Gene Therapies Now FDA-Approved for Use: What You Need to Know to Address Safety and IP Considerations – Plus an Update on Biosimilars

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Syllabus

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SUPREME COURT OF THE UNITED STATES

Syllabus

SANDOZ INC. *v.* AMGEN INC. ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 15–1039. Argued April 26, 2017—Decided June 12, 2017*

The Biologics Price Competition and Innovation Act of 2009 (BPCIA or Act) provides an abbreviated pathway for obtaining Food and Drug Administration (FDA) approval of a drug that is biosimilar to an already licensed biological product (reference product). 42 U. S. C. §262(k). It also provides procedures for resolving patent disputes between biosimilar manufacturers (applicants) and manufacturers of reference products (sponsors). §262(*l*). The Act treats the mere submission of a biosimilar application as an "artificial" act of infringement, enabling parties to bring patent infringement actions at certain points in the application process even if the applicant has not committed a traditional act of patent infringement. See 35 U. S. C. §§271(e)(2)(C)(i), (ii).

Under §262(*l*)(2)(A), an applicant seeking FDA approval of a biosimilar must provide its application and manufacturing information to the sponsor within 20 days of the date the FDA notifies the applicant that it has accepted the application for review. This triggers an exchange of information between the applicant and sponsor designed to create lists of relevant patents and flesh out potential legal arguments. §262(*l*)(3). The BPCIA then channels the parties into two phases of patent litigation. In the first, the parties collaborate to identify patents on the lists for immediate litigation. The second phase—triggered when the applicant, pursuant to §262(*l*)(8)(A), gives the sponsor notice at least 180 days before commercially marketing the biosimilar—involves any listed patents not litigated in the first phase. The applicant has substantial control over the timing and

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*Together with No. 15–1195, *Amgen Inc. et al.* v. *Sandoz Inc.*, also on certiorari to the same court.

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scope of both phases of litigation.

Failure to comply with these procedural requirements may lead to two consequences relevant here. Under §262(*l*)(9)(C), if an applicant fails to provide its application and manufacturing information to the sponsor under §262(*l*)(2)(A), then the sponsor, but not the applicant, may immediately bring an action "for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." And under §262(*l*)(9)(B), if an applicant provides the application and manufacturing information but fails to complete a subsequent step in the process, the sponsor, but not the applicant, may bring a declaratory-judgment action with respect to any patent included on the sponsor's list of relevant patents.

Neupogen is a filgrastim product marketed by Amgen, which claims to hold patents on methods of manufacturing and using filgrastim. Sandoz sought FDA approval to market a biosimilar filgrastim product under the brand name Zarxio, with Neupogen as the reference product. A day after the FDA informed Sandoz that its application had been accepted for review, Sandoz notified Amgen that it had submitted an application and that it intended to market Zarxio immediately upon receiving FDA approval. It later informed Amgen that it did not intend to provide the application and manufacturing information required by §262(*l*)(2)(A) and that Amgen could sue immediately for infringement under §262(*l*)(9)(C).

Amgen sued Sandoz for patent infringement and also asserted that Sandoz engaged in "unlawful" conduct in violation of California's unfair competition law. This latter claim was predicated on two alleged violations of the BPCIA: Sandoz's failure to provide its application and manufacturing information under §262(*l*)(2)(A), and its provision of notice of commercial marketing under §262(*l*)(8)(A) prior to obtaining licensure from the FDA. Amgen sought injunctions to enforce both BPCIA requirements. Sandoz counterclaimed for declaratory judgments that the asserted patent was invalid and not infringed and that it had not violated the BPCIA.

While the case was pending, the FDA licensed Zarxio, and Sandoz provided Amgen a further notice of commercial marketing. The District Court subsequently granted partial judgment on the pleadings to Sandoz on its BPCIA counterclaims and dismissed Amgen's unfair competition claims with prejudice. The Federal Circuit affirmed in part, vacated in part, and remanded. The court affirmed the dismissal of Amgen's state-law claim based on Sandoz's alleged violation of §262(*l*)(2)(A), holding that Sandoz did not violate the BPCIA in failing to disclose its application and manufacturing information and that the BPCIA provides the exclusive remedies for failure to comply

with this requirement. The court also held that under §262(*l*)(8)(A) an applicant must provide notice of commercial marketing after obtaining licensure, and that this requirement is mandatory. It thus enjoined Sandoz from marketing Zarxio until 180 days after the date it provided its second notice.

Held: Section 262(*l*)(2)(A) is not enforceable by injunction under federal law, but the Federal Circuit on remand should determine whether a state-law injunction is available. An applicant may provide notice under §262(*l*)(8)(A) prior to obtaining licensure. Pp. 10–18.

(a) Section 262(*l*)(2)(A)'s requirement that an applicant provide the sponsor with its application and manufacturing information is not enforceable by an injunction under federal law. The Federal Circuit reached the proper result on this point, but its reasoning was flawed. It cited §271(e)(4), which expressly provides the "only remedies" for an act of artificial infringement. In light of this language, the court reasoned that no remedy other than those specified in the text—such as an injunction to compel the applicant to provide its application and manufacturing information—was available. The problem with this reasoning is that Sandoz's failure to disclose was not an act of artificial infringement remediable under §271(e)(4). Submitting an application constitutes an act of artificial infringement; failing to disclose the application and manufacturing information required by §262(*l*)(2)(A) does not.

Another provision, §262(*l*)(9)(C), provides a remedy for an applicant's failure to turn over its application and manufacturing information. It authorizes the sponsor, but not the applicant, to bring an immediate declaratory-judgment action for artificial infringement, thus vesting in the sponsor the control that the applicant would otherwise have exercised over the scope and timing of the patent litigation and depriving the applicant of the certainty it could have obtained by bringing a declaratory-judgment action prior to marketing its product. The presence of this remedy, coupled with the absence of any other textually specified remedies, indicates that Congress did not intend sponsors to have access to injunctive relief, at least as a matter of federal law, to enforce the disclosure requirement. See *Great-West Life & Annuity Ins. Co.* v. *Knudson*, 534 U. S. 204, 209. Statutory context further confirms that Congress did not authorize courts to enforce §262(*l*)(2)(A) by injunction. Pp. 10–13.

(b) The Federal Circuit should determine on remand whether an injunction is available under state law to enforce §262(*l*)(2)(A). Whether Sandoz's conduct was "unlawful" under California's unfair competition statute is a question of state law, and the Federal Circuit thus erred in attempting to answer that question by referring only to the BPCIA. There is no dispute about how the federal scheme actual-

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ly works on the facts of this case: Sandoz failed to disclose the requisite information under §262(*l*)(2)(A), and was accordingly subject to the consequence specified in §262(*l*)(9)(C). As a result, there is nothing to decide on this point as a matter of federal law. The court on remand should determine whether California law would treat noncompliance with §262(*l*)(2)(A) as "unlawful," and whether the BPCIA pre-empts any additional state-law remedy for failure to comply with §262(*l*)(2)(A). Pp. 13–15.

(c) An applicant may provide notice of commercial marketing before obtaining a license. Section 262(*l*)(8)(A) states that the applicant "shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." Because the phrase "of the biological product licensed under subsection (k)" modifies "commercial marketing" rather than "notice," "commercial marketing" is the point in time by which the biosimilar must be "licensed." Accordingly, the applicant may provide notice either before or after receiving FDA approval. Statutory context confirms that §262(*l*)(8)(A) contains a single timing requirement (180 days before marketing), rather than the two requirements posited by the Federal Circuit (after licensing, and 180 days before marketing). "Had Congress intended to" impose two timing requirements in §262(*l*)(8)(A), "it presumably would have done so expressly as it did in the" adjacent provision, §262(*l*)(8)(B). *Russello* v. *United States*, 464 U. S. 16, 23. Amgen's contrary arguments are unpersuasive, and its various policy arguments cannot overcome the statute's plain language. Pp. 15–18.

794 F. 3d 1347, vacated in part, reversed in part, and remanded.

THOMAS, J., delivered the opinion for a unanimous Court. BREYER, J., filed a concurring opinion.

SUPREME COURT OF THE UNITED STATES

Nos. 15–1039 and 15–1195

SANDOZ INC., PETITIONER
15–1039 *v.*
AMGEN INC., ET AL.

AMGEN INC., ET AL., PETITIONERS
15–1195 *v.*
SANDOZ INC.

ON WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 12, 2017]

JUSTICE THOMAS delivered the opinion of the Court.

These cases involve 42 U. S. C. §262(*l*), which was enacted as part of the Biologics Price Competition and Innovation Act of 2009 (BPCIA), 124 Stat. 808. The BPCIA governs a type of drug called a biosimilar, which is a biologic product that is highly similar to a biologic product that has already been approved by the Food and Drug Administration (FDA). Under §262(*l*), an applicant that seeks FDA approval of a biosimilar must provide its application materials and manufacturing information to the manufacturer of the corresponding biologic within 20 days of the date the FDA notifies the applicant that it has accepted the application for review. The applicant then must give notice to the manufacturer at least 180 days before marketing the biosimilar commercially.

The first question presented by these cases is whether

the requirement that an applicant provide its application and manufacturing information to the manufacturer of the biologic is enforceable by injunction. We conclude that an injunction is not available under federal law, but we remand for the court below to decide whether an injunction is available under state law. The second question is whether the applicant must give notice to the manufacturer after, rather than before, obtaining a license from the FDA for its biosimilar. We conclude that an applicant may provide notice before obtaining a license.

I

The complex statutory scheme at issue in these cases establishes processes both for obtaining FDA approval of biosimilars and for resolving patent disputes between manufacturers of licensed biologics and manufacturers of biosimilars. Before turning to the questions presented, we first explain the statutory background.

A

A biologic is a type of drug derived from natural, biological sources such as animals or microorganisms. Biologics thus differ from traditional drugs, which are typically synthesized from chemicals.[1] A manufacturer of a biologic may market the drug only if the FDA has licensed it pursuant to either of two review processes set forth in §262. The default pathway for approval, used for new biologics, is set forth in §262(a). Under that subsection, the FDA may license a new biologic if, among other things, the manufacturer demonstrates that it is "safe, pure, and potent." §262(a)(2)(C)(i)(I). In addition to this default route, the statute also prescribes an alternative, abbreviated route for FDA approval of biosimilars, which is set

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[1] FDA, What Are "Biologics" Questions and Answers (Aug. 5, 2015), http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm (as last visited June 6, 2017).

forth in §262(k).

To obtain approval through the BPCIA's abbreviated process, the manufacturer of a biosimilar (applicant) does not need to show that the product is "safe, pure, and potent." Instead, the applicant may piggyback on the showing made by the manufacturer (sponsor) of a previously licensed biologic (reference product). See §262(k)(2)(A)(iii). An applicant must show that its product is "highly similar" to the reference product and that there are no "clinically meaningful differences" between the two in terms of "safety, purity, and potency." §§262(i)(2)(A), (B); see also §262(k)(2)(A)(i)(I). An applicant may not submit an application until 4 years after the reference product is first licensed, and the FDA may not license a biosimilar until 12 years after the reference product is first licensed. §§262(k)(7)(A), (B). As a result, the manufacturer of a new biologic enjoys a 12-year period when its biologic may be marketed without competition from biosimilars.

B

A sponsor may hold multiple patents covering the biologic, its therapeutic uses, and the processes used to manufacture it. Those patents may constrain an applicant's ability to market its biosimilar even after the expiration of the 12-year exclusivity period contained in §262(k)(7)(A).

The BPCIA facilitates litigation during the period preceding FDA approval so that the parties do not have to wait until commercial marketing to resolve their patent disputes. It enables the parties to bring infringement actions at certain points in the application process, even if the applicant has not yet committed an act that would traditionally constitute patent infringement. See 35 U. S. C. §271(a) (traditionally infringing acts include making, using, offering to sell, or selling any patented invention within the United States without authority to do so). Specifically, it provides that the mere submission of a

biosimilar application constitutes an act of infringement. §§271(e)(2)(C)(i), (ii). We will refer to this kind of preapproval infringement as "artificial" infringement. Section 271(e)(4) provides remedies for artificial infringement, including injunctive relief and damages.

C

The BPCIA sets forth a carefully calibrated scheme for preparing to adjudicate, and then adjudicating, claims of infringement. See 42 U. S. C. §262(*l*). When the FDA accepts an application for review, it notifies the applicant, who within 20 days "shall provide" to the sponsor a copy of the application and information about how the biosimilar is manufactured. §262(*l*)(2)(A). The applicant also "may provide" the sponsor with any additional information that it requests. §262(*l*)(2)(B). These disclosures enable the sponsor to evaluate the biosimilar for possible infringement of patents it holds on the reference product (*i.e.*, the corresponding biologic). §262(*l*)(1)(D). The information the applicant provides is subject to strict confidentiality rules, enforceable by injunction. See §262(*l*)(1)(H). The first question presented by these cases is whether §262(*l*)(2)(A)'s requirement—that the applicant provide its application and manufacturing information to the sponsor—is itself enforceable by injunction.

After the applicant makes the requisite disclosures, the parties exchange information to identify relevant patents and to flesh out the legal arguments that they might raise in future litigation. Within 60 days of receiving the application and manufacturing information, the sponsor "shall provide" to the applicant "a list of patents" for which it believes it could assert an infringement claim if a person without a license made, used, offered to sell, sold, or imported "the biological product that is the subject of the [biosimilar] application." §262(*l*)(3)(A)(i). The sponsor must also identify any patents on the list that it would be

willing to license. §262(*l*)(3)(A)(ii).

Next, within 60 days of receiving the sponsor's list, the applicant may provide to the sponsor a list of patents that the applicant believes are relevant but that the sponsor omitted from its own list, §262(*l*)(3)(B)(i), and "shall provide" to the sponsor reasons why it could not be held liable for infringing the relevant patents, §262(*l*)(3)(B)(ii). The applicant may argue that the relevant patents are invalid, unenforceable, or not infringed, or the applicant may agree not to market the biosimilar until a particular patent has expired. *Ibid.* The applicant must also respond to the sponsor's offers to license particular patents. §262(*l*)(3)(B)(iii). Then, within 60 days of receiving the applicant's responses, the sponsor "shall provide" to the applicant its own arguments concerning infringement, enforceability, and validity as to each relevant patent. §262(*l*)(3)(C).

Following this exchange, the BPCIA channels the parties into two phases of patent litigation. In the first phase, the parties collaborate to identify patents that they would like to litigate immediately. The second phase is triggered by the applicant's notice of commercial marketing and involves any patents that were included on the parties' §262(*l*)(3) lists but not litigated in the first phase.

At the outset of the first phase, the applicant and the sponsor must negotiate to determine which patents included on the §262(*l*)(3) lists will be litigated immediately. See §§262(*l*)(4)(A), (*l*)(6). If they cannot agree, then they must engage in another list exchange. §262(*l*)(4)(B). The applicant "shall notify" the sponsor of the number of patents it intends to list for litigation, §262(*l*)(5)(A), and, within five days, the parties "shall simultaneously exchange" lists of the patents they would like to litigate immediately. §262(*l*)(5)(B)(i). This process gives the applicant substantial control over the scope of the first phase of litigation: The number of patents on the sponsor's

list is limited to the number contained in the applicant's list, though the sponsor always has the right to list at least one patent. §262(*l*)(5)(B)(ii).

The parties then proceed to litigate infringement with respect to the patents they agreed to litigate or, if they failed to agree, the patents contained on the lists they simultaneously exchanged under §262(*l*)(5). §§262(*l*)(6)(A), (B). Section 271(e)(2)(C)(i) facilitates this first phase of litigation by making it an act of artificial infringement, with respect to any patent included on the parties' §262(*l*)(3) lists, to submit an application for a license from the FDA. The sponsor "shall bring an action" in court within 30 days of the date of agreement or the simultaneous list exchange. §§262(*l*)(6)(A), (B). If the sponsor brings a timely action and prevails, it may obtain a remedy provided by §271(e)(4).

The second phase of litigation involves patents that were included on the original §262(*l*)(3) lists but not litigated in the first phase (and any patents that the sponsor acquired after the §262(*l*)(3) exchange occurred and added to the lists, see §262(*l*)(7)). The second phase is commenced by the applicant's notice of commercial marketing, which the applicant "shall provide" to the sponsor "not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k)." §262(*l*)(8)(A). The BPCIA bars any declaratory judgment action prior to this notice. §262(*l*)(9)(A) (prohibiting, in situations where the parties have complied with each step of the BPCIA process, either the sponsor or the applicant from seeking a "declaration of infringement, validity, or enforceability of any patent" that was included on the §262(*l*)(3) lists but not litigated in the first phase "prior to the date notice is received under paragraph (8)(A)"). Because the applicant (subject to certain constraints) chooses when to begin commercial marketing and when to give notice, it wields substantial control over the

timing of the second phase of litigation. The second question presented is whether notice is effective if an applicant provides it prior to the FDA's decision to license the biosimilar.

In this second phase of litigation, *either* party may sue for declaratory relief. See §262(*l*)(9)(A). In addition, prior to the date of first commercial marketing, the sponsor may "seek a preliminary injunction prohibiting the [biosimilar] applicant from engaging in the commercial manufacture or sale of [the biosimilar] until the court decides the issue of patent validity, enforcement, and infringement with respect to any patent that" was included on the §262(*l*)(3) lists but not litigated in the first phase. §262(*l*)(8)(B).

D

If the parties comply with each step outlined in the BPCIA, they will have the opportunity to litigate the relevant patents before the biosimilar is marketed. To encourage parties to comply with its procedural requirements, the BPCIA includes various consequences for failing to do so. Two of the BPCIA's remedial provisions are at issue here. Under §262(*l*)(9)(C), if an applicant fails to provide its application and manufacturing information to the sponsor—thus effectively pretermitting the entire two-phase litigation process—then the sponsor, but not the applicant, may immediately bring an action "for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." Section 271(e)(2)(C)(ii) facilitates this action by making it an artificial act of infringement, with respect to any patent that *could* have been included on the §262(*l*)(3) lists, to submit a biosimilar application. Similarly, when an applicant provides the application and manufacturing information but fails to complete a subsequent step, §262(*l*)(9)(B) provides that the sponsor, but not the applicant, may bring a declaratory-judgment action

with respect to any patent included on the sponsor's §262(*l*)(3)(A) list of patents (as well as those it acquired later and added to the list). As noted, it is an act of artificial infringement, with respect to any patent on the §262(*l*)(3) lists, to submit an application to the FDA. See §271(e)(2)(C)(i).

II

These cases concern filgrastim, a biologic used to stimulate the production of white blood cells. Amgen, the respondent in No. 15–1039 and the petitioner in No. 15–1195, has marketed a filgrastim product called Neupogen since 1991 and claims to hold patents on methods of manufacturing and using filgrastim. In May 2014, Sandoz, the petitioner in No. 15–1039 and the respondent in No. 15–1195, filed an application with the FDA seeking approval to market a filgrastim biosimilar under the brand name Zarxio, with Neupogen as the reference product. The FDA informed Sandoz on July 7, 2014, that it had accepted the application for review. One day later, Sandoz notified Amgen both that it had submitted an application and that it intended to begin marketing Zarxio immediately upon receiving FDA approval, which it expected in the first half of 2015. Sandoz later confirmed that it did not intend to provide the requisite application and manufacturing information under §262(*l*)(2)(A) and informed Amgen that Amgen could sue for infringement immediately under §262(*l*)(9)(C).

In October 2014, Amgen sued Sandoz for patent infringement. Amgen also asserted two claims under California's unfair competition law, which prohibits "any unlawful . . . business act or practice." Cal. Bus. & Prof. Code Ann. §17200 (West 2008). A "business act or practice" is "unlawful" under the unfair competition law if it violates a rule contained in some other state or federal statute. *Rose* v. *Bank of America, N. A.*, 57 Cal. 4th 390,

396, 304 P. 3d 181, 185 (2013). Amgen alleged that Sandoz engaged in "unlawful" conduct when it failed to provide its application and manufacturing information under §262(*l*)(2)(A), and when it provided notice of commercial marketing under §262(*l*)(8)(A) before, rather than after, the FDA licensed its biosimilar. Amgen sought injunctions to enforce both requirements. Sandoz counterclaimed for declaratory judgments that the asserted patent was invalid and not infringed and that it had not violated the BPCIA.

While the case was pending in the District Court, the FDA licensed Zarxio, and Sandoz provided Amgen a further notice of commercial marketing. The District Court subsequently granted partial judgment on the pleadings to Sandoz on its BPCIA counterclaims and dismissed Amgen's unfair competition claims with prejudice. 2015 WL 1264756, *7–*9 (ND Cal., Mar. 19, 2015). After the District Court entered final judgment as to these claims, Amgen appealed to the Federal Circuit, which granted an injunction pending appeal against the commercial marketing of Zarxio.

A divided Federal Circuit affirmed in part, vacated in part, and remanded. First, the court affirmed the dismissal of Amgen's state-law claim based on Sandoz's alleged violation of §262(*l*)(2)(A). It held that Sandoz did not violate the BPCIA in failing to disclose its application and manufacturing information. It further held that the remedies contained in the BPCIA are the exclusive remedies for an applicant's failure to comply with §262(*l*)(2)(A). 794 F. 3d 1347, 1357, 1360 (2015).

Second, the court held that an applicant may provide effective notice of commercial marketing only *after* the FDA has licensed the biosimilar. *Id.,* at 1358. Accordingly, the 180-day clock began after Sandoz's second, post-licensure notice. The Federal Circuit further concluded that the notice requirement is mandatory and extended its

injunction pending appeal to bar Sandoz from marketing Zarxio until 180 days after the date it provided its second notice. *Id.,* at 1360–1361.

We granted Sandoz's petition for certiorari, No. 15–1039, and Amgen's conditional cross-petition for certiorari, No. 15–1195, and consolidated the cases. 580 U. S. ___ (2017).

III

The first question we must answer is whether §262(*l*)(2)(A)'s requirement that an applicant provide the sponsor with its application and manufacturing information is enforceable by an injunction under either federal or state law.

A

We agree with the Federal Circuit that an injunction under federal law is not available to enforce §262(*l*)(2)(A), though for slightly different reasons than those provided by the court below. The Federal Circuit held that "42 U. S. C. §262(*l*)(9)(C) and 35 U. S. C. §271(e) expressly provide the only remedies" for a violation of §262(*l*)(2)(A), 794 F. 3d, at 1357, and neither of those provisions authorizes a court to compel compliance with §262(*l*)(2)(A). In concluding that the remedies specified in the BPCIA are exclusive, the Federal Circuit relied primarily on §271(e)(4), which states that it provides "'the only remedies which may be granted by a court for an act of [artificial] infringement.'" *Id.,* at 1356 (emphasis deleted).

The flaw in the Federal Circuit's reasoning is that Sandoz's failure to disclose its application and manufacturing information was not an act of artificial infringement, and thus was not remediable under §271(e)(4). Submitting an application constitutes an act of artificial infringement. See §§271(e)(2)(C)(i), (ii) ("It shall be an act of infringement to submit . . . an application seeking ap-

proval of a biological product"). Failing to disclose the application and manufacturing information under §262(*l*)(2)(A) does not.

In reaching the opposite conclusion, the Federal Circuit relied on §271(e)(2)(C)(ii), which states that "[i]t shall be an act of infringement to submit[,] *if the applicant for the application fails to provide the application and information required under [§262(l)(2)(A)]*, an application seeking approval of a biological product for a patent that could be identified pursuant to [§262(*l*)(3)(A)(i)]." (Emphasis added.) The court appeared to conclude, based on the italicized language, that an applicant's noncompliance with §262(*l*)(2)(A) is an element of the act of artificial infringement (along with the submission of the application). 794 F. 3d, at 1356. We disagree. The italicized language merely assists in identifying which patents will be the subject of the artificial infringement suit. It does not define the act of artificial infringement itself.

This conclusion follows from the structure of §271(e)(2)(C). Clause (i) of §271(e)(2)(C) defines artificial infringement in the situation where the parties proceed through the list exchange process and the patents subject to suit are those contained in the §262(*l*)(3) lists, as supplemented under §262(*l*)(7). That clause provides that it is an act of artificial infringement to submit, "*with respect to a patent that is identified in the list of patents described in [§262(l)(3)] (including as provided under [§262(l)(7)])*, an application seeking approval of a biological product." (Emphasis added.) Clause (ii) of §271(e)(2)(C), in contrast, defines artificial infringement in the situation where an applicant fails to disclose its application and manufacturing information altogether and the parties never prepare the §262(*l*)(3) lists. That clause provides that the submission of the application represents an act of artificial infringement with respect to any patent that *could* have been included on the lists.

In this way, the two clauses of §271(e)(2)(C) work in tandem. They both treat submission of the application as the act of artificial infringement for which §271(e)(4) provides the remedies. And they both identify the patents subject to suit, although by different means depending on whether the applicant disclosed its application and manufacturing information under §262(*l*)(2)(A). If the applicant made the disclosures, clause (i) applies; if it did not, clause (ii) applies. In neither instance is the applicant's failure to provide its application and manufacturing information an element of the act of artificial infringement, and in neither instance does §271(e)(4) provide a remedy for that failure. See Brief for Amgen Inc. et al. 66–67 (conceding both points).

A separate provision of §262, however, does provide a remedy for an applicant's failure to turn over its application and manufacturing information. When an applicant fails to comply with §262(*l*)(2)(A), §262(*l*)(9)(C) authorizes the sponsor, but not the applicant, to bring an immediate declaratory-judgment action for artificial infringement as defined in §271(e)(2)(C)(ii). Section 262(*l*)(9)(C) thus vests in the sponsor the control that the applicant would otherwise have exercised over the scope and timing of the patent litigation. It also deprives the applicant of the certainty that it could have obtained by bringing a declaratory-judgment action prior to marketing its product.

The remedy provided by §262(*l*)(9)(C) excludes all other federal remedies, including injunctive relief. Where, as here, "a statute expressly provides a remedy, courts must be especially reluctant to provide additional remedies." *Karahalios* v. *Federal Employees*, 489 U. S. 527, 533 (1989). The BPCIA's "carefully crafted and detailed enforcement scheme provides strong evidence that Congress did *not* intend to authorize other remedies that it simply forgot to incorporate expressly." *Great-West Life & Annu-*

ity Ins. Co. v. *Knudson*, 534 U. S. 204, 209 (2002) (internal quotation marks omitted). The presence of §262(*l*)(9)(C), coupled with the absence of any other textually specified remedies, indicates that Congress did not intend sponsors to have access to injunctive relief, at least as a matter of federal law, to enforce the disclosure requirement.

Statutory context further confirms that Congress did not authorize courts to enforce §262(*l*)(2)(A) by injunction. Section 262(*l*)(1)(H) provides that "the court shall consider immediate injunctive relief to be an appropriate and necessary remedy for any violation or threatened violation" of the rules governing the confidentiality of information disclosed under §262(*l*). We assume that Congress acted intentionally when it provided an injunctive remedy for breach of the confidentiality requirements but not for breach of §262(*l*)(2)(A)'s disclosure requirement. Cf. *Touche Ross & Co.* v. *Redington*, 442 U. S. 560, 572 (1979) ("[W]hen Congress wished to provide a private damage remedy, it knew how to do so and did so expressly").[2] Accordingly, the Federal Circuit properly declined to grant an injunction under federal law.

B

The Federal Circuit rejected Amgen's request for an injunction under state law for two reasons. First, it interpreted California's unfair competition law not to provide a remedy when the underlying statute specifies an "expressly . . . exclusive" remedy. 794 F. 3d, at 1360 (citing Cal.

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[2] In holding that §262(*l*)(9)(C) represents the exclusive remedy for an applicant's failure to provide its application and manufacturing information, we express no view on whether a district court could take into account an applicant's violation of §262(*l*)(2)(A) (or any other BPCIA procedural requirement) in deciding whether to grant a preliminary injunction under 35 U. S. C. §271(e)(4)(B) or §283 against marketing the biosimilar. See *Winter* v. *Natural Resources Defense Council, Inc.*, 555 U. S. 7, 20 (2008) (court should consider "balance of equities" in deciding whether to grant a preliminary injunction).

Bus. & Prof. Code Ann. §17205; *Loeffler* v. *Target Corp.*, 58 Cal. 4th 1081, 1125–1126, 324 P. 3d 50, 76 (2014)). It further held that §271(e)(4), by its text, "provides 'the only remedies'" for an applicant's failure to disclose its application and manufacturing information. 794 F. 3d, at 1360 (quoting §271(e)(4)). The court thus concluded that no state remedy was available for Sandoz's alleged violation of §262(*l*)(2)(A) under the terms of California's unfair competition law.

This state-law holding rests on an incorrect interpretation of federal law. As we have explained, failure to comply with §262(*l*)(2)(A) is not an act of artificial infringement. Because §271(e)(4) provides remedies only for artificial infringement, it provides no remedy at all, much less an "expressly . . . exclusive" one, for Sandoz's failure to comply with §262(*l*)(2)(A).

Second, the Federal Circuit held in the alternative that Sandoz's failure to disclose its application and manufacturing information was not "unlawful" under California's unfair competition law. In the court's view, when an applicant declines to provide its application and manufacturing information to the sponsor, it takes a path "expressly contemplated by" §262(*l*)(9)(C) and §271(e)(2)(C)(ii) and thus does not violate the BPCIA. 794 F. 3d, at 1357, 1360. In their briefs before this Court, the parties frame this issue as whether the §262(*l*)(2)(A) requirement is mandatory in all circumstances, see Brief for Amgen Inc. et al. 58, or merely a condition precedent to the information exchange process, see Reply Brief for Sandoz Inc. 33. If it is only a condition precedent, then an applicant effectively has the option to withhold its application and manufacturing information and does not commit an "unlawful" act in doing so.

We decline to resolve this particular dispute definitively because it does not present a question of federal law. The BPCIA, standing alone, does not require a court to decide

whether §262(*l*)(2)(A) is mandatory or conditional; the court need only determine whether the applicant supplied the sponsor with the information required under §262(*l*)(2)(A). If the applicant failed to provide that information, then the sponsor, but not the applicant, could bring an immediate declaratory-judgment action pursuant to §262(*l*)(9)(C). The parties in these cases agree—as did the Federal Circuit—that Sandoz failed to comply with §262(*l*)(2)(A), thus subjecting itself to that consequence. There is no dispute about how the federal scheme actually works, and thus nothing for us to decide as a matter of federal law. The mandatory or conditional nature of the BPCIA's requirements matters *only* for purposes of California's unfair competition law, which penalizes "unlawful" conduct. Whether Sandoz's conduct was "unlawful" under the unfair competition law is a state-law question, and the court below erred in attempting to answer that question by referring to the BPCIA alone.

On remand, the Federal Circuit should determine whether California law would treat noncompliance with §262(*l*)(2)(A) as "unlawful." If the answer is yes, then the court should proceed to determine whether the BPCIA pre-empts any additional remedy available under state law for an applicant's failure to comply with §262(*l*)(2)(A) (and whether Sandoz has forfeited any pre-emption defense, see 794 F. 3d, at 1360, n. 5). The court is also of course free to address the pre-emption question first by assuming that a remedy under state law exists.

IV

The second question at issue in these cases is whether an applicant must provide notice *after* the FDA licenses its biosimilar, or if it may also provide effective notice before licensure. Section 262(*l*)(8)(A) states that the applicant "shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial

marketing of the biological product licensed under subsection (k)." The Federal Circuit held that an applicant's biosimilar must already be "licensed" at the time the applicant gives notice. 794 F. 3d, at 1358.

We disagree. The applicant must give "notice" at least 180 days "before the date of the first commercial marketing." "[C]ommercial marketing," in turn, must be "of the biological product licensed under subsection (k)." §262(*l*)(8)(A). Because this latter phrase modifies "commercial marketing" rather than "notice," "commercial marketing" is the point in time by which the biosimilar must be "licensed." The statute's use of the word "licensed" merely reflects the fact that, on the "date of the first commercial marketing," the product must be "licensed." See §262(a)(1)(A). Accordingly, the applicant may provide notice either before or after receiving FDA approval.

Statutory context confirms this interpretation. Section 262(*l*)(8)(A) contains a single timing requirement: The applicant must provide notice at least 180 days prior to marketing its biosimilar. The Federal Circuit, however, interpreted the provision to impose two timing requirements: The applicant must provide notice after the FDA licenses the biosimilar *and* at least 180 days before the applicant markets the biosimilar. An adjacent provision expressly sets forth just that type of dual timing requirement. See §262(*l*)(8)(B) ("*After* receiving notice under subparagraph (A) and *before* such date of the first commercial marketing of such biological product, the reference product sponsor may seek a preliminary injunction" (emphasis added)). But Congress did not use that structure in §262(*l*)(8)(A). "Had Congress intended to" impose two timing requirements in §262(*l*)(8)(A), "it presumably would have done so expressly as it did in the immediately following" subparagraph. *Russello* v. *United States*, 464 U. S. 16, 23 (1983).

We are not persuaded by Amgen's arguments to the contrary. Amgen points out that other provisions refer to "'the biological product *that is the subject of*'" the application, rather than the "'biological product *licensed under* subsection (k).'" Brief for Amgen Inc. et al. 28 (emphasis added). In its view, this variation "is a strong textual indication that §262(*l*)(8)(A), unlike the other provisions, refers to a product that has already been 'licensed' by the FDA." *Ibid.*

Amgen's interpretation is not necessary to harmonize Congress' use of the two different phrases. The provision upon which Amgen primarily relies (and that is generally illustrative of the other provisions it cites) requires the applicant to explain why the sponsor's patents are "'invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product that is the subject of the subsection (k) application.'" *Id.,* at 29–30 (quoting §262(*l*)(3)(B)(ii)(I); emphasis deleted). This provision uses the phrase "subject of the subsection (k) application" rather than "product licensed under subsection (k)" because the applicant can evaluate validity, enforceability, and infringement with respect to the biosimilar only as it exists *when the applicant is conducting the evaluation*, which it does before licensure. The applicant cannot make the same evaluation with respect to the biosimilar as it will exist after licensure, because the biosimilar's specifications may change during the application process. See, *e.g.,* 794 F. 3d, at 1358. In contrast, nothing in §262(*l*)(8)(A) turns on the precise status or characteristics of the biosimilar application.

Amgen also advances a host of policy arguments that prelicensure notice is undesirable. See Brief for Amgen Inc. et al. 35–42. Sandoz and the Government, in turn, respond with their own bevy of arguments that Amgen's concerns are misplaced and that prelicensure notice affirmatively furthers Congress' intent. See Brief for

Sandoz Inc. 39–42, 56; Brief for United States as *Amicus Curiae* 28–29. The plausibility of the contentions on both sides illustrates why such disputes are appropriately addressed to Congress, not the courts. Even if we were persuaded that Amgen had the better of the policy arguments, those arguments could not overcome the statute's plain language, which is our "primary guide" to Congress' preferred policy. *McFarland* v. *Scott*, 512 U. S. 849, 865 (1994) (THOMAS, J., dissenting).

In sum, because Sandoz fully complied with §262(*l*)(8)(A) when it first gave notice (before licensure) in July 2014, the Federal Circuit erred in issuing a federal injunction prohibiting Sandoz from marketing Zarxio until 180 days after licensure. Furthermore, because Amgen's request for state-law relief is predicated on its argument that the BPCIA forbids prelicensure notice, its claim under California's unfair competition law also fails. We accordingly reverse the Federal Circuit's judgment as to the notice provision.

* * *

For the foregoing reasons, the judgment of the Court of Appeals is vacated in part and reversed in part, and the cases are remanded for further proceedings consistent with this opinion.

It is so ordered.

SUPREME COURT OF THE UNITED STATES

Nos. 15–1039 and 15–1195

15–1039 SANDOZ INC., PETITIONER *v.* AMGEN INC., ET AL.

15–1195 AMGEN INC., ET AL., PETITIONERS *v.* SANDOZ INC.

ON WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

[June 12, 2017]

JUSTICE BREYER, concurring.

The Court's interpretation of the statutory terms before us is a reasonable interpretation, and I join its opinion. In my view, Congress implicitly delegated to the Food and Drug Administration authority to interpret those same terms. That being so, if that agency, after greater experience administering this statute, determines that a different interpretation would better serve the statute's objectives, it may well have authority to depart from, or to modify, today's interpretation, see *National Cable & Telecommunications Assn.* v. *Brand X Internet Services*, 545 U. S. 967, 982–984 (2005), though we need not now decide any such matter.

United States Court of Appeals for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING LIMITED,
Plaintiffs-Appellants

v.

SANDOZ INC.,
Defendant-Appellee

2015-1499

Appeal from the United States District Court for the Northern District of California in No. 3:14-cv-04741-RS, Judge Richard Seeborg.

Decided: December 14, 2017

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Before NEWMAN, LOURIE, and CHEN, *Circuit Judges*.

LOURIE, *Circuit Judge*.

This appeal has returned to us on remand from the Supreme Court of the United States. In their earlier appearance in this court, Amgen Inc. and Amgen Manufacturing Ltd. (collectively, "Amgen") appealed from the decision of the United States District Court for the Northern District of California (1) granting partial judgment on the pleadings to Sandoz Inc. ("Sandoz") on its counterclaims seeking a declaratory judgment interpreting the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010) (codified as amended at 42 U.S.C. § 262, 35 U.S.C. § 271(e), 28 U.S.C. § 2201(b), 21 U.S.C. § 355 et seq.); (2) dismissing with prejudice Amgen's unfair competition claims asserting unlawful business practices under California Business & Professions Code § 17200 et seq. ("UCL") and conversion claims (collectively, the "state law claims"); and (3) denying Amgen's motion for a preliminary injunction based on its state law claims. *Amgen Inc. v. Sandoz Inc.*, No. 14-cv-04741, 2015 WL 1264756 (N.D. Cal. Mar. 19, 2015) ("*Opinion*").

Following full briefing and oral argument, we affirmed the dismissal of Amgen's state law claims, vacated the judgment on Sandoz's counterclaims, directed the district court to enter judgment on those counterclaims consistent with our opinion, and remanded for further

proceedings. *See Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015), *rev'd in part, vacated in part*, 137 S. Ct. 1664 (2017).

In particular, we held that under 42 U.S.C. § 262(*l*)(8)(A) "a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product." *Id.* at 1357. In addition, we held that the "shall" provision in paragraph (*l*)(2)(A) did not mean "must" and concluded that "when a subsection (k) applicant fails the disclosure requirement [of § 262(*l*)(8)(A)], 42 U.S.C. § 262(*l*)(9)(C) and 35 U.S.C. § 271(e) expressly provide the only remedies as those being based on a claim of patent infringement." *Id.* at 1355–57.

Both parties petitioned for rehearing en banc, which this court denied. *See Amgen Inc. v. Sandoz Inc.*, No. 15-1499, slip op. (Fed. Cir. Oct. 16, 2015). Sandoz then filed a petition for a writ of certiorari in the Supreme Court presenting the following questions: "Whether notice of commercial marketing given before FDA approval can be effective and whether, in any event, treating Section 262(*l*)(8)(A) as a standalone requirement and creating an injunctive remedy that delays all biosimilars by 180 days after approval is improper." Petition for a Writ of Certiorari at ii, *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017) (No. 15-1039).

Amgen subsequently filed a conditional cross-petition for a writ of certiorari presenting the following questions:

> Is an Applicant required by 42 U.S.C. § 262(*l*)(2)(A) to provide the Sponsor with a copy of its biologics license application and related manufacturing information, which the statute says the Applicant "shall provide," and, where an Applicant fails to provide that required information, is the Sponsor's sole recourse to commence a declaratory-judgment action under 42 U.S.C.

> § 262(*l*)(9)(C) and/or a patent-infringement action under 35 U.S.C. § 27l(e)(2)(C)(ii)?

Conditional Cross-Petition for a Writ of Certiorari at ii, *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017) (No. 15-1195). The Supreme Court granted both Sandoz's petition and Amgen's conditional cross-petition and consolidated the cases for briefing and oral argument. *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 808 (2017). The United States filed a brief and argued as amicus curiae.

On June 12, 2017, the Court announced its decision. *Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017). The Court held that an injunction under federal law is not available to enforce 42 U.S.C. § 262(*l*)(2)(A); and a biosimilar applicant may provide the notice required by 42 U.S.C. § 262(*l*)(8)(A) either before or after receiving FDA approval, *i.e.*, the applicant need not defer giving notice of commercial marketing until FDA licensure of the biosimilar in order to begin the running of the 180-day clock. *Id.* at 1674, 1677. The Court reversed our decision in part and vacated it in part and remanded the case for further proceedings consistent with its opinion. The Court directed:

> On remand, the Federal Circuit should determine whether California law would treat noncompliance with § 262(*l*)(2)(A) as "unlawful." If the answer is yes, then the court should proceed to determine whether the BPCIA pre-empts any additional remedy available under state law for an applicant's failure to comply with § 262(*l*)(2)(A) (and whether Sandoz has forfeited any pre-emption defense, see 794 F.3d, at 1360, n. 5). The court is also of course free to address the pre-emption question first by assuming that a remedy under state law exists.

Id. at 1676–77.

Following remand, we recalled our mandate, reopened the appeal, and directed supplemental briefing on July 26, 2017. Both parties responded with supplemental briefing, which, *inter alia*, addressed the question whether Sandoz waived any preemption defense it had to Amgen's state law claims.

Because Sandoz did not forfeit its preemption defense and the BPCIA preempts state law remedies for an applicant's failure to comply with § 262(*l*)(2)(A), we now affirm the district court's dismissal of Amgen's state law claims.

BACKGROUND

In 2010, as part of the Patient Protection and Affordable Care Act, Congress enacted the BPCIA, which established an abbreviated pathway for regulatory approval of follow-on biological products that are "highly similar" to a previously approved product ("reference product"). Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. at 815. Congress established such "a biosimilars pathway balancing innovation and consumer interests." BPCIA, Pub. L. No. 111-148, § 7001(b), 124 Stat. at 804.

The BPCIA has certain similarities in its goals and procedures to the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act"), Pub. L. No. 98-417, 98 Stat. 1585 (1984), but it has several obvious differences. We note this as a matter of historical interest, but otherwise do not comment on those similarities and differences.

Under the governing statutory scheme, the Food and Drug Administration ("FDA") approves a biological product for commercial marketing by granting a biologics license under 42 U.S.C. § 262(a). An applicant filing an original biologics license application ("BLA") typically must provide clinical data to demonstrate the safety and efficacy of its product. In contrast, under the abbreviated regulatory approval pathway created by the BPCIA,

codified at 42 U.S.C. § 262(k), an applicant filing an abbreviated biologics license application ("aBLA" or "biosimilar application") instead submits information to demonstrate that its product is "biosimilar" to or "interchangeable" with a previously approved reference product, together with "publicly-available information regarding the [FDA]'s previous determination that the reference product is safe, pure, and potent." *Id.* § 262(k)(2)–(5); *see also id.* § 262(i). The BPCIA thus permits a biosimilar applicant to rely in part on the approved license of a reference product.

To balance the goals of innovation and price competition, Congress enacted the BPCIA to provide a four-year and a twelve-year exclusivity period to a reference product, both beginning on the date of first licensure of the reference product. Specifically, a biosimilar application "may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a)," *id.* § 262(k)(7)(B), and approval of a biosimilar application "may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a)," *id.* § 262(k)(7)(A). Thus, a sponsor of an approved reference product (the "reference product sponsor" or "RPS") receives up to twelve years of exclusivity against follow-on products, regardless of patent protection.

The BPCIA established a biosimilar patent dispute resolution regime by amending Titles 28, 35, and 42 of the United States Code. The BPCIA amended the Patent Act to create an artificial "act of infringement," similar to that of 35 U.S.C. § 271(e)(2)(A), and to allow infringement suits to begin based on the filing of a biosimilar application prior to FDA approval and prior to marketing of the biological product. *See* 35 U.S.C. § 271(e)(2)(C), (e)(4), (e)(6). The BPCIA also established a unique and elaborate process for information exchange between the biosim-

ilar applicant and the RPS in order to help resolve biosimilar patent disputes. *See* 42 U.S.C. § 262(*l*).

Under that process, codified at 42 U.S.C. § 262(*l*), the biosimilar applicant provides the RPS confidential access to its aBLA and to the manufacturing information pertaining to the biosimilar product no later than 20 days after the FDA accepts its application for review. *Id.* § 262(*l*)(1)–(2). The parties may then exchange lists of patents for which they believe a claim of patent infringement could reasonably be asserted by the RPS, as well as their respective positions on infringement, validity, and enforceability of those patents. *Id.* § 262(*l*)(3). Following that exchange period, the parties negotiate to formulate a list of patents ("listed patents") that would be expected to be the subject of an immediate patent infringement action, *id.* § 262(*l*)(4)–(5), and the RPS then may sue the biosimilar applicant within 30 days, *id.* § 262(*l*)(6). The information exchange and negotiation thus contemplate an immediate infringement action brought by the RPS based only on listed patents.

Subsection 262(*l*) also provides that the applicant give notice of commercial marketing to the RPS at least 180 days prior to commercial marketing of its product licensed under subsection (k). The RPS thus has a period of time to seek a preliminary injunction based on patents that the parties initially identified during information exchange, but which were not selected for an immediate infringement action, as well as any newly issued or licensed patents (collectively, "non-listed patents"). *Id.* § 262(*l*)(7)–(8).

Subsection 262(*l*) additionally provides, in paragraph (*l*)(9)(A), that if the applicant discloses the information "required under paragraph (2)(A)," then neither the RPS nor the applicant may bring a declaratory judgment action based on the non-listed patents prior to the date on which the RPS receives the notice of commercial market-

ing under paragraph (*l*)(8)(A). *Id.* § 262(*l*)(9)(A). Paragraphs (*l*)(9)(B) and (*l*)(9)(C), however, permit the RPS, but not the applicant, to seek declaratory relief with respect to infringement, validity, or enforceability of certain patents in the event that the applicant fails to comply with certain provisions of subsection (*l*). *Id.* § 262(*l*)(9)(B)–(C). "The remedy provided by § 262(*l*)(9)(C) excludes all other federal remedies, including injunctive relief," for failure to comply with § 262(*l*)(2)(A). *Sandoz*, 137 S. Ct. at 1675.

Amgen has marketed filgrastim under the brand name Neupogen® ("Neupogen") since 1991. In May 2014, Sandoz filed an aBLA, seeking FDA approval of a biosimilar filgrastim product, for which Neupogen was the reference product. On July 7, 2014, Sandoz received notification from the FDA that it had accepted Sandoz's application for review.

Immediately thereafter, on July 8, 2014, Sandoz notified Amgen that it: had filed the biosimilar application referencing Neupogen; believed that the application would be approved in "Q1/2 of 2015"; and intended to launch its biosimilar product immediately upon FDA approval. J.A. 1472. Later in July, in response to an inquiry from Amgen, Sandoz confirmed that the FDA had accepted its application for review; it informed Amgen that it had "opted not to provide Amgen with Sandoz's biosimilar application within 20 days of the FDA's notification of acceptance" but that Amgen was entitled to sue Sandoz under § 262(*l*)(9)(C) "to require Sandoz to disclose [its] biosimilar application." J.A. 1495–96. Sandoz thus did not disclose its aBLA or its product's manufacturing information to Amgen according to § 262(*l*)(2)(A).

Accordingly, in October 2014, Amgen sued Sandoz in the Northern District of California, asserting claims of (1) unfair competition by engaging in unlawful business practices under the UCL, based on two alleged violations

of the BPCIA; (2) conversion for allegedly wrongful use of Amgen's approved license on Neupogen; and (3) infringement of Amgen's U.S. Patent 6,162,427 ("the '427 patent"), which claims a method of using filgrastim. Amgen alleged that Sandoz violated the BPCIA by failing to disclose the information required under § 262(*l*)(2)(A) and by giving a premature, ineffective, notice of commercial marketing under § 262(*l*)(8)(A) before FDA approval of its biosimilar product. Sandoz counterclaimed for a declaratory judgment that the BPCIA permitted its actions, that Amgen's state law claims were unlawful and/or preempted, and that the '427 patent was invalid and not infringed. Sandoz also asserted in its answer as an affirmative defense preemption of the state law claims by the BPCIA.

In January 2015, the parties filed cross-motions for judgment on the pleadings on Amgen's state law claims and Sandoz's counterclaims regarding its actions under the BPCIA. In February 2015, Amgen also filed a motion for a preliminary injunction to enjoin Sandoz from launching its biosimilar product, Zarxio, after FDA approval, based solely on its state law claims. Also, in February 2015, through discovery, Amgen obtained access to Sandoz's biosimilar application.

On March 19, 2015, the district court granted partial judgment on the pleadings to Sandoz on its counterclaims to the extent that Sandoz's interpretation of the BPCIA statute was consistent with the court's interpretation. Specifically, the district court concluded that: (1) the BPCIA renders permissible a biosimilar applicant's decision not to disclose its aBLA and the manufacturing information to the RPS, subject only to the consequences set forth in 42 U.S.C. § 262(*l*)(9)(C); (2) such a decision alone does not offer a basis for the RPS to obtain injunctive relief, restitution, or damages against the applicant; and (3) the applicant may give notice of commercial

marketing under § 262(*l*)(8)(A) before FDA approval. *Opinion*, 2015 WL 1264756, at *8, *11.

Based on its interpretation of the BPCIA, the district court then dismissed Amgen's unfair competition and conversion claims with prejudice, concluding that Sandoz did not violate the BPCIA or act unlawfully. *Id.* at *8–9. Sandoz did not then argue, and the district court did not address, its preemption counterclaim or affirmative defense. J.A. 1876–77. The court also denied Amgen's motion for a preliminary injunction based on its state law claims, noting that Amgen "has yet to proceed on its remaining claim for patent infringement." *Opinion*, 2015 WL 1264756, at *10.

On the parties' joint motion, on March 25, 2015, the district court entered final judgment as to Amgen's unfair competition and conversion claims and as to Sandoz's BPCIA counterclaims under Rule 54(b) of the Federal Rules of Civil Procedure.

On October 15, 2015, Amgen filed its First Amended and Supplemental Complaint, which added a claim for infringement of Amgen's U.S. Patent 8,940,878 ("the '878 patent"). On September 13, 2017, the district court entered a stipulated judgment of noninfringement of the '427 patent. The parties' claims and counterclaims relating to infringement, validity, and enforceability of the '878 patent remain pending at the district court.

Meanwhile, on March 6, 2015, the FDA approved Sandoz's aBLA for all approved uses of Amgen's Neupogen. Although Sandoz did not launch its filgrastim product at that time, it eventually did so after our decision on appeal.

Amgen timely appealed from the March 25, 2015 final judgment as to Amgen's unfair competition and conversion claims and as to Sandoz's BPCIA counterclaims, and from the denial of a preliminary injunction. We have

jurisdiction under 28 U.S.C. § 1295(a)(1) and § 1292(a)(1) and (c)(1).

DISCUSSION

We apply the procedural law of the regional circuit, here the Ninth Circuit, when reviewing a district court's grant of a motion for judgment on the pleadings. *Merck & Co. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1320 (Fed. Cir. 2007). The Ninth Circuit reviews the grant of judgment on the pleadings *de novo*, *Peterson v. California*, 604 F.3d 1166, 1169 (9th Cir. 2010), and "accept[s] all material allegations in the complaint as true and construe[s] them in the light most favorable to [the non-moving party]," *Turner v. Cook*, 362 F.3d 1219, 1225 (9th Cir. 2004) (third alteration in original).

Amgen argues that (1) Sandoz waived its preemption defense to its state law claims in this appeal; (2) the BPCIA does not preempt state law remedies for failure to comply with § 262(*l*)(2)(A); and (3) failure to comply with § 262(*l*)(2)(A) is both "unlawful" under the UCL and an act of conversion. Sandoz responds that (1) we have discretion to address preemption now; (2) both field and conflict preemption bar Amgen's state law claims; (3) Amgen's state law claims fail under California law; and (4) Amgen abandoned its conversion claim. We will address the parties' arguments in turn.[1]

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[1] Because we conclude that Sandoz did not waive its preemption defense and Amgen's state law claims are preempted, we do not reach the parties' arguments relating to (1) whether Sandoz preserved its conversion claims; or (2) whether failure to comply with § 262(*l*)(2)(A) is "unlawful" under the UCL or an act of conversion. *See Sandoz*, 137 S. Ct. at 1677 ("The court is also of course free to address the pre-emption question first by assuming that a remedy under state law exists.").

I.

We first address the parties' waiver arguments. "Under the usual rule, an affirmative defense is deemed waived if it has not been raised in a pleading, by motion, or at trial." *Daingerfield Island Protective Soc'y v. Babbitt*, 40 F.3d 442, 445 (D.C. Cir. 1994) (internal quotation marks omitted); *see also* Fed. R. Civ. P. 12(h)(2) (listing "[f]ailure to state a claim upon which relief can be granted" as a defense that may be raised "in any pleading allowed or ordered under Rule 7(a)"; "by a motion under Rule 12(c)"; or "at trial").

Neither the district court nor this court in its prior decision addressed preemption on the merits. The Supreme Court has observed that as a "general rule . . . a federal appellate court does not consider an issue not passed upon below." *Singleton v. Wulff*, 428 U.S. 106, 120 (1976). Appellate courts, however, have discretion to decide when to deviate from this general waiver rule. *See id.* at 121 ("The matter of what questions may be taken up and resolved for the first time on appeal is one left primarily to the discretion of the courts of appeals, to be exercised on the facts of individual cases."). We have previously articulated five reasons that may justify an appellate court's consideration of an issue not argued to the district court:

> (i) the issue involves a pure question of law and refusal to consider it would result in a miscarriage of justice; (ii) the proper resolution is beyond any doubt; (iii) the appellant had no opportunity to raise the objection at the district court level; (iv) the issue presents significant questions of general impact or of great public concern; or (v) the interest of substantial justice is at stake.

L.E.A. Dynatech, Inc. v. Allina, 49 F.3d 1527, 1531 (Fed. Cir. 1995) (internal quotation marks and alteration omitted); *see also Interactive Gift Express, Inc. v. Com-*

puserve Inc., 256 F.3d 1323, 1344–45 (Fed. Cir. 2001) (citing *L.E.A.*, 49 F.3d at 1531). We consider subcategory iv especially compelling here. The issue of preemption is a significant question regarding the interpretation of the BPCIA.

Amgen argues that Sandoz waived its preemption defense by not arguing it before the district court. According to Amgen, "preemption is an affirmative defense that can be waived." Appellants' Suppl. Br. 8 (citing *Teutscher v. Woodson*, 835 F.3d 936, 945 n.1 (9th Cir. 2016); *Russian Media Grp., LLC v. Cable Am. Inc.*, 598 F.3d 302, 309 (7th Cir. 2010); *Wood v. Milyard*, 566 U.S. 463, 470 (2012)). Amgen stresses that we previously declined to address preemption in this case. Amgen further contends that we should not remand the issue of preemption to the district court.

Sandoz responds that we have discretion to address its preemption defense now. Sandoz contends that "this is a case of great importance" and "preemption will have been 'fully briefed' and is a pure 'matter of law.'" Appellee's Suppl. Br. 8 (quoting *Interactive Gift*, 256 F.3d at 1345). Sandoz further argues that Amgen will not be prejudiced by our consideration of preemption because Sandoz can assert preemption in the district court later as it preserved the defense in its answer.

We agree with Sandoz that we have discretion to address preemption in this appeal and should exercise that discretion. The Supreme Court expressly invited us to do so, and to assume that a remedy under state law would exist if there were not preemption. *See Sandoz*, 137 S. Ct. at 1676–77. We hereby make that assumption.

Preemption is a legal question that the parties have fully briefed. This appeal, and its remand, require us to consider whether state law claims may play a role in enforcing compliance with § 262(*l*)(2)(A). Preemption in this case thus presents "a significant question[] of general

impact or of great public concern." *See Hall v. Bed Bath & Beyond, Inc.*, 705 F.3d 1357, 1371 (Fed. Cir. 2013) (holding party did not waive preemption argument by failing to raise it in its Rule 12(b)(6) motion because "waiver is generally inapplicable to 'significant questions of general impact or of great public concern.'" (quoting *Interactive Gift*, 256 F.3d at 1345)).

Moreover, even if we declined to reach preemption now, Sandoz could raise the defense on remand before the district court. Sandoz preserved its ability to assert preemption by pleading the defense in its answer. *See Daingerfield*, 40 F.3d at 445 (holding defense pled in answer not waived even though defendant failed to assert the defense before the prior appeal); 5 C. Wright & A. Miller, Federal Practice and Procedure § 1277 (3d ed. 2017) (explaining "the failure to raise an affirmative defense by motion will not result in a waiver as long as it is interposed in the answer"); *see also* Fed. R. Civ. P. 12(h)(2). We thus discern no prejudice to Amgen by resolving the preemption issue now.

Amgen's cited cases are readily distinguishable. In *Teutscher*, the Ninth Circuit "decline[d] to consider [preemption] sua sponte." 835 F.3d at 945 n.1. Here, preemption has been fully briefed and the Supreme Court expressly invited us to address the issue on remand. *See Sandoz*, 137 S. Ct. at 1676–77.

In *Russian Media*, the Seventh Circuit declined to address preemption for the first time on appeal in reviewing a district court's grant of a preliminary injunction where preemption had not been timely raised at the district court. *See* 598 F.3d at 309 ("It is not appropriate for this court to overturn an injunction on the basis of a defense that the district court had no opportunity to consider."). The court "express[ed] no opinion on whether the preemption defense is preserved for further proceedings in the district court." *Id.* Here, we are not reviewing the grant

of a preliminary injunction and Sandoz timely raised the defense in its answer.

In *Wood*, the Supreme Court stated the general rule that "[a]n affirmative defense, once forfeited, is excluded from the case, and, as a rule, cannot be asserted on appeal," 566 U.S. at 470 (internal citations and alternations omitted), and went on to recognize an exception to that general rule in the case, *id.* at 473. Here, we have determined that Sandoz has not forfeited its preemption defense, so the general rule has no applicability.

II.

We therefore turn to the question whether Amgen's state law claims are preempted by the BPCIA. We apply our own law to determine whether the BPCIA preempts the state law claims. *See Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356, 1360–61 (Fed. Cir. 1999) (en banc in relevant part) ("In order to fulfill our obligation of promoting uniformity in the field of patent law, it is equally important to apply our construction of patent law to the questions whether and to what extent patent law preempts or conflicts with other causes of action."), *abrogated on other grounds by TrafFix Devices, Inc. v. Mktg. Displays, Inc.*, 532 U.S. 23, 28 (2001). Preemption is a question of law that we review *de novo*. *Ultra-Precision Mfg., Ltd. v. Ford Motor Co.*, 411 F.3d 1369, 1376 (Fed. Cir. 2005).

A.

The Supremacy Clause states a clear rule that federal law "shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. The Supremacy Clause preempts state law by means of express preemption, field preemption, or conflict preemption. *See English v. Gen. Elec. Co.*, 496 U.S. 72, 78–79 (1990). "Pre-

emption fundamentally is a question of congressional intent and when Congress has made its intent known through explicit statutory language, the courts' task is an easy one." *Id.* (internal citation omitted). Express preemption is not at issue in this appeal, so we focus only on the latter two forms of preemption.

Under field preemption, "state law is pre-empted where it regulates conduct in a field that Congress intended the Federal Government to occupy exclusively." *Id.* at 79. We may infer such a congressional intent from a "scheme of federal regulation . . . so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it," or where an Act of Congress "touch[es] a field in which the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject." *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947). "Where Congress occupies an entire field . . . even complementary state regulation is impermissible." *Arizona v. United States*, 567 U.S. 387, 401 (2012).

State laws are also preempted when they conflict with federal law. *Id.* at 399. Conflict preemption occurs "where it is impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *English*, 496 U.S. at 79 (internal citation and quotation marks omitted).

Additionally, where Congress has legislated "in [a] field which the States have traditionally occupied," "we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." *Rice*, 331 U.S. at 230. No such "presumption against finding federal pre-emption of a state law cause of action" applies, however, where the field is not "'a field

which the States have traditionally occupied.'" *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2001) (quoting *Rice*, 331 U.S. at 230). We conclude that both field and conflict preemption exist here.

B.

Amgen argues that the BPCIA does not preempt state law remedies for failure to comply with § 262(*l*)(2)(A). Amgen contends that we have "held that patent law does not fully preempt related state-law doctrines," including "state unfair-competition laws." Appellants' Suppl. Br. 15 (citing *Hunter Douglas, Inc. v. Harmonic Design, Inc.*, 153 F.3d 1318, 1333 (Fed. Cir. 1998), *overruled on other grounds by Midwest Indus.*, 175 F.3d 1356). According to Amgen, field preemption does not apply to its state law claims because "the federal statute does not provide a meaningful remedy for the state-recognized interests that have been injured by Sandoz's failure to comply with 42 U.S.C. § 262(*l*)(2)(A)." *Id.* at 16.

Sandoz responds that field preemption bars Amgen's state law claims because the BPCIA's comprehensive framework demonstrates Congressional intent that federal law exclusively occupy the field of patent dispute resolution triggered by the filing of a biosimilar application. According to Sandoz, the inference of Congressional intent to occupy the field is particularly strong because the scheme "touch[es] a field in which the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject." Appellee's Suppl. Br. 12 (alternation in original) (quoting *Rice*, 331 U.S. at 230). Sandoz also contends that no presumption against preemption applies here.

We agree with Sandoz that the BPCIA preempts state law claims predicated on an applicant's failure to comply with § 262(*l*)(2)(A). As an initial matter, no presumption against preemption applies in this case because biosimilar patent litigation "is hardly 'a field which the States have

traditionally occupied.'" *Buckman*, 531 U.S. at 347 (quoting *Rice*, 331 U.S. at 230). Indeed, patents are "inherently federal in character" because a patent "originates from, is governed by, and terminates according to federal law." *Id.* In keeping with this federal character, Congress has granted federal courts "exclusive jurisdiction over cases 'arising under any Act of Congress relating to patents.'" *Gunn v. Minton*, 568 U.S. 251, 253 (2013) (quoting 28 U.S.C. § 1338(a)); *see also* 28 U.S.C. § 1338(a) ("No State court shall have jurisdiction over any claim for relief arising under any Act of Congress relating to patents, plant variety protection, or copyrights."). Similarly, the FDA has exclusive authority to license biosimilars pursuant to the provisions of 42 U.S.C. § 262. *See* 42 U.S.C. § 262(a)(1).

The BPCIA is a "complex statutory scheme . . . [that] establishes processes both for obtaining FDA approval of biosimilars and for resolving patent disputes between manufacturers of licensed biologics and manufacturers of biosimilars." *Sandoz*, 137 S. Ct. at 1669. It "sets forth a carefully calibrated scheme for preparing to adjudicate, and then adjudicating, claims of [patent] infringement." *Id.* at 1670 (citing 42 U.S.C. § 262(*l*)). Congress established this scheme as part of its careful "balancing [of] innovation and consumer interests." BPCIA, Pub. L. No. 111-148, § 7001(b), 124 Stat. at 804.

Similar to the federal alien registration system in *Arizona* that the Supreme Court held preempted that field, the scheme here is "comprehensive" and "provide[s] a full set of standards governing" the exchange of information in biosimilar patent litigation, "including the punishment for noncompliance." *Arizona*, 567 U.S. at 401. The Supreme Court has held that "[t]he remedy provided by § 262(*l*)(9)(C) excludes all other federal remedies, including injunctive relief," for failure to comply with § 262(*l*)(2)(A). *Sandoz*, 137 S. Ct. at 1675. The Court has described the BPCIA as possessing a "carefully crafted

and detailed enforcement scheme" and stated that this scheme "provides strong evidence that Congress did *not* intend to authorize other remedies that it simply forgot to incorporate expressly." *Id.* at 1675 (emphasis in original) (internal quotations omitted). The BPCIA's comprehensive, carefully calibrated "scheme of federal regulation . . . [is] so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it." *Rice*, 331 U.S. at 230.

Moreover, Amgen seeks through California law to impose penalties on Sandoz for failure to comply with § 262(*l*)(2)(A), *e.g.*, injunctive relief and damages, that the BPCIA does not provide. Section 262(*l*)(9)(C) permits the RPS, but not the applicant, to bring an action "for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product." Because § 262(*l*)(9)(C) provides the exclusive federal remedy for failure to comply with § 262(*l*)(2)(A), federal law does not permit injunctive relief or damages for such failure. *See Sandoz*, 137 S. Ct. at 1675. "Permitting the State to impose its own penalties for the [alleged violation of federal law] here would conflict with the careful framework Congress adopted." *Arizona*, 567 U.S. at 402; *cf. Amalgamated Ass'n of St., Elec. Ry. & Motor Coach Emps. of Am. v. Lockridge*, 403 U.S. 274, 287 (1971) (holding state law claim preempted and explaining "[t]he technique of administration and the range and nature of those remedies that are and are not available is a fundamental part and parcel of the operative legal system established by the [preempting] Act"). This conflict in available remedies between federal and state law "underscore[s] the reason for field preemption." *Arizona*, 567 U.S. at 403.

Amgen's reliance on *Hunter Douglas* is misplaced. In *Hunter Douglas*, we held that "federal patent law" did not preempt "the field pertaining to state unfair competition law." 153 F.3d at 1333. But our recognition that patent

law does not preempt all related state law claims does not dictate the outcome in this case. *See Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 154, 167 (1989) (stating that "all state regulation of potentially patentable but unpatented subject matter is not *ipso facto* preempted by the federal patent laws" and holding preempted the particular state law at issue, which "enter[ed] a field of regulation which the patent laws have reserved to Congress"). The field here is biosimilar patent litigation, not patent law generally. As explained above, the federal government has fully occupied this field.

Additionally, Amgen's assertion that the BPCIA "does not provide a meaningful remedy for the state-recognized interests that have been injured by Sandoz's failure to comply with 42 U.S.C. § 262(*l*)(2)(A)," Appellants' Suppl. Br. 16, misunderstands the relevant inquiry. The Supreme Court has explained that "[p]re-emption fundamentally is a question of congressional intent," *English*, 496 U.S. at 78–79, and reiterated that "'[t]he purpose of Congress is the ultimate touchstone' in every pre-emption case," *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (alternation in original) (quoting *Retail Clerks v. Schermerhorn*, 375 U.S. 96, 103 (1963)). As discussed *supra*, this "scheme of federal regulation . . . [is] so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it." *Rice*, 331 U.S. at 230. Thus, assuming *arguendo* that there are any state-recognized interests in play here, California law must "give way to federal law." *See Arizona*, 567 U.S. at 399.

C.

Amgen also argues that the BPCIA does not conflict with Amgen's state law claims. First, Amgen contends, the state law claims "do not 'clash' with the objectives of the BPCIA and federal patent laws." Appellants' Suppl. Br. 12 (quoting *Sears, Roebuck & Co. v. Stiffel Co.*, 376

U.S. 225, 231 (1964)). Second, according to Amgen, the state law claims include additional elements not addressed by the BPCIA or found in the patent litigation facilitated by the BPCIA. *See Rodime PLC v. Seagate Tech., Inc.*, 174 F.3d 1294, 1306 (Fed. Cir. 1999). Third, Amgen argues that the state law claims do not depend on the resolution of Amgen's patent disputes and that the relief sought is both different from and independent of the remedy provided by the BPCIA and patent law.

Sandoz responds that the state law remedies conflict with the intricate federal scheme. According to Sandoz, such remedies "would disrupt the balance struck by the BPCIA's express consequences for noncompliance with its procedural steps," Appellee's Suppl. Br. 13, frustrating "Congress's deliberate omission of an injunction to compel disclosure of an application, and its provision of only the Section 262(*l*)(9)(C) consequence," *id.* at 14. Sandoz contends that this "disruption to the federal scheme would be compounded by the multiplicity of remedies different states might make available for 'violations' of the BPCIA." *Id.* at 15–16.

We agree with Sandoz that conflict preemption also bars Amgen's state law claims. Contrary to Amgen's assertions, its state law claims "clash" with the BPCIA, and the differences in remedies between the federal scheme and state law claims support concluding that those claims are preempted. As the Supreme Court has recognized, a "[c]onflict in technique can be fully as disruptive to the system Congress erected as conflict in overt policy." *Amalgamated Ass'n*, 403 U.S. at 287. Additionally, compliance with the BPCIA's "detailed regulatory regime in the shadow of 50 States' tort regimes," and unfair competition standards, could "dramatically increase the burdens" on biosimilar applicants beyond those contemplated by Congress in enacting the BPCIA. *Buckman*, 531 U.S. at 350.

As previously discussed, Amgen seeks through state law to impose penalties on Sandoz unavailable under the BPCIA for failure to comply with § 262(*l*)(2)(A)'s disclosure requirements. This "conflict in the method of enforcement" between the BPCIA and state law creates "an obstacle to the regulatory system Congress chose." *Arizona*, 567 U.S. at 406. We must assume that Congress acted intentionally when it did not provide an injunctive remedy for breach of § 262(*l*)(2)(A)'s disclosure requirements. *See Sandoz*, 137 S. Ct. at 1675. Where, as here, "Congress made a deliberate choice not to impose" certain penalties for noncompliance with federal law, state laws imposing those penalties "would interfere with the careful balance struck by Congress." *Arizona*, 567 U.S. at 405–06.

Amgen's reliance on *Rodime* is misplaced. In *Rodime*, we determined that the patent laws did not preempt patentee's state law claims for tortious interference with prospective economic advantage and unfair competition based on the accused infringer's alleged efforts to dissuade other companies from taking a license to the asserted patent. 174 F.3d at 1306. Our statement, applied to the facts of *Rodime*, that "[t]he patent laws will not preempt such claims if they include additional elements not found in the federal patent law cause of action and if they are not an impermissible attempt to offer patent-like protection to subject matter addressed by federal law," *id.*, does not immunize state law claims in other types of cases from ordinary principles of preemption. As discussed *supra*, the preemption analysis here demonstrates that Amgen's state law claims conflict with the BPCIA and intrude upon a field, biosimilar patent litigation, that Congress reserved for the federal government.

We have considered Amgen's remaining arguments but find them to be unpersuasive.

CONCLUSION

For the foregoing reasons, we affirm the dismissal of Amgen's unfair competition and conversion claims. Amgen's state law claims are preempted on both field and conflict grounds.

AFFIRMED

COSTS

Each party shall bear its own costs.

Center for Drug Evaluation and Research

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125118	abatacept	Orencia	12/23/05				
103575	abciximab	ReoPro	12/22/94	NA	NA		
125274	abobotulinumtoxinA	Dysport	04/29/09				
125057	adalimumab	Humira	12/31/02	NA	NA		
761058	adalimumab-adbm	Cyltezo	08/25/17			B	
761024	adalimumab-atto	Amjevita	09/23/16			B	
125427	ado-trastuzumab emtansine	Kadcyla	02/22/13				
125387	aflibercept	Eylea	11/18/11				
103979	agalsidase beta	Fabrazyme	04/24/03	NA	NA		
125431	albiglutide	Tanzeum	04/15/14				
103293	aldesleukin	Proleukin	05/05/92	NA	NA		
103948	alemtuzumab	Campath, Lemtrada	05/07/01	NA	NA		
125141	alglucosidase alfa	Myozyme	04/28/06				
125291	alglucosidase alfa	Lumizyme	05/24/10				
125559	alirocumab	Praluent	07/24/15				
103172	alteplase, cathflo activase	Activase	11/13/87	NA	NA		
103950	anakinra	Kineret	11/14/01	NA	NA		
125513	asfotase alfa	Strensiq	10/23/15				
101063	asparaginase	Elspar	01/10/78	NA	NA		
125359	asparaginase erwinia chrysanthemi	Erwinaze	11/18/11				
761034	atezolizumab	Tecentriq	05/18/16				
761049	avelumab	Bavencio	03/23/17				
103764	basiliximab	Simulect	05/12/98	NA	NA		
103691	becaplermin	Regranex	12/16/97	NA	NA		
125288	belatacept	Nulojix	06/15/11				
125370	belimumab	Benlysta	03/09/11				
761043	belimumab	Benlysta	07/20/17				
761070	benralizumab	Fasenra	11/14/17				
125085	bevacizumab	Avastin	02/26/04	NA	NA		
761028	bevacizumab-awwb	Mvasi	09/14/17			B	
761046	bezlotoxumab	Zinplava	10/21/16				
125557	blinatumomab	Blincyto	12/03/14				
125388	brentuximab vedotin	Adcetris	08/19/11				
761032	brodalumab	Siliq	02/15/17				
125319	canakinumab	Ilaris	06/17/09				
103608	capromab pendetide	ProstaScint	10/28/96	NA	NA		
761052	cerliponase alfa	Brineura	04/27/17				
125160	certolizumab pegol	Cimzia	04/22/08				
125084	cetuximab	Erbitux	02/12/04	NA	NA		
101995	collagenase	Santyl	06/04/65	NA	NA		
125338	collagenase clostridium histolyticum	Xiaflex	02/02/10				
103749	daclizumab	Zenapax	12/10/97	NA	NA		Yes
761029	daclizumab	Zinbryta	05/27/16				
761036	daratumumab	Darzalex	11/16/15				
103951	darbepoetin alfa	Aranesp	09/17/01	NA	NA		
103767	denileukin diftitox	Ontak	02/05/99	NA	NA		
125320	denosumab	Prolia, Xgeva	06/01/10				
125516	dinutuximab	Unituxin	03/10/15				
103532	dornase alfa	Pulmozyme	12/30/93	NA	NA		
125469	dulaglutide	Trulicity	09/18/14				
761055	dupilumab	Dupixent	03/28/17				

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761069	durvalumab	Imfinzi	05/01/17				
125277	ecallantide	Kalbitor	12/01/09				
125166	eculizumab	Soliris	03/16/07				
125460	elosulfase alfa	Vimizim	02/14/14				
761035	elotuzumab	Empliciti	11/30/15				
761083	emicizumab-kxwh	Hemlibra	11/16/17				
103234	epoetin alfa	Epogen/Procrit	06/01/89	NA	NA		
103795	etanercept	Enbrel	11/02/98	NA	NA		
761042	etanercept-szzs	Erelzi	08/30/16			B	
125522	evolocumab	Repatha	08/27/15				
103353	filgrastim	Neupogen	02/20/91	NA	NA		
125553	filgrastim-sndz	Zarxio	03/06/15			B	
125117	galsulfase	Naglazyme	05/31/05	NA	NA		
761060	gemtuzumab ozogamicin	Mylotarg	09/01/17				
125327	glucarpidase	Voraxaze	01/17/12				
125289	golimumab	Simponi	04/24/09				
125433	golimumab injection, for IV use	Simponi Aria	07/18/13				
761061	guselkumab	Tremfya	07/13/17				
125019	ibritumomab tiuxetan	Zevalin	02/19/02	NA	NA		
761025	idarucizumab	Praxbind	10/16/15				
125151	idursulfase	Elaprase	07/24/06				
125360	incobotulinumtoxinA	Xeomin	07/30/10				
103772	infliximab	Remicade	08/24/98	NA	NA		
761054	infliximab-abda	Renflexis	04/21/17			B	
125544	infliximab-dyyb	Inflectra	04/05/16			B	
761072	infliximab-qbtx	Ixifi	12/13/17			B	
761040	inotuzumab ozogamicin	Besponsa	08/17/17				
103132	interferon alfa-2b	Intron A	06/04/86	NA	NA		
103158	interferon alfa-n3	Alferon N Injection	10/10/89	NA	NA		
103628	interferon beta-1a	Avonex	05/17/96	NA	NA		
103780	interferon beta-1a	Rebif	03/07/02	NA	NA		
103471	interferon beta-1b	Betaseron	07/23/93	NA	NA		
125290	interferon beta-1b	Extavia	08/14/09				
103836	interferon gamma-1b	Actimmune	02/25/99	NA	NA		
125377	ipilimumab	Yervoy	03/25/11				
125521	ixekizumab	Taltz	03/22/16				
125058	laronidase	Aldurazyme	04/30/03	NA	NA		
125526	mepolizumab	Nucala	11/04/15				
125164	methoxy polyethylene glycol-epoetin beta	Mircera	11/14/07				
125390	metreleptin	Myalept	02/24/14				
125104	natalizumab	Tysabri	11/23/04	NA	NA		
125547	necitumumab	Portrazza	11/24/15				
125554	nivolumab	Opdivo	12/22/14				
125509	obiltoxaximab	Anthim	03/18/16				
125486	obinutuzumab	Gazyva	11/01/13				
761053	ocrelizumab	Ocrevus	03/28/17				
125422	ocriplasmin	Jetrea	10/17/12				
125326	ofatumumab	Arzerra	10/26/09				
761038	olaratumab	Lartruvo	10/19/16				
103976	omalizumab	Xolair	06/20/03	NA	NA		
103000	onabotulinumtoxinA	Botox	12/29/89	NA	NA		

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103694	oprelvekin	Neumega	11/25/97	NA	NA		Yes
125103	palifermin	Kepivance	12/15/04	NA	NA		
103770	palivizumab	Synagis	06/19/98	NA	NA		
125147	panitumumab	Vectibix	09/27/06				
125511	parathyroid hormone	Natpara	01/23/15				
103411	pegaspargase	Oncaspar	02/01/94	NA	NA		
125031	pegfilgrastim	Neulasta	01/31/02	NA	NA		
103964	peginterferon alfa-2a	Pegasys	10/16/02	NA	NA		
125083	peginterferon alfa-2a co-packaged with ribavirin	Pegasys Copegus Combination Pack	06/04/04	NA	NA		Yes
103949	peginterferon alfa-2b	PegIntron, Sylatron	01/19/01	NA	NA		
125499	peginterferon beta-1a	Plegridy	08/15/14				
125293	pegloticase	Krystexxa	09/14/10				
125514	pembrolizumab	Keytruda	09/04/14				
125409	pertuzumab	Perjeta	06/08/12	06/08/12	06/08/24		
125477	ramucirumab	Cyramza	04/21/14				
125156	ranibizumab	Lucentis	06/30/06				
103946	rasburicase	Elitek	07/12/02	NA	NA		
125349	raxibacumab	raxibacumab	12/14/12				
761033	reslizumab	Cinqair	03/23/16				
103786	reteplase	Retavase	10/30/96	NA	NA		
125249	rilonacept	Arcalyst	02/27/08				
103846	rimabotulinumtoxinB	Myobloc	12/08/00	NA	NA		
103705	rituximab	Rituxan	11/26/97	NA	NA		
761064	rituximab and hyaluronidase human	Rituxan Hycela	06/22/17				
125268	romiplostim	Nplate	08/22/08				
103362	sargramostim	Leukine	03/05/91	NA	NA		
761037	sarilumab	Kevzara	05/22/17				
125561	sebelipase alfa	Kanuma	12/08/15				
125504	secukinumab	Cosentyx	01/21/15				
125496	siltuximab	Sylvant	04/23/14				
125294	tbo-filgrastim	Granix	08/29/12	08/29/12	08/29/24		
103909	tenecteplase	TNKase	06/02/00	NA	NA		
125276	tocilizumab	Actemra	01/08/10				
125472	tocilizumab	Actemra	10/21/13				
103792	trastuzumab	Herceptin	09/25/98	NA	NA		
761074	trastuzumab-dkst	Ogivri	12/01/17			B	
125261	ustekinumab	Stelara	09/25/09				
761044	ustekinumab	Stelara	09/23/16				
125476	vedolizumab	Entyvio	05/20/14				
761047	vestronidase alfa-vjbk	Mepsevii	11/15/17				
125418	ziv-aflibercept	Zaltrap	08/03/12				

Center for Drug Evaluation and Research

List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date

BLA STN	PRODUCT (PROPER) NAME	PROPRIETARY NAME	DATE OF LICENSURE (mo/day/yr)	DATE OF FIRST LICENSURE (mo/day/yr)	REFERENCE PRODUCT EXCLUSIVITY EXPIRY DATE (mo/day/yr)	INTERCHANGEABLE (I)/ BIOSIMILAR (B)	WITHDRAWN

Key -

BLA STN: Biologic License Application Submission Tracking Number

Product (Proper) Name: The nonproprietary name designated by FDA for a biological product at the time of licensure under the PHS Act (section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k) of the FD&C Act).

Proprietary Name: Brand/Trade Name

Date of Licensure: The date the application was approved/licensed for marketing. Date of licensure for each application was identified through FDA records.

Date of First Licensure: The date from which reference product exclusivity began to run. Under 351(k)(7)(C), the date of first licensure will not be the date a particular application was licensed if that application is a subsequent application filed by the same or related sponsor of the biological product for a change (not including a modification to the structure of its previously approved biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength, or if the change is a modification to the structure of the previously approved biological product that does not result in a change in safety, purity, or potency.

FDA will generally make a determination of date of first licensure for reasons of regulatory necessity and/or at the request of the 351(a) application license holder.

The Agency will denote the date of first licensure as "not applicable" (NA) if:

- The product was licensed under 351(a) and the date it was licensed falls under any exclusion identified in 351(k)(7)(C) or
- More than 12 years (or 12 years and 6 months in the case of a product that has earned pediatric exclusivity) have passed since the date of licensure of the product, and thus any reference product exclusivity that the product may have had would have expired, thus obviating the need for a determination of whether any exclusion under 351(k)(7)(C) applies.

In such cases, a corresponding NA notation will also be placed in the next column, "Reference Product Exclusivity Expiry Date".

Reference Product Exclusivity Expiry Date: The reference product exclusivity expiry date indicates (1) the date that is 12 years from the date of first licensure as described in 351(k)(7); plus (2) any pediatric exclusivity granted pursuant to section 505(A) of the FD&C Act, if applicable. The reference product exclusivity expiry date is the date on which a 351(k) application referencing the reference product may be licensed assuming it is not blocked by orphan exclusivity and otherwise meets the requirements for licensure under 351(k). To determine whether there is unexpired orphan exclusivity for an indication for which the reference product is licensed, please refer to the searchable database for Orphan Designated and/or Approved Products (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm).

For the explanation of the notation "NA," please see the definition of "Date of First Licensure" above.

Interchangeable (I)/Biosimilar (B): Identification of those biological products approved/licensed under 351(k) that were licensed as either interchangeable with or biosimilar to the reference product. Such products will be listed under the 351(a) BLA referenced in the 351(k) application. Biosimilarity has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in the biosimilar product's Full Prescribing Information.

Withdrawn: The BLA has been withdrawn or is no longer being marketed. This does not specify whether withdrawn for reasons of safety and/or effectiveness.

Note: The List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations reflects all BLAs that were active at the time the "Purple Book" was originally published on September 9, 2014. FDA will continue to update the list when FDA licenses a biological product under section 351(a) or section 351(k) of the PHS Act and/or makes a determination regarding date of first licensure for a biological product licensed under section 351(a) of the PHS Act, and to reflect other changes in the status of these biological products, as appropriate.

FDA-Approved Biosimilar Products

Drug Name	Approval Date	More Information
Zarxio (Filgrastim-sndz)	March 2015	Zarxio information Press Release: FDA approves first biosimilar
Inflectra (Infliximab-dyyb)	April 2016	Inflectra information Press Release: FDA approves Inflectra
Erelzi (Etanercept-szzs)	August 2016	Erelzi information Press Release: FDA approves Erelzi
Amjevita (Adalimumab - atta)	September 2016	Amjevita information Press Release: FDA approves Amjevita
Renflexis (Infliximab-abda)	May 2017	Renflexis information
Cyltezo (Adalimumab-adbm)	August 2017	Cyltezo information
Mvasi (Bevacizumab-awwb)	September 2017	Mvasi information Press Release: FDA approves first biosimilar for the treatment of cancer
Ogivri (trastuzumab-dkst)	December 2017	Ogivri information Press Release: FDA approves first biosimilar for the treatment of certain breast and stomach cancers
Ixifi (infliximab-qbtx)	December 2017	Ixifi information

Learn More

Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations
The “Purple Book” lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act.

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Reference IV

Selected File History
US 8,399,654

WHAT IS CLAIMED IS:

1. A chimeric receptor comprising an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, a hinge and transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain.

2. The chimeric receptor of claim 1, wherein the 4-1BB signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

3. The chimeric receptor of claim 2, wherein the cytoplasmic domain further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

4. The chimeric receptor of claim 3, wherein the hinge and transmembrane domain is the hinge and transmembrane domain of CD8α.

5. The chimeric receptor of claim 4, wherein the extracellular ligand-binding domain further comprises a signal peptide of CD8α.

6. A polynucleotide encoding the chimeric receptor of claim 1.

7. A vector comprising a polynucleotide encoding the chimeric receptor of claim 1 operatively linked to at least one regulatory element for expression of the chimeric receptor.

8. A host cell comprising a polynucleotide encoding the chimeric receptor of claim 1.

9. The host cell of claim 8 which is a T lymphocyte or an NK cell.

10. The host cell of claim 9 which is a T lymphocyte.

11. A host cell comprising the chimeric receptor of claim 1.

12. The host cell of claim 11 which is a T lymphocyte or an NK cell.

13. The host cell of claim 11 which is a T lymphocyte.

14. A method of enhancing a T lymphocyte or an NK cell activity in an individual comprising introducing into the individual a T lymphocyte or NK cell, which T lymphocyte or NK cell comprises a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, (b) a hinge and transmembrane domain, and (c) a cytoplasmic domain comprising a 4-1BB signaling domain.

15. The method of claim 14 wherein the 4-1BB signaling domain of the chimeric receptor comprises amino acids 214-255 of SEQ ID NO:2.

16. The method of claim 15 wherein the cytoplasmic domain of the chimeric receptor further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

17. The method claim 16, wherein the hinge and transmembrane domain of the chimeric receptor is a CD8α hinge and transmembrane domain.

18. The method of claim 17, wherein the extracellular ligand-binding domain of the chimeric receptor further comprises a signal peptide of CD8α.

19. The method of claim 14, wherein the individual is suffering from a cancer of B-cell origin.

20. The method of claim 19, wherein the cancer is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma.

21. The method of claim 14, wherein the individual is suffering from lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer,

neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma, acute lymphoblastic leukemia, small cell lung cancer, Hodgkin's lymphoma, or childhood acute lymphoblastic leukemia.

22. A method for treating an individual suffering from cancer comprising introducing into the individual a T lymphocyte or an NK cell, which T lymphocyte or NK cell comprises a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 scFv domain; (b) a hinge region and transmembrane domain of CD8α; and (c) a cytoplasmic domain comprising a signaling domain of 4-1BB.

23. The method of claim 22, wherein the 4-1BB signaling domain of the chimeric receptor comprises amino acids 214-255 of SEQ ID NO:2.

24. The method of claim 23, wherein the cytoplasmic domain of the chimeric receptor further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

25. The method claim 24, wherein the hinge and transmembrane domain of the chimeric receptor is a CD8α hinge and transmembrane domain.

26. The method of claim 25, wherein the extracellular ligand-binding domain of the chimeric receptor further comprises a signal peptide of CD8α.

27. The method of claim 22, wherein the individual is suffering from a cancer of B-cell origin.

28. The method of claim 27, wherein the cancer is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma.

29. The method of claim 22, wherein the cancer is selected from the group consisting of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma, acute

lymphoblastic leukemia, small cell lung cancer, Hodgkin's lymphoma, and childhood acute lymphoblastic leukemia.

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NEW YORK NY 10017

MAILED

AUG 08 2012

OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/548,148

1. THE REQUEST FILED July 12, 2012 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to JoAnne Burke at 571-272-4584. In his/her absence, calls may be directed to Brian Brown, 571-272-5338.

/JoAnne Burke/
[*Signature*]

Petitions Examiner
(Title)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,148	07/12/2012	Dario CAMPANA	13213-005-999	1261

20583 7590 08/09/2012

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER
OUSPENSKI, ILIA I

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/09/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/548,148	CAMPANA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-29* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-29* are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Restriction Requirement

1. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5, drawn to a polypeptide, classified in Class 530, subclass 350.

II. Claims 6-13, drawn to a nucleic acid, vector and host cell, classified in Class 536, subclass 23.5, for example.

III. Claims 14-29, drawn to a method comprising administering a host cell to a subject, classified in Class 424, subclass 93.2.

2. Groups I and II are different products. The products are patentably distinct because their structures, physicochemical properties and/or mode of action are different, and they do not share a common structure that is disclosed to be essential for common utility. Furthermore, they require non-coextensive searches in the scientific literature. Therefore, each product is patentably distinct, and searching of these Inventions would impose an undue burden.

Groups II and III are related as product and process of using. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the host cell of Group II can be used in *in vitro* assays, in addition to the recited methods.

3. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Species Election

4. This application contains claims directed to the following patentably distinct Species of the claimed Invention III, wherein the cancer is one of those recited in claims 21 and 29. Applicant is required under 35 U.S.C. 121 to elect a single specific type of cancer for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

These species are distinct because the pathological conditions differ in etiologies, molecular and cellular mechanisms, symptoms and therapeutic endpoints; thus each condition represents patentably distinct subject matter. Furthermore, the examination of the species would require different searches in the scientific literature, and the pathological conditions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. As such, it would be burdensome to examine these Species together.

5. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

6. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. *Process claims that depend from or otherwise include all the limitations of the patentable product* will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain

dependency on the product claims or to otherwise include the limitations of the product claims. *Failure to do so may result in a loss of the right to rejoinder.*

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

7. Applicant is reminded that upon the cancellation of claims to a non-elected inventions, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel E. Kolker can be reached on 571-272-3181. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ILIA OUSPENSKI/

ILIA OUSPENSKI, Ph.D.
Primary Examiner
Art Unit 1644

REMARKS

In the Office Action, the Examiner has required a restriction to one of the following groups of inventions:

1. Claims 1-5, drawn to a polypeptide;
2. Claims 6-13, drawn to a nucleic acid, vector and host cell, and
3. Claims 14-29, drawn to a method comprising administering a host cell to a subject.

In response, Applicants elect the invention of **Group 2**. Applicants believe that claims 6-13, which recite a polynucleotide, vector and host cells, read on the elected group to be examined.

It is requested that the enclosed election and remarks be made of record in the file of the above-identified application.

Respectfully submitted,

/Eileen E. Falvey/ 46,097

Date August 30, 2012

Eileen E. Falvey (Reg. No.)
JONES DAY
222 East 41st Street
New York, New York 10017
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Enclosures

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,148	07/12/2012	Dario CAMPANA	13213-005-999	1261

108842 7590 10/11/2012

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EXAMINER	
OUSPENSKI, ILIA I	
ART UNIT	PAPER NUMBER
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10/11/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/548,148	CAMPANA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-29* is/are pending in the application.

5a) Of the above claim(s) *1-5 and 11-29* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *6-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *12 July 2012* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/30/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group II (claims 6-13) in the reply filed on 08/30/2012 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Upon reconsideration, it is determined that claims 11-13 correspond to Group I as set forth in the restriction requirement of 08/09/2012, because they are drawn to a host cell comprising the polypeptide of Group I, rather than the polynucleotide of Group II.

Claims 1-5 and 11-29 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 6-10 are presently under consideration.

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 35 U.S.C. 119(e) as follows: the record of priority application USSN 10/981,352 does not contain a reference to provisional application USSN 60/517,507 in the specification or in Application Data Sheet, as required by 37 CFR 1.78. See MPEP 201.11.

Therefore, the instant claims are accorded the priority date of 11/04/2004, i.e. the filing date of USSN 10/981,352.

3. Claims 6-10 are objected to as being dependent on a non-elected claim. It is suggested that Applicant rewrite the claims in independent form to include the limitations of the non-elected base claim.

4. **35 U.S.C. § 101** reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

5. Claims 8-10 are rejected under **35 USC §101** because the claimed invention is directed to non-statutory subject matter.

The claims are directed to a "host cell" comprising the recited polynucleotide. The instant specification discloses at page 8, paragraph [0034], that the term "host cell" means any cell of any organism, but does not specify whether the cells are in vitro or in vivo. Therefore, the term "host cell" in the instant claims is interpreted to encompass, inter alia, a cell present in a human being, and therefore being inseparable from the human being itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. Applicant is invited to amend the claims to recite "isolated" and/or "non-human" host cell. See 1077 O.G. 24, April 21, 1987.

6. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 6-10 are rejected under **35 U.S.C. 102(a)** as being anticipated by Imai et al. (Blood, 102 (11): p 66a-67a; November 16, 2003) or Imai et al. (Journal of Biological Regulators and Homeostatic Agents, 18 (1): p 62-71; January 2004; abstract only).

As addressed in section 2 above, the instant claims have been accorded the priority date of 11/04/2004.

Since the plurality of authors of the cited references is not coextensive with the plurality of inventors of the instant application, the references are “by others.”

Both references teach chimeric receptors “anti-CD19-BB-zeta,” comprising an anti-CD19 scFv domain, hinge and transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain (see the Abstract of both publications). Since the chimeric receptor is recombinantly produced, the teachings of the references inherently comprise a polynucleotide encoding the receptor, as well as a vector and host cell

comprising the polynucleotide. Furthermore, both references teach T lymphocytes transduced to express the chimeric receptor.

At least in view of the above, the teachings of the reference anticipate the instantly claimed invention.

8. Claims 6-10 are rejected under **35 U.S.C. 102(a) and 35 U.S.C. 102(a)** as being anticipated by Sadelain et al. (US 2004/0043401; see entire document).

Sadelain teaches in Example 8 and 7 a chimeric receptor comprising an extracellular anti-cd19 scFv domain [0051] and intracellular 4-1BB signaling domain [0053]). Example 1 at [0038] clarifies that the scFv and the signaling domain are connected via a hinge and transmembrane sequences. The polynucleotide sequence (SEQ ID NO:15) encoding the chimeric receptor comprising intracellular 4-1BB signaling domain is taught at [0018]. Figure 1 shows a vector comprising the polynucleotide, and [0028] teaches T cells comprising the polynucleotide.

At least in view of the above, the teachings of the reference anticipate the instantly claimed invention.

9. The following is a quotation of **35 U.S.C. 103(a)** which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 6-10 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Jensen et al. (US 2004/0126363 ['363]; see entire document) in view of Jensen (US 2003/0215427 ['427]; see entire document).

Jensen '363 teaches a chimeric receptor comprising an extracellular anti-CD19 scFv, a portion of an IgG constant region (i.e. a hinge), a transmembrane domain and a cytoplasmic signaling domain for an effector function of an immune cell, such as the cytoplasmic signaling domain of zeta chain of CD3 (e.g. the Abstract, and claim 1). Jensen '363 further teaches a DNA construct (i.e. a polynucleotide) encoding the chimeric receptor (e.g. claim 17) and a vector comprising the construct (e.g. claim 18). Jensen '363 further teaches genetically engineered immune cells, such as T lymphocytes and NK cells, expressing the chimeric receptor (e.g. claim 2), i.e. comprising the polynucleotide encoding the receptor.

Examples of cytoplasmic signaling domains envisioned by Jensen '363 include the zeta chain of the T cell receptor or any of its homologs (e.g., eta, delta, gamma or epsilon), MB1 chain, B29, Fc RIII and Fc RI and the like. Intracellular signaling portions of other members of the families of activating proteins can be used, such as Fc.gamma.RIII and Fc.epsilon.RI [0050].

Jensen '363 further teaches that T cells or NK cells expressing the chimeric receptor are useful in treating CD19-expressing malignancies, wherein the cytoplasmic signaling domain mediates activation of the cells (e.g. [0051-0065]).

Jensen '363 does not specifically exemplify a 4-1BB signaling domain as the cytoplasmic signaling domain.

Jensen '427 teaches a chimeric receptor comprising an extracellular anti-CE3 scFv, a hinge domain, a transmembrane domain and a cytoplasmic signaling domain of 4-1BB (see e.g. the claims, in particular claims 1, 4, 7, 9, and 10). Jensen '427 further teaches a DNA construct (i.e. a polynucleotide) encoding the chimeric receptor (e.g. claim 17) and a vector comprising the construct (e.g. claim 18). Jensen '427 further teaches genetically engineered immune cells, such as T lymphocytes and NK cells, expressing the chimeric receptor (e.g. claim 3), i.e. comprising the polynucleotide encoding the receptor.

Jensen '427 further teaches that T cells or NK cells expressing the chimeric receptor are useful in treating CE3-expressing malignancies, wherein the cytoplasmic signaling domain mediates activation of the cells (e.g. claims 19-21).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the anti-CD19 scFv of the chimeric receptor taught by Jensen '363 for the scFv of the chimeric receptor taught by Jensen '427, to produce the instantly recited receptor and the corresponding polynucleotide and host cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, in view of the teachings of both references that that such chimeric receptors are useful in treating malignancies expressing the target of the extracellular scFv domain of the chimeric receptor.

One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success in producing the polynucleotides encoding such chimeric receptors and T cells expressing the receptors, based on the detailed guidance provided in both publications, and further in view of the routine nature of the experimentation involved.

Furthermore, "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…. [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See MPEP 2144.06.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The teachings made of record and not presently relied upon are considered pertinent to Applicant's disclosure: Koehler et al. (Advances in Hematology, Volume 2012, Article ID 595060, 13 pages; doi:10.1155/2012/595060; see entire document). The reference teaches that CD19-specific chimeric receptors comprising a 4-1BB signaling domain either alone or in combination with CD3 zeta signaling domain may induce superior activation of the T cells relative to only the CD3 zeta signaling domain (e.g. pages 2-3 and 8-9).

12. Conclusion: no claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel E. Kolker can be reached on 571-272-3181. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ILIA OUSPENSKI/

ILIA OUSPENSKI, Ph.D.
Primary Examiner
Art Unit 1644

Electronic Filing

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Campana *et al.*	Confirmation No.:	1261
Application No.:	13/548,148	Art Unit:	1644
Filed:	July 12, 2012	Examiner:	Ilia I. Ouspenski
For:	CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN	Attorney Docket No.:	13213-005-999

RESPONSE TO OFFICE ACTION UNDER 37 CFR 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed October 11, 2012, in connection the above-identified application, Applicants submit herewith: (1) a Combined Declaration under 37 C.F.R. §§ 1.131 and 1.132, with Exhibits A-I; (2) Appendix 1: Milone *et al.*, 2009, Molecular Therapy 17:1453-1464; and (3) Appendix 2: Porter et al., N. Eng. J. Med. 365; 8: 725-733.

No fee is believed to be due in connection with this submission. Should any fee be required, however, the Commissioner is authorized to charge any required fees to Jones Day Deposit Account No. 50-3013.

Amendments to the Claims begin at page 2 of this paper.

Remarks/Arguments begin at page 5 of this paper.

AMENDMENTS TO THE CLAIMS:

This Listing of Claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS:

1 – 5. (Canceled)

6. (Currently amended) A polynucleotide encoding ~~the~~ a chimeric receptor ~~of claim 1~~ comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

7. (Currently amended) A vector comprising a polynucleotide encoding ~~the~~ a chimeric receptor ~~of claim 1~~ comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, (b) a transmembrane domain, and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, wherein the polynucleotide encoding the chimeric receptor is operatively linked to at least one regulatory element for expression of the chimeric receptor.

8. (Currently amended) ~~A~~ An isolated host cell comprising a polynucleotide encoding ~~the~~ a chimeric receptor ~~of claim 1~~ comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

9. (Currently amended) The isolated host cell of claim 8 which is a T lymphocyte or an NK cell.

10. (Currently amended) The isolated host cell of claim 8 which is a T lymphocyte.

11– 29. (Canceled)

30. (New) The polynucleotide of claim 6 wherein the signaling domain is a human 4-1BB signaling domain.

31. (New) The polynucleotide of claim 30, wherein the 4-1BB signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

32. (New) The polynucleotide of claim 31, wherein the nucleotide sequence encoding the human 4-1BB signaling domain comprises nucleotide residues 129-893 of SEQ ID NO:1.

33. (New) The polynucleotide of claim 6, wherein the transmembrane domain is the transmembrane domain of CD8α.

34. (New) The polynucleotide of claim 33, wherein the extracellular ligand-binding domain further comprises a signal peptide of CD8α.

35. (New) The vector of claim 7 which is a viral vector.

36. (New) The vector of claim 35 which is a retroviral vector.

37. (New) The isolated host cell of claim 8 which is an NK cell.

38. (New) The isolated host cell of claim 8 which is an autologous cell isolated from a patient having a cancer of B cell origin.

39. (New) The isolated host cell of claim 38, wherein the autologous cell is an autologous T lymphocyte.

40. (New) The isolated host cell of claim 39, wherein the autologous T lymphocyte is derived from a blood or tumor sample of a patient having a cancer of B cell origin and activated and expanded *in vitro*.

41. (New) The isolated host cell of claim 10, wherein the T lymphocyte is an activated T lymphocyte.

42. (New) The isolated host cell of claim 10, wherein the T lymphocyte is isolated from a blood or tumor sample of a patient having a cancer of B cell origin.

43. (New) The isolated host cell of claim 42 wherein the host cell is isolated from a patient having lymphoblastic leukemia, B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma.

44. (New) The polynucleotide of claim 6, wherein the chimeric receptor further comprises a hinge domain.

45. (New) The vector of claim 7, wherein the chimeric receptor further comprises a hinge domain.

46. (New) The isolated cell of claim 8, wherein the chimeric receptor further comprises a hinge domain.

REMARKS/ARGUMENTS

Claims 1-29 were pending in the present application. By this amendment, Claims 1-5 and 11-29, which were withdrawn by the Examiner as being drawn to nonelected inventions, have now been canceled without prejudice to Applicants' right to pursue the subject matter of the canceled claims, and Claims 6-10 have been amended. In addition, new Claims 30-46, which recite specific polynucleotides encoding an anti-CD19 BB-ζ chimeric receptor comprising an anti-CD19 scFv domain, a transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, and vectors and host cells comprising such polynucleotides, have been added. Thus, upon entry of the present amendment, claims 6-10 and 30-46 (*i.e.*, 3 independent claims and 19 dependent claims) will be pending.

Support for the amendments and newly added claims is found in the specification as filed. In particular, claim 6 has been amended to specify a polynucleotide, *i.e.*, an anti-CD19-BB-ζ polynucleotide that encodes a chimeric receptor comprising a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, a transmembrane domain, and/or an extracellular ligand-binding domain; and dependant claims 30-35 further specify that the polynucleotide of claim 6: encodes a human 4-1BB signaling domain (claim 30), encodes a human 4-1BB signaling domain comprising amino acids 214-255 of SEQ ID NO:2 (claim 31), nucleotide residues 129-893 of SEQ ID NO:1 (claim 32), encodes a transmembrane domain of CD8α (claim 33), encodes an extracellular ligand-binding which further comprises a signal peptide of CD8α (claim 34), or further encodes a hinge domain (claim 44). Support for these amendments is found in the specification as originally filed, particularly, for example, at ¶¶ 16,

17, 19, 26, and 49-61 of the specification (wherein ¶ numbering is in reference is to the paragraph numbering in Substitute Specification filed 9/21/12). Claim 7 has been amended, and new claims 35-37 and 45 have been added, to specify particular vectors; support for these new claims and amendments is found in the specification as originally filed, particularly, for example, at ¶¶16, 34, 49, 52, and 54-65 of the specification. Claims 8-10 have been amended to specify isolated host cells, and new claims 38-43, and 46 have been added, to specify particular isolated host cells; support for these new claims and amendments is found in the specification as originally filed, particularly, for example, at ¶¶16, 34 and 49, 52, and 54-65 of the specification.

As such, no new matter has been added by these amendments.

I. The Rejections Under U.S.C. § 101 Should Be Withdrawn

The Examiner has rejected Claims 8-10 as being directed to non-statutory subject matter under 35 U.S.C. § 101. According to the Examiner, Claims 8-10 are directed to a "host cell" comprising the recited polynucleotide without specifying whether the cells are *in vitro* or *in vivo*, and could therefore be interpreted to encompass, *inter alia*, a cell present in a human being and thus inseparable from the human being itself, and therefore nonstatutory subject matter.

In response, Claims 8-10 have been amended, and new Claims 38-42 have been added, to require that the claimed host cells be isolated. Support for these amendments and new claims may be found, *inter alia*, at ¶¶34 and 54 of the application. As such, the claimed host cells are *in vitro*, not *in vivo*, and cannot be interpreted to encompass a cell present in a human being. Therefore, Applicant submits that the isolated host cells of Claims 8-10 and new Claims 38-42 are statutory subject matter and do not contravene 35 U.S.C. § 101.

II. The Rejection Under 35 U.S.C. § 102(a) For Anticipation by Imai I and Imai II Should Be Withdrawn

The Examiner has rejected Claims 6-10 as being anticipated under 35 U.S.C. § 102(a) by Imai *et al.*, Blood, 102 (11): pp. 66a - 67a; November 16, 2003 ("Imai I") or Imai *et al.*, Journal of Biological Regulators and Homeostatic Agents, 18 (1): p. 62-71; January 2004. According to the Examiner, since the plurality of authors of the cited references is not coextensive with the plurality of inventors of the instant application, the references are "by others."

At the outset, it is noted that the second Imai *et al.* reference identified above lists only two authors, C. Imai and D. Campana, who are the applicants and named inventors of the instant application. As such, the second Imai *et al.* reference cited by the Examiner is not "by others." During a conference call on 10/22/2012, the Examiner informed Applicants' attorney that the second Imai *et al.* reference used in this rejection was mis-identified and should be replaced by Imai *et al.*, Leukemia, 18 (1): p. 676-684; February 2004 (abstract only) ("Imai II").

Both Imai I and Imai II list a plurality of authors, including C. Imai and D. Campana, the applicants and named inventors of the instant application, as well as other coauthors. However, Imai I and Imai II describe the applicants' own work, as established by the Combined Declaration under 37 C.F.R. §§ 1.131 and 1.132 and Exhibits A-I ("the Declaration") submitted herewith and discussed in detail below.

According to the Examiner, both Imai I and Imai II teach anti-CD19 BB-ζ chimeric receptors comprising an anti-CD19 scFv domain, a transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain, as well as T lymphocytes transduced to express the chimeric receptor. The Examiner further alleges that the references inherently comprise a

polynucleotide encoding the receptor, as well as a vector and host cell comprising the polynucleotide.

Applicants respectfully request that the Examiner consider the Declaration (including Exhibits A-I), which provides documentary evidence establishing that the invention of the claimed subject matter (*i.e.*, a polynucleotide encoding an anti-CD19 BB-ζ chimeric receptor comprising an anti-CD19 scFv domain, a transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain; isolated host cells (*e.g.*, T lymphocytes) comprising a polynucleotide encoding an anti-CD19 BB-ζ chimeric receptor; and a vector and a host cell comprising a polynucleotide encoding an anti-CD19 BB-ζ chimeric receptor) was reduced to practice by the inventors, Drs. Imai and Campana, in the United States prior to May 28, 2003, a date which is prior to the effective publication dates of both of Imai I and Imai II. In particular, the Declaration provides evidence that the inventors conceived of the idea of developing a cell-based immunotherapy of CD19-positive leukemia using genetically modified human primary lymphocytes grafted with an anti-CD19 BB-ζ chimeric receptor. To this end, a polynucleotide encoding an anti-CD19 BB-ζ chimeric receptor was constructed as described in the Declaration (and in Example 1 at ¶ [0078] of the instant application) by obtaining the known genetic components and using polymerase chain reaction technology and splicing by overlapping extension (PCR and SOE-PCR) to generate and assemble the genetic fragments to create a polynucleotide that encodes anti-CD19 BB-ζ. In addition, the Declaration demonstrates that vectors and host cells comprising those polynucleotides were constructed in the United States prior to May 28, 2003, and that such polynucleotides, vectors and cells work

for their intended purpose. As such, the Declaration establishes that the claimed subject matter was invented prior to the effective publication dates of Imai I and Imai II.

Therefore, Applicants submit that Imai I and Imai II do not anticipate the claimed subject matter under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request that the claim rejections under 35 U.S.C. § 102(a) over Imai I and Imai II be withdrawn.

III. The Rejection Under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e) For Anticipation by Sadelain Should Be Withdrawn

The Examiner has rejected Claims 6-10 as being anticipated under 35 U.S.C. § 102(a) and 35 U.S.C. § 102(e)[1] by Pub. No. US 2004/0043401 ("Sadelain"). In particular, the Examiner contends that Sadelain teaches: (1) a chimeric receptor comprising an extracellular anti-CD19 scFv domain and intracellular 4-1BB signaling domain in Examples 8 and 7; (2) the scFv and the signaling domain are connected via transmembrane sequences (Example 1); (3) the polynucleotide sequence SEQ ID NO:15 encoding the chimeric receptor comprising intracellular 4-1BB signaling domain; (4) a vector comprising the polynucleotide; and (5) T cells comprising the polynucleotide.

As a initial observation, Applicants respectfully point out that Sadelain's priority application, provisional application No. 60/383,872 filed May 28, 2002 ("Sadelain provisional") does not contain the disclosure relied on by the Examiner in making this rejection. In particular, the Sadelain provisional does not include Example 8 or 7, and does not teach or suggest the claimed polynucleotide encoding a chimeric receptor comprising an extracellular ligand-binding

[1] During a conference call with Applicant's attorney on 10/22/2012, the Examiner clarified that "35 U.S.C. 102(a) and 35 U.S.C. 102 (a)" was a typographical error, and that it should be read as "35 U.S.C. 102(a) and 35 U.S.C. 102 (e)".

domain comprising an anti-CD19 scFv domain, a transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain. As such, Sadelain's earliest possible effective filing date applicable to the instantly claimed invention under 35 U.S.C. § 102(a) or 102(e) is the May 28, 2003 filing date of U.S. Application No. 10/448,256.

Without conceding to the propriety of the Examiner's rejection or characterization of the disclosure of Sadelain, Applicants respectfully request that the Examiner consider the amended claims (directed to polynucleotides encoding an anti-CD19 BB-ζ chimeric receptor comprising, *inter alia*, a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, and vectors and host cells comprising such polynucleotides) and the Declaration (including Exhibits A-I) submitted herewith, which establishes that the claimed invention was reduced to practice in the United States by the inventors prior to May 28, 2003, as discussed in Section II, above. In particular, the Declaration provides documentary evidence that establishes that, prior to May 28, 2003, the inventors conceived of the idea of developing a cell-based immunotherapy of CD19-positive leukemia using genetically modified human primary lymphocytes grafted with an anti-CD19 BB-ζ chimeric receptor. The Declaration further establishes that, to this end, a polypeptide encoding a chimeric receptor comprising an extracellular anti-CD19 scFv domain and intracellular 4-1BB signaling domain, wherein the scFv and the signaling domain are connected via a transmembrane domain, and a polynucleotide encoding a chimeric receptor comprising an intracellular 4-1BB signaling domain and a CD3ζ signaling domain, and a vector and T-cells comprising such polynucleotide, was reduced to practice in the United States by the inventors prior to May 28, 2003. As such, the inventors have established that the claimed subject matter was invented prior to the effective date of Sadelain.

Therefore, Applicants respectfully submit that Sadelain does not anticipate the claimed subject matter under 35 U.S.C. §§ 102(a) or 102(e). Accordingly, Applicants request that the claim rejections under 35 U.S.C. §§ 102(a) and 102(e) over Sadelain be withdrawn.

IV. The Rejection Under 35 U.S.C. § 103(a) As Being Unpatentable Over Jensen et al. in View of Jenson Should Be Withdrawn

The Examiner has rejected Claims 6-10 as being unpatentable over US 2004/0126363 ("Jenson et al. '363") in view of US 2003/0215427 ("Jenson '427").

In particular, the Examiner contends that Jenson et al. '363 teaches a chimeric receptor comprising an extracellular anti-CD19 scFv, a portion of an IgG constant region (*i.e.*, a hinge), a transmembrane domain and a cytoplasmic signaling domain for an effector function of an immune cell such as the cytoplasmic signaling domain of zeta chain CD3, a DNA polynucleotide encoding the chimeric receptor and a vector comprising the DNA construct, and genetically engineered immune cells such as T lymphocytes and NK cells, expressing the chimeric receptor, *i.e.*, comprising the polynucleotide encoding the receptor.

The Examiner admits that Jenson et al. '363 does not exemplify a 4-1BB signaling domain. However, the Examiner contends that, based on the teaching of Jensen '427 of a chimeric receptor comprising an extracellular anti-CE3 scFv, a hinge domain, a transmembrane domain and a cytoplasmic signaling domain of 4-1BB, a DNA polynucleotide encoding the chimeric receptor and a vector comprising the construct, and its further teaching of genetically engineered immune cells, such as T lymphocytes and NK cells, expressing the chimeric receptor, *i.e.*, comprising the polynucleotide encoding the receptor; and the teaching that T cells or NK cells expressing the chimeric receptor are useful in treating CE3 malignancies, wherein the

cytoplasmic signaling domain mediates activation of the cells, that it would be obvious to a person of ordinary skill in the art at the time the invention was made to substitute the anti-CD19 of the chimeric receptor taught by Jenson '363 for the scFv of the chimeric receptor taught by Jenson '427 to produce the instantly recited receptor and the corresponding polynucleotide and host cells.

Without conceding to the propriety of the rejection, the claims have been amended to recite polynucleotides encoding an anti-CD19 BB-ζ chimeric receptor comprising an anti-CD19 scFv domain, a transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, and isolated host cells and vectors comprising such polynucleotides.

Neither Jenson et al. '363 nor Jenson '427 teach or suggest a polynucleotide encoding a chimeric receptor that has both a 4-1BB signaling domain and a CD3ζ signaling domain, or even any chimeric receptor having two signaling domains, much less the claimed anti-CD19-BB-ζ polynucleotides encoding a chimeric receptor comprising a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain. Thus, substituting the anti-CD19 of the chimeric receptor of Jenson et al. '363 for the scFv of the chimeric receptor of Jenson '427 to produce a new chimeric receptor, as suggested by the Examiner, would not result in the presently claimed polynucleotides, vectors, and host cells.

Moreover, the claimed anti-CD19-BB-ζ polynucleotides encoding such chimeric receptors and isolated host cells and vectors comprising such polynucleotides have demonstrated unexpectedly superior anti-leukemic efficacy when expressed in T cells. For example, as described in the application, expression of anti-CD19-BB-ζ receptor in T cells resulted in

cytotoxic activity toward $CD19^+$ leukemic cells at low concentration in an environment critical for B-lineage leukemia cell growth (see ¶57 of specification), and caused higher levels of TRAIL (T-Receptor Apopotosis-Inducing Ligand) stimulation than the level of TRAIL stimulation caused by a chimeric receptor comprising the CD19 receptor but lacking a 4-1BB signaling domain (see ¶58 of specification).

Further evidence of the unexpected efficacy of the anti-CD19-BB-ζ chimeric antigen receptor ("CAR") is found in Milone *et al.*, 2009, "Chimeric Receptors Containing CD137 Signal Transduction Domains Mediate Enhanced Survival of T Cells and Increased Antileukemic Efficacy In Vivo," Molecular Therapy 17: 1453-1464 (Appendix 1). Using an immune-deficient mouse model of primary human pre-B-cell acute lymphoblastic leukemia (ALL), Milone *et al.* compared the proliferative capacity of T cells expressing CARs having different types of activator domains, and demonstrated that human T cells expressing anti-CD19-BB-ζ surprisingly exhibited the greatest anti-leukemic efficacy, prolonged survival *in vivo*, and were significantly more effective than CARs expressing either a TCR-ζ activating domain without the 4-1BB domain, or a dual CD28-ζ signaling domain. (*See* Milone et al., p. 1456, Fig. 4, and Abstract).

Finally, the results of a recently reported clinical trial in which a patient with chronic lymphocytic leukemia (CLL) was treated with modified T-cells comprising polynucleotides encoding an anti-CD19-BB-ζ CAR demonstrated remarkable and unexpected efficacy of anti-CD19-BB-ζ CAR T-cell therapy in treating CLL. *See* Porter et al., "Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia," N. Eng. J. Med. 365; 8: 725-733 (Appendix 2). A patient treated with a very low dose (1.5×10^5 per kg) of autologous T cells genetically

modified with a vector expressing an anti-CD19-BB-ζ CAR demonstrated delayed development of the tumor lysis syndrome and complete remission (*Id.*, Abstract). The unexpectedly low dosage of infused anti-CD19-BB-ζ CAR T cells needed to achieve a clinically evident antitumor response was particularly remarkable as it was several orders of magnitude below doses used in previous CAR-modified T cell therapy studies (*Id.* at p. 731).

Therefore, Applicants submit that the claimed subject matter is not obvious under 35 U.S.C. § 103(a) over Jenson et al. '363 in view of Jenson '427. Accordingly, Applicants respectfully request that the claim rejections under 35 U.S.C. § 103(a) over Jenson et al. '363 in view of Jenson '427 be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks made herein be considered and made of record in the instant application.

Respectfully submitted,

Date January 11, 2013

/Eileen E. Falvey/ 46,097

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NOTICE OF ALLOWANCE AND FEE(S) DUE

108842 7590 01/23/2013

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222 East 41st Street
New York, NY 10017

EXAMINER
OUSPENSKI, ILIA I

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/23/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,148	07/12/2012	Dario CAMPANA	13213-005-999	1261

TITLE OF INVENTION: CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$0	$0	$885	04/23/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

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B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,148	07/12/2012	Dario CAMPANA	13213-005-999	1261

TITLE OF INVENTION: CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$885	$0	$0	$885	04/23/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
OUSPENSKI, ILIA I	1644	536-023400

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

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☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

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Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,148	07/12/2012	Dario CAMPANA	13213-005-999	1261

108842 7590 01/23/2013

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New York, NY 10017

EXAMINER	
OUSPENSKI, ILIA I	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/23/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/548,148	CAMPANA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *01/11/2013*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *6-10 and 30-46*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ILIA OUSPENSKI/
Primary Examiner, Art Unit 1644

US008399645B2

(12) **United States Patent**
Campana et al.

(10) **Patent No.: US 8,399,645 B2**
(45) **Date of Patent: Mar. 19, 2013**

(54) **CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN**

(75) Inventors: **Dario Campana**, Germantown, TN (US); **Chihaya Imai**, Niigata (JP)

(73) Assignee: **St. Jude Children's Research Hospital, Inc.**, Memphis, TN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/548,148**

(22) Filed: **Jul. 12, 2012**

(65) **Prior Publication Data**

US 2012/0282256 A1 Nov. 8, 2012

Related U.S. Application Data

(63) Continuation of application No. 13/244,981, filed on Sep. 26, 2011, now abandoned, which is a continuation of application No. 12/206,204, filed on Sep. 8, 2008, now Pat. No. 8,026,097, which is a continuation of application No. 11/074,525, filed on Mar. 8, 2005, now Pat. No. 7,435,596, which is a continuation-in-part of application No. 10/981,352, filed on Nov. 4, 2004, now abandoned.

(60) Provisional application No. 60/517,507, filed on Nov. 5, 2003.

(51) **Int. Cl.**
C07H 21/04 (2006.01)
C12N 15/00 (2006.01)

(52) **U.S. Cl.** **536/23.4**; 435/320.1; 435/455

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to a chimeric receptor capable of signaling both a primary and a co-stimulatory pathway, thus allowing activation of the co-stimulatory pathway without binding to the natural ligand. The cytoplasmic domain of the receptor contains a portion of the 4-1BB signaling domain. Embodiments of the invention relate to polynucleotides that encode the receptor, vectors and host cells encoding a chimeric receptor, particularly including T cells and natural killer (NK) cells and methods of use.

22 Claims, 2 Drawing Sheets

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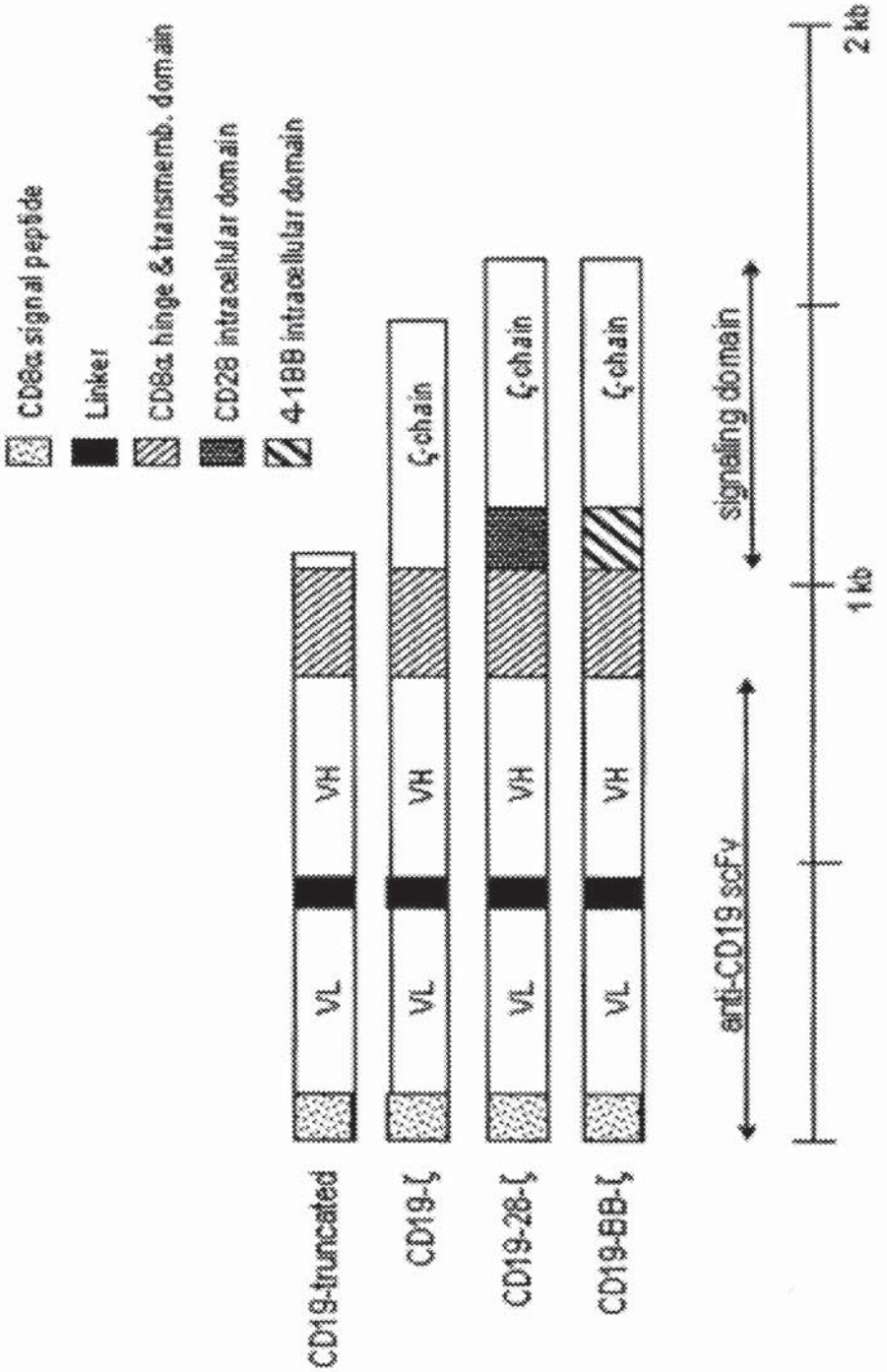
CD8α signal peptide
Linker
CD8α hinge & transmemb. domain
CD28 intracellular domain
4-1BB intracellular domain
CD19-truncated
CD19-ζ
CD19-28-ζ
CD19-BB-ζ
VL
VH
ζ chain
anti-CD19 scFv
signaling domain
1 kb
2 kb

Figure 1

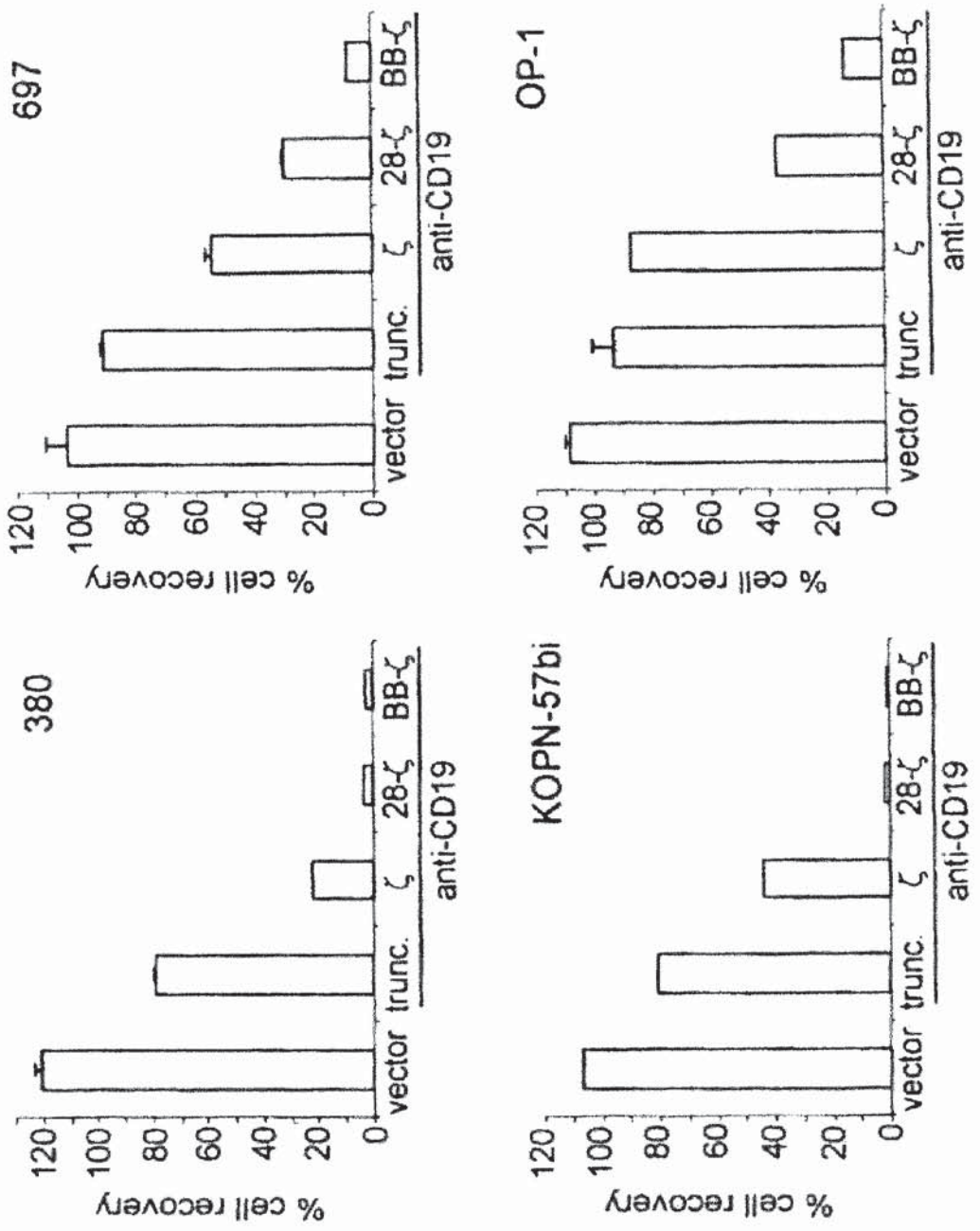
697
380
OP-1
KOPN-57bi
% cell recovery
120
100
80
60
40
20
0
vector
trunc.
ζ
28-ζ
BB-ζ
anti-CD19

Figure 2

CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN

2. CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/244,981, filed Sep. 26, 2011 now abandoned, which is a continuation of U.S. patent application Ser. No. 12/206,204, filed on Sep. 8, 2008 (granted as U.S. Pat. No. 8,026,097), which is a continuation of U.S. patent application Ser. No. 11/074,525, filed on Mar. 8, 2005 (granted as U.S. Pat. No. 7,435,596), which is a continuation-in-part of U.S. patent application Ser. No. 10/981,352 filed Nov. 4, 2004 (abandoned), which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/517,507 filed on Nov. 5, 2003, each of which is incorporated herein by reference in its entirety.

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. The Sequence Listing is being concurrently submitted via EFS-Web as an ASCII text file named 13213-005-999_Sequence_Listing.txt, created Jul. 12, 2012, and being 16,298 bytes in size.

1. GOVERNMENT INTEREST

This invention was made in part with U.S. Government support under National Institutes of Health grant No. CA 58297. The U.S. Government may have certain rights in this invention.

3. FIELD OF THE INVENTION

This invention relates to chimeric cell membrane receptors, particularly chimeric T-cell receptors. This invention further relates to activation and expansion of cells for therapeutic uses, in particular for activation and expansion of NK cells for chimeric receptor-based cell therapy.

4. BACKGROUND

Regulation of cell activities is frequently achieved by the binding of a ligand to a surface membrane receptor comprising an extracellular and a cytoplasmic domain. The formation of the complex between the ligand and the extracellular portion of the receptor results in a conformational change in the cytoplasmic portion of the receptor which results in a signal transduced within the cell. In some instances, the change in the cytoplasmic portion results in binding to other proteins, where other proteins are activated and may carry out various functions. In some situations, the cytoplasmic portion is autophosphorylated or phosphorylated, resulting in a change in its activity. These events are frequently coupled with secondary messengers, such as calcium, cyclic adenosine monophosphate, inositol phosphate, diacylglycerol, and the like. The binding of the ligand to the surface membrane receptor results in a particular signal being transduced.

For T-cells, engagement of the T-cell receptor (TCR) alone is not sufficient to induce persistent activation of resting naive or memory T cells. Full, productive T cell activation requires a second co-stimulatory signal from a competent antigen-presenting cell (APC). Co-stimulation is achieved naturally by the interaction of the co-stimulatory cell surface receptor on the T cell with the appropriate counter-receptor on the surface of the APC. An APC is normally a cell of host origin which displays a moiety which will cause the stimulation of

an immune response. APCs include monocyte/macrophages, dendritic cells, B cells, and any number of virally-infected or tumor cells which express a protein on their surface recognized by T cells. To be immunogenic APCs must also express on their surface a co-stimulatory molecule. Such APCs are capable of stimulating T cell proliferation, inducing cytokine production, and acting as targets for cytolytic T cells upon direct interaction with the T cell. See Linsley and Ledbetter, Ann. Rev. Immunol. 4:191-212 (1993); Johnson and Jenkins, Life Sciences 55:1767-1780 (1994); June et al., Immunol. Today 15:321-331 (1994); and Mondino and Jenkins, J. Leuk. Biol. 55:805-815 (1994).

Engagement of the co-stimulatory molecule together with the TCR is necessary for optimal levels of IL-2 production, proliferation and clonal expansion, and generation of effector functions such as the production of immunoregulatory cytokines, induction of antibody responses from B cells, and induction of cytolytic activity. More importantly, engagement of the TCR in the absence of the co-stimulatory signal results in a state of non-responsiveness, called anergy. Anergic cells fail to become activated upon subsequent stimulation through the TCR, even in the presence of co-stimulation, and in some cases may be induced to die by a programmed self-destruct mechanism.

In certain situations, for example where APCs lack the counter-receptor molecules necessary for co-stimulation, it would be beneficial to have the co-stimulatory signal induced by virtue of employing a ligand other than the natural ligand for the co-stimulatory receptor. This might be, for example, the same ligand as that recognized by the TCR (i.e., the same moiety, such that if one signal is received, both signals will be received), or another cell surface molecule known to be present on the target cells (APCs).

Several receptors that have been reported to provide co-stimulation for T-cell activation, including CD28, OX40, CD27, CD2, CD5, ICAM-1, LFA-1 (CD11a/CD18), and 4-1BB. The signaling pathways utilized by these co-stimulatory molecules share the common property of acting in synergy with the primary T cell receptor activation signal.

Previously the signaling domain of CD28 has been combined with the T-cell receptor to form a co-stimulatory chimeric receptor. See U.S. Pat. No. 5,686,281; Geiger, T. L. et al., *Blood* 98: 2364-2371 (2001); Hombach, A. et al., *J Immunol* 167: 6123-6131 (2001); Maher, J. et al. *Nat Biotechnol* 20: 70-75 (2002); Haynes, N. M. et al., *J Immunol* 169: 5780-5786 (2002); Haynes, N. M. et al., *Blood* 100: 3155-3163 (2002). These co-stimulatory receptors provide a signal that is synergistic with the primary effector activation signal, i.e. the TCR signal or the chimeric effector function receptor signal, and can complete the requirements for activation under conditions where stimulation of the TCR or chimeric effector function receptor is suboptimal and might otherwise be detrimental to the function of the cell. These receptors can support immune responses, particularly of T cells, by permitting the use of ligands other than the natural ligand to provide the required co-stimulatory signal.

Chimeric receptors that contain a CD19 specific single chain immunoglobulin extracellular domain have been shown to lyse CD19+ target cells and eradicate CD19+ B cell lymphomas engrafted in mice [Cooper L J, et al., Blood 101:1637-1644 (2003) and Brentjens R J, et al., Nature Medicine 9:279-286 (2003)]. Cooper et al. reported that T-cell clones transduced with chimeric receptors comprising anti-CD19 scFv and CD3ζ produced approximately 80% specific lysis of B-cell leukemia and lymphoma cell lines at a 1:1 effector to target ratio in a 4-hour Cr release assay; at this ratio, percent specific lysis of one primary B-lineage ALL

sample tested was approximately 30%. Brentjens et al. reported that T-cells bearing anti-CD19 scFv and CD3ζ chimeric receptors could be greatly expanded in the presence of exogenous IL-15 and artificial antigen-presenting cells transduced with CD19 and CD80. The authors showed that these T cells significantly improved the survival of immunodeficient mice engrafted with the Raji B-cell lymphoma cell line. Their results also confirmed the importance of co-stimulation in maximizing T-cell-mediated anti-leukemic activity. Only cells expressing the B7 ligands of CD28 elicited effective T-cell responses. This could be a major obstacle in the case of B-lineage ALL because leukemic lymphoblasts typically do not express B7 molecules.

In addition to T cell immune responses, natural killer (NK) cell responses appear to be clinically relevant. While T cells recognize tumor associated peptide antigen expressed on surface HLA class I or class II molecules, antigen nonspecific immune responses are mediated by NK cells that are activated by the failure to recognize cognate "self" HLA class I molecules. The graft-versus-tumor effect of transplants using HLA matched donors is mediated by antigen specific T cells, while transplantation using HLA mismatched donors can also lead to donor NK cells with potent antitumor activity. HLA mismatched haplo-identical transplants can exert a powerful anti-leukemia effect based on expansion of antigen nonspecific donor NK cells.

Immunotherapy with NK cells has been limited by the inability to obtain sufficient numbers of pure NK cells suitable for manipulation and expansion. The established methods for cell expansion favor T cell expansion and even after T cells are depleted, residual T cells typically become prominent after stimulation. Thus there is a need for better methods to expand NK cells from a population without expanding T cells.

5. SUMMARY OF THE INVENTION

The present invention provides a chimeric receptor containing a co-stimulatory signal by incorporation of the signaling domain of the 4-1BB receptor. The chimeric receptor comprises an extracellular ligand binding domain, a transmembrane domain and a cytoplasmic domain wherein the cytoplasmic domain comprises the signaling domain of 4-1BB. In one embodiment of the invention the signaling domain of 4-1BB used in the chimeric receptor is of human origin. In a preferred embodiment, human 4-1BB consists of SEQ ID NO:2. In another embodiment the signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

In another embodiment of the invention the cytoplasmic domain of the chimeric receptor comprises the signaling domain of CD3ζ in addition to the signaling domain of 4-1BB. In another embodiment the extracellular domain comprises a single chain variable domain of an anti-CD19 monoclonal antibody. In another embodiment the transmembrane domain comprises the hinge and transmembrane domains of CD8α. In a most preferred embodiment of the invention the extracellular domain comprises a single chain variable domain of an anti-CD19 monoclonal antibody, the transmembrane domain comprises the hinge and transmembrane domain of CD8α, and the cytoplasmic domain comprises the signaling domain of CD3ζ and the signaling domain of 4-1BB.

Other aspects of the invention include polynucleotide sequences, vectors and host cells encoding a chimeric receptor that comprises the signaling domain of 4-1BB. Yet other aspects include methods of enhancing T lymphocyte or natural killer (NK) cell activity in an individual and treating an individual suffering from cancer by introducing into the individual a T lymphocyte or NK cell comprising a chimeric receptor that comprises the signaling domain of 4-1BB. These aspects particularly include the treatment of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. Preferred cancer targets for use with the present invention are cancers of B cell origin, particularly including acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma.

A different but related aspect of the present invention provides a method for obtaining an enriched NK cell population suitable for transduction with a chimeric receptor that comprises the signaling domain of 4-1BB. This method comprises the expansion of NK cells within a mixed population of NK cells and T cells by co-culturing the mixed population of cells with a cell line that activates NK cells and not T lymphocytes. This NK activating cell line is composed of cells that activate NK cells, but not T lymphocytes, and which express membrane bound interleukin-15 and a co-stimulatory factor ligand. In a particular embodiment the NK activating cell line is the K562 myeloid leukemia cell line or the Wilms tumor cell line HFWT. In another embodiment of the invention the co-stimulatory factor ligand is CD137L.

Another aspect of the present invention is based on the concept that expression of chimeric receptors on NK cells could overcome HLA-mediated inhibitory signals, thus endowing the cells with cytotoxicity against otherwise NK-resistant cells. The invention provides a method that allows specific and vigorous preferential expansion of NK cells lacking T-cell receptors ($CD56^+$ $CD3^-$ cells) and their highly efficient transduction with chimeric receptors.

6. DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID No. 1 is the nucleotide sequence for human 4-1BB mRNA. The coding sequence for the human 4-1BB protein begins at position 129 and ends at position 893.

SEQ ID No. 2 is the amino acid sequence of human 4-1BB. The signaling domain begins at position 214 and ends at position 255.

SEQ. ID. No. 3 is the nucleotide sequence for murine 4-1BB mRNA. The coding sequence for the murine 4-1BB protein begins at position 146 and ends at position 916.

SEQ ID. No. 4 is the amino acid sequence of murine 4-1BB. The signaling domain begins at position 209 and ends at position 256.

7. DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic representation of the CD19-truncated, CD19-ζ, CD19-28-ζ and CD19-BB-ζ receptor constructs.

FIG. **2** shows the percent of CD19-positive leukemia cell recovery in four different cell lines (380, 697, KOPN-57bi and OP-1) after 24 hours of culture with NK cells with or without a chimeric receptor at a 1:1 ratio relative to cultures with no NK cells. The bars represent each of the 4 cell lines that are co-cultured with NK cells containing either "vector" which is MSCV-IRES GFP only; "trunc." which is vector containing truncated anti-CD19; "ζ" which is vector containing anti-CD19-CD3ζ; "28 ζ" which is vector containing anti-CD19-CD28α-CD3ζ; or "BB-ζ" which is vector containing anti-CD19-4-1BB intracellular domain-CD3ζ. This figure

shows that chimeric receptors confer anti-ALL activity to NK cells which is improved by the addition of the co-stimulatory molecules CD28 or 4-1BB.

8. DETAILED DESCRIPTION OF THE INVENTION

Definitions

4-1BB: The term "4-1BB" refers to a membrane receptor protein also termed CD137, which is a member of the tumor necrosis factor receptor (TNFR) superfamily expressed on the surface of activated T-cells as a type of accessory molecule [Kwon et al., Proc. Natl. Acad. Sci. USA 86:1963 (1989); Pollok et al., J. Immunol. 151:771 (1993)]. 4-1BB has a molecular weight of 55 kDa, and is found as a homodimer. It has been suggested that 4-1BB mediates a signal transduction pathway from outside of the cell to inside [Kim et al., J. Immunol. 151:1255 (1993)].

A human 4-1BB gene (SEQ ID NO:1) was isolated from a cDNA library made from activated human peripheral T-cell mRNA [Goodwin et al., Eur. J. Immunol. 23:2631 (1993);]. The amino acid sequence of human 4-1BB (SEQ ID NO: 2) shows 60% homology to mouse 4-1BB (SEQ ID NO:4) [Kwon et al., Proc. Natl. Acad. Sci. USA 86:1963 (1989); Gen Bank No: NM_011612] which indicates that the sequences are highly conserved. As mentioned supra, 4-1BB belongs to the TNFR superfamily, along with CD40, CD27, TNFR-I, TNFR-II, Fas, and CD30 [Alderson et al., Eur. J. Immunol. 24:2219 (1994)]. When a monoclonal antibody is bound to 4-1BB expressed on the surface of mouse T-cells, anti-CD3 T-cell activation is increased many fold [Pollok et al., J. Immunol. 150:771 (1993)].

4-1BB binds to a high-affinity ligand (4-1BB, also termed CD137L) expressed on several antigen-presenting cells such as macrophages and activated B cells [Pollok et al., J. Immunol. 150:771 (1993) Schwarz et al., Blood 85:1043 (1995)). The interaction of 4-1BB and its ligand provides a co-stimulatory signal leading to T cell activation and growth [Goodwin et al., Eur. J. Immunol. 23:2631 (1993); Alderson et al., Eur. J. Immunol. 24:2219 (1994); Hurtado et al., J. Immunol. 155:3360 (1995); Pollock et al., Eur. J. Immunol. 25:488 (1995); DeBenedette et al., J. Exp. Med. 181:985 (1995)]. These observations suggest an important role for 4-1BB in the regulation of T cell-mediated immune responses [Ignacio et al., Nature Med. 3:682 (1997)].

4-1BB ligand (CD137L) is claimed and described in U.S. Pat. No. 5,674,704.

The term IL-15 (interleukin 15) refers to a cytokine that stimulates NK cells [Fehniger T A, Caligiuri M A. Blood 97(1):14-32 (2001)]. It has become apparent that IL-15 presented through cell-to-cell contact has a higher NK stimulating activity than soluble IL-15 [Dubois S, et al., Immunity 17(5):537-547 (2002); Kobayashi H, et al., Blood (2004) PMID: 15367431; Koka R, et al., J Immunol 173(6):3594-3598 (2004); Burkett P R, et al., J Exp Med 200(7):825-834 (2004)]. To express membrane-bound IL-15 a construct consisting of human IL-15 mature peptide (NM 172174) was fused to the signal peptide and transmembrane domain of human CD8α.

To specifically or preferentially expand NK cells means to culture a mixed population of cells that contains a small number of NK cells so that the NK cells proliferate to numbers greater than other cell types in the population.

To activate T cells and NK cells means to induce a change in their biologic state by which the cells express activation markers, produce cytokines, proliferate and/or become cytotoxic to target cells. All these changes can be produced by primary stimulatory signals. Co-stimulatory signals amplify the magnitude of the primary signals and suppress cell death following initial stimulation resulting in a more durable activation state and thus a higher cytotoxic capacity.

The terms T-cell and T lymphocyte are interchangeable and used synonymously herein.

The term "chimeric receptor" as used herein is defined as a cell-surface receptor comprising an extracellular ligand binding domain, a transmembrane domain and a cytoplasmic co-stimulatory signaling domain in a combination that is not naturally found together on a single protein. This particularly includes receptors wherein the extracellular domain and the cytoplasmic domain are not naturally found together on a single receptor protein. The chimeric receptors of the present invention are intended primarily for use with T cells and natural killer (NK) cells.

The term "host cell" means any cell of any organism that is selected, modified, transformed, grown, used or manipulated in any way, for the production of a substance by the cell, for example the expression by the cell of a gene, a DNA or RNA sequence, a protein or an enzyme. Host cells of the present invention include T cells and NK cells that contain the DNA or RNA sequences encoding the chimeric receptor and express the chimeric receptor on the cell surface. Host cells may be used for enhancing T lymphocyte activity, NK cell activity, treatment of cancer, and treatment of autoimmune diseases.

The terms "express" and "expression" mean allowing or causing the information in a gene or DNA sequence to become manifest, for example producing a protein by activating the cellular functions involved in transcription and translation of a corresponding gene or DNA sequence. A DNA sequence is expressed in or by a cell to form an "expression product" such as a protein. The expression product itself, e.g. the resulting protein, may also be said to be "expressed" by the cell. An expression product can be characterized as intracellular, extracellular or transmembrane. The term "intracellular" means something that is inside a cell. The term "extracellular" means something that is outside a cell. The term transmembrane means something that has an extracellular domain outside the cell, a portion embedded in the cell membrane and an intracellular domain inside the cell.

The term "transfection" means the introduction of a foreign nucleic acid into a cell using recombinant DNA technology. The term "transformation" means the introduction of a "foreign" (i.e. extrinsic or extracellular) gene, DNA or RNA sequence to a host cell, so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein or enzyme coded by the introduced gene or sequence. The introduced gene or sequence may also be called a "cloned" or "foreign" gene or sequence, may include regulatory or control sequences, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The gene or sequence may include nonfunctional sequences or sequences with no known function. A host cell that receives and expresses introduced DNA or RNA has been "transformed" and is a "transformant" or a "clone." The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or species.

The term "transduction" means the introduction of a foreign nucleic acid into a cell using a viral vector.

The terms "vector", "cloning vector" and "expression vector" mean the vehicle by which a DNA or RNA sequence (e.g. a foreign gene) can be introduced into a host cell, so as to transform the host and promote expression (e.g. transcription

and translation) of the introduced sequence. Vectors include plasmids, phages, viruses, etc.

A solid support means any surface capable of having an agent attached thereto and includes, without limitation, metals, glass, plastics, polymers, particles, microparticles, copolymers, colloids, lipids, lipid bilayers, cell surfaces and the like. Essentially any surface that is capable of retaining an agent bound or attached thereto. A prototypical example of a solid support used herein, is a particle such as a bead.

The term "substantially free of" means a population of cells, e.g. NK cells, that is at least 50% free of non-NK cells, or in certain embodiments at least 60, 70, 80, 85, or 90% free of non-NK cells.

A "co-stimulatory signal" refers to a signal, which in combination with a primary signal, such as TCR/CD3 ligation, leads to NK cell proliferation and/or upregulation or downregulation of key molecules.

Description of the Invention

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, e.g., Sambrook et al, "Molecular Cloning: A Laboratory Manual" (1989); "Current Protocols in Molecular Biology" Volumes [-III [Ausubel, R. M., ed. (1994)]; "Cell Biology: A Laboratory Handbook" Volumes I-III [J. E. Celis, ed. (1994))]; "Current Protocols in Immunology" Volumes I-III [Coligan, J. E., ed. (1994)]; "Oligonucleotide Synthesis" (M. J. Gait ed. 1984); "Nucleic Acid Hybridization" [B. D. Haines & S. J. Higgins eds. (1985)]; "Transcription And Translation" [B. D. Haines & S. J. Higgins, eds. (1984)]; "Animal Cell Culture" [R. I. Freshney, ed. (1986)]; "Immobilized Cells And Enzymes" [IRL Press, (1986)]; B. Perbal, "A Practical Guide To Molecular Cloning" (1984); CURRENT PROTOCOLS IN IMMUNOLOGY Q. E. Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, eds., 1991); ANNUAL REVIEW OF IMMUNOLOGY; as well as monographs in journals such as ADVANCES IN IMMUNOLOGY. All patents, patent applications, and publications mentioned herein are hereby incorporated herein by reference.

Primary T cells expressing chimeric receptors specific for tumor or viral antigens have considerable therapeutic potential as immunotherapy reagents. Unfortunately, their clinical value is limited by their rapid loss of function and failure to expand in vivo, presumably due to the lack of co-stimulator molecules on tumor cells and the inherent limitations of signaling exclusively through the chimeric receptor.

The chimeric receptors of the present invention overcome this limitation wherein they have the capacity to provide both the primary effector activity and the co-stimulatory activity upon binding of the receptor to a single ligand. For instance, binding of the anti-CD19-BB-ζ receptor to the CD19 ligand provides not only the primary effector function, but also a proliferative and cytolytic effect.

T cells transduced with anti-CD19 chimeric receptors of the present invention which contain co-stimulatory molecules have remarkable anti-ALL capacity. However, the use of allogenic receptor-modified T cells after hematopoietic cell transplantation might carry the risk of severe graft-versus-host disease (GvHD). In this setting, the use of CD3-negative NK cells is attractive because they are not expected to cause GvHD.

Studies suggest an anti-tumor effect of NK cells and Zeis et al., Br J Haematol 96: 757-61 (1997) have shown in mice that NK cells contribute to a graft-versus-leukemia effect, without inducing GvHD.

Expanding NK cells which can then be transfected with chimeric receptors according to this method represents another aspect of the present invention.

The chimeric receptors of the present invention comprise an extracellular domain, a transmembrane domain and a cytoplasmic domain. The extracellular domain and transmembrane domain can be derived from any desired source for such domains.

As described in U.S. Pat. Nos. 5,359,046, 5,686,281 and 6,103,521, the extracellular domain may be obtained from any of the wide variety of extracellular domains or secreted proteins associated with ligand binding and/or signal transduction. The extracellular domain may be part of a protein which is monomeric, homodimeric, heterodimeric, or associated with a larger number of proteins in a non-covalent complex. In particular, the extracellular domain may consist of an Ig heavy chain which may in turn be covalently associated with Ig light chain by virtue of the presence of CH1 and hinge regions, or may become covalently associated with other Ig heavy/light chain complexes by virtue of the presence of hinge, CH2 and CH3 domains. In the latter case, the heavy/light chain complex that becomes joined to the chimeric construct may constitute an antibody with a specificity distinct from the antibody specificity of the chimeric construct. Depending on the function of the antibody, the desired structure and the signal transduction, the entire chain may be used or a truncated chain may be used, where all or a part of the CH1, CH2, or CH3 domains may be removed or all or part of the hinge region may be removed.

Wherein an antitumor chimeric receptor is utilized, the tumor may be of any kind as long as it has a cell surface antigen which may be recognized by the chimeric receptor. In a specific embodiment, the chimeric receptor may be for any cancer for which a specific monoclonal antibody exists or is capable of being generated. In particular, cancers such as neuroblastoma, small cell lung cancer, melanoma, ovarian cancer, renal cell carcinoma, colon cancer, Hodgkin's lymphoma, and childhood acute lymphoblastic leukemia have antigens specific for the chimeric receptors.

The transmembrane domain may be contributed by the protein contributing the multispecific extracellular inducer clustering domain, the protein contributing the effector function signaling domain, the protein contributing the proliferation signaling portion, or by a totally different protein. For the most part it will be convenient to have the transmembrane domain naturally associated with one of the domains. In some cases it will be desirable to employ the transmembrane domain of the .zeta., .eta. or Fc.epsilon.R1.gamma. chains which contain a cysteine residue capable of disulfide bonding, so that the resulting chimeric protein will be able to form disulfide linked dimers with itself, or with unmodified versions of the .zeta., .eta. or Fc.epsilon.R1.gamma. chains or related proteins. In some instances, the transmembrane domain will be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. In other cases it will be desirable to employ the transmembrane domain of .zeta., .eta., Fc.epsilon. R1-.gamma. and -.beta., MB1 (Ig.alpha.), B29 or CD3-.gamma., .zeta., or .epsilon., in order to retain physical association with other members of the receptor complex.

The cytoplasmic domain of the chimeric receptors of the invention will comprise the 4-1BB signaling domain by itself or combined with any other desired cytoplasmic domain(s) useful in the context of this chimeric receptor type. In a most preferred embodiment of the invention the extracellular domain comprises a single chain variable domain of an anti-CD19 monoclonal antibody, the transmembrane domain comprises the hinge and transmembrane domain of CD8α, and the cytoplasmic domain comprises the signaling domain of CD3ζ and the signaling domain of 4-1BB. The extracellular domain of the preferred embodiment contains the anti-CD19 monoclonal antibody which is described in Nicholson IC, et al., Mol Immunol 34:1157-1165 (1997) plus the 21 amino acid signal peptide of CD8α (translated from 63 nucleotides at positions 26-88 of GenBank Accession No. NM_001768). The CD8α hinge and transmembrane domain consists of 69 amino acids translated from the 207 nucleotides at positions 815-1021 of GenBank Accession No. NM_001768. The CD3ζ signaling domain of the preferred embodiment contains 112 amino acids translated from 339 nucleotides at positions 1022-1360 of GenBank Accession No. NM_000734.

Antigen-specific cells can be expanded in vitro for use in adoptive cellular immunotherapy in which infusions of such cells have been shown to have anti-tumor reactivity in a tumor-bearing host. The compositions and methods of this invention can be used to generate a population of T lymphocyte or NK cells that deliver both primary and co-stimulatory signals for use in immunotherapy in the treatment of cancer, in particular the treatment of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. Immunotherapeutics, generally, rely on the use of immune effector cells and molecules to target and destroy cancer cells. The effector may be a lymphocyte carrying a surface molecule that interacts, either directly or indirectly, with a tumor cell target. Various effector cells include cytotoxic T cells and NK cells. The compositions and methods described in the present invention may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth.

In adoptive immunotherapy, the patient's circulating lymphocytes, or tumor infiltrated lymphocytes, are isolated in vitro, activated by lymphokines such as IL-2 or transduced with genes for tumor necrosis, and readministered [Rosenberg et al., N. Engl. J. Med. 319:1767 (1988)]. To achieve this, one would administer to an animal, or human patient, an immunologically effective amount of activated lymphocytes genetically modified to express a tumor-specific chimeric receptor gene as described herein. The activated lymphocytes will most preferably be the patient's own cells that were earlier isolated from a blood or tumor sample and activated and expanded in vitro. In aspects of the present invention T lymphocytes or NK cells from a patient having a cancer of B cell origin such as lymphoblastic leukemia, B-cell chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma would be isolated and transduced with the CD19-BB-ζ polynucleotide so that a chimeric receptor containing 4-1BB in the cytoplasmic domain is express on the cell surface of the T cell or NK cell. The modified cells would then be readministered into the patient to target and kill the tumor cells.

As shown in one Example infra, primary T-cells were transduced with the anti-CD19-BB-ζ receptor of the present invention. One week after transduction the T-cells had expanded 3-4 fold in contrast to cells that were transduced with a chimeric receptor that lacked 4-1BB. After 3 weeks in culture the T-cells had expanded by more than 16-fold.

T-cells that were transduced with the anti-CD19-BB-ζ receptor and cultured in 200 IU/mL of IL-2 for two weeks, then removed from IL-2 and exposed to irradiated OP-1 cells underwent apoptosis. However, cells cultured in 10 IU/mL of IL-2 and exposed to irradiated OP-1 cells for two weeks after transduction remained viable. T-cells that were transduced with CD19 chimeric receptors that lacked 4-1BB underwent apoptosis under these same conditions. These results show that 4-1BB co-stimulation confers a survival advantage on lymphocytes, which overcomes a major obstacle with current chimeric receptors used in immunotherapy.

To determine if T-cells transduced with the anti-CD19-BB-ζ receptor exhibited cytotoxic activity under conditions necessary for immunotherapy, their cytotoxic activity at low effector:target (E:T) ratios were measured. As described in the Example infra, T-cells transduced with the anti-CD19-BB-ζ receptor and control vectors were expanded in vitro for two weeks and mixed with OP-1 cells at various E:T ratios (1:1, 0.1:1, and 0.01:1). Viable leukemic cells were counted after one week of culture. T-cells expressing the anti-CD19-BB-ζ receptor exhibited cytotoxic activity at the 1:1 and 0.1:1 ratios against all $CD19^+$ cell lines tested. The anti-CD19-BB-ζ receptor was not effective at the 0.01:1 ratio. The CD19 chimeric receptor that lacked 4-1BB showed cytotoxic activity at the 1:1 ratio, but at the 0.1:1 ratio the results were inferior to the anti-CD19-BB-ζ receptor.

A surprising result obtained with the anti-CD19-BB-ζ receptor was that the T-cells transduced with the receptor exhibited cytotoxic activity toward $CD19^+$ leukemic cells at a ratio of 0.01:1 when the leukemic cells were co-cultured with bone marrow-derived mesenchymal cells. This result shows that T-cells transduced with the anti-CD19-BB-ζ receptor exhibit cytotoxic activity in an environment critical for B-lineage leukemic cell growth. Another unexpected result was that expression of the anti-CD19-BB-ζ receptor caused higher levels of TRAIL stimulation.

Furthermore, IL-2, which causes $CD8^+$ cells to expand more vigorously, levels in cells expressing the anti-CD19-BB-ζ receptor were higher than in cells expressing the other receptors tested. These results further support the use of the anti-CD19-BB-ζ receptor for immunotherapy.

Construction of the Anti-CD19-BB-ζ Receptor

The present invention provides a chimeric receptor construct which contains the signaling domain of 4-1BB and fragments thereof. In a preferred embodiment of the invention, the genetic fragments used in the chimeric receptor were generated using splicing by overlapping extension by PCR (SOE-PCR), a technique useful for generating hybrid proteins of immunological interest. [Warrens A N, et al. Gene 20; 186: 29-35 (1997)]. Other procedures used to generate the polynucleotides and vector constructs of the present invention are well known in the art.

Transduction of T-Cells

As shown in the Examples, infra, a polynucleotide expressing a chimeric receptor capable of providing both primary effector and co-stimulatory activities was introduced into T-cells and NK cells via retroviral transduction. References describing retroviral transduction of genes are Anderson et al., U.S. Pat. No. 5,399,346; Mann et al., Cell 33:153 (1983); Temin et al., U.S. Pat. No. 4,650,764; Temin et al., U.S. Pat. No. 4,980,289; Markowitz et al., J. Virol. 62:1120 (1988); Temin et al., U.S. Pat. No. 5,124,263; International Patent Publication No. WO 95/07358, published Mar. 16, 1995, by Dougherty et al.; and Kuo et al., Blood 82:845 (1993). International Patent Publication No. WO 95/07358 describes high efficiency transduction of primary B lymphocytes.

Expansion of NK Cells

The present invention shows that human primary NK cells may be expanded in the presence of a myeloid cell line that has been genetically modified to express membrane bound IL-15 and 4-1BB ligand (CD137L). A cell line modified in this way which does not have MHC class I and II molecules is highly susceptible to NK cell lysis and activates NK cells.

For example, K562 myeloid cells can be transduced with a chimeric protein construct consisting of human IL-15 mature peptide fused to the signal peptide and transmembrane domain of human CD8α and GFP. Transduced cells can then be single-cell cloned by limiting dilution and a clone with the highest GFP expression and surface IL-15 selected. This clone can then be transduced with human CD137L, creating a K562-mb15-137L cell line.

To preferentially expand NK cells, peripheral blood mononuclear cell cultures containing NK cells are cultured with a K562-mb15-137L cell line in the presence of 10 IU/mL of IL-2 for a period of time sufficient to activate and enrich for a population of NK cells. This period can range from 2 to 20 days, preferably about 5 days. Expanded NK cells may then be transduced with the anti-CD19-BB-ζ chimeric receptor.

Administration of Activated T Cells and NK Cells

Methods of re-introducing cellular components are known in the art and include procedures such as those exemplified in U.S. Pat. Nos. 4,844,893 and 4,690,915. The amount of activated T cells or NK cells used can vary between in vitro and in vivo uses, as well as with the amount and type of the target cells. The amount administered will also vary depending on the condition of the patient and should be determined by considering all appropriate factors by the practitioner.

Obtaining an enriched population of NK cells for use in therapy has been difficult to achieve. Specific NK cell expansion has been problematic to achieve with established methods, where CD3+ T cells preferentially expand. Even after T cell depletion, residual T cells typically become prominent after stimulation. However, in accordance with the teachings of the present invention NK cells may be preferentially expanded by exposure to cells that lack or poorly express major histocompatibility complex I and/or II molecules and which have been genetically modified to express membrane bound IL-15 and 4-1BB ligand (CDI37L). Such cell lines include, but are not necessarily limited to, K562 [ATCC, CCL 243; Lozzio et al., Blood 45(3): 321-334 (1975); Klein et al., Int. J. Cancer 18: 421-431 (1976)], and the Wilms tumor cell line HFWT. [Fehniger T A, Caligiuri M A. Int Rev Immunol 20(3-4):503-534 (2001); Harada H, et al., Exp Hematol 32(7):614-621 (2004)], the uterine endometrium tumor cell line HHUA, the melanoma cell line HMV-II, the hepatoblastoma cell line HuH-6, the lung small cell carcinoma cell lines Lu-130 and Lu-134-A, the neutoblastoma cell lines NB 19 and N1369, the embryonal carcinoma cell line from testis NEC 14, the cervix carcinoma cell line TCO-2, and the bone marrow-metastated neuroblastoma cell line TNB 1 [Harada H., et al., Jpn. J. Cancer Res 93: 313-319 (2002)]. Preferably the cell line used lacks or poorly expresses both MHC I and II molecules, such as the K562 and HFWT cell lines.

A solid support may be used instead of a cell line. Such supports will have attached on its surface at least one molecule capable of binding to NK cells and inducing a primary activation event and/or a proliferative response or capable of binding a molecule having such an affect thereby acting as a scaffold. The support may have attached to its surface the CD137 ligand protein, a CD137 antibody, the IL-15 protein or an IL-15 receptor antibody. Preferably, the support will have IL-15 receptor antibody and CD137 antibody bound on its surface.

The invention is intended to include the use of fragments, mutants, or variants (e.g., modified forms) of the IL-15 and/or CD137 ligand proteins or antigens that retain the ability to induce stimulation and proliferation of NK cells. A "form of the protein" is intended to mean a protein that shares a significant homology with the IL-15 or CD137 ligand proteins or antigen and is capable of effecting stimulation and proliferation of NK cells. The terms "biologically active" or "biologically active form of the protein," as used herein, are meant to include forms of the proteins or antigens that are capable of effecting enhanced activated NK cell proliferation. One skilled in the art can select such forms based on their ability to enhance NK cell activation and proliferation upon introduction of a nucleic acid encoding said proteins into a cell line. The ability of a specific form of the IL-15 or CD137 ligand protein or antigen to enhance NK cell proliferation can be readily determined, for example, by measuring cell proliferation or effector function by any known assay or method.

Antigen-specific cells can be expanded in vitro for use in adoptive cellular immunotherapy in which infusions of such cells have been shown to have anti-tumor reactivity in a tumor-bearing host. The compositions and methods of this invention can be used to generate a population of NK cells that deliver both primary and co-stimulatory signals for use in immunotherapy in the treatment of cancer, in particular the treatment of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. The compositions and methods described in the present invention may be utilized in conjunction with other types of therapy for cancer, such as chemotherapy, surgery, radiation, gene therapy, and so forth.

9. EXAMPLES

9.1 Example 1

Introduction

In approximately 20% of children and 65% of adults with acute lymphoblastic leukemia (ALL), drug-resistant leukemic cells survive intensive chemotherapy and cause disease recurrence. [Pui C H et al, Childhood acute lymphoblastic leukemia—Current status and future perspectives. Lancet Oncology2:597-607 (2001); Verma A, Stock W. Management of adult acute lymphoblastic leukemia: moving toward a risk-adapted approach. Curr Opin Oncol 13:14-20T (2001)] lymphocyte-based cell therapy should bypass cellular mechanisms of drug resistance. Its potential clinical value for leukemia is demonstrated by the association between T-cell-mediated graft-versus-host disease (GvHD) and delay or suppression of leukemia recurrence after allogeneic stem cell transplantation. [Champlin R. T-cell depletion to prevent graft-versus-host disease after bone marrow transplantation. Hematol Oncol Clin North Am 4:687-698 (1990); Porter D L, Antin J H. The graft-versus-leukemia effects of allogeneic cell therapy. Annu Rev Med 50:369-86.:369-386 (1999); Appelbaum F R. Haematopoietic cell transplantation as immunotherapy. Nature 411:385-389 (2001)] Manipulation of GvHD by infusion of donor lymphocytes can produce a measurable anti-leukemic effect. [Porter D L, et al. Induction of graft-versus-host disease as immunotherapy for relapsed chronic myeloid leukemia. N Engl J Med 330:100-106 (1994); Kolb H J, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood 6:2041-2050 (1995); Slavin S, et al. Allogeneic cell therapy with donor peripheral blood cells and recombinant human

interleukin-2 to treat leukemia relapse after allogeneic bone marrow transplantation. Blood 87:2195-2204 (1996); Collins R H, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 15:433-444 (1997)] However, in patients with ALL this effect is often limited, [Kolb H J, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood 86:2041-2050 (1995); Verdonck L F, et al. Donor leukocyte infusions for recurrent hematologic malignancies after allogeneic bone marrow transplantation: impact of infused and residual donor T cells. Bone Marrow Transplant 22:1057-1063 (1998); Collins R H, Jr., et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant 26:511-516 (2000)] possibly reflecting inadequate T-cell stimulation by leukemic lymphoblasts.

T lymphocyte specificity can be redirected through expression of chimeric immune receptors consisting of an extracellular antibody-derived single-chain variable domain (scFv) and an intracellular signal transduction molecule (e.g., the signaling domain of CD3ζ or FcγRIII). [Geiger T L, Jyothi M D. Development and application of receptor-modified T lymphocytes for adoptive immunotherapy. Transfus Med Rev 15:21-34 (2001); Schumacher T N. T-cell-receptor gene therapy. Nat Rev Immunol. 2:512-519 (2002); Sadelain M, et al. Targeting tumours with genetically enhanced T lymphocytes. Nat Rev Cancer 3:35-45 (2003)] Such T lymphocytes can be activated by cell surface epitopes targeted by the scFv and can kill the epitope-presenting cells. The first requirement to redirect T cells against ALL cells is the identification of target molecules that are selectively expressed by leukemic cells. In B-lineage ALL, CD19 is an attractive target, because it is expressed on virtually all leukemic lymphoblasts in almost all cases. [Campana D, Behm F G. Immunophenotyping of leukemia. J Immunol Methods 243:59-75 (2000)] It is not expressed by normal non-hematopoietic tissues, and among hematopoietic cells, it is expressed only by B-lineage lymphoid cells. [Campana D, Behm F G. Immunophenotyping of leukemia. J Immunol Methods 243:59-75 (2000); Nadler L M, et al. B4, a human B lymphocyte-associated antigen expressed on normal, mitogen-activated, and malignant B lymphocytes. J Immunol 131:244-250 (1983)] Recent studies have shown that T-cells expressing anti-CD19 scFv and CD3ζ signaling domain can proliferate when mixed with $CD19^+$ cells and can lyse $CD19^+$ target cells. [Cooper L J, et al. T-cell clones can be rendered specific for CD19: toward the selective augmentation of the graft-versus-B-lineage leukemia effect. Blood 101:1637-1644 (2003); Brentjens R J, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 9:279-286 (2003)]

A prerequisite for the success of T-cell therapy is the capacity of the engineered T lymphocytes to expand and produce a vigorous and durable anti-leukemic response in vivo. The engagement of the TCR, although necessary, is not sufficient to fully activate T cells; a second signal, or co-stimulus, is also required. [Liebowitz D N, et al. Costimulatory approaches to adoptive immunotherapy. Curr Opin Oncol 10:533-541 (1998); Allison J P, Lanier L L. Structure, function, and serology of the T-cell antigen receptor complex. Annu Rev Immunol 5:503-540 (1987); Salomon B, Bluestone J A. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. Annu Rev Immunol 19:225-52.:225-252 (2001)] This could be a major obstacle for chimeric receptor-based therapy of B-lineage ALL, because B-lineage leukemic lymphoblasts generally lack B7 molecules that bind to CD28 on T-lymphocytes and trigger the CD28-mediated co-stimulatory pathway. [Cardoso A A, et al. Pre-B acute lymphoblastic leukemia cells may induce T-cell anergy to alloantigen. Blood 88:41-48 (1996)] This limitation might be overcome by incorporating the signal transduction domain of CD28 into chimeric receptors. [Eshhar Z, et al. Functional expression of chimeric receptor genes in human T cells. J Immunol Methods 2001; 248:67-76 (2001); Hombach A, et al. Tumor-specific T cell activation by recombinant immunoreceptors: CD3 zeta signaling and CD28 costimulation are simultaneously required for efficient IL-2 secretion and can be integrated into one combined CD28/CD3 zeta signaling receptor molecule. J Immunol 167: 6123-6131 (2001); Geiger T L, et al. Integrated src kinase and costimulatory activity enhances signal transduction through single-chain chimeric receptors in T lymphocytes. Blood 98:2364-2371 (2001); Maher J, et al. Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRzeta/CD28 receptor. Nat Biotechnol 20:70-75 (2002)] Murine T cells bearing such receptors have shown a greater capacity to inhibit cancer cell growth and metastasis in mice than those with chimeric receptors lacking this domain. [Haynes N M, et al. Rejection of syngeneic colon carcinoma by CTLs expressing single-chain antibody receptors codelivering CD28 costimulation. J Immunol 169:5780-5786 (2002); Haynes N M, et al. Single-chain antigen recognition receptors that costimulate potent rejection of established experimental tumors. Blood 100:3155-3163 (2002)]

A second co-stimulatory pathway in T cells, independent of CD28 signaling, is mediated by 4-1BB (CD137), a member of the tumor necrosis factor (TNF) receptor family. [Sica G, Chen L. Modulation of the immune response through 4-1BB. In: Habib N, ed. Cancer gene therapy: past achievements and future challenges. New York: Kluwer Academic/Plenum Publishers; 355-362 (2000)] 4-1BB stimulation significantly enhances survival and clonal expansion of CD8+ T-lymphocytes, and CD8+ T-cell responses in a variety of settings, including viral infection, allograft rejection, and tumor immunity. [Shuford W W, et al. 4-1BB costimulatory signals preferentially induce CD8+ T cell proliferation and lead to the amplification in vivo of cytotoxic T cell responses. J Exp Med 186:47-55 (1997); Melero I, et al. Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med 3:682-685 (1997); Melero I, et al. Amplification of tumor immunity by gene transfer of the co-stimulatory 4-1BB ligand: synergy with the CD28 co-stimulatory pathway. Eur J Immunol 28:1116-1121 (1998); Takahashi C, et al. Cutting edge: 4-1BB is a bona fide CD8 T cell survival signal. J Immunol 162:5037-5040 (1999); Martinet O, et al. T cell activation with systemic agonistic antibody versus local 4-1BB ligand gene delivery combined with interleukin-12 eradicate liver metastases of breast cancer. Gene Ther 9:786-792 (2002); May K F, Jr., et al. Anti-4-1BB monoclonal antibody enhances rejection of large tumor burden by promoting survival but not clonal expansion of tumor-specific CD8+ T cells. Cancer Res 62:3459-3465 (2002)] However, the natural ligand of 4-1BB is weakly and heterogeneously expressed in B-lineage ALL cells (C. Imai, D. Campana, unpublished observations). Therefore, it is likely that this important co-stimulatory signal, like CD28, can become operational only if 4-1BB is added to chimeric receptors. However, it is not known whether such receptors would help deliver effective T-cell responses to cancer cells and, if so, whether these would be equivalent to those elicited by receptors containing CD28.

We constructed a chimeric T-cell receptor specific for CD19 that contains a 4-1BB signaling domain. We determined whether T cells transduced with these receptors could

effectively destroy B-lineage ALL cell lines and primary leukemic cells under culture conditions that approximate the in vivo microenvironment where leukemic cells grow. We compared the properties of T-cells expressing the 4-1BB-containing receptor to those of T-cells expressing an equivalent receptor lacking 4-1BB or containing CD28 instead.

Materials and Methods

Cells

Available in our laboratory were the human B-lineage ALL cell line OP-1, developed from the primary leukemic cells of a patient with newly diagnosed B-lineage ALL with the t(9;22)(q34;q11) karyotype and the BCR-ABL gene fusion; [Manabe A, et al. Interleukin-4 induces programmed cell death (apoptosis) in cases of high-risk acute lymphoblastic leukemia. Blood 83:1731-1737 (1994)] the B-lineage ALL cell lines RS4;11, [Stong R C, et al. Human acute leukemia cell line with the t(4;11) chromosomal rearrangement exhibits B lineage and monocytic characteristics. Blood 1985; 65:21-31 (1985)] and REH [Rosenfeld C, et al. Phenotypic characterisation of a unique non-T, non-B acute lymphoblastic leukaemia cell line. Nature 267:841-843 (1977)]; the T-cell lines Jurkat [Schneider U, et al. Characterization of EBV-genome negative "null" and "T" cell lines derived from children with acute lymphoblastic leukemia and leukemic transformed non-Hodgkin lymphoma. Int J Cancer 1977; 19:621-626 (1977)] and CEM-C7 [Harmon J M, et al. Dexamethasone induces irreversible G1 arrest and death of a human lymphoid cell line. J Cell Physiol 98:267-278 (1979)]; and the myeloid cell lines K562 [Koeffler H P, Golde D W. Acute myelogenous leukemia: a human cell line responsive to colony-stimulating activity. Science 200:1153-1154 (1978)] and U-937. [Sundstrom C, Nilsson K. Establishment and characterization of a human histiocytic lymphoma cell line (U-937). Int J Cancer 1976; 17:565-577 (1976)] Cells were maintained in RPMI-1640 (Gibco, Grand Island, N.Y.) with 10% fetal calf serum (FCS; BioWhittaker, Walkersville, Md.) and antibiotics. Human adenocarcinoma HeLa cells and embryonic kidney fibroblast 293T cells, maintained in DMEM (MediaTech, Herndon, Va.) supplemented with 10% FCS and antibiotics, were also used.

We used primary leukemia cells obtained from 5 patients with newly diagnosed B-lineage ALL with the approval of the St. Jude Children's Research Hospital Institutional Review Board and with appropriate informed consent. The diagnosis of B-lineage ALL was unequivocal by morphologic, cytochemical, and immunophenotypic criteria; in each case, more than 95% of leukemic cells were positive for CD19. Peripheral blood samples were obtained from 7 healthy adult donors. Mononuclear cells were collected from the samples by centrifugation on a Lymphoprep density step (Nycomed, Oslo, Norway) and were washed two times in phosphate-buffered saline (PBS) and once in AIM-V medium (Gibco).

Plasmids

The plasmid encoding anti-CD19 scFv was obtained from Dr. I. Nicholson (Child Health Research Institute, Adelaide, Australia). [Nicholson I C, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. Mol Immunol 34:1157-1165 (1997)] The pMSCV-IRES-GFP, pEQPAM3(-E), and pRDF were obtained from Dr. E. Vanin at our institution. Signal peptide, hinge and transmembrane domain of CD8α, and intracellular domains of 4-1BB, CD28, CD3ζ and CD19 were subcloned by polymerase chain reaction (PCR) using a human spleen cDNA library (from Dr. G. Neale, St. Jude Children's Research Hospital) as a template. FIG. **1** shows a schematic representation of the anti-CD19-ζ, anti-CD19-BB-ζ anti-CD19-28-sand anti-CD19-truncated (control) constructs. We used splicing by overlapping extension by PCR (SOE-PCR) to assemble several genetic fragments. [Warrens A N, et al. Splicing by overlap extension by PCR using asymmetric amplification: an improved technique for the generation of hybrid proteins of immunological interest. Gene 20; 186:29-35 (1997)] The sequence of each genetic fragment was confirmed by direct sequencing. The resulting expression cassettes were subcloned into EcoRI and XhoI sites of MSCV-IRES-GFP.

To transduce CD19-negative K562 cells with CD19, we constructed a MSCV-IRES-DsRed vector. The IRES and DsRed sequences were subcloned from MSCV-IRES-GFP and pDsRedN1 (Clontech, Palo Alto, Calif.), respectively, and assembled by SOE-PCR. The IRES-DsRed cassette was digested and ligated into XhoI and NotI sites of MSCV-IRES-GFP. The expression cassette for CD19 was subsequently ligated into EcoRI and XhoI sites of MSCV-IRES-DsRed vector.

Virus Production and Gene Transduction

To generate RD114-pseudotyped retrovirus, we used calcium phosphate DNA precipitation to transfect 3×10^6 293T cells, maintained in 10-cm tissue culture dishes (Falcon, Becton Dickinson, Franklin Lakes, N.J.) for 24 hours, with 8 μg of one of the vectors anti-CD19-ζ, anti-CD19-BB-ζ, anti-CD19-28-ζ**0** or anti-CD19-truncated, 8 μg of pEQ-PAM3(-E) and 4 μg of pRDF. After 24 hours, medium was replaced with RPMI-1640 with 10% FCS and antibiotics. Conditioned medium containing retrovirus was harvested 48 hours and 72 hours after transfection, immediately frozen in dry ice, and stored at −80° C. until use. HeLa cells were used to titrate virus concentration.

Peripheral blood mononuclear cells were incubated in a tissue culture dish for 2 hours to remove adherent cells. Non-adherent cells were collected and prestimulated for 48 hours with 7 μg/mL PHA-M (Sigma, St. Louis, Mo.) and 200 IU/mL human IL-2 (National Cancer Institute BRB Preclinical Repository, Rockville, Md.) in RPMI-1640 and 10% FCS. Cells were then transduced as follows. A 14-mL polypropylene centrifuge tube (Falcon) was coated with 0.5 mL of human fibronectin (Sigma) diluted to 100 μg/mL for 2 hours at room temperature and then incubated with 2% bovine serum albumin (Sigma) for 30 minutes. Prestimulated cells (2×10^5) were resuspended in the fibronectin-coated tube in 2-3 mL of virus-conditioned medium with polybrene (4 μg/mL; Sigma) and centrifuged at 2400×g for 2 hours. The multiplicity of infection (4 to 8) was identical in each experiment comparing the activity of different chimeric receptors. After centrifugation, cells were left undisturbed for 24 hours in a humidified incubator at 37° C., 5% CO_2. The transduction procedure was repeated on two successive days. Cells were then washed twice with RPMI-1640 and maintained in RPMI-1640, 10% FCS, and 200 IU/mL of IL-2 until use.

A similar procedure was used to express chimeric receptors in Jurkat cells, except that cells were not prestimulated. K562 cells expressing CD19 were created by resuspending 2×10^5 K562 cells in 3 mL of MSCV-CD19-IRES-DsRed virus medium with 4 μg/mL polybrene in a fibronectin-coated tube; the tube was centrifuged at 2400×g for 2 hours and left undisturbed in an incubator for 24 hours. Control cells were transduced with the vector only. These procedures were repeated on 3 successive days. After confirming CD19 and DsRed expression, cells were subjected to single-cell sorting with a fluorescence-activated cell sorter (MoFlo, Cytomation, Fort Collins, Colo.). The clones that showed the highest expression of DsRed and CD19 and of DsRed alone were selected for further experiments.

Detection of Chimeric Receptor Expression

Transduced Jurkat and peripheral blood cells were stained with goat anti-mouse (Fab)2 polyclonal antibody conjugated with biotin (Jackson Immunoresearch, West Grove, Pa.) followed by streptavidin conjugated to peridinin chlorophyll protein (PerCP; Becton Dickinson, San Jose, Calif.). Patterns of CD4, CD8, and CD28 expression were also analyzed by using anti-CD4 and anti-CD28 conjugated to PE and anti-CD8 conjugated to PerCP (antibodies from Becton Dickinson, and Pharmingen, San Diego, Calif.). Antibody staining was detected with a FACScan flow cytometer (Becton Dickinson).

For Western blotting, 2×10^7 cells were lysed in 1 mL RIPA buffer (PBS, 1% Triton-X100, 0.5% sodium deoxycholate, 0.1% SDS) containing 3 μg/mL of pepstatin, 3 μg/mL of leupeptin, 1 mM of PMSF, 2 mM of EDTA, and 5 μg/mL of aprotinin. Centrifuged lysate supernatants were boiled with an equal volume of loading buffer with or without 0.1 M DTT, then were separated by SDS-PAGE on a precast 12% acrylamide gel (BioRad, Hercules, Calif.). The proteins were transferred to a PVDF membrane, which was incubated with primary mouse anti-human CD3ζ monoclonal antibody (clone 8D3; Pharmingen), 1 μg/mL for 12 hours at 4° C. Membranes were then washed, incubated with a 1:500 dilution of goat anti-mouse IgG horseradish peroxidase-conjugated second antibody for 1 hour, and developed by using the ECP kit (Pharmacia, Piscataway, N.J.).

Changes in Gene Expression and Cytokine Production after Receptor Ligation

Jurkat cells transduced with the chimeric receptors were cocultured with OP-1 leukemic cells fixed with 0.5% paraformaldehyde at an effector:target (E:T) ratio of 1:1. RNA was extracted using Trizol Reagent (Invitrogen, Carlsbad, Calif.). Gene expression of Jurkat cells was analyzed using HG-U133A GeneChip microarrays (Affymetrix, Santa Clara, Calif.) as previously described. [Yeoh E J, et al. Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell 2002; 1:133-143 (2002); Ross M E, et al. Classification of pediatric acute lymphoblastic leukemia by gene expression profiling. Blood. May 2003; 10.1182/blood-2003-01-0338 (2003)] Arrays were scanned using a laser confocal scanner (Agilent, Palo Alto, Calif.) and analyzed with Affymetrix Microarray suite 5.0. We used an arbitrary factor of 2 or higher to define gene overexpression. IL-2, TNF-related apoptosis-inducing ligand (TRAIL), OX40, IL-3 and μ-actin transcripts were detected by semi-quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) using Jurkat cells stimulated as above; primers were designed using the Primer3 software developed by the Whitehead Institute for Biomedical Research.

For cytokine production, Jurkat cells and primary lymphocytes (2×10^5 in 200 μl) expressing chimeric receptors were stimulated with OP-1 cells at a 1:1 E:T ratio for 24 hours. Levels of IL-2 and IFNγ in culture supernatants were determined with a Bio-Plex assay (BioRad). Lymphocytes before and after stimulation were also labeled with anti-TRAIL-PE (Becton Dickinson).

Expansion and Purification of Receptor-Transduced Primary T Cells

Receptor-transduced lymphocytes (3×10^5) were co-cultured with 1.5×10^5 irradiated OP-1 cells in RPMI-1640 with 10% FCS with or without exogenous IL-2. Cells were pulsed weekly with irradiated target cells at an E:T ratio of 2:1. Cells were counted by Trypan-blue dye exclusion and by flow cytometry to confirm the presence of GFP-positive cells and the absence of CD19-positive cells. To prepare pure populations of $CD8^+$ cells expressing chimeric receptors, we labeled cells with a PE-conjugated anti-CD8 antibody (Becton Dickinson) that had been previously dialyzed to remove preservatives and then sterile-filtered. $CD8^+$ GFP+ cells were isolated using a fluorescence-activated cell sorter (MoFlo).

Cytotoxicity Assays

The cytolytic activity of transductants was measured by assays of lactate dehydrogenase (LDH) release using the Cytotoxicity Detection Kit (Roche, Indianapolis, Ind.) according to the manufacturer's instructions. Briefly, 2×10^4 target cells were placed in 96-well V-bottom tissue culture plates (Costar, Cambridge, Mass.) and cocultured in triplicate in RPMI-1640 supplemented with 1% FCS, with primary lymphocytes transduced with chimeric receptors. After 5 hours, cell-free supernatant was harvested and immediately analyzed for LDH activity. Percent specific cytolysis was calculated by using the formula: (Test—effector control—low control/high control—low control)×100, in which "high control" is the value obtained from supernatant of target cells exposed to 1% Triton-X-100, "effector control" is the spontaneous LDH release value of lymphocytes alone, "low control" is the spontaneous LDH release value of target cells alone; background control (the value obtained from medium alone) was subtracted from each value before the calculation.

The anti-leukemic activity of receptor-transduced lymphocytes was also assessed in 7-day cultures using lower E:T ratios. For this purpose, we used bone marrow-derived mesenchymal cells to support the viability of leukemic cells. [Nishigaki H, et al. Prevalence and growth characteristics of malignant stem cells in B-lineage acute lymphoblastic leukemia. Blood 89:3735-3744 (1997); Mihara K, et al. Development and functional characterization of human bone marrow mesenchymal cells immortalized by enforced expression of telomerase. Br J Haematol 120:846-849 (2003)] Briefly, 2×10^4 human mesenchymal cells immortalized by enforced expression of telomerase reverse transcriptase were plated on a 96-well tissue culture plate precoated with 1% gelatin. After 5 days, 1×10^4 CD19+ target cells (in case of cell lines) or 2×10^5 CD19+ target cells (in case of primary ALL cells) were plated on the wells and allowed to rest for 2 hours. After extensive washing to remove residual IL-2-containing medium, receptor-transduced primary T cells were added to the wells at the proportion indicated in Results. Cultures were performed in the absence of exogenous IL-2. Plates were incubated at 37° C. in 5% CO_2 for 5-7 days. Cells were harvested, passed through a 19-gauge needle to disrupt residual mesenchymal-cell aggregates, stained with anti-CD19-PE antibody, and assayed by flow cytometry as previously described. [Ito C, et al. Hyperdiploid acute lymphoblastic leukemia with 51 to 65 chromosomes: A distinct biological entity with a marked propensity to undergo apoptosis. Blood 93:315-320 (1999); Srivannaboon K, et al. Interleukin-4 variant (BAY 36-1677) selectively induces apoptosis in acute lymphoblastic leukemia cells. Blood 97:752-758 (2001)] Expression of DsRed served as a marker of residual K562 cells. Experiments were done in triplicate.

Results

Transduction of Primary Human T Lymphocytes with Anti-CD19-BB-ζ Chimeric Receptors

In preliminary experiments, transduction of lymphocytes stimulated with PHA (7 μg/mL) and IL-2 (200 IU/mL) for 48 hours, followed by centrifugation (at 2400×g) of the activated lymphocytes with retroviral supernatant in tubes coated with fibronectin, consistently yielded a high percentage of chimeric receptor and GFP expression; this method was used in all subsequent experiments. In 75 transduction experiments, 31% to 86% (median, 64%) of mononuclear cells expressed

GFP. In experiments with cells obtained from 6 donors, we tested the immunophenotype of the cells transduced with anti-CD19-BB-ζ receptors. Fourteen days after transduction a mean (±SD) of 89.6%±2.3% (n=6) of GFP cells also expressed CD3; 66.2%±17.9% of CD3 T lymphocytes were transduced. Among GFP^+ cells, 21.1%±8.8% (n=6) were $CD4^+$, 68.1%±8.1% (n=6) were $CD8^+$, 38.1%±16.1% (n=3) were $CD28^+$ and 24.2%±11.6% (n=3) were $CD8^+CD28^+$. These proportions were similar to those obtained with the anti-CD19-ζ receptors lacking 4-1BB. In this case, 85.4%±11.0% (n=6) of GFP^+ cells expressed CD3; 60.8%±10.1% of $CD3^+$ cells were transduced. Among GFP^+ cells, 18.0%±8.7% (n=6) were $CD4^+$, 66.1%±11.7% (n=6) were $CD8^+$, 41.2%±12.2% (n=3) were $CD28^+$ and 20.6%±11.3% (n=3) were $CD8^+CD28^+$. In these experiments, median transduction efficiency was 65% (range, 31% to 86%) for anti-CD19-BB-ζ receptors, and 65% (range, 37% to 83%) for anti-CD19-ζ receptors.

The surface expression of the chimeric receptors on GFP^+ cells was confirmed by staining with a goat anti-mouse antibody that reacted with the scFv portion of anti-CD19. Expression was detectable on most GFP^+ cells and was not detectable on GFP cells and vector-transduced cells. The level of surface expression of anti-CD19-BB-ζ was identical to that of the receptor lacking 4-1BB. Expression was confirmed by Western blot analysis; under non-reducing conditions, peripheral blood mononuclear cells transduced with the chimeric receptors expressed them mostly as monomers, although dimers could be detected.

Signaling Function of Anti-CD19-BB-ζ Chimeric Receptors

To test the functionality of the anti-CD19-BB-ζ chimeric receptor, we used the T-cell line Jurkat and the CD19+ ALL cell line OP-1. After transduction, >95% Jurkat cells were GFP+. Exposure of irradiated OP-1 cells to Jurkat cells transduced with anti-CD19-BB-ζ triggered transcription of IL-2. Notably, in parallel experiments with Jurkat cells transduced with the anti-CD19-ζ receptor lacking 4-1BB, the level of IL-2 transcription was much lower. No IL-2 transcription was detected in Jurkat cells transduced with the anti-CD19-truncated control receptor lacking CD3ζ.

To identify further changes in molecules associated with T-cell activation, survival or cytotoxicity induced by anti-CD19-BB-ζ receptors, Jurkat cells were either transduced with these receptors or with anti-CD19-ζ receptors and then stimulated with paraformadehyde-fixed OP-1 cells. After 12 hours of stimulation, we screened the cells' gene expression using Affymetrix HG-U133A chips. Genes that were overexpressed by a factor of 2 or higher in cells with anti-CD19-BB-ζ included the member of the TNF family TRAIL, the TNF-receptor member OX40, and IL-3. Overexpression of these molecules after stimulation was validated using RT-PCR. In cells bearing the anti-CD19-ζ receptor, there were no overexpressed genes with a known function associated with T-cells. Therefore, anti-CD19-BB-ζ receptors elicit transcriptional responses that are distinct from those triggered by receptors lacking 4-1BB.

Expansion of T Cells Expressing Anti-CD19-BB-ζ Receptors in the Presence of $CD19^+$ Cells

To measure the ability of anti-CD19-BB-ζ transduced lymphocytes to survive and expand in vitro, we first analyzed primary T cells (obtained from 2 donors), 7 days after transduction. Transduction efficiency with the 3 receptors was similar: 72% and 67% for anti-CD19-BB-ζ, 63% and 66% for anti-CD19-ζ and 67% and 68% for the truncated anti-CD19 receptor. When cocultured with irradiated OP-1 ALL cells in the absence of exogenous IL-2, cells transduced with anti-CD19-BB-ζ expanded: after only 1 week of culture, GFP^+ cells recovered were 320% and 413% of input cells. T cells that expressed the anti-CD19-ζ receptor but lacked 4-1BB signaling capacity remained viable but showed little expansion (cell recovery: 111% and 160% of input cells, respectively), whereas those that expressed the truncated anti-CD19 receptor underwent apoptosis (<10% of input cells were viable after 1 week). Lymphocytes transduced with anti-CD19-BB-ζ continued to expand in the presence of irradiated OP-1 cells. After 3 weeks of culture, they had expanded by more than 16-fold, with 98% of the cells at this point being GFP^+. By contrast, cells transduced with only anti-CD19-ζ survived for less than 2 weeks of culture.

We performed the next set of experiments with T cells (obtained from 3 donors) 14 days after transduction with anti-CD19-BB-ζ, anti-CD19-ζ or anti-CD19-truncated, and expanded with high-dose IL-2 (200 IU/mL). Recovery of lymphocytes of each donor with anti-CD19-BB-ζ receptors was significantly higher than that of lymphocytes with anti-CD19-ζ receptors in all 3 comparisons ($P<0.005$). When IL-2 was removed, exposure of the transduced cells to irradiated OP-1 cells induced apoptosis, irrespective of the chimeric receptor expressed. This was in contrast to results with cells 7 days post-transduction, and in accord with the loss of T cell functionality after prolonged culture in IL-2 observed by others. [Brentjens R J, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 9:279-286 (2003); Rossig C. et al. Targeting of G(D2)-positive tumor cells by human T lymphocytes engineered to express chimeric T-cell receptor genes. Int J Cancer 94:228-236 (2001)] However, low-dose IL-2 (10 IU/mL) was sufficient to maintain most lymphocytes transduced with anti-CD19-BB-ζ viable after 2 weeks of culture with irradiated OP-1 cells, but did not prevent apoptosis of cells transduced with the other receptors. Taken together, these data indicate that 4-1BB-mediated costimulation confers a survival advantage on lymphocytes.

Cytotoxicity Triggered by Anti-CD19-BB-ζ Chimeric Receptors

Lymphocytes obtained from two donors and transduced with anti-CD19-BB-ζ and anti-CD19-ζ exerted dose-dependent cytotoxicity, as shown by a 5-hour LDH release assay using the OP-1 B-lineage ALL cell line as a target. Transduction efficiencies were 41% and 73% for empty vector, 40% and 67% for anti-CD19-truncated, 43% and 63% for anti-CD19-ζ, and 46% and 72% for anti-CD19-BB-ζ. No differences in cytotoxicities mediated by the two receptors were detectable with this assay. Although no lysis of target cells was apparent at a 1:1 ratio in the 5-hour LDH assay, most leukemic cells were specifically killed by lymphocytes expressing signaling chimeric receptors when the cultures were examined at 16 hours by flow cytometry and inverted microscopy.

To better mimic the application of T-cell therapy, we determined whether T cells expressing the chimeric receptor would exert significant anti-leukemic activity when present at low E:T ratios in prolonged culture. Lymphocytes from various donors were expanded in vitro for 14 days after transduction and were mixed at different ratios with OP-1, RS4;11, or REH B-lineage ALL cells, or with K562 (a CD19-negative myeloid cell line that lacks HLA antigens) transduced with CD19 or with vector alone. Co-cultures were maintained for 7 days, and viable leukemic cells were counted by flow cytometry. As observed in short term cultures, at a 1:1 ratio, T cells expressing signaling chimeric receptors eliminated virtually all leukemic cells from the cultures. At a 0.1:1 ratio, however, T cells transduced with anti-CD19-BB-ζ receptors

were markedly more effective than those lacking 4-1BB signaling. Chimeric receptor-transduced T cells had no effect on cells lacking CD19. The presence of 4-1BB in the chimeric receptor did not increase background, non-CD19-mediated cytotoxicity, in experiments using CEM-C7, U-937 and K-562. As in other experiments, transduction efficiencies with the two chimeric receptors were equivalent, and range from 62% to 73% for anti-CD19-ζ and from 60% to 70% for anti-CD19-BB-ζ.

Cells present in the bone marrow microenvironment may decrease T-cell proliferation in a mixed lymphocyte reaction. [Bartholomew A, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 30:42-48 (2002); Krampera M, et al. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 101:3722-3729 (2003); Le Blanc K, et al. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 57:11-20 (2003)] To test whether these cells would also affect T-cell-mediated antileukemic activity, we repeated the experiments with OP-1 in the presence of bone marrow-derived mesenchymal cell layers. [Mihara K, et al. Development and functional characterization of human bone marrow mesenchymal cells immortalized by enforced expression of telomerase. Br J Haematol 2003; 120:846-849 (2003)] T-cell cytotoxicity under these conditions was even greater than that observed in cultures without mesenchymal cells. Remarkably, T cells transduced with anti-CD19-BB-ζ were markedly cytotoxic even at a ratio of 0.01:1 in this assay, whereas those transduced with anti-CD19-ζ were not.

Effect of Receptor-Transduced T Cells on Primary Leukemic Cells

We co-cultured primary B-lineage ALL cells with bone marrow-derived mesenchymal cells, which are essential to preserve their viability in vitro. [Nishigaki H, et al. Prevalence and growth characteristics of malignant stem cells in B-lineage acute lymphoblastic leukemia. Blood 1997; 89:3735-3744 (1997); Mihara K, et al. Development and functional characterization of human bone marrow mesenchymal cells immortalized by enforced expression of telomerase. Br J Haematol 120:846-849 (2003)] We tested the effect of T cells expressing anti-CD19-BB-ζ on primary leukemic cells obtained from 5 patients at the time of diagnosis; these patients included 3 who had B-lineage ALL with 11q23 abnormalities, a karyotype associated with drug resistance. [Pui C H, et al. Childhood acute lymphoblastic leukemia—Current status and future perspectives. Lancet Oncology 2:597-607 (2001)] Mesenchymal cells supported ALL cell survival in vitro: in cultures not exposed to exogenous T cells, recovery of leukemic cells from the 5 patients after 5 days of culture ranged from 100.1% to 180.7% of the input cell number. Leukemic cells incubated at a 0.1:1 ratio with lymphocytes expressing anti-CD19-BB-ζ were virtually eliminated in all 5 cultures. Remarkable cytotoxicity was also seen at a 0.01:1 ratio. Importantly, at this ratio, lymphocytes expressing anti-CD19-BB-ζ were consistently more cytotoxic than those expressing the anti-CD19-ζ receptor alone ($P<0.01$ by t test for all comparisons).

Comparisons Between Chimeric Receptors Containing Signaling Domains of 4-1BB and of CD28

We compared responses induced by anti-CD19-BB-ζ to those of an equivalent receptor in which 4-1BB signaling domains were replaced by CD28 signaling domains (FIG. **1**). Expression of the latter was similar to that of anti-CD19-BB-ζ and anti-CD19-ζ receptors: >95% Jurkat cells were consistently GFP+ after transduction with anti-CD19-28-ζ and most of these cells had detectable receptors on the cell surface. In 6 experiments with primary lymphocytes, transduced cells ranged from 42% to 84% (median, 72%).

We tested production of IL-2 in Jurkat cells transduced with the three receptors and stimulated with the CD19+ ALL cell line OP-1. Production of IL-2 was the highest in cells expressing anti-CD19-BB-ζ ($P<0.05$). Production of IL-2 was also tested in primary lymphocytes, which were transduced with the chimeric receptors and then expanded for 5 weeks with pulses of OP-1. The pattern of IL-2 production was similar to that observed in Jurkat cells. Cells expressing anti-CD19-BB-ζ produced higher levels of IL-2 ($P<0.01$). Chimeric receptors containing the co-stimulatory molecules induced a higher IFN-γ production in primary lymphocytes. IFN-γ levels were the highest with the anti-CD19-28-ζ receptor ($P<0.05$). Finally, we tested surface expression of TRAIL protein in primary lymphocytes by staining with a specific antibody. Levels of TRAIL were the highest in cells transduced with the anti-CD19-BB-ζ receptor. These results indicate that anti-CD19-BB-ζ receptors are functionally distinct from those lacking co-stimulatory molecules or containing CD28 instead of 4-1BB.

Next, we compared the cytotoxicity exerted by primary T cells transduced with anti-CD19-BB-ζ receptors to those exerted by T cells bearing receptors lacking 4-1BB. For these experiments, we transduced primary lymphocytes from 2 donors with anti-CD19-BB-ζ anti-CD19-28-ζ, anti-CD19-ζ and anti-CD19-truncated, we expanded them for 2-3 weeks with IL-2, and then purified $CD8^+$, GFP^+ cells by fluorescence activated cell sorting. Confirming our previous results with unsorted cells, $CD8^+$ cells expressing anti-CD19-BB-ζ receptors were significantly more effective than those with anti-CD19-ζ receptors, and were as effective as those with anti-CD19-BB-ζ Finally, we determined the capacity of the purified CD8 cells transduced with the various receptors to expand in the presence of low dose (10 U/mL) IL-2. Cells transduced with anti-CD19-BB-ζ receptor had a significantly higher cell growth under these conditions than those bearing the other receptors ($P<0.001$).

Discussion

Results of this study indicate that anti-CD19-BB-ζ receptors could help achieve effective T-cell immunotherapy of B-lineage ALL. Lymphocytes expressing anti-CD19-BB-ζ survived and expanded better than those with equivalent receptors lacking 4-1BB. These lymphocytes also had higher anti-leukemic activity and could kill B-lineage ALL cells from patients at E:T ratios as low as 0.01:1, suggesting that the infusion of relatively low numbers of transduced T cells could have a measurable anti-leukemic effect in patients. Finally, lymphocytes transduced with anti-CD19-BB-ζ were particularly effective in the presence of bone marrow-derived mesenchymal cells which form the microenvironment critical for B-lineage ALL cell growth, further supporting their potential for immunotherapy.

Two recently reported studies used anti-CD19 scFv as a component of a chimeric receptor for T-cell therapy of B-cell malignancies. Cooper et al. Blood 101:1637-1644 (2003) reported that T-cell clones transduced with chimeric receptors comprising anti-CD19 scFv and CD3ζ produced approximately 80% specific lysis of B-cell leukemia and lymphoma cell lines at a 1:1 E:T ratio in a 4-hour ^{51}Cr release assay; at this ratio, percent specific lysis of one primary B-lineage ALL sample tested was approximately 30%. Brentjens et al. Nat Med 279-286 (2003) reported that T-cells bearing anti-CD19 scFv and CD3ζ chimeric receptors could be greatly expanded in the presence of exogenous IL-15 and artificial antigen-

presenting cells transduced with CD19 and CD80. The authors showed that these T cells significantly improved the survival of immunodeficient mice engrafted with the Raji B-cell lymphoma cell line. Their results demonstrated the requirement for co-stimulation in maximizing T-cell-mediated anti-leukemic activity: only cells expressing the B7 ligands of CD28 elicited effective T-cell responses. However, B-lineage ALL cells typically do not express B7-1(CD80) and only a subset expresses B7-2 (CD86) molecules. [Cardoso A A, et al. Pre-B acute lymphoblastic leukemia cells may induce T-cell anergy to alloantigen. Blood 88:41-48 (1996)]

4-1BB, a tumor necrosis factor-receptor family member, is a co-stimulatory receptor that can act independently from CD28 to prevent activation-induced death of activated T cells. [Kim Y J, et al. Human 4-1BB regulates CD28 co-stimulation to promote Th1 cell responses. Eur J Immunol 28:881-890 (1998); Hurtado J C, et al. Signals through 4-1BB are costimulatory to previously activated splenic T cells and inhibit activation-induced cell death. J Immunol 158:2600-2609 (1997); DeBenedette M A, et al. Costimulation of CD28– T lymphocytes by 4-1BB ligand. J Immunol 1997; 158:551-559 (1997); Bukczynski J, et al. Costimulation of human CD28– T cells by 4-1BB ligand. Eur J Immunol 33:446-454 (2003)] In our study, we found that chimeric receptors containing 4-1BB can elicit vigorous signals in the absence of CD28– mediated co-stimulation. Cytotoxicity against $CD19^+$ cells mediated by these receptors was as good as that mediated by CD28-containing receptors and was clearly superior to that induced by receptors lacking co-stimulatory molecules. It is known that, in contrast to CD28, 4-1BB stimulation results in a much larger proliferation of $CD8^+$ cells than CD4+ cells. [Shuford W W, et al. 4-1BB costimulatory signals preferentially induce $CD8^+$ T cell proliferation and lead to the amplification in vivo of cytotoxic T cell responses. J Exp Med 1997; 186:47-55 (1997)] We found that T cells expressing the anti-CD19-BB-ζ receptor produced more IL-2 upon stimulation, and that $CD8^+$ cells expanded in the presence of low-dose IL-2 more vigorously than those expressing receptors lacking 4-1BB domains, including those containing CD28. Therefore, the presence of 4-1BB in the chimeric receptors may support more durable T cell responses than those induced by other receptors.

Experimental evidence indicates that harnessing 4-1BB signaling could have useful application in antitumor therapy. Melero et al. Nat Med 3:682-685 (1997) found that antibodies to 4-1BB significantly improved long-lasting remission and survival rates in mice inoculated with the immunogenic P815 mastocytoma cell line. Moreover, immunogenic murine tumor cells made to express 4-1BB ligand were readily rejected and induced long term immunity. [Melero I, et al. Chen L. Amplification of tumor immunity by gene transfer of the co-stimulatory 4-1BB ligand: synergy with the CD28 co-stimulatory pathway. Eur J Immunol 28:1116-1121 (1998)] Dramatic results were also observed in vaccination experiments using other tumor cell lines expressing 4-1BB ligands. [Ye Z, et al. Gene therapy for cancer using single-chain Fv fragments specific for 4-1BB. Nat Med 8:343-348 (2002); Mogi S, et al. Tumour rejection by gene transfer of 4-1BB ligand into a CD80(+) murine squamous cell carcinoma and the requirements of co-stimulatory molecules on tumour and host cells. Immunology 101:541-547 (2000); Yoshida H, et al. A novel adenovirus expressing human 4-1BB ligand enhances antitumor immunity. Cancer Immunol Immunother 52:97-106 (2003)] Of note, experiments with the poorly immunogenic Ag104A fibrosarcoma cell line provided some evidence that 4-1BB could be superior to CD28 in eliciting anti-tumor responses: 80% of mice showed tumor regression with 4-1BB stimulation and 50% of mice with widespread metastasis were cured, [Melero I, Shuford W W, Newby S A, et al. Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors. Nat Med 3:682-685 (1997)] whereas CD28 costimulation was not effective alone and required simultaneous CD2 stimulation. [Li Y, et al. Costimulation by CD48 and B7-1 induces immunity against poorly immunogenic tumors. J Exp Med 1996; 183:639-644 (1996)] These data, together with our results, indicate that the addition of 4-1BB to the chimeric receptor should significantly increase the probability that transduced T-cells will survive and continue to proliferate when the receptor is engaged in vivo. We think it noteworthy that T cells with chimeric receptors containing 4-1BB expressed the highest levels of TRAIL upon stimulation, given the known tumoricidal activity of this molecule. [Schmaltz C, et al. T cells require TRAIL for optimal graft-versus-tumor activity. Nat Med 8:1433-1437 (2002)]

Clinical precedents, such as administration of T-cell clones that target CMV epitopes [Walter E A, et al. Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. N Engl J Med. 333:1038-1044 (1995)] or EBV-specific antigens, [Rooney C M, et al. Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr-virus-related lymphoproliferation. Lancet 345:9-13 (1995)] attest to the clinical feasibility of adoptive T-cell therapy. Transfer of chimeric receptor-modified T cells has the added advantage of permitting immediate generation of tumor-specific T-cell immunity. Subsequently, therapeutic quantities of antigen-specific T cells can be generated quite rapidly by exposure to target cells and/or artificial antigen-presenting cells, in the presence of ligands of co-stimulatory molecules and/or exogenous cytokines such as IL-2, IL-7, and IL-15. [Geiger T L, Jyothi M D. Development and application of receptor-modified T lymphocytes for adoptive immunotherapy. Transfus Med Rev 15:21-34 (2001); Schumacher T N. T-cell-receptor gene therapy. Nat Rev Immunol. 2:512-519 (2002); Sadelain M, et al. Targeting tumours with genetically enhanced T lymphocytes. Nat Rev Cancer 3:35-45 (2003); Brentjens R J, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 9:279-286 (2003)] A specific risk of the strategy proposed here relates to the transforming potential of the retrovirus used to transduce chimeric receptors. [Baum C, Dullmann J, Li Z, et al. Side effects of retroviral gene transfer into hematopoietic stem cells. Blood 101:2099-2114 (2003)] We therefore envisage the coexpression of suicide genes as a safety measure for clinical studies. [Marktel S, et al. Immunologic potential of donor lymphocytes expressing a suicide gene for early immune reconstitution after hematopoietic T-cell-depleted stem cell transplantation. Blood 101:1290-1298 (2003)] This approach would also ensure that the elimination of normal $CD19^+$ B-lineage cells is temporary and should therefore have limited clinical consequences.

In view of the limited effectiveness and the high risk of the currently available treatment options for chemotherapy-refractory B-lineage ALL and other B cell malignancies, the results of our study provide compelling justification for clinical trials using T cells expressing anti-CD19-BB-ζ receptors. Donor-derived T cells endowed with chimeric receptors could replace infusion of non-specific lymphocytes post-transplant. To reduce the risk of GvHD mediated by endogenous T-cell receptors, it may be beneficial to use T cells with restricted endogenous specificity, for example, Epstein-Barr-

virus-specific cytotoxic T-lymphocyte lines. [Rossig C, et al. Epstein-Barr virus-specific human T lymphocytes expressing antitumor chimeric T-cell receptors: potential for improved immunotherapy. Blood. 99:2009-2016 (2002)] Therefore, it would be important to test the effects of adding 4-1BB to chimeric receptors transduced in these lines. The reinfusion of autologous T cells collected during clinical remission could also be considered in patients with persistent minimal residual disease. In our experiments, T cells expressing anti-CD19-BB-ζ receptors completely eliminated ALL cells at E:T ratios higher than 1:1, and autologous B lymphocytes became undetectable shortly after transduction of anti-CD19-BB-ζ, suggesting that the potential leukemic cell contamination in the infused products should be greatly reduced or abrogated by the procedure.

9.2 Example 2

T lymphocytes transduced with anti-CD19 chimeric receptors have remarkable anti-ALL capacity in vitro and in vivo, suggesting the clinical testing of receptor-modified autologous T cells in patients with persistent minimal residual disease. However, the use of allogeneic receptor-modified T lymphocytes after hematopoietic cell transplantation (HCT) might carry the risk of severe graft-versus-host disease (GvHD). In this setting, the use of CD3-negative natural killer (NK) cells is attractive because they should not cause GvHD.

Spontaneous cytotoxicity of NK cells against ALL is weak, if measurable at all. To test whether anti-CD19 chimeric receptors could enhance it, we developed methods to specifically expand human primary NK cells and induce high levels of receptor expression. Specific NK cell expansion has been problematic to achieve with established methods which favor CD3+ T cell expansion. Even after T-cell depletion, residual T cells typically become prominent after stimulation.

We overcame this obstacle by generating a genetically-modified K562 myeloid leukemia cell line that expresses membrane-bound interleukin-15 (IL-15) and 4-1BB ligand (CD137L) (K562-mb15-137L). The K562-mb15-137 cell line was generated by retrovirally transducing K562 cells with a chimeric protein construct consisting of human IL-15 mature peptide fused to the signal peptide and transmembrane domain of human CD8 alpha, as well as GFP. Transduced cells were single cell-cloned by limiting dilution and a clone with the highest expression of GFP and membrane-bound (surface) IL-15 was selected. Then, the clone was transduced with human CD137L.

Peripheral blood mononuclear cells from 8 donors were cultured with K562-mb15-137L in the presence of 10 IU/mL IL-2. After 1 week of culture with K562-mb15-137L, NK cells expanded by 16.3±5.9 fold, whereas T cells did not expand. The stimulatory effect of K562-mb15-137L was much higher than that of K562 cells transduced with control vectors, K562 expressing membrane-bound IL-15 or CD137L alone, or K562 expressing wild-type IL-15 instead of membrane-bound IL-15.

NK cells expanded with K562-mb15-137L were transduced with a retroviral vector and the anti-CD19-BB-ζ chimeric receptor. In 27 experiments, mean transduction efficiency (±SD) after 7-14 days was 67.5%±16.7%. Seven to fourteen days after transduction, 92.3% (range 84.7%-99.4%) of cells were CD3-CD56+ NK cells; expression of receptors on the cell surface was high. NK cells expressing anti-CD19-BB-ζ had powerful cytotoxicity against NK-resistant B-lineage ALL cells. NK cells transduced with anti-CD19-BB-ζ had consistently higher cytotoxicity than those transduced with receptors lacking 4-1BB.

Transduction of NK Cells with Chimeric Receptors

Peripheral blood mononuclear cells were stimulated with the K562-mb15-137L cells prior to their exposure to retroviral vectors containing anti-CD19 receptor constructs and GFP. In 10 experiments, median percent of NK cells was 98.4% (93.7-99.4%) 7-11 days after transduction; 77.4% (55.2-90.0%) of these cells were GFP+. We observed high levels of surface expression of the anti-CD19 chimeric receptors.

NK activity against the CD19-negative cells K562 and U937 was not affected by the expression of anti-CD19 receptors. The receptors, however, markedly increased NK activity against $CD19^+$ ALL cells. The following summarizes results obtained with NK cells from 2 donors. At an E:T ratio of 1:1, NK cells from donor 1 lacked cytotoxicity against $CD19^+$ RS4;11 cells and exerted ~50% cytoxicity against $CD19^+$697 cells after 24 hours. NK cells from donor 2 had no cytotoxicity against RS4;11 or 697 cells. Expression of the anti-CD19-CD3ϵ receptor overcame NK resistance. NK cells from donor 1 became cytotoxic to RS4;11 cells and those from donor 2 become cytotoxic to both RS;11 and 697 cells. Moreover, when control cells had some cytotoxicity, this was significantly augmented by expression of signaling anti-CD19 receptor.

Subsequently, we found that addition of the co-stimulatory CD28 or 4-1BB to the anti-CD19 receptor markedly enhanced NK cytotoxicity against NK-resistant ALL cells (FIG. **2**). For example, after 24 hours of culture at 1:1 E:T ratio, the cytotoxicity mediated by the anti-CD19-BB-ζ receptor against the NK-resistant $CD19^+$ ALL cell lines 380, 697, KOPN57bi and OP1 ranged from 86.5% to 99.1%. Therefore, the inclusion of co-stimulatory molecules enhances not only the cytoxicity of T lymphocytes but also that of NK cells.

9.3 Example 3

Artificial Antigen Producing Cells (APCs) Pave the Way for Clinical Application by Potent Primary in Vitro Induction

Materials and Methods

Cells

The CD19 human B-lineage ALL cell lines RS4;11, OP-1, 380, 697, and KOPN57bi; the T-cell line GEM-C7; and the myeloid cell lines K562 and U-937 were available in our laboratory. Cells were maintained in RPMI-1640 (Gibco, Grand Island, N.Y.) supplemented with 10% fetal calf serum (FCS; BioWhittaker, Walkersville, Md.) and antibiotics.

Primary leukemia cells were obtained with appropriate informed consent and Institutional Review Board (M) approval from nine patients with B-lineage ALL; from four of these patients, we also studied (with IRB approval) cryopreserved peripheral blood samples obtained during clinical remission. An unequivocal diagnosis of B-lineage ALL was established by morphologic, cytochemical, and immunophenotypic criteria; in each case, more than 95% of the cells were positive for CD19. Peripheral blood was obtained from eight healthy adult donors. Mononuclear cells collected from the samples by centrifugation on a Lymphoprep density step (Nycomed, Oslo, Norway) were washed twice in phosphate-buffered saline (PBS) and once in AIM-V medium (Gibco).

Plasmids and Retrovirus Production

The anti-CD19-ζ, anti-CD19-BB-i and anti-CD19-truncated (control) plasmids are described in Imai, C, et al., Leukemia 18:676-684 (2004). The pMSCV-IRES-GFP, pEQ-PAM3(-E), and pRDF constructs were obtained from the St.

Jude Vector Development and Production Shared Resource. The intracellular domains of human DAP 10, 4-1BB ligand and interleukin-15 (IL-15) with long signal peptide were subcloned by polymerase chain reaction (PCR) with a human spleen cDNA library (from Dr. G. Neale, St. Jude Children's Research Hospital) used as a template. An antiCD19-DAP 10 plasmid was constructed by replacing the intracellular domain of anti-CD19-ζ with that of DAP 10, using the SOE-PCR (splicing by overlapping extension by PCR) method. The signal peptide of CD8 cc, the mature peptide of IL-15 and the transmembrane domain of CDBα were assembled by SOE-PCR to encode a "membrane-bound" form of IL-15. The resulting expression cassettes were subcloned into EcoRI and XhoI sites of MSCV-IRES-GFP.

The RD114-pseudotyped retrovirus was generated as described in Imai, C, et al., Leukemia 18:676-684 (2004). We used calcium phosphate DNA precipitation to transfect 293T cells with anti-CD19-ζ, anti-CD19-DAP10, anti-CD19-BB-ζ, or anti-CD19-truncated; pEQ-PAM3(-E); and pRDF. Conditioned medium containing retrovirus was harvested at 48 hours and 72 hours after transfection, immediately frozen in dry ice, and stored at −80° C. until use.

Development of K562 Derivatives, Expansion of NK Cells and Gene Transduction

K562 cells were transduced with the construct encoding the "membrane-bound" form of IL-15. Cells were cloned by limiting dilution, and a single-cell clone with high expression of GFP and of surface IL-15 ("K562-mb15") was expanded. This clone was subsequently transduced with human 4-1BB ligand and designated as "K562-mb15-41BBL". K562 cells expressing wild-type IL-15 ("K562-wt15") or 4-IBBL ("K562-41BBL") were produced by a similar procedure. Peripheral blood mononuclear cells (1.5×106) were incubated in a 24-well tissue culture plate with or without 106 K562-derivative stimulator cells in the presence of 10 N/mL human IL-2 (National Cancer Institute BRB Preclinical Repository, Rockville, Md.) in RPMI-1640 and 10% FCS.

Mononuclear cells stimulated with K562-mb15-41BBL were transduced with retroviruses, as previously described for T cells [Melero I, et al., NK1.1 cells express 4-iBB (CDw137) costimulatory molecule and are required for tumor immunity elicited by anti-4-1BB monoclonal antibodies. Cell Immunol 190:167-172 (1998)]. Briefly, 14-mL polypropylene centrifuge tubes (Falcon) were coated with human fibronectin (100 μg/mL; Sigma, St. Louis, Mo.) or RetroNectin (50 μg/mL; TaKaRa, Otsu, Japan). Prestimulated cells (2×10^5) were resuspended in the tubes in 2-3 mL of virus-conditioned medium with polybrene (4 μg/mL; Sigma) and centrifuged at 2400×g for 2 hours (centrifugation was omitted when RetroNectin was used). The multiplicity of infection (4 to 6) was identical in each experiment comparing the activity of different chimeric receptors. After centrifugation, cells were left undisturbed for 24 hours in a humidified incubator at 37° C., 5% CO_2. The transduction procedure was repeated on two successive days. After a second transduction, the cells were re-stimulated with K562-mb 15-4 1BBL in the presence of 10 IU/mL of IL-2. Cells were maintained in RPMI-1640, 10% FCS, and 10 IU/mL IL-2.

Detection of Chimeric Receptor Expression and Immunophenotyping

Transduced NK cells were stained with goat anti-mouse $(Fab)^2$ polyclonal antibody conjugated with biotin (Jackson Immunoresearch, West Grove, Pa.) followed by streptavidin conjugated to peridinin chlorophyll protein (PerCP; Becton Dickinson, San Jose, Calif.). For Western blotting, cells were lysed in RIPA buffer (PBS, 1% Triton-X100, 0.5% sodium deoxycholate, 0.1% SDS) containing 3 μg/mL of pepstatin, 3 μg/mL of leupeptin, 1 mM of PMSF, 2 mM of EDTA, and 5 μg/mL of aprotinin. Centrifuged lysate supernatants were boiled with an equal volume of loading buffer with or without 0.1 M DTT, and then separated by SDS PAGE on a precast 10-20% gradient acrylamide gel (BioRad, Hercules, Calif.). The proteins were transferred to a PVDF membrane, which was incubated with primary mouse anti-human CD3ζ monoclonal antibody (clone 8D3; Pharmingen). Membranes were then washed, incubated with a goat anti-mouse IgG horseradish peroxidase-conjugated second antibody, and developed by using the ECP kit (Pharmacia, Piscataway, N.J.).

The following antibodies were used for immunophenotypic characterization of expanded and transduced cells: anti-CD3 conjugated to fluorescein isothiocyanate (FITC), to peridinin chlorophyll protein (PerCP) or to energy-coupled dye (ECD); anti-CD10 conjugated to phycoerythrin (PE); anti-CD19 PE; anti-CD22 PE; anti-CD56 FITC, PE or allophycocyanin (AFC); anti-CD16 CyChrome (antibodies from Becton Dickinson; Pharmingen, San Diego; or Beckman-Coulter, Miami, Fla.); and anti-CD25 PE (Dako, Carpinteria, Calif.). Surface expression of KIR and NK activation molecules was determined with specific antibodies conjugated to FIX or PE (from Beckman-Coulter or Becton-Dickinson), as previously described [Brentjens R J, Latouche J B, Santos E, et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 9:279-286 (2003)]. Antibody staining was detected with a FACScan or a LSR II flow cytomete (Becton Dickinson).

Cytotoxicity Assays and Cytokine Production

Target cells (1.5×105) were placed in 96-well U-bottomed tissue culture plates (Costar, Cambridge, Mass.) and incubated with primary NK cells transduced with chimeric receptors at various effector:target (E:T) ratios in RPMI-1640 supplemented with 10% FCS; NK cells were cultured with 1000 U/mL IL-2 for 48 hours before the assay. Cultures were performed in the absence of exogenous IL-2. After 4 hours and 24 hours, cells were harvested, labeled with CD10 PE or CD22 PE and CD56 FITC, and assayed by flow cytometry as previously described. The numbers of target cells recovered from cultures without NK cells were used as a reference.

For cytokine production, primary NK cells (2×10^5 in 200 μl) expressing chimeric receptors were stimulated with various target cells at a 1:1 ratio for 24 hours. The levels of IFN-γ and GM-CSF in cell-free culture supernatants were determined with a Bio-Plex assay (BioRad).

Statistical Analysis

A test of equality of mean NK expansion with various stimuli was performed using analysis of variance for a randomized complete block design with each donor considered a random block. Tukey's honest significant difference procedure was used to compute simultaneous confidence intervals for each pairwise comparison of the differences of treatment means. Differences in cytotoxicities and cytokine production among NK cells bearing different chimeric receptors were analyzed by the paired Student's t test.

Results

Culture Conditions that Favor the Expansion of Primary NK Cells

To transduce chimeric receptors into primary NK cells, we searched for stimuli that would induce specific NK cell proliferation. In preliminary experiments, peripheral blood mononuclear cells of $CD3^+$ T lymphocytes were depleted and the remaining cells were stimulated with IL-2 (1000 U/mL) or IL-15 (10 ng/mL). Under these culture conditions there was no expansion of NK cells, which in fact progressively declined in numbers. With PHA (7 mg/mL) and IL-2 (1000

U/mL) as stimuli, we observed a 2- to 5-fold expansion of $CD56^+$ $CD3^-$ NK cells after 1 week of culture. However, despite the low proportion of contaminating $CD3^+$ cells (<2% in two experiments) at the beginning of the cultures, these cells expanded more than NK cells (>30-fold expansion), and after 1 week of culture represented approximately 35% of the cell population.

NK cells can be stimulated by contact with the human leukemia cell line K562, which lacks HLA-antigen expression, [Robertson M J, Cameron C, Lazo S, Cochran K J, Voss S D, Ritz J. Costimulation of human natural killer cell proliferation: role of accessory cytokines and cell contact-dependent signals. Nat Immun 15:213-226 (1996)] and genetically modified K562 cells have been used to stimulate cytotoxic T lymphocytes [Maus M V, Thomas A K, Leonard D G, et al. Ex vivo expansion of polyclonal and antigen-specific cytotoxic T lymphocytes by artificial APCs expressing ligands for the T-cell receptor, CD28 and 4-1BB. Nat Biotechnol 20:143-148 (2002)]. We tested whether the NK-stimulatory capacity of K562 cells could be increased through enforced expression of additional NK-stimulatory molecules, using two molecules that are not expressed by K562 cells and are known to stimulate NK cells. One molecule, the ligand for 4-1BB (4-1BBL), triggers activation signals after binding to 4-1BB (CD137), a signaling molecule expressed on the surface of NK cells [Melero I, Johnston J V, Shufford W W, Mittler R S, Chen L. NK1.I cells express 4-IBB (CDw137) costimulatory molecule and are required for tumor immunity elicited by anti-4-IBB monoclonal antibodies. Cell Immunol 190:167-172 (1998)]. The other molecule, IL-15, is a cytokine known to promote NK-cell development and the survival of mature NK cells [Carson W E, Fehniger T A, Haldar S, et al. A potential role for interleukin-15 in the regulation of human natural killer cell survival J Clin Invest. 99:937-943 (1997); Cooper M A, Bush J E, Fehniger T A, et al. In vivo evidence for a dependence on interleukin 15 for survival of natural killer cells. Blood 100:3633-3638 (2002); Fehniger T A, Caligiuri M A. Ontogeny and expansion of human natural killer cells: clinical implications. Int Rev Immunol 20:503-534 (2001); Wu J, Lanier L L. Natural killer cells and cancer. Adv Cancer Res 90:127-56.:127-156 (2003)]. Since IL-15 has greater biological activity when presented to NK cells bound to IL-15Rα on the cell membrane of stimulatory cells, rather than in its soluble form, we made a construct containing the human IL-15 gene fused to the gene encoding the human CD8α, transmembrane domain, and used it to transduce K562 cells. Expression of IL-15 on the surface of K562 cells was more than five times higher with the IL-15-CD8α construct than with wild-type IL-15.

To test whether the modified K562 cells expressing both 4-11313L and IL-I5 (K562mb15-41BBL cells) promote NK cell expansion, we cultured peripheral blood mononuclear cells from seven donors in the presence of low-dose (10 U/mL) IL-2 as well as irradiated K562 cells transduced with 4-1BBL and/or IL-15, or with an empty control vector. Expression of either 4-1BBL or IL-15 by K562 cells improved the stimulation of NK-stimulatory capacity of K562 in some cases but not overall, whereas simultaneous expression of both molecules led to a consistent and striking amplification of NK cells (median recovery of $CD56^+$ $CD3^-$ cells at 1 week of culture, 2030% of input cells [range, 1020%-2520%] compared with a median recovery of 250% [range, 150%-640%] for K562 cells lacking 4-1BBL and IL-15; $P<0.0001$). In 24 experiments with cells from 8 donors, NK-cell expansion after 3 weeks of culture with K562 cells expressing both stimulatory molecules ranged from 309-fold to 12,409 fold (median, 1089-fold). Neither the modified nor unmodified K562 cells caused an expansion of T lymphocytes. Among expanded $CD56^+$ $CD3^-$ NK cells, expression of CD56 was higher than that of unstimulated cells; expression of CD16 was similar to that seen on unstimulated NK cells (median CD16+ NK cells in 7 donors: 89% before expansion and 84% after expansion). We also compared the expression of KIR molecules on the expanded NK cells with that on NK cells before culture, using the monoclonal antibodies CD158a (against KIR 2DL1), CD158b (2DL2), NKBI (3DL1) and NKAT2 (2DL3). The prevalence of NK subsets expressing these molecules after expansion resembled that of their counterparts before culture, although the level of expression of KIR molecules was higher after culture. Similar results were obtained for the inhibitory receptor CD94, while expression of the activating receptors NKp30 and NKp44 became detectable on most cells after culture. In sum, the immunophenotype of expanded NK cells reiterated that of activated NK cells, indicating that contact with K562-mb1541BBL cells had stimulated expansion of all subsets of NK cells.

Transduction of NK Cells with Chimeric Receptors

Before transducing peripheral blood mononuclear cells with retroviral vectors containing chimeric receptor constructs and GFP, we stimulated them with K562-mb15-41BBL cells. In 27 experiments, the median percentage of NK cells that were GFP^+ at 7-11 days after transduction was 69% (43%-93%). Chimeric receptors were expressed at high levels on the surface of NK cells and, by Western blotting, were in both monomeric and dimeric configurations.

To identify the specific signals required to stimulate NK cells with chimeric receptors, and overcome inhibitory signals mediated by KIR molecules and other NK inhibitory receptors that bind to HLA class I molecules, we first compared two types of chimeric receptors containing different signaling domains: CD3ζ, a signal-transducing molecule containing three immunoreceptor tyrosine-based activation motifs (ITAMs) and linked to several activating receptors expressed on the surface of NK cells [Farag S S, Fehniger T A, Ruggeri L, Velardi A, Caligiuri M A. Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect. Blood 100:1935-1947 (2002); Moretta L, Moretta A. Unravelling natural killer cell function: triggering and inhibitory human NK receptors. EMBO J 23:255-259 (2004)], and DAP 10, a signal transducing molecule with no ITAMs linked to the activating receptor NKG2D and previously shown to trigger NK cytotoxicity [Farag S S, Fehniger T A, Ruggeri L, Velardi A, Caligiuri M A. Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect. Blood 100:1935-1947 (2002); Moretta L, Moretta A. Unravelling natural killer cell function: triggering and inhibitory human NK receptors. EMBO J 23:255-259 (2004); Billadeau D D, Upshaw J L, Schoon R A, Dick C J, Leibson P J. NKG2D-DAPIO triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. Nat ImmuNo. 4:557-564 (2003)]. As a control, we used NK cells transduced with a vector containing an antiCD19 receptor but no signaling molecules or containing GFP alone.

NK cells were challenged with the $CD19^+$ leukemic cell lines 380, 697 and RS4;11, all of which express high levels of HLA-class I molecules by antibody staining By genotyping, RS4;11 is Cw4/Cw3, Bw4 and A3; 380 is Cw4/Cw4, Bw4; and 697 is Cw3/Cw3. Hence, these cell lines were fully capable of inhibiting NK cell cytotoxicity via binding to NK inhibitory receptors.

Expression of receptors without signaling molecules did not increase NK-mediated cytotoxicity over that exerted by NK cells transduced with the vector containing only GFP. By

contrast, expression of anti-CD19-ζ receptors markedly enhanced NK cytotoxicity in all experiments, regardless of the intrinsic ability of donor NK cells to kill leukemic targets. For example, 380 cells were highly resistant to NK cells from donors 2 and 3, but were killed when these donor cells expressed anti-CD19-ζ receptors. Similar observations were made for RS4;11 cells and the NK cells of donor 1 and for 697 cells and NK cells of donor 2. Moreover, the anti-CD19-ζ receptors led to improved killing of target cells even when natural cytotoxicity was present. In all experiments, the cytotoxicity triggered by the anti-CD19-ζ receptor was enhanced over that achieved by replacing CD3ζ with DAP 10 ($P<0.001$).

4-1BB-Mediated Costimulatory Signals Enhance NK Cytotoxicity

Previous studies have shown that the addition of costimulatory molecules to chimeric receptors enhances the proliferation and cytotoxicity of T lymphocytes [Imai C, Mihara K, Andreansky M, Nicholson I C, Pui C H, Campana D. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia 18:676-684 (2004)]. Of the two best known costimulatory molecules in T lymphocytes, CD28 and 4-1BB, only 4-1BB is expressed by NK cells [Melero I, Johnston J V, Shufford W W, Mittler R S, Chen L. NKLI cells express 4-1BB (CDw137) costimulatory molecule and are required for tumor immunity elicited by anti-4-1BB monoclonal antibodies. Cell Immunol 1998; 190:167-172 (1998); Lang S, Vujanovic N L, Wollenberg B, Whiteside T L. Absence of B7.1-CD28/CTLA-4 mediated co-stimulation in human NK cells. Eur J Immunol 28:780-786 (1998); Goodier M R, Londei M. CD28 is not directly involved in the response of human CD3CD56+ natural killer cells to lipopolysaccharide: a role for T cells. Immunology 111:384-390(2004)]. We determined whether the addition of 4-1BB to the anti-CD19-ζ receptor would enhance NK cytotoxicity. In a 4 hour-cytotoxicity assay, cells expressing the 41BB-augmented receptor showed a markedly better ability to kill $CD19^+$ cells than did cells lacking this modification. The superiority of NK cells bearing the anti-CD19-BB-ζ receptor was also evident in 24-hour assays with NK cells from different donors cultured at a 1:1 ratio with the leukemia cell lines 697, KOPN57bi and OP-1.

Next, we determined whether the antileukemic activity of NK cells expressing anti-CD19-BB-ζ receptors extended to primary leukemic samples. In five samples from children with different molecular species of ALL, NK cells expressing the 4-1BB receptors exerted strong cytotoxicity that was evident even at low E:T ratios (e.g., <1:1; FIG. **7**) and uniformly exceeded the activity of NK cells expressing signaling receptors that lacked 4-1BB. Even when donor NK cells had natural cytotoxicity against ALL cells and CD3ζ receptor did not improve it, addition of 4-1BB to the receptor significantly enhanced cytotoxicity. Consistent with their increased cytotoxicity, NK cells expressing anti-CD19-BB-ζ mediated more vigorous activation signals. Forty-six percent of NK cells bearing this receptor expressed the IL2 receptor a chain CD25 after 24 hours of coculture with $CD19^+$ ALL cells, compared with only 17% of cells expressing the anti-CD19-ζ receptor and <1% for cells expressing receptors that lacked stimulatory capacity. Moreover, anti-CD19-BB-C receptors induced a much higher production of IFN-g and GM-CSF upon contact with $CD19^+$ cells than did receptors without 41BB.

We asked whether the expression of signaling chimeric receptors would affect spontaneous NK activity against NK-sensitive cell lines not expressing CD19. Spontaneous cytotoxicity of NK cells from three donors against the $CD19^-$ leukemia cell lines K562, U937 and CEM-C7 was not diminished by expression of chimeric receptors, with or without 4-1BB.

Anti-CD19 Chimeric Receptors Induce NK Cytotoxicity Against Autologous Leukemic Cells

To determine whether the NK cell expansion and transduction system that we developed would be applicable to clinical samples, we studied peripheral blood samples that had been obtained (and cryopreserved) from four patients with childhood B-lineage ALL in clinical remission, 25-56 weeks from diagnosis. NK cell expansion occur in all four samples: recovery of after one week of culture with K562-mb15-41BBL cells, recovery of $CD56^+$ $CD3^-$ NK cells ranged from 1350% to 3680% of the input.

After transduction with chimeric receptors, we tested the cytotoxicity of the NK cells against autologous leukemic lymphoblasts obtained at diagnosis. Expression of anti-CD19-BB-ζ receptors overcame NK cell resistance of autologous cells; NK cells expressing the receptors exerted cytotoxicity which was as powerful as that observed with allogeneic targets.

Discussion

In this study, we demonstrated that the resistance of cancer cells to NK cell activity can be overcome by chimeric receptors expressed on primary NK cells. The stimulatory signals triggered by the receptors upon contact with target cells predominated over inhibitory signals and induced powerful cytotoxicity against NK-resistant leukemic cell lines and primary leukemic cells. We found that the type of stimulatory signal delivered by the chimeric receptor was a key factor in inducing cytotoxicity. Although DAP 10 signaling can elicit NK cytotoxicity, chimeric receptors containing this molecule in our study induced weaker NK cell activity than that generated by CD3ζ-containing receptors, despite identical levels of surface expression. We also found that addition of the costimulatory molecule 4-1BB to the chimeric receptors markedly augmented cytotoxicity, and that receptors containing both CD3ζ and 4-1BB triggered a much more robust NK cell activation and cytokine production than did those containing only CD3ζ.

The important contribution of 4-1BB signals agrees with findings that anti-4-1BB antibodies activate murine NK cells [Pan P Y, et al., Regulation of dendritic cell function by NK cells: mechanisms underlying the synergism in the combination therapy of IL-12 and 4-1BB activation. J Immunol 172: 4779-4789 (2004)], and enhance their anti-tumor activity. Leukemic lymphoid cells usually do not express 4-1BB ligand: only 2 of 284 diagnostic B-lineage ALL samples studied by gene arrays at our institution expressed 4-1BB ligand transcripts [Yeoh E J, et al., Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. Cancer Cell 1:133-143 (2002)]. Hence, 4-1BB signals can be delivered to NK cells only if the molecule is incorporated into the receptor.

Efficient and stable transduction of primary NK cells is notoriously difficult, prompting us to devise a new gene transduction method for the present study. Most investigators have demonstrated efficient gene transfer only in continuously growing NK cell lines [Roberts M R, et al., Antigen-specific cytolysis by neutrophils and NK cells expressing chimeric immune receptors bearing zeta or gamma signaling domains. J Immunol. 161:375-384 (1998); Nagashima S, et al., Stable transduction of the interleukin-2 gene into human natural killer cell lines and their phenotypic and functional characterization in vitro and in vivo. Blood 91:3850-3861(1998)] or

reported methods yielding only transient gene expression [Billadeau D D, et al., NKG2D-DAP 10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. Nat ImmuNo. 4:557-564 (2003); Trompeter H I, et al., Rapid and highly efficient gene transfer into natural killer cells by nucleofection. J Immunol Methods 274:245-256 (2003); Schroers R, et al., Gene transfer into human T lymphocytes and natural killer cells by Ad5/F35 chimeric adenoviral vectors. Exp Hematol 32:536-546(2004)]. We achieved stable expression of chimeric receptors in primary $CD56^+$ $CD3^-$ NK cells by using an RD114-pseudotyped retroviral vector and specifically expanding primary $CD56^+$ $CD3^-$ NK cells before they were exposed to the retrovirus, a step that allowed highly efficient gene expression. Although several cytokines such as IL-2, IL-12 and IL-15 have been reported to stimulate NK cells [Carson W E, et al., A potential role for interleukin-15 in the regulation of human natural killer cell survival J Clin Invest. 99:937-943 (1997); Trinchieri G, et al., Response of resting human peripheral blood natural killer cells to interleukin 2 J Exp Med 1984; 160: 1147-1169 (1984); Naume B, et al., A comparative study of IL-12 (cytotoxic lymphocyte maturation factor)-, IL-2-, and IL-7-induced effects on immunomagnetically purified CD56+ NK cells. J Immunol 148:2429-2436 (1992)], their capacity to induce proliferation of resting $CD56^+$ CD3 cells has been poor, unless accessory cells are present in the cultures. Perussia et al. Nat Immun Cell Growth Regul 6:171-188 (1987), found that contact with irradiated B-lymphoblastoid cells induced as high as a 25-fold expansion of NK cells after 2 weeks of stimulation, while Miller et al. Blood; 80:2221-2229 (1992) reported an approximate 30-fold expansion of NK cells after 18 days of culture with 1000 U/mL IL-2 and monocytes. However, these culture conditions are likely to promote the growth of $CD3^+$ T lymphocytes as well as NK cells. Since our ultimate aim is to generate pure preparations for out donor NK cells devoid of $CD3^+$ T lymphocytes, that can be infused into recipients of allogeneic hematopoietic stem cell transplants, we searched for methods that would maximize NK cell expansion without producing T-cell mitogenicity.

Contact with K562 cells (which lack MHC-class I molecule expression and hence do not trigger KIR-mediated inhibitory signals in NK cells) is known to augment NK cell proliferation in response to IL-15. We found that membrane-bound IL-15 and 4-1BBL, coexpressed by K562 cells, acted synergistically to augment K562-specific NK stimulatory capacity, resulting in vigorous expansion of peripheral blood $CD56^+$ $CD3^-$ NK cells without concomitant growth of T lymphocytes. After 2-3 weeks of culture, we observed NK cell expansions of up to 10,000-fold, and virtually pure populations of NK cells could be obtained, even without the need for T-cell depletion in some cases. NK cells expanded in this system retained the immunophenotypic diversity seen among peripheral blood subsets of NK cells, as well as their natural cytotoxicity against sensitive target cells, even after transduction with different chimeric receptors. Hence, this system should help studies of NK cell biology which require specific cell expansion and/or gene transduction, but it should also be adaptable to clinical applications after generating K562mb 15-4 1 BBL cells that comply with current good manufacturing practices for clinical trials. Recently, Harada et al. reported that expansions of $CD56^+$ $CD3^-$ cells (up to 400-fold after 2 weeks) were apparently superior after contact with another HLA class I-negative cell line, the Wilms tumor cell line HFWT [Harada H, Saijo K, Watanabe S, et al. Selective expansion of human natural killer cells from peripheral blood mononuclear cells by the cell line, HFWT. Jpn J Cancer Res 93:313 (2002)]. Future studies should determine whether HFWT cells express 41BBL or whether enforced expression of 4-1BBL together with IL-15 results in a greater specific expansion of NK cells than seen with modified K562 cells.

In the context of allogeneic hematopoietic stem cell transplantation, infusions of activated donor T cells would carry an unacceptably high risk of severe GvHD, particularly in recipients of haploidentical or mismatched transplants. By contrast, infusions of pure CD56 CD3 NK cells should not impose that risk [Ruggeri L, et al., Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 295:2097-2100 (2002)]. Most clinical studies of the therapeutic effects of NK cells have been performed in an autologous setting and have yielded only moderately promising results [Farag S S, et al., Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect. Blood 100:1935-1947 (2002); Chiorean E G, Miller J S. The biology of natural killer cells and implications for therapy of human disease. J Hematother Stem Cell Res 10:451-463 (2001)]. This is not surprising because NK cell activity is inhibited by surface receptors that recognize autologous HLA molecules expressed by both normal and neoplastic cells. Allogeneic NK cells may be more effective, but even in an allogeneic setting the capacity of NK cells to kill malignant lymphoid cells is generally modest and often negligible [Caligiuri M A, Velardi A, Scheinberg D A, Borrello I M. Immunotherapeutic approaches for hematologic malignancies. Hematology (Am Soc Hematol Educ Program) 337-353 (2004)]. Leung et al. [J Immunol 172:644-650 (2004)] detected NK cytotoxicity against an ALL cell line expressing particularly low levels of inhibitory HLA molecules, but cytotoxicity was much lower than that observed against the NK-cell target K562: only about 50% of the ALL cells were killed at an effector:target ratio of 40:1. In that study, RS4;11 cells, which express HLA-C alleles that bind the most commonly expressed KIRs, were NK-resistant, whereas these cells, as well as autologous leukemic cells, were highly sensitive to NK cells expressing anti-CD19 signaling receptors in our study. NK cells expressing signaling chimeric receptors have much more powerful antileukemic activity than unmodified NK cells, and can kill target cells irrespective of their HLA profile. An increased understanding of the signals leading to immune cell activation, together with progress in gene cloning and transfer, have made the treatment of cancer with "adoptively acquired immunity" a realistic goal. Clinical precedents, such as administration of T-cell clones that target cytomegalovirus epitopes [Walter E A, et al., Reconstitution of cellular immunity against cytomegalovirus in recipients of allogeneic bone marrow by transfer of T-cell clones from the donor. N Engl J Med 1995; 333: 1038-1044 (1995)] or EBV-specific antigens [Rooney C M, et al., Use of gene-modified virus-specific T lymphocytes to control Epstein-Barr-virus-related lymphoproliferation. Lancet 345:9-13(1995)], attest to the clinical feasibility of adoptive immune cell therapy. Nonetheless, there are potential limitations that may affect the effectiveness of cell therapy guided by chimeric receptors. One is that the murine scFv portion of the chimeric receptor or the fusion sites of the human regions that compose it may trigger a host immune response leading to elimination of the modified cells [Sadelain M, et al., Targeting tumours with genetically enhanced T lymphocytes. Nat Rev Cancer 3:35-45 (2003)]. Although the impact of such an event in a clinical setting remains to be determined, we anticipate that immune responses against modified NK cells will be limited in immune-suppressed patients after hematopoietic stem cell transplantation. Another potential limitation is that adoptively transferred

cells may have inadequate persistence in vivo, although a recent study showed that NK cells obtained from haploidentical donors and activated ex vivo could expand in patients when infused after administration of high-dose cyclophosphamide and fludarabine, which caused an increased in endogenous IL-15 [Miller J S, et al., Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in cancer patients. Blood; in press (2005)]. We speculate that such expansions would also occur with genetically-modified NK cells, and suggest that further studies to identify signaling molecules that promote NK cell proliferation when incorporated into chimeric receptors are warranted. In patients at a high risk of leukemia or lymphoma relapse, the expected benefits of genetically-modified NK cells will outweigh the risk of insertional oncogenesis posed by the use of retroviruses for chimeric receptor transduction [Baum C, et al., Side effects of retroviral gene transfer into hematopoietic stem cells. Blood 101:2099-2114 (2003)]. We also predict that the coexpression of suicide genes will become a useful safety measure in clinical studies [Marktel S, et al., Immunologic potential of donor lymphocytes expressing a suicide gene for early immune reconstitution after hematopoietic T-cell-depleted stem cell transplantation. Blood 101:1290-1298 (2003)]; this strategy would also ensure that the elimination of normal $CD19^+$ B-lineage cells is only temporary.

Novel therapies that bypass cellular mechanisms of drug resistance are urgently needed for patients with refractory leukemia and lymphoma. NK cell alloreactivity is a powerful new tool for improving the therapeutic potential of allogeneic hematopoietic stem cell transplantation. The results of this study indicate that signaling receptors can enhance the efficacy of NK cell alloreactivity and widen its applicability. We envisage initial clinical trials in which donor NK cells, collected by apheresis, are expanded ex vivo as described here, transduced with chimeric receptors and then infused after transplantation in patients with B-lineage ALL. The target molecule for the chimeric receptors, CD19, was selected because it is one of the most widely expressed surface antigens among B-cell malignancies, including ALL, CLL and NHL. In these malignancies, CD19 is highly expressed on the surface of virtually all cells but has limited or no expression in normal tissues [Campana D, Behm F G. Immunophenotyping of leukemia. J Immunol Methods 243:59-75 (2000)]. However, the NK-cell strategy of immunotherapy we describe would not have to be directed to the CD19 antigen, but could be applied to any of the numerous molecules identified as potential targets for chimeric receptor-based cell therapy in cancer patients.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification, including but not limited to U.S. patent application Ser. No. 09/960,264, filed Sep. 20, 2001; and U.S. application Ser. No. 10/981,352, filed Nov. 4, 2004, are incorporated herein by reference, in their entirety. All of references, patents, patent applications, etc. cited above, are incorporated herein in their entirety.

SEQUENCE LISTING

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15                  20                  25                  30

tgc cca gct ggt aca ttc tgt gat aat aac agg aat cag att tgc agt      266
Cys Pro Ala Gly Thr Phe Cys Asp Asn Asn Arg Asn Gln Ile Cys Ser
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gac ata tgc agg cag tgt aaa ggt gtt ttc agg acc agg aag gag tgt      362
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gaa ctg aca aaa aaa ggt tgt aaa gac tgt tgc ttt ggg aca ttt aac      506
Glu Leu Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn
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gat cag aaa cgt ggc atc tgt cga ccc tgg aca aac tgt tct ttg gat      554
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gga aag tct gtg ctt gtg aat ggg acg aag gag agg gac gtg gtc tgt      602
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cct gcc cct gcg aga gag cca gga cac tct ccg cag atc atc tcc ttc      698
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ata ttc aaa caa cca ttt atg aga cca gta caa act act caa gag gaa      842
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Leu
255

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Cys Arg Gln Cys Lys Gly Val Phe Arg Thr Arg Lys Glu Cys Ser Ser
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Thr Ser Asn Ala Glu Cys Asp Cys Thr Pro Gly Phe His Cys Leu Gly
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Ala Gly Cys Ser Met Cys Glu Gln Asp Cys Lys Gln Gly Gln Glu Leu
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Thr Lys Lys Gly Cys Lys Asp Cys Cys Phe Gly Thr Phe Asn Asp Gln
115 120 125

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Ser Val Leu Val Asn Gly Thr Lys Glu Arg Asp Val Val Cys Gly Pro
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Arg Phe Ser Val Val Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
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gga ttc cat tgc ttg ggg cca cag tgc acc aga tgt gaa aag gac tgc      460
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ttc ccc cac ata ttc aag caa cca ttt aag aag acc act gga gca gct      844
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caa gag gaa gat gct tgt agc tgc cga tgt cca cag gaa gaa gaa gga      892
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Pro Ser Thr Phe Ser Ser Ile Gly Gly Gln Pro Asn Cys Asn Ile Cys
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Arg Val Cys Ala Gly Tyr Phe Arg Phe Lys Lys Phe Cys Ser Ser Thr
65                  70                  75                  80

His Asn Ala Glu Cys Glu Cys Ile Glu Gly Phe His Cys Leu Gly Pro
                85                  90                  95

Gln Cys Thr Arg Cys Glu Lys Asp Cys Arg Pro Gly Gln Glu Leu Thr
            100                 105                 110

Lys Gln Gly Cys Lys Thr Cys Ser Leu Gly Thr Phe Asn Asp Gln Asn
        115                 120                 125

Gly Thr Gly Val Cys Arg Pro Trp Thr Asn Cys Ser Leu Asp Gly Arg
    130                 135                 140

Ser Val Leu Lys Thr Gly Thr Thr Glu Lys Asp Val Val Cys Gly Pro
145                 150                 155                 160

Pro Val Val Ser Phe Ser Pro Ser Thr Thr Ile Ser Val Thr Pro Glu
                165                 170                 175

Gly Gly Pro Gly Gly His Ser Leu Gln Val Leu Thr Leu Phe Leu Ala
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225                 230                 235                 240

Cys Arg Cys Pro Gln Glu Glu Glu Gly Gly Gly Gly Gly Tyr Glu Leu
                245                 250                 255
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What is claimed is:

1. A polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

2. A vector comprising a polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, (b) a transmembrane domain, and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, wherein the polynucleotide encoding the chimeric receptor is operatively linked to at least one regulatory element for expression of the chimeric receptor.

3. An isolated host cell comprising a polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

4. The isolated host cell of claim **3** which is a T lymphocyte or an NK cell.

5. The isolated host cell of claim **3** which is a T lymphocyte.

6. The polynucleotide of claim **1** wherein the signaling domain is a human 4-1BB signaling domain.

7. The polynucleotide of claim **6**, Wherein the 4-1BB signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

8. The polynucleotide of claim **7**, wherein the nucleotide sequence encoding the human 4-1BB signaling domain comprises nucleotide residues 129-893 of SEQ ID NO:1.

9. The polynucleotide of claim **1**, wherein the transmembrane domain is the transmembrane domain of CD8α.

10. The polynucleotide of claim **9**, wherein the extracellular ligand-binding domain further comprises a signal peptide of CD8α.

11. The vector of claim **2** which is a viral vector.

12. The vector of claim **11** which is a retroviral vector.

13. The isolated host cell of claim **3** which is an NK cell.

14. The isolated host cell of claim **3** which is an autologous cell isolated from a patient having a cancer of B cell origin.

15. The isolated host cell of claim **14**, wherein the autologous cell is an autologous T lymphocyte.

16. The isolated host cell of claim **15**, wherein the autologous T lymphocyte is derived from a blood or tumor sample of a patient having a cancer of B cell origin and activated and expanded in vitro.

17. The isolated host cell of claim **5**, wherein the T lymphocyte is an activated T lymphocyte.

18. The isolated host cell of claim **5**, wherein the T lymphocyte is isolated from a blood or tumor sample of a patient having a cancer of B cell origin.

19. The isolated host cell of claim **18** wherein the host cell is isolated from a patient having lymphoblastic leukemia, B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma.

20. The polynucleotide of claim **1**, wherein the chimeric receptor further comprises a hinge domain.

21. The vector of claim **2**, wherein the chimeric receptor further comprises a hinge domain.

22. The isolated cell of claim **3**, wherein the chimeric receptor further comprises a hinge domain.

* * * * *

Reference III

Selected Documents - Dispute

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	:	NO. 12-4122

MEMORANDUM

Dalzell, J. April 12, 2013

I. Introduction

We consider here a motion by St. Jude Children's Research Hospital ("St. Jude") to dismiss Count I of the complaint filed by the Trustees of the University of Pennsylvania ("Penn" or "the University"), a Count which alleges tortious interference with contractual relations.[1] St. Jude argues first that the claim is barred by the Noerr-Pennington doctrine, and that, if it is not, the University has failed to state a claim on which relief can be granted.

[1] Also pending before the Court is St. Jude's motion to dismiss Count I of the counterclaim the University filed in response to the Tennessee action, now consolidated here. In a December 14, 2012 epistolary submission to the Court, St. Jude asks us to consider the motions to dismiss together because they are "essentially identical." We will do so, and our analysis here will apply to St. Jude's motion to dismiss the University's counterclaim as well.

a. Factual History

This action between the University and St. Jude concerns two Materials Transfer Agreements ("MTAs" or "Agreements") between the parties, one executed in 2003 and the other in 2007.

The Agreements arose out of research that doctors at each institution had been conducting on immunotherapy cancer treatment. The University avers that Carl H. June, M.D., a Professor of Pathology and Laboratory Medicine at Penn, had developed a "CD19 ScFv DNA lentiviral construct" (the "June Construct") that "causes T cells to express chimeric antigen receptors (CARs) in patients such that their cancer is treated". Am. Comp. ¶ 8.

According to the University's amended complaint, Dario Campana, M.D., Ph.D., a doctor at St. Jude[2], had also developed "an anti-CD19 BB-ζ chimeric receptor construct" (the "Campana Construct"). Id. at ¶ 11. St. Jude claims that this construct is a molecule that "can be expressed on the surface of a normal human immune T-cell, and . . . causes the T-cell to recognize and attack certain leukemic cancer cells". MTD at 3. Dr. June and Dr. Campana met at a conference in 2003, after which Dr.

[2] The University alleges that Dr. Campana no longer works at St. Jude and currently serves as a professor at the National University of Singapore, Department of Pediatrics. Am. Comp. ¶ 14.

June asked Dr. Campana to provide him with a sample of the Campana Construct. Am. Comp. ¶ 12.

In order to facilitate this exchange, the parties entered into the first MTA at issue here on December 17, 2003. Id. at ¶ 13. That Agreement defined the "Material" St. Jude was transferring as "the anti-CD19-BB-ζ chimeric T-cell receptor construct, including any progeny, portions, unmodified derivatives and any accompanying know-how or data". 2003 MTA at ¶ 1, Am. Comp. Ex. D. The Agreement provided that "the Material will only be used to create a lentiviral chimeric T-cell receptor construct to be used in pre-clinical studies", id. at ¶ 3, and "may not be used in humans" or "for any commercial purpose." Id. at ¶ 4. It further provided that the University would "not commercialize any product that contains Material without the prior written approval of St. Jude." Id. at ¶ 8.

By 2007, Dr. June wished to use the June Construct to conduct human clinical trials, Am. Comp. ¶ 17, and so in February 2008, the parties executed a second MTA, dated October 2, 2007[3], allowing the product to be used in such clinical trials. 2007 MTA at ¶ 3, Am. Comp. Ex. E. That agreement contained the same definition of "Material" as found in the 2003 agreement. Id. at ¶ 1.

[3] We refer to this agreement, as the parties do, as the 2007 agreement.

In August 2011, Dr. June described the results of his study in an article in The New England Journal of Medicine, New Eng. J. Med. 8:725-733 (2011) and in Science Translational Medicine, 2011; 3(95):95ra73. Id. ¶ 23. St. Jude, in a complaint we will discuss below, avers that the University did not submit the Science Translational Medicine article to it for approval and that Penn and Dr. June failed to acknowledge that the Material the article referred to had come from St. Jude. St. Jude Comp. ¶ 49.

In a November 22, 2011 letter, the University informed St. Jude that it wished to terminate the MTA[4]. Am. Comp. Ex. F.

The University contends that it "contractually agreed to exclusively negotiate with Novartis regarding a ground-breaking collaboration that would develop Dr. June's cellular immunotherapy for general cancer patient use." Id. ¶ 27. According to the amended complaint, "The University . . . actively negotiated with Novartis a collaboration under which the University would receive funding that would allow it to continue with clinical trials of the Penn Immunotherapy without undue delay", and "[a]s of July 10, 2012, the University and Novartis had made substantial progress towards reaching an

[4] In its amended complaint, the University says this letter informed St. Jude it wished to terminate the 2003 MTA, but the letter refers to the 2007 MTA in its subject line and does not make clear which MTA the University seeks to terminate. The distinction does not affect our decision here.

agreement that would allow continued development of the Penn Immunotherapy Technology." Id. ¶¶ 28-29.

According to the University's complaint, "[s]tarting in August 2011, St. Jude and the University had ongoing discussions regarding St. Jude's contention that the University allegedly breached the 2003 and 2007 MTAs." Id. ¶ 30. St. Jude claims that by January of 2012 it "had learned that the University had breached both the 2003 MTA and the 2007 MTA by publishing experimental results without the required acknowledgment of St. Jude and without sharing the proposed publication with St. Jude beforehand", and by "engaging in prohibited commercialization efforts", MTD at 5.

As a result, St. Jude's General Counsel, Clinton Hermes, and outside counsel, Glenn Krinsky, spoke to University General Counsel Wendy White by telephone on January 20, 2012. Id. While they were speaking, Krinsky sent White an e-mail, explaining:

> Mr. Hermes and I telephoned you several minutes ago to inform you that St. Jude intended to file suit today against the Trustees of the University of Pennsylvania ("Penn") in connection with disputes arising under that certain Collaboration and Materials Transfer Agreement . . . As an alternative to filing suit, Mr. Hermes offered Penn the opportunity to enter into a "Stand Still Agreement" with St. Jude to enable the parties to discuss the disputes arising under the MTAs with the hopes of resolving those disputes and obviating the

> need for a lawsuit . . . In exchange . . . you have agreed on behalf of Penn that Penn will not file a lawsuit or initiate any other type of judicial or administrative proceeding . . . until no earlier than Friday February 3rd, 2012. On behalf of Penn, you explicitly acknowledge that there are no restrictions on St. Jude's ability to initiate legal proceedings related to the MTAs including, but not limited to, a federal court lawsuit against Penn in the Western District of Tennessee at any time after 3:00pm EST on Tuesday January 31, 2012 in the event that Penn has not executed a Stand Still Agreement . . .

Id. at 5-6. According to St. Jude, White responded that she "Understood and confirmed" the terms of the e-mail, and when the deadline for settlement passed, the parties had not reached an agreement. Id. at 6.

b. Procedural History

On July 11, 2012, St. Jude filed a breach of contract action against the University in the Western District of Tennessee. See St. Jude Comp., MTD Ex. A-1. St. Jude sought eight forms of preliminary and permanent injunctive relief: (1) specific performance of the 2003 and 2007 MTAs and to instruct the University to make submissions to journals crediting Dr. Campana and St. Jude's with the use of chimeric antigen receptors ("CAR"), St. Jude Comp. at ¶ 85 (1)-(4), and (2) an order that (a) the University enter into a Joint Materials Transfer Agreement covering the distribution of materials that

contain the CAR, (b) the University not enter into an agreement to commercialize any product containing the CAR without St. Jude's approval, and (c) directs the University to provide St. Jude with a list of everyone to whom it had distributed the CAR or CAR coding sequence and a copy of all patent applications for inventions containing the CAR or the CAR coding sequence. Id. at ¶ 85 (5)-(8). Finally, St. Jude sought actual, compensatory, and punitive damages, as well as the imposition of a constructive trust or lien on "the Materials, and any construct, progeny, portions, replications or derivatives of the Materials". Id. at ¶ 85 (9)-(10).

On August 2, 2012, the University moved to dismiss the Tennessee action for lack of personal jurisdiction, or, in the alternative, to transfer the action to this District. See Penn MTD, St. Jude MTD Ex. C-1.

Meanwhile, in July of 2012, the University filed a complaint in this Court, which it amended in September of that year. In its amended complaint, the University alleges tortious interference with prospective contractual relations and seeks a declaratory judgment stating that it has not materially breached the 2003 and 2007 agreements and that the 2003 agreement has been terminated.

St. Jude moved to dismiss the entire action without prejudice on the ground that the Tennessee action was pending

and asserted that the University's claims were compulsory counterclaims in that action. St. Jude alternatively moved this Court to dismiss Count I of the University's complaint which alleged tortious interference with prospective contractual relations for failure to state a claim on which relief can be granted, arguing first that Noerr-Pennington barred the claim, and also that the University had failed to allege sufficient facts to support its claim, see Def. MTD at 1, 16, 24.

On October 10, 2012, the United States District Court for the Western District of Tennessee transferred its case to this Court pursuant to 28 U.S.C. § 1404(a). We soon after consolidated the actions.

As St. Jude acknowledges, "[t]he transfer moots the first part of St. Jude's Motion to Dismiss or Stay, which seeks dismissal or stay of this action pursuant to the first filed and compulsory counterclaim rules". St. Jude Reply at 1. We thus consider the second part of St. Jude's motion, by which it aims to dismiss Count I of the amended complaint.

II. Analysis

The gravamen of the University's complaint is that "St. Jude first asserted an interest in the June Construct in 2011, but delayed litigation until the middle of 2012, when the University and Novartis were actively involved in negotiation of

a major collaboration agreement." Am. Comp. ¶ 37. The University further argues that St. Jude knew it was not entitled to the relief it sought, including the injunctive relief, id. at ¶ 43, and instead, "St. Jude filed the Tennessee Complaint with the intent that the public disclosure of its baseless allegations and requests for injunctive relief therein would disrupt the negotiations between the University and Novartis." Id. at ¶ 47.

St. Jude responds that this claim is barred by the Noerr-Pennington doctrine, and, in the alternative, that the University's amended complaint fails to state a claim for tortious interference with contractual relations on which relief can be granted. MTD at 16, 24.

a. Choice of Law

The parties dispute whether Tennessee law or Pennsylvania law governs the University's tort claim. As a federal court sitting in diversity, we are to apply the choice of law rules of our forum state, Pennsylvania. Lacey v. Cessna Aircraft Co., 932 F.2d 170, 187 (3d Cir. 1991) (citing Klaxon Co. v. Stentor Electric Mfg. Co., 313 U.S. 487 (1941)).

Under Pennsylvania's choice of law scheme, we must first determine whether a true conflict exists between the laws of the two states.[5] If it does, we consider "the governmental interests underlying the issue and determine which state has the

[5] With regard to whose substantive law Pennsylvania's choice of law rules would direct us to use, St. Jude contends that where a party alleges the tortious filing of a lawsuit "Pennsylvania courts have generally applied the law of the state in which the allegedly wrongful litigation was filed." MTD at 24. (citing, inter alia, Rosen v. Tesoro Petroleum Corp., 582 A.2d 27, 31 (Pa. Super. Ct. 1990)).

The University argues that the Pennsylvania conflicts-of-law analysis focuses on which state has the greater interest in the application of its law, see Univ. Resp. at 23 n.5 (citing Toledo Mack Sales & Serv. v. Mack Trucks, Inc., No. Civ. 02-CV-4373, 2005 WL 724117, at *11 (E.D. Pa. Mar. 29, 2005)), and that Pennsylvania courts considering tortious interference claims "have routinely found that the state with the greatest interest in application of its law is the state where the business relationship at issue transpires." Id. (emphasis in original) (citing KDH Electronic Systems, Inc. v. Curtis Tech. Ltd., 826 F. Supp. 2d 782, 801 (E.D. Pa. 2011)). The University concludes that "[n]o part of the business relationship involves Tennessee" and so "Pennsylvania has the greatest interest in application of its laws under Pennsylvania conflicts of law principles." Id.

As we discuss, there is no true conflict between Tennessee and Pennsylvania law on tortious interference with contractual relations.

greater interest in the application of its law." Rosen v. Tesoro Petroleum Corp., 399 Pa. Super. 226, 231 (Pa. Super. Ct. 1990) (citing Cipolla v. Shaposka, 439 Pa. 563 (1970)).

Trau-Med of America, Inc. v. Allstate Ins. Co., 71 S.W.3d 691 (Tenn. 2002) set forth the elements of the tort of intentional interference with business relationships in Tennessee. In order to state such a claim, a plaintiff in Tennessee must show:

> (1) an existing business relationship with specific third parties or a prospective relationship with an identifiable class of third persons; (2) the defendant's knowledge of that relationship and not a mere awareness of the plaintiff's business dealings with others in general; (3) the defendant's intent to cause the breach or termination of the business relationship; (4) the defendant's improper motive or improper means; and finally (5) damages resulting from the tortious interference.

Id. at 701 (emphasis in original) (internal quotations and citations omitted).

The Tennessee Supreme Court observed that Tennessee courts had long recognized that "a defendant's malicious conduct preventing a third person from conducting business with the plaintiff was tortious and therefore actionable", id. at 698, but it expressed concern that "because this tort extends beyond situations in which there exists a valid contractual relationship, it could potentially infringe upon the principle

of free competition by holding liable those individuals engaged in legitimate business practices." Id. at 699. In order to address this concern, the court limited liability to "improper conduct extending beyond the bounds of doing business in a freely competitive economy." Id. at 700 (emphasis in original).

Pennsylvania law also recognizes a tort for intentional interference with prospective contractual relations whose elements are: "(1) a prospective contractual relation; (2) the purpose or intent to harm the plaintiff by preventing the relation from occurring; (3) the absence of privilege or justification on the part of the defendant; and (4) the occasioning of actual damage resulting from the defendant's conduct." Thompson Coal Co. v. Pike Coal Co., 488 Pa. 198, 208 (Pa. 1979) (citing Glenn v. Point Park College, 441 Pa. 474 (1971)). See also Kernaghan v. BCI Communications, 802 F. Supp. 2d 590, 596 (E.D. Pa. 2011) (reciting the same elements).

The elements of the tort under Pennsylvania law are similar to those under Tennessee law: the first and second elements of the Pennsylvania formula track the first three elements of the Tennessee approach, and the damages prong in both tests is much the same. As to the fourth requirement of the Tennessee formula -- that the defendant act with "improper motive or improper means" -- the Tennessee Supreme Court elaborated on this element by giving examples of improper means:

"those means that are illegal or independently tortious . . . and those methods that violate an established standard of a trade or profession, or otherwise involve unethical conduct." Trau-Med, 71 S.W.3d at 701 n.5. This prong is therefore cognate with the third prong of the Pennsylvania test.

The Pennsylvania Supreme Court in Glenn distinguished actions taken without "privilege or justification" from those "interferences which are sanctioned by the rules of the game which society has adopted" and actions within "the area of socially acceptable conduct which the law regards as privileged". Glenn, 441 Pa. at 482 (internal quotations omitted). Moreover, the policy underlying the two tests is similar: as Glenn's reasoning shows, the goal of the Pennsylvania scheme is to make actionable conduct that is outside of the "rules of the game" while insulating those engaged in legitimate business practices.

There is thus no true conflict between Tennessee and Pennsylvania law and we would not disserve Tennessee's interests by applying Pennsylvania law to the University's tortious interference claim. Cf. Rosen, 399 Pa. Super. at 233 (finding a true conflict where "either state's interests would be disserved by the application of the other state's law"). We will thus apply Pennsylvania law.

b. Noerr-Pennington Applicability

St. Jude argues that the University's claim is barred by the Noerr-Pennington doctrine, which protects parties who petition governments for redress from claims arising in response to that petitioning. See Cheminor Drugs, Ltd. v. Ethyl Corp., 168 F.3d 119, 122 (3d Cir. 1999) (citing Eastern R.R. Presidents Conference v. Noerr Motor Freight, 365 U.S. 127 (1961); United Mine Workers of Am. v. Pennington, 381 U.S. 657, (1965)). In California Motor Transport Co. v. Trucking Unlimited, 404 U.S. 508, 510 (1972), the Supreme Court extended Noerr-Pennington to include protection for citizens who petition for relief through the courts. See also Professional Real Estate Investors, Inc. v. Columbia Pictures Indus., 508 U.S. 49, 56-57 (1993) ("PRE").

To be sure, Noerr-Pennington immunity arose in the antitrust context, but as our Court of Appeals has explained it has "by analogy extended the Noerr-Pennington doctrine to offer protection to citizens' petitioning activities in contexts outside the antitrust area as well." We, Inc. v. City of Philadelphia, 174 F.3d 322, 326-27 (3d Cir. 1999).

Noerr-Pennington does not, however, protect "sham" petitioning, that is, "petitioning activity 'ostensibly directed toward influencing governmental action [but that] is a mere sham to cover . . . an attempt to interfere directly with the

business relationships of a competitor." PRE, 508 U.S. at 56 (quoting Noerr, 365 U.S. at 144). Thus, Noerr-Pennington covers the conduct St. Jude engaged in here -- an issue the University disputes, as we discuss below -- and so we must determine whether that conduct was a "sham" precluding immunity.

1. Noerr-Pennington And The Right To Petition

The University first argues that Noerr-Pennington does not protect St. Jude because our Court of Appeals has limited the doctrine's application outside of the antitrust field to protecting the right to petition. Univ. Resp. at 19. In support, the University cites We, Inc., id., in which the court explained that "the purpose of Noerr-Pennington as applied in areas outside the antitrust field is the protection of the right to petition." Id. at 327. The University's argument assumes that this case does not implicate that right.

But courts for decades have held that the right to petition encompasses the right to bring a lawsuit. As the Supreme Court explained over forty years ago in in California Motor Transport, "Certainly the right to petition extends to all departments of the Government. The right of access to the courts is indeed but one aspect of the right of petition." Id.

at 510 (citing Johnson v. Avery, 393 U.S. 483, 485 (1969)).[6] See also Cheminor Drugs, 168 F.3d at 122 ("[Noerr-Pennington] immunity extends to persons who petition all types of government entities - legislatures, administrative agencies, and courts"); Brownsville Golden Age Nursing Home, Inc. v. Wells, 839 F.2d 155, 160 (3d Cir. 1988) (explaining that the right to petition protected by the Noerr-Pennington line includes the right to bring suit). We thus do not find support in the caselaw for the distinction the University seeks to draw between petitioning and bringing a lawsuit. To the contrary, it remains black letter law that lawsuits constitute a form of protected petitioning under Noerr-Pennington.

The University next argues that its tortious interference claim is not only based on St. Jude's filing of the lawsuit, but also on "the fact that St. Jude made a baseless and

[6] Of late the breadth of this holding has not gone unquestioned. In Borough of Duryea v. Guarnieri, 131 S. Ct. 2488 (2011), Justices Scalia and Thomas expressed doubt in their concurring opinions that the Petition Clause encompasses lawsuits. See id. at 2503 (Scalia, J., concurring) ("I find the proposition that a lawsuit is a constitutionally protected 'Petition' quite doubtful"). But as Justice Kennedy, writing for the seven-Justice majority in Guarnieri, explained, "[t]his Court's precedents confirm that the Petition Clause protects the right of individuals to appeal to courts and other forums established by the government for resolution of legal disputes." Id. at 2494 (quoting, inter alia, Sure-Tan, Inc. v. NLRB, 467 U.S. 883, 896-97 (1984), for the proposition that "the right of access to courts for redress of wrongs is an aspect of the First Amendment right to petition the government."). We thus conclude that Guarnieri does not foreclose the application of Noerr-Pennington to petitions that take the form of lawsuits.

unfounded demand for preliminary injunctive relief in the Tennessee Action that is unwarranted by the MTAs at issue, and it made this demand with the specific purpose of interfering with the Univer[s]ity's business relations." Univ. Resp. at 22. The University contends that "St. Jude has come forward with no authority that supports that unfounded requests for injunctive relief, made with bad motive, are immunized under Noerr-Pennington." Id. St. Jude's request for injunctive relief was part of the lawsuit, so the University's argument -- that the allegedly "baseless and unfounded demand" is a separate activity not protected under Noerr-Pennington -- does not persuade. Instead, the University's contention bears on the determination of whether the suit was a sham so as not to warrant Noerr-Pennington protection, and we will consider it later during our analysis of that question below.

2. Deciding Noerr-Pennington Based On A Motion To Dismiss

We next turn to the University's argument that "it would be inappropriate for this Court to dismiss the University's common law tort claim at the motion to dismiss phase based on St. Jude's assertion of an affirmative Noerr-Pennington defense." Univ. Resp. at 20.

This contention appears to rest on two arguments. First, the University claims that because Noerr-Pennington is an affirmative defense it cannot form the basis for a Rule 12(b)(6) motion. Id. at 20. Next, the University suggests that whether Noerr-Pennington applies is a question of fact that cannot be decided at the motion to dismiss stage. Id. We address each argument in turn.

The University relies on In re Adams Golf, Inc. Securities Litig., 381 F.3d 267 (3d Cir. 2004), for the proposition that "an affirmative defense may not be used to dismiss a plaintiff's complaint under Rule 12(b)(6)." Id. at 277. Jones v. Bock, 549 U.S. 199 (2007), makes clear that this principle is not unvarying -- an affirmative defense may form the basis for dismissal on a 12(b)(6) motion:

> A complaint is subject to dismissal for failure to state a claim if the allegations, taken as true, show the plaintiff is not entitled to relief. If the allegations, for example, show that relief is barred by the applicable statute of limitations, the

> complaint is subject to dismissal for failure to state a claim; that does not make the statute of limitations any less an affirmative defense . . . Whether a particular ground for opposing a claim may be the basis for dismissal for failure to state a claim depends on whether the allegations in the complaint suffice to establish that ground, not on the nature of the ground in the abstract.

Id. at 215. Adams Golf thus does not carry the weight the University claims it does.[7]

[7] Adams Golf is also distinguishable from this case in that in that case the defendant bore the burden of proving the asserted defense, loss causation. The plaintiffs had brought an action alleging materially false or misleading statements in violation of Sections 11 and 12(a)(2) of the Securities Act of 1933. Those Sections do not require a plaintiff to prove loss causation in order to state a claim, but a defendant may argue as an affirmative defense that any misstatements did not cause a loss. See Adams Golf, 381 F.3d at 277. Our Court of Appeals found that the district court had improperly granted the defendant's motion to dismiss based on this affirmative defense because "[u]nder sections 11 and 12(a)(2), plaintiffs do not bear the burden of proving causation." Adams Golf, 381 F.3d at 277.

A Noerr-Pennington defense differs from the negative causation defense at issue in Adams Golf in that under Noerr-Pennington the plaintiff bears the burden of proving that the petitioning activity is a sham undeserving of Noerr-Pennington protection. As the Supreme Court explained in PRE, because "[t]he existence of probable cause to institute legal proceedings precludes a finding that an antitrust defendant has engaged in sham litigation", proving that litigation is a sham "requires the plaintiff to prove that the defendant lacked probable cause to institute an unsuccessful civil lawsuit and that the defendant pressed the action for an improper, malicious purpose", PRE, 508 U.S. at 62. See also In re Flonase Antitrust Litig., 795 F. Supp. 2d 300, 311 (E.D. Pa. 2011) ("under PRE, the burden falls on the party invoking the sham exception, here the Plaintiffs, to show that the conduct at issue constitutes a sham").

Instead, as the Supreme Court stressed in the language from Jones v. Bock quoted above, the question of whether an affirmative defense may form the basis for dismissal under Rule 12(b)(6) is one of whether a court can determine, taking all allegations as true, that the plaintiff is not entitled to relief as a matter of law. This question brings us to the University's second argument -- that Noerr-Pennington applicability is a question of fact that cannot be decided at this stage.

In deciding a motion to dismiss, we "accept all factual allegations as true, construe the complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the complaint, the plaintiff may be entitled to relief." Grammer v. John J. Kane Reg'l Ctrs.-Glen Hazel, 570 F.3d 520, 523 (3d Cir. 2009). We may grant a motion to dismiss under Rule 12(b)(6) if a complaint does not "contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" Ashcroft v. Iqbal, 556 U.S. 662, 678 (2009).

To be sure, the question of whether litigation is a sham can be a fact question for the jury, see In re Flonase, 795 F. Supp. 2d at 311. But as the Supreme Court explained in PRE, when "there is no dispute over the predicate facts of the underlying legal proceeding, a court may decide probable cause

[and thus Noerr-Pennington applicability] as a matter of law,"[8] PRE, 508 U.S. at 63. District courts in other circuits have recognized this and granted motions to dismiss on Noerr-Pennington grounds. See, e.g., Pennwalt Corp. v. Zenith Labs., Inc., 472 F. Supp. 413, 424 (E.D. Mich. 1979); Nursing Registry, Inc. v. Eastern North Carolina Regional Emergency Medical Services Consortium, Inc., 959 F. Supp. 298, 305 (E.D.N.C. 1997).

Here, all facts relevant to the determination of Noerr-Pennington applicability are undisputed and contained within the record we may consider in deciding this motion to dismiss. As our Court of Appeals explained in Pryor v. National Collegiate Athletic Ass'n, 288 F.3d 548, 560 (3d. Cir. 2002), in deciding a motion to dismiss under Rule 12(b)(6) we may consider "documents which are attached to or submitted with the complaint, as well as legal arguments presented in memorandums or briefs and arguments of counsel. Further, documents whose contents are alleged in the complaint and whose authenticity no party questions . . . may be considered." Id. (emphasis in original) (citation omitted). We may also consider matters of

[8] Cheminor confirms that courts may in some cases make Noerr-Pennington determinations as a matter of law. There, our Court of Appeals affirmed the grant of summary judgment with regard to state tort claims on the basis that such claims were barred by Noerr-Pennington. See Cheminor, 168 F.3d at 128-29.

public record. See Pension Benefit Guar. Corp. v. White Consol. Indus., Inc., 998 F.2d 1192, 1196 (3d Cir. 1993).

What gave rise to the claim of tortious interference -- the suit that St. Jude filed in the Western District of Tennessee -- is contained within the record of that earlier suit, which we have now consolidated with this action. Moreover, identical copies of the contracts giving rise to that first suit -- the 2003 and 2007 MTAs -- are attached to the University's complaint and to St. Jude's motion to dismiss, and neither party disputes the authenticity of these documents.

The only factual issue that the parties seem to dispute regarding the claim is St. Jude's intent in filing the motion, but, as we will soon discuss, the question of intent would only be relevant if we were to find that the action itself was a sham, which we do not. Thus, we find that we may consider the application of Noerr-Pennington at this stage.

3. Noerr-Pennington's Application To Pennsylvania Tort Claims

Finally, we turn to the University's argument that courts have never applied Noerr-Pennington to Pennsylvania state law tort claims in an action that does not also involve state or federal antitrust claims. Univ. Resp. at 20-21. As we explained above, we will decide the University's tort claim according to Pennsylvania state law.

The University argues that in Cheminor, the "Third Circuit applied the doctrine to New Jersey state law claims in conjunction with its application of the doctrine to federal and state antitrust claims." Id. at 20. It contends that Cheminor is thus distinguishable from the instant case where "there are no state or [federal] antitrust claims" and "the activity that underlies the University's common law tort claim is outside of the antitrust context." Id. at 21. The University argues that Cheminor relied on a "prediction that the New Jersey Supreme Court would so apply the doctrine to tort claims under New Jersey law", and "no court has made a similar prediction as to what the Pennsylvania Supreme Court would do". Id.

St. Jude counters that the University "offers no basis for determining that a Pennsylvania court would reach any conclusion different from the New Jersey courts on this question." St. Jude Reply at 5.

The distinction between Pennsylvania law here and New Jersey law in Cheminor is unconvincing. First, the Third Circuit in Cheminor did not rely on existing New Jersey state law in reaching its conclusion. Instead, it found that "New Jersey has not yet decided whether the Noerr-Pennington doctrine 'extends beyond antitrust law to tort liability'", but found "no persuasive reason why these state tort claims, based on the same petitioning activity as the federal claims, would not be barred by the Noerr-Pennington doctrine." Cheminor, 168 F.3d at 128. Although here the state tort claim does not accompany antitrust claims, Pennsylvania courts have recognized that Noerr-Pennington immunity extends beyond the anti-trust context. See, e.g., Wawa, Inc. v. Alexander J. Litwornia & Assoc., 817 A.2d 543, 546 (Pa. Super. 2003); DeSimone, Inc. v. Philadelphia Authority for Indus. Dev., No. 002707, 2003 WL 21390632, at *5 n.7 (Pa. Com. Pl. June 10, 2003).

The limited Pennsylvania jurisprudence regarding Noerr-Pennington suggests that the Pennsylvania courts hew closely to the Third Circuit's interpretation of the doctrine. In Wawa, Inc. v. Alexander J. Litwornia & Assoc., 817 A.2d 543 (Pa. Super. 2003), for example, the Superior Court adopted the reasoning of the Third Circuit governing Noerr-Pennington on several grounds. See id. at 547-48 (quoting Barnes Foundation v. Twp. of Lower Merion, 242 F.3d 151

(3d Cir. 2001), for the impact of Noerr-Pennington on suits brought to stifle First Amendment activity and citing Cheminor for the principle that a material misrepresentation affecting the core of a litigant's case may preclude Noerr-Pennington immunity). See also, e.g., Sudarkasa v. Glanton, 57 Pa. D. & C. 4th 472, 500-01 (Pa. Com. Pl. 2002) (relying on Barnes Foundation).

Importantly, the Pennsylvania courts have followed our Court of Appeals in applying Noerr-Pennington in Pennsylvania tort cases outside the antitrust context. In Brownsville Golden Age Nursing Home v. Wells, 839 F.2d 155 (3d Cir. 1988), for example, our Court of Appeals upheld the dismissal of the plaintiff's tort law claims of malicious abuse of process and tortious interference with contractual relationships, finding that Noerr-Pennington barred liability for "damage caused by inducing legislative, administrative, or judicial action", id. at 160.

In Sudarkasa, the Philadelphia Court of Common Pleas upheld a trial court's nonsuit verdict on the reasoning that Noerr-Pennington barred the plaintiff's tortious interference with contract claim. Id. at 498-501. In doing so, the Court relied on the principle articulated in Brownsville Golden Age Nursing Home that "actions giving rise to the interference with contractual relations are not improper where

they 'foster a social interest of greater public import than is the social interest invaded'" and "[o]f great social interest is the exercise of the First Amendment right to petition the government." Sudarkasa, 57 Pa. D. § C. 4th at 500 (quoting Brownsville, 839 F.2d at 159).

We predict that the Pennsylvania courts would likely find Noerr-Pennington applicable to the University's tort claim here, and St. Jude will be immune from suit based on its claim originally made in the Western District of Tennessee unless that litigation is a sham.

c. Whether St. Jude's Litigation Was A "Sham"

The Supreme Court outlined a two-part definition of "sham" activity in PRE, explaining that the inquiry is initially -- and often finally -- an objective one. In order for a suit to be a "sham," it "must be objectively baseless in the sense that no reasonable litigant could realistically expect success on the merits. If an objective litigant could conclude that the suit is reasonably calculated to elicit a favorable outcome, the suit is immunized under Noerr", PRE, 508 U.S. at 60. See also Columbia v. Omni Outdoor Advertising, Inc., 499 U.S. 365, 381 (1991) (whether an activity is a sham is determined by objective criteria). Only if the suit is objectively without merit can a court consider a litigant's subjective motivation:

"Under this second part of our definition of sham, the court should focus on whether the baseless lawsuit conceals an attempt to interfere directly with the business relationships of a competitor, through the use [of] the governmental process -- as opposed to the outcome of that process . . . .", PRE, 508 U.S. at 60-61 (emphasis in original) (internal citations and quotations omitted).

A suit is objectively baseless if the litigant did not have probable cause to institute legal proceedings. See id. at 62 ("[t]he existence of probable cause to institute legal proceedings precludes a finding that an antitrust defendant has engaged in sham litigation"). Probable cause "requires no more than a reasonable belief that there is a chance that a claim may be held valid upon adjudication". Id. at 62-63 (internal citations, quotations and alterations omitted).

Under PRE, the party alleging that the litigation is not protected by Noerr-Pennington bears the burden of demonstrating that the challenged conduct was a sham, and "[i]f an objective litigant could conclude that the suit is reasonably calculated to elicit a favorable outcome, the suit is immunized under Noerr, and a[] claim premised on the sham exception must fail." Id. at 60.

As we described at length above, the action giving rise to the University's tort claim was the breach of contract

claim St. Jude originally filed in the Western District of Tennessee seeking eight forms of preliminary and permanent injunctive relief as well as actual, compensatory, and punitive damages and the imposition of a constructive trust or lien on the Materials and their derivatives. See St. Jude Comp., MTD Ex. A-1.

St. Jude points out that the 2003 and 2007 MTAs apply to "any progeny, portions, [and] unmodified derivatives" of the Campana Construct, 2003 MTA, Am. Comp. Ex. D at ¶ 1, and the 2007 MTA requires that the University confer with St. Jude to determine St. Jude's ownership interests before filing a patent application or commercializing any "product which contains a portion of the Materials, is derived from the Materials, or which could not have been produced but for the use of the Materials." 2007 MTA, Am. Comp. Ex. E at ¶ 5. St. Jude thus argues that in order to meet its burden of showing that the Tennessee litigation was a sham, the University would have to allege facts that, if proven, would show that no reasonable litigant could have believed that any portion of Dr. June's research included progeny, portions, or unmodified derivatives of the Campana Construct or contained, incorporated, used, included a portion of, was derived from, or could not have been produced but for the use of the Campana Construct. MTD at 18-19.

St. Jude contends that instead of alleging facts to support these claims, the amended complaint suggests that the Campana Construct was used in developing the Penn Immunotherapy. St. Jude points to paragraph twelve of the amended complaint where the University avers that "Dr. June asked Dr. Campana for a sample of the Campana Construct that his laboratory could modify to create a lentiviral vector for pre-clinical, non-human testing for cancer", Am. Comp. ¶ 12. It also points to paragraph fifteen where the University explains that Dr. June's research involved "modification of excised segments of the Campana Construct and development of the Penn Immunotherapy." Id. ¶ 15. St. Jude also notes that in its November 22, 2011 letter seeking to terminate the MTA, the University wrote that "Dr. June's construct has been significantly modified from that provided by Dr. Campana and is currently in use in clinical trials." Id. Ex. F at 2.

St. Jude argues that in light of these contentions, and although the University may argue with regard to the breach of contract and declaratory relief claims either that it did not publish or seek to commercialize the Campana Construct, or that its use of the Construct was not encompassed in the MTAs, "it is preposterous to contend that it is 'objectively unreasonable' for St. Jude to have alleged in the [Tennessee action] that the MTAs' references to 'progeny' and 'portions' of the Materials,

constructs 'derived from' the Materials, and 'use' of the Materials, bring these modifications within the Agreements' scope." MTD at 20.

We agree. Rather tellingly, Count II of the University's amended complaint on its face bolsters St. Jude's position that there was ambiguity about the role of the Campana Construct in the research on which Dr. June published and the products the University sought to commercialize. Such ambiguity gives rise to a "reasonable belief that there is a chance that a claim may be held valid upon adjudication", PRE, 508 U.S. at 62-63.

In this Count, the University seeks a declaratory judgment that it "has not materially breached the 2003 MTA", that "the 2003 MTA has been terminated", and that "the University has not materially breached the 2007 MTA." Am. Comp. ¶ 75 (b)-(d). In support of its claim the University maintains that "[t]here is a real and actual controversy between the parties as to whether the University has materially breached the Agreements as alleged in the Tennessee Complaint." Id. ¶ 71. St. Jude's complaint, which alleges a material breach of the MTAs, see St. Jude Comp. ¶¶ 69-72, 82-84, confirms this position. Indeed, St. Jude's breach of contract claim and the University's prayer for declaratory judgment perform cognate functions of determining the parties' rights under their

contracts. See, e.g., Note, Developments in the Law: Declaratory Judgments, 1941-1949, 62 Harv. L. Rev. 787, 805-17 (1949) ("The declaratory judgment comprises an authoritative judicial statement of the jural relationships between parties to a controversy" and a prayer for declaratory relief is justiciable if "a coercive cause of action has already accrued to one of the parties with respect to that issue, or if it is relatively certain that coercive litigation will eventually ensue between the same parties if a declaration is refused"); E. Borchard, Declaratory Judgments 279 (the "broad objective" of declaratory judgments is "to settle and afford relief from uncertainty and insecurity") (2d ed. 1941) (internal quotations omitted). By bringing a declaratory judgment action, the University implicitly but necessarily acknowledges an ambiguity as to contractual rights that makes reasonable St. Jude's belief that its claims would be held valid upon adjudication.

In contending that the litigation does not deserve Noerr-Pennington protection, the University does not specifically argue that the Tennessee litigation was a sham, but it does say that "St. Jude made a baseless and unfounded demand for preliminary injunctive relief in the Tennessee Action that is unwarranted by the MTAs at issue, and it made this demand with the specific purpose of interfering with the Univer[s]ity's business relations." Univ. Reply at 22.

As an example of the putative baselessness of the relief sought, the University notes that St. Jude requested a preliminary injunction ordering the University not to enter into any agreement to commercialize the Materials without St. Jude's permission despite St. Jude's concession that the damage it would suffer from unpermitted contracts was a deprivation of income. Id. at 22 n.4. Pointing to the well-established principle that an injunction is inappropriate where the potential injury is monetary loss, see, e.g., ECRI v. McGraw-Hill, Inc., 809 F.2dd 223, 226 (3d Cir. 1987), the University argues that "[t]his admission in and of itself demonstrates that the demand for relief was objectively meritless and unfounded." Univ. Reply at 22 n.4.

St. Jude persuasively responds that whether that prayer for injunctive relief lacks merit "is beside the point" because "[c]ourts have routinely held that as long as some of the claims in a complaint have a proper basis, the lawsuit is not a sham for Noerr-Pennington purposes." St. Jude Reply at 5 n.5. St. Jude points to Dentsply Int'l, Inc. v. New Tech. Co., No. 96-272 MMS, 1996 WL 756766 (D. Del. 1996), where Judge Schwartz held that "litigation will not be considered a 'sham' so long as at least one claim in the lawsuit has objective merit." Id. at *2. Dentsply relied on the language in PRE that in order to be a sham, the "lawsuit must be objectively

baseless," PRE, 508 U.S. at 60, and it cited Eden Hannon & Co. v. Sumitomo Trust & Banking Co., 914 F.2d 556 (4th Cir. 1990), where the Fourth Circuit found that a suit where the plaintiff succeeded on one of four claims was "hardly a sham." Id. at 565. Dentsply's reasoning is convincing, particularly since we are mindful of the "very narrow scope" of the sham exception. VIM, Inc. v. Somerset Hotel Ass'n, 19 F. Supp. 2d 422, 426 (W.D. Pa. 1998). We will not find that the Tennessee litigation -- which sought to determine the very rights that the University seeks to be decided here -- was a sham.

Finally, the University's allegations suggest that the timing of St. Jude's litigation in the Western District of Tennessee reveals a bad ulterior motive: "St. Jude improperly sought an injunction for which it had no basis and timed the Tennessee Action to disrupt the University's collaboration with Novartis." Univ. Resp. at 25. Because we have found that the Tennessee litigation was not a sham, we need not consider St. Jude's motive in filing that now-consolidated suit. See, e.g., PRE, 508 U.S. at 60 ("Only if challenged litigation is objectively meritless may a court examine the litigant's subjective motivation.").

III. Conclusion

For the foregoing reasons, we will grant St. Jude's motion to dismiss Count I of the University's complaint and its motion to dismiss Count I of the University's counterclaim.

BY THE COURT:

/S/ STEWART DALZELL, J.

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE'S CHILDREN'S RESEARCH HOSPITAL	:	NO. 12-4122

ORDER

AND NOW, this 12th day of April, 2013, upon consideration of defendant St. Jude Children's Research Hospital's motion to dismiss Count I of the amended complaint filed by the Trustees of the University of Pennsylvania (docket entry # 9), St. Jude's motion for leave to file a reply brief (docket entry # 19), and St. Jude's motion to dismiss Count I of the University's counterclaim (docket entry # 21), it is hereby ORDERED that:

1. St. Jude's motion to dismiss (docket entry # 9) is GRANTED;

2. St. Jude's motion for leave to file a reply brief (docket entry # 19) is GRANTED;

3. Defendant's second motion to dismiss (docket entry # 21) is GRANTED; and

4. By noon on April 26, 2013, St. Jude shall ANSWER the University's complaint.

BY THE COURT:

/S/ STEWART DALZELL, J.
Stewart Dalzell, J.

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	:	NO. 12-4122

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	:	NO. 13-1502

MEMORANDUM

Dalzell, J. November 13, 2013

I. Introduction

These actions concern the nature of an immunotherapy for cancer treatment that Dr. Carl June, M.D., Director of the Translational Research Program and a professor at the University of Pennsylvania ("the University" or "Penn"), developed. The parties' claims sound in patent and contract law, and the dispute centers on the question of whether Dr. June's immunotherapy (the "June Construct") contains "material" within the meaning of two Materials Transfer Agreements the University executed with St. Jude Children's Research Hospital ("St. Jude").

We here consolidate the earlier contract action (C.A. No. 12-4122) and the later patent action (C.A. No. 13-1502) and consider St. Jude's motion for partial summary judgment in the contract action and Penn's partial motion to dismiss St. Jude's counterclaims in the patent action.[1] We also consider St. Jude's motion for a separate trial. For the reasons discussed herein, we will deny in part the motion to dismiss, deny the summary judgment motion, and deny the motion for a separate trial. We will then set a schedule for discovery and trial.

II. Procedural History

On April 12, 2013, we issued an opinion in which we detailed the procedural and factual history of this dispute. Trustees of Univ. of Pennsylvania v. St. Jude Children's Research Hosp., No. 12-4122, 2013 WL 1499518 (E.D. Pa. Apr. 12, 2013). Because those histories guide our consideration of the instant motions, and because the parties' recent submissions provide more information about the facts giving rise to the conflict, we will rehearse the procedural history briefly and the factual history in detail.

[1] We have jurisdiction over the contract claims pursuant to 28 U.S.C. § 1332 because the parties are diverse -- St. Jude is a citizen of Tennessee and the University is a citizen of Pennsylvania, see C.A. No. 12-4122 Am. Comp. ¶¶ 1-2, and the amount in controversy exceeds $75,000. We have jurisdiction over the patent action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

On July 11, 2012 St. Jude filed a breach of contract action against the University in the Western District of Tennessee seeking injunctive relief and damages on the ground that the University had breached two Materials Transfer Agreements ("MTAs" or "Agreements") the parties had executed. Apr. 20, 2013 Mem. at 6-7.

Eight days later, the University filed a breach of contract action here. It then submitted an amended complaint in that action in September of 2012.[2] On October 10, 2012 the United States District Court for the Western District of Tennessee transferred the St. Jude case to this District pursuant to 28 U.S.C. § 1404(a), and we consolidated the actions.

On March 19, 2013, the United States Patent and Trademark Office issued U.S. Patent No. 8,399,645, (the "'645 patent") entitled "Chimeric Receptors with 4-1BB Stimulatory Signaling Domain" to St. Jude. Three days later the University filed a separate action in this Court seeking a declaration that it was not infringing on that patent and that the patent was

[2] The amended complaint sought damages for tortious interference with prospective contractual relations and a declaratory judgment that the University did not materially breach the 2003 and 2007 Agreements and that the 2003 Agreement had been terminated. We dismissed the tort claim in our April 2013 Memorandum.

invalid, see C.A. No. 13-1502, Comp. ¶¶ 9, 34-39. St. Jude moved to dismiss, and on June 10, 2013 the University filed an amended complaint in which it again sought our declaration of its non-infringement and the patent's invalidity. See C.A. No. 13-1502, Am. Comp. ¶¶ 34-39.[3]

St. Jude filed an Answer and Counterclaims, asserting that Penn is infringing and contributorily infringing on the '645 patent by using and commercializing the June Construct, and that this infringement is willful. Through its counterclaims St. Jude seeks a judgment in its favor in C.A. No. 13-1502, a declaration that the patent is valid and enforceable and that Penn is infringing upon it and that such infringement has been willful and deliberate. It also seeks an injunction from further infringement or contributory infringement, and damages. See C.A. No. 13-1502 Counterclaims ¶¶ 22-34. Penn moves to dismiss the willful infringement claim. See C.A. No. 13-1502 Penn MTD.

When the University filed the patent action, we directed the parties to show cause why we should not consolidate it with the contract action, see C.A. No. 13-1502, Docket No. 4.

[3] St. Jude's motion to dismiss the original complaint is thus moot. See Fed. R. Civ. P. 15(a)(1)(B) (a party may amend its pleading once as a matter of course within twenty-one days after service of a motion under Rule 12(b)).

The University responded that it did not oppose consolidation, see April 26, 2013 epistolary submission. St. Jude responded by submitting a motion for partial summary judgment and positing that by the time the parties had submitted briefing in the patent case the contract case might be resolved by summary judgment. St. Jude Resp. to Order to Show Cause.

As an alternative to summary judgment, St. Jude moved for a separate trial on "[t]he question of whether the June Construct incorporates and was made with Material" under the MTAs. St. Jude MSJ at 23.

We thus consider here our initial suggestion of consolidation, the University's motion to dismiss St. Jude's counterclaim for willful infringement, and St. Jude's motion for partial summary judgment or, in the alternative, a separate trial.

III. Factual History

This action between the University and St. Jude concerns two MTAs between the parties, the "2003 MTA" and the "2007 MTA". We will describe the undisputed facts as the parties have presented them.[4]

[4] Where we draw the facts from one party's pleading, we will note any factual dispute by the other party.

A. The Campana Construct

The MTAs arose out of immunotherapy research Dr. Dario Campana and Dr. Chihaya Imai[5] conducted at St. Jude. In the early 2000s Dr. Campana developed a protein molecule called an "anti-CD19 chimeric antigen receptor" ("CAR"). Through a genetic process we will recount below, Dr. Campana inserted the CAR into T cells, a type of white blood cell that directs immune responses and attacks infected or cancerous cells.[6] One end of the CAR protruded from the T cell, enabling it to latch onto a tumor cell "antigen." St. Jude MSJ at 4 (citing Declaration of Dr. John Gray, Ex. to St. Jude MSJ, at ¶ 6). When the T cell connected with the antigen, the other end of the CAR directed the T cell to "attack and destroy" the target cell. Id.

[5] St. Jude, in its motion for summary judgment, refers to Drs. Campana and Imai collectively as "Campana". Though we recognize Dr. Imai's contributions -- and his existential independence from Dr. Campana -- we will adopt that convention here for the sake of simplicity in a matter that is already quite complex. We also note that Dr. Campana is no longer with St. Jude and now works as a professor in the Department of Pediatrics at the National University of Singapore. Campana Dec., Ex. to St. Jude MSJ, at ¶ 1.

[6] For more information, see, e.g., National Institute of Allergy and Infectious Diseases, "Immune System", available at http://www.niaid.nih.gov/topics/immunesystem/immunecells/pages/tcells.aspx.

Dr. Campana reproduced this result by developing a cDNA, a DNA[7] molecule containing a nucleotide[8] sequence encoding the structure of the CAR, and inserting it into the DNA of a T cell. Thus, when the T cell replicated, the new T cells also included the CAR. Id. Through this process Dr. Campana "creat[ed] a population of T cell progeny that can be used to treat CD19+ B-cell cancers, such as acute and chronic leukemia and non-Hodgkin's lymphoma". St. Jude MSJ at 5. In order to insert the CAR-encoded cDNA into the T cell DNA, Dr. Campana used a "retroviral 'vector'" as a "molecular delivery vehicle". Id.

[7] When James Watson and Francis Crick introduced the world to their depiction to the now-iconic double helix of DNA in their brief note in the 25 April 1953 issue of Nature, "Molecular Structure of Nucleic Acids: A Structure for Deoxyribase Nucleic Acid", they ended their short article with what is almost certainly the most striking understatement in the history of science: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." Their work won them the Nobel Prize in Medicine and Physiology on December 10, 1962. The Nature note and its double helix are reproduced in Horace Freeland Judson, The Eighth Day of Creation 196-98 (1979) (hereinafter "Judson").

[8] As Judson points out at 29, nucleic acids' "presence in all cells was as quickly demonstrated" as their chemistry was, but "[t]heir function remained unknown." By the beginning of the twentieth century "the three constituents of nucleic acids had been described," id., and the last, known as a base, was a "three-piece subassembly . . . called a nucleotide, a homely word, precise, indispensable, and ubiquitous in this science, indeed much like the word 'iamb' in poetics, for it expresses not just a particular sort of construction but a unit of length and even a category of significance." Id.

Dr. Campana presented his findings at an American Society of Hematology conference in San Diego, California, in December of 2003. St. Jude MSJ at 5; Penn Opp. at 3. After the conference, Dr. June wrote to Dr. Campana saying,

> Your data at ASH with the CD19 ScFv was striking. I was wondering if you might want to have an inter-institutional collaboration to test this? . . . I think that retroviruses are going to be problematic as vectors due to the leukemic risk, and the higher efficiency of the lentivirus is another reason making it attractive to switch. Would you consider letting my lab create the lentiviral vector from your construct, and then I can ship you transduced T cells to compare to the retroviral vector?

Dec. 10, 2003 E-mail from June to Campana, Campana Dec., Ex. to St. Jude MSJ, Ex. 4.

In order to facilitate this exchange, the parties entered into the first MTA at issue here on December 17, 2003. Id. at ¶ 13. That Agreement defined the "Material" St. Jude was transferring as "the anti-CD19-BB-ζ chimeric T-cell receptor construct, including any progeny, portions, unmodified derivatives and any accompanying know-how or data". 2003 MTA at ¶ 1, St. Jude MSJ Ex. A. The Agreement provided that "the Material will only be used to create a lentiviral chimeric T-cell receptor construct to be used in pre-clinical studies", id.

at ¶ 3, and "may not be used in humans" or "for any commercial purpose." Id. at ¶ 4. It further provided that the University would "not commercialize any product that contains Material without the prior written approval of St. Jude", id. at ¶ 8, that the University would jointly publish any "result[s] from the collaborative research study" with St. Jude, id. at ¶ 6, and that it would "notify St. Jude within sixty (60) days of filing any patent application which claims subject matter that contains or incorporates the Material or which claims a method of manufacture or use of the Material." Id. at ¶ 8.

Pursuant to the MTA, St. Jude sent the anti-CD19-BB-ζ chimeric receptor construct to the University, St. Jude MSJ at 7, Penn Resp. in Opp. at 7. After receiving the construct, Drs. Milone and June sent e-mails requesting information about the gene sequence to Drs. Campana and Imai. Dr. June requested a sequence of the plasmid, and he asked, "how do you detect surface expression of the scfv; do you have an antibody to [do] it?" Dec. 17, 2003 E-mail from June to Campana, Campana Dec. Ex. 5. Dr. Campana responded by sending the sequence of the anti-CD19-BB-ζ and explained, "We detect surface expression with a goat-anti-mouse F(ab)2 biotin from Jackson Immunoresearch, followed by streptavidin PerCP from Becton Dickinson." Dec. 17,

2003 E-mail from Campana to June, Campana Dec. Ex. 5. Dr. Milone then wrote, "I realized that the sequence for the CD19-truncated receptor is likely to have a different 3' end compared with the other 2 constructs. We need to use PCR to transfer it to our lentivirus system. Could you tell me what sequence is at the 3' end of the CD19-truncated?" Dec. 23, 2003 E-mail from Milone to Imai, Campana Dec. Ex. 5. Dr. Imai responded with "files containing sequence for anti-CD19-truncated and MSCV-IRES-GFP retroviral vector." Dec. 23, 2003 E-mail from Imai to Milone, Campana Dec. Ex. 5.

Penn does not contest that St. Jude sent the construct and the gene sequence, but it argues that the sequence and the other information did not constitute "know-how" under the MTA because

> The sequence of a plasmid or DNA sequence, such as the CD19-BB-z CAR sequence included in the Attachment, is readily obtainable by a person skilled in the art of molecular biology using commonly employed sequencing techniques, as were widely available at the time the materials were received from St. Jude.

Penn Resp. in Opp. at 9, citing Milone Dep., Ex. C to Penn Resp. in Opp., at ¶ 7. Dr. Milone avers that it is "common practice amongst scientific and academic research institutions that, when one institution sends biological material such as a plasmid to

another, it also sends a text version of DNA sequences . . . so the recipient scientist does not have to independently sequence" the material, but that had St. Jude not provided the sequence, Dr. Milone "otherwise could have derived [the information] from [his] own sequencing of the biological materials provided by St. Jude." Milone Dep. at ¶ 7.

B. The June Construct

When Dr. June proposed using a lentiviral vector, rather than a retroviral vector, he and others at Penn, including Dr. Michael Milone, were "the first researchers to work with a lentiviral vector (a modified form of HIV-1) for immunotherapy in cancer patients, having determined that the use of a lentivirus was the most effective way to accomplish genetic modification of human T cells". Penn Resp. in Opp. at 7. Penn contends that Drs. Milone and June could not use the St. Jude CAR cDNA because it was designed to be introduced through a retroviral vector, and it thus "lacked the required sequences at the beginning and end of the DNA anti-CD19-BB-z chain to allow it to recombine into the University's pre-existing lentiviral vector." Penn Resp. in Opp. at 8, citing Milone Dec. Ex. C, at ¶ 11. Instead, Penn avers that Dr. Milone developed a separate "primer-based polymerase chain reaction ("PCR")" that would

generate a DNA sequence similar to the one that Dr. Campana had constructed but modified to contain "appropriate restriction enzyme sites on the ends to facilitate recombination into the University's lentiviral vector." Campana Dec. at ¶ 12. Thus, Penn alleges that this new sequence differed from the sequence in the Campana Construct in that it "included five nucleotide differences at the ends of the sequence" to facilitate incorporation into the lentiviral vector. Id. at ¶ 13.

Moreover, Penn contends that the new sequence differed from the sequence in the Campana Construct in that it contained a modified nucleotide in the CAR sequence leading to "an amino acid change from the original amino acid sequence encoded by the Campana construct." Id.

Dr. Milone also avers that "[t]he modified anti-CD19-BB-z did not contain any physical part of the Campana Construct. It was composed completely of nucleotides from Dr. June's laboratory during the PCR reaction", and "after the PCR process . . . the original Campana Construct physically existed as it did before the process." Id. at ¶ 14. Drs. Milone and June completed the June Construct by incorporating the modified anti-CD19-BB-ζ sequence into a lentiviral plasmid that had been created earlier in Dr. June's laboratory. Id. at ¶ 15. The

University thus describes the June Construct as a "modified derivative" of the Campana Construct. Penn Resp. in Opp. at 7.

St. Jude's account of the genetic makeup of the June construct appears similar to Penn's account in fact, if not in emphasis. St. Jude describes the June Construct as a "lentiviral vector clone" consisting of "the anti-CD19 cDNA provided by St. Jude, incorporated into a lentiviral vector delivery vehicle", St. Jude MSJ at 8. St. Jude asserts that "[t]he cDNA of the June Construct consisted of the identical approximately 1,500-base-pair sequence provided by St. Jude, with the exception of a single-base-pair difference that appears to be the kind of 'copying error' (or mutation) that can occur in a process called PCR amplification." Id. (emphasis in original). The "exception" to which St. Jude refers appears to be the difference Dr. Milone cited as causing an amino acid change. St. Jude thus concludes that "even with the base pair difference, the June Construct contains the largest possible nucleotide 'portion' -- all but one base pair out of approximately 1,500 -- of the anti-CD19 cDNA 'Material' St. Jude provided, and it was made with the accompanying data and know-how St. Jude provided." Id. at 8-9.

With regard to the five nucleotide differences at the end of the sequence, St. Jude contends that "all Penn did with

the anti-CD19 CAR cDNA it received from St. Jude was to copy it exactly using common polymerase chain reaction ("PCR") techniques, and to add five nucleotide base pairs at each end so the cDNA could be spliced into a lentiviral vector." St. Jude Reply at 4[9].

C. The 2007 MTA

In 2007 St. Jude sent Penn an e-mail saying that it had "reason to believe Dr. June may have sent the receptor to an investigator outside the University of Pennsylvania" and noted that it needed to determine whether "Dr. June is planning to conduct clinical trials using St. Jude materials", Jan. 11, 2007 e-mail from Hawkins to Donohue, Hawkins Dec., Ex. to St. Jude MSJ, Ex. 1.

Kurt Schwinghammer, then Director of Licensing at Penn, responded that Dr. June was planning to conduct a clinical trial, and that he had told Dr. Campana that he intended to do so. Feb. 5, 2007 E-mail from Schwinghammer to Hawkins, Hawkins Dec. Ex. 2. Three days later, St. Jude replied that Dr. Campana

[9] Penn opposed St. Jude's motion for leave to file a reply brief, and it objects to our consideration of that brief on a number of grounds, including that the brief's exhibits contain hearsay statements that we may not consider in deciding a motion for summary judgment. Penn Resp. in Opp. to Reply at 5. We will grant St. Jude leave to reply, and we will consider the legal arguments it raises in that brief, but we will not consider the exhibits appended to its reply.

would not object to clinical trials moving forward, but that from St. Jude's standpoint "a new clinical trial agreement will need to be executed between the University and St. Jude before clinical trials proceed." St. Jude MSJ at 9-10, quoting Feb. 8, 2007 e-mail from Hawkins to Schwinghammer, Hawkins Dec. Ex. 3. On February 28, 2007, St. Jude again wrote to Penn that "a new MTA for clinical use must be executed between the University and St. Jude to provide St. Jude with the appropriate protections." Id.

On April 16, 2007, Donald T. Deyo, Director of Corporate Contracts in Penn's Office of Research Services, wrote, "[w]e acknowledge the necessity of a new MTA since the anti-CD19-BB-zeta receptor materials are now to be used in a clinical trial." Apr. 16, 2007 E-mail from Deyo to Hawkins, Hawkins Dec. Ex. 5.

On or about February 8, 2008, the parties executed a second MTA, dated it October 2, 2007[10], allowing Dr. June to proceed with clinical trials. 2007 MTA, St. Jude MSJ Ex. B; Penn Resp. in Opp. at 4. That agreement contained the same

[10] We refer to this agreement, as the parties do, as the 2007 MTA.

definition of "Material" as found in the 2003 agreement.[11] 2007 MTA at ¶ 1.

D. Penn's Alleged Breaches

In April of 2009, Dr. Campana and Dr. June, with others, co-authored an article in Molecular Therapy, Campana Dec. ¶ 6, in which they noted that "[t]he cDNA for the CARs that contain a truncated form of the TCR-ζ intracellular domain . . . were generated at St[.] Jude's Children[;]s Research Hospital. These complete CAR sequences were amplified directly from the provided plasmids by PCR."[12] Campana Dec. Ex. 1 at 8.

In August 2011 Dr. June described the results of his clinical trials in articles in The New England Journal of Medicine, New Eng. J. Med. 8:725-733 (2011) and Science Translational Medicine, 2011; 3(95):95ra73. See St. Jude MSJ at 12, Exs. C and D. St. Jude contends, and Penn does not dispute, that "neither article . . . acknowledge[d] St. Jude as the source of the anti-CD19 CAR cDNA", St. Jude MSJ at 12. St. Jude wrote to Penn asking if the receptor used in the trials the articles described was the same receptor St. Jude had provided.

[11] The term in the 2007 Agreement is "Materials", rather than "Material", but the definition is the same.

[12] "PCR", or Polymerase Chain Reaction, is a method used to make large numbers of copies of specific DNA segments. See St. Jude MSJ at 8 n.5.

Hawkins Dep., Ex. to St. Jude MSJ, Ex. 6. Responding to this (and other inquiries) from St. Jude, Penn's director of legal affairs, Kathryn A. Donohue, wrote to St. Jude and said, "We incorporated the cDNA from Dr. Campana/St. Jude into the vector." St. Jude MSJ at 13 (quoting Sept. 22, 2011 E-mail from Donohue to Marsh, Watts Dec., Ex. to St. Jude MSJ, Ex. 2). Donohue included a diagram, above which she wrote, "In the schema below (from the NEJM paper), the large circle represents the entire vector, and **the portion of the vector that represents the St. Jude sequence** is circled in blue." Id. (emphasis in original). Donohue continued that the paper in which Dr. Campana was included as a co-author was "incorporated as ref #5 of the NEJM paper, and is an acknowledgment of Dr. Campana and St. Jude." Id. The parties dispute the significance of these communications, as we will discuss below.

St. Jude points out that when other researchers asked Dr. June for the construct, he told them they needed to obtain permission from Dr. Campana and St. Jude, see, e.g., Esther Allay Dec., Ex. to St. Jude MSJ, Ex. 6 (Nov. 19, 2011 e-mail from Dr. June to Dr. Stephen Gottschalk saying, "I would be happy to send you the BBz CAR. You would also need to get permission from dario campana [sic] at St. Jude. He sent us a retroviral plasmid in 2003, and we modified the CAR and adapted

for lentivirus."); Ex. 3 (Sept. 27, 2011 e-mail from Dr. June to a researcher at the National Cancer Center in Korea saying "[i]t turns out that you also need an MTA from Dr. Dario Campana at St. Jude/Singagpore [sic], or at least his permission, for me to send you the plasmid. We originally made the CD19:BB:Z lentiviral vector from a retroviral vector that Dario made.").

Dr. June's declaration suggests a different understanding. He avers that "[a]t no point have I ever understood the [MTAs] . . . to restrict the transfer of the June Construct, developed in my laboratory at the University, since the June Construct does not physically contain any of the Material provided by St. Jude under the 2003 MTA." June Dec., Ex. A to Penn Resp. in Opp., at ¶ 14. Dr. June says that before August 29, 2011 he "sent samples of the June Construct to researchers at other universities . . . without directing them to St. Jude for permission." Id. at ¶ 15.

On August 29, 2011, an Associate General Counsel for St. Jude, McGehee Marsh, sent a letter to Donohue referring to Dr. June's recent publications and saying, "[w]e simply need to know if the receptor used in the clinical trial is the one obtained from St. Jude. If it was, we would like to understand why Dr. June did not acknowledge St. Jude's contribution . . . ." Aug. 29, 2011 Letter from Marsh to Donohue, June Dec. Ex. 1.

After Penn received this letter, Dr. June avers that "solely in order to avoid a legal dispute and out of an abundance of caution," he "directed any researchers who wanted [him] to send them the June Construct to St. Jude so that St. Jude would not later take issue with such transfer." June Dec. ¶ 16.

In a November 22, 2011 letter, the University informed St. Jude that it wished to terminate the MTA[13]. No. 12-4122 Am. Comp. Ex. F.

The University contends that it "contractually agreed to exclusively negotiate with Novartis regarding a ground-breaking collaboration that would develop Dr. June's cellular immunotherapy for general cancer patient use." Id. ¶ 27. According to the amended complaint, "The University . . . actively negotiated with Novartis a collaboration under which the University would receive funding that would allow it to continue with clinical trials of the Penn Immunotherapy without undue delay", and "[a]s of July 10, 2012, the University and Novartis had made substantial progress towards reaching an

[13] In its amended complaint the University says this letter informed St. Jude it wished to terminate the 2003 MTA, but the letter refers to the 2007 MTA in its subject line and does not make clear which MTA the University sought to terminate. In any event, the distinction does not affect our decision here.

agreement that would allow continued development of the Penn Immunotherapy Technology." Id. ¶¶ 28-29.

In St. Jude's counterclaims in the patent action, St. Jude avers, and Penn does not dispute, that Penn "entered an 'alliance' and 'an exclusive global research and licensing agreement' with Novartis in August 2012 to commercialize the cells, lentiviral vectors, and CARs that Penn now calls 'CTL019'", St. Jude Counterclaim ¶ 15, Ex. B. See also Press Release, Perelman School of Medicine, University of Pennsylvania, "University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients" (Aug. 6, 2012) (available at http://www.uphs.upenn.edu/news/News_Releases/2012/08/novartis/).

On January 10, 2013, in-Pharma Technologist.com, a Web site that provides "Breaking News on Global Pharmaceutical Technology & Manufacturing", reported that Novartis had purchased a manufacturing plant with "the technological competence and equipment to support both clinical and commercial production for CTL019 as well as other therapies in the area of human autologous cellular immunotherapy products." Id., St. Jude Answer, Ex. C, available at http://www.in-pharmatechnologist.com/content/view/print/728836. The article explained that "CTL019 is Novartis' first candidate CAR therapy

and is currently being studied as a test pilot at the University of Pennsylvania." Id. St. Jude avers that "one or more applications have been filed" with the U.S. Food and Drug Administration for the CTL019 cells, CTL019 lentiviral vectors, and CTL019 CARs. St. Jude Counterclaims ¶ 17.

St. Jude applied for a patent for the Campana Construct on July 12, 2012, and it received a patent on March 19, 2013, United States Patent No. 8,399,645, entitled "Chimeric Receptors with 4-1BB Stimulatory Signaling Domain" (the "'645 patent"). See St. Jude Counterclaims ¶¶ 8, 18, 21. According to St. Jude, "The ['645 patent] generally discloses compositions and methods for genetically modifying human immune cells to enable them to manufacture chimeric antigen receptors . . . and then to recognize and attack certain types of cancer cells." Id. at ¶ 9.

IV. Consolidation

Under Fed. R. Civ. P. 42(a), we have "broad power" to consolidate cases that share "common question[s] of law or fact." Ellerman Lines, Ltd. v. Atlantic & Gulf Stevedores, Inc., 339 F.2d 673, 675 (3d Cir. 1964). Here, the facts underlying the patent suit are almost identical to those underlying the contract action. Indeed, in the amended

complaint in the patent action, Penn avers that "[t]he subject matter of the '645 patent directly relates to the same subject matter at issue in the [contract action]." No. 13-1502 Am. Comp. ¶ 27.

St. Jude opposed consolidation, apparently on the theory that its motion for summary judgment in the contract case was such a slam dunk that we would readily grant it, thereby clearing the path for victory in the subsequent patent case. Because, as we discuss below, we do not find that summary judgment is warranted, we are not persuaded by St. Jude's proposed approach.

We will thus consolidate the actions.

V. Penn's Motion to Dismiss

Penn moves to dismiss the allegations of willful infringement in St. Jude's counterclaim under Fed. R. Civ. P. 12(b)(6).

A. Standard of Review

Under Fed. R. Civ. P. 12(b)(6), a defendant may move the Court to dismiss a complaint on the ground that it fails to "state a claim upon which relief can be granted", and the moving defendant bears the burden of proving that this is so, see Fed.

R. Civ. P. 12(b)(6), see also Hedges v. United States, 404 F.3d 744, 750 (3d Cir. 2005).

As the Supreme Court held in Bell Atlantic Corp. v. Twombly, 550 U.S. 544 (2007) and Ashcroft v. Iqbal, 556 U.S. 662 (2009), in order to survive a Rule 12(b)(6) motion, "a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face'", Iqbal, 556 U.S. at 678 (quoting Twombly, 550 U.S. at 570). A claim is plausible "when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged", Iqbal, 556 U.S. at 678.

Penn argues here that St. Jude has failed to allege sufficient facts to state a claim for willful infringement.

As our Court of Appeals has explained post-Twombly and Iqbal, when considering a motion to dismiss under Fed. R. Civ. P. 12(b)(6), the district courts must engage in a two-part analysis:

> First, the factual and legal elements of a claim should be separated. The District Court must accept all of the complaint's well-pleaded facts as true, but may disregard any legal conclusions. Second, a District Court must then determine whether the facts alleged in the complaint are sufficient to show that the plaintiff has a "plausible claim for relief."

Fowler v. UPMC Shadyside, 578 F.3d 203, 210-11 (3d Cir. 2009). For the first part of this test, we refer to the facts as we have recounted them above.

In In re Seagate Technology, LLC, 497 F.3d 1360 (Fed. Cir. 2007), the Court of Appeals for the Federal Circuit held that in the patent context "to establish willful infringement, a patentee must show by clear and convincing evidence that the infringer acted despite an objectively high likelihood that its actions constituted infringement of a valid patent", id. at 1371. The Federal Circuit also held that if a patent holder demonstrated that the alleged infringer's conduct had met this objective test, the holder must then show that the risk "was either known or so obvious that it should have been known to the accused infringer." Id.[14]

St. Jude makes much of the issue of whether Seagate announced a new standard for pleading or for proving a claim of willful infringement, see St. Jude Resp. in Opp. at 5-7, arguing that the case "set forth a heightened standard for proving willfulness at trial, not for pleading it." Id. at 5. Penn

[14] The Federal Circuit's decisions on patent law are binding on our resolution of the dispute, as the Federal Circuit has exclusive appellate jurisdiction over cases in which our jurisdiction is based on federal patent law. Christianson v. Colt Industries Operating Corp., 486 U.S. 800, 807-08 (1988).

does not directly argue that Seagate does establish a heightened pleading standard for willful infringement claims, instead urging us to analyze St. Jude's claim under Fed. R. Civ. P. 8, see Penn MTD at 1.

Courts applying Seagate in the motion to dismiss context have not treated it as establishing a heightened pleading standard, but have instead found it to be an explanation of the elements of the cause of action of willful infringement. Under this reading, a plaintiff states a claim for willful infringement if it pleads sufficient factual matter, accepted as true, to allow us to "draw the reasonable inference that the defendant is liable", Iqbal, 556 U.S. at 678, for "act[ing] despite an objectively high likelihood that its actions constituted infringement of a valid patent" where the risk was either known or was so obvious that it should have been known. Seagate, 497 F.3d at 1371. See, e.g., MONEC Holding AG v. Motorola Mobility, Inc., 897 F. Supp. 2d 225, 235-36 (D. Del. 2012) (discussing Seagate as outlining the standard a plaintiff must meet in "prov[ing] a cause of action for willful infringement" and finding, in light of Seagate, that "a plaintiff alleging a cause of action for willful infringement must 'plead facts giving rise to at least a showing of objective recklessness of the infringement risk'", which requires

allegations of "'factual circumstances in which the patents-in-suit are called to the attention' of the defendants", id. at 236 (quoting St. Clair Intellectual Prop. Consultants, Inc. v. Hewlett-Packard Co., No. 10-425, 2012 WL 1134318, at *2-3 (D. Del. Mar. 28, 2012) (internal alterations omitted)).

We will thus apply the 12(b)(6) analysis we described above, treating Seagate as announcing the elements of the claim of willful infringement.

B. Discussion

1. Willful Infringement Claim

There can be no question that Penn knew of the patent -- Penn filed its action for non-infringement and non-enforceability on March 22, 2013, three days after the patent issued.

As we described above, St. Jude has alleged facts regarding Penn's partnership with Novartis that, if taken as true, demonstrate that Penn was commercializing CTL019 T cells, polynucleotides encoding CTL019 CARs, and CTL019 lentiviral vectors whose compositions are covered by the '645 patent. These facts suffice to state a claim that Penn acted in the face of an "objectively high likelihood" that it was infringing on a valid patent. This finding is consistent with other courts' analyses of motions to dismiss willful infringement claims.

See, e.g., Medtrica Solutions, Ltd. v. Cygnus Medical, LLC, No. 12-538, 2012 WL 5726799, at *1 (W.D. Wash., Nov. 15, 2012) ("The allegations that Medtrica has had notice of the '023 Patent since 2011 and has continued to make and sell the Appli-Kit and Revital-Ox . . . are sufficient to 'make out the barest factual assertion' to state a claim for willful infringement") (quoting IpVenture, Inc. v. Cellco P'ship, No. 10-4755, 2011 WL 207978, at *2 (N.D. Cal. Jan. 21, 2011)); Oracle Corp. v. DrugLogic, Inc., 807 F. Supp. 2d 885, 902 (N.D. Cal. 2011) (finding that plaintiff had stated a claim where it alleged that defendant was aware of the disputed patent and had "actual notice" of the infringement claims) (citing Milwaukee Elec. Tool Corp. v. Hitachi Koki, Ltd., No. 09-948, 2011 WL 665439, at *5 (E.D. Wis. Feb. 14, 2011) for the proposition that the "allegation that the defendants were aware of the plaintiffs' five patents and that the defendants allegedly had infringed and continued to infringe upon, is sufficient to plead willful infringement").

Penn's filing of C.A. No. 13-1502 fortifies our assessment. In its amended complaint, Penn alleges -- as it had to in order to demonstrate the propriety of a declaratory judgment -- that "a substantial and continuing controversy exists between the University and St. Jude regarding whether the

University is liable for infringing the '645 patent." No. 13-1502 Am. Comp. ¶ 33.

We will therefore deny in part Penn's motion to dismiss the claim of willful infringement.

2. Pre-Filing Conduct vs. Post-Filing Conduct

We deny the motion to dismiss only "in part" because the finding that St. Jude has alleged facts sufficient to state a claim for willful infringement by no means ends our analysis -- we must also consider, under Seagate, whether St. Jude's failure to seek a preliminary injunction is fatal to a willfulness claim for the "post-filing" period, and, if so, whether the post-filing period begins to run at the date Penn filed the action or the date St. Jude filed its counterclaims.

In Seagate, the Federal Circuit explained that "in ordinary circumstances, willfulness will depend on an infringer's prelitigation conduct." Seagate, 497 F.3d at 1374. The Court noted that while "a willfulness claim asserted in the original complaint must necessarily be grounded exclusively in the accused infringer's pre-filing conduct", when an accused infringer acts willfully after a patent holder has filed a complaint, the patentee may "move for a preliminary injunction, which generally provides an adequate remedy for combating post-

filing willful infringement." Id. The Federal Circuit reasoned that a patentee who does not attempt to exercise his right to prevent further infringement in this way "should not be allowed to accrue enhanced damages based solely on the infringer's post-filing conduct." Id.

Penn accurately notes that "St. Jude has made no motion to preliminarily enjoin the University from engaging in the accused infringing activities", and it argues that "[t]he absence of a motion for preliminary injunction is fatal to the viability of St. Jude's claim that the University's activities are and continue to be willful." Penn MTD at 6. Penn thus takes Seagate to mean that "an allegation of willful infringement must either be made based on the accused infringer's pre-litigation knowledge, or be maintained only if the patentee seeks a preliminary injunction", id.

St. Jude characterizes the Seagate language as dictum, and it argues that although "[d]istrict courts are divided over whether Seagate announced a per se requirement that a preliminary injunction motion be filed . . . no such motion is necessary where willfulness is premised on pre-suit knowledge of the asserted point." St. Jude Resp. in Opp. at 9 (emphasis in original). St. Jude also points out an important distinction between the instant matter and the Seagate line -- in those

cases, the patentee filed the suit alleging infringement, and so the suit itself often notified the alleged infringer of the patent. For example, in McRO, Inc. v. Namco Bandai Games America, Inc., CV 12-10322-CW (FFMx) (C.D. Cal. Jul. 11, 2013), on which Penn relies, Penn MTD Ex. A, the Court considered whether plaintiff could bring a willfulness claim where "the alleged knowledge of the patent resulted only from the filing of the original complaint in the action and the plaintiff has not sought a preliminary injunction." Id. at 9. The Court found that the plaintiff could not sustain such a claim because Seagate "drastically limit[ed] the availability of willfulness claims when notice is delivered via lawsuit." Id. at 10. McRO Inc. does not apply here, as there is no question that Penn knew of the patent before either party filed suit.

But Seagate's reasoning is not limited to such a situation. As we noted above, Seagate also suggests that a patentee for whom a preliminary injunction remedy is available should not sleep on his rights and thereby accrue greater damages after filing suit. Seagate, 497 F.3d at 1374. See also Anascape, Ltd. v. Microsoft Corp., No. 9:06-158, 2008 WL 7182476, at *3 (E.D. Tex. Apr. 25, 2008) (denying willful infringement claim where patentee "did not even attempt to stop any alleged infringing activity" by moving for a preliminary

injunction). That logic does extend to this dispute, and we thus find that St. Jude's failure to seek a preliminary injunction limits Penn's liability for alleged willful infringement.

The question of when the "post-suit" timeline begins is complicated in this matter where Penn -- the alleged infringer -- sued first, seeking to vindicate its claim that it was not infringing on any valid patent St. Jude held, and where the willful infringement claim came later, in St. Jude's counterclaims. In a typical case, where the patentee files suit, courts have found that a patentee's obligation to seek a preliminary injunction begins upon the filing of the willful infringement claim, see, e.g., LML Holdings, Inc. v. Pacific Coast Dist. Inc., No. 11-6173, 2012 WL 1965878, at *5-6 (N.D. Cal. May 30, 2012); Clouding, IP, LLC v. Amazon.com, Inc., No. 12-641, 642, 675, 2013 WL 2293452 (D. Del. May 24, 2013) (finding that the "post-filing" period began when the patentee filed an amended complaint containing a willfulness claim, not when the patentee filed the original complaint).

Without acknowledging that this case diverges from the usual pattern, Penn assumes that the "post-filing" period commenced when it filed its suit, see Penn MTD at 7. St. Jude argues that the post-filing period did not begin until it filed

its counterclaims alleging willful infringement, see St. Jude Resp. in Opp. at 10.

St. Jude's suggested approach is consistent with caselaw finding that the post-filing period begins at the time a patentee files a willful infringement claim. We agree. Moreover, a contrary finding would have the bizarre effect of encouraging alleged infringers to file declaratory actions immediately after the issuance of a patent so that they could infringe on valid patents with no fear of a willfulness claim. This result is inconsistent with the damages scheme the Federal Circuit established in Beatrice Foods Co. v. New England Printing & Lithographing Co., 923 F.2d 1576 (Fed. Cir. 1991)[15] and clarified in Seagate.

We thus find that St. Jude is not entitled to damages for willful infringement for the period beginning on June 27, 2013, when it filed its counterclaims, and we will grant Penn's motion to dismiss insofar as it relates to this period.

[15] Beatrice Foods Co. established the principle that in order to receive an award of enhanced damages a patentee must make a showing of willful infringement. 923 F.2d at 1578.

VI. St. Jude's Motion for Summary Judgment

We turn to St. Jude's motion for partial summary judgment, initially filed in C.A. No. 12-4122, in which St. Jude asks us to determine, as a matter of law, that

> [t]he "lentiviral vector clone" (that Penn's pleadings call the "June Construct"), which Penn made from biological material and accompanying data and know-how provided by St. Jude pursuant to the Collaboration and Materials Transfer Agreement dated December 10, 2003 (the "2003 MTA"), and which it has used in clinical trials pursuant to the Materials Transfer Agreement dated October 2, 2007 (the "2007 MTA"), contains and was made with "Material" within the plain meaning of the two MTAs.

St. Jude MSJ at 1 (emphasis added).

A. Standard of Review

As is well-settled, a party moving for summary judgment bears the initial burden of informing the district court of the basis for its argument that there is no genuine issue of material fact by "identifying those portions of 'the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any,' which it believes demonstrate the absence of a genuine issue of material fact", Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986).

If the moving party carries this initial burden, the Rules then oblige "the nonmoving party to go beyond the pleadings and by [his] own affidavits, or by the 'depositions, answers to interrogatories, and admissions on file,' designate 'specific facts showing that there is a genuine issue for trial.'" Id. at 324 (quoting Fed. R. Civ. P. 56).

A factual dispute is genuine

> [I]f the evidence is such that a reasonable jury could return a verdict for the nonmoving party. . . . The mere existence of a scintilla of evidence in support of the plaintiff's position will be insufficient; there must be evidence on which the jury could reasonably find for the plaintiff.

Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248, 252 (1986). A fact is "material" if it "might affect the outcome of the suit under the governing law". Id. at 248.

We "must draw all reasonable inferences in favor of the nonmoving party, and [we] may not make credibility determinations or weigh the evidence." Reeves v. Sanderson Plumbing Prods., Inc., 530 U.S. 133, 150 (2000), cited in Amour v. County of Beaver, PA, 271 F.3d 417, 420 (3d Cir. 2001)).

B. Discussion

1. The Parties Do Not Dispute The Physical Make-Up of the June Construct

According to Penn, we should deny summary judgment on the question of whether the June Construct contains "materials" under the MTA because there exists "a genuine issue of fact regarding the makeup of the June Construct", Penn Resp. in Opp. at 13. Penn argues that "St. Jude's motion for summary judgment is premised on the factual assertion that the June Construct has a portion of the Campana Construct in it" because St. Jude makes assertions such as, "[t]he 'lentiviral vector clone' of the CAR that Penn made pursuant to the 2003 MTA consisted of the anti-CD19 cDNA provided by St. Jude, incorporated into a lentiviral vector delivery vehicle." Id.

But the dispute as to the physical make-up of the June Construct appears to be rhetorical rather than factual. The parties seem to agree that the June Construct contains a copy of the cDNA sequence from the Campana Construct, with one base pair difference and a change to accommodate the lentiviral vector. St. Jude refers to the June Construct as containing an "exact copy of all but one of the approximately 1,500 base pairs comprising the cDNA supplied by St. Jude", St. Judge MSJ at 20, and describes it as a "lentiviral vector clone", id. at 8 (emphases added). St. Jude thus does not appear to contend that the June Construct contains a physical portion of the Campana

Construct -- instead, St. Jude argues that by using a gene sequence identical to that of the Campana Construct, except for the differences we just mentioned, Dr. June has created a construct that "contains" a "portion" of the anti-CD19-BB-ζ and is thus subject to the commercialization and crediting restrictions of the MTAs.

Thus, whether the copy of the Campana Construct sequence in the June Construct constitutes a "portion" under the MTA is a matter not of factual dispute but of contract interpretation.

2. Pennsylvania Contract Law

Under Pennsylvania contract law[16], we seek to ascertain "the intent of the parties", Kripp v. Kripp, 849 A.2d 1159, 1163

[16] St. Jude assumes in its motion that Pennsylvania law applies. See St. Jude MSJ at 19-20. The University responds by arguing Pennsylvania law, but it maintains that "[s]uch response should not be construed as an admission that Pennsylvania law is the appropriate law under a choice of law analysis." Penn Resp. in Opp. at 15 n.3. As we noted above, Penn is a citizen of Pennsylvania, see No. 12-4122 Am. Comp. ¶ 1, and it appears that Dr. June's actions took place in Pennsylvania. St. Jude is a Tennessee citizen, see No. 12-4122 Am. Comp. ¶ 2. The MTAs contain no choice of law clause, and in our April 4, 2013 Memorandum we conducted a choice of law analysis with regard to Penn's tort claim, and, finding no real conflict between Pennsylvania and Tennessee law, applied Pennsylvania law. Here, the only non-Pennsylvania citizen, St. Jude, has argued under Pennsylvania law and neither party has given us any reason to believe Pennsylvania law does not apply. We will thus apply Pennsylvania law here.

(Pa. 2004), and where there is a written contract whose terms are "clear and unambiguous, the intent of the parties is to be ascertained from the document itself." Id. (citing Hutchison v. Sunbeam Coal Corp., 519 A.2d 385, 390 (Pa. 1986)).

A contract is ambiguous if "it is reasonably susceptible of different constructions and capable of being understood in more than one sense", id. As Pennsylvania courts have made clear, "the mere fact that the parties do not agree upon the proper construction" does not render a contract ambiguous, Metzger v. Clifford Realty Corp., 476 A.2d 1, 5 (Pa. Super. Ct. 1984) (quoting Commonwealth State Highway and Bridge Auth. v. E.J. Albrecht Co., 430 A.2d 328, 330 (Pa. 1981)).

If a contract is unambiguous, we interpret it as a matter of law, but if we find that it is ambiguous its meaning is a question for the finder of fact. Id. See also, e.g., Ins. Adjustment Bureau, Inc. v. Allstate Ins. Co., 905 A.2d 462, 469 (Pa. 2006).

In Pennsylvania, "the course of the parties' performance under a contract is always relevant in interpreting that contract." Matthews v. Unisource Worldwide, Inc., 748 A.2d 219, 222 (Pa. Super. Ct. 2000) (citing Atlantic Richfield Co. v. Razumic, 390 A.2d 736, 741 n.6 (1978)). See also, e.g., Restatement (Second) of Contracts § 202(5) ("Wherever

reasonable, the manifestations of intention of the parties to a promise or agreement are interpreted as consistent with each other and with any relevant course of performance, course of dealing, or usage of trade.").

3. The Language of the MTAs

St. Jude argues that the terms of the MTAs are unambiguous. According to St. Jude, "[t]he 2003 MTA and the 2007 MTA each plainly define Material to include 'any' 'portions' and 'accompanying know-how and data'", and "a 'portion' is 'a part of a whole'". St. Jude MSJ at 20 (quoting Oxford Dictionaries, available at http://oxforddictionaries.com/definition/english/portion?q=portion).[17] "Data" are "facts or statistics collected together for reference or analysis", id., while "know-how" is "practical knowledge or skill; expertise", id. Thus, on St. Jude's

[17] We typically rely upon the peerless The Oxford English Dictionary for what Simon Winchester rightly described as The Meaning of Everything in the title of his 2003 history of the OED, but because the OED includes the similar definition, "a part of any whole", as one of nine ways of using "portion" as a noun, we defer here to St. Jude's source. XII Oxford English Dictionary 154-55, def. II.5.a (2d ed. 1989). We note that another of the nine definitions the OED offers is "[t]he part (of anything) allotted or belonging to one person; a share", id. at 154, def. I.1.a., as in, "**1772** Junius Lett. lxviii. (1820) 338 The study of the law requires but a moderate portion of abilities." Only on this one point do we diverge from James Murray and his learned team.

reading, "an exact copy of all but one of the approximately 1,500 base pairs comprising the cDNA supplied by St. Jude was a 'portion' of the Material", and "the data files and technical information that St. Jude's Imai sent to Penn's Milone . . . were 'accompanying know-how and data'". Id.

Penn suggests, without concluding, that the contract is ambiguous, see Penn Resp. in Opp. at 15-16, and it offers an alternative interpretation of the contract language. According to Penn, the phrase "progeny, portions, unmodified derivatives and any accompanying know-how or data" does not encompass the June Construct because the June Construct is a "modified derivative," or "a substance created from all or part of another, but . . . requir[ing] a change relative to the original substance during the creation process", Penn Resp. in Opp. at 16. Penn contrasts this with an unmodified derivative, which the agreement specifically includes and which Penn describes as "a substance that can be formed directly from another without a change to the original substance". Id. Penn argues that the contract's definition of materials "does not broadly encompass any and all derivatives of the biological materials provided", but instead "specifies very limited types of derivatives of the biological materials to be included", of which "modified derivatives" is not one. Id.

Reading modified derivatives as excluded from the MTA is also appropriate, Penn contends, in light of paragraph three of the 2007 MTA where Penn agreed that "the Materials are provided for the sole purpose of allowing [Penn] to use Materials to produce a molecular lentiviral vector clone incorporating Materials . . . for application in ex vivo autologous cell modification . . . ." 2007 MTA ¶ 3; Penn Resp. in Opp. at 17 (emphasis added). This passage does not refer to the lentiviral clone as itself a "material", and the commercialization constraints in the 2003 MTA and 2007 MTA do not refer to products "incorporating Materials", but those "contain[ing] materials" (2003 MTA) or "contain[ing] a portion of the Materials, . . . derived from the Materials, or which could not have been produced but for the use of the Materials." (2007 MTA). Penn argues that the June Construct does not contain a "portion" of the materials because it does not contain "a physical part of the whole provided by St. Jude", Penn Resp. in Opp. at 20, but instead contains a modified derivative.

Penn also points to paragraph five of the 2007 MTA which provides that with regard to patents "[o]wnership shall follow inventorship according to US patent law." Penn reads this as demonstrating a "clear intent . . . to allow the University to research and create a new substance in which it

would presumably have its own rights", while under St. Jude's interpretation, "even a copy of a single nucleotide, molecule, or even atom from the Campana Construct would constitute a 'portion' of the Materials", Penn Resp. in Opp. at 20-21.

St. Jude and Penn reach contrary conclusions about the scope of the definition of "materials", and we find that both are reasonable. The contract is thus facially ambiguous. See, e.g., Ins. Adjustment Bureau, Inc., 905 A.2d at 469 (finding that opposing parties' interpretations were both reasonable and so "the Agreement on its face is ambiguous").

We now consider evidence of the course of performance and trade usage to determine whether these shed sufficient light on the matter to resolve the ambiguity.

4. Course of Performance

St. Jude argues that "[o]ver nearly eight years, Penn repeatedly performed, acknowledged, and admitted its obligations under the 2003 MTA and the 2007 MTA Agreements in accordance with its full agreement that the June Construct contained and was made with Materials." St. Jude MSJ at 20-21. St. Jude points to Dr. June's crediting of Dr. Campana, Deyo's e-mail acknowledging "the necessity of a new MTA" before proceeding with clinical trials of the June Construct, and Donahue's e-mail

diagramming the lentiviral vector, including the portion of the vector that represented the Campana Construct.

Penn argues that the fact that Dr. June occasionally gave credit to Dr. Campana does not capture the course of performance because other articles -- indeed, the articles that form the basis for St. Jude's breach of contract action -- did not credit Dr. Campana, as we discussed above. According to Penn, Dr. June did not always credit Dr. Campana because he did not believe he had a contractual obligation to do so -- instead, he did so in order to comply with "standard practice in the field of academic research [of] identify[ing] the source of biological sequences." Penn Resp. in Opp. at 23.

With regard to Donahue's letter, Penn argues persuasively that the "portion" to which Donahue referred was not a "portion" of the Campana Construct within the meaning of the MTA, but the portion of the June Construct which contained the gene sequence from the Campana Construct. That reading seems plainly accurate, and under it Donahue's statement does not shed light on Penn's understanding of whether the June Construct contained "material" within the meaning of the MTAs.

Penn does not dispute St. Jude's recounting of Deyo's e-mail.[18]

The evidence Penn presents -- including evidence of Dr. June's varied treatment of the June Construct in crediting St. Jude and in sharing materials -- does demonstrate a genuine dispute of fact as to Penn's understanding of the scope of the MTAs. Though Dr. June's occasional efforts to credit Dr. Campana and to seek Dr. Campana's permission before sharing the June Construct may shed light on Penn's understanding of the agreements, these efforts do not elucidate the agreements' terms. See, e.g., J.W.S. Delavau, Inc. v. Eastern America Transport & Warehousing, Inc., 810 A.2d 672, 684 (Pa. Super. Ct. 2002) ("Pennsylvania case law indicates 'course of performance' can only be used to interpret, but not to supplement, the terms of an existing agreement.").

St. Jude dismisses Penn's evidence as "self-serving declarations of undisclosed intent", St. Jude Reply at 8, but the credibility of witnesses precisely presents a question for a finder of fact. It is of course well-settled that we may not make credibility determinations in deciding a motion for summary judgment. See, e.g., Marino v. Indus. Crating Co., 358 F.3d

[18] As St. Jude puts it, Penn is "deathly silent" on this issue. St. Jude Reply at 7.

241, 247 (3d Cir. 2004). In light of this evidence, Deyo's e-mail is insufficient to demonstrate that there is no genuine issue of material fact with respect to Penn's understanding. We thus find that the course of performance does not resolve the contracts' facial ambiguity.

5. Trade Usage

Penn claims that we must read the terms of the MTAs in light of their trade usage. As the United States Supreme Court long ago explained, "[t]he proper office of a custom or usage in trade is to ascertain and explain the meaning and intention of the parties to a contract . . . which could not be done without the aid of this extrinsic evidence." Barnard v. Kellogg, 77 U.S. 383, 390 (1870). Whether a trade usage exists is a question of fact for the jury, see, e.g., Albus v. Toomey, 116 A. 917, 918 (Pa. 1922); Simon Wrecking Co. v. AIU Ins. Co., 530 F. Supp. 2d 706, 715 (E.D. Pa. 2008) (Brody, J.). See also Restatement (Second) of Contracts § 222(2) ("The existence and scope of a usage of trade are to be determined as questions of fact.").

St. Jude objects that "the mere injection of purported trade usage into a party's opposition to a motion for summary judgment will not defeat the motion", St. Jude Reply at 14, and,

although we agree as a general matter, we find that here Penn has pointed to sufficient evidence to give rise to a genuine issue of material fact as to whether a trade usage affected the parties' understanding of the agreements' terms.

Penn argues that reading "materials" in the MTAs not to include the June Construct is consistent with the purpose of MTAs within the medical research field. Penn produces an affidavit of Dr. Wesley D. Blakeslee, the Executive Director of Johns Hopkins Technology Transfer at Johns Hopkins University, who avers that "[a]s a general matter, MTAs between scientific research institutions are drafted to govern the exchange of tangible materials . . . and are not intended to govern concepts, ideas or future intellectual property derived from the use of the tangible materials." Blakeslee Dec., Penn Resp. in Opp. Ex. B, at ¶ 8.

St. Jude objects that Blakeslee's Declaration is "conclusory" and "sweeping" in its opinions, and it suggests that Penn has introduced "scant factual evidence" to support its trade usage theory. St. Jude demonstrates considerable chutzpa in objecting to the volume of Penn's evidence when St. Jude moved for summary judgment before discovery, and its argument does not accord with our role as a court reviewing a summary judgment motion. As the Supreme Court has made clear, we may

not "weigh the evidence", and we must "draw all reasonable inferences in favor of the nonmoving party", Reeves, 530 U.S. at 150, when ruling on a summary judgment motion. We thus cannot discard the evidence Penn has provided on the ground that Penn did not provide enough support for its argument.

St. Jude next objects to Blakeslee's interpretation on the ground that it would render the 2007 MTA "meaningless", and so a construction based on it must fail as a matter of law. St. Jude Reply at 18. Blakeslee suggests that the MTA governed only the physically transferred materials, and St. Jude argues that if this were true there would be no need for the 2007 MTA, which did not accompany a physical materials transfer, and which the parties reached ostensibly so that Penn could use the June Construct in clinical trials. If the June Construct did not contain or was not made using "material" within the meaning of the 2003 MTA, St. Jude's argument goes, the parties would not have needed to execute a second MTA for the materials' use in clinical trials. But St. Jude makes this argument before conducting any discovery that would shed light on the parties' understanding of the scope of the materials used during the clinical trials and the purpose of the 2007 MTA. Without further evidence of the parties' understanding at the time they entered into the second MTA, we cannot say as a matter of law

that Blakeslee's interpretation would render the 2007 MTA meaningless and would thus be useless in shedding light on the question of whether there is a dispute as to trade usage.

6. Penn Has Demonstrated A Genuine Issue of Material Fact As To The Meaning of the Contract

The agreement is facially ambiguous, and the parties' conduct under it does not resolve that ambiguity. Moreover, there is a question of fact as to what the trade usage is and whether it affected the parties' understanding of the MTAs' terms. Summary judgment is thus unwarranted.

VII. St. Jude's Motion for a Separate Trial

St. Jude moves in the alternative for a separate trial on the issue of whether the June Construct contained and was made with "material" within the meaning of the 2003 and 2007 MTAs. St. Jude MSJ at 23. Penn opposes this motion on the ground that "piecemeal resolution of issues in separate trials will only serve to prolong the parties' dispute, not accelerate its resolution." Penn Resp. in Opp. at 26.

We agree with St. Jude that an expeditious resolution of the threshold question of whether the June Construct contains and was made with "material" within the meaning of the MTAs will help resolve the case. But we do not agree that separate trials

are necessary in order to accomplish this aim. Instead, in the accompanying Order, we will establish a brief discovery schedule followed by a trial on all claims. Because the case involves both legal and equitable claims, we address the parties' jury trial rights below.

The Seventh Amendment provides that "[i]n Suits at common law, where the value in controversy shall exceed twenty dollars, the right of trial by jury shall be preserved." The United States Supreme Court has explained that this Amendment gives a litigant a right to a jury trial for actions "analogous to 'Suits at common law.'" Tull v. United States, 481 U.S. 412, 417 (1987). The jury trial right does not extend to suits that would have been brought in equity, and so in order to determine whether a litigant has that right courts must "examine both the nature of the action and of the remedy sought." Id.

Where a case includes both legal and equitable claims, if the issues underlying the two are common, "the legal claims involved in the action must be determined prior to any final court determination of respondents' equitable claims." Dairy Queen, Inc. v. Wood, 369 U.S. 469, 479 (1962).

Although "[d]etermination of whether a claim stated by the complaint is triable by the court or by a jury will normally not be dependent upon the 'legal' or 'equitable' character of

the counterclaim", there are cases, such as one where "the plaintiff seeks a declaration of invalidity or non-infringement of a patent, in which the relief sought by the counterclaim will determine the nature of the entire case." Beacon Theatres, Inc. v. Westover, 359 U.S. 500, 519 n.13 (1959) (Stewart, J., dissenting) (citing Moore's Federal Practice (2d ed.) § 38.29) (emphasis added).

Penn's amended complaint in C.A. No. 12-4122 seeks a declaratory judgment. St. Jude's complaint, originally filed in the Western District of Tennessee and now consolidated with C.A. No. 12-4122, contains only a breach of contract claim for which St. Jude seeks damages. Both parties included a jury demand in their complaints in that action.

In C.A. No. 13-1502, Penn seeks determinations of non-infringement and invalidity, and St. Jude counterclaims, seeking declaratory relief and damages. Both parties again include jury demands.

As our Court of Appeals has explained, a declaratory judgment action is neither legal nor equitable in nature, and if it "does not fit into one of the existing equitable patterns but is essentially an inverted law suit -- an action brought by one who would have been a defendant at common law -- then the parties have a right to a jury", AstenJohnson, Inc. v. Columbia

Cas. Co., 562 F.3d 213, 223 (3d Cir. 2009) (quoting Owens-Illinois, Inc. v. Lake Shore Land Co., 610 F.2d 1185, 1189 (3d Cir. 1979)). In order to determine whether the action falls under this category, we are to consider "in what kind of suit the claim would have come to court if there were no declaratory judgment remedy", Owens-Illinois, Inc., 610 F.2d at 1189.

Penn's declaratory judgment claims in the contract case would have come -- and did come, in St. Jude's Tennessee complaint -- in the form of a breach of contract action. To the extent that such an action seeks damages it is a legal claim and requires a jury trial. See, e.g., 9 Charles Allen Wright & Arthur R. Miller, Federal Practice and Procedure § 2316 (3d ed., updated April 2013) ("An action for damages for breach of contract is legal in nature and therefore triable to a jury"); Wills v. Young, 255 F.2d 65, 67 (3d Cir. 1958) (contrasting "an action at law for damages for breach of contract" with "an action in equity for specific performance"). Penn and St. Jude are thus entitled to a jury determination on St. Jude's breach of contract claim for damages and Penn's declaratory judgment claims in C.A. No. 12-4122.

With regard to St. Jude's claim for a preliminary injunction, this is an equitable remedy that we will consider. See, e.g., N.A.A.C.P. v. North Hudson Regional Fire & Rescue,

707 F. Supp. 2d 520, 541 (D.N.J. 2010) (Debevoise, J.) ("a preliminary injunction is an equitable remedy, which the Court, in its discretion, considers by balancing and weighing the various factors"). Under Dairy Queen, we will dispose of the equitable claims after a jury considers the legal claims.

Penn also seeks a declaratory judgment in the patent suit. In In re Lockwood, 50 F.3d 966 (Fed. Cir. 1995), the Federal Circuit observed that "declaratory judgment actions are, for Seventh Amendment purposes, only as legal or equitable in nature as the controversies on which they are founded." Id. at 973.[19] The Federal Circuit found that a declaratory judgment action by a potential infringer should be considered "as a suit for patent infringement in which the affirmative defense of invalidity has been pled", id. at 974. Lockwood looked to the nature of patent actions in the eighteenth century and found that "[i]n eighteenth-century England, allegations of patent

[19] As the Northern District of Illinois summarized, the Supreme Court vacated the Federal Circuit's decision in Lockwood after Lockwood withdrew its jury demand, American Airlines, Inc. v. Lockwood, 515 U.S. 1182 (1995); Barry S. Wilson, Patent Invalidity and the Seventh Amendment; Is the Jury Out?, 34 San Diego L.Rev. 1787, 1796 (1997), and so Lockwood is not binding, but it is persuasive as a "source of guidance" and as an indication of the Federal Circuit's likely position on the Seventh Amendment question. Pfizer Inc. v. Novopharm Ltd., No. 00 C 1475, 2001 WL 477163, at *3 (N.D. Ill. May 3, 2001) (citing Christianson v. Colt Indus. Operating Corp., 870 F.2d 1292, 1298–99, n. 7 (7th Cir.1989)).

infringement could be raised in both actions at law and suits in equity", id. at 975, and "[t]he choice of forum and remedy, and thus of the method of trial, was left with the patentee." Id. The Federal Circuit reasoned that "[u]nder both English and American practice . . . it was the patentee who decided in the first instance whether a jury trial on the factual questions relating to validity would be compelled", and so the patentee retained the option of a jury trial even when "the validity of his patents comes before the court in a declaratory judgment action for invalidity rather than as a defense in an infringement suit." Id. at 976.

In Tegal Corp. v. Tokyo Electron America, Inc., 257 F.3d 1331 (Fed. Cir. 2001), the Federal Circuit cited Lockwood's canvass of eighteenth century patent law and explained that "[i]f the patentee sought an injunction and an accounting, the patentee went to a court of equity. If, however, the patentee sought only damages, a court of law was used." Id. at 1340 (internal citations omitted).

Thus, under the Federal Circuit's jurisprudence the remedy the patentee seeks determines the nature of the action. See also, e.g., Kao Corp. v. Unilever U.S., Inc., No 01-680, 2003 WL 1905635, at *3 (D. Del. Apr. 17, 2003) ("the patentee's

infringement case is the linchpin of the Federal Circuit's Seventh Amendment analyses").

Here, where St. Jude's counterclaims seek damages, the action is necessarily legal and the parties may try their patent claims to a jury. As mentioned, we will make a determination as to the equitable relief they seek after a jury trial.

VIII. Conclusion

For the reasons stated herein, we will consolidate the actions, deny as moot St. Jude's motion to dismiss Penn's initial patent complaint, grant in part and deny in part Penn's motion to dismiss St. Jude's willful infringement counterclaim, and deny St. Jude's motion for partial summary judgment and motion for separate trial. In the accompanying Order, we set a discovery and trial schedule.

BY THE COURT:

/S/ STEWART DALZELL

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	:	NO. 12-4122

TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA	:	CIVIL ACTION
v.	:	
ST. JUDE CHILDREN'S RESEARCH HOSPITAL	:	NO. 13-1502

ORDER

AND NOW, this 13th day of November, 2013, upon consideration of defendant St. Jude Children's Research Hospital's ("St. Jude") response to our Order to Show Cause, its motion to for partial summary judgment and alternative motion for a separate trial (C.A. No. 12-4122, docket entry # 28), the response in opposition thereto filed by plaintiff Trustees of the University of Pennsylvania ("Penn"), St. Jude's motion for leave to file a reply in support of that motion (C.A. No. 12-4122, docket entry # 35), Penn's opposition in response thereto, Penn's original complaint in C.A. No. 13-1502, St. Jude's motion to dismiss that complaint (C.A. No. 13-1502, docket entry # 12),

Penn's amended complaint, St. Jude's answer and counterclaims, Penn's partial motion to dismiss (C.A. No. 13-1502, docket entry # 18), and St. Jude's response in opposition thereto, and for the reasons discussed in the accompanying Memorandum, it is hereby ORDERED that:

1. The Clerk of Court shall CONSOLIDATE C.A. No. 12-4122 and C.A. No. 13-1502 as C.A. No. 13-1502;

2. All papers filed in C.A. No. 12-4122 are to be placed in the file for C.A. No. 13-1502 and the Clerk shall CLOSE C.A. No. 12-4122 statistically;

3. St. Jude's motion for partial summary judgment and alternative motion for a separate trial (C.A. No. 12-4122, docket entry # 28) is DENIED;

4. St. Jude's motion for leave to file a reply in support of its motion for summary judgment or a new trial (C.A. No. 12-4122, docket entry # 35) is GRANTED;

5. St. Jude's motion to dismiss (C.A. No. 13-1502, docket entry # 12) is DENIED AS MOOT;

6. Penn's motion to dismiss St. Jude's counterclaim of willful infringement (C.A. No. 13-1502, docket entry # 18) is GRANTED IN PART and DENIED IN PART, as follows:

a. With respect to the period beginning on June 27, 2013 the motion is GRANTED; and

b. With respect to the period from March 19, 2013 through June 26, 2013 the motion is DENIED;

7. The parties shall COMPLETE discovery by January 24, 2014[20];

8. Trial in this matter, not to exceed four days of evidence per side, shall COMMENCE on Monday, February 10, 2014, at 9:30 a.m. in Courtroom 15-B;

9. Any motions in limine shall be FILED in conformance with the Court's Standing Order (attached) by noon on January 28, 2014, with any motion responses due by noon on January 31, 2014;

10. The parties shall SUBMIT a stipulation of facts, as comprehensive and detailed as possible, by noon on January 28, 2014; and

11. Proposed jury instructions and proposed jury verdict forms shall be FILED by January 31, 2014.

BY THE COURT:
/s/ Stewart Dalzell, J.

[20] We trust given the parties' high level of sophistication that there will be no Daubert issues to resolve before trial. If our trust proves to be misplaced, we may have to revisit the trial date set herein.

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UNITED ST ATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPOR T PURSUANT T O SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2015

OR

☐ TRANSITION REPOR T PURSUANT T O SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period fr om _____ to _____

Commission File Number: 001-36781

Juno Therapeutics, Inc.
(Exact name of r egistrant as specified in its charter)

Delawar e	46-3656275
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
307 Westlake A venue North, Suite 300 Seattle, W A	98109
(Address of principal executive offices)	(Zip Code)

(206) 582-1600
(Registrant's telephone number, including area code)

Securities r egister ed pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common stock, par value $0.0001 per shar e	The NASDAQ Global Select Market

Securities r egister ed pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Securities Exchange Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☒ Accelerated filer ☐

Non-accelerated filer ☐ (Do not check if a smaller reporting company) Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates as of June 30, 2015 was $2,833,756,799.

The number of shares outstanding of the registrant's common stock as of February 18, 2016 was 104,059,558.

DOCUMENTS INCORPORA TED BY REFERENCE:

Portions of the registrant's Proxy Statement for the registrant's 2016 Annual Meeting of Stockholders will be filed with the Commission within 120 days after the close of the registrant's 2015 fiscal year and are incorporated by reference in Part III.

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Juno Therapeutics, Inc.
Annual Report on Form 10-K
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PART I

Forward-Looking Statements and Market Data

This Annual Report on Form 10-K contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. All statements other than statements of historical facts contained in this report are forward-looking statements. In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "aim," "potential," "continue," "ongoing," "goal," or the negative of these terms or other similar expressions, although not all forward-looking statements contain these words.

These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this report, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain. Forward-looking statements in this report include, but are not limited to, statements about:

- the success, cost and timing of our product development activities and clinical trials;
- our ability and the potential to successfully advance our technology platform to improve the safety and effectiveness of our existing product candidates;
- the potential for our identified research priorities to advance our chimeric antigen receptor ("CAR") and T cell receptor ("TCR") technologies;
- the potential of our collaboration with Celgene and the ability and willingness of Celgene to be our commercialization partner outside of North America;
- the ability and willingness of our third-party research institution collaborators to continue research and development activities relating to our product candidates;
- the potential of our other research and development and strategic collaborations, including our collaborations with Editas Medicine, Inc., Fate Therapeutics, Inc., and MedImmune Limited;
- our ability to obtain orphan drug designation or breakthrough status for our CD19 product candidates and any other product candidates, or to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate;
- the ability to license additional intellectual property relating to our product candidates;
- our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates;
- our ability to commercialize our products in light of the intellectual property rights of others;
- our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates;
- our plans to research, develop and commercialize our product candidates;
- the potential of the technologies we have acquired through strategic transactions, such as the acquisition of Stage Cell Therapeutics GmbH, X-Body, Inc., and AbVitro Inc.;
- the size and growth potential of the markets for our product candidates, and our ability to serve those markets;
- regulatory developments in the United States and foreign countries;

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- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our plans to develop our own manufacturing facilities, including our manufacturing facility in Bothell, Washington;
- the success of competing therapies that are or may become available;
- our ability to attract and retain key scientific or management personnel;
- the accuracy of our estimates regarding expenses, success payments, future revenue, capital requirements, profitability, and needs for additional financing;
- fluctuations in the trading price of our common stock;
- the anticipated benefits of our litigation settlement with the Trustees of the University of Pennsylvania and Novartis;
- our plans regarding our corporate headquarters; and
- our use of the proceeds from our initial public offering and proceeds received from Celgene.

In addition, you should refer to Part I—Item 1A—"Risk Factors" in this report for a discussion of other important factors that may cause actual results to differ materially from those expressed or implied by the forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this report will prove to be accurate. Furthermore, if the forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This report also contains estimates, projections and other information concerning our industry, our business, and the markets for our products and product candidates, including data regarding the estimated size of those markets, their projected growth rates, the perceptions and preferences of patients and physicians regarding certain therapies and other prescription, prescriber and patient data, as well as data regarding market research, estimates and forecasts prepared by our management. We obtained the industry, market and other data throughout this report from our own internal estimates and research, as well as from industry publications and research, surveys and studies conducted by third parties.

Unless the context requires otherwise, in this report the terms "Juno," "we," "us" and "our" refer to Juno Therapeutics, Inc. and its wholly-owned subsidiaries on a consolidated basis.

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ITEM 1. BUSINESS.

Overview

We are building a fully-integrated biopharmaceutical company focused on re-engaging the body's immune system to revolutionize the treatment of cancer. Founded on the vision that the use of human cells as therapeutic entities will drive one of the next important phases in medicine, we are developing cell-based cancer immunotherapies based on our CAR and high-affinity TCR technologies to genetically engineer T cells to recognize and kill cancer cells. We have shown compelling clinical responses in clinical trials using multiple cell-based product candidates to address refractory B cell lymphomas and leukemias, and we also have a number of ongoing trials exploring our platform in solid-organ cancers and in combination with various strategies to overcome the immune-suppressive effects of cancer. Longer term, we aim to improve and leverage our cell-based platform to develop additional product candidates to address a broad range of cancers and human diseases, including moving forward our pre-clinical product candidates that target additional hematologic and solid-organ cancers.

In the third quarter of 2015, we began a Phase II trial of JCAR015 that could support accelerated U.S. regulatory approval in adult relapsed/refractory ("r/r") B cell acute lymphoblastic leukemia ("ALL") as early as 2017. We also began a Phase I trial with JCAR017 in adult r/r aggressive B cell non-Hodgkin lymphoma ("NHL"), with the potential to move to a registration trial for that product candidate in 2016 or early 2017. We are continuing to enroll patients in an ongoing Phase I/II trial for JCAR014 in B cell malignancies, and although we do not plan to move JCAR014 into registration trials, we plan to use this trial to explore important questions that may improve our platform overall. To date, data from the JCAR014 trial have provided encouraging early insights on how to improve our efficacy and safety in patients with ALL, NHL, and chronic lymphocytic leukemia ("CLL"). The IND has cleared for and we plan to enroll patients through 2016 in a Phase Ib clinical trial combining JCAR014 with MedImmune's investigational programmed death ligand 1 ("PD-L1") immune checkpoint inhibitor, durvalumab, for the treatment of adult r/r B cell NHL. We have also begun Phase I trials for five additional product candidates that target different cancer-associated proteins in hematological and solid organ cancers. We also expect to commence a Phase I trial through our collaborator MSK of a CD19/4-1BBL "armored" CAR in 2016 and a Phase I trial for one or both of CD19/CD40L and CD19/IL-12 "armored" CARs in 2016 or 2017.

Cancer is a leading cause of death in developed countries. Cancer is characterized by the uncontrolled proliferation of abnormal cells. Cancer cells contain mutated proteins and may overexpress other proteins normally found in the body at low levels. The immune system typically recognizes abnormal protein expression and eliminates these cells in a highly efficient process known as immune surveillance. Cancer cells' ability to evade immune surveillance is a key factor in their growth, spread, and persistence. In the last five years, there has been substantial scientific progress in countering these evasion mechanisms using immunotherapies, or therapies that activate the immune system. Immunotherapies are increasingly recognized as an important part of today's frontier in the treatment of cancer.

A central player in cancer immunotherapy is a type of white blood cell known as the T cell. In healthy individuals, T cells identify and kill infected or abnormal cells, including cancer cells. We leverage two technologies—CARs and TCRs—to activate a patient's own T cells so that they attack cancer cells. Through genetic engineering, we insert a gene for a particular CAR or TCR construct into the T cell that enables it to recognize cancer cells. Our CAR technology directs T cells to recognize cancer cells based on the expression of specific proteins located on the cell surface, whereas our TCR technology provides the T cells with a specific T cell receptor to recognize protein fragments derived from either the surface or inside the cell.

We are investing substantially in manufacturing processes that we believe will be commercially scalable for both CARs and TCRs, and plan to manufacture clinical trial material from a Juno-operated manufacturing facility in Bothell, Washington, beginning in the first quarter of 2016. We harvest blood cells from a cancer patient, separate the appropriate T cells, activate the cell, insert the gene sequence for the CAR or TCR construct into the

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cell's DNA, and grow these modified T cells to the desired dose level. The modified T cells can then be infused into the patient or frozen and stored for later infusion. Once infused, the T cells are designed to multiply, through a process known as cell expansion, when they encounter the targeted proteins and to kill the targeted cancer cells.

Our scientific founders and their institutions include world leaders in oncology, immunology, and cell therapy, and they actively contribute towards developing our product candidates and technologies. Collectively, these stakeholders share our commitment to bringing our product candidates to market and our vision of revolutionizing medicine through developing a broadly applicable cell-based platform. We have also entered into a number of strategic collaborations with commercial companies that we believe will help us manufacture and commercialize our product candidates around the world or develop additional or improved product candidates, including Celgene, Editas Medicine, Inc. ("Editas"), Fate Therapeutics, Inc. ("Fate Therapeutics"), and MedImmune Limited ("MedImmune").

Clinical-Stage CD19 Product Candidates

Our most advanced product candidates, JCAR015, JCAR017, and JCAR014, leverage CAR technology to target CD19, a protein expressed on the surface of almost all B cell leukemias and lymphomas. Despite significant advances over the past two decades, lymphoma and leukemia are estimated to account for approximately 45,000 annual deaths in the United States.

- ALL Progress and Strategy. JCAR015, in data presented at the American Society of Hematology ("ASH") meeting in December 2015 ("ASH 2015"), achieved an 82% complete remission ("CR") rate in 45 evaluable adult patients with r/r ALL who received our CAR T cell product candidate in an ongoing Phase I clinical trial, as of a data cutoff date of November 2, 2015. The complete molecular remission ("CRm") rate by flow cytometry, a more stringent measure of a response defined by the absence of minimal residual disease ("MRD"), was 67%. This patient population has disease that has recurred despite multiple prior intensive chemotherapy and/or antibody regimens. Historical long-term complete remission rates without JCAR015 in a similar population are approximately 10% using standard of care therapy. We initiated a Phase II trial in 2015 exploring JCAR015 in adult r/r ALL that could support accelerated U.S. regulatory approval.

  JCAR014, in investigator-reported data presented at ASH 2015 in patients with r/r ALL, showed that since the change to a fludarabine/cyclophosphamide ("flu/cy") pre-conditioning chemotherapy regimen, 17 out of 17 patients, or 100%, have achieved both a CR and CRm. While more follow-up is needed, data to date suggest that JCAR014 plus this pre-conditioning regimen has improved durability of response. We do not plan to move JCAR014 into registration studies, but we plan to apply its insights into pre-conditioning regimens and the importance of both depth of response and cell persistence across our portfolio.

  JCAR017, in data presented at the 4th International Conference on Immunotherapy in Pediatric Oncology ("CIPO") in September 2015 ("CIPO 2015"), achieved an 91% CR rate and 91% CRm rate in 32 evaluable patients with pediatric r/r ALL in the Phase I portion of an ongoing Phase I/II trial, as of a data cutoff date in September 2015. In this trial, JCAR017 has shown the highest cell expansion and longest cell persistence in patients of any of our CD19-directed product candidates prior to the introduction of flu/cy conditioning. We believe that product candidates with greater cell expansion and cell persistence are likely to lead to improved clinical benefit. We are currently enrolling more patients in this trial and exploring the impact of a flu/cy conditioning regimen on JCAR017's efficacy and safety in this setting.

- NHL Progress and Strategy. Data presented at ASH 2015 from the Phase I portion of an ongoing Phase I/II trial with JCAR014 demonstrated that using a flu/cy pre-conditioning regimen prior to treatment with JCAR014 led to significantly greater expansion and longer persistence of the CAR T cells in the body in patients with r/r NHL. The improved expansion and persistence translated into better patient outcomes, particularly at the dose we plan to use going forward. At this dose, 7 of 11 r/r

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NHL patients, or 64%, had a complete response, and in those r/r NHL patients with diffuse large B cell lymphoma ("DLBCL"), 6 out of 8 patients, or 75%, had a complete response. Patients from this portion of the trial have been followed for between two and nine months, and as of the data cut-off date of December 1, 2015, all patients with a complete response remained in remission. We plan to continue treating patients with JCAR014 in 2016 in order to explore various treatment strategies to improve the cell expansion and cell persistence of the CAR T cells in the body, as well as test JCAR014 in combination with other agents, including a Phase Ib trial with the MedImmune checkpoint inhibitor durvalumab in which we plan to enroll adult r/r NHL patients in 2016.

Based upon these JCAR014 data, data on expansion and persistence for JCAR017, and insights from across our CD19 trials, we initiated a multi-center, Phase I trial exploring JCAR017 in r/r NHL in 2015, with the potential to advance to a registration trial in 2016 or early 2017 that may support accelerated U.S. regulatory approval.

- CLL Progress and Strategy. Data presented at ASH 2015 from an ongoing Phase I/II trial of JCAR014 with our current dosing and pre-conditioning strategy demonstrated a complete response in four out of seven, or 57%, r/r CLL patients, and seven out of seven, or 100%, had either a complete or partial response. As of the data cutoff date of December 1, 2015, all of these responses were ongoing at time points ranging from two to 14 months. We plan to enroll more r/r CLL patients in this trial in early 2016, and if the data remain consistent with these early findings, move toward a registration trial as rapidly as possible.

We also expect to commence a Phase I trial through our collaborator Memorial Sloan Kettering Cancer Center ("MSK") of a CD19/4-1BBL "armored" CAR in 2016 in one or more B cell malignancies and a Phase I trial for one or both of CD19/CD40L and CD19/IL-12 "armored" CARs in 2016 or 2017. We also intend to begin a Phase I trial for our fully human CD19 CAR in 2016 in one or more B cell malignancies.

JCAR015, JCAR017, and JCAR014 differ in multiple respects, including the types of T cells used, sites of engagement, and activation signal within the cells. We believe clinical experience with multiple CD19 CARs in patients with B cell malignancies gives us the opportunity to learn about the product characteristics that lead to the best patient outcomes. We intend to apply these learnings as rapidly as we can to improve our future product candidates. Our goal is to bring best-in-class therapies to market across a range of B cell malignancies, focusing on improving efficacy, safety, and patient experience.

Additional Product Candidates and Research Strategy

We have begun Phase I trials for four additional product candidates using our CAR technology, directed against CD22, L1CAM, MUC-16, and ROR-1. We also began a new Phase I clinical trial for a fifth product candidate, using our TCR technology, directed against WT-1. CD22, L1CAM, MUC-16, ROR-1, and WT-1 are proteins that are overexpressed on certain cancer cells.

At ASH 2015, we reported initial data from a Phase I trial exploring our CD22-directed CAR T cell product candidate in patients with r/r ALL. CD22 is expressed by most B cell malignancies, including NHL, ALL, and CLL. Within these CD22 positive malignancies, it is generally expressed on all of a patient's cancer cells. Additionally, as experience grows with CD19-directed CAR T cell product candidates, CD19 epitope loss has been recognized as an important mechanism of patient relapse after treatment with a CD19-directed CAR T cell, particularly in pediatric ALL. CD22 is expressed on the vast majority of these tumors, and may provide an alternative treatment for these patients. In this dose escalation trial, we saw initial signs of activity, with 2 out of 7, or 29% of patients achieving a CR and no dose-limiting toxicities. These data include only one patient enrolled above the lowest dose in this trial. We recently achieved the first clinical milestone under our license agreement with Opus Bio, Inc. ("Opus Bio") for this product candidate, for which we paid Opus Bio a milestone payment in equity. We plan to enroll more patients and present additional data from this trial during 2016. Combining CD19

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and CD22 may increase the selection pressure on the cancer and significantly reduce the overall risk of relapse. As a result, we also plan to investigate combination approaches.

The trials for the product candidates targeting L1CAM, MUC-16, ROR-1, and WT-1 may provide greater insights into our technologies' applicability to a wider range of patients including those with common solid tumors. Our MUC-16 directed product candidate is an "armored" CAR that secretes the cytokine IL-12, which we believe may help overcome the inhibitory effects that the tumor micro-environment can have on T cell activity. We also plan to begin Phase I testing of our first CD19-directed "armored" CAR in one or more B cell malignancies within the next several months. We expect to have initial data from all of these product candidates over the next six to 18 months.

We believe there are a number of areas for ongoing research that may significantly impact our long-term success with CARs and TCRs, including:

- Cell Selection and Composition. We believe that a defined cell composition has the potential to improve the consistency, potency, cell persistence, and tolerability of CAR and TCR based treatments. The greater product composition consistency achieved with defined cell composition may also facilitate regulatory approval. We are exploring defined cell composition with several of our product candidates, including JCAR014 and JCAR017, which consist of a defined composition of T cells known as CD8+ and CD4+ T cells. We are continuing to focus on improving our understanding of the different types of T cells in an effort to identify the subsets of T cells that optimize efficacy and safety. We intend to leverage our experience with these product candidates as we advance our pipeline. Our acquisition of Stage Cell Therapeutics GmbH ("Stage") in 2015 gives us access to potential best-in-class cell selection technologies.
- Cell Persistence. We believe the persistence of our engineered T cells, meaning the duration of time CARs or TCRs have anti-tumor activity in the body, has a meaningful impact on clinical outcomes. We are continuing to invest in technologies to optimize the cell persistence of our genetically-engineered T cells, including technologies related to cell composition, cell signaling, non-immunogenic fully human single chain variable fragments ("scFvs"), and modulation of a patient's immune system. We are building internal capabilities through both hiring and via acquisitions such as X-Body, Inc. ("X-Body") and AbVitro, and collaborations with companies such as Editas and Fate Therapeutics.
- Target Protein Selection. We are using bioinformatics, in vitro analyses, animal data, and clinical experience to identify additional target tumor proteins. Our CAR and TCR technologies enable us to explore target proteins located inside cells ("intracellular proteins") and proteins located on the cell surface ("extracellular proteins"), giving us the potential to treat a wide array of cancers. We are also investing in technologies that have the potential to accelerate our generation of TCRs and CARs to new targets. For instance, our acquisition of AbVitro Inc. in early 2016 gave us access to a leading next-generation single cell sequencing platform that allows for the identification of full-length, natively paired antibodies and T cell receptors across millions of single cells simultaneously from patient tumor or blood samples.
- Cell Signaling. Researchers have used CAR T cells for more than two decades in the treatment of cancer. A key insight over the past decade was the addition of a costimulatory domain to the construct. The costimulatory domain amplifies intracellular signaling after the binding domain interacts with a target protein, magnifying the activation of the T cell. We are advancing two next-generation CAR technologies, which we refer to as bispecific CARs and "armored" CARs. Bispecific CARs incorporate a second binding domain on the CAR T cell designed to either amplify or inhibit signaling, a feature that may increase the CAR T cells' ability to distinguish between cancer cells and normal cells. "Armored" CARs deliver cytokines or other stimulatory signals to modify the tumor microenvironment. We believe these technologies may be important for the treatment of solid tumors.

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The following table summarizes our product candidate pipeline and our active and planned clinical trials:

Program	Description
CD19: JCAR015 (Adult ALL and Adult NHL)	• Adult ALL Phase I • Adult NHL (Post Autologous Tx) Phase I • Adult ALL Phase II Pivotal Study
CD19: JCAR017 (Pediatric ALL and Adult NHL)	• Pediatric ALL Phase I / II • Adult NHL Phase I
CD19: JCAR014 (Adult B Cell Malignancies)	• Adult B Cell Malignancies Phase I / II • Exploratory Pathway (Cell Population, Immune Modulation, Others) Phase I
CD19: JCAR021 Fully Human scFv (B Cell Malignancies)	• Adult B Cell Malignancies Phase I
CD19: "Armored" CAR (B Cell Malignancies)	• Adult B Cell Malignancies Phase I / II
CD19: Combination of JCAR014 with PD-L1 checkpoint inhibitor (Adult NHL)	• Adult NHL Phase I
CD22: JCAR018 Fully Human scFv (B Cell Malignancies)	• Pediatric ALL / NHL Phase I
WT-1: JTCR016 (AML, NSCLC)	• Adult AML Phase I / II • Adult NSCLC Phase I
L1CAM: JCAR023 (Neuroblastoma)	• Pediatric Neuroblastoma Phase I
MUC16 & IL-12: JCAR020 "Armored" CAR (Ovarian)	• Ovarian Phase I
ROR-1: JCAR024 (CLL, Solid Organ Tumors)	• ROR-1 Expressing Tumors Phase I

Our Strategy

Our current focus is to create best-in-class cancer therapies using human T cells. We believe that genetically-engineered T cells have the potential to meaningfully improve survival and quality of life for cancer patients. Key elements of our strategy include:

Expedite clinical development, regulatory approval, and commercialization of our CD19 product candidates. We began a Phase II trial in adult r/r ALL in mid-2015 with JCAR015 and a Phase I trial in adult r/r NHL in 2015 with JCAR017, with a potential to move to a registration trial in adult r/r NHL with JCAR017 in 2016 or early 2017. We believe data from these trials, if positive, may lead to an accelerated U.S. regulatory approval for the treatment of adult r/r ALL as early as 2017 and NHL thereafter. If approved in r/r ALL, we plan to commercialize this CD19 product candidate in the U.S. with our own specialty sales force. We expect that data from our U.S. registration trials for our CD19 product candidates will also serve as part of our European Union ("EU") regulatory package. We have begun dialogues with EU regulators and expect to enroll our first patients in clinical studies in the EU in 2016 or 2017. Celgene has an option to license certain assets, including immune-oncology product candidates, from our pipeline. If Celgene exercises this option, it will serve as our primary commercialization partner outside of North America and China.

Invest in our platform to maximize the beneficial outcomes for cancer patients. Because our CAR and TCR technologies are designed to target both proteins on the cell surface and inside the cell, we believe we have the potential to treat a wide array of cancers, including solid tumors. We believe there are multiple ways to continue to improve efficacy and tolerability of each of these technologies. We have begun Phase I trials for four product

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candidates targeting cancer-associated proteins other than CD19, and we expect to begin a fifth in early 2016. We plan to begin Phase I testing of our first CD19-directed “armored” CAR in one or more B cell malignancies within the next several months. As data emerge from these studies, we may advance one or more of these product candidates beyond proof of concept trials. We, together with our collaborators, intend to advance multiple additional product candidates into clinical testing over the next five years, with an increasing focus on addressing solid tumors, which cause the vast majority of cancer-related deaths in the developed world. Additionally, we believe that there may be multiple opportunities to improve the efficacy or safety of our product candidates by manipulating the genome, RNA, cell signaling pathways within a cell, or cell surface proteins. To that end, we have made substantial internal investments in these capabilities and entered into collaborations with companies such as Editas, Fate Therapeutics, and Celgene. We expect to continue to build our internal capabilities and to look to access best-in-class technologies outside the company with the goal of making better products for patients.

Develop process development and manufacturing capabilities to be a competitive advantage. We are investing significant resources to optimize process development and manufacturing. We believe these efforts will lead to better product characterization, a more efficient production cycle, and greater flexibility in implementing manufacturing enhancements. In turn, these improvements may lead to a lower cost of manufacturing, streamlined regulatory reviews, greater convenience for patients and physicians, and better patient outcomes. Additionally, this investment in characterizing and controlling our process has the potential to allow us to better exploit future biologic insights into what cell types improve patient outcomes. We have used contract manufacturing organizations (“CMOs”) to provide speed, flexibility and limit upfront capital investment, and successfully brought a CMO on-line to manufacture JCAR015. We have also established a Juno-run manufacturing facility in Bothell, Washington, and are in the process of completing the necessary steps for regulatory approval for this facility. We plan to begin manufacturing clinical trial material from this facility in 2016 and commercial products, subject to the required regulatory approvals, during 2017. In addition, in 2015 we acquired Stage, a company with potential best-in-class cell selection and cell activation technologies as well as automation technologies. We are integrating these technologies into our manufacturing platform. Our overall goal in process development and manufacturing is to maximize patient benefit and carefully manage our cost structure.

Leverage our relationships with our founding institutions, scientific founders and other scientific advisors. Our world-renowned scientific founders and founding institutions, have a history of seminal discoveries and significant experience in oncology, immunology, and cell therapy. We intend to be a science-driven company in all our strategic decision-making and to continue to use our scientific founders’ insights, discoveries, and know-how as we develop our pipeline and technologies.

Background

Immune System and T Cells

The immune system recognizes danger signals and responds to threats at a cellular level. It is often described as having two arms. The first arm is known as the innate immune system, which recognizes non-specific signals of infection or abnormalities as a first line of defense. The innate immune system is the initial response to an infection, and the response is the same every time regardless of prior exposure to the infectious agent. The second arm is known as the adaptive immune system, which is composed of highly specific, targeted cells and provides long-term recognition and protection from infectious agents and abnormal processes such as cancer. The adaptive immune response is further subdivided into humoral, or antibody-based, and cellular, which includes T cell-based immune responses.

The most significant components of the cellular aspect of the adaptive immune response are T cells, so called because they generally mature in the thymus. T cells are involved in both sensing and killing infected or abnormal cells, as well as coordinating the activation of other cells in an immune response. These cells can be

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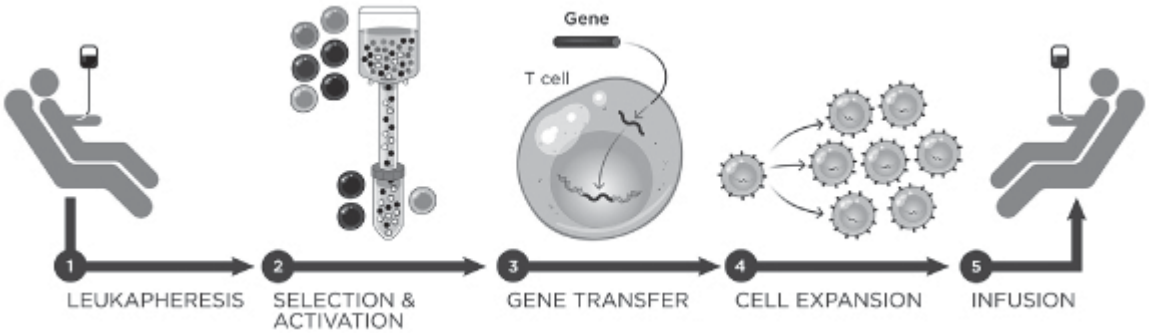
classified into two major subsets, CD4+ T cells and CD8+ T cells, based on cell surface expression of CD4 or CD8 glycoprotein. Both subsets of T cells have specific functions in mounting an immune response capable of clearing an infection or eliminating cancerous cells. CD4+ T cells, or helper T cells, are generally involved in coordinating the immune response by enhancing the activation, expansion, migration, and effector functions of other types of immune cells. CD8+ T cells, or cytotoxic T cells, can directly attack and kill cells they recognize as infected or otherwise abnormal, and are aided by CD4+ T cells. Both types of T cells are activated when their T cell receptor recognizes and binds to a specific protein structure expressed on the surface of another cell. This protein structure is composed of the major histocompatibility complex ("MHC") and a small protein fragment, or peptide, derived from either proteins inside the cell or on the cell surface. Circulating CD4+ and CD8+ T cells survey the body differentiating between MHC/peptide structures containing "foreign" peptides and those containing "self" peptides. A foreign peptide may signal the presence of an immune threat, such as an infection or cancer, causing the T cell to activate, recruit other immune cells, and eliminate the targeted cell.

Although the immune system is designed to identify foreign or abnormal proteins expressed on tumor cells, this process is often defective in cancer patients. The defective process sometimes occurs when the cancer cells closely resemble healthy cells and go unnoticed or if tumors lose their protein expression. Additionally, cancer cells employ a number of mechanisms to escape immune detection to suppress the effect of the immune response. Some tumors also encourage the production of regulatory T cells that block cytotoxic T cells that would normally attack the cancer.

Our CAR and TCR Technologies

Our CAR and TCR technologies alter T cells ex vivo, or outside the body, so that the T cells can recognize specific proteins on the surface or inside cancer cells or other diseased cells in order to kill those diseased cells. As depicted below, with both our CAR and TCR technologies, we (1) harvest a patient's white blood cells in a process called leukapheresis, and while ex vivo we (2) select and activate certain T cells of interest. (3) Gene sequences for the CAR or TCR construct are transferred into the T cell DNA using a viral vector, such as a lentivirus or a gamma retrovirus. The number of cells is (4) expanded until it reaches the desired dose. These genetically engineered cells are (5) infused back into the patient.



When the engineered T cell engages the target protein on the cancer cell, it triggers further multiplication of the cells in the body and activation of a cytotoxic, or cell-killing, response against the cancer cell. These T cells have an "auto-regulatory" capability that stimulates their multiplication in the presence of the target protein and a reduction in the number of such cells as the target protein declines.

The genetically-engineered CARs and TCRs are designed to help a patient's immune system overcome survival mechanisms employed by cancer cells. CAR technology directs T cells to recognize cancer cells based on expression of specific cell surface proteins, whereas high-affinity TCR technology provides the T cells with a specific T cell receptor that recognizes protein fragments derived from either intracellular or extracellular proteins. The differences in these two technologies may enable us to develop immunotherapies targeting a broad array of cancer-associated proteins, including those expressed by solid organ cancers.

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For both the CAR and TCR technologies, we believe that the T cell subsets used in treatment may have a significant impact on cell persistence, efficacy, and/or tolerability. We are investing significant resources in understanding the optimal cells and cell conditions for treatment. Animal data have shown that using a defined composition of CD8+ cells and CD4+ cells can improve the frequency, robustness, and duration of an anti-tumor response. Animal data have also shown that certain CD8+ T cells, when implanted, are more likely to persist as part of the T cell memory pool with the capability of self-renewal, which may lead to a longer duration of the therapeutic effect in patients. We believe our focus on optimizing cells and cellular conditions increases our probability of generating best-in-class therapeutics. Moreover, we believe that the enhanced product characterization that results from a defined cell population may provide greater consistency across patients and give us an improved process development and a potential advantage with clinicians, patients, and regulators.

In some patients, it may be important to control the proliferation and survival of the engineered T cells after they are infused. Our scientific founders have developed technology that inserts a gene into the cell that leads to expression of an inactive truncated EGF receptor ("EGFRt"). Commercially available antibodies, such as cetuximab, can bind to EGFRt and initiate a process that leads to rapid killing, or ablation, of the engineered T cells. This killing effect with cetuximab has been observed in animal studies, but not yet in human studies. Several of our product candidates, including JCAR014 and JCAR017, incorporate this technology. In some of our manufacturing processes, we also use EGFRt as means of identifying the T cells that have been genetically modified to include the CAR construct.

Differences between CARs and TCRs

There are three main differences between CARs and TCRs:

- Site of Protein Recognition. CARs recognize proteins expressed on the cell's surface, whereas TCRs recognize peptide fragments from proteins expressed either inside the cell or on the cell's surface. TCRs are capable of targeting a broader range of proteins and may be able to more selectively target cancer cells or target a broader array of tumor types.
- MHC Restriction. TCRs recognize proteins that are presented to the immune system as a peptide bound to an MHC, and are therefore restricted to a certain MHC type. MHC types vary across the human population. It is estimated that approximately 80% of the U.S. population has one of the four most common MHC types. Due to this variability, multiple different TCR product candidates will be needed to address any given target protein for a broad population. In contrast, CARs are capable of recognizing the target protein regardless of MHC type. Additionally, most of the TCR product candidates developed in the field to date have been designed to recognize peptides in the context of Class I MHC, which activates CD8+ cells and not CD4+ cells. The implications of the preferential CD8+ activation are not clear, but given the importance of CD8+ and CD4+ cells in a typical immune response, activation of a CD4+ cellular response is likely important in generating maximum efficacy.
- Maturity of the Technology. The life sciences industry has been developing antibodies for several decades and we believe scientific advances made with this technology can be leveraged to rapidly and predictably generate scFvs to incorporate into a CAR construct and enable it to target a specific protein. Industrial production of TCRs is relatively new, and we are investing in improving our understanding of important variables such as the optimal binding efficiency and structure.

CARs

There are several key components to our CAR technology, each of which may have a significant impact on its utility in cancer immunotherapy:

- Targeting Element. Our CAR construct typically uses an scFv, also referred to as a binding domain, to recognize a protein of interest. The scFv is derived from the portion of an antibody that specifically recognizes a target protein, and when it is expressed on the surface of a CAR T cell and subsequently binds to a target protein on a cancer cell, it is able to maintain the CAR T cell in proximity to the

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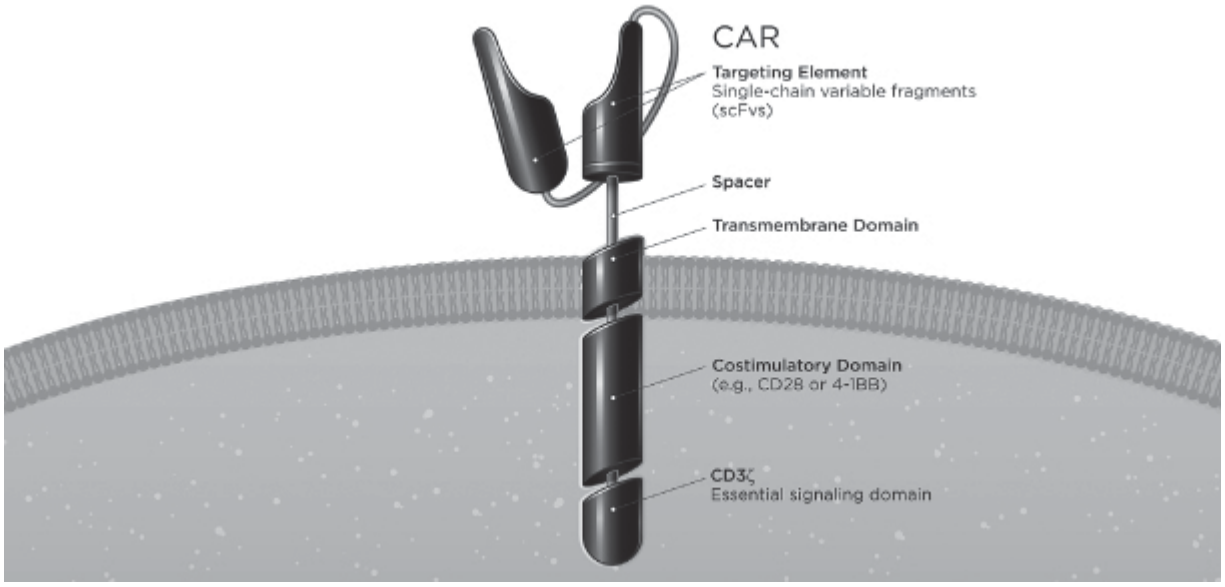
cancer cell and trigger the activation of the T cell. For example, our most clinically-advanced CAR T cell programs use an scFv from a mouse-derived antibody to target a cell surface protein called CD19. Through our 2015 acquisition of X-Body, we have access to a library of fully human scFvs and our AbVitro acquisition enables us to identify naturally occurring antibodies. We plan to use both of these technologies in the development of future product candidates.

- Spacer and Transmembrane Domain. The spacer connects the extracellular scFv targeting element to the transmembrane domain, which transverses the cell membrane and connects to the intracellular signaling domain. Data from our scientific founders suggest that the spacer may need to be varied to optimize the potency of the CAR T cell toward the cancer cell due to factors such as the size of the target protein, the region of the target protein where the scFv binds, and the size and affinity of the scFv. Through our collaborations, we have access to a library of spacer constructs.
- Costimulatory Domains. Upon recognition and binding of the scFv of the CAR T cell to the cancer cell, there is a conformational change that leads to an activation signal to the cell through CD3-zeta, an intracellular signaling protein. Our current CAR constructs also include either a CD28 or 4-1BB costimulatory signaling domain to mimic a "second signal" that amplifies the activation of the CAR T cells, leading to a more robust signal to the T cell to multiply and kill the cancer cell. Additionally, we are exploring the use of a "third signal" in improving the efficacy of our CAR T technology. In 2016, we intend to begin human testing of an "armored CAR" that include adding both a CD28 co-stimulatory domain and another signal through 4-1BB ligand.



Next-Generation CAR Technology

We are investing significant resources and are developing deep expertise on how each element of the CAR construct affects the potency and durability of the T cell response that ensues, as we believe these will be the key determinants for the long-term ability to create novel CAR T cell products with improved patient benefit.

As we build on the specificity of our technologies and our understanding of mechanisms of immune evasion used by cancer cells, we are advancing two next-generation CAR technologies that incorporate mechanisms to either dampen or amplify T cell activation signals present on the cancer cells or in the tumor microenvironment. Our "armored" CAR technology can incorporate the production or expression of locally acting signaling proteins to amplify the immune response within the tumor microenvironment with the goal of minimizing systemic side effects. An example of such a signaling protein is interleukin 12 ("IL-12"), which can stimulate T cell activation

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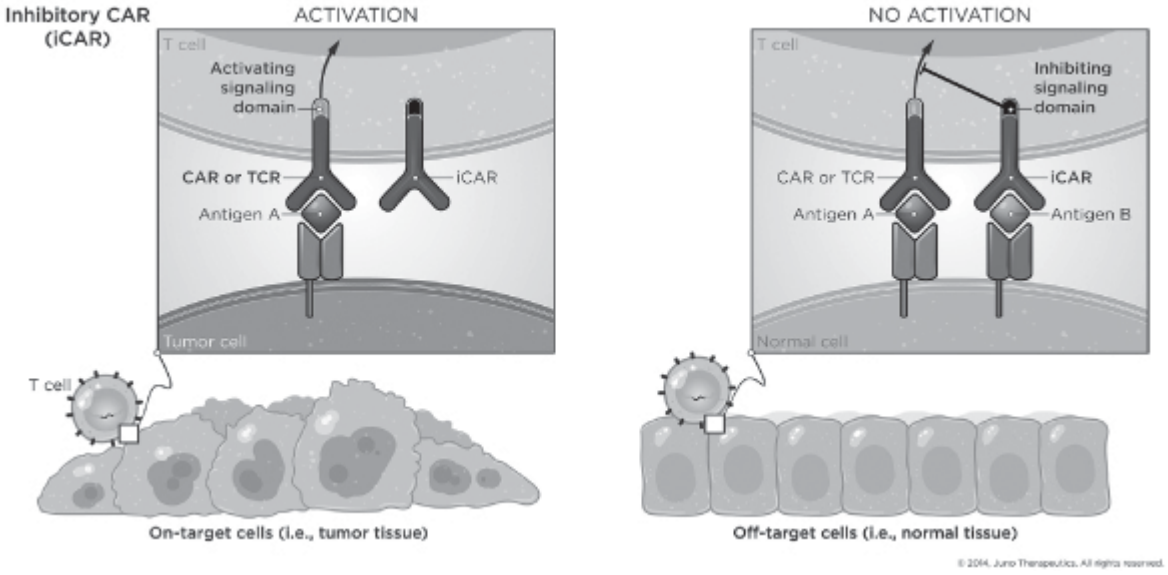
and recruitment. We believe “armored” CAR technology will be especially useful in solid tumor indications, in which microenvironment and potent immunosuppressive mechanisms have the potential to make the establishment of a robust anti-tumor response more challenging.

Our bispecific CAR technology, which includes a second binding domain on the CAR T cell designed to either amplify or inhibit signaling, a feature that may increase our CAR T cells’ ability to distinguish between cancer cells and normal cells. For example, a CAR T cell can be engineered such that it would be triggered in the presence of one target protein, but if a second protein is present it would be inhibited. Alternatively, it could also be engineered such that two target proteins would be required for maximal activation. These approaches may increase the specificity of the CAR for tumor relative to normal tissue.

The exhibit below shows a bispecific CAR, in this case an inhibitory CAR (“iCAR”) that employs an inhibitory signal to improve specificity.



We are also exploring a number of technologies that modulate T cell biology and their biologic properties in patients. For example, we have partnered with Editas, a leader in applying genome editing such as CRISPR/Cas9 and Talon technologies to create human therapeutics, and Fate Therapeutics, a leader in using pharmacologic modulators such as small molecules to alter the properties of cells while they are ex vivo. With Editas, we are exploring the biologic implication on our engineered T cell technologies of knocking-out or altering the function of a number of human genes. With Fate Therapeutics, we are exploring the potential for these modulators to alter intracellular signaling pathways, with the potential to alter the subtype of T cell or the state of the T cell. The goal of these modifications is to improve efficacy and safety of our products.

TCRs

Much like our CAR technology, our high-affinity TCR technology is designed to activate a potent immune response against cancer through the introduction of engineered T cells. The gene sequence we introduce with our TCR technology encodes for the proteins required to assemble a TCR that recognizes a specific MHC/peptide structure. Modified T cells expressing a TCR construct have the potential advantage of recognizing peptides from cancer-associated proteins expressed either on the surface of or inside the tumor cell, which may allow us to target a broad range of tumors. Beyond the fact that TCRs can recognize peptides derived from intracellular proteins, another advantage of TCRs is that they are fully human and therefore may be less likely to elicit an immune response against the infused TCR cells.

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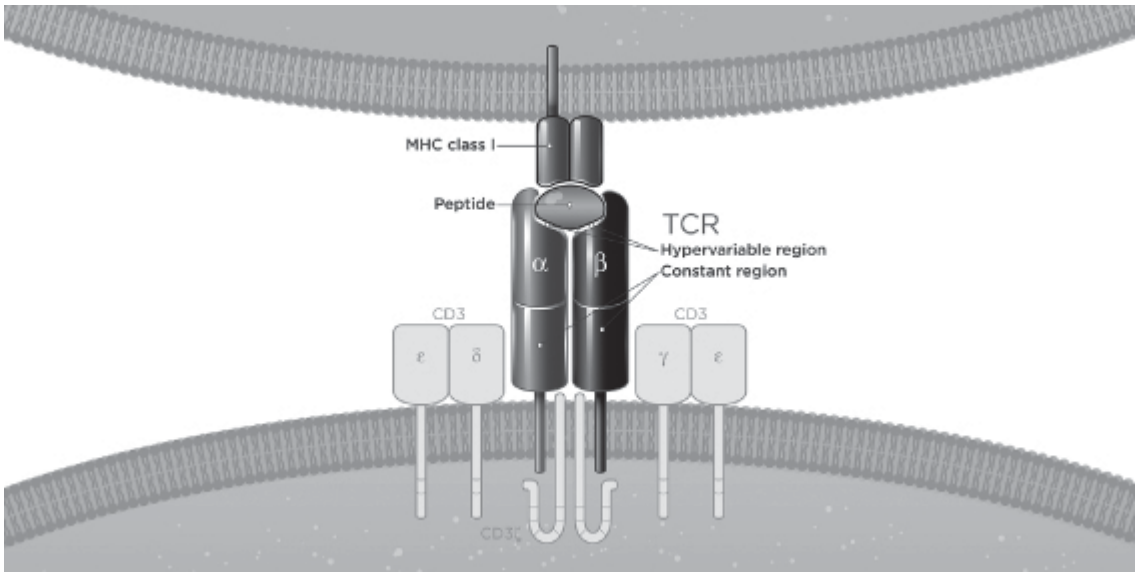
The engagement of a TCR is restricted to a certain MHC type. Due to the variability of MHC types across the human population, different TCRs will be required for various segments of the population. Our TCR constructs are selected by screening healthy donors for naturally-occurring high-affinity TCRs against a MHC/ peptide combination of interest. Depending on the binding affinity of the selected TCR construct, it is either used directly or modified by mutating a specific region, the hypervariable domain, of the TCR binding pocket to create a higher affinity construct. Based on the limited number of patients who have received any TCR treatment to date, these TCR cells appear to behave like endogenous T cells after re-infusion back into the patient. They undergo a process similar to an endogenous T cell of cell expansion and cytotoxic activation upon recognition of their defined cancer-associated proteins.



Important areas of investment for us going forward will be industrializing the creation and manufacturing of TCRs, improving screening processes to better ensure that TCR constructs do not cross-react with normally expressed or other proteins, and finding costimulatory signals to enhance the potency of the genetically engineered cells.

We recently acquired AbVitro, a company based in Boston, Massachusetts with technology to perform next-generation, high throughput, single cell sequencing. This technology allows us to interrogate millions of cells per experiment. An important application for this technology will be to find high affinity, naturally occurring, matched chain TCRs from the normal human immune repertoire, which we believe have a lower risk of unexpected off-target binding than TCRs that have manipulated or mutagenized during development. We believe this technology will significantly improve the speed at which we find these TCRs, allowing us to optimize binding affinity and develop TCRs for a larger percentage of the population.

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Product Pipeline

CD19-Directed Product Candidates

Overview

Our three most advanced clinical candidates, JCAR015, JCAR017, and JCAR014, use CAR T cell technology to target CD19. We have worldwide rights to commercialize each of these product candidates. These product candidates differ in several respects as outlined below. We believe our access to and clinical experience with multiple CD19 CARs in patients with B cell malignancies gives us the opportunity to bring best-in-class therapies to market across a range of different blood cancers. We have treated over 250 patients with anti-CD19 CAR T cells.

CD19-Directed Clinical Product Pipeline Overview

	JCAR015	JCAR017	JCAR014
Binding Domain	SJ25C1	FMC63	FMC63
Indications	Adult ALL	Pediatric ALL Adult aggressive NHL	NHL, Adult ALL, CLL
Costimulatory Domain	CD28	4-1BB	4-1BB
Cell Population	CD4+ & CD8+ upfront selection	CD4+ & CD8+ in a defined ratio	CD4+ & CD8+ in a defined ratio
Ablation Technology	None	EGFRt	EGFRt
Viral Vector	Gamma Retroviral	Lentiviral	Lentiviral

We believe CD19 presents an attractive immunotherapeutic target for our technology for a number of reasons:

- CD19 is expressed by most B cell malignancies including NHL, ALL, and CLL. Within these CD19 positive malignancies, it is generally expressed on all of a patient's cancer cells.
- CD19 is expressed on all stages of B lineage cells, and it is present in the vast majority of precursor B cell ALL cases.
- CD19 is not known to be expressed on any healthy tissue other than B cells. Although treatment with a CD19-directed therapy has the potential to deplete B cells, experience with Rituxan has shown that humans can live with B cell depletion for a prolonged period. Further, CD19 is not expressed on hematopoietic stem cells, and therefore B cells should return when the CAR T cell is no longer present.

B Cell Acute Lymphoblastic Leukemia

ALL is an uncontrolled proliferation of lymphoblasts, which are immature white blood cells. The lymphoblasts, which are produced in the bone marrow, cause damage and death by inhibiting the production of normal cells. Approximately 6,000 patients are diagnosed with ALL in the United States each year, and although just over half of the new diagnoses are in adult patients, the vast majority of the approximately 1,400 deaths per year occur in adults. There are two main types of ALL, B cell ALL and T cell ALL. Approximately 80% of cases of ALL are B cell ALL, which we aim to address with our CD19 product candidates.

Treatment outcomes for ALL patients can be distinguished between CR and CRm rates. CR occurs when there is no clinical evidence of the disease based on less than 5% blast cells in the marrow, blood cell counts within normal limits, and no signs or symptoms of the disease. CRm occurs when a patient has all of the above outcomes and there is no evidence of ALL cells in the marrow when using sensitive tests such as polymerase chain reaction ("PCR") and/or flow cytometry. CR rates are the typical regulatory standard, but recent evidence suggests patients that achieve a CRm have a better long-term prognosis.

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Current standard-of-care treatment for both adults and children involves multi-drug chemotherapeutic regimens, and in some cases hematopoietic stem cell transplant ("HSCT"). In adults with ALL, approximately 80% of patients will demonstrate a complete remission with their initial course of chemotherapy. However, approximately 60% of patients who have so demonstrated a complete remission with their initial course of chemotherapy will relapse. Most patients that relapse after the first course of chemotherapy will die in well under a year, and patients that have failed at least two salvage therapies have a median survival that is typically around three months. Allogeneic HSCT, which uses hematopoietic stem cells from a matched donor, offers the potential for disease eradication in some individuals, however, the option is available only to approximately a third of patients due to the lack of compatible stem cell source, general health, or the high risk of complications. Even with HSCT, approximately 20-30% of patients die of treatment-related complications and the median disease-free survival is less than six months.

ALL Efficacy with Current Standard of Care Therapy

ALL Treatment Course	CR Rate (Complete Remission)
1st Induction	80-90%
1st Salvage Chemotherapy	31-44%
>1st Salvage Chemotherapy	20-23%
>2nd Salvage Chemotherapy	5-8%

Antibody-based platforms, including bispecific T cell enhancers ("BiTEs") and antibody–drug conjugates ("ADCs") have also been explored in this disease setting. The FDA granted accelerated approval in late 2014 to blinatumomab, a CD19 BiTE given by continuous infusion due to its short serum half life, for treatment of individuals with r/r Philadelphia-chromosome negative ALL. Despite a CR rate of 42% and a CRm rate of 31%, which represent a meaningful improvement versus historical standards, the median duration of response was just under 6 months. Another novel agent, inotuzumab ozogamicin ("inotuzumab"), a CD22 monoclonal ADC conjugated to calicheamicin, has been studied in adults with r/r ALL. The reported results from a Phase III randomized trial of inotuzumab plus induction chemotherapy, as compared against induction chemotherapy on its own, demonstrated a CR rate of 81% but a median duration of response of 4.6 months. Although these novel agents have improved CR rates, such outcomes are not uniform with later relapses, higher burden disease, or in all age groups. Thus, significant unmet need remains. Of note, the majority of inotuzumab treated patients were in first relapse, while the blinatumomab data and data for JCAR015 are primarily in patients after a second or greater relapse.

B Cell Non-Hodgkin Lymphomas

NHL is the most common cancer of the lymphatic system. NHL is not a single disease, but rather a group of several closely related cancers. Although the various types of NHL have some things in common, they differ in their appearance under the microscope, their molecular features, their growth patterns, their impact on the body, and treatment. Over 70,000 cases of NHL are diagnosed annually in the United States, and 85% derive from B cell lineages, which express CD19. B cell NHLs are a large group of cancers that are typically divided into aggressive (fast-growing) and indolent (slow-growing) types.

Aggressive NHL also represents a collection of lymphoma subtypes. The most common histologic type of aggressive lymphoma is diffuse large B cell lymphoma ("DLBCL"), which is also the most common subtype of all NHLs, and represents approximately 40% of new cases annually. Unlike indolent lymphomas, which have a median survival time as long as 20 years, DLBCL, if left untreated, may have survival measured in weeks to months. Patients often present with a rapidly enlarging mass in a lymphatic region. Extranodal involvement or

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associated constitutional symptoms are uncommon, although the presence of these symptoms indicates a more aggressive phenotype. Patients with DLBCL who are unable to undergo autologous HSCT and are treated solely with chemotherapy have a poor prognosis with a median survival of approximately six months, compared to a median survival of approximately 12 months for patients who are able to undergo autologous HSCT.

The indolent lymphomas represent a wide group of tumors that often have a long natural history characterized by frequent relapses; together, the indolent lymphomas account for approximately 55% of NHL incidence in the United States. Although these malignancies are treated routinely with a combination of chemotherapy and antibodies, there is no standard of care for relapsed indolent NHL. The typical treatment approaches include multiple rounds of induction chemotherapy or more aggressive salvage therapies, including autologous HSCT, which uses the patient's own hematopoietic stem cells. Unfortunately, these treatments are generally not curative. Patients with recurrent or progressive indolent lymphoma may be candidates for allogeneic HSCT, which can provide long-term disease free survival to some.

Chronic Lymphocytic Leukemia

CLL is the most common type of leukemia, and it occurs most frequently in older individuals, with diagnoses in persons under 30 years of age occurring only rarely. Each year, approximately 21,000 patients are diagnosed with CLL in the United States. Nearly all CLL is characterized by CD5+ B cells, which express CD19. Approximately 80–85% of individuals with CLL have standard risk disease at diagnosis, and for them the level of disease burden determines both prognosis and the need for immediate treatment or "watchful waiting" before the initiation of any therapy. Over time, CLL develops poor risk features, including expression of CD38, ZAP70, unmutated immunoglobulin heavy chain sequences, or cytogenetic abnormalities or gene mutations. Approximately 15–20% of CLL patients can initially present with poor risk disease. Median progression-free survival in these high risk groups is often under 12 to 18 months after frontline therapy, and less than 12 months in relapsed/refractory disease.

The goal of therapy in CLL for individuals with both treatment naïve and relapsed/refractory disease is a clinical complete response. Strong correlations have been demonstrated between depth of response, specifically to levels below detectable MRD by flow cytometry, and survival. An array of therapies have been evaluated and approved for use in treatment naive and relapsed/refractory CLL, including combination chemotherapy, chemoimmunotherapy, ibrutinib, idelalisib, alemtuzumab, and ofatumumab, and several others continue in development. However, the enthusiasm for these agents has generally been tempered by the low likelihood of complete responses, challenging toxicities, and limited duration of disease responses. Individuals with CLL are generally not considered candidates for allogeneic or autologous transplantation due in part to the median age of 71 years at diagnosis. Therefore, significant opportunity exists for novel therapies to address this unmet need with agents that are tolerated in this patient population.

JCAR015

Overview. JCAR015 is our most advanced development product candidate, and in an ongoing Phase I study, it has demonstrated clinically meaningful complete remission rates in adult patients with r/r ALL. As a result, we have begun a Phase II, multicenter pivotal trial in this setting. JCAR015 uses a CD28 costimulatory domain and a CD4+ and CD8+ selection step to select out T cells from peripheral blood mononuclear cells ("PBMC"). This combined CD4+ and CD8+ selection process significantly reduces B cell leukemia contamination. JCAR015 was originally developed at MSK. The trials for JCAR015 have not employed any manufacturing screening assay to exclude patients from treatment, which may broaden the scope of any eventual marketing approval of JCAR015 as compared to others' CD19 directed product candidates where such assays have been used.

Clinical Experience. JCAR015 continues enrolling r/r ALL patients in a single-center, Phase I open label clinical trial. This trial was initiated in January 2010. An investigational new drug ("IND") application for JCAR015 was submitted in January 2007 by MSK, the Phase I trial sponsor for the treatment of relapsed/refractory CLL. The

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IND was amended in September 2009 to add a protocol for the treatment of r/r ALL in adults. The main goals of the trial are to determine the safety and appropriate dose of the modified T cells in patients with B cell malignancies. We have focused our efforts in this trial and with this therapy towards patients with r/r ALL, a patient population with few or no alternatives. Initially, patients enrolled in this trial received low-intensity conditioning chemotherapy prior to receiving their CAR T cell dose, but more recently, the trial has also evaluated alternative pre-conditioning regimens and novel cell dosing schedules for use in our pivotal Phase II trial.

As of a data cutoff date of November 2, 2015, 82% of the 45 evaluable patients receiving CAR T cells achieved CR and 67% of patients achieved a CRm using PCR and/or flow cytometry in a population relapsed or refractory to prior intensive chemotherapy and/or novel antibody regimens.

Summary of Clinical Data
JCAR015

	Disease Burden(1)		
	Minimal Residual	Morphologic(2)	Total
Number of Patients	21	25(3)	46(3)
Complete Remission(4)	19/21 (90%)	18/24 (75%)	37/45 (82%)
Complete Molecular Remission(5)	15/21 (71%)	15/24 (63%)	30/45 (67%)
Severe CRS(6)	0/21 (0%)	11/25 (44%)	11/46 (24%)
Grade 3 and Above Neurotoxicity	3/21 (14%)	10/25 (40%)	13/46 (28%)

(1) Minimal residual disease = presence of no more than 5% lymphoblasts in a patient's bone barrow; morphologic disease = more than 5% lymphoblasts in a patient's bone marrow
(2) Includes one subject with extra-medullary disease only
(3) Includes one subject who was evaluable for safety outcomes, but not for efficacy
(4) Includes both complete remission and complete remission with incomplete hematological recovery
(5) Measured by flow cytometry or PCR
(6) Defined as requiring mechanical ventilator or significant vasopressor support

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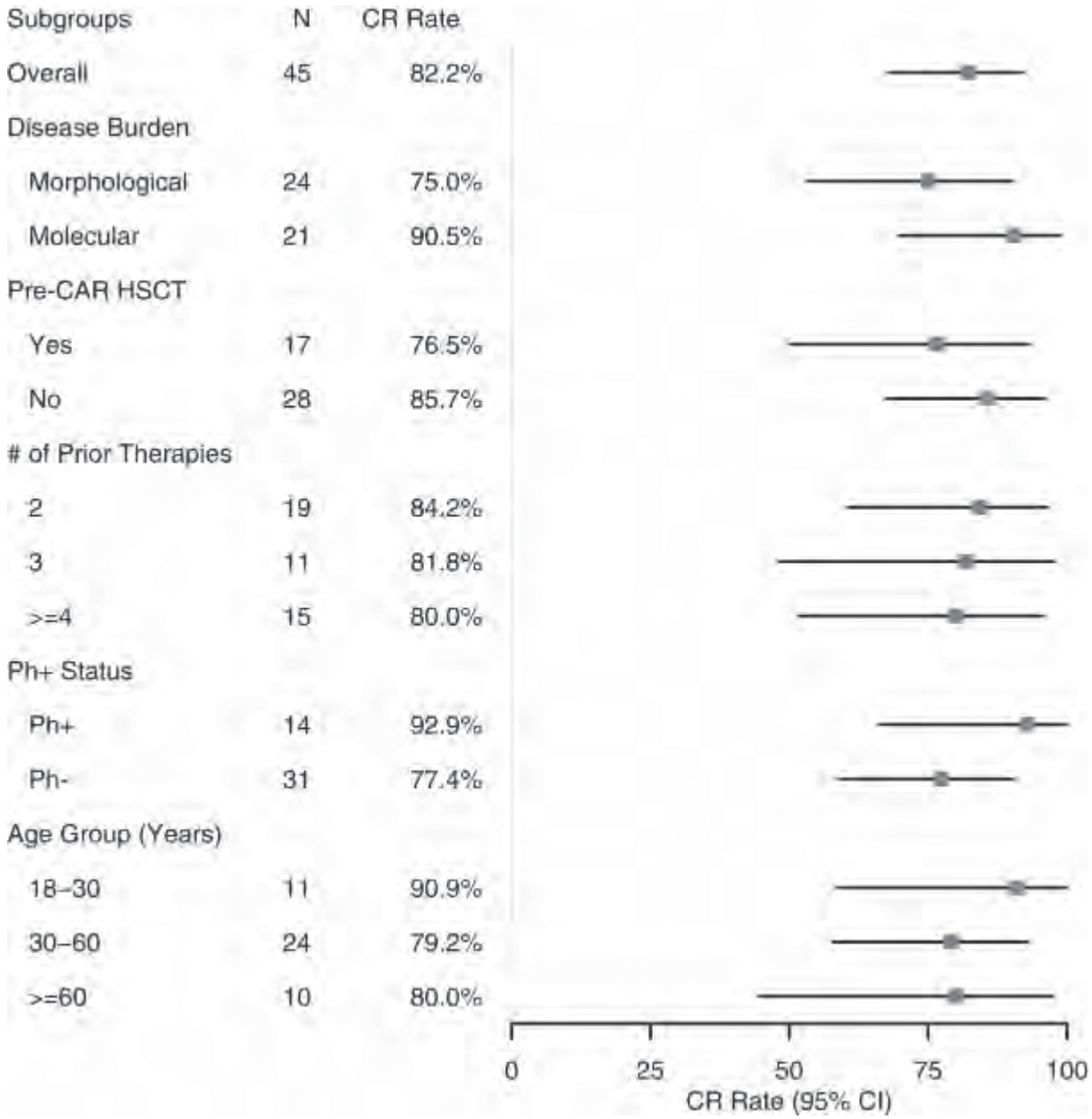
As demonstrated by the following chart, CR rates were consistent across demographic and disease characteristics.

Summary of CR by Subgroups
JCAR015



The notable side effects of JCAR015 are severe cytokine release syndrome ("sCRS") and severe neurotoxicity. sCRS is a condition that, by convention, is currently defined clinically by certain side effects, including hypotension, or low blood pressure, when such side effects are serious enough to lead to intensive care unit care with mechanical ventilation or significant vasopressor support. CRS is generally believed to result from the release of inflammatory proteins in the body as the CAR T cells rapidly multiply in the presence of the target tumor proteins. Severe neurotoxicity can have several clinical manifestations, including confusion, aphasia, encephalopathy, myoclonus and generalized seizure.

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Severe neurotoxicity is defined as events having grade 3 or higher severity as defined by Common Terminology Criteria for Adverse Events ("CTCAE") for each manifestation. These severe neurotoxicity events may require ICU level care. As of a data cutoff date of November 2, 2015, approximately 24% of 46 adult r/r ALL patients experienced sCRS, with a rate of 0% in patients with minimal residual disease and 44% in patients with morphologic disease. Approximately 28% of 46 adult r/r ALL patients experienced severe neurotoxicity, with a rate of 14% in patients with minimal residual disease and 40% in patients with morphologic disease. We define minimal residual disease as the presence of no more than 5% lymphoblasts in a patient's bone marrow and morphologic disease as more than 5% lymphoblasts in a patient's bone marrow. Among the patients with sCRS, there have been two deaths that we believe were either directly or indirectly related to sCRS. Other than sCRS and severe neurotoxicity, JCAR015 has been generally well tolerated.

The following table identifies the prevalence of adverse events that are at least possibly related to JCAR015 based on clinical data through November 2, 2015 that are CTCAE grade 3 or higher.

Grade 3 or Higher Treatment-Emergent Adverse Events that Are at Least Possibly Related to Study Treatment
JCAR015

	Total Treated (N=46)
Any AE as Specified	40 (87.0%)
Blood and lymphatic system disorders	21 (45.7%)
Febrile neutropenia	21 (45.7%)
Cardiac disorders	5 (10.9%)
Atrial fibrillation	1 (2.2%)
Atrial tachycardia	1 (2.2%)
Sinus tachycardia	3 (6.5%)
Left ventricular dysfunction	1 (2.2%)
General disorders and administration site conditions	5 (10.9%)
Pyrexia	3 (6.5%)
Chills	1 (2.2%)
Fatigue	1 (2.2%)
Infections and infestations	3 (6.5%)
Pneumonia	1 (2.2%)
Sepsis	1 (2.2%)
Sinusitis	1 (2.2%)
Investigations	16 (34.8%)
Alanine aminotransferase increased	6 (13.0%)
Blood alkaline phosphatase increased	6 (13.0%)
Aspartate aminotransferase increased	6 (13.0%)
Blood bilirubin increased	5 (10.9%)
Blood creatinine increased	2 (4.3%)
Blood creatine phosphokinase increased	1 (2.2%)
Neutrophil count	1 (2.2%)
Neutrophil count decreased	1 (2.2%)
Metabolism and nutrition disorders	32 (69.6%)
Hypocalcaemia	21 (45.7%)
Hypophosphataemia	25 (54.3%)
Hyperglycaemia	10 (21.7%)
Hypokalaemia	11 (23.9%)
Hyponatraemia	6 (13.0%)

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	Total Treated (N=46)
Hyperkalaemia	4 (8.7%)
Hypermagnesaemia	2 (4.3%)
Hypertriglyceridaemia	1 (2.2%)
Hypoalbuminaemia	1 (2.2%)
Nervous system disorders	14 (30.4%)
Encephalopathy	14 (30.4%)
Paraesthesia	1 (2.2%)
Peripheral motor neuropathy	1 (2.2%)
Seizure	1 (2.2%)
Respiratory, thoracic and mediastinal disorders	8 (17.4%)
Hypoxia	6 (13.0%)
Dyspnoea	3 (6.5%)
Respiratory failure	2 (4.3%)
Skin and subcutaneous tissue disorders	1 (2.2%)
Dermatitis acneiform	1 (2.2%)
	1 (3.6%)
Erythema multiforme	1 (2.2%)
	1 (3.6%)
Vascular disorders	14 (30.4%)
Hypotension	14 (30.4%)
	9 (32.1%)
Hypertension	1 (2.2%)
Gastrointestinal disorders	1 (2.2%)
Small intestinal haemorrhage	1 (2.2%)
Renal and urinary disorders	1 (2.2%)
Acute kidney injury	1 (2.2%)
Uncoded Events	1 (2.2%)
Muscle weakness - extremity-lower	1 (2.2%)
Immune system disorders	3 (6.5%)
Cytokine release syndrome	3 (6.5%)

Several protocol changes were made in April 2014 after treatment-emergent adverse events led to the death of two patients. The most important changes included using a lower dose of CAR T cells (1x10^6/kg vs 3x10^6/kg) in patients with morphologic r/r ALL, excluding patients with Class III or IV congestive heart failure as defined by the New York Heart Association, excluding patients with active central nervous system leukemia or symptomatic central nervous system leukemia within 28 days, adding sCRS as a dose limiting toxicity, and restricting a patient from receiving a second treatment of JCAR015 if the patient experienced any non-hematologic CTCAE grade 4 toxicities, including sCRS, with the prior JCAR015 treatment. Prior to the protocol changes, patients typically received a dose of 3x10^6 CAR T cells/kg regardless of the level of disease burden. We continue to examine the effect of a second scheduled dose delivered approximately three weeks following the first dose and the use of alternative pre-conditioning regimens containing fludarabine and cyclophosphamide. We expect to have additional data from this trial over the next six to 18 months.

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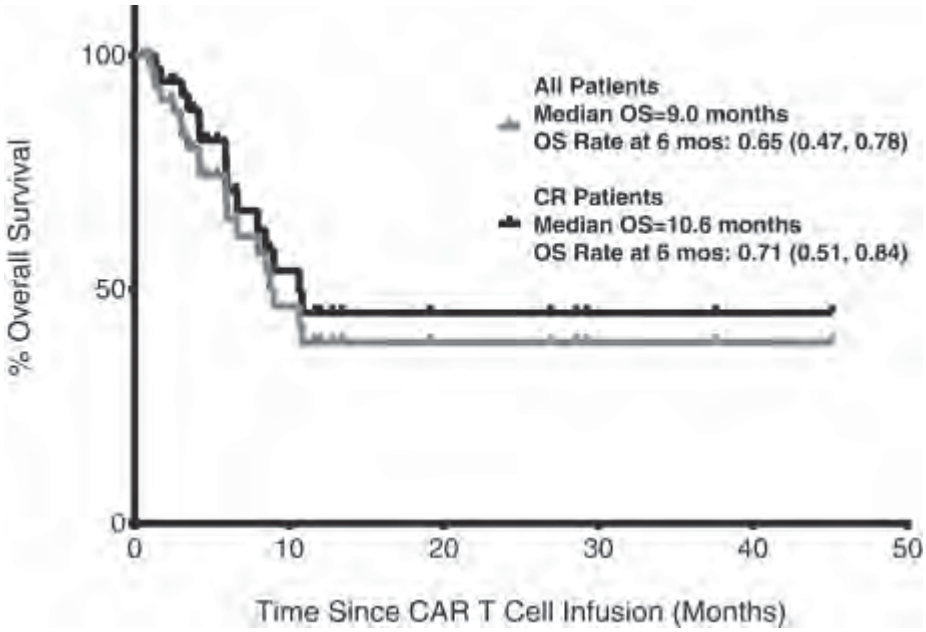
In the following figure, we show the investigator-reported survival rate as of November 2, 2015 of the 45 evaluable r/r ALL patients treated with JCAR015. Although it is difficult to compare across trials, the survival rate compares favorably to historical controls, which have a median survival of approximately three months, and one-year overall survival of approximately 14%. In this single arm Phase I trial, individuals achieving a CR demonstrated a plateau in overall survival of approximately 50% at one year and beyond (Kaplan-Meier estimate of OS rate at 12 months is 0.45 with 95% confidence interval of [0.25, 0.63]).

Overall Survival: All JCAR015 Patients



Source: MSK ASH 2015 Presentation

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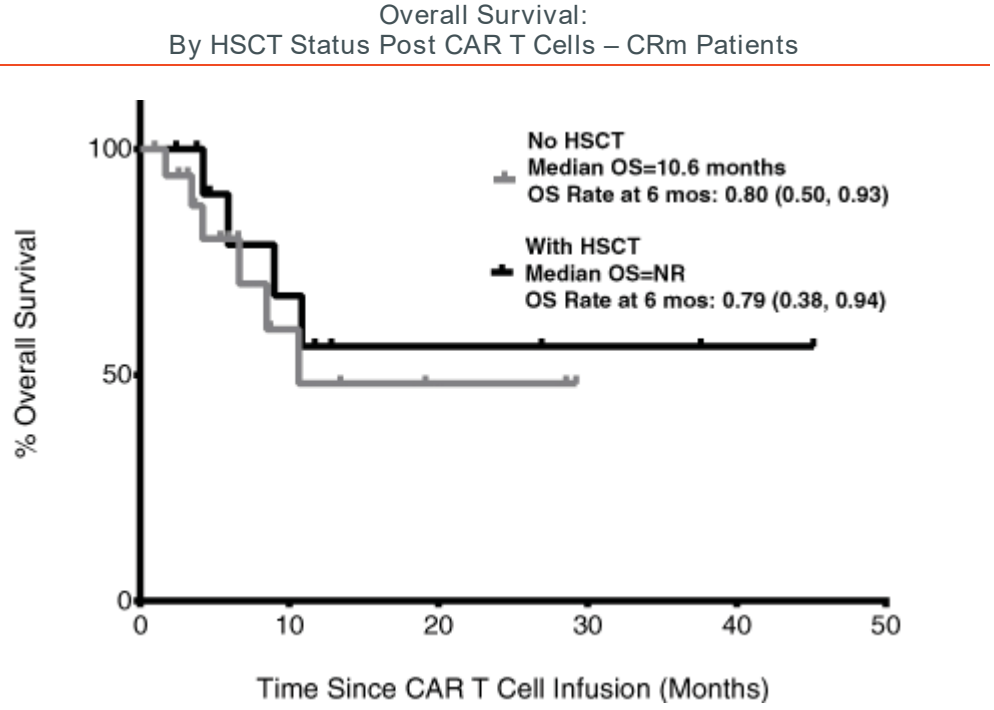
Patients with r/r ALL who achieve a CR with treatment may proceed to an allogeneic HSCT. In this trial, 13 patients have, as of a data cutoff date of November 2, 2015, received an allogeneic HSCT after attaining a CR with JCAR015. In the figure below, we show the investigator-reported survival rate as of November 2, 2015 of r/r ALL patients treated with JCAR015 that responded to treatment, with separate curves for patients that receive an allogeneic HSCT at some point after treatment and those that do not.



Source: MSK ASH 2015 Presentation.

We began a Phase II, multicenter, pivotal trial in 2015 under a Juno-sponsored IND. We plan to treat approximately 90 adult r/r ALL patients with JCAR015 across more than 15 world-class cancer centers in order to have approximately 50 evaluable patients, which is defined as r/r ALL patients with morphologic ALL at the time of JCAR015 infusion. The trial design includes optimized dosing schedule and pre-conditioning. The primary endpoint is overall response rate, defined as the proportion of subjects with CR or CR with incomplete hematological recovery. Patients will also be evaluated and followed for several secondary endpoints, including but not limited to safety, durability of responses, cellular kinetics, disease control rate, and comparability of Phase II manufacturing product to Phase I manufacturing product.

JCAR017

Overview. JCAR017 also targets CD19, but differs from JCAR015 in several important respects. JCAR017 uses the 4-1BB costimulatory domain, a different scFv binding domain and a defined cell composition made up of a 1:1 ratio of CD4+ T cells and CD8+ T cells. This defined cell composition is attained by using separate CD4+ and CD8+ selection and processing and then controlling for the number of each cell subtype in the final product. This minimizes the leukemia contamination risk and provides a consistent T cell phenotype ratio.

JCAR017 is currently in development for pediatric patients with r/r ALL, and more recently, for adults with r/r aggressive NHL. In the Phase I/II pediatric r/r ALL trial, the Phase I portion initially enrolled patients whose leukemia has recurred after an allogeneic HSCT, but later the entry criteria were broadened to include all

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pediatric patients with r/r ALL. JCAR017 was originally developed at Seattle Children's Research Institute ("SCRI"). A Phase I NHL trial began in 2015 and is enrolling adults with r/r aggressive NHL to explore this product candidate's efficacy in this setting and to explore multi-dose schedules.

Clinical Experience. JCAR017 is being evaluated in a Phase I/II clinical trial in pediatric r/r ALL. An IND application for JCAR017 was submitted in November 2013 by SCRI, the Phase I/II trial sponsor, for the treatment of CD19 positive pediatric leukemia. The trial was initiated in January 2014. The Phase I/II trial is designed to evaluate four dose levels: 5x10^5 T cells/kg, 1x10^6 T cells/kg, 5x10^6 T cells/kg, and 1x10^7 T cells/kg. The primary endpoints of the trial are to evaluate the preliminary toxicity, safety, and efficacy of JCAR017, and the feasibility of manufacturing and releasing JCAR017, in children and young adults with CD19- positive pediatric leukemia. The secondary endpoints of the trial include assessing persistence of the modified T cells and potentially assessing the efficacy of cetuximab to eliminate the modified T cells. Patients enrolled in this trial initially received low-intensity chemotherapy prior to receiving their CAR T cell dose, and maximum tolerated dose was determined to be 5x10^6 T cells/kg. More recently, a much lower cell dose of 5x10^5 T cells/kg has been tested with intensified pre-conditioning, and early results with this regimen have demonstrated an improved risk/benefit profile for this agent.

Based on investigator-reported data presented at the American Association for Cancer Research Annual Meeting held in April 2015 ("AACR 2015"), as of a data cutoff date of April 10, 2015, 22 patients had been treated in the Phase I portion of the trial, of which 91% experienced a CRm, as represented by the following table:

Summary of Clinical Data
JCAR017

Number of Patients	22
CR	21/22 (95%)(1)
CRm(2)	20/22 (91%)(1)
sCRS(3)	6/22 (27%)
Severe Neurotoxicity	4/22 (18%)

(1) One non-responder received steroids at line placement for apheresis
(2) Measured by flow cytometry
(3) Defined as requiring mechanical ventilator or significant vasopressor support

Source: SCRI AACR 2015 Presentation.

In an investigator-reported update of outcomes presented at CIPO 2015, as of a data cutoff date in September 2015, 91% (29/32) patients have experienced a CRm.

Patients treated in this trial have experienced the highest cell expansion and longest cell persistence in the body of any of our CD19-directed product candidates prior to the introduction of flu/cy conditioning. Improving cell expansion and persistence translates into an increase in exposure of cancer cells in the body to the CAR T cells, the active ingredient in our treatment. Increasing this exposure is an important goal of our basic and translational research. We believe, and data from studies for product candidates such as JCAR014 show, that increasing this exposure translates into improved clinical benefit. Additionally, JCAR017 is a defined cell product that has a number of manufacturing related advantages compared to JCAR014 that may translate into both better clinical results and long-term cost of goods. Because of these potential advantages in both exposure and manufacturing, we have chosen to move forward with JCAR017 as the backbone for our multi-center, Phase I trial in r/r NHL. We also plan to study it across a number of additional treatment settings if results continue to support these potential advantages.

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We began a multicenter Phase I trial in 2015 of JCAR017 in adults with r/r aggressive NHL under a Juno-sponsored IND. We plan to treat approximately 48 r/r NHL patients in this Phase I trial. The primary endpoints of the trial are to evaluate preliminary toxicity, safety, and cell expansion and cell persistence of JCAR017. The secondary endpoints of the trial include assessing efficacy, durability of responses, progression-free survival, and overall survival.

JCAR014

Overview. JCAR014 also targets CD19. JCAR014 uses the 4-1BB costimulatory domain and is composed of CD8+ T cells and CD4+ T cells in a defined ratio. JCAR014 was originally developed at the Fred Hutchinson Cancer Research Center ("FHCRC").

Clinical Experience. JCAR014 is being evaluated in a Phase I/II trial as a treatment for adults with any of several B cell malignancies, including ALL, NHL, and CLL, in patients relapsed or refractory to standard therapies. An IND application for JCAR014 was submitted in March 2013 by FHCRC's Stanley Riddell, the Phase I/II trial sponsor, for the treatment of CD19-positive advanced B cell malignancies. The trial was initiated in May 2013. The Phase I/II trial is designed to evaluate three dose levels: 2x10^5 T cells/kg, 2x10^6 T cells/kg, and 2x10^7 T cells/kg. The highest dose level of 2x10^7 T cells/kg has been discontinued as it exceeded the maximum tolerated dose as defined by the study. The primary endpoint of the trial is to evaluate the feasibility and preliminary safety of using JCAR014 to treat CD19-positive advanced B cell malignancies. The secondary endpoints of the trial include assessing the duration of persistence of the modified T cells, determining whether the modified T cells traffic in the bone marrow and function in vivo, determining if the modified T cells have antitumor activity in patients with measurable tumor burden prior to T cell transfer, and determining if the treatment is associated with tumor lysis syndrome. As of a data cutoff date of December 1, 2015, 71 patients have been treated in the Phase I portion of the trial, of which 30 patients had r/r ALL, 32 patients had r/r NHL, and nine patients had r/r CLL. Patients enrolled in this trial initially received low-intensity chemotherapy prior to receiving their CAR T cell dose. This trial has systematically evaluated alternative pre-conditioning regimens and established a flu/cy pre-conditioning regimen that supports significantly improved cell expansion, cell persistence, and complete response rates. The combination of this regimen and the JCAR014 defined cell product also demonstrated relatively low frequency of severe CRS and neurotoxicity at lower dosing levels for all diseases.

A key finding of the early phase of the trial was that patients with greater cell expansion and longer cell persistence generally derived better clinical benefit. Data for JCAR014 using a flu/cy pre-conditioning regimen were presented at ASH 2015 and demonstrated improved cell expansion and cell persistence in individuals with r/r ALL, r/r NHL, and r/r CLL.

In r/r ALL, 17 patients have been treated with JCAR014 using a flu/cy pre-conditioning regimen, with 100% achieving a CR and a CRm based upon investigator-reported interim data. The reported follow-up was relatively short, but clearly was showing improved durability of response.

In r/r NHL, the JCAR014 experience with flu/cy pre-conditioning in 18 evaluable patients demonstrated a complete response rate of 50%, as defined by International Working Group Criteria [2007], and produced severe CRS in 20% and severe neurotoxicity in 35% of patients. At the currently planned dose for r/r NHL patients, 2x10^6 T cells/kg, in 11 evaluable patients, JCAR014 has achieved a 64% complete response rate and 82% complete or partial response rate. In the eight r/r NHL patients with DLBCL, 75% had a complete response and 100% of patients had a complete or partial response. At this dose, 9% of r/r NHL patients experienced sCRS and 18% of r/r NHL patients had severe neurotoxicity. For the JCAR014 trial, sCRS is defined as the occurrence of certain side effects, which can include hypotension or respiratory distress that required ICU level care. Patients from this portion of the trial have been followed for between two and nine months, and as of the data cut-off date of December 1, 2015, all patients with a complete response remained in remission.

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In r/r CLL, seven patients have been treated with JCAR014 using a flu/cy pre-conditioning regimen. All seven had either a complete or partial response, with four, or 57%, having a complete response. As of the December 1, 2015 cutoff date, no patient in this portion of the trial had had their cancer progress with follow-up of between two and 14 months.

As presented at ASH 2015, in the full Phase I portion of the trial, this defined cell product candidate displayed a side effect profile that is similar to our other CD19-directed product candidates in the types of adverse events observed. In this trial, 13% of patients with r/r NHL have experienced sCRS and 28% of r/r NHL patients experienced severe neurotoxicity, 23% of r/r ALL patients experienced sCRS and 50% of r/r ALL patients experienced severe neurotoxicity, and 11% of patients with r/r CLL have experienced sCRS and 33% of patients with r/r CLL have experienced severe neurotoxicity. There have been two patient deaths in r/r ALL patients treated with JCAR014—one at the highest dose, 2x10^7 T cells/kg, and one at the middle dose, 2x10^6 T cells/kg—that we believe were either directly or indirectly related to sCRS or severe neurotoxicity. There have also been two patient deaths in r/r NHL patients treated with JCAR014, both at the highest dose, that we believe were either directly or indirectly related to sCRS or severe neurotoxicity. As a result of the patient deaths, the highest dose level is no longer being used on the trial and the middle dose level is no longer being used in r/r ALL patients.

Overall in this study, as of December 1, 2015, we have treated 30 patients with r/r ALL with various conditioning regimens. Based on investigator-reported interim data, 100% of the 29 evaluable patients had a CR and 93% of the 29 evaluable patients had a CRm.

We have treated 32 patients with r/r NHL. Based on investigator-reported interim data, 63% of the 30 evaluable patients had a partial or complete response.

We have treated 9 patients with r/r CLL. Based on investigator-reported interim data, 89% of the 9 patients had a partial or complete response.

The following figure compares the experience in r/r NHL with JCAR014 as of a data cutoff date of December 1, 2015, comparing the data for patients who received a flu/cy conditioning regimen to those who did not, and comparing the data for the three dose levels used in the patients who received flu/cy conditioning:

JCAR014: NHL Experience Provides Important Insights

Conditioning Regimen	Non-Flu/Cy	Flu/Cy		
Dose Level	All Doses N=12	$2*10^5$/kg N=3	$2*10^6$/kg N=11	$2*10^7$/kg N=4–6
Efficacy				
CR	1/12 (8%)	1/3 (33%)	7/11 (64%)	1/4 (25%)
CR/PR	6/12 (50%)	1/3 (33%)	9/11 (82%)	3/4 (75%)
Toxicity				
sCRS	0/12 (0%)	0/3 (0%)	1/11 (9%)	3/6 (50%)
Severe Neurotoxicity	2/12 (17%)	1/3 (33%)	2/11 (18%)	4/6 (67%)

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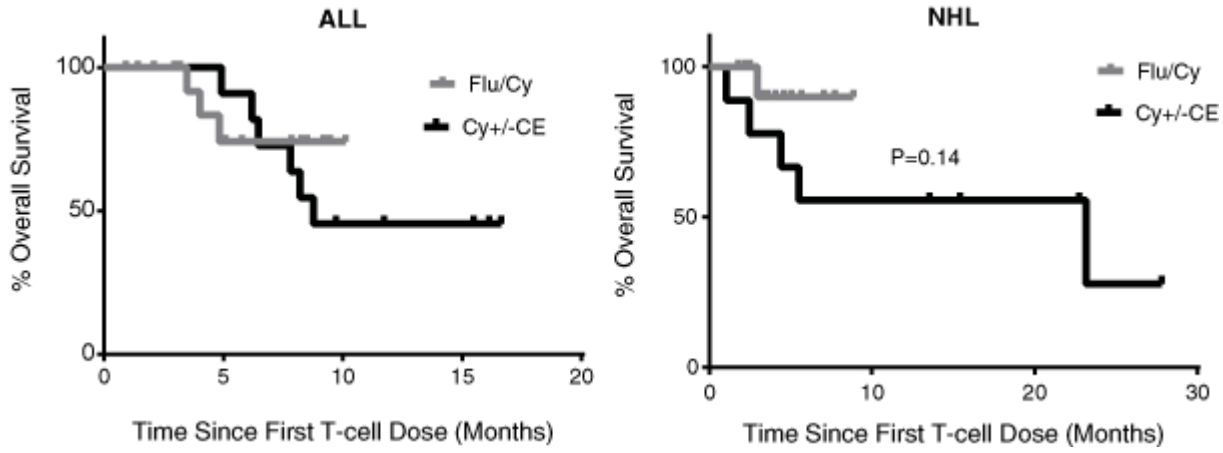
Adding fludarabine to our pre-treatment chemotherapy regimen has meaningfully impacted the cell expansion and cell persistence of JCAR014, and these early clinical data show an improved clinical benefit. The exact mechanism of this effect from fludarabine is not yet known, but several hypotheses include:

- an impact on the patient's own, or endogenous, CD8+, cytotoxic T cells, which can lead to a lower risk of a patient immune response to JCAR014;
- a decrease in endogenous CD4+ regulatory T cells, which may help the CAR T cells grow better and persist in an active state for longer;
- a decrease in endogenous T cells leading to an increase in cytokine production that is favorable to CAR T cell growth and survival; and/or
- a direct effect on lymph node architecture, which improves access of CAR T cells to the cancer.

CR, CRm, and complete responses are important surrogate markers for patients. Ultimately, survival is the most important measure of clinical benefit for cancer patients. While the results are not from a randomized trial, and longer follow-up is necessary, the figures below show that the improvement in cell exposure is translating into improved response rates and into improved survival, as of a data cutoff date of December 1, 2015. These figures show the overall survival of r/r ALL and r/r NHL patients who received JCAR014 at dose levels 1 and 2, comparing those who received flu/cy pre-conditioning and those who did not. We believe that the level of any plateau on an overall survival curve can be important information for physicians and patients.

Overall Survival After CAR T Cell Infusion in ALL and NHL Patients at Dose Levels 1 & 2



Based on data from this trial, the depth and duration of response in r/r NHL, r/r CLL, and /r ALL with JCAR014 appear to correlate with the cell expansion and cell persistence of the product candidate in the patient's body. With JCAR014, we have seen significant antitumor responses together with relatively low frequency of severe CRS and neurotoxicity, even with intensified chemotherapy regimens, suggesting that defined ratio CD4+ and CD8+ T cell products may have potential cell dose control advantages, which may improve potency and safety.

JCAR017, like JCAR014, is a defined cell product, but JCAR017 has a number of manufacturing-related advantages. Hence, our current plan is to develop JCAR017 rather than JCAR014. However, we plan to continue enrolling patients in the ongoing Phase I/II trial for JCAR014 in 2016 in order to explore additional treatment strategies to improve the exposure of the CAR T cells. We expect to have additional data from this trial in 2016. In addition, the IND has cleared for and we plan to enroll patents through 2016 in a Phase Ib trial, sponsored by FHCRC, in r/r NHL patients using the combination of JCAR014 with MedImmune's PD-L1 checkpoint inhibitor durvalumab. We believe that this and other combination trials will provide key insights on the next set of development trials in lymphoma and CLL. These trials may also potentially inform strategies for solid organ tumor settings and next generation CAR constructs.

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CD19 Strategy and Development Plans

With respect to adult r/r ALL, we are currently enrolling our multicenter Phase II potential registration trial for JCAR015. Data from this trial may allow for FDA accelerated approval as early as 2017.

With respect to r/r NHL, we initiated our multi-center Phase I trial for JCAR017 in adults in 2015. This product candidate appears to have the highest cell expansion and longest cell persistence in the absence of flu/cy conditioning, and most favorable therapeutic window of any of our CD19-directed product candidates based on the data generated to date. If data from this trial continue to show favorable expansion and persistence as well as clinical responses, we plan to utilize this drug candidate in our r/r NHL and r/r CLL trials moving forward. We continue to enroll patients in the ongoing Phase I/II trial for JCAR014 in r/r NHL, and we plan to use the ongoing Phase I/II trial to explore important questions that will inform our clinical strategy for other product candidates and improve our platform overall, such as exploring alternative chemotherapy preparation regimens and immune-modulatory strategies to improve cell persistence. In 2016, we expect to have additional data from the Phase I/II JCAR014 trial and initial data from our Phase I JCAR017 trial. Depending upon the results of these trials, we intend to begin registration trials in aggressive r/r NHL and r/r CLL in 2016 or early 2017 to support U.S. regulatory approval.

We believe our access to and clinical experience with multiple CD19 trials gives us the opportunity to bring best-in-class therapies to market across a range of B cell malignancies, as well as to make technology improvements to create better products over time. Key areas of focus include investigating the effect of varying cell compositions, the “armored” CAR approach, combinations with other immuno-oncology agents, and human binding domains.

We are planning Phase I trials in one or more B cell malignancies for up to three different “armored” CAR product candidates that target CD19. These product candidates are designed to explore the potential for synergistic effects of a CD19-directed CAR T cell and the production or expression of locally acting signaling proteins by the CAR T cell, specifically 4-1BBL, CD40L, and IL-12. We expect to commence a Phase I trial through our collaborator MSK of a CD19/4-1BBL “armored” CAR in 2016, and a Phase I trial for one or both of CD19/CD40L and CD19/IL-12 “armored” CARs in 2016 or 2017.

The IND has cleared for and we plan enrollment through 2016 for a Phase Ib trial, sponsored by FHCRC, in r/r NHL patients using the novel combination of JCAR014 with MedImmune’s PD-L1 checkpoint inhibitor durvalumab. We believe that this, and other combination trials will provide key insights on the next set of development trials in lymphoma and solid tumor settings, and also potentially inform next generation CAR constructs. Also, we are also planning to initiate a Phase I trial in one or more B cell malignancies in 2016 using a CD19-directed CAR product candidate that uses a fully human scFv. We expect several generations of product improvements for this target over the coming years, as we work to optimize patient outcomes for patients with lymphoma or leukemia.

As described in more detail under the caption “Licenses and Third-Party Collaborations” below, Celgene has the right to opt in to our CD19 program and thereby exclusively license our CD19 product candidates for development and commercialization outside of North America and China. Celgene has an opt-in decision on our CD19 program in 2016, and should Celgene exercise this option, we expect that we, along with Celgene, will outline more of our strategy in these geographies. Should Celgene not exercise its option, we will either develop and commercialize our CD19 portfolio ourselves or seek another partner in some or all of these geographies.

Additional Product Candidates

We are exploring the potential of our CAR and TCR technologies against targets that have the potential to treat cancers not currently targeted by CD19-directed products—in particular, difficult-to-treat solid organ tumors such as certain breast, lung, and pancreatic cancers, as well as B cell malignancies that do not express CD19. We

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and our collaborators are working on a number of product candidates in early clinical or late-stage pre-clinical development that target different cancer proteins. We began clinical testing of four candidates in 2015 targeting cancer-associated proteins other than CD19 and plan to begin clinical testing of a fifth in early 2016, and these trials will continue to enroll patients in 2016.

JCAR018: CD22

CD22 is a cell surface protein widely expressed on B lymphocytes. It is expressed by most B cell malignancies, including NHL, ALL, and CLL. Within these CD22 positive malignancies, it is generally expressed on all of a patient's cancer cells. Additionally, treatment with CD19-directed therapies has led to the emergence in some patients of CD19-negative cancer cells. To date, these patients' cancer cells have retained CD22 expression, potentially making a CD22-directed CAR T cell product candidate an important potential treatment for these patients. Similar to CD19, CD22 is not known to be expressed on any healthy tissue other than B cells. It is also not expressed on hematopoietic stem cells, and therefore B cells should return when the CAR T cell is no longer present.

JCAR018 is the CD22-directed CAR product candidate with respect to which we have licensed technology from Opus Bio. This product candidate was originally developed at the NCI. It has a fully human scFv and a 4-1BB costimulatory domain. Data from mouse models suggest that JCAR018 will have comparable efficacy in lymphoma and leukemia as CD19-directed CAR T cells. Patient enrollment has commenced in a Phase I trial sponsored by the NCI. This Phase I trial will enroll patients one year to 30 years in age that have CD22-positive r/r ALL or r/r NHL. The trial is open to patients who have either CD19-negative or CD19-positive disease and who have or have not received previous CAR T cell treatment. Preliminary results with the lowest JCAR018 cell dose, as well as one patient at the next highest dose, were presented at ASH 2015. JCAR018 demonstrated anti-tumor activity in r/r ALL patients, including both patients that had previously been treated with an anti-CD19 CAR therapy and those who had not, with two out of seven achieving a CRm. The product candidate had generally manageable adverse events. The dose escalation portion of this trial will continue during 2016. We recently achieved the first clinical milestone under our license agreement for this product candidate, for which paid Opus Bio a milestone payment in equity. We plan to present additional data from this trial later in 2016.

JCAR023: L1CAM (CD171)

L1CAM, also known as CD171, is a cell-surface adhesion molecule that plays an important role in the development of a normal nervous system. It is overexpressed in neuroblastoma, and there is increasing evidence of aberrant expression in a variety of solid organ tumors, including glioblastoma and lung, pancreatic, and ovarian cancers.

JCAR023 is our L1CAM directed CAR T cell product candidate, which was originally developed at SCRI. It has a defined cell composition. Preliminary data from a non-human primate study has shown no evidence of reactivity of JCAR023 to normal tissues at cell doses 10-100 fold higher than the anticipated target dose in humans. SCRI is conducting a Phase I trial of JCAR023 in in patients with refractory or recurrent pediatric neuroblastoma, under a SCRI-sponsored IND. The Phase I protocol-defined dose-escalation will continue during 2016.

JCAR020: MUC-16 / IL-12

MUC-16 is a protein overexpressed in the majority of ovarian cancers, but not on the surface of normal ovary cells. CA-125 is a protein found in the blood of ovarian cancer patients that results from the cleavage of MUC-16. CA-125 levels in the blood are a common test for ovarian cancer progression because they correlate with cancer progression. Our MUC-16/IL-12 product candidate, JCAR020, which was originally developed at MSK, has a binding domain that recognizes an extracellular domain of MUC-16 that remains following cleavage of CA-125.

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JCAR020 is our first development candidate that uses our "armored CAR" technology. IL-12 is a cytokine that can help overcome the inhibitory effects that the tumor micro-environment can have on T cell activity. Systemic delivery of IL-12 has been limited to date by severe side effects, which have included severe hematological toxicity, severe hepatic dysfunction, and immune reactive events such as colitis, some of which resulted in deaths and trial stoppage. However, we believe local delivery to the tumor may provide efficacy while avoiding these side effects. JCAR020 secretes IL-12. Because CAR T cells aggregate at the target protein, IL-12 delivery is likely to concentrate in areas with significant MUC-16 protein expression, in this case, MUC-16 expressing cancers. We believe the armored CAR utilizing IL-12 has the potential to enhance T cell potency and persistence. MSK is conducting a Phase I trial of JCAR020 in ovarian cancer, under an MSK-sponsored IND. The Phase I trial for JCAR020 opened for enrollment in 2015, and the trial will continue to enroll patients at ascending doses in 2016. In addition to assessing safety and preliminary efficacy, the trial is designed to provide potential biomarker and translational insights.

JCAR024: ROR-1

ROR-1 is a protein expressed in the formation of embryos, but in normal adult cells its surface expression is predominantly found at low levels on adipocytes, or fat cells, and briefly on precursors to B cells, or pre-B cells, during normal B cell maturation. ROR-1 is overexpressed on a wide variety of cancers including a subset of non-small cell lung cancer, triple negative breast cancer, pancreatic cancer, and prostate cancer. It is highly expressed on B cell chronic lymphocytic leukemia and mantle cell lymphoma.

JCAR024 is our ROR-1-directed CAR T cell product candidate, which was originally developed at FHCRC. It has a defined cell composition. Preliminary data in non-human primates has shown no evidence of acute clinically relevant side effects at cell doses exceeding the anticipated target dose in humans. We began a Phase I trial in early 2016 of JCAR024 in patients with ROR-1 expressing cancers, under a FHCRC-sponsored IND. We are also developing a next generation ROR-1-directed CAR T cell product candidate.

JTCR016: WT-1

Our lead high-affinity TCR T cell product candidate, JTCR016, targets WT-1, an intracellular protein that is overexpressed in a number of cancers, including adult myeloid leukemia ("AML") and non-small cell lung, breast, pancreatic, ovarian, and colorectal cancers. This product candidate was originally developed at FHCRC. An IND application for JTCR016 was submitted in May 2012 by FHCRC's Aude Chapuis, the sponsor of a Phase I/II trial for this product candidate, for the treatment of high risk or relapsed AML, myelodysplasic syndrome, and chronic myeloid leukemia in patients who have received an allogeneic HSCT.

Based on investigator-reported interim data presented at CIPO 2015 from the Phase I portion of this trial, JTCR016 has been generally well tolerated and has demonstrated no off-target effects. JTCR016 has also demonstrated TCR cell persistence beyond one year in a majority of subjects. This trial continues to monitor for AML disease relapse in this high risk population. We expect additional data from this trial in 2016.

The following adverse events of CTCAE grades 3 or 4 were experienced by more than one patient, whether or not treatment related, based on investigator-reported interim data as of November 10, 2014: lymphopenia, thrombocytopenia, anemia, hypotension, neutrophil count decreased, hyponatremia, hypophosphatemia, fever, fatigue, and infection. There were no observed events of sCRS or severe neurotoxicity in these patients.

We are also enrolling patients in a separate FHCRC-sponsored Phase I trial of JTCR016 in advanced NSCLC patients and are planning another FHCRC-sponsored Phase I trial of JTCR016 in earlier-stage AML patients.

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Process Development and Manufacturing

We are devoting significant resources to process development and manufacturing in order to optimize the safety and efficacy of our product candidates, as well as to reduce our per unit manufacturing costs. The manufacture of our product candidates involves complex processes, including the separation of the appropriate T cells from blood product collected from the patient, the activation of the T cells, the insertion of the gene sequence for the CAR or TCR construct into the cell's DNA, and the growth in the number of these modified T cells to the desired dose level. We have established a semi-automated, closed platform for this process, and we are investing further resources in improving and further automating the process so as to reduce the cost of manufacturing.

We continue to leverage our relationships with our academic partner institutions for manufacturing for some of our Phase I/II clinical trials. Doing so has significantly accelerated our ability to advance clinical trials, gain insights into the multiple manufacturing processes, and establish an infrastructure for future Phase I and II trials.

Our manufacturing strategy is designed to meet the demand needs of clinical supply and commercial launch. We have successfully brought on-line a CMO to manufacture JCAR015 and are in the final stages of establishing our own manufacturing facility to support manufacturing under established current good manufacturing practices ("cGMP"). This approach will position us to support multicenter clinical trials and commercialization.

Our goal is to carefully manage our cost structure, maximize optionality, and drive long-term cost of goods as low as possible. As such, we established manufacturing capabilities at a CMO to increase the speed at which we could bring cGMP capacity on-line to support our JCAR015 clinical program. We plan to complement the use of the CMO by establishing our own cGMP manufacturing facility. In 2015 we entered into a ten-year lease for a facility in Bothell, Washington, which we have comprehensively remodeled to enable cGMP manufacturing. We are in the process of completing the necessary steps for regulatory approval for this facility, and we plan to begin manufacturing clinical trial material from this facility in 2016 and commercial products, subject to the required regulatory approvals, during 2017. We believe that operating our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, will enable the more rapid implementation of process changes, and will allow for better long-term margins.

Our manufacturing strategy is currently structured to support our U.S. development plans. Although we believe the general manufacturing strategy developed for the United States will be applicable in other geographies, specific strategies for other geographies will be developed as part of our clinical and commercial plans for such other geographies. As such, we are currently developing our strategy for geographies outside of the U.S., in collaboration with Celgene and other potential partners.

Commercialization Plan

We currently have no sales, marketing or commercial product distribution capabilities and have no experience as a company in marketing products. We intend to build our own global commercialization capabilities over time as well as to leverage Celgene's global capabilities in certain geographies on assets that Celgene opts into.

According to Decision Resources Group's projections, the combined global market for ALL, DLBCL, and CLL combined is expected to exceed $20 billion by 2025. In the United States alone, there are approximately 6,000 patients diagnosed with ALL, 42,000 patients diagnosed with NHL and another 21,000 diagnosed with CLL each year. If any of our CD19 product candidates are approved, we expect to commercialize those products in the United States with an experienced sales, marketing, payer access and distribution organization including a national specialty hematology sales force.

Outside the United States, we have not yet defined our regulatory and commercial strategy for our CD19 product candidates. Based on the collaboration agreement Juno entered into with Celgene, if Celgene exercises its option for the CD19 program, we would expect to outline our global plan for further development and commercialization of

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our CD19 product candidates in partnership with Celgene in 2016. With respect to product candidates arising out of other programs that Celgene opts in to, we would expect to leverage Celgene's global development and commercial capabilities in those territories where Celgene receives development and commercialization rights. With respect to product candidates arising from programs for which Celgene chooses not to exercise its option, we would expect to identify strategic partners for ongoing global commercialization of such product candidates, which may include biopharmaceutical partners, distributors, and contract sales and marketing organizations, or we may decide to establish our own commercial infrastructure. We plan to further evaluate these alternatives as we approach approval for one of our product candidates.

As additional product candidates advance through our pipeline, our commercial plans will evolve as we consider elements such as the market potential, the unmet clinical need, the competitive landscape, development costs, etc., in order to efficiently and successfully commercialize our assets.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from our collaborators or other third parties. Our policy is to seek to protect our proprietary position by, among other methods, filing patent applications in the United States and in jurisdictions outside of the United States related to our proprietary technology, inventions, improvements, and product candidates that are important to the development and implementation of our business. We also rely on trade secrets and know-how relating to our proprietary technology and product candidates, continuing innovation, and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of immunotherapy. We additionally rely on data exclusivity, market exclusivity, and patent term extensions when available, and plan to seek and rely on regulatory protection afforded through orphan drug designations. Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for our technology, inventions, and improvements; to preserve the confidentiality of our trade secrets; to maintain our licenses to use intellectual property owned by third parties; to defend and enforce our proprietary rights, including our patents; and to operate without infringing on the valid and enforceable patents and other proprietary rights of third parties.

We have developed and in-licensed numerous patents and patent applications and possess substantial know-how and trade secrets relating to the development and commercialization of immunotherapy product candidates, including related manufacturing processes and technology. Many of these in-licensed patents and patent applications claim the inventions of investigators at MSK, FHCRC, SCRI, NIH, City of Hope, and St. Jude, as described in more detail below under the caption "Licenses and Third-Party Collaborations." As of January 31, 2016, our owned and licensed patent portfolio consists of approximately 22 licensed U.S. issued patents, approximately 26 licensed U.S. pending patent applications, approximately 38 owned U.S. issued patents, and approximately 35 owned U.S. pending patent applications covering certain of our proprietary technology, inventions, and improvements and our most advanced product candidates, as well as approximately five owned patents issued in jurisdictions outside the United States, approximately 39 licensed patents issued in jurisdictions outside of the United States, approximately 169 licensed patent applications pending in jurisdictions outside of the United States (including eight licensed pending Patent Cooperation Treaty applications), and approximately 61 owned patent applications pending in jurisdictions outside of the United States (including 14 owned pending Patent Cooperation Treaty applications) that, in many cases, are counterparts to the foregoing U.S. patents and patent applications. For example, these patents and patent applications include claims directed to:

- proprietary CARs, T cell receptors and antibodies;
- proprietary CAR constructs, including those with customized spacer domains for improved tumor recognition;
- engineered transgenes for T cell selection and in vivo ablation;

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- proprietary gene transfer vectors;
- reversible reagents for cell selection, expansion and engineering;
- systems and processes for generating and manufacturing cells for adoptive immunotherapy;
- adoptive immunotherapy using defined T cell compositions;
- multispecific cellular therapy approaches, including bispecific CARs, cells and compositions;
- formulations, dosages, and treatment methods for adoptive immunotherapy, including those for reducing toxicity associated with adoptive immunotherapy;
- approaches for improving exposure to therapeutic cell product and promoting resistance to factors of tumor microenvironments; and
- libraries and high throughput methods for the discovery of antigen-binding molecules and targets.

As for the immunotherapy products and processes we develop and commercialize, in the normal course of business, we intend to pursue, when possible, composition, method of use, dosing and formulation patent protection. We may also pursue patent protection with respect to manufacturing and drug development processes and technology. The patents and patent applications outside of the United States in our portfolio are held primarily in Europe, Canada, Japan, and Australia.

Individual patents extend for varying periods of time, depending upon the date of filing of the patent application, the date of patent issuance, and the legal term of patents in the countries in which they are obtained. Generally, patents issued for applications filed in the United States are effective for 20 years from the earliest effective filing date. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period. The restoration period cannot be longer than five years and the total patent term, including the restoration period, must not exceed 14 years following FDA approval. The duration of patents outside of the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. Our issued patents will expire on dates ranging from 2019 to 2031. If patents are issued on our pending patent applications, the resulting patents are projected to expire on dates ranging from 2021 to 2037. However, the actual protection afforded by a patent varies on a product-by-product basis, from country-to-country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country, and the validity and enforceability of the patent.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the scope of claims allowable in patents in the field of immunotherapy has emerged in the United States. The patent situation outside of the United States is even more uncertain. Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions and enforce our intellectual property rights, and more generally could affect the value of our intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell, or importing products that infringe our intellectual property will depend in part on our success in obtaining and enforcing patent claims that cover our technology, inventions, and improvements. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our products and the methods used to manufacture those products. Moreover, even our issued patents do not guarantee us the right to practice our technology in relation to the commercialization of our products. We have conducted analyses of the patent landscape with respect to our CD19 product candidates, and based on these analyses, we believe we will have freedom to operate with respect to our most advanced CD19 product candidates, by which we mean we believe that we will be able to commercialize them. However, the area of patent and other intellectual property rights in biotechnology is an

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evolving one with many risks and uncertainties, and third parties may have blocking patents that could be used to prevent us from commercializing our patented product candidates and practicing our proprietary technology. Our issued patents and those that may issue in the future may be challenged, invalidated, or circumvented, which could limit our ability to stop competitors from marketing related products or limit the length of the term of patent protection that we may have for our product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies. For these reasons, we may have competition for our product candidates. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any particular product candidate can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of the patent.

Patent disputes are sometimes interwoven into other business disputes. For example, we were a party in a lawsuit captioned Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn.), which concerned both a contractual dispute between St. Jude Children's Research Hospital ("St. Jude") and the Trustees of the University of Pennsylvania ("Penn"), and a dispute about U.S. Patent No. 8,399,645 (the "'645 Patent"), which St. Jude has exclusively licensed to us. This lawsuit settled in April 2015.

As of December 31, 2015, our registered trademark portfolio currently contains 32 registered trademarks and pending trademark applications, consisting of four pending trademark applications in the United States, and 17 registered trademarks and 11 pending trademark applications in Australia, Canada, China, the European Community (including Germany), India, Japan, Korea, and Singapore, and under the Madrid Protocol. We may also rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect our technology and product candidates, in part, by entering into confidentiality agreements with those who have access to our confidential information, including our employees, contractors, consultants, collaborators, and advisors. We also seek to preserve the integrity and confidentiality of our proprietary technology and processes by maintaining physical security of our premises and physical and electronic security of our information technology systems. Although we have confidence in these individuals, organizations, and systems, agreements or security measures may be breached and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or may be independently discovered by competitors. To the extent that our employees, contractors, consultants, collaborators, and advisors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For this and more comprehensive risks related to our proprietary technology, inventions, improvements and products, please see the section captioned "Risks Related to Intellectual Property" in Part I—Item 1A—"Risk Factors" of this report.

Licenses and Third-Party Collaborations

Celgene Corporation

Collaboration Agreement

In June 2015, we entered into a master research and collaboration agreement (the "Celgene Collaboration Agreement") with Celgene Corporation and a wholly owned subsidiary of Celgene Corporation (collectively, "Celgene") pursuant to which Juno and Celgene will research, develop and commercialize novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. The Celgene Collaboration Agreement became effective on July 31, 2015 and was amended and restated in August 2015 to clarify certain procedural aspects relating to a party's exercise of an option for a given program, and to provide additional detail regarding a party's entry into the applicable development and commercialization agreement thereafter. Pursuant to the collaboration, each of Celgene and Juno will conduct independent programs to research, develop, and commercialize such product candidates (including, in the case of Juno, our CD19 and CD22 programs). As detailed below, each party has certain options

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to obtain either an exclusive license to develop and commercialize specified product candidates arising from specified types of programs conducted by the other party within the scope of the collaboration, or the right to participate in the co-development and co-commercialization of specified product candidates arising from such programs.

The parties may exercise their options with respect to specified product candidates arising under programs within the scope of the collaboration until July 31, 2025, which is the tenth anniversary of the effective date of the Celgene Collaboration Agreement (the "Research Collaboration Term"), subject to a tail period applicable to certain programs, for which options have not yet been exercised as of the expiration of the Research Collaboration Term. For therapeutic product candidates that are directed to the target of a program for which an option is exercised, but for which the party exercising its option has not elected to obtain rights upon option exercise, each party is obligated during the remainder of the Research Collaboration Term to continue to offer the other party the right to exercise an additional option to obtain rights to develop and commercialize such other product candidates in such program until commencement of a pivotal clinical trial, upon terms set forth in the Celgene Collaboration Agreement. If a party does not exercise its option with respect to a program that is subject to the other party's exclusive right to exercise an option prior to the expiration of all applicable option exercise periods for such product candidates in such program, the option with respect to such product candidates and such program will expire and the party required to offer such product candidates and program to the other party is free to develop and commercialize such product candidates independently.

Pursuant to the Celgene Collaboration Agreement, each party is solely responsible for research and development activities conducted under its programs prior to the other party's exercise of an option. Following a party's exercise of its option for a program, the parties will enter into an agreed form of license agreement or co-development and co-commercialization agreement for such program, as applicable, which agreement will set forth the allocation of rights and responsibilities as between the parties for development and commercialization activities for product candidates arising out of such program in the Celgene Territory and the Juno Territory, as applicable (as each is defined below).

Options under Celgene Collaboration Agreement

First, we granted Celgene options to obtain an exclusive license with respect to Juno's internally conducted programs, to develop and commercialize specified types of immuno-oncology and immunology therapeutics that are selected by Celgene at the time it exercises such options and are directed to the molecular targets that are the subject of the relevant Juno programs. Juno will retain the right to develop and commercialize product candidates arising from such programs in the United States, Canada and Mexico, and for cellular therapy product candidates, China (such countries, the "Juno Territory" and all other countries, the "Celgene Territory"). Celgene may exercise the foregoing options on a program-by-program basis at various time points through completion of certain clinical trials with respect to product candidates in each program. Upon Celgene's exercise of such option for specified product candidates for a program, the parties are obligated to enter into either a license agreement or a co-development and co-commercialization agreement as specified below.

If Celgene exercises an option with respect to our internally developed programs within the scope of the collaboration, including our CD19 and CD22 programs, Juno and Celgene will enter into an agreed form of a license agreement pursuant to which Celgene receives an exclusive, royalty-bearing license to develop and commercialize, at Celgene's cost, specified therapeutic product candidates directed to the targets of such Juno programs in the Celgene Territory, and Juno retains all rights to develop further and commercialize, at Juno's cost, such therapeutic product candidates in the Juno Territory, subject to Celgene's right to exercise an option for a specified number of such programs, excluding the CD19 program and the CD22 program, to co-promote such product candidates in the Juno Territory (in which case the parties would execute a co-development and co-commercialization agreement as specified below). Under all such license agreements, Juno has the right to participate in specified commercialization activities arising from such programs in certain major European markets.

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For internally developed Juno programs for which Celgene exercises one of its specified number of rights to co-develop and co-commercialize product candidates arising in such program, as described above, the parties shall enter into an agreed form of co-development and co-commercialization agreement, pursuant to which Celgene shall have the right to co-develop and co-commercialize such product candidates, with the parties each entitled to bear and receive an equal share of the profits and losses arising out of such programs following the exercise of such co-promote right. In general, under such agreements, Juno will be the lead party for development and commercialization activities for such product candidates in the Juno Territory, and Celgene will be the lead party for development and commercialization activities for such product candidates in the Celgene Territory. Under such agreements, Celgene has the right to elect to participate in up to a specified percentage of specified commercialization activities for such product candidates in the Juno Territory, and Juno has the right to elect to participate in up to a specified percentage of specified commercialization activities for such product candidates in certain major European markets.

If Juno exercises its option with respect to specified product candidates arising in internally developed Celgene programs within the scope of the collaboration, the parties are obligated to enter into a co-development and co-commercialization agreement pursuant to which Juno bears thirty percent (30%) and Celgene bears seventy percent (70%) of global profits and losses. Under such co-development and co-commercialization agreements, Celgene is the lead party for all development and commercialization activities for such product candidates worldwide, subject to Juno's right to participate in up to a specified percentage of specified commercialization activities in North America under certain circumstances and in certain major European countries.

Furthermore, each party will have the exclusive right to exercise options to co-develop and co-commercialize product candidates arising out of programs for which the other party in-licenses or acquires rights that are within the scope of their collaboration, where such rights are available to be granted, with the parties each bearing an equal share of the profits and losses arising out of such programs following the exercise of such option. In general, for such programs where the rights are in-licensed or acquired by Juno and for which Celgene exercises its options, Juno will be the lead party for development and commercialization of product candidates arising from such programs in the Juno Territory, subject to Celgene's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory, and Celgene will be the lead party for development and commercialization of product candidates arising in such programs in the Celgene Territory, subject to Juno's right to elect to participate in certain commercialization activities for such product candidates in certain major European markets. Conversely, for such programs where the rights are in-licensed or acquired by Celgene and for which Juno exercises its options, Celgene will be the lead party for development and commercialization activities for product candidates arising from such programs on a worldwide basis, subject to Juno's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory and in certain major European markets. The party exercising an option for these in-licensed or acquired programs is required to pay to the other party an upfront payment equal to one half of the costs incurred by other party in connection with the acquisition of rights to such programs.

In addition to an upfront cash payment of approximately $150.2 million under the Celgene Collaboration Agreement, Celgene is required to pay to Juno an additional upfront fee if Celgene exercises its option for each of the CD19 Program and the CD22 Program, totaling, if the options are exercised for both programs during the initial opt-in window, $100.0 million. Upon a party's exercise of the option for any other program (other than certain in-licensed or acquired programs where a party exercises its option at the time such program is acquired), the party exercising the option is required to pay to the other party an upfront payment at the time of exercise of its option, calculated as a multiple of the costs incurred by the other party in relation to the development activities for such program prior to the exercise of the option, with such multiple based on the point in development of such product at which such party exercises such option. For programs for which the parties have entered into a license agreement, Juno will also receive royalties from Celgene, for product candidates arising from the CD19 and CD22 programs, at a percentage in the mid-teens of net sales of such product candidates in the Celgene Territory, and for product candidates arising from other Juno programs that are subject to a license agreement,

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tiered royalties on net sales of such product candidates in the Celgene Territory, at percentages ranging from the high single digits to the mid-teens, calculated based on the stage of development at which Celgene exercises its option for such program.

In addition to each party's rights with respect to development and commercialization of product candidates arising from programs in the collaboration as set forth above, the parties have agreed to enter into a manufacturing and supply agreement that will govern the terms of manufacture and supply of cellular therapy product candidates and other product candidates included within collaboration programs following the exercise of an option for each such program. Under this agreement, Juno would manufacture and supply cellular therapy product candidates for the Juno Territory, and provide certain support for the manufacture and supply of cellular therapy product candidates for the Celgene Territory. Celgene would be responsible for the supply of other types of product candidates for which options are exercised.

The Celgene Collaboration Agreement will terminate upon the later of the last-to-expire of all option exercise periods, or, if an option is exercised by a party for one or more programs in the collaboration, upon the termination or expiration of the last-to-exist license agreement or co-development and co-commercialization agreement, as applicable, for any such program. The Celgene Collaboration Agreement may be terminated by either party for the insolvency of, or for an uncured material breach of the Celgene Collaboration Agreement by, the other party. Celgene may terminate the Celgene Collaboration Agreement in its entirety for any reason by providing Juno with prior written notice if there are no active development and commercialization agreements in place. Juno may terminate the Celgene Collaboration Agreement if Juno exercises its termination rights under the Voting and Standstill Agreement (as defined below) between the Parties for Celgene's breach of certain covenants therein, or if either party terminates the Purchase Agreement (as defined below) other than as a result of a failure by Juno to meet specified closing conditions under such agreement. Either party also has the right to terminate the Celgene Collaboration Agreement on a program-by-program basis if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under the Celgene Collaboration Agreement.

On a program-by-program basis and prior to the exercise of an option, either party may terminate the Celgene Collaboration Agreement either in its entirety or with respect to one or more programs on prior written notice to the other party in the case of an uncured material breach by the other party that frustrates the fundamental purpose of the Celgene Collaboration Agreement,. On a program-by-program basis following the exercise of an option for a program, either Party may also terminate any license agreement, or co-development and co-commercialization agreement for such program upon prior notice for an uncured material breach by the other party with respect to such program that frustrates the fundamental purpose of such agreement. Either party may terminate a license agreement or co-development and co-commercialization agreement upon the bankruptcy or insolvency of the other party. Either party also has the right to terminate the license agreement or the co-development and co-commercialization agreement if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under such agreement.

Equity Placement

In June 2015, we also entered into a share purchase agreement (the "Purchase Agreement") with Celgene. Pursuant to the Purchase Agreement, we agreed to sell 9,137,672 shares of our common stock to Celgene at an aggregate cash price of approximately $849.8 million, or $93.00 per share of common stock, at an initial closing. The initial closing occurred on August 4, 2015.

First Period Top-Up Rights

Starting in 2016 and until June 29, 2020, Celgene has the annual right, following the filing of each Annual Report on Form 10-K filed by Juno (including this report), to purchase additional shares from Juno at a market average price, allowing it to "top up" to an ownership interest equal to 10% of the then-outstanding shares (after

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giving effect to such purchase), subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). Based on the number of shares of common stock outstanding as of February 18, 2016 as set forth on the cover of this report, we estimate that Celgene will have the right to acquire approximately 1,268,283 shares of our common stock if exercises the "top up" right triggered by the filing of this report.

First Acquisition Right

During the period beginning on June 29, 2019 and ending on June 28, 2020, subject to Celgene opting in to a certain number of Juno programs under the Celgene Collaboration Agreement, Celgene will have the right (the "First Acquisition Right") to purchase up to 19.99% of the then-outstanding shares of Juno's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market (currently The NASDAQ Global Select Market) on the date of exercise (the "FAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.

Second Period Top-Up Rights

After the closing of the purchase of shares upon the exercise of the First Acquisition Right until the SAR Termination Date (as defined below), in the event that Celgene has been diluted after exercising the First Acquisition Right, Juno will, following the filing of each Annual Report on Form 10-K filed by Juno, offer Celgene the right to purchase additional shares from Juno at 105% of market average price, allowing Celgene to "top up" to an ownership interest (after giving effect to such purchase) equal to the percentage ownership of shares that Celgene obtained upon exercise of the First Acquisition Right, subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any year in which it is offered such right by Juno, then the percentage of ownership targeted for a top-up stock purchase for the next year it is offered such top-up right will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). The "SAR Termination Date" is the later of (a) June 29, 2025, and (b) the earlier of (x) the date that is 6 months following the date that the conditions to the exercise of the Second Acquisition Right (as defined herein) are satisfied and (y) December 29, 2025.

Second Acquisition Right

During the period beginning on June 29, 2024 and ending on the SAR Termination Date, subject to each of Celgene and Juno opting into a certain number of programs under the Celgene Collaboration Agreement, and provided that Celgene exercised the First Acquisition Right so as to obtain a percentage ownership of 17% of Juno, Celgene will have the right (the "Second Acquisition Right") to purchase up to 30% of the then-outstanding shares of Juno's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market on the date of exercise (the "SAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.

Final Top-Up Rights

Following the closing of the purchase of shares upon the exercise of the Second Acquisition Right and until the Celgene Collaboration Agreement expires or is terminated, Celgene would have the annual right, in the event that Celgene has been diluted after exercising the Second Acquisition Right, following the filing of each Annual Report on Form 10-K filed by Juno, to purchase additional shares from Juno at a price equal to 105% of market average price, allowing it to "top up" to the percentage ownership it had attained upon exercising the Second Acquisition Right, less 250 basis points, subject to adjustment downward in certain circumstances. If Celgene

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does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise).

These rights and the other described top-up rights, as well as the First Acquisition Right and Second Acquisition Right, may be limited or eliminated in certain circumstances when and if Celgene disposes of any of its shares.

Conditions to Closing; Termination; Stockholder Approval

Closings of top-up rights, the First Acquisition Right, and the Second Acquisition Right, are subject to customary closing conditions, including termination or expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended. We have the ability to terminate Celgene's future purchase rights under the Purchase Agreement in the event that Celgene breaches certain of its obligations under the Voting and Standstill Agreement (described below), Celgene undergoes a change in control, or the Celgene Collaboration Agreement terminates or expires.

The Purchase Agreement limits the aggregate number of shares that may be issued thereunder to 19.99% of Juno's common stock outstanding immediately prior to the entry into the Purchase Agreement, unless stockholder approval is obtained for additional issuances of Juno stock in accordance with NASDAQ rules. We have agreed to submit the additional equity issuances for approval by our stockholders at our 2016 annual meeting of stockholders.

Voting and Standstill Agreement

In connection with the Purchase Agreement, we entered into a voting and standstill agreement (the "Voting and Standstill Agreement") with Celgene in June 2015. Pursuant to the Voting and Standstill Agreement, until the later of the fifth anniversary of the date of the Voting and Standstill Agreement and the expiration or earlier termination of the Celgene Collaboration Agreement, Celgene will be bound by certain "standstill" provisions which generally will prevent it from purchasing outstanding shares of Juno common stock or common stock equivalents, making a tender offer or encouraging or supporting a third party tender offer, calling a meeting of Juno's stockholders, nominating a director whose nomination has not been approved by Juno's board of directors (the "Board"), soliciting proxies in opposition to the recommendation of the Board, depositing shares of common stock in a voting trust, assisting a third party in taking such actions, entering into discussions with a third party as to such actions, or requesting or proposing in writing to the Board or any member thereof that Juno amend or waive any of these limitations. Celgene has also agreed not to dispose of any shares of common stock beneficially owned by it during certain specified lock-up periods, other than under certain exceptions. Following the expiration of such lock-up periods, Celgene may sell shares subject to certain manner of sale and volume limitations, as well as restrictions on sales to persons defined as "competitors." Celgene has agreed generally to vote its shares in accordance with the recommendations of the majority of Juno's Board.

We have agreed to give Celgene certain Board designation rights until at least June 29, 2020, and thereafter for as long as Celgene and its affiliates beneficially own at least 7.5% of the voting power of Juno's outstanding shares. Dr. Thomas O. Daniel is Celgene's current designee on the Board. Juno has agreed to nominate Dr. Daniel for election and reelection as a director on the Board, provided in each case that Dr. Daniel is reasonably acceptable to the nominating and governance committee of the Board. Celgene may designate another nominee to replace Dr. Daniel upon Dr. Daniel's departure from the Board or as a replacement nominee for election at a meeting of stockholders at which such position is up for election. Except for the first such subsequent designee, any such subsequent designee may not be an employee or officer of Celgene, must be independent under NASDAQ rules, and must be reasonably acceptable to the nominating and governance committee of the Board. The first subsequent designee may be an "officer" of Celgene Corporation for purposes of Section 16 of the Securities Exchange Act of 1934, as amended, within the meaning of Rule 16a-1(f) thereunder, provided that such designee is reasonably acceptable to the nominating and governance committee of the Board.

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The rights and restrictions applicable to Celgene under the Voting and Standstill Agreement are subject to termination upon the occurrence of certain events, including certain events involving a change of control, or potential change of control, of Juno.

Registration Rights Agreement

In connection with the Purchase Agreement, we also entered into a registration rights agreement (the "Celgene Registration Rights Agreement") with Celgene in June 2015. Pursuant to the Celgene Registration Rights Agreement, if and as Celgene is permitted to sell shares under the Voting and Standstill Agreement, Juno has agreed to, upon the written request of Celgene, prepare and file with the Securities and Exchange Commission a registration statement on Form S-3 for purposes of registering the resale of the shares specified in Celgene's written request or, if Juno is not at such time eligible for the use of Form S-3, use its commercially reasonable efforts to prepare and file a registration statement on a Form S-1 or alternative form that permits the resale of the shares. Juno has also agreed, among other things, to indemnify Celgene under the registration statement from certain liabilities and to pay all fees and expenses (excluding any legal fees of the selling holder(s) above $10,000 per registration statement, and any underwriting discounts and selling commissions) incident to the Juno's obligations under the Celgene Registration Rights Agreement.

Fred Hutchinson Cancer Research Center License and Collaboration Agreement

In October 2013, we entered into a license agreement with FHCRC that grants us an exclusive, worldwide, sublicensable license under certain patent rights, and a non-exclusive, worldwide, sublicensable license under certain technology, to research, develop, manufacture, improve, and commercialize products and processes covered by such patent rights or incorporating such technology for all therapeutic uses for the treatment of human cancer. This agreement was amended and restated in November 2014. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including target specific constructs and customized spacer regions, TCR constructs, and their use for immunotherapy. Pursuant to this license agreement, as of January 31, 2016, we have rights to five pending U.S. patent applications, one pending Patent Cooperation Treaty application, and a number of other patent applications in jurisdictions outside the United States. We paid to FHCRC an upfront payment of $250,000 upon entering into this agreement. We are required to pay to FHCRC an annual maintenance fee of $50,000 for the first four years of the agreement's term and thereafter minimum annual royalties of $100,000 per year, with such payments reduced by the amount of running royalties paid to FHCRC in the applicable prior year. We may be obligated to pay to FHCRC up to a maximum of $6.75 million per licensed product, which includes JCAR014 and JCAR017, upon our achievement of certain specified clinical and regulatory milestones. In addition, the license agreement provides that we are required to pay to FHCRC low single-digit royalties based on annual net sales of the licensed products by us and by our sublicensees. We are also required to pay to FHCRC a portion of the payments that we receive from sublicensees of the rights licensed to us by FHCRC, on a tiered basis, up to a cap. In addition, we have agreed to use a set amount of these sublicensee payments to support the research and development of licensed products, and if, by the fifth anniversary of the license agreement, we have received at least such amount in sublicensee payments but have spent less than such amount on such research and development activities, we must pay to FHCRC the difference between such set amount and the actual amounts we have spent on such activities.

The license agreement will expire on the later of the expiration of the last to expire of the licensed patents rights covering a licensed product, on a country-by-country basis, or 15 years following the regulatory approval of the first licensed product. We may terminate the agreement at will upon 90 days' notice, in its entirety, on a country-by-country basis, or with respect to any aspect of any licensed patent. FHCRC has the right to terminate the agreement upon 90 days' notice in the event of our uncured breach, but upon 45 days' notice if such breach is of a payment or reporting obligation, and upon written notice if we are more than three days late with any payment obligation on any two occasions within a 12-month period. FHCRC may also terminate the agreement upon 30 days' written notice if we challenge, or notify FHCRC that we intend to challenge, the validity or enforceability of any of the licensed patent rights, and the agreement will terminate automatically in the event of our

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bankruptcy or insolvency. Upon termination, but not expiration, of the agreement, we are required, upon FHCRC's request, to timely enter into good faith negotiations with FHCRC's future licensees for the purpose of granting licensing rights to our modifications to or improvements upon the licensed patents or technologies.

Also in October 2013, we entered into a collaboration agreement with FHCRC relating to the research and development of cellular immunotherapy products. The research is conducted under project orders containing plans and budgets approved by the parties. We have an exclusive option to obtain a royalty-bearing license to intellectual property owned by FHCRC that is developed in connection with the work conducted under the collaboration agreement, such license to be exclusive with respect to patents and patent applications and non- exclusive with respect to any other intellectual property. In addition, FHCRC granted us an exclusive, perpetual, royalty-free, sublicenseable license to any such intellectual property that constitutes an improvement to any process used to manufacture any human cellular and tissue-based collaboration study product, for the development and/or commercialization of cellular immunotherapy products.

The term of the collaboration agreement shall continue for six years from the effective date, unless earlier terminated. Either party may terminate the collaboration agreement, in its entirety or with respect to a particular collaboration project, upon 30 days' prior written notice in the case of the other party's uncured material breach. Either we or FHCRC may also terminate upon written notice in the event of the other party's bankruptcy or insolvency.

In connection with the collaboration agreement in October 2013, we entered into a letter agreement with FHCRC pursuant to which we issued to FHCRC 3,274,998 shares of our common stock and also agreed to make success payments to FHCRC, payable in cash or publicly-traded equity at our discretion. In December 2015, we amended this letter agreement to make certain clarifying amendments thereto. These success payments are based on increases in the per share fair market value of our common stock during the term of the success payment agreement, which is a period of time that begins on the date of our collaboration agreement with FHCRC and ends on the later of: (1) the eighth anniversary of that date and (2) the earlier of (a) the eleventh anniversary of that date and (b) the third anniversary of the first date on which the FDA issues formal written approval for us to market a pharmaceutical or biologic product developed at least in part by our company. Success payments are owed (if applicable) after measurement of the value of our common stock in connection with the following valuation measurement dates during the term of the success payment agreement: (1) December 19, 2014 (the date our common stock first became publicly traded upon our initial public offering); (2) the date on which we sell, lease, transfer, or exclusively license all or substantially all of our assets to another company; (3) the date on which we merge or consolidate with or into another entity (other than a merger in which our pre-merger stockholders own a majority of the shares of the surviving entity); (4) any date on which ARCH Venture Fund VII, L.P. or C.L. Alaska L.P. transfers a majority of its shares of company capital stock held by it on such date to a third party; (5) every second anniversary of any event described in the preceding clauses (1), (2), (3) or (4), but only upon a request by FHCRC made within 20 calendar days after receiving written notice from us of such event; and (6) the last day of the term of the success payment agreement. Any success payment will generally be made within 90 days after the applicable valuation measurement date, except that (1) in the case of an initial public offering, the payment was required on December 21, 2015, which was the first business day following the first anniversary of the date our common stock first became publicly traded upon our initial public offering, and (2) in the case of a merger or sale of all of our company's assets, the success payment will be made on the earlier of the 90th day following the transaction or the first date that transaction proceeds are paid to any of our stockholders. In the case of an initial public offering, the value of our common stock for determining whether a success payment was owed was determined by the average closing price of a share of our common stock over the consecutive 90 calendar day period preceding December 19, 2015, which was the first anniversary of the date our common stock first became publicly traded following our initial public offering. In the case of a valuation measurement date triggered by each second anniversary of our stock first becoming publicly traded, the value of our common stock for determining whether a success payment is owed will be determined by the average closing price of a share of our common stock over the consecutive 90 calendar day period preceding such anniversary date, so long as our common stock is publicly tradeable during such 90 calendar day period. On all other

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valuation measurement dates (if any), the value will be determined either, in the case of a merger or stock sale, by the consideration paid in the transaction for each share of our stock or, in all other cases, by a baseball arbitration process. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending from $20.00 per share to $160.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending from $10 million at $20.00 per share to $375 million at $160.00 per share, payable if such threshold is reached. Any previous success payments made to FHCRC are credited against the success payment owed as of any valuation measurement date, so that FHCRC does not receive multiple success payments in connection with the same threshold. The success payments paid to FHCRC will not exceed, in aggregate, $375 million, which would be owed only when the value of the common stock reaches $160.00 per share. In June 2014, we entered into an agreement with FHCRC to provide that certain indirect costs related to the collaboration projects conducted by FHCRC are creditable against any success payments, and we amended this agreement in December 2015. If we elect to make a success payment in shares of our common stock, the number of shares to be issued is computed by dividing the dollar amount of the success payment by the volume weighted average trading price of a share of our common stock on the trading day preceding the date on which the success payment is made.

In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million. We elected to make the payment in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015.

Memorial Sloan Kettering License and Research Agreement

In November 2013, we entered into a license agreement with MSK that grants us a worldwide, sublicensable license to certain patent rights and intellectual property rights related to certain know-how to develop, make, and commercialize licensed products and to perform services for all therapeutic and diagnostic uses, which license is exclusive with respect to such patent rights and tangible materials within such know-how, and nonexclusive with respect to such know-how and related intellectual property rights. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including bispecific and armored CARs, and their use for immunotherapy. Pursuant to this license agreement, as of January 31, 2016, we have rights to three issued U.S. patents, four pending U.S. patent applications, and a number of other patents and patent applications in jurisdictions outside the United States. Upon entering the agreement, we paid MSK an upfront payment of $6.9 million, and we are required to pay to MSK annual minimum royalties of $100,000 commencing on the fifth anniversary of the license agreement, with such payments creditable against royalties. The license agreement requires us to pay to MSK mid-to-high single-digit royalties based on annual net sales of licensed products or the performance of licensed services by us and our affiliates and sublicensees, which royalty will be reduced in the case of licensed products or services that are not covered by a valid patent in the country in which such products or services are manufactured or commercialized. In addition, if the first product we commercialize contains a chimeric antigen receptor T cell that is not a licensed product under the terms of the agreement, we are required to pay to MSK a below-single-digit royalty on net sales of such product for ten years after the first commercial sale of such product. We may also be obligated to pay to MSK up to a maximum of $6.75 million in clinical and regulatory milestone payments for each licensed product, which includes JCAR015. In addition, we are required to pay to MSK a percentage of certain payments that we receive from sublicensees of the rights licensed to us by MSK, which percentage will be based upon the date we receive such payments, the commitments we make for the development of licensed products under the agreement, or the achievement of certain clinical milestones.

The license agreement will expire, on a country-by-country and licensed-product-by-licensed-product and/or licensed-service-by-licensed-service basis, until the later of the expiration of the last to expire of the patents and patent applications covering such licensed product or service, the expiration of any market exclusivity period granted by a regulatory authority for such licensed product or service in such country, ten years from the first commercial sale of such licensed product or service in such country, or ten years from the first commercial sale of such licensed product or service in such country, where such product or service was never covered by a valid

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patent or patent application in such country. Upon the expiration of the agreement in any country for a particular licensed product, we will retain a nonexclusive, royalty-free license in such country to the licensed know-how useful to manufacture or commercialize such product. MSK may terminate the license agreement upon 90 days' notice in the event of our uncured material breach, or upon 30 days' notice if such breach is of a payment obligation. MSK may also terminate the agreement upon written notice in the event of our bankruptcy or insolvency or our conviction of a felony relating to the licensed products, or if we challenge the validity or enforceability of any licensed patent right. In addition, we have the right to terminate the agreement in its entirety at will upon 30 days' notice to MSK, but if we have commenced the commercialization of licensed products we can only terminate at will if we cease all development and commercialization of licensed products.

Also in November 2013, we entered into a master sponsored research agreement, which we refer to as the MSRA, with MSK focused on research and development relating to chimeric antigen receptor T cell technology. The research is conducted under project orders containing plans and budgets approved by the parties. We have an exclusive option to obtain an exclusive, worldwide, royalty-bearing, sublicensable license to intellectual property owned by MSK developed in connection with the work conducted under the MSRA, and an exclusive option to obtain an exclusive, worldwide, sublicensable license to MSK's interest in any improvements to the intellectual property licensed by us to MSK for conducting a research project. If the exclusive license agreement with MSK described above is still in effect, any such intellectual property licensed by us pursuant to our exercise of either such option shall be included within the rights licensed to us under the exclusive license agreement, although we may agree to additional diligence and other obligations. The term of the MSRA shall continue until the activities set forth in each statement of work entered into under the MSRA are completed. The MSRA may be terminated by either party upon 90 days' notice in the event of the other party's uncured material breach. MSK may terminate the MSRA upon 30 days' notice in the event of our uncured failure to make a payment.

Also in November 2013, we entered into a master clinical study agreement, which we refer to as the MCSA, for clinical studies to be conducted at MSK on our behalf. Each such clinical study will be conducted in accordance with a written plan and budget and protocol approved by the parties. We have an exclusive option to obtain an exclusive, worldwide, royalty-bearing, sublicensable license to intellectual property owned by MSK developed in connection with the work conducted under the MCSA, and an exclusive option to obtain an exclusive, worldwide, sublicensable license to MSK's interest in any improvements to the intellectual property licensed by us to MSK to conduct any clinical study under the MCSA. If the exclusive license agreement with MSK described above is still in effect, any such intellectual property licensed by us pursuant to our exercise of either such option shall be automatically included within the rights licensed to us under the exclusive license agreement. The MCSA has a term of five years and may be terminated by either party upon 30 days' notice in the event of the other party's uncured material breach, or upon written notice in the event of the other party's bankruptcy or insolvency.

In connection with these arrangements, in November 2013 we entered into a letter agreement with MSK pursuant to which we issued to MSK 500,000 shares of our common stock and agreed to make success payments to MSK, payable in cash or publicly-traded equity at our discretion. In December 2015, we amended this letter agreement to make certain clarifying amendments thereto. These success payments are based on increases in the per share fair market value of our common stock during the term of the success payment agreement, which is a period of time that begins on the date of our research agreement with MSK and ends on the later of (1) the eighth anniversary of that date and (2) the earlier of (a) the 11th anniversary of that date and (b) the third anniversary of the first date on which the FDA issues formal written approval for us to market a pharmaceutical or biologic product developed at least in part by our company. Success payments will be owed (if applicable) after measurement of the value of our common stock in connection with the following valuation measurement dates during the term of the success payment agreement: (1) December 19, 2014 (the date our common stock first became publicly traded upon our initial public offering); (2) the date on which we sell, lease, transfer, or exclusively license all or substantially all of our assets to another company; (3) the date on which we merge or consolidate with or into another entity (other than a merger in which our pre-merger stockholders own a majority of the shares of the surviving entity); (4) any date on which ARCH Venture Fund VII, L.P. or C.L. Alaska L.P.

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transfers a majority of its shares of company capital stock held by it on such date to a third party; (5) every second anniversary of any event described in the preceding clauses (1), (2), (3) or (4); and (6) the last day of the term of the success payment agreement. Any success payment will generally be made within 90 days after the applicable valuation measurement date, except that (1) in the case of an initial public offering, the payment will be made on March 19, 2016, which the date that is 90 days after the first anniversary of the date our common stock first became publicly traded upon our initial public offering, and (2) in the case of a merger or sale of all of our company's assets, the success payment will be made on the earlier of the 90th day following the transaction or the first date that transaction proceeds are paid to any of our stockholders. In the case of an initial public offering, the value of our common stock for determining whether a success payment was owed was determined by the average closing price of a share of our common stock over the consecutive 90 calendar day period preceding December 19, 2015, which was the first anniversary of the date our common stock first became publicly traded following our initial public offering. In the case of a valuation measurement date triggered by each second anniversary of our stock first becoming publicly traded, the value of our common stock for determining whether a success payment is owed will be determined by the average closing price of a share of our common stock over the consecutive 90 calendar day period preceding such anniversary date, so long as our common stock is publicly tradeable during such 90 calendar day period. On all other valuation measurement dates (if any), the value will be determined either, in the case of a merger or stock sale, by the consideration paid in the transaction for each share of our stock or, in all other cases, by a baseball arbitration process. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending from $10 million at $40.00 per share to $150 million at $120.00 per share, payable if such threshold is reached. Any previous success payments made to MSK are credited against the success payment owed as of any valuation measurement date, so that MSK does not receive multiple success payments in connection with the same threshold. The success payments paid to MSK will not exceed, in aggregate, $150 million, which would be owed only when the value of the common stock reaches $120.00 per share. In October 2015, we entered into an agreement with MSK to provide that certain indirect costs related to certain clinical studies and research projects are creditable against any success payments, and we amended this agreement in December 2015. If we elect to make a success payment in shares of our common stock, the number of shares to be issued is computed by dividing the dollar amount of the success payment by the volume weighted average trading price of a share of our common stock on the trading day preceding the date on which the success payment is made.

In December 2015, a success payment to MSK was triggered in the amount of $10.0 million, which is required to be paid, less indirect cost offsets, on March 18, 2016.

Seattle Children's Research Institute License and Collaboration Agreement

In February 2014, we entered into a license agreement with SCRI that grants to us an exclusive, worldwide, royalty-bearing sublicensable license to certain patent rights to develop, make, and commercialize licensed products and to perform licensed services for all therapeutic, prophylactic, and diagnostic uses. The patents and patent applications covered by this agreement are directed, in part, to regulated transgene expression and CAR constructs, including bispecific CARs and customized spacer regions, and their use for immunotherapy. Pursuant to this license agreement, as of January 31, 2016, we have rights to one pending U.S. patent application, five pending Patent Cooperation Treaty applications, and a number of other pending patent applications in jurisdictions outside the United States. Under the terms of the agreement, we paid SCRI an upfront payment of $200,000 and are required to pay to SCRI annual license maintenance fees, creditable against royalties and milestone payments due to SCH, of $50,000 per year for the first five years and $200,000 per year thereafter. Pursuant to the license agreement, we are obligated to pay to SCRI low single-digit royalties based on annual net sales of licensed products and licensed services by us and our affiliates and sublicensees. Based on the progress we make in the advancement of licensed products, including JCAR014 and JCAR017, we may be required to make clinical and regulatory milestone payments totaling up to $13.3 million in the aggregate per licensed

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product and up to $3.0 million in commercial milestone payments. In addition, we are required to pay to SCRI a percentage of the payments that we receive from sublicensees of certain rights licensed to us by SCRI, up to an aggregate of $15 million, which percentage will be based upon the date we receive such payments and the achievement of certain clinical and regulatory milestones. The term of the license agreement will continue until the expiration or abandonment of all licensed patents and patent applications. We have the right to terminate the agreement at will upon 60 days' written notice to SCRI. SCRI may terminate the agreement upon 90 days' notice in the event of our uncured material breach, or upon 30 days' notice if such breach is of a payment obligation. SCRI may terminate the agreement immediately if we challenge the enforceability, validity, or scope of any licensed patent right or assist a third party to do so. The agreement will terminate immediately in the event of our bankruptcy or insolvency.

Also in February 2014, we entered into a sponsored research agreement with SCRI. The research is conducted under project orders containing plans and budgets approved by the parties. We have an exclusive option to obtain an exclusive license to certain improvements, inventions, and other intellectual property rights owned by SCRI developed in connection with the work conducted under the sponsored research agreement. In some circumstances, we may be required to pay an option exercise fee to SCRI of up to $100,000 per improvement. When improvements provide substantial new functionality or commercial benefit and can be practiced without a license to any of the patents already licensed under the license agreement, we may agree to additional royalties, development milestones, and diligence obligations. The initial term of the sponsored research agreement was five years, and has since been extended through April 2020. SCRI may terminate the agreement for any reason upon 180 days' notice, or immediately if the principal investigator is unable to continue performing the research and there is no successor acceptable to both parties. Either party may terminate the agreement upon 30 days' notice in the event of the other party's uncured material breach.

City of Hope License Agreement

In November 2009, ZetaRx LLC ("ZetaRx") entered into a license agreement with City of Hope ("COH") pursuant to which ZetaRx was granted an exclusive, worldwide, royalty-bearing license under certain patent rights to manufacture and commercialize products involving genetically engineered white blood cells for the treatment or prevention of disease in humans. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including bispecific CARs and T cell ablation technologies, and their use for immunotherapy. Pursuant to this license agreement, as of January 31, 2016, we have rights to 12 issued U.S. patents, three pending U.S. patent applications, and a number of other patents and patent applications in jurisdictions outside the United States. The license is sublicensable with consent, and our sublicensees cannot grant further sublicenses. This license agreement was assumed by us in connection with our acquisition of certain of ZetaRx's assets in October 2013. Under the terms of the license agreement, we are required to pay COH an annual license maintenance fee of $25,000, which payment is creditable against any other royalties due for the applicable year. In addition, the license agreement requires us to pay COH low single-digit royalties on annual net sales by us and our sublicensees. In addition, we are required to pay COH a fixed percentage of certain payments we receive from sublicensees of the technology licensed to us by COH.

The license agreement shall expire, on a country-by-country basis, upon the expiration of the last to expire of the patent rights licensed to us in such country. The agreement may be terminated by either party upon 30 days' prior written notice in the event of the other party's uncured material breach. In addition, COH may terminate the agreement immediately upon written notice in the event of bankruptcy or insolvency of our company, or if we do not reach certain clinical milestones by certain dates.

St. Jude Children's Research Hospital Agreement; Sublicense to Penn and Novartis

In December 2013, we entered into an agreement with St. Jude (the "St. Jude License Agreement") pursuant to which we (1) obtained control over, and are obliged to pursue and defend, St. Jude's causes of action in a pending litigation in the Eastern District of Pennsylvania, Trustees of the University of Pennsylvania v. St. Jude

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Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (the "Penn litigation"), in which we and St. Jude were each adverse to Penn and Novartis, and (2) acquired an exclusive, worldwide, royalty-bearing license under certain patent rights owned by St. Jude, including the '645 Patent, to develop, make, and commercialize licensed products and services for all therapeutic, diagnostic, preventative, and palliative uses. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs capable of signaling both a primary and a co-stimulatory pathway. Pursuant to the St. Jude License Agreement, as of January 31, 2016, we have rights to one issued U.S. patent and three pending U.S. patent applications. The Penn litigation concerned both the '645 Patent and a contractual dispute between St. Jude and Penn. We also obtained settlement authority in the Penn litigation, subject to certain conditions.

Upon entering into this the St. Jude License Agreement, we made an initial payment to St. Jude of $25 million. In addition, the agreement requires us to pay St. Jude low single-digit royalties on net sales of licensed products and services. We are also obligated to pay a $100,000 minimum annual royalty for the first two years of the agreement, and a $500,000 minimum royalty thereafter through the term of the agreement. In addition, we are required to make milestone payments of up to an aggregate of $62.5 million upon the achievement of specified clinical, regulatory, and commercialization milestones for licensed products, which includes JCAR014 and JCAR017. In addition, we are required to pay St. Jude a percentage of certain payments we receive from sublicensees of the rights licensed to us by St. Jude or in settlement of litigation with respect to such rights. We were also required to pay a percentage of St. Jude's reasonable legal fees incurred in connection with the Penn litigation.

The term of the St. Jude License Agreement will expire, on a country-by-country basis, upon the expiration of the last to expire of the licensed patents and patent applications in such country. The agreement may be terminated by either party in the event of the other party's bankruptcy or insolvency, or upon advance written notice in the event of the other party's uncured breach. We may terminate the agreement at will, in its entirety or with respect to any particular licensed patent or patent application, upon advance written notice to St. Jude.

In April 2015, St. Jude and we agreed to settle the litigation with Penn and Novartis. In connection with such settlement, we entered into a sublicense agreement (the "Penn/Novartis Sublicense Agreement") with Penn and an affiliate of Novartis pursuant to which Juno granted to Novartis a non-exclusive, royalty-bearing sublicense under certain patent rights, including the '645 Patent, to develop, make and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative and palliative uses. This sublicense is not sublicensable without our prior written consent, although Novartis may authorize third parties to act on its behalf with respect to the manufacture, development or commercialization of Novartis' licensed products and licensed services. Pursuant to the Penn/Novartis Sublicense Agreement, Novartis paid Juno $12.3 million upon the effectiveness of such agreement, which amount was first applied to cover certain predetermined litigation expenses incurred by St. Jude, with the remainder divided between Juno and St. Jude at a fixed ratio. In addition, Novartis is also required to pay mid-single digit royalties on the U.S. net sales of products and services related to the disputed contract and patent claims (the "Novartis Royalty Payments"), a low double digit percentage of the royalties Novartis pays to Penn for global net sales of those products (the "Penn Royalty Payments"), and milestone payments upon the achievement of specified clinical, regulatory and commercialization milestones for licensed products (the "Novartis Milestone Payments"). If Juno achieves any of the milestones prior to Novartis, the related Novartis Milestone Payment will be reduced by 50%. In addition, if Juno achieves any milestone after Novartis, Juno will reimburse Novartis 50% of any Novartis Milestone Payment previously paid by Novartis to Juno in respect of such milestone. These milestones largely overlap with the milestones for which Juno may owe a payment to St. Jude under the St. Jude License Agreement and the Novartis Milestone Payments would in effect serve to partially offset Juno's obligations to St. Jude with respect to such milestones.

The term of the Penn/Novartis Sublicense Agreement will expire when there are no remaining payment obligations due under the agreement. The Penn/Novartis Sublicense Agreement may be terminated by either party in the event of the other party's bankruptcy or insolvency or upon the occurrence of certain specified breaches, or upon advance written notice in the event of the other party's uncured material breach. Novartis may terminate the Penn/Novartis Sublicense Agreement at will upon advance written notice to Juno.

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In connection with the settlement, Juno also amended the St. Jude License Agreement to provide the terms by which the Penn/Novartis Sublicense Agreement would be treated under the St. Jude License Agreement. The net effect of the Penn/Novartis Sublicense Agreement and amendment to the St. Jude License Agreement is that (1) Juno will pass through a percentage of the Novartis Royalty Payments to St. Jude, and (2) Juno will pass through a portion of the Penn Royalty Payments and Novartis Milestone Payments to St. Jude.

In the first quarter of 2016, Novartis paid us $5.8 million upon the achievement of a clinical milestone by Novartis, $5.0 million of which we are required to pass on to St. Jude. In the event we separately achieve the same clinical milestone in the future, we will be required to reimburse Novartis $2.9 million.

License Agreements with Fred Hutchinson Cancer Research Center assumed from ZetaRx

We assumed two license agreements with FHCRC in connection with our acquisition of certain of ZetaRx's assets in October 2013. ZetaRx entered into these license agreements with FHCRC in 2009 (the "2009 FHCRC Agreement") and 2012 (the "2012 FHCRC Agreement"). These agreements were amended and restated in November 2014. Under each of these license agreements, we received an exclusive, worldwide, sublicensable license under patent and technology rights to make, manufacture, use, and commercialize products (and, under the 2009 FHCRC Agreement only, services) for all fields of use. The patents and patent applications covered by these agreements are directed, in part, to defined T cell compositions and their use for immunotherapy. Pursuant to these license agreements, as of January 31, 2016, we have rights to one issued U.S. patent, four pending U.S. patent applications, one issued patent in a jurisdiction outside the United States, one pending Patent Cooperation Treaty application, and a number of other patent applications in jurisdictions outside the United States. Pursuant to each of the agreements, we are required to pay FHCRC a low single-digit running royalty based on annual net sales of licensed products (and, under the 2009 FHCRC Agreement only, licensed services) by us and by our affiliates and sublicensees. In addition, under each agreement, we are required to pay to FHCRC a minimum annual royalty of $5,000 until we receive FDA approval of a licensed product, and a minimum annual royalty of $20,000 thereafter for the remainder of the applicable agreement term, which payments will be creditable against any running royalties due to FHCRC under the respective license agreements. Under the 2012 FHCRC Agreement, we are required to pay to FHCRC up to an aggregate of $1.35 million upon our achievement of certain clinical and regulatory milestones relating to the licensed products, which includes JCAR014 and JCAR017. In addition, under each of the license agreements, we are required to pay FHCRC a fixed percentage of certain payments that we receive from sublicensees of the rights licensed to us by FHCRC, up to a cap.

Unless earlier terminated, each of these license agreements will expire upon the expiration of the last to expire of the patent rights licensed to us under the respective agreements. Each agreement may be terminated by FHCRC upon 90 days' written notice if we fail to provide satisfactory written evidence that we have submitted an IND application to the FDA, by June 2015 in the case of the 2009 FHCRC Agreement, and by January 2017 in the case of the 2012 FHCRC Agreement. We have the right to terminate each of the agreements at will, in part or in their entirety, upon 60 days' written notice to FHCRC. Each of the license agreements may also be terminated by FHCRC in the event of our bankruptcy or insolvency, upon 90 days' written notice in the event of our uncured material breach, and upon 30 days' written notice in the event of our uncured breach of a payment or reporting obligation. Upon termination, but not expiration, of either of these license agreements, we must grant to FHCRC a royalty-bearing, non-exclusive, non-sublicensable license with respect to any improvements we make based on the patents or technology licensed to us under the respective agreements.

Royalty and Milestone Obligations for JCAR015 and JCAR017

Under our existing license agreements, our overall royalty burden for net sales of each of JCAR015 and JCAR017 in the United States is less than 10%. We anticipate that the royalty burden will be lower outside of the United States. As of the date of this report, based on our planned manufacturing processes for JCAR015 and JCAR017, the aggregate maximum amount of milestone payments we could be required to make under our existing license and collaboration agreements is $19.3 million and $95.5 million for JCAR015 and JCAR017,

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respectively. Included in the foregoing figures for JCAR015 and JCAR017 are $5.7 million and $67.4 million, respectively, in milestone payments that would be paid only for the first product candidate to meet the associated milestone. The amount of overlap among JCAR015 and JCAR017 with respect to milestones that would be paid only for the first product candidate to achieve the associated milestone is $5.7 million for JCAR015 and JCAR017, such that the combined aggregate maximum amount of milestone payments for JCAR015 and JCAR017 is $109.1 million. Certain milestones would be paid in euros, which have been estimated in U.S. dollars for the foregoing figures based on the exchange rate as of December 31, 2015.

Opus Bio License Agreement

In December 2014, we entered into a license agreement with Opus Bio pursuant to which we were granted an exclusive, worldwide, sublicensable license under certain patent rights and data to research, develop, make, have made, use, have used, sell, have sold, offer to sell, import and otherwise exploit products that incorporate or use engineered T cells directed against CD22 and that are covered by such patent rights or use or incorporate such data. Certain of the licensed patent rights are in-licensed by Opus Bio from the National Institutes of Health ("NIH"). The patents and patent applications covered by this agreement are directed, in part, to various human monoclonal antibodies specific for CD22 and their use in immunotherapy. Pursuant to this license agreement, as of January 31, 2016, we have rights to four issued U.S. patents, three pending U.S. patent applications, and a number of other patents and patent applications in jurisdictions outside the United States. The licensed data was generated under an agreement between Opus Bio and the National Cancer Institute ("NCI") and Opus Bio's rights to the licensed data are not exclusive. Our rights to such data are therefore exclusive only as between us and Opus, and non-exclusive as between us and third parties, who may license such data from the NCI. Our license from Opus Bio is limited to the field of treating B cell malignancies that express CD22 on their cell surface using CARs containing certain specified antibody binding fragments. Under the agreement, we will be required to use commercially reasonable efforts to research, develop, and commercialize licensed products. Such development must be in accordance with the timelines provided in the license agreement for achievement of certain clinical, regulatory, and commercial benchmarks, and with the development plans set forth in Opus Bio's agreements with the NIH. In November 2015, the license agreement was amended to adjust certain of these timelines.

Upon the effectiveness of this license in December 2014, we made an upfront payment to Opus Bio of $20.0 million in cash and issued to Opus Bio 1,602,564 shares of our common stock. Upon our achievement of certain clinical, regulatory, and commercial milestones set forth in the license agreement, we will be obligated to pay Opus Bio additional consideration. The consideration due upon achievement of the first three clinical milestones would consist of additional shares of our common stock in an amount equal to the dollar value specified for the applicable milestone, which is $52.5 million in the aggregate for the three milestones, divided by the greater of $10.92 and the arithmetic average of the daily volume-weighted average price of our common stock on The NASDAQ Global Select Market over the 30 trading days preceding the achievement of the milestone, up to a maximum of 4,807,692 shares in the aggregate (this minimum per share value and maximum number of shares subject, in each case, to adjustment for any stock dividend, stock split, combination of shares, or other similar events). Upon our achievement of any subsequent milestones, we will be obligated to pay Opus Bio cash consideration, which potential milestone payments total $215.0 million in the aggregate. Once certain milestones have been achieved, we will be required to spend at least $2.5 million per year on development and commercialization of licensed products. In January 2016, the first clinical milestone of $20.0 million was achieved, and we issued 408,068 shares of our common stock as payment. The license agreement further provides that we are required to pay to Opus Bio tiered royalties based on annual net sales of licensed products by us and by our sublicensees, at rates ranging from the low-single to mid-single digits. We will also be required to make certain pass-through payments owed by Opus Bio to NIH under its NIH license agreements, including certain patent costs, development and commercial milestones of up to $2.8 million in the aggregate, and low single-digit royalties based on annual net sales.

Our obligations to pay royalties to Opus Bio will expire, on a country-by-country and licensed-product- by-licensed-product basis, upon the later of the expiration of the last-to-expire patent covering such product in such

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country and the expiration of the period of data protection or market exclusivity or similar protection granted by the regulatory authority in such country for such product. The license agreement will expire on the expiration of our payment obligations to Opus Bio and to the NIH. We may terminate the agreement at will upon 30 days' prior written notice. Opus Bio has the right to terminate the agreement immediately in the event of our material breach, including our failure to meet certain regulatory, clinical, and commercial deadlines, that remains uncured after a period of notice from Opus Bio, and immediately upon notice in the event of our bankruptcy or insolvency. If we terminate for convenience, or if Opus Bio terminates due to our material breach, then we will be subject to obligations allowing Opus Bio to continue to develop licensed products, including transfer of certain materials and products, transfer of ownership of certain regulatory documents and any approved trademarks or brand names, the assignment of third-party agreements solely related to the licensed products and necessary for the research, development, or commercialization of the licensed products, our continued manufacture of the licensed products, and the grant of certain non-exclusive licenses under certain technology controlled by us. If we terminate the license agreement for convenience and Opus elects to continue to develop the licensed products, then we have the option to resume our rights under the license agreement in exchange for additional payment obligations to Opus.

Other Licenses and Third-Party Collaboration Agreements

We have entered into a number of other license agreements and collaboration agreements with third parties in connection with our preclinical and clinical research and development activities. These include, among others:

- A collaboration and license agreement with Fate Therapeutics to identify and utilize small molecules to modulate our genetically-engineered T cell product candidates to improve their therapeutic potential for cancer patients.
- A collaboration and license agreement with Editas to pursue research programs utilizing Editas' genome editing technologies with Juno's CAR and TCR technologies.
- A clinical study collaboration agreement with MedImmune to conduct combination clinical trials in immuno-oncology with one of our investigational CD19-directed CAR product candidates and MedImmune's investigational PD-L1 immune checkpoint inhibitor, MEDI4736.

Acquisitions

During 2015 and early 2016, we have completed three business acquisitions to augment our research and development capabilities and to improve our supply chain and long-term cost of goods.

Stage Cell Therapeutics

In May 2015, we acquired Stage, a company focused on developing technology platforms, including novel reagents and automation technologies, that enable the development and production of cell therapeutics. The acquisition of Stage is intended to provide us access to transformative cell selection and activation capabilities, next generation manufacturing automation technologies, enhanced control of our supply chain, and lower expected long-term cost of goods.

As consideration for the Stage acquisition, we paid €52.5 million in cash and issued an aggregate of 486,279 shares of common stock to the selling shareholders. We also agreed to pay additional amounts of up to an aggregate of €135.0 million in cash based on the achievement of certain technical, clinical, regulatory, and commercial milestones related to novel reagents (€40.0 million), advanced automation technology (€65.0 million), and Stage's existing clinical pipeline (€30.0 million).

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X-Body

In June 2015, we acquired X-Body, a company focused on the discovery of human monoclonal antibodies and discovery of TCR binding domains. The X-Body acquisition is intended to augment our capabilities to create best-in-class engineered T cells against a broad array of cancer targets.

As consideration for the X-Body acquisition, we paid $21.3 million in cash and issued an aggregate of 366,434 shares of common stock to the former X-Body stockholders. We also agreed to pay additional amounts in cash upon the realization of specified milestones substantially as follows, with respect to products generated using the X-Body technology: $5.0 million per target upon the achievement, during a specified period, of a certain regulatory milestone for products that utilize a certain type of binding mechanism; up to $30.0 million upon the achievement, during a specified period, of regulatory and clinical milestones for the first product using another type of binding mechanism (any product using such type of binding mechanism, a “Type X Product”); $5.0 million per product upon the achievement, during a specified period, of a certain regulatory milestone for a certain number of subsequent Type X Products; $50.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain specified binding properties (a “Type Y Product”); and $20.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain other specified binding properties. If a Type X Product or a Type Y Product is commercialized, we can choose either to make a commercialization milestone payment for such a product or to pay a low single-digit royalty on net sales of such a product.

AbVitro

In January 2016, we acquired AbVitro, a company with a leading next-generation single cell sequencing platform. The AbVitro acquisition is intended to augment our capabilities to create best-in-class engineered T cells against a broad array of cancer targets. We will initially use this technology in our translation research assays, to find and generate fully-human TCRs and antibodies, and to find novel targets.

As consideration for the AbVitro acquisition, we paid approximately $78 million in cash and issued 1,289,188 shares of our common stock. There are no milestone payment obligations under the terms of the AbVitro acquisition.

We and Celgene have agreed in principle to enter into an agreement to license Celgene a subset of the acquired AbVitro technology and to grant Celgene options to certain related potential product rights emanating from the acquired technology.

Competition

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large biopharmaceutical companies, midsize/smaller public and privately-held biotechnology firms, academic research institutions, governmental agencies, and public and private research institutions.

In addition to the current standard of care treatments for patients, a large number of commercial and academic clinical trials are being pursued by variety of parties in the field of immunotherapy. Early positive clinical results from these trials have fueled continued interest in the field of immunotherapy. In the CAR and TCR space, our competitors include, but are not limited to, Novartis / Penn, Kite Pharma / Amgen / NCI, Cellectis / Pfizer / Servier, Johnson & Johnson / Transposagen Biopharmaceuticals, bluebird bio, Bellicum, Celyad, NantKwest, Intrexon / Ziopharm / MD Anderson Cancer Center, Unum Therapeutics, Adaptimmune / GlaxoSmithKline, ImmunoCellular Therapeutics, and Autolus. We also face competition from non-cell based treatments offered by companies such as Amgen, Pfizer, Abbvie, AstraZeneca, Bristol-Myers, Incyte, Merck, and Roche. For instance,

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the FDA approved Amgen's blinotumomab for the treatment of r/r ALL in 2014, and that product has achieved a complete remission rate of approximately 40% in clinical trials. We also anticipate Pfizer's inotuzumab to be approved for the treatment of r/r ALL as early as 2016, which has shown a CR rate of approximately 80% in clinical trials. Many of our larger current or potential competitors, either alone or with their collaboration partners, have greater financial resources and deeper expertise in manufacturing, preclinical testing, clinical trial execution, regulatory matters and commercializing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and gene therapy industries may result in even more resources being concentrated among a smaller number of very capable competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining experienced scientific and management personnel, patient enrollment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs' success.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that alone or in combination have better efficacy, less toxicity, more convenience, or are less expensive than the products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we do, which may also include broader labels, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our programs are likely to be their efficacy, safety, and convenience, along with our ability to simply operationalize the use of our products.

Government Regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring, and post-approval reporting of biologics such as those we are developing. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

The process required by the FDA before biologic product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's current Good Laboratory Practices ("GLP") regulation;
- submission to the FDA of an IND which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent Institutional Review Board ("IRB") or ethics committee at each clinical site before the trial is commenced;
- performance of adequate and well-controlled human clinical trials to establish the safety, purity and potency of the proposed biologic product candidate for its intended purpose;
- preparation of and submission to the FDA of a BLA after completion of all pivotal clinical trials;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with cGMP and to assure that the

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facilities, methods and controls are adequate to preserve the biological product's continued safety, purity and potency, and of selected clinical investigations to assess compliance with Good Clinical Practices ("GCP"); and

- FDA review and approval of the BLA to permit commercial marketing of the product for particular indications for use in the United States.

The testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Prior to beginning the first clinical trial with a product candidate, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

When a trial using genetically engineered cells is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation is submitted to and the study is registered with the NIH Office of Biotechnology Activities ("OBA") pursuant to the NIH Guidelines for Research Involving Recombinant DNA Molecules ("NIH Guidelines"). Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, and many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the Recombinant DNA Advisory Committee ("RAC"), a federal advisory committee that discusses protocols that raise novel or particularly important scientific, safety, or ethical considerations at one of its quarterly public meetings. The OBA will notify the FDA of the RAC's decision regarding the necessity for full public review of a protocol. RAC proceedings and reports are posted to the OBA web site and may be accessed by the public. If the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies, including our Phase II trial for JCAR015, also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

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For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap.

- Phase I—The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- Phase II—The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase II clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase III clinical trials.
- Phase III—The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.
- Phase IV—In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so- called Phase IV studies may be made a condition to approval of the BLA.

Phase I, Phase II and Phase III testing may not be completed successfully within a specified period, if at all, and there can be no assurance that the data collected will support FDA approval or licensure of the product. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

BLA Submission and Review by the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from pertinent preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by investigators. The submission of a BLA requires payment of a substantial User Fee to FDA, and the sponsor of an approved BLA is also subject to annual product and establishment user fees. These fees are typically increased annually. A waiver of user fees may be obtained under certain limited circumstances.

Once a BLA has been submitted, the FDA's goal is to review the application within ten months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency.

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The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all, and we may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals, which could delay or preclude us from marketing our products. After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may request additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy (“REMS”) plan to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing regulatory standards is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product’s safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies. In addition, new government requirements, including those resulting from new legislation, may be established, or the FDA’s policies may change, which could delay or prevent regulatory approval of our products under development.

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA’s review and approval of new drugs and biological products that meet certain criteria. Specifically, new drugs and biological products are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. For a fast track product, the FDA may consider sections of the BLA for review on a rolling basis before the complete application is submitted if relevant criteria are met. A fast track designated product candidate may also qualify for priority review, under which the FDA sets the target date for FDA action on the BLA at six months after the FDA accepts the application for filing. Priority review is granted when there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious disease or condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of 10 months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

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Under the accelerated approval program, the FDA may approve a BLA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing studies or completion of ongoing studies after marketing approval are generally required to verify the biologic's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety and Innovation Act ("FDASIA"), which was enacted and signed into law in 2012, established the new breakthrough therapy designation. A sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the product candidate is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Sponsors may request the FDA to designate a breakthrough therapy at the time of or any time after the submission of an IND, but ideally before an end-of-phase II meeting with FDA. If the FDA designates a breakthrough therapy, it may take actions appropriate to expedite the development and review of the application, which may include holding meetings with the sponsor and the review team throughout the development of the therapy; providing timely advice to, and interactive communication with, the sponsor regarding the development of the drug to ensure that the development program to gather the nonclinical and clinical data necessary for approval is as efficient as practicable; involving senior managers and experienced review staff, as appropriate, in a collaborative, cross-disciplinary review; assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor; and considering alternative clinical trial designs when scientifically appropriate, which may result in smaller trials or more efficient trials that require less time to complete and may minimize the number of patients exposed to a potentially less efficacious treatment. Breakthrough therapy designation comes with all of the benefits of fast track designation, which means that the sponsor may file sections of the BLA for review on a rolling basis if certain conditions are satisfied, including an agreement with FDA on the proposed schedule for submission of portions of the application and the payment of applicable user fees before the FDA may initiate a review. We plan to seek designation as a breakthrough therapy for some or all of our CD19 product candidates, as qualification permits. Our collaborator MSK obtained breakthrough therapy designation for JCAR015 for r/r ALL, but we will have to seek such designation separately under our own IND.

Fast Track designation, priority review and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 individuals in the United States and when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a full BLA, to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does

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not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the BLA application user fee.

A designated orphan drug many not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or, as noted above, if the second applicant demonstrates that its product is clinically superior to the approved product with orphan exclusivity or the manufacturer of the approved product is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. We plan to seek orphan drug designation for some or all of our CD19 product candidates in specific orphan indications in which there is a medically plausible basis for the use of these products. We have obtained orphan drug designation for each of JCAR015 and JCAR014 for the treatment of ALL.

Post-Approval Requirements

Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data. Biologic manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance. We cannot be certain that we or our present or future suppliers will be able to comply with the cGMP regulations and other FDA regulatory requirements. If our present or future suppliers are not able to comply with these requirements, the FDA may, among other things, halt our clinical trials, require us to recall a product from distribution, or withdraw approval of the BLA.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our product candidates, and expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved BLA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;

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- fines, warning letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of biologics. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Other Healthcare Laws and Compliance Requirements

Our sales, promotion, medical education and other activities following product approval will be subject to regulation by numerous regulatory and law enforcement authorities in the United States in addition to FDA, including potentially the Federal Trade Commission, the Department of Justice, the Centers for Medicare and Medicaid Services, other divisions of the Department of Health and Human Services and state and local governments. Our promotional and scientific/educational programs must comply with the federal Anti-Kickback Statute, the Foreign Corrupt Practices Act, the False Claims Act, the Veterans Health Care Act, physician payment transparency laws, privacy laws, security laws, and additional state laws similar to the foregoing.

The federal Anti-Kickback Statute prohibits, among other things, the offer, receipt, or payment of remuneration in exchange for or to induce the referral of patients or the use of products or services that would be paid for in whole or part by Medicare, Medicaid or other federal health care programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced price items and services. The government has enforced the Anti-Kickback Statute to reach large settlements with healthcare companies based on sham research or consulting and other financial arrangements with physicians. Further, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act. Many states have similar laws that apply to their state health care programs as well as private payors.

The False Claims Act ("FCA"), imposes liability on persons who, among other things, present or cause to be presented false or fraudulent claims for payment by a federal health care program. The FCA has been used to prosecute persons submitting claims for payment that are inaccurate or fraudulent, that are for services not provided as claimed, or for services that are not medically necessary. Actions under the FCA may be brought by the Attorney General or as a qui tam action by a private individual in the name of the government. Violations of the FCA can result in significant monetary penalties and treble damages. The federal government is using the FCA, and the accompanying threat of significant liability, in its investigation and prosecution of pharmaceutical and biotechnology companies throughout the country, for example, in connection with the promotion of products for unapproved uses and other sales and marketing practices. The government has obtained multi-million and multibillion dollar settlements under the FCA in addition to individual criminal convictions under applicable criminal statutes. In addition, companies have been forced to implement extensive corrective action plans, and have often become subject to consent decrees or corporate integrity agreements, restricting the manner in which

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they conduct their business. The federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA") also created federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Given the significant size of actual and potential settlements, it is expected that the government will continue to devote substantial resources to investigating healthcare providers' and manufacturers' compliance with applicable fraud and abuse laws.

In addition, there has been a recent trend of increased federal and state regulation of payments made to physicians and other healthcare providers. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the "Affordable Care Act"), among other things, imposed new reporting requirements on drug manufacturers for payments or other transfers of value made by them to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (or up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers must submit reports by the 90th day of each calendar year. Certain states also mandate implementation of commercial compliance programs, impose restrictions on drug manufacturer marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians and other healthcare professionals.

We may also be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology and Clinical Health Act ("HITECH"), and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, imposes specified requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities that create, receive, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect.

If our operations are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, civil and criminal penalties, damages, fines, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

Also, the U.S. Foreign Corrupt Practices Act and similar worldwide anti-bribery laws generally prohibit companies and their intermediaries from making improper payments to foreign officials for the purpose of obtaining or retaining business. We cannot assure you that our internal control policies and procedures will protect us from reckless or negligent acts committed by our employees, future distributors, partners, collaborators or agents. Violations of these laws, or allegations of such violations, could result in fines, penalties or prosecution and have a negative impact on our business, results of operations and reputation.

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Coverage and Reimbursement

Sales of pharmaceutical products depend significantly on the availability of third-party coverage and reimbursement. Third-party payors include government health administrative authorities, managed care providers, private health insurers, integrated delivery networks, and other organizations. Although we currently believe that third-party payors will provide coverage and reimbursement for our product candidates, if approved, these third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services. In addition, significant uncertainty exists as to the reimbursement status of newly approved healthcare products. We may need to conduct expensive clinical studies to demonstrate the comparative cost-effectiveness of our products. The product candidates that we develop may not be considered cost-effective. It is time consuming and expensive for us to seek coverage and reimbursement from third-party payors. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis.

Healthcare Reform

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

By way of example, in March 2010, the Affordable Care Act was signed into law, intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Among the provisions of the Affordable Care Act of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013, and, due to subsequent legislative amendments, will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our product candidates, if approved, and, accordingly, our financial operations.

We expect that the Affordable Care Act, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products to the extent we choose to develop or sell any products outside of the United States. The approval process varies from country to country and the time may be longer or shorter than that required to obtain FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country.

In the EU, member states require both regulatory clearances by the national competent authority and a favorable ethics committee opinion prior to the commencement of a clinical trial. Under the EU regulatory systems, marketing authorization applications may be submitted under either a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU member states. It is compulsory for medicines produced by certain biotechnological processes. Because our products are produced in that way, we would be subject to the centralized process. Under the centralized procedure, pharmaceutical companies submit a single marketing authorization application to the European Medicines Agency (“EMA”). Once granted by the European Commission, a centralized marketing authorization is valid in all EU member states, as well as the European Economic Area countries Iceland, Liechtenstein and Norway. By law, a company can only start to market a medicine once it has received a marketing authorization.

Employees

As of December 31, 2015, we had 306 employees globally. None of our employees are represented by a labor union or covered under a collective bargaining agreement. We consider our employee relations to be good.

Research and Development

Our research and development costs were $205.2 million, $204.5 million, and $46.2 million for the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013, respectively. See Part II—Item 7—“Management’s Discussion and Analysis of Financial Condition and Results of Operations” of this report for additional detail regarding our research and development activities.

Geographic Information

Revenues generated outside of the United States and long-lived assets located outside of the United States were not material for the year ended and as of December 31, 2015, respectively.

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Financial Information about Segments

We operate in one business segment. See Note 2 to our audited consolidated financial statements included in this report. For financial information regarding our business, see Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations" of this report and our audited consolidated financial statements and related notes included elsewhere in this report.

About Juno

Juno was incorporated in Delaware on August 5, 2013. Our principal executive offices are located at 307 Westlake Avenue North, Suite 300, Seattle, Washington 98109. Our telephone number is (206) 582-1600. Our website address is www.junotherapeutics.com. Information contained on the website is not incorporated by reference into this report, and should not be considered to be part of this report.

We use Juno Therapeutics®, the Juno Therapeutics logo, and other marks as trademarks in the United States and other countries. This report contains references to our trademarks and service marks and to those belonging to other entities. Solely for convenience, trademarks and trade names referred to in this report, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate in any way that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other entities' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, any other entity.

Available Information

We file electronically with the Securities and Exchange Commission ("SEC") our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). We make available on our website at www.junotherapeutics.com, free of charge, copies of these reports, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The public may read or copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street NE, Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that website is www.sec.gov. The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this filing. Further, our references to the URLs for these websites are intended to be inactive textual references only.

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ITEM 1A. RISK FACTORS

The following section includes the most significant factors that may adversely affect our business and operations. You should carefully consider the risks and uncertainties described below and all information contained in this report, including our consolidated financial statements and the related notes and Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

Risks Related to Our Business and Industry

We are a clinical-stage company and have a very limited operating history, which may make it difficult to evaluate our current business and predict our future performance.

We are a clinical-stage biopharmaceutical company that was formed in August 2013. We have no cell-therapy products approved for commercial sale and as of December 31, 2015 had not generated any revenue from such products. We are focused on developing products that use human cells as therapeutic entities and, although there have been significant advances in cell- based immunotherapy, our T cell technologies are new and largely unproven. Our limited operating history, particularly in light of the rapidly evolving cancer immunotherapy field, may make it difficult to evaluate our current business and predict our future performance. Our very short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer.

We have incurred net losses in each period since our inception and anticipate that we will continue to incur net losses in the future.

We are not profitable and have incurred losses in each period since our inception. For the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013, we reported a net loss of $239.4 million, $243.4 million, and $51.8 million, respectively. As of December 31, 2015, we had an accumulated deficit of $585.7 million, which includes $51.1 million related to non-cash deemed dividends, $159.4 million in upfront fees to acquire technology, of which $85.5 million was paid in cash and $73.9 million was paid through the issuance of common stock, non-cash expense of $136.5 million associated with the change in the estimated fair value and elapsed service period for our potential and actual success payment liability to FHCRC and MSK, and $10.7 million of expense associated with our convertible preferred stock options. We expect these losses to increase as we continue to incur significant research and development and other expenses related to our ongoing operations, seek regulatory approvals for our product candidates, scale-up manufacturing capabilities and hire additional personnel to support the development of our product candidates and to enhance our operational, financial and information management systems.

A critical aspect of our strategy is to invest significantly in our technology platform to improve the efficacy and safety of our product candidates. Even if we succeed in commercializing one or more of these product candidates, we will continue to incur losses for the foreseeable future relating to our substantial research and development expenditures to develop our technologies. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital. Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period to period comparison of our results of operations may not be a good indication of our future performance.

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We expect to continue to incur significant losses for the foreseeable future. We expect these losses and our cash utilization to increase in the near term as we continue to conduct clinical trials, file additional IND filings for additional product candidates, and conduct research and development of our other product candidates.

We are collaborating with Celgene pursuant to a collaboration agreement, under which we and Celgene will research, develop and commercialize novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. Contingent upon the payment of certain upfront payments, Celgene may exercise options to acquire exclusive licenses to certain therapeutics we develop and each party may exercise certain options to co-develop and co-commercialize product candidates developed, or acquired or in-licensed, by the other party. If Celgene does not exercise its options, or if our collaboration with Celgene terminates, we will be responsible for funding further development of the relevant product candidates, which would cause our expenses to increase, unless we enter into another collaboration for such product candidates, which may not be possible within an acceptable timeframe, or on suitable terms. Similarly, our expenses would increase if we exercise an option to co-develop and co-commercialize any product candidate developed, or in-licensed or acquired, by Celgene. If any of these were to occur, our losses could increase.

We have never generated any revenue from sales of cell-therapy products and our ability to generate revenue from cell-therapy product sales and become profitable depends significantly on our success in a number of factors.

We have no cell-therapy products approved for commercial sale, have not generated any revenue from cell-therapy product sales, and do not anticipate generating any revenue from cell-therapy product sales until some time after we have received regulatory approval for the commercial sale of a product candidate. Our ability to generate revenue and achieve profitability depends significantly on our success in many factors, including:

- completing research regarding, and nonclinical and clinical development of, our product candidates;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for our product candidates, including establishing and maintaining commercially viable supply relationships with third parties and establishing our own manufacturing capabilities and infrastructure;
- launching and commercializing product candidates for which we obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor;
- obtaining market acceptance of our product candidates as viable treatment options, and obtaining adequate coverage, reimbursement, and pricing by third-party payors, integrated delivery networks, and government authorities;
- addressing any competing technological and market developments;
- Celgene exercising any of its options under our collaboration agreement with Celgene, and Celgene’s efforts to further develop and commercialize the associated product candidates;
- identifying, assessing, acquiring and/or developing new product candidates;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

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Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical, or other types of studies in addition to those that we currently anticipate. If we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. If we are not able to generate revenue from the sale of any approved products, we may never become profitable.

Our technology platform, including our CAR and high-affinity TCR technologies are new approaches to cancer treatment that present significant challenges.

We have concentrated our research and development efforts on T cell immunotherapy technology, and our future success is highly dependent on the successful development of T cell immunotherapies in general and our CAR and TCR technologies and product candidates in particular. Our approach to cancer treatment aims to alter T cells ex vivo through genetic modification using certain viruses designed to reengineer the T cells to recognize specific proteins on the surface or inside cancer cells. Because this is a new approach to cancer immunotherapy and cancer treatment generally, developing and commercializing our product candidates subjects us to a number of challenges, including:

- obtaining regulatory approval from the FDA and other regulatory authorities that have very limited experience with the commercial development of genetically modified T cell therapies for cancer;
- developing and deploying consistent and reliable processes for engineering a patient's T cells ex vivo and infusing the engineered T cells back into the patient;
- conditioning patients with chemotherapy in conjunction with delivering each of our products, which may increase the risk of adverse side effects of our products;
- educating medical personnel regarding the potential side effect profile of each of our products, such as the potential adverse side effects related to cytokine release;
- developing processes for the safe administration of these products, including long-term follow-up for all patients who receive our product candidates;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a manufacturing process and distribution network with a cost of goods that allows for an attractive return on investment;
- establishing sales and marketing capabilities after obtaining any regulatory approval to gain market acceptance, and obtaining adequate coverage, reimbursement, and pricing by third-party payors and government authorities; and
- developing therapies for types of cancers beyond those addressed by our current product candidates.

We cannot be sure that our T cell immunotherapy technologies will yield satisfactory products that are safe and effective, scalable, or profitable.

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Additionally, because our technology involves the genetic modification of patient cells ex vivo using a virus, we are subject to many of the challenges and risks that gene therapies face, including:

- Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. To date, only one product that involves the genetic modification of patient cells has been approved in the United States and only one has been approved in the EU.
- Genetically modified products in the event of improper insertion of a gene sequence into a patient's chromosome could lead to lymphoma, leukemia or other cancers, or other aberrantly functioning cells.
- Although our viral vectors are not able to replicate, there is a risk with the use of retroviral or lentiviral vectors that they could lead to new or reactivated pathogenic strains of virus or other infectious diseases.
- The FDA recommends a 15 year follow-up observation period for all patients who receive treatment using gene therapies, and we may need to adopt such an observation period for our product candidates.
- Clinical trials using genetically modified cells conducted at institutions that receive funding for recombinant DNA research from the NIH, are subject to review by the RAC. Although the FDA decides whether individual protocols may proceed, the RAC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and approved its initiation.

Moreover, public perception of therapy safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to subscribe to the novel treatment mechanics. Physicians, hospitals and third-party payors often are slow to adopt new products, technologies and treatment practices that require additional upfront costs and training. Physicians may not be willing to undergo training to adopt this novel and personalized therapy, may decide the therapy is too complex to adopt without appropriate training and may choose not to administer the therapy. Based on these and other factors, hospitals and payors may decide that the benefits of this new therapy do not or will not outweigh its costs.

Our near term ability to generate product revenue is dependent on the success of one or more of our CD19 product candidates, each of which are in clinical development and will require significant additional clinical testing before we can seek regulatory approval and begin commercial sales.

Our near term ability to generate product revenue is highly dependent on our ability to obtain regulatory approval of and successfully commercialize one or more of our CD19 product candidates. Our most advanced product candidates, JCAR015, JCAR017, and JCAR014, are in clinical development, have been tested in a relatively small number of patients, and will require additional clinical and nonclinical development, regulatory review and approval in each jurisdiction in which we intend to market the products, substantial investment, access to sufficient commercial manufacturing capacity, and significant marketing efforts before we can generate any revenue from product sales. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity, and potency of the product candidates in humans. We cannot be certain that any of our product candidates will be successful in clinical studies and they may not receive regulatory approval even if they are successful in clinical studies.

In addition, because JCAR015, JCAR017, and JCAR014 are our most advanced product candidates, and because our other product candidates are based on similar technology, if JCAR015, JCAR017, or JCAR014 encounter safety or efficacy problems, developmental delays, regulatory issues, reagent supply issues, or other problems, our development plans and business could be significantly harmed. Further, competitors who are developing products with similar technology may experience problems with their products that could identify problems that would potentially harm our business.

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Prior to the Juno-sponsored Phase I trial of JCAR017 and the Phase II clinical trial of JCAR015 that began in 2015, third parties had sponsored and conducted all clinical trials of our CD19 product candidates and other product candidates, and our ability to influence the design and conduct of such trials has been limited. We have assumed control over the future clinical and regulatory development of JCAR015 and, for NHL, JCAR017, and may do so for other product candidates, which will entail additional expenses and may be subject to delay. Any failure by a third party to meet its obligations with respect to the clinical and regulatory development of our product candidates may delay or impair our ability to obtain regulatory approval for our products and result in liability for our company.

Prior to the Juno-sponsored Phase I clinical trial of JCAR017 and the Phase II clinical trial of JCAR015, both of which began in 2015, we had not sponsored any clinical trials relating to our CD19 product candidates or other product candidates. Instead, faculty members at our third-party research institution collaborators, or those institutions themselves, sponsored all clinical trials relating to these product candidates, in each case under their own INDs. We have now assumed control of the overall clinical and regulatory development of JCAR015 and, for NHL, JCAR017 for future clinical trials. We may assume control over the clinical and regulatory development of other product candidates in the future, in which case we will need to obtain sponsorship of the INDs or file new Juno-sponsored INDs. Failure to obtain, or delays in obtaining, sponsorship of INDs or in filing new Juno-sponsored INDs for these or any other product candidates we determine to advance could negatively affect the timing of our potential future clinical trials. Additionally, although MSK received breakthrough therapy designation for JCAR015 from the FDA, we will separately need to request breakthrough therapy designation from the FDA under our own IND, which designation we may not be successful in obtaining, which could adversely affect the timing of future clinical trials and regulatory review and approval. Any such impacts on timing could increase research and development costs and could delay or prevent obtaining regulatory approval for our most advanced product candidates, either of which could have a material adverse effect on our business.

Further, even in the event that the IND sponsorship is or has been obtained for existing and new INDs, we did not control the design or conduct of the previous trials. It is possible that the FDA will not accept these previous trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any of one or more reasons, including the safety, purity, and potency of the product candidate, the degree of product characterization, elements of the design or execution of the previous trials or safety concerns, or other trial results. We may also be subject to liabilities arising from any treatment-related injuries or adverse effects in patients enrolled in these previous trials. As a result, we may be subject to unforeseen third-party claims and delays in our potential future clinical trials. We may also be required to repeat in whole or in part clinical trials previously conducted by our third-party research institution collaborators, which will be expensive and delay the submission and licensure or other regulatory approvals with respect to any of our product candidates. Any such delay or liability could have a material adverse effect on our business.

Although we have assumed control of the overall clinical and regulatory development of JCAR015 and, for NHL, JCAR017 going forward, we expect to be dependent on our contractual arrangements with third-party research institution collaborators for ongoing and planned trials for our other product candidates, and for JCAR017 other than in NHL, until we determine to assume control of the clinical and regulatory development of those candidates. Such arrangements provide us certain information rights with respect to certain previous, planned, or ongoing trials with respect to our product candidates, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from such trials. Even after we assume control of the overall clinical and regulatory development of a product candidate, including JCAR015 and JCAR017, we will still remain dependent on such contractual data rights for use in our clinical and regulatory development activities. If these obligations are breached by our third-party research institution collaborators, or if the data, or our data rights, prove to be inadequate compared to the first-hand knowledge we might have gained had the completed trials been Juno-sponsored trials, then our ability to design and conduct our corporate-sponsored clinical trials may be adversely affected. Additionally, the FDA may disagree with the sufficiency of our right to reference the preclinical, manufacturing, or clinical data generated by these prior investigator-sponsored trials, or our interpretation of preclinical, manufacturing, or clinical data from these clinical trials. If

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so, the FDA may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may begin our planned trials and/or may not accept such additional data as adequate to begin our planned trials.

Additionally, we may remain dependent on our third-party research institution collaborators for other support services in connection with our Juno-sponsored clinical trials. For instance, we will be dependent on SCRI for the manufacture of JCAR017 for our Juno-sponsored Phase I trial in r/r NHL until we transition the manufacturing of such product candidate to our Juno-operated manufacturing facility later in 2016. Transferring the process to our Juno-operated facility may also prove more difficult or take more time than we currently estimate, and it may not occur in 2016 or ever. This dependence on SCRI for the manufacture of JCAR017 will subject us to risks such as those described below under "—We expect to rely on third parties to manufacture our clinical product supplies, and we intend to rely on third parties for at least a portion of the manufacturing process of our product candidates, if approved. Our business could be harmed if those third parties fail to provide us with sufficient quantities of product or fail to do so at acceptable quality levels or prices."

We may encounter substantial delays in our clinical trials, or may not be able to conduct our trials on the timelines we expect.

Clinical testing is expensive, time consuming, and subject to uncertainty. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. We expect that the early clinical work performed by our third-party research institution collaborators will help support the filing with the FDA of multiple INDs for product candidates in the next five years. However, we cannot be sure that we will be able to submit INDs at this rate, and we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin. Moreover, even if these trials begin, issues may arise that could suspend or terminate such clinical trials. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Events that may prevent successful or timely completion of clinical development include:

- inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation of clinical studies;
- delays in sufficiently developing, characterizing, or controlling a manufacturing process suitable for advanced clinical trials;
- delays in reaching a consensus with regulatory agencies on study design;
- the FDA may not allow us to use the clinical trial data from a research institution to support an IND if we cannot demonstrate the comparability of our product candidates with the product candidate used by the relevant research institution in its clinical studies;
- delays in reaching agreement on acceptable terms with prospective contract research organizations ("CROs") and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites;
- delays in obtaining required IRB approval at each clinical study site;
- imposition of a temporary or permanent clinical hold by regulatory agencies for a number of reasons, including after review of an IND application or amendment, or equivalent application or amendment; as a result of a new safety finding that presents unreasonable risk to clinical trial participants; a negative finding from an inspection of our clinical study operations or study sites; developments on trials conducted by competitors for related technology that raises FDA concerns about risk to patients of the technology broadly; or if FDA finds that the investigational protocol or plan is clearly deficient to meet its stated objectives;
- delays in recruiting suitable patients to participate in our clinical studies;
- difficulty collaborating with patient groups and investigators;

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- failure by our CROs, other third parties, or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's GCP requirements, or applicable regulatory guidelines in other countries;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- patients dropping out of a study;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- the cost of clinical studies of our product candidates being greater than we anticipate;
- clinical studies of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical studies or abandon product development programs;
- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by either a CMO or by us, and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process;
- transfer of manufacturing processes to Celgene or any other commercialization partner for the manufacture of product candidates in trials outside of the United States;
- delays or failure to secure supply agreements with suitable reagent suppliers, or any failures by suppliers to meet our quantity or quality requirements for necessary reagents; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates, we may be required to or we may elect to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical study delays could also shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

We have entered into collaborations, including our Celgene collaboration, and may form or seek collaborations or strategic alliances or enter into additional licensing arrangements in the future, and we may not realize the benefits of such alliances or licensing arrangements.

We have entered into a number of research and development collaborations, including with Celgene, Fate Therapeutics, Editas Medicine, and MedImmune, and these collaborations are subject to numerous risks, which may include the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to a collaboration;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial

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results, changes in their strategic focus due to the acquisition of competitive products, availability of funding, or other external factors, such as a business combination that diverts resources or creates competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to their marketing and distribution;
- collaborators may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- disputes may arise between us and a collaborator that cause the delay or termination of the research, development or commercialization of our product candidates, or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates; and
- collaborators may own or co-own intellectual property covering our products that results from our collaborating with them, and in such cases, we would not have the exclusive right to commercialize such intellectual property.

In particular, if Celgene opts to exercise its options to license any product candidates under the collaboration agreement with us, we may have limited influence or control over their approaches to development and commercialization in the territories in which they lead development and commercialization. Although we will still lead development and commercialization activities in North America for our product candidates arising from programs for which Celgene has exercised an option, Celgene's development and commercialization activities in the territories where it is the lead party may adversely impact our own efforts in North America. Failure by Celgene to meet its obligations under the collaboration agreement and any co-development or co-commercialization agreement we enter into, or failure by Celgene to apply sufficient efforts at developing and commercializing collaboration products, may materially adversely affect our business and our results of operations. Celgene could independently develop, or develop with its other third party collaborators, products or product candidates that compete directly or indirectly with our products or product candidates, and that competition could adversely impact Celgene's willingness to exercise an option under our collaboration or Celgene's level of diligence for our collaboration products for which it has exercised an option. For instance, Celgene and bluebird bio are collaborating on an anti-BCMA CAR T product candidate. Additionally, Celgene's exercise of an option for a program that includes a given product candidate may also lead to changes to clinical and regulatory development strategy for such product candidate that may impact previously announce development timelines for such product candidate, which may or may not adversely affect our stock price. Celgene will also require some level of assistance from us with respect to product candidates it opts into, and this assistance could be burdensome on our organization and resources and disrupt our own development and commercialization activities for product candidates for which we retain rights or in geographies where we are responsible for leading development and commercialization.

We may form or seek further strategic alliances, create joint ventures or collaborations, or enter into additional licensing arrangements with third parties that we believe will complement or augment our development and commercialization efforts with respect to our product candidates and any future product candidates that we may

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develop. Such alliances will be subject to many of the risks set forth above. Moreover, any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex.

As a result of these risks, we may not be able to realize the benefit of our existing collaborations or any future collaborations or licensing agreements we may enter into. Any delays in entering into new collaborations or strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates in certain geographies for certain indications, which would harm our business prospects, financial condition, and results of operations.

The FDA or comparable foreign regulatory authorities may disagree with our regulatory plans, including our plans to seek accelerated approval, and we may fail to obtain regulatory approval of our product candidates.

We have begun a trial in adult relapsed/refractory ALL with JCAR015 that could support accelerated U.S. regulatory approval. We also have begun a Phase I trial in adult relapsed/refractory NHL with JCAR017, with the potential to move to a registration trial in 2016 or early 2017. We intend to conduct each of these clinical trials in the United States. If the results of these trials are sufficiently compelling, we intend to discuss with the FDA filing BLAs for accelerated approval of such CD19 product candidates as a treatment for patients who are refractory to currently approved treatments in these indications.

The FDA generally requires a BLA to be supported by two adequate and well-controlled Phase III studies or one large and robust, well-controlled Phase III study in the patient population being studied that provides substantial evidence that a biologic is safe, pure and potent. Phase III clinical studies typically involve hundreds of patients, have significant costs and take years to complete. However, product candidates studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA may require a sponsor of a drug or biologic receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug or biologic may be subject to withdrawal procedures by the FDA that are more accelerated than those available for regular approvals. We believe our accelerated approval strategy is warranted given the currently limited alternative therapies for patients with relapsed/refractory ALL and relapsed/refractory NHL, but the FDA may not agree or alternative therapies may enter the market that cause the FDA to determine that the accelerated approval framework is no longer appropriate in those indications. The FDA may ultimately require one or multiple Phase III clinical trials prior to approval, particularly because our product candidates are novel and personalized treatments.

As part of its marketing authorization process, the EMA may grant marketing authorizations on the basis of less complete data than is normally required, when, for certain categories of medicinal products, doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use (“CHMP”) to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating diseases or life-threatening diseases and those designated as orphan medicinal products.

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A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete nonclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public-health threats.

Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a conditional marketing authorization will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product are generated, submitted, assessed and acted upon. Although we may seek a conditional marketing authorization for one or more of our product candidates by the EMA, the EMA or CHMP may ultimately not agree that the requirements for such conditional marketing authorization have been satisfied. Even if conditional marketing authorization is granted, we cannot guarantee that the EMA or CHMP will renew the authorization annually. We do intend, alone or with Celgene, to seek conditional marketing approval in the EU for our CD19-directed CAR T programs.

Our clinical trial results may also not support approval, whether accelerated approval, conditional marketing authorizations, or regular approval. The results of preclinical and clinical studies may not be predictive of the results of later-stage clinical trials, and product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through preclinical studies and initial clinical trials. In addition, our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- we may be unable to demonstrate that our product candidates' risk-benefit ratios for their proposed indications are acceptable;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that the clinical and other benefits of our product candidates outweigh their safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a BLA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;

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- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, our own manufacturing facilities, or a third-party manufacturer's facilities with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Further, failure to obtain approval for any of the above reasons may be made more likely by the fact that the FDA and other regulatory authorities have very limited experience with commercial development of genetically engineered T cell therapies for cancer. Failure to obtain regulatory approval to market any of our product candidates would significantly harm our business, results of operations, and prospects.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which would prevent or delay regulatory approval and commercialization.

The clinical trials of our product candidates are, and the manufacturing and marketing of our products will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and market our product candidates. Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. In particular, because our product candidates are subject to regulation as biological drug products, we will need to demonstrate that they are safe, pure, and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use. The risk/benefit profile required for product licensure will vary depending on these factors and may include not only the ability to show tumor shrinkage, but also adequate duration of response, a delay in the progression of the disease, and/or an improvement in survival. For example, response rates from the use of our product candidates may not be sufficient to obtain regulatory approval unless we can also show an adequate duration of response. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. The results of studies in one set of patients or line of treatment may not be predictive of those obtained in another. We expect there may be greater variability in results for products processed and administered on a patient-by-patient basis, as anticipated for our product candidates, than for "off-the-shelf" products, like many other drugs. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising results in earlier trials. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization.

Data from studies conducted by the third-party research institutions that are our collaboration partners, FHCRC, MSK, and SCRI, should not be relied upon as evidence that later or larger-scale clinical trials will succeed. Some future trials may have different patient populations than current studies and will test our product candidates in different indications, among other differences. In addition, our proposed manufacturing processes for our CD19 product candidates include what we believe will be process improvements that are not part of the production processes that are currently being used in the clinical trials being conducted by the research institutions. Accordingly, our results with our CD19 product candidates may not be consistent with the results of the clinical trials being conducted by our research institute collaborators.

In addition, even if such trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we submit our

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product candidates for approval. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates.

Our product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences.

As with most biological drug products, use of our product candidates could be associated with side effects or adverse events which can vary in severity from minor reactions to death and in frequency from infrequent to prevalent. Undesirable side effects or unacceptable toxicities caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical trials. We have seen severe neurotoxicity or sCRS, in some cases leading to death, in a number of patients with ALL, NHL, or CLL using each of JCAR015, JCAR017, and JCAR014. Severe neurotoxicity is a condition that, by convention, is currently defined clinically by confusion or other central nervous system side effects, when such side effects are serious enough to lead to intensive care unit care. The exact cause of severe neurotoxicity in connection with treatment with CAR T cells is not fully understood at this time. sCRS is a condition that, by convention, is currently defined clinically by certain side effects, which can include fever, chills, and hypotension, or low blood pressure, related to the release of inflammatory proteins in the body as the CAR T cells rapidly multiply in the presence of the target tumor protein, when such side effects are serious enough to lead to intensive care unit care with mechanical ventilation or significant vasopressor support. In early 2014, two patient deaths in the JCAR015 trial, which we believe were either directly or indirectly related to sCRS, resulted in the FDA placing the trial on clinical hold. Several JCAR015 protocol changes were made after those deaths, the most important of which include using a lower dose in patients with morphologic relapsed/refractory ALL, excluding patients with Class III or IV congestive heart failure as defined by the New York Heart Association, excluding patients with active central nervous system leukemia or symptomatic central nervous system leukemia within 28 days, adding sCRS as a dose limiting toxicity, and restricting a patient from receiving a second treatment of JCAR015 if the patient experienced any non-hematologic grade 4 toxicities, including sCRS, with the prior JCAR015 treatment. The protocol changes resulted in the FDA removing the clinical hold. However, these protocol changes may reduce efficacy and may not result in a better tolerability profile. The FDA or comparable foreign regulatory authorities could delay or deny approval of our product candidates for any or all targeted indications and negative side effects could result in a more restrictive label for any product that is approved. Side effects such as toxicity or other safety issues associated with the use of our product candidates could also require us or our collaborators to perform additional studies or halt development or sale of these product candidates.

Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete the trial, or could result in potential product liability claims. In addition, these side effects may not be appropriately or timely recognized or managed by the treating medical staff, particularly outside of the research institutions that collaborate with us, as toxicities resulting from personalized T cell therapy are not normally encountered in the general patient population and by medical personnel. We expect to have to train medical personnel using our product candidates to understand their side effect profiles, both for our planned clinical trials and upon any commercialization of any product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in adverse effects to patients, including death. Any of these occurrences may materially and adversely harm our business, financial condition and prospects.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, including during any long-term follow-up observation period recommended or required for patients who receive treatment using our products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;

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- we may be required to create a REMS plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, and/or other elements to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of the foregoing could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations, and prospects.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol;
- the size of the study population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials for similar therapies or other new therapeutics not involving T cell based immunotherapy;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will not complete a clinical trial.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. Moreover, because our product candidates represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such as chemotherapy and hematopoietic cell transplantation, rather than enroll patients in any future clinical trial.

Even if we are able to enroll a sufficient number of patients in our clinical trials, delays in patient enrollment may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of our product candidates.

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Clinical trials are expensive, time-consuming and difficult to design and implement, and our clinical trial costs may be higher than for more conventional therapeutic technologies or drug products.

Clinical trials are expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. Because our product candidates are based on new technologies and manufactured on a patient-by-patient basis, we expect that they will require extensive research and development and have substantial manufacturing costs. In addition, costs to treat patients with relapsed/refractory cancer and to treat potential side effects that may result from our product candidates can be significant. Some clinical trial sites may not bill, or obtain coverage from, Medicare, Medicaid, or other third-party payors for some or all of these costs for patients enrolled in our clinical trials, and we may be required by those trial sites to pay such costs. Accordingly, our clinical trial costs are likely to be significantly higher per patient than those of more conventional therapeutic technologies or drug products. In addition, our proposed personalized product candidates involve several complex and costly manufacturing and processing steps, the costs of which will be borne by us. Depending on the number of patients we ultimately enroll in our trials, and the number of trials we may need to conduct, our overall clinical trial costs may be higher than for more conventional treatments.

Research and development of biopharmaceutical products is inherently risky. We may not be successful in our efforts to use and enhance our technology platform and CAR and TCR technologies to create a pipeline of product candidates and develop commercially successful products, or we may expend our limited resources on programs that do not yield a successful product candidate and fail to capitalize on product candidates or diseases that may be more profitable or for which there is a greater likelihood of success. If we fail to develop additional product candidates, our commercial opportunity will be limited.

Although our most advanced product candidates are JCAR015, JCAR017, and JCAR014, we and our collaborators are simultaneously pursuing clinical development of additional product candidates developed employing our CAR and TCR technologies. We are at an early stage of development and our technology platform has not yet led, and may never lead, to approved or commercially successful products.

Even if we are successful in continuing to build our pipeline, obtaining regulatory approvals and commercializing additional product candidates may require substantial additional funding and are prone to the risks of failure inherent in medical product development.

Investment in biopharmaceutical product development involves significant risk that any potential product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval, and become commercially viable. We cannot provide you any assurance that we will be able to successfully advance any of these additional product candidates through the development process. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development or commercialization for many reasons, including the following:

- our platform may not be successful in identifying additional product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- our product candidates may not succeed in preclinical or clinical testing;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- the market for a product candidate may change during our program so that the continued development of that product candidate is no longer reasonable;

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- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Even if we receive FDA approval to market additional product candidates, whether for the treatment of cancers or other diseases, we cannot assure you that any such product candidates will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. Further, because of our limited financial and managerial resources, we are required to focus our research programs on certain product candidates and on specific diseases. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases that may later prove to have greater commercial potential, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights. For additional information regarding the factors that will affect our ability to achieve revenue from product sales, see the risk factor above "—We have never generated any revenue from sales of cell-therapy products and our ability to generate revenue from cell-therapy product sales and become profitable depends significantly on our success in a number of factors."

Our product candidates are biologics and the manufacture of our product candidates is complex and we may encounter difficulties in production, particularly with respect to process development or scaling-out of our manufacturing capabilities. If we, Celgene, or any of our third-party manufacturers encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

Our product candidates are biologics and the process of manufacturing our products is complex, highly-regulated and subject to multiple risks. The manufacture of our product candidates involves complex processes, including harvesting T cells from patients, genetically modifying the T cells ex vivo, multiplying the T cells to obtain the desired dose, and ultimately infusing the T cells back into a patient's body. As a result of the complexities, the cost to manufacture biologics in general, and our genetically modified cell product candidates in particular, is generally higher than traditional small molecule chemical compounds, and the manufacturing process is less reliable and is more difficult to reproduce. Our manufacturing process will be susceptible to product loss or failure due to logistical issues associated with the collection of white blood cells, or starting material, from the patient, shipping such material to the manufacturing site, shipping the final product back to the patient, and infusing the patient with the product, manufacturing issues associated with the differences in patient starting materials, interruptions in the manufacturing process, contamination, equipment or reagent failure, improper installation or operation of equipment, vendor or operator error, inconsistency in cell growth, and variability in product characteristics. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects, and other supply disruptions. If for any reason we lose a patient's starting material or later-developed product at any point in the process, the manufacturing process for that patient will need to be restarted and the resulting delay may adversely affect that patient's outcome. If microbial, viral, or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. Because our product candidates are manufactured for each particular patient, we will be required to maintain a chain of identity with respect to materials as they move from the patient to the manufacturing facility, through the manufacturing process, and back to the patient. Maintaining

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such a chain of identity is difficult and complex, and failure to do so could result in adverse patient outcomes, loss of product, or regulatory action including withdrawal of our products from the market. Further, as product candidates are developed through preclinical to late stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

Historically, our product candidates have been manufactured using unoptimized processes by our third-party research institution collaborators that we do not intend to use for more advanced clinical trials or commercialization. Although we are working to develop commercially viable processes, doing so is a difficult and uncertain task, and there are risks associated with scaling to the level required for advanced clinical trials or commercialization, including, among others, cost overruns, potential problems with process scale-out, process reproducibility, stability issues, lot consistency, and timely availability of reagents or raw materials. As a result of these challenges, we may experience delays in our clinical development and/or commercialization plans. We may ultimately be unable to reduce the cost of goods for our product candidates to levels that will allow for an attractive return on investment if and when those product candidates are commercialized.

In some circumstances, changes in the manufacturing process may require us to perform ex vivo comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials. For instance, changes we made to the manufacturing process, including changes in reagents and in the viral vector, in preparation for our Phase II trial for JCAR015 will require us to show the comparability of the Phase II product to Phase I product. We have provided the FDA with comparability evidence from ex vivo experimental studies comparing Phase I product to Phase II product, and plan to provide the FDA with clinical comparability data from our ongoing Phase II trial. We may also make further changes to our manufacturing process before or after commercialization, and such changes may require us to show the comparability of the resulting product to the product used in the clinical trials using the earlier process. We may be required to collect additional clinical data from any modified process prior to obtaining marketing approval for the product candidate produced with such modified process. If clinical data are not ultimately comparable to that seen in the earlier trials in terms of safety or efficacy, we may be required to make further changes to our process and/or undertake additional clinical testing, either of which could significantly delay the clinical development or commercialization of JCAR015.

We expect our manufacturing strategy will involve the use of one or more CMOs as well as establishing our own capabilities and infrastructure, including a manufacturing facility to manufacture our product candidates. We also plan to manufacture certain of the reagents used for making our product candidates ourselves. We expect that development of our own manufacturing facility, as well as manufacturing some of our own reagents, will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company manufacturing product candidates for use in the clinic, and only limited experience (through our German subsidiary) manufacturing reagents, and may never be successful in operating our own manufacturing facility or in manufacturing reagents in sufficient quantities or with sufficient quality for clinical or commercial use. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly.

Even if we are successful in developing our manufacturing capabilities sufficient for clinical and commercial supply, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, operator error, natural disasters, power failures, availability of qualified personnel, difficulties with logistics and shipping, problems regarding yields or stability of product, contamination or other quality control issues, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business. Furthermore, if contaminants are discovered in our supply of our product candidates or in our manufacturing facilities or those of our CMOs, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the

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contamination. We cannot assure you that any stability failures or other issues relating to the manufacture of our product candidates will not occur in the future. Additionally, we and our CMOs may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If we or our CMOs were to encounter any of these difficulties, our ability to provide our product candidate to patients in clinical trials, or to provide product for treatment of patients once approved, would be jeopardized.

In addition, the manufacturing process for any products that we may develop is subject to FDA and foreign regulatory authority approval process, and we will need to meet, and our CMOs will need to meet, all applicable FDA and foreign regulatory authority requirements on an ongoing basis. If we or our CMOs are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

If and when Celgene opts into any of our product candidates, we also expect that we will need to assist Celgene with the transfer of our manufacturing processes to geographies outside of the United States. The transfer of process to Celgene would be subject to the same types of risk as set forth above and may not ultimately be successful or may take longer to succeed than expected, which could delay development and commercialization activities in those geographies, which would have an adverse effect on our business. Such transfer activities may also require a significant amount of attention from our personnel, which may disrupt our other development and commercialization activities, which may have an adverse effect on our business. Additionally, in the interim we may need to manufacture product candidates out of our existing facilities for use in clinical trials in the Celgene territories, which may disrupt our own clinical activities and, to the extent we are not able to produce product candidate in the volumes required by Celgene, may also lead to delays in development plans in such Celgene territories.

We expect to rely on third parties to manufacture our clinical product supplies, and we intend to rely on third parties for at least a portion of the manufacturing process of our product candidates, if approved. Our business could be harmed if those third parties fail to provide us with sufficient quantities of product or fail to do so at acceptable quality levels or prices.

We currently rely on outside vendors to manufacture supplies and process our product candidates, which is and will need to be done on a patient-by-patient basis. We have not yet caused our product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. Although our manufacturing and processing approach is based upon the current approach undertaken by our third-party research institution collaborators, we have limited experience in managing the T cell engineering process, and our process may be more difficult or expensive than the approaches currently in use. We will make changes as we work to optimize the manufacturing process, and we cannot be sure that even minor changes in the process will not result in significantly different T cells that may not be as safe and effective as any T cell therapy deployed by our third-party research institution collaborators.

Although we are in the final stages of bringing our own manufacturing facility online, we also intend to continue to use third parties as part of our manufacturing process and for filling some or our product candidate manufacturing requirements. Our anticipated reliance on a limited number of third-party manufacturers exposes us to the following risks:

- We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and the FDA must approve any manufacturers. This approval would

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require new testing and good manufacturing practices compliance inspections by FDA. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our products.

- Our manufacturers may have little or no experience with autologous cell products, which are products made from a patient's own cells, and therefore may require a significant amount of support from us in order to implement and maintain the infrastructure and processes required to manufacture our product candidates.
- Our third-party manufacturers might be unable to timely manufacture our product or the custom materials or reagents used in the manufacture thereof, or produce the quantity and quality required to meet our clinical and commercial needs, if any.
- Contract manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately.
- Our future contract manufacturers may not perform as agreed, may not devote sufficient resources to us, or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store, and distribute our products or the custom materials or reagents used in the manufacture thereof.
- Manufacturers are subject to ongoing periodic unannounced inspection by the FDA and corresponding state agencies to ensure strict compliance with cGMPs and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards.
- We may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our products, or in the manufacture of the custom materials or reagents used in the manufacture thereof.
- Our third-party manufacturers could breach or terminate their agreement with us.
- Raw materials and components used in the manufacturing process, particularly those for which we have no other source or supplier, may not be available or may not be suitable or acceptable for use due to material or component defects.
- Our contract manufacturers and critical reagent suppliers may be subject to inclement weather, as well as natural or man-made disasters.
- Our contract manufacturers may have unacceptable or inconsistent product quality success rates and yields.

Each of these risks could delay or prevent the completion of our clinical trials or the approval of any of our product candidates by the FDA, result in higher costs or adversely impact commercialization of our product candidates.

In addition, we will rely on third parties to perform certain specification tests on our product candidates prior to delivery to patients. If these tests are not appropriately done and test data are not reliable, patients could be put at risk of serious harm and the FDA could require additional clinical trials or place significant restrictions on our company until deficiencies are remedied.

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Cell-based therapies rely on the availability of reagents, specialized equipment, and other specialty materials, which may not be available to us on acceptable terms or at all. For some of these reagents, equipment, and materials, we rely or may rely on sole source vendors or a limited number of vendors, which could impair our ability to manufacture and supply our products.

Manufacturing our product candidates will require many reagents, which are substances used in our manufacturing processes to bring about chemical or biological reactions, and other specialty materials and equipment, some of which are manufactured or supplied by small companies with limited resources and experience to support commercial biologics production. We currently depend on a limited number of vendors for certain materials and equipment used in the manufacture of our product candidates. Some of these suppliers may not have the capacity to support commercial products manufactured under cGMP by biopharmaceutical firms or may otherwise be ill-equipped to support our needs. We also do not have supply contracts with many of these suppliers and may not be able to obtain supply contracts with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key materials and equipment to support clinical or commercial manufacturing.

For some of these reagents, equipment, and materials, we rely and may in the future rely on sole source vendors or a limited number of vendors. An inability to continue to source product from any of these suppliers, which could be due to regulatory actions or requirements affecting the supplier, adverse financial or other strategic developments experienced by a supplier, labor disputes or shortages, unexpected demands, or quality issues, could adversely affect our ability to satisfy demand for our product candidates, which could adversely and materially affect our product sales and operating results or our ability to conduct clinical trials, either of which could significantly harm our business.

As we continue to develop and scale our manufacturing process, we expect that we will need to obtain rights to and supplies of certain materials and equipment to be used as part of that process. We may not be able to obtain rights to such materials on commercially reasonable terms, or at all, and if we are unable to alter our process in a commercially viable manner to avoid the use of such materials or find a suitable substitute, it would have a material adverse effect on our business. Even if we are able to alter our process so as to use other materials or equipment, such a change may lead to a delay in our clinical development and/or commercialization plans. If such a change occurs for product candidate that is already in clinical testing, the change may require us to perform both ex vivo comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials.

We are and will continue to rely in significant part on outside scientists and their third-party research institutions for research and development and early clinical testing of our product candidates. These scientists and institutions may have other commitments or conflicts of interest, which could limit our access to their expertise and harm our ability to leverage our technology platform.

We rely to a large extent at present on our third-party research institution collaborators for research and development capabilities. Currently, MSK is conducting Phase I clinical trials using JCAR015 to address adult ALL and pediatric ALL and a Phase I trial with JCAR020 to address ovarian cancer; SCRI is conducting a Phase I/II clinical trial using JCAR017 to address pediatric ALL and a Phase I trial using JCAR023 to address refractory or recurrent pediatric neuroblastoma; and FHCRC is conducting a Phase I/II clinical trial using JCAR014 to address ALL, NHL, and CLL, a Phase I trial using JCAR024 to address ROR-1 expressing cancers, a Phase I/II trial using JTCR016 to address high risk or relapsed AML, myelodysplasic syndrome, and chronic myeloid leukemia, and a Phase I trial using JTCR016 to address advanced NSCLC. Each of these clinical trials addresses a limited number of patients. We expect to use the results of these trials, if favorable, to help support the filing with the FDA of INDs to conduct more advanced clinical trials with the corresponding product candidates. To date, we have filed, and the FDA has cleared, a Juno-sponsored IND for the Phase I clinical trial of JCAR017 in adult aggressive r/r NHL and a Juno-sponsored IND for the Phase II clinical trial of JCAR015 in adult r/r ALL, and these Juno-sponsored trials have begun.

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With respect to our CD22 product candidate, JCAR018, the NCI is conducting a clinical trial of the product candidate for the treatment of pediatric relapsed/refractory ALL and relapsed/refractory NHL. If the results of this trial are compelling, we expect to use the results of the NCI's clinical trial to support the filing with the FDA of a Juno-sponsored IND to conduct more advanced clinical trials of JCAR018 or another CD22-directed product candidate.

We also fund research and development under agreements with FHCRC, MSK, and SCRI. However, the research we are funding constitutes only a small portion of the overall research of each research institution. Other research being conducted by these institutions may at times receive higher priority than research on the programs we are funding.

The outside scientists who conduct the clinical testing of our current product candidates, and who conduct the research and development upon which our product candidate pipeline depends, are not our employees; rather they serve as either independent contractors or the primary investigators under research collaboration agreements that we have with their sponsoring academic or research institution. Such scientists and collaborators may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if an actual or potential conflict of interest between their work for us and their work for another entity arises, we may lose their services. These factors could adversely affect the timing of the clinical trials, the timing of receipt and reporting of clinical data, the timing of Juno-sponsored IND filings, and our ability to conduct future planned clinical trials. It is also possible that some of our valuable proprietary knowledge may become publicly known through these scientific advisors if they breach their confidentiality agreements with us, which would cause competitive harm to, and have a material adverse effect on, our business.

Our existing agreements with our collaboration partners may be subject to termination by the counterparty upon the occurrence of certain circumstances as described in more detail under the caption "Licenses and Third-Party Collaborations" in Part I—Item 1 —"Business" of this report. If any of our collaboration partners terminates their collaboration agreement, the research and development of the relevant product candidate would be suspended, and we may be unable to research, develop, and license future product candidates. We may be required to devote additional resources to the development of our product candidates or seek a new collaboration partner, and the terms of any additional collaborations or other arrangements that we establish may not be favorable to us. In addition, there is a natural transition period when a new third-party begins work. In addition, switching or adding third parties to conduct our clinical trials involves substantial cost and requires extensive management time and focus. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines.

We will be highly dependent on the NCI for early clinical testing of JCAR018.

In December 2014, we entered into an exclusive license agreement with Opus Bio pursuant to which Opus Bio has granted us an exclusive, worldwide, sublicenseable license under certain patent rights related to a CD22-directed CAR product candidate, JCAR018. In connection therewith, the NCI agreed to separate the activities that are exclusively related to CD22 under its agreement with Opus Bio and to enter into a separate agreement with us (the "Juno CRADA"), on the same terms as such agreement and incorporate such activities into its agreement with us.

The NCI has commenced a Phase I clinical trial of JCAR018 for the treatment of pediatric relapsed/refractory ALL and relapsed/refractory NHL. If the results of this trial are compelling, we expect to use the results of the NCI's clinical trial to support the filing with the FDA of a Juno-sponsored IND to conduct more advanced clinical trials of JCAR018 or another CD22-directed product candidate. However, we will have limited control over the nature or timing of the NCI's clinical trial and limited visibility into their day-to-day activities. For example, the clinical trial will constitute only a small portion of the NCI's overall research and the research of the principal investigators. Other research being conducted by the principal investigators may at times receive

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higher priority than research on JCAR018. We will also be dependent on the NCI to provide us with data, include batch records, to support the filing of our IND. These factors could adversely affect the timing of our IND filing.

The NCI may unilaterally terminate our rights under the Juno CRADA at any time for any reason or for no reason upon at least 60 days prior written notice. If the NCI unilaterally terminates the Juno CRADA, the research and development under the Juno CRADA would be suspended and we may lose certain of our data rights, which may impair our ability to obtain regulatory approval of JCAR018.

Our results of operations and financial position could be negatively impacted if our tax positions are challenged by tax authorities.

We are a U.S.-based multinational company subject to tax in certain U.S. and foreign tax jurisdictions. United States federal, state and local, as well as international tax laws and regulations are extremely complex and subject to varying interpretations. Although we believe that our tax estimates and tax positions are reasonable, there can be no assurance that our tax positions will not be challenged by relevant tax authorities or that we would be successful in any such challenge. If we are unsuccessful in such a challenge, the relevant tax authorities may assess additional taxes, which could result in adjustments to, or impact the timing or amount of, taxable income, deductions or other tax allocations, which may adversely affect our results of operations and financial position.

If we fail to obtain additional financing, we may be unable to complete the development and commercialization of our product candidates.

Our operations have required substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the clinical development of our product candidates, including our ongoing and planned clinical trials for our CD19 product candidates. If approved, we will require significant additional amounts in order to launch and commercialize our product candidates.

As of December 31, 2015, we had $1.2 billion in cash, cash equivalents, and marketable securities. In August 2015, we received $1.0 billion from Celgene from the sale of common stock to Celgene and from the initial payment under our collaboration agreement. We believe that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our operations for at least the next 12 months. However, changing circumstances or business opportunities, within or beyond our control, may lead us to use our capital faster than we currently anticipate. We may ultimately need to raise additional funds for the further development and commercialization of our product candidates or to pursue strategic transactions and other business opportunities that arise.

We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. Our license and collaboration agreements may also be terminated if we are unable to meet the payment obligations under the agreements. We could be required to seek additional collaborators for our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to our product candidates in markets where we otherwise would seek to pursue development or commercialization ourselves.

If Celgene declines to exercise its option with respect to one or more product candidates covered by our collaboration agreement with Celgene, or terminates the collaboration agreement with us, we will need to secure funding to advance development of those programs on our own or secure relationships with collaborators that have the necessary capital and expertise. In addition, we may need additional funding to advance product candidates prior to Celgene’s decisions regarding option exercise with respect to such product candidate if development of that program is not discontinued. In addition, if we exercise our option to any of Celgene’s in-

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licensed programs to co-develop and co-commercialize products, then we may need to secure additional funding to support our obligations to pay one-half of the acquisition costs of any such in-licensed program.

If we are unable to obtain sufficient financing when needed, it could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

Any future revenue from the license agreement with Penn and Novartis is highly dependent upon milestone and contingent royalty payments generated from the efforts of Penn and Novartis, over which we have no control, and we may not realize the intended benefits of this agreement.

On April 4, 2015, the parties to Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn.), agreed to settle the case, which was dismissed on April 7, 2015. In connection with this settlement we entered into a sublicense agreement with Penn and an affiliate of Novartis pursuant to which we granted Novartis a non-exclusive, royalty-bearing sublicense under certain patent rights, including U.S. Patent No. 8,399,645, to develop, make and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative and palliative uses. In exchange for this sublicense, Novartis is obligated to pay us mid-single digit royalties on the U.S. net sales of products and services related to the disputed contract and patent claims, a low double digit percentage of the royalties Novartis pays to Penn for global net sales of those products, and milestone payments upon the achievement of specified clinical, regulatory and commercialization milestones for licensed products. The sublicense agreement with Novartis and Penn is terminable by Novartis at will without notice to us and without our consent.

Our receipt of royalty and milestone payments from Novartis is subject to many risks and uncertainties. In particular, these payments are dependent upon Novartis' ability to make U.S. and global sales of its products and services, and its ability to achieve clinical, regulatory and commercialization milestones for the licensed products. We will have no control over the nature or timing of Novartis' efforts towards making these sales or achieving these milestones. Furthermore, in the course of developing and commercializing its products, Novartis and Penn will likely be subject to many risks and uncertainties similar to those faced by our company and our product candidates as described in this section, and may be subject to other risks specific to Novartis and Penn. Additionally, if Novartis or Penn breaches our sublicense agreement, we may determine to terminate the agreement, or may be required to do so by St. Jude pursuant to the terms of our license agreement with St. Jude. To the extent Novartis fails, for any of the reasons outlined above or any other reason, to remit royalty payments or milestone payments under our sublicense agreement, or fails to remit these payments in the amount anticipated, or to the extent that our sublicense agreement with Novartis and Penn is terminated, we may not realize the potential benefits of the sublicense agreement with Penn and Novartis.

We may never formalize our agreement in principle with Celgene to license Celgene a subset of the acquired AbVitro technology or the final terms of the agreement may not be as favorable to us as expected.

We and Celgene have agreed in principle to enter into an agreement to license Celgene a subset of the acquired AbVitro technology and to grant Celgene options to certain related potential product rights emanating from the acquired technology. However, we may never come to agreement with Celgene on the formal terms of such an agreement, in which case we will not receive the financial benefits of such an agreement. Even if we do come to agreement with Celgene, it may not be on terms that are favorable to us as expected.

We will rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize our product candidates.

We will depend upon independent investigators to conduct our clinical trials under agreements with universities, medical institutions, CROs, strategic partners, and others. At present, we contract directly with all of our trial sites, and therefore have to negotiate budgets and contracts with each trial site, which may result in delays to our

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development timelines and increased costs. If we transition to a CRO to manage the conduct of our clinical trials, we will also have to negotiate budgets and contracts with such CRO, which may similarly lead to delays and increased costs.

We will rely heavily on third parties over the course of our clinical trials, and as a result will have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to how they are providing and administering T cell therapy. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory, and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators, and trial sites. If we or any of these third parties fail to comply with applicable GCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional nonclinical or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the GCP regulations. In addition, our clinical trials must be conducted with biologic product produced under cGMP regulations and will require a large number of test patients. Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any third parties conducting our clinical trials are not and will not be our employees and, except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing preclinical, clinical, and nonclinical programs. These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical studies or other drug development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed, or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed. We have disclosed in this report and various corporate presentations certain third party investigator-reported interim data from some of our trials, including interim data for which we have not yet independently reviewed the source data. We also sometimes rely on such investigator-reported interim data in making business decisions. Independent review of the data could fail to confirm the investigator-reported interim data, which may lead to revisions in disclosed clinical trial results in the future. Any such revisions that reveal more negative data than previously disclosed investigator-reported interim data could have an adverse impact on our business prospects and the trading price of our common stock. Such revisions could also reduce investor confidence in investigator-reported interim data that we disclose in the future.

If any of our relationships with trial sites, or any CRO that we may use in the future, terminate, we may not be able to enter into arrangements with alternative trial sites or CROs or do so on commercially reasonable terms. Switching or adding additional trial sites or CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines, and such delays could have a material adverse impact on our business, financial condition, and prospects.

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The market opportunities for our product candidates may be limited to those patients who are ineligible for or have failed prior treatments and may be small.

Cancer therapies are sometimes characterized as first line, second line, or third line, and the FDA often approves new therapies initially only for third line use. When cancer is detected early enough, first line therapy is sometimes adequate to cure the cancer or prolong life without a cure. Whenever first line therapy, usually chemotherapy, hormone therapy, surgery, or a combination of these, proves unsuccessful, second line therapy may be administered. Second line therapies often consist of more chemotherapy, radiation, antibody drugs, tumor targeted small molecules, or a combination of these. Third line therapies can include bone marrow transplantation, antibody and small molecule targeted therapies, more invasive forms of surgery, and new technologies. We expect to initially seek approval of our product candidates as a third line therapy for patients who have failed other approved treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval as a second line therapy and potentially as a first line therapy, but there is no guarantee that our product candidates, even if approved, would be approved for second line or first line therapy. In addition, we may have to conduct additional clinical trials prior to gaining approval for second line or first line therapy.

Our projections of both the number of people who have the cancers we are targeting, as well as the subset of people with these cancers in a position to receive third line therapy and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these cancers. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. For instance, with our CD19 product candidates we expect to initially target a small patient population that suffers from ALL and certain types of aggressive NHL. Even if we obtain significant market share for our product candidates, because the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications, including use as a first or second line therapy.

Our market opportunities may also be limited by competitor treatments that may enter the market. See the risk factor below "—We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively."

We plan to seek orphan drug designation for some or all of our CD19 product candidates, but we may be unable to obtain such designations or to maintain the benefits associated with orphan drug designation, including market exclusivity, which may cause our revenue, if any, to be reduced.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval of that particular product for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a BLA, to market the same

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biologic (meaning, a product with the same principal molecular structural features) for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan drug exclusivity or if FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. As a result, even if one of our product candidates receives orphan exclusivity, the FDA can still approve other biologics that do not have the same principal molecular structural features for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product or if a subsequent applicant demonstrates clinical superiority over our product.

We plan to seek orphan drug designation for some or all of our CD19 product candidates in specific orphan indications in which there is a medically plausible basis for the use of these products, including relapsed/ refractory ALL and relapsed/refractory NHL indications. We have obtained orphan drug designation for each of JCAR015 and JCAR014 for the treatment of ALL. Even when we obtain orphan drug designation, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication and may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. In addition, although we intend to seek orphan drug designation for other product candidates, we may never receive such designations.

We plan to seek but may fail to obtain breakthrough therapy designation for some or all of our CD19 product candidates.

In 2012, the FDA established a breakthrough therapy designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases when “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.” The designation of a product candidate as a breakthrough therapy provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate and ensure collection of appropriate data needed to support approval; more frequent written correspondence from FDA about such things as the design of the proposed clinical trials and use of biomarkers; intensive guidance on an efficient drug development program, beginning as early as Phase I; organizational commitment involving senior managers; and eligibility for rolling review and priority review.

Breakthrough therapy designation does not change the standards for product approval. We intend to seek breakthrough therapy designation for some or all of our CD19 product candidates that may qualify for such designation. Our collaborator MSK obtained breakthrough therapy designation for JCAR015 for relapsed/refractory ALL, but we will have to seek such designation separately under our own IND, which designation we may not receive. In addition, although we intend to seek breakthrough therapy designation for other product candidates, we may never receive such designations.

We currently have no marketing and sales organization and have no experience in marketing products. If we are unable to establish marketing and sales capabilities on our own or through our collaboration with Celgene or enter into agreements with third parties to market and sell our product candidates, we may not be able to generate product revenue.

We currently have no sales, marketing, or commercial product distribution capabilities and have no experience as a company in marketing products. We intend to develop an in-house marketing organization and sales force, which will require significant capital expenditures, management resources, and time. We will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, and retain marketing and sales personnel.

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Under our collaboration with Celgene, for Juno-developed programs that Celgene opts into, Celgene will lead development and commercialization activities outside of North America and, for cellular therapy product candidates, China, but we will still be responsible for leading such activities in North America and, for cellular therapy product candidates, China. If Celgene does not opt into a program for one of our product candidates that we move to commercialization, we will alone be responsible for commercialization activities worldwide, unless we find another collaborator to assist with the sales and marketing of our products.

If we are unable or decide not to establish internal sales, marketing and commercial distribution capabilities for any or all products we develop, we will likely pursue further collaborative arrangements regarding the sales and marketing of our products. However, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend upon the efforts of such third parties, which may not be successful. We may have little or no control over the marketing and sales efforts of such third parties, and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates.

There can be no assurance that we will be able to develop in-house sales and commercial distribution capabilities or establish or maintain relationships with third-party collaborators to successfully commercialize any product in the United States or overseas, and as a result, we may not be able to generate product revenue.

A variety of risks associated with operating our business internationally could materially adversely affect our business.

As a result of the Stage acquisition, we acquired a German subsidiary with employees in Germany. We also plan to seek regulatory approval of our product candidates outside of the United States. Accordingly, we expect that we, and any potential collaborators that have operations in foreign jurisdictions, will be subject to additional risks related to operating in foreign countries, including:

- differing regulatory requirements in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls, and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with applicable tax, employment, immigration, data privacy, and labor laws for employees living or traveling abroad, including for our German employees;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign laws;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

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These and other risks associated with our planned international operations may materially adversely affect our ability to attain or maintain profitable operations.

We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry, and the rapidly evolving market for developing genetically engineered T cells in particular, is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, universities, and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations as well as established sales forces. Smaller or early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborative partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized, or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products.

Specifically, genetically engineering T cells faces significant competition in both the CAR and TCR technology space from multiple companies and their collaborators, such as Novartis / Penn, Kite Pharma / Amgen / NCI, Cellectis / Pfizer / Servier, Johnson & Johnson / Transposagen Biopharmaceuticals, bluebird bio, Bellicum, Celyad, NantKwest, Intrexon / Ziopharm / MD Anderson Cancer Center, Unum Therapeutics, Adaptimmune / GlaxoSmithKline, ImmunoCellular Therapeutics, and Autolus. We also face competition from non-cell based treatments offered by companies such as Amgen, Pfizer, Abbvie, AstraZeneca, Bristol-Myers, Incyte, Merck, and Roche. For instance, in 2014 the FDA approved Amgen’s blinotumomab for the treatment of r/r ALL, and that product has achieved a CR rate of approximately 40% in clinical trials. We also anticipate Pfizer’s inotuzumab to be approved for the treatment of r/r ALL as early as 2016, which has shown a CR rate of approximately 80% in clinical trials.

Even if we obtain regulatory approval of our product candidates, we may not be the first to market and that may affect the price or demand for our product candidates. Additionally, the availability and price of our competitors’ products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances. Additionally, a competitor could obtain orphan product exclusivity from the FDA with respect to such competitor’s product. If such competitor product is determined to be the same product as one of our product candidates, that may prevent us from obtaining approval from the FDA for such product candidate for the same indication for seven years, except in limited circumstances.

For additional information regarding our competition, see the section captioned “Competition” in Part I—Item 1—“Business” located elsewhere in this report.

We are highly dependent on our key personnel, and if we are not successful in attracting, motivating and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly

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dependent on our management, particularly our chief executive officer, Hans Bishop, and our scientific and medical personnel. The loss of the services of any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements, could result in delays in product development and harm our business.

We conduct most of our operations at our facility in Seattle, Washington, in a region that is headquarters to many other biopharmaceutical companies and many academic and research institutions. As a result of our acquisition of X-Body and Stage, we have also expanded our operations into Massachusetts and Germany and currently have employees in both geographies. Competition for skilled personnel is intense in all of these geographies and the turnover rate can be high, which may limit our ability to hire and retain highly qualified personnel on acceptable terms or at all. We expect that we will need to recruit talent from outside of the regions in which we currently operate, and doing so may be costly and difficult. Further expansion into additional states or countries could also increase our regulatory and legal risks.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided restricted stock and stock option grants that vest over time. The value to employees of these equity grants that vest over time may be significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. Although we have employment agreements with our key employees, these employment agreements provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice. We do not maintain “key man” insurance policies on the lives of all of these individuals or the lives of any of our other employees.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

As of December 31, 2015, we had 306 employees worldwide, most of whom are full time. As our development and commercialization plans and strategies develop, and as we transition into operating as a public company, we must add a significant number of additional research and development, managerial, operational, sales, marketing, financial, and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining, and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for our product candidates, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems, and procedures.

Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities. Our efforts to manage our growth are complicated by the fact that all of our executive officers other than our chief executive officer have joined us since January 2014. This lack of long-term experience working together may adversely impact our senior management team’s ability to effectively manage our business and growth.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services. There can be no assurance that the services of these independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any

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reason, our clinical trials may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, if at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development, and commercialization goals.

We have engaged in and may in the future engage in acquisitions or strategic partnerships, which could divert management's attention, increase our capital requirements, dilute our stockholders, be difficult to integrate, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We have made or entered into several acquisitions or strategic partnerships, and we may continue to evaluate various acquisitions and strategic partnerships, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. For instance, in May 2015, we acquired all the outstanding equity interests in Stage, in connection with which we paid €52.5 million in cash and issued 486,279 shares of common stock as an upfront payment, with potential earn out payments of up to €135.0 million in cash based on the achievement of certain technical, clinical, regulatory, and commercial milestones.

Any acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities, including earn-out milestones;
- the issuance of our equity securities;
- assimilation of operations, intellectual property and products of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing product programs and initiatives in pursuing such a strategic merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- expense or diversion of efforts related to the development of acquired technology under any diligence obligation required of us with respect to earn out milestones for an acquisition transaction, where we may not undertake such expense or efforts absent such diligence obligations;
- risk that the other party or parties to an acquisition transaction may claim that we have not satisfied any earn out diligence obligation and seek damages or other legal or equitable relief;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we undertake additional acquisitions, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. We also cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Moreover, we may not be able to locate suitable

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acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business.

Our success payment obligations to FHCRC and MSK may result in dilution to our stockholders, may be a drain on our cash resources, or may cause us to incur debt obligations to satisfy the payment obligations.

We have agreed to make success payments to each of FHCRC and MSK pursuant to the terms of our agreements with each of those entities. These success payments will be based on increases in the estimated fair value of our common stock, payable in cash or publicly-traded equity at our discretion. The term of these obligations may last up to 11 years. Success payments will be owed (if applicable) after measurement of the value of our common stock in connection with the following valuation measurement dates during the term of the success payment agreement: (1) December 19, 2014, which was the date our common stock first became publicly traded; (2) the date on which we sell, lease, transfer or exclusively license all or substantially all of our assets to another company; (3) the date on which we merge or consolidate with or into another entity (other than a merger in which our pre-merger stockholders own a majority of the shares of the surviving entity); (4) any date on which ARCH Venture Fund VII, L.P. or C.L. Alaska L.P. transfers a majority of its shares of company capital stock held by it on such date to a third party; (5) every second anniversary of any event described in the preceding clauses (1), (2), (3) or (4), but, in the case of FHCRC, only upon a request by FHCRC made within 20 calendar days after receiving written notice from us of such event; and (6) the last day of the 11 year period. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending, in the case of FHCRC, from $20.00 per share to $160.00 per share and, in the case of MSK, from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending, in the case of FHCRC, from $10 million at $20.00 per share to $375 million at $160.00 per share and, in the case of MSK, from $10 million at $40.00 per share to $150 million at $120.00 per share, payable if such threshold is reached. The maximum aggregate amount of success payments to FHCRC is $375 million and to MSK is $150 million, in each case subject to certain indirect cost offsets related to our cash payments for collaboration activities. In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million, and a success payment to MSK was triggered in the amount of $10.0 million, less indirect cost offsets that will be determined at the time of payment in March 2016. We elected to make the payment to FHCRC in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015. The MSK success payment is required to be made, in cash or shares of our common stock at our election, on March 18, 2016. See the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” in this report for further discussion of these success payments.

The next anticipated valuation measurement date at which success payments may be triggered is December 19, 2016. Success payments will only be triggered on that date to the extent the average closing price of a share of our common stock over the consecutive 90 calendar day period preceding December 19, 2016 meets or exceeds $60.00, subject to adjustment for any stock dividend, stock split, combination of shares, and other similar events.

In order to satisfy our obligations to make these success payments, if and when they are triggered, we may issue equity securities that may cause dilution to our stockholders, or we may use our existing cash or incur debt obligations to satisfy the success payment obligation in cash, which may adversely affect our financial position.

The success payment obligations to FHCRC and MSK may cause GAAP operating results to fluctuate significantly from quarter to quarter, which may reduce the usefulness of our GAAP financial statements.

Our success payment obligations to FHCRC and MSK are recorded as a liability on our balance sheet. Under generally accepted accounting principles in the United States (“GAAP”), we are required to estimate the fair value of this liability as of each quarter end and changes in estimated fair value are amortized to expense using the accelerated attribution method over the remaining term of the collaboration agreement. Factors that may lead

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to increases or decreases in the estimated fair value of this liability include, among others, changes in the value of the common stock, change in volatility, changes in the applicable term of the success payments, changes in the risk free rate, and changes in the estimated indirect costs that are creditable against FHCRC and MSK success payments. As a result, our operating results and financial condition as reported by GAAP may fluctuate significantly from quarter to quarter and from year to year and may reduce the usefulness of our GAAP financial statements. In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million. We elected to make the payment in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015. In December 2015, a success payment to MSK was triggered in the amount of $10.0 million, less indirect cost offsets that will be determined at the time of payment in March 2016. The success payment obligation to MSK is required to be paid, in cash or shares of our common stock at our election, on March 18, 2016. As of December 31, 2015 the estimated fair values of the success payment liabilities on the consolidated balance sheets after giving effect to the success payments achieved by FHCRC and MSK were $33.8 million and $31.0 million related to FHCRC and MSK, respectively.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships, and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. The incurrence of indebtedness would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

If we, our CROs or our CMOs use hazardous and biological materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of potentially hazardous substances, including chemical and biological materials, by us or third parties, such as CROs and CMOs. We and such third parties are subject to federal, state, and local laws and regulations in the United States governing the use, manufacture, storage, handling, and disposal of medical and hazardous materials. Although we believe that our and such third parties' procedures for using, handling, storing, and disposing of these materials comply with legally prescribed standards, we cannot completely eliminate the risk of contamination or injury resulting from medical or hazardous materials. As a result of any such contamination or injury, we may incur liability or local, city, state, or federal authorities may curtail the use of these materials and interrupt our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. We do not have any insurance for liabilities arising from medical or hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, prospects, financial condition, or results of operations.

Our internal computer systems, or those used by our third-party research institution collaborators, CROs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs and other contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. Although to our knowledge we have not experienced any such material system failure or security breach to date,

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if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on our third-party research institution collaborators for research and development of our product candidates and other third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our third-party research institution collaborators, CROs, CMOs, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. Our headquarters and our Juno-operated manufacturing facility are both located in King County, Washington, and therefore could both be similarly affected by the same event. In addition, we rely on our third-party research institution collaborators for conducting research and development of our product candidates, and they may be affected by government shutdowns or withdrawn funding. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers in part to produce and process our product candidates or to supply us with certain reagents or specialized equipment or materials used our manufacturing process. Our ability to obtain clinical or commercial supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. Damage or extended periods of interruption to our corporate, development, research, or manufacturing facilities due to fire, natural disaster, power loss, communications failure, unauthorized entry or other events could cause us to cease or delay development of some or all of our product candidates. Although we maintain property damage and business interruption insurance coverage, our insurance might not cover all losses under such circumstances and our business may be seriously harmed by such delays and interruption.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;

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- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- a decline in our share price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaborators. Although we currently carry $10.0 million of clinical trial insurance, the amount of such insurance coverage may not be adequate, we may be unable to maintain such insurance, or we may not be able to obtain additional or replacement insurance at a reasonable cost, if at all. Our insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

As of December 31, 2015, we had U.S. federal net operating loss carryforwards of approximately $167.3 million, which will begin to expire in 2033. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50-percentage- point cumulative change (by value) in the equity ownership of certain stockholders over a rolling three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income or taxes may be limited. As a result of our transactions that have occurred since our incorporation in August 2013, including our initial public offering, we may have experienced such an "ownership change." We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which changes are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

Risks Related to Government Regulation

The FDA regulatory approval process is lengthy, time-consuming, and inherently unpredictable, and we may experience significant delays in the clinical development and regulatory approval, if any, of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing, and distribution of drug products, including biologics, are subject to extensive regulation by the FDA and other regulatory authorities in the United States. We are not permitted to market any biological drug product in the United States until we receive a Biologics License from the FDA. We have not previously submitted a BLA to the FDA, or similar approval filings to comparable foreign authorities. A BLA must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe, pure, and potent for each desired indication. The BLA must also include significant information regarding the chemistry, manufacturing, and controls for the product, and the manufacturing facilities must complete a successful pre-license inspection. We expect the novel nature of our product candidates to create further challenges in obtaining regulatory approval. For example, the FDA has limited experience with commercial development of genetically-modified T cell

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therapies for cancer. The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support licensure. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain licensure of the product candidates based on the completed clinical trials. Accordingly, the regulatory approval pathway for our product candidates may be uncertain, complex, expensive, and lengthy, and approval may not be obtained.

In addition, clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- obtaining regulatory approval to begin a trial, if applicable;
- the availability of financial resources to begin and complete the trials;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining approval at each clinical trial site by an independent IRB;
- recruiting suitable patients to participate in a trial in a timely manner;
- having patients complete a trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol, not complying with GCPs, or dropping out of a trial;
- addressing any patient safety concerns that arise during the course of a trial;
- addressing any conflicts with new or existing laws or regulations;
- adding new clinical trial sites; or
- manufacturing qualified materials under cGMPs for use in clinical trials.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors. See the risk factor above "—If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected" for additional information on risks related to patient enrollment. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such trials are being conducted, the data safety monitoring board for such trial, or the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Some studies, including our Phase II trial for JCAR015, also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. If we experience termination of, or delays in the completion of, any clinical trial of our product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Our third-party research institution collaborators may also experience similar difficulties in completing ongoing clinical trials and conducting future clinical trials of product candidates. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

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Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we receive regulatory approval of our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post- marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to cGMP, and in certain cases Good Tissue Practices regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, other marketing application, and previous responses to inspectional observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with requirements including submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and GCPs for any clinical trials that we conduct post-approval.

The FDA may impose consent decrees or withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of

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previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters, or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention, or refusal to permit the import or export of our product candidates; and
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. The policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

In addition, if we were able to obtain accelerated approval of any of our CD19 product candidates, the FDA would require us to conduct a confirmatory study to verify the predicted clinical benefit and additional safety studies. The results from the confirmatory study may not support the clinical benefit, which would result in the approval being withdrawn. While operating under accelerated approval, we will be subject to certain restrictions that we would not be subject to upon receiving regular approval.

Even if we obtain regulatory approval of our product candidates, the products may not gain market acceptance among physicians, patients, hospitals, cancer treatment centers, and others in the medical community.

The use of engineered T cells as a potential cancer treatment is a recent development and may not become broadly accepted by physicians, patients, hospitals, cancer treatment centers, and others in the medical community. We expect physicians in the large bone marrow transplant centers to be particularly influential, and we may not be able to convince them to use our product candidates for many reasons. For example, certain of the product candidates that we will be developing target a cell surface marker that may be present on cancer cells as well as non-cancerous cells. It is possible that our product candidates may kill these non-cancerous cells, which may result in unacceptable side effects, including death. Additional factors will influence whether our product candidates are accepted in the market, including:

- the clinical indications for which our product candidates are approved;
- physicians, hospitals, cancer treatment centers, and patients considering our product candidates as a safe and effective treatment;
- the potential and perceived advantages of our product candidates over alternative treatments;

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- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA or other regulatory authorities;
- limitations or warnings contained in the labeling approved by the FDA;
- the timing of market introduction of our product candidates as well as competitive products;
- the cost of treatment in relation to alternative treatments;
- the amount of upfront costs or training required for physicians to administer our product candidates;
- the availability of adequate coverage, reimbursement, and pricing by third-party payors and government authorities;
- the willingness of patients to pay out-of-pocket in the absence of coverage and reimbursement by third-party payors and government authorities;
- relative convenience and ease of administration, including as compared to alternative treatments and competitive therapies; and
- the effectiveness of our sales and marketing efforts.

In addition, although we are not utilizing embryonic stem cells or replication competent vectors, adverse publicity due to the ethical and social controversies surrounding the therapeutic use of such technologies, and reported side effects from any clinical trials using these technologies or the failure of such trials to demonstrate that these therapies are safe and effective may limit market acceptance our product candidates. If our product candidates are approved but fail to achieve market acceptance among physicians, patients, hospitals, cancer treatment centers or others in the medical community, we will not be able to generate significant revenue.

Even if our products achieve market acceptance, we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our products, are more cost effective or render our products obsolete.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

Successful sales of our product candidates, if approved, depend on the availability of adequate coverage and reimbursement from third-party payors. In addition, because our product candidates represent new approaches to the treatment of cancer, we cannot accurately estimate the potential revenue from our product candidates.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, commercial payors, and integrated delivery networks are critical to new product acceptance.

Government authorities and third-party payors, such as private health insurers, health maintenance organizations, and integrated delivery networks decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

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In the United States, no uniform policy of coverage and reimbursement for products exists among third- party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our genetically modified products. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates have a higher cost of goods than conventional therapies, and may require long- term follow up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of biologics is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for our product candidates and may be affected by existing and future health care reform measures.

Healthcare legislative reform measures, or public focus on product pricing, may have a material adverse effect on our business and results of operations.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government’s comparative effectiveness research.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and, due to subsequent legislative amendments, will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare.

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For instance, there have recently been public hearings in the U.S. Congress concerning pharmaceutical product pricing. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

There has also been, and may in the future be, public attention on product pricing, and that may result in political, interest group, or media criticism of companies whose pricing or potential pricing is perceived by the public as high. If we were to become subject to such criticism, it could harm our reputation, create adverse publicity, and impact our relationships with our suppliers, collaborators, medical providers, and patients, each which could adversely affect our business and results of operations.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud, misconduct or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards we have established; comply with healthcare fraud and abuse laws in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices.

These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other third-party payors that are false or fraudulent or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;
- the federal Health Insurance Portability and Accountability Act of 1996, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- the federal Physician Payment Sunshine Act, created under the Affordable Care Act, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Risks Related to Intellectual Property

We depend on intellectual property licensed from third parties and termination of any of these licenses could result in the loss of significant rights, which would harm our business.

We are dependent on patents, know-how, and proprietary technology, both our own and licensed from others. Any termination of these licenses could result in the loss of significant rights and could harm our ability to commercialize our product candidates. See the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” of this report for additional information regarding our license agreements.

Disputes may also arise between us and our licensors regarding intellectual property subject to a license agreement, including those relating to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the license agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- whether we are complying with our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates; and
- the allocation of ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and by us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. We are generally also subject to all of the same risks with respect to protection of intellectual property that we license as we are for intellectual property that we own, which are described below. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

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We depend, in part, on our licensors to file, prosecute, maintain, defend, and enforce patents and patent applications that are material to our business.

Patents relating to our product candidates are controlled by certain of our licensors. Each of our licensors generally has rights to file, prosecute, maintain, and defend the patents we have licensed from such licensor. We generally have the first right to enforce our patent rights, although our ability to settle such claims often requires the consent of the licensor. If our licensors or any future licensees having rights to file, prosecute, maintain, and defend our patent rights fail to conduct these activities for patents or patent applications covering any of our product candidates, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using, or selling competing products. We cannot be certain that such activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents or other intellectual property rights. Pursuant to the terms of the license agreements with some of our licensors, the licensors may have the right to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents and, even if we are permitted to pursue such enforcement or defense, we cannot ensure the cooperation of our licensors. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. Even if we are not a party to these legal actions, an adverse outcome could harm our business because it might prevent us from continuing to license intellectual property that we may need to operate our business. In addition, even when we have the right to control patent prosecution of licensed patents and patent applications, enforcement of licensed patents, or defense of claims asserting the invalidity of those patents, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to or after our assuming control.

We may not be successful in obtaining or maintaining necessary rights to product components and processes for our product development pipeline.

We own or license from third parties certain intellectual property rights necessary to develop our product candidates. The growth of our business will likely depend in part on our ability to acquire or in-license additional proprietary rights. For example, our programs may involve additional product candidates that may require the use of additional proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently. These formulations may be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license under such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us.

Additionally, we sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution’s rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to

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commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire.

We are dependent on intellectual property sublicensed to us by Opus Bio from the NIH for development of JCAR018. Failure to meet our own obligations to Opus Bio and the NIH may result in the loss of our rights to such intellectual property, which could harm our business.

Under our license agreement with Opus Bio, we are obligated to make certain pass-through payments to the NIH as well as to meet certain development benchmarks within certain time periods. We may be unable to make these payments or meet these benchmarks or may breach our other obligations under this license agreement, which could lead to the termination of the license agreement.

In addition, the NIH has the right to require us to grant mandatory sublicenses to the intellectual property licensed from the NIH under certain specified circumstances, including if it is necessary to meet health and safety needs that we are not reasonably satisfying or if it is necessary to meet requirements for public use specified by federal regulations. Any required sublicense of these licenses could result in the loss of significant rights and could harm our ability to commercialize licensed products.

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products or product candidates.

We anticipate that we will file additional patent applications both in the United States and in other countries, as appropriate. However, we cannot predict:

- if and when any patents will issue;
- the degree and range of protection any issued patents will afford us against competitors, including whether third parties will find ways to invalidate or otherwise circumvent our patents;
- whether others will apply for or obtain patents claiming aspects similar to those covered by our patents and patent applications; or
- whether we will need to initiate litigation or administrative proceedings to defend our patent rights, which may be costly whether we win or lose.

Composition of matter patents for biological and pharmaceutical products such as CAR or TCR product candidates are generally considered to be the strongest form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of use. We cannot be certain, however, that the claims in our pending patent applications covering the composition of matter of our product candidates will be considered patentable by the United States Patent and Trademark Office ("USPTO"), or by patent offices in foreign countries, or that the claims in any of our issued patents will be considered valid and enforceable by courts in the United States or foreign countries. Method of use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label" for those uses that are covered by our method of use patents. Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The strength of patents in the biotechnology and pharmaceutical field can be uncertain, and evaluating the scope of such patents involves complex legal and scientific analyses. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates or uses thereof in the United States or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the

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validity, enforceability, or scope thereof, which may result in such patents being narrowed, invalidated, or held unenforceable. For example, on August 13, 2015, Kite Pharma filed a petition with the USPTO for inter partes review of U.S. Patent No. 7,446,190, a patent that we have exclusively licensed from MSK. If Kite Pharma is successful in the resulting proceedings at the USPTO, the patent could be narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing their products to avoid being covered by our claims. If the breadth or strength of protection provided by the patent applications we hold with respect to our product candidates is threatened, this could dissuade companies from collaborating with us to develop, and could threaten our ability to commercialize, our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced. Because patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Furthermore, for U.S. applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third party or instituted by the USPTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. For U.S. applications containing a claim not entitled to priority before March 16, 2013, there is a greater level of uncertainty in the patent law in view of the passage of the America Invents Act, which brought into effect significant changes to the U.S. patent laws, including new procedures for challenging pending patent applications and issued patents.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce, and any other elements of our product discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. Trade secrets, however, may be difficult to protect. We seek to protect our proprietary processes, in part, by entering into confidentiality agreements with our employees, consultants, outside scientific advisors, contractors, and collaborators. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, outside scientific advisors, contractors, and collaborators might intentionally or inadvertently disclose our trade secret information to competitors. In addition, competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, or misappropriation of our intellectual property by third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results, and financial condition.

Third-party claims of intellectual property infringement against us or our collaborators may prevent or delay our product discovery and development efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. Recently, due to changes in U.S. law referred to as patent reform, new procedures including inter partes review and post-grant review have been implemented. As stated above, this reform adds uncertainty to the possibility of challenge to our patents in the future.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries

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expand and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others.

Although we have conducted analyses of the patent landscape with respect to our CD19 product candidates, and based on these analyses, we believe that we will be able to commercialize our CD19 product candidates, third parties may nonetheless assert that we infringe their patents, or that we are otherwise employing their proprietary technology without authorization, and may sue us. For instance, Novartis Pharmaceutical Corporation has asserted in writing its belief that we infringe the following patents controlled by Novartis Pharmaceutical Corporation: U.S. Patent Nos. 7,408,053, 7,205,101, 7,527,925, and 7,442,525. There may be third-party patents of which we are currently unaware with claims to compositions, formulations, methods of manufacture, or methods of use or treatment that cover our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies or the manufacture, use, or sale of our product candidates infringes upon these patents. If any such third-party patents were held by a court of competent jurisdiction to cover our technologies or product candidates, the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business.

Third parties asserting their patent rights against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties, or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly.

We have limited foreign intellectual property rights and may not be able to protect our intellectual property rights throughout the world.

We have limited intellectual property rights outside the United States, and, in particular, some of our patents directed to CAR constructs do not extend outside of the United States. Filing, prosecuting, maintaining and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can have a different scope and strength than do those in the United States. In addition, the laws of some foreign countries, such as China, Brazil, Russia, India, and South Africa, do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or adequate to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, such as China, Brazil, Russia, India, and South Africa, do not favor the enforcement of patents, trade secrets and other intellectual property, particularly those

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relating to biopharmaceutical products, which could make it difficult in those jurisdictions for us to stop the infringement or misappropriation of our patents or other intellectual property rights, or the marketing of competing products in violation of our proprietary rights. Proceedings to enforce our patent and other intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Furthermore such proceedings could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims of infringement or misappropriation against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To cease such infringement or unauthorized use, we may be required to file patent infringement claims, which can be expensive and time- consuming. In addition, in an infringement proceeding or a declaratory judgment action against us, a court may decide that one or more of our patents is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceeding could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business.

Interference or derivation proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to, or the correct inventorship of, our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation, interference, or derivation proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or before the USPTO or comparable foreign authority.

If we or one of our licensing partners initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, inter partes review, post-grant review, and equivalent proceedings in foreign jurisdictions, such as opposition or derivation proceedings. Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity of our patents, for example, we

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cannot be certain that there is no invalidating prior art of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves, both technological and legal complexity, and is therefore costly, time-consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, in Assoc. for Molecular Pathology v. Myriad Genetics, Inc., the U.S. Supreme Court held that certain claims to naturally-occurring substances are not patentable. Although we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress, or the USPTO may impact the value of our patents.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants, or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent application process. Although an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In any such event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

The lives of our patents may not be sufficient to effectively protect our products and business.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after its first effective filing date. Although various extensions may be available, the life of a patent, and the protection

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it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from biosimilar or generic medications. Our issued patents will expire on dates ranging from 2019 to 2031, subject to any patent extensions that may be available for such patents. If patents are issued on our pending patent applications, the resulting patents are projected to expire on dates ranging from 2021 to 2037. In addition, although upon issuance in the United States a patent's life can be increased based on certain delays caused by the USPTO, this increase can be reduced or eliminated based on certain delays caused by the patent applicant during patent prosecution. If we do not have sufficient patent life to protect our products, our business and results of operations will be adversely affected.

We may face competition from biosimilars, which may have a material adverse impact on the future commercial prospects of our product candidates.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This new pathway could allow competitors to reference data from innovative biological products 12 years after the time of approval of the innovative biological product. This data exclusivity does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. Data exclusivity only assures that another company cannot rely upon the data within the innovator's application to support the biosimilar product's approval. In his proposed budget for fiscal year 2014, President Obama proposed to cut this 12-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity due to minor changes in product formulations, a practice often referred to as "evergreening." It is possible that Congress may take these or other measures to reduce or eliminate periods of exclusivity. The Biologics Price Competition and Innovation Act of 2009 is complex and only beginning to be interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning is subject to uncertainty. Although it is uncertain when any such processes may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our product candidates.

In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to get it on the market until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products.

If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators, or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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Risks Related to Our Common Stock

We expect that our stock price will fluctuate significantly.

The trading price of our common stock may be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- adverse results or delays in the clinical trials of our product candidates or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- regulatory or legal developments in the United States and other countries, especially changes in laws or regulations applicable to our products, including clinical trial requirements for approvals;
- our inability to obtain or delays in obtaining adequate product supply for any approved product or inability to do so at acceptable prices;
- any failure to commercialize our product candidates or if the size and growth of the markets we intend to target fail to meet expectations;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to cancer immunology or the use of our product candidates;
- introductions or announcements of new products offered by us or significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our collaborators or our competitors and the timing of such introductions or announcements;
- announcements relating to future collaborations or our existing collaboration with Celgene, including decisions regarding the exercise by Celgene or us of any of our or their options thereunder, or any exercise or non-exercise by Celgene of a right to purchase shares of our common stock;
- our ability to effectively manage our growth;
- our ability to successfully treat additional types of cancers or at different stages;
- changes in the structure of healthcare payment systems;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- publication of research reports about us or our industry, or immunotherapy in particular, or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- market conditions in the pharmaceutical and biotechnology sectors or the economy generally;
- our ability or inability to raise additional capital through the issuance of equity or debt or collaboration arrangements and the terms on which we raise it;
- trading volume of our common stock;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies; and
- significant lawsuits, including patent or stockholder litigation.

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The stock market in general, and market prices for the securities of biopharmaceutical companies like ours in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common stock, regardless of our operating performance. In several recent situations when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.

An active trading market for our common stock may not be sustained.

Prior to our initial public offering in December 2014, there was no public market for our common stock. Although our common stock is listed on The NASDAQ Global Select Market, the market for our shares has demonstrated varying levels of trading activity. Furthermore, an active trading market may not be sustained in the future. The lack of an active market may impair investors' ability to sell their shares at the time they wish to sell them or at a price that they consider reasonable, may reduce the market value of their shares and may impair our ability to raise capital.

If securities or industry analysts do not publish research reports about our business, or if they issue an adverse opinion about our business, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us issues an adverse opinion about our company, our stock price would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Future sales of our common stock in the public market could cause our stock price to fall.

Our stock price could decline as a result of sales of a large number of shares of our common stock or the perception that these sales could occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

As of December 31, 2015, we had 102,400,503 shares of common stock outstanding, including 5,153,445 shares of restricted stock that remained subject to vesting requirements. In connection with the sale of shares to Celgene, all 9,137,672 shares acquired by Celgene on August 4, 2015, representing 9.1% of our common stock outstanding as of the date of issuance (after giving effect to such issuance), are subject to a market standoff agreement for 364 days from the date of acquisition. Any subsequent acquisitions of shares of our common stock by Celgene will commence another 364 day market standoff period, subject to certain exceptions.

We have also registered the offer and sale of all shares of common stock that we may issue under our equity compensation plans, including upon the exercise of stock options. These shares can be freely sold in the public market upon issuance.

As of December 31, 2015, the holders of as many as 37.3 million shares, or 36.4% of our common stock outstanding as of December 31, 2015, have rights, subject to some conditions, under the investor rights agreement with such holders to require us to file registration statements covering the sale of their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. Once we register the offer and sale of shares for the holders of registration rights, they can be freely sold in the public market. In connection with the collaboration agreement with Celgene, we have also entered into a registration rights agreement, pursuant to which upon the written request of Celgene at certain times and subject to the

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satisfaction of certain conditions, we have agreed to prepare and file with the SEC a registration statement on Form S-3 for purposes of registering the resale of the shares specified in Celgene's written request or, if we are not at such time eligible for the use of Form S-3, use commercially reasonable efforts to prepare and file a registration statement on a Form S-1 or alternative form that permits the resale of the shares.

In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise, including up to 30% of shares of our outstanding common stock to Celgene. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

Our executive officers, directors and our 10% or greater stockholders, together with their respective affiliates, beneficially owned approximately 51.4% of our capital stock as of December 31, 2015, excluding shares underlying outstanding options. Accordingly, such persons and entities, if they acted together, would be able to determine the composition of the board of directors, retain the voting power to approve many matters requiring stockholder approval, including mergers and other business combinations, and continue to have significant influence over our operations. In addition, other than in connection with a change of control, in any vote or action by written consent of our stockholders, including, without limitation, with respect to the election of directors, Celgene has agreed to vote or execute a written consent with respect to all of our voting securities held by Celgene in accordance with the recommendation of our board of directors, limiting the ability of Celgene to contrary to our board of directors that you otherwise may believe is in your best interest as our stockholder. This concentration of ownership amongst our significant holders, including Celgene, could have the effect of delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us that you may believe are in your best interests as one of our stockholders. This in turn could have a material adverse effect on our stock price and may prevent attempts by our stockholders to replace or remove the board of directors or management.

In connection with the entry into the Celgene collaboration agreement, Celgene acquired 9.1% of our outstanding shares of common stock and subject to certain conditions, may purchase additional shares annually to obtain and maintain a 10% ownership percentage through June 29, 2020. Furthermore, between June 29, 2019 and June 29, 2025 and between June 29, 2024 and the expiration of the collaboration agreement, subject to certain conditions, Celgene has the option to acquire and maintain an ownership of up to 19.99% and up to 30%, respectively, of our then outstanding shares of common stock. We have also entered into a voting and standstill agreement with Celgene, pursuant to which we have agreed to give Celgene certain board designation rights until at least June 29, 2020, and thereafter for as long as Celgene and its affiliates beneficially own at least 7.5% of the voting power of our outstanding shares. As a result of the concentration of ownership, Celgene could have the ability to delay or prevent a change in our control or otherwise discourage a potential acquirer from attempting to obtain control of us that you may believe are in your best interests as our stockholder.

Anti-takeover provisions in our charter documents and under Delaware or Washington law could make an acquisition of us difficult, limit attempts by our stockholders to replace or remove our current management and adversely affect our stock price.

Provisions of our certificate of incorporation and bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our stock. Among other things, the certificate of incorporation and bylaws will:

- permit the board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate;

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- provide that the authorized number of directors may be changed only by resolution of the board of directors;
- provide that all vacancies, including newly-created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- divide the board of directors into three classes;
- provide that a director may only be removed from the board of directors by the stockholders for cause;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be taken by written consent;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner, and meet specific requirements as to the form and content of a stockholder's notice;
- prevent cumulative voting rights (therefore allowing the holders of a plurality of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose);
- require that, to the fullest extent permitted by law, a stockholder reimburse us for all fees, costs and expenses incurred by us in connection with a proceeding initiated by such stockholder in which such stockholder does not obtain a judgment on the merits that substantially achieves the full remedy sought;
- provide that special meetings of our stockholders may be called only by the chairman of the board, our chief executive officer (or president, in the absence of a chief executive officer) or by the board of directors; and
- provide that stockholders will be permitted to amend the bylaws only upon receiving at least two- thirds of the total votes entitled to be cast by holders of all outstanding shares then entitled to vote generally in the election of directors, voting together as a single class.

Furthermore, pursuant to the voting and standstill agreement with Celgene, until the later of the fifth anniversary of the date of such agreement and the expiration or earlier termination of our collaboration agreement with Celgene, it will be bound by certain "standstill" provisions which generally will prevent it from purchasing outstanding shares of our common stock, making a tender offer or encouraging or supporting a third party tender offer, nominating a director whose nomination has not been approved by our board of directors, soliciting proxies in opposition to the recommendation of our board of directors or assisting a third party in taking such actions, entering into discussions with a third party as to such actions, or requesting or proposing in writing to our board of directors or any member thereof that we amend or waive any of these limitations. As a result, the ability of Celgene to act in contrary to our board of directors is severely limited and any attempts by Celgene to acquire us or encourage a third party to acquire us are prohibited by this voting and standstill agreement. In addition, subject to certain exceptions—including a vote in connection with a change in control of our company—Celgene has agreed to vote or execute a written consent with respect to all of our voting securities held by Celgene in accordance with the recommendation of our board of directors, limiting the ability of Celgene to contrary to our board of directors that you otherwise may believe is in your best interest as our stockholder.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with any "interested" stockholder for a period of three years following the date on which the stockholder became an "interested" stockholder. Likewise, because our principal executive offices are located in Washington, the anti-takeover provisions of the Washington Business Corporation Act may apply to us under certain circumstances now or in the future. These provisions prohibit a "target corporation"

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from engaging in any of a broad range of business combinations with any stockholder constituting an "acquiring person" for a period of five years following the date on which the stockholder became an "acquiring person."

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws, any action to interpret, apply, enforce, or determine the validity of our certificate of incorporation or bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Complying with the laws and regulations affecting public companies has increased and will increase our costs and the demands on management and could harm our operating results.

As a public company, we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company, including costs associated with public company reporting requirements. We also anticipate that we will incur costs associated with relatively recently adopted corporate governance requirements, including requirements of the SEC and NASDAQ. We expect these rules and regulations to increase our legal and financial compliance costs and to make some activities more time-consuming and costly. We also expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified individuals to serve on our board of directors or as executive officers. We are currently evaluating and monitoring developments with respect to these rules, and we cannot predict or estimate the amount of additional costs we may incur or the timing of such costs.

Starting January 1, 2016, we are no longer an "emerging growth company" and we will no longer be able to avail ourselves of exemptions from various reporting requirements applicable to other public companies but not to "emerging growth companies." For example, the Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and the effectiveness of our disclosure controls and procedures quarterly. Section 404 of the Sarbanes-Oxley Act ("Section 404") requires us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm potentially to attest to, the effectiveness of our internal control over financial reporting. We previously availed ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. However, beginning on January 1, 2016, we are no longer avail ourselves of this exemption. Our independent registered public accounting firm is now required to undertake an assessment of our internal control over financial reporting, and as a result the cost of our compliance with Section 404 will correspondingly increase. Our compliance with applicable provisions of Section 404 will require that we incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in

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our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources. Furthermore, investor perceptions of our company may suffer if deficiencies are found, and this could cause a decline in the market price of our stock. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal control over financial reporting from our independent registered public accounting firm.

Our management team has broad discretion to use the net proceeds from the initial payments to us under our collaboration agreement with Celgene and from the sale of our shares to Celgene and its investment of these proceeds may not yield a favorable return. We may invest the proceeds of the Celgene transaction and any remaining proceeds from our initial public offering in December 2014 in ways with which investors disagree.

Our management has broad discretion over the use of proceeds from the initial payments to us under our collaboration agreement with Celgene and from the sale of our shares to Celgene, as well as any remaining proceeds from our December 2014 initial public offering, and we could spend the proceeds from these transactions in ways our stockholders may not agree with or that do not yield a favorable return, if at all. In addition, until the proceeds are used, they may be placed in investments that do not produce significant income or that may lose value. If we do not invest or apply the proceeds in ways that improve our operating results, we may fail to achieve expected financial results, which could cause our stock price to decline.

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ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

The following table summarizes the facilities we lease as of December 31, 2015, including the location and size of the facilities, and their designated use.

Location	Approximate Square Feet	Operation	Lease Expiration Dates
Seattle, Washington	70,800	Administrative, Clinical, Commercial, Process Development, Quality, Regulatory, Research	April 2017 – July 2017
Bothell, Washington	67,800	Manufacturing	March 2025
Waltham, Massachusetts	3,500	Research	September 2016
Munich, Germany	17,600	Manufacturing, Process Development, Research	September 2025
Göttingen, Germany	700	Administrative, Research	December 2017

The foregoing table does not reflect two additional leases that we have entered into, but for which the lease term has not yet commenced. The first is a lease for approximately 161,400 square feet of office and laboratory space in a to-be-constructed building located in Seattle, Washington. The anticipated commencement date of the lease is in or about April 2017 with an initial term of 84 months. We intend for this space to serve as our corporate headquarters. The second is a lease for approximately 20,100 square feet of office and laboratory space located in Waltham, Massachusetts with a commencement date of June 2016 and an initial term of 120 months.

We believe that our existing facilities are adequate for our near-term needs, but expect to need additional space as we grow and expand our operations. We believe that suitable additional or alternative office, laboratory, and manufacturing space would be available as required in the future on commercially reasonable terms.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we may become involved in litigation or proceedings relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

In August 2015, Kite Pharma filed a petition with the USPTO for inter partes review of U.S. Patent No. 7,446,190, a patent that we have exclusively licensed from MSK. In February 2016, the USPTO determined to initiate the inter partes review proceedings, in Kite Pharma, Inc. v. Sloan Kettering Institute for Cancer Research, Case IPR2015-01719. As the exclusive licensor, we have opted to exercise our right to control the defense of the patent in the proceedings. We will incur expenses associated with this defense, which expenses may be substantial. If we are unsuccessful, the patent could be narrowed or invalidated, but we do not expect that this would have a material adverse effect on our business.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Our common stock has been listed on The NASDAQ Global Select Market under the symbol "JUNO" since December 19, 2014. Prior to that date, there was no public trading market for our common stock. The following table sets forth the high and low intraday sales price per share of our common stock as reported on The NASDAQ Global Select Market for the period indicated:

	High	Low
Year Ended December 31, 2015		
First Quarter 2015	$64.55	$38.00
Second Quarter 2015	$69.28	$40.60
Third Quarter 2015	$56.29	$33.00
Fourth Quarter 2015	$57.82	$39.36
Year Ended December 31, 2014		
Fourth Quarter (from December 19, 2014)	$56.50	$34.71

Holders of Common Stock

As of February 18, 2016, there were 139 holders of record of our common stock.

Dividend Policy

We have never declared or paid any cash dividends on our common stock or any other securities. We anticipate that we will retain all available funds and any future earnings, if any, for use in the operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, future debt instruments may materially restrict our ability to pay dividends on our common stock. Payment of future cash dividends, if any, will be at the discretion of the board of directors after taking into account various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements of current or then-existing debt instruments and other factors the board of directors deems relevant.

Performance Graph

This graph is not "soliciting material," is not deemed "filed" with the SEC and is not to be incorporated by reference into any filing of Juno Therapeutics, Inc. under the Securities Act of 1933, as amended (the "Securities Act"), or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

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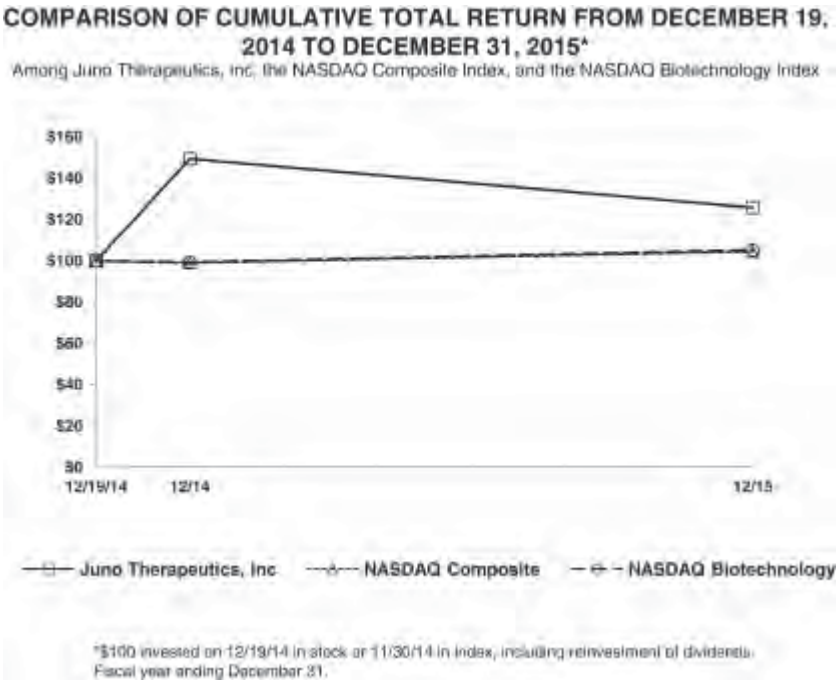
The following graph shows the total stockholder return of an investment of $100 in cash at market close on December 19, 2014 (the first day of trading of our common stock) through December 31, 2015 for (1) our common stock, (2) the NASDAQ Composite Index (U.S.) and (3) the NASDAQ Biotechnology Index. Pursuant to applicable Securities and Exchange Commission rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder return shown on the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



	12/19/2014	12/31/2014	12/31/2015
Juno Therapeutics, Inc	100.00	149.20	125.63
NASDAQ Composite	100.00	98.81	104.66
NASDAQ Biotechnology	100.00	99.34	105.20

Recent Sales of Unregistered Securities

We did not sell any unregistered securities during the year ended December 31, 2015 other than those sales that have previously been disclosed in a Quarterly Report on Form 10-Q or a Current Report on Form 8-K.

Use of Proceeds from Registered Securities

On December 23, 2014, we closed our initial public offering, in which we sold an aggregate of 12,676,354 shares of common stock at a price to the public of $24.00 per share. The offer and sale of all of the shares in the initial

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public offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-200293), which was declared effective by the SEC on December 18, 2014 (the "Registration Statement"), and a registration statement on Form S-1 (File No. 333-201062), which became effective immediately upon filing with the SEC on December 18, 2014.

There has been no material change in the planned use of proceeds from our initial public offering as described in the Registration Statement. We invested the funds received in short-term, interest-bearing investment-grade securities and government securities. As of December 31, 2015, we have used approximately $217.9 million of the net proceeds from the IPO primarily to fund the costs to advance JCAR015 through a Phase II clinical trial, to advance JCAR017 through a Phase I clinical trial and into a potential registration trial in relapsed/refractory NHL, to further develop additional product candidates, to expand our internal research and development capabilities, to establish manufacturing capabilities, to acquire, license and invest in complementary products, technologies and businesses, and other general corporate purposes. None of the offering proceeds were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates.

Issuer Purchases of Equity Securities

We did not repurchase any shares of our common stock during the fiscal quarter ended December 31, 2015.

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ITEM 6. SELECTED FINANCIAL DATA.

The selected statement of operations data for the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013, and the selected balance sheet data as of December 31, 2015, 2014, and 2013 are derived from our audited consolidated financial statements included elsewhere in this report. Our cash provided by operations during the year ended December 31, 2015 was $7.3 million and we ended 2015 with $1.2 billion in cash, cash equivalents, and marketable securities. Cash used in operations during the year ended December 31, 2014 and during the period from August 5, 2013 to December 31, 2013 was $82.5 million and $30.5 million, respectively.

Included in net loss attributable to common stockholders in the year ended December 31, 2015 are non-cash expenses of an aggregate of $57.8 million related to the change in the estimated value and elapsed service period for our potential and actual success payment liabilities to FHCRC and MSK ($51.6 million) and stock-based compensation expense related to a former co-founding director who became a consultant upon his departure from the board of directors ($6.2 million). Included in net loss attributable to common stockholders in the year ended December 31, 2014 are non-cash expenses of an aggregate of $229.7 million related to the change in the estimated value and elapsed service period for our success payment liabilities to FHCRC and MSK ($84.9 million), non-cash deemed dividends recorded upon issuance of our convertible preferred stock ($67.5 million), the non-cash portion of an upfront fee to acquire technology from Opus Bio related to our CD22-directed product candidate JCAR018 ($64.1 million), changes in the fair value of our Series A and Series A-2 convertible preferred stock options ($10.7 million), and stock-based compensation expense related to a former co-founding director who became a consultant upon his departure from the board of directors ($2.5 million).

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Our historical results are not necessarily indicative of the results that may be expected in the future. Refer to the selected historical financial data below in conjunction with Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations" of this report and the audited consolidated financial statements and related notes included elsewhere in this report.

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
	(in thousands, except share and per share amounts)		
Consolidated statements of operations data:			
Revenue	$ 18,215	$ —	$ —
Operating expenses:			
Research and development (1)	205,160	204,511	46,245
General and administrative (2)	51,130	19,529	4,238
Litigation	6,025	8,718	1,195
Total operating expenses	262,315	232,758	51,678
Loss from operations	(244,100)	(232,758)	(51,678)
Interest income, net	1,730	69	—
Other income (expenses), net	234	(10,718)	(142)
Loss before income taxes	(242,136)	(243,407)	(51,820)
Benefit for income taxes	2,760	—	—
Net loss	$ (239,376)	$ (243,407)	$ (51,820)
Net loss attributable to common stockholders:			
Net loss	$ (239,376)	$ (243,407)	$ (51,820)
Deemed dividends upon issuance of convertible preferred stock, non-cash	—	(67,464)	—
Net loss attributable to common stockholders	$ (239,376)	$ (310,871)	$ (51,820)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.72)	$ (36.82)	$ (14.16)
Weighted average common shares outstanding, basic and diluted	88,145,424	8,442,947	3,658,687

(1) Research and development expense for the year ended December 31, 2015 includes non-cash expense of $51.6 million associated with our actual and potential success payment liability to FHCRC and MSK attributable to the change in the estimated value and elapsed service period, and $30.8 million associated with the acquisition of new technology. In December 2015, success payment obligations to FHCRC were triggered in the amount of $75.0 million less indirect cost offsets of $3.3 million and to MSK of $10.0 million less indirect cost offsets that will be determined at the time of payment in March 2016. We elected to make the payment to FHCRC in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015. The success payment obligation to MSK is required to be paid on March 18, 2016, in cash or shares of our common stock at our election.

Research and development expense for the year ended December 31, 2014 includes non-cash expense of $84.9 million associated with the portion of the success payment liability to FHCRC and MSK attributable to the elapsed service period, $64.1 million for the non-cash portion of the upfront fee to acquire technology related to JCAR018, and $20.0 million for the cash portion of the upfront fee to acquire technology related to JCAR018.

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(2) General and administrative expense for the year ended December 31, 2015 includes $9.7 million of expenses related to the Celgene, Stage, X-Body and other business development transactions.

	As of December 31,		
	2015	2014	2013
		(in thousands)	
Consolidated balance sheets data:			
Cash, cash equivalents, and marketable securities	$1,216,299	$ 474,051	$ 35,966
Working capital	832,111	338,642	25,007
Total assets	1,445,128	489,163	40,094
Total liabilities	303,595	100,631	11,193
Common stock and additional paid-in capital	1,733,273	734,903	8,138
Accumulated deficit (1)	(585,657)	(346,281)	(51,820)
Total stockholders' equity	$1,141,533	$ 388,532	$(43,682)

(1) Accumulated deficit as of December 31, 2015 includes $51.1 million related to non-cash deemed dividends, $159.4 million in upfront fees to acquire technology, of which $85.5 million was paid in cash and $73.9 million was paid through the issuance of common stock, and non-cash expense of $136.5 million associated with the change in the estimated fair value and elapsed service period for our potential and actual success payment liability to FHCRC and MSK.

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ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

You should read the following discussion in conjunction with our consolidated financial statements and related notes included elsewhere in this report. This discussion contains forward-looking statements that involve risks and uncertainties, as described in the section of this report captioned "Forward-Looking Statements and Market Data." As a result of many factors, such as those set forth in Part I—Item 1A—"Risk Factors" of this report and elsewhere in this report, our actual results may differ materially from those anticipated in these forward-looking statements.

Overview

We are building a fully-integrated biopharmaceutical company focused on re-engaging the body's immune system to revolutionize the treatment of cancer. Founded on the vision that the use of human cells as therapeutic entities will drive one of the next important phases in medicine, we are developing cell-based cancer immunotherapies based on our CAR and high-affinity TCR technologies to genetically engineer T cells to recognize and kill cancer cells. We have shown compelling clinical responses in clinical trials using multiple cell-based product candidates to address refractory B cell lymphomas and leukemias, and we also have a number of ongoing trials exploring our platform in solid-organ cancers and in combination with various strategies to overcome the immune-suppressive effects of cancer. Longer term, we aim to improve and leverage our cell-based platform to develop additional product candidates to address a broad range of cancers and human diseases, including moving forward our pre-clinical product candidates that target additional hematologic and solid-organ cancers.

In the third quarter of 2015, we began a Phase II trial of JCAR015 that could support accelerated U.S. regulatory approval in adult r/r B cell ALL as early as 2017. We also began a Phase I trial with JCAR017 in adult r/r aggressive B cell NHL, with the potential to move to a registration trial for that product candidate in 2016 or early 2017. We are continuing to enroll patients in an ongoing Phase I/II trial for JCAR014 in B cell malignancies, and although we do not plan to move JCAR014 into registration trials, we plan to use this trial to explore important questions that may improve our platform overall. To date, data from the JCAR014 trial have provided encouraging early insights on how to improve our efficacy and safety in patients with ALL, NHL, and CLL. The IND has cleared for and we plan to enroll patients through 2016 in a Phase Ib clinical trial combining JCAR014 with MedImmune's investigational PD-L1 immune checkpoint inhibitor, durvalumab, for the treatment of adult r/r B cell NHL. We have also begun Phase I trials for five additional product candidates that target different cancer-associated proteins in hematological and solid organ cancers. We also expect to commence a Phase I trial through our collaborator MSK of a CD19/4-1BBL "armored" CAR in 2016 and a Phase I trial for one or both of CD19/CD40L and CD19/IL-12 "armored" CARs in 2016 or 2017.

We believe that the quality of our people will have a strong and positive impact on our ability to develop and capitalize on our technology. In that vein we have assembled a talented group of scientists, engineers, clinicians, directors, and other advisors who develop and consolidate technologies and intellectual property from some of the world's leading research institutions, including FHCRC, MSK, SCRI, and the NCI. Our scientific founders and their institutions include world leaders in oncology, immunology, and cell therapy, and they actively contribute towards developing our product candidates and technologies. Collectively, these stakeholders share our commitment to bringing our product candidates to market and our vision of revolutionizing medicine through developing a broadly applicable cell-based platform. We have also entered into a number of strategic collaborations with commercial companies that we believe will help us manufacture and commercialize our product candidates around the world or develop additional or improved product candidates, including Celgene, Editas, Fate Therapeutics, and MedImmune.

We are devoting significant resources to optimizing process development and manufacturing. We believe that these efforts will lead to better product characterization, a more efficient production cycle, and greater flexibility

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in implementing enhancements to product candidates. In turn, these improvements may lead to a lower cost of manufacturing, streamlined regulatory reviews, greater convenience for patients and physicians, and better patient outcomes. We have used CMOs to provide speed, flexibility and limit upfront capital investment in manufacturing, and successfully brought a CMO on-line to manufacture JCAR015. We have also established a Juno-run manufacturing facility in Bothell, Washington. We plan to manufacture clinical trial material from this facility beginning in the first quarter of 2016, and commercial products, subject to the required regulatory approvals, beginning in 2017, with the goal of improving long-term margins and enabling more rapid implementation of innovative changes.

In June 2015 we entered into a ten-year, global collaboration agreement with Celgene Corporation for the development and commercialization of immunotherapies. In connection with this collaboration agreement, Celgene paid us a $150 million upfront payment, and under a Share Purchase Agreement, we sold Celgene 9,137,672 shares of our common stock for an aggregate cash price of approximately $850 million, or $93.00 per share.

We completed three business acquisitions in 2015 and early 2016 to augment our research and development capabilities and to improve our supply chain and long-term cost of goods.

In May 2015, we acquired Stage, a company focused on developing technology platforms, including novel reagents and automation technologies, that enable the development and production of cell therapeutics. The acquisition of Stage is intended to provide us access to transformative cell selection and activation capabilities, next generation manufacturing automation technologies, enhanced control of our supply chain, and lower expected long-term cost of goods.

In June 2015, we acquired X-Body, a company focused on the discovery of human monoclonal antibodies and discovery of TCR binding domains. The X-Body acquisition is intended to augment our capabilities to create best-in-class engineered T cells against a broad array of cancer targets.

In January 2016, we acquired AbVitro, a company with a leading next-generation single cell sequencing platform. The AbVitro acquisition is intended to augment our capabilities to create best-in-class engineered T cells against a broad array of cancer targets. We and Celgene have agreed in principle to enter into an agreement to license Celgene a subset of the acquired technology and to grant Celgene options to certain related potential product rights emanating from the acquired technology.

As of December 31, 2015, we generated revenue of $5.1 million from the Celgene Collaboration Agreement. In addition, we generated revenue of $12.3 million in 2015 from an upfront license payment in connection with the Penn/Novartis Sublicense Agreement entered into in April 2015. In the future, we may generate revenue from product sales, collaboration agreements, strategic alliances and licensing arrangements, or a combination of these. We expect that any revenue we generate will fluctuate from quarter to quarter and year to year as a result of the timing and amount of license fees, milestones, reimbursement of costs incurred and other payments and product sales, to the extent any are successfully commercialized. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval of them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

We have agreed to make success payments to each of FHCRC and MSK pursuant to the terms of our collaboration agreements with each of those entities. In December 2015, success payment obligations to FHCRC were triggered in the amount of $75.0 million less indirect cost offsets of $3.3 million and to MSK of $10.0 million less indirect cost offsets that will be determined at the time of payment in March 2016. We elected to make the payment to FHCRC in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015. The success payment obligation to MSK is required to be paid, in cash or shares of our common stock at our election, on March 18, 2016. For additional information regarding these success payments, see the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” located elsewhere in this report.

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As of December 31, 2015, we had cash, cash equivalents, and marketable securities of $1.2 billion compared with $474 million as of December 31, 2014. Cash provided by operations for the year ended December 31, 2015 was $7.3 million and includes a $150.2 million upfront payment from the Celgene Collaboration Agreement, offset by $30.8 million in costs to acquire technology in the Editas and Fate Therapeutics collaborations, and cash used to grow our business, including the hiring of key talent. Included in net cash used in investing activities in 2015 is $77.7 million of net cash used to acquire Stage and X-Body and $7.2 million used to acquire the investment in Fate Therapeutics. Cash provided by financing activities in 2015 includes $849.8 million from Celgene for the purchase of 9,137,672 shares of our common stock.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported revenue generated and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Revenue

We recognize revenue for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue in our consolidated balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue in current liabilities. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, less current portion.

We analyze agreements with more than one element, or deliverable, based on the guidance in Accounting Standards Codification ("ASC 605-25"). We identify the deliverables within the agreement and evaluate which deliverables represent separate units of accounting. Analyzing the agreement to identify deliverables requires the use of judgment. A deliverable is considered a separate unit of accounting when the deliverable has value to the collaborator or licensee on a standalone basis based on the consideration of the relevant facts and circumstances for each agreement. In assessing whether an item has standalone value, we consider factors such as the research, manufacturing, and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, we consider whether the other deliverable(s) can be used for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there are other vendors that can provide the undelivered element(s).

Consideration received is allocated at the inception of the agreement to all identified units of accounting based on their relative selling price. The relative selling price for each deliverable is estimated using objective evidence if

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it is available. If objective evidence is not available, we use our best estimate of the selling price for the deliverable. Management may be required to exercise considerable judgment in estimating the selling prices of identified units of accounting under its agreements.

Options for future deliverables are considered substantive if, at the inception of the arrangement, we are at risk as to whether the collaboration partner will choose to exercise the option. Factors that we consider in evaluating whether an option is substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the option, the cost to exercise the option and the likelihood that the option will be exercised. For arrangements under which an option is considered substantive, we do not consider the item underlying the option to be a deliverable at the inception of the arrangement and the associated option fees are not included in the initial consideration, assuming the option is not priced at a significant and incremental discount. Conversely, for arrangements under which an option is not considered substantive or if an option is priced at a significant and incremental discount, we would consider the item underlying the option to be a deliverable at the inception of the arrangement and a corresponding amount would be included in the initial consideration.

The consideration received is allocated among the separate units of accounting, and the applicable revenue recognition criteria are applied to each of the separate units. We recognize the revenue allocated to each unit of accounting over the period of performance. Revenue is recognized using either a proportional performance or straight-line method, depending on whether we can reasonably estimate the level of effort required to complete our performance obligations under an arrangement.

Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the net amount of identifiable assets acquired and liabilities assumed in a business combination measured at fair value. We evaluate goodwill for impairment annually during the fourth quarter and upon the occurrence of triggering events or substantive changes in circumstances that could indicate a potential impairment by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that the fair value of net asset are below their carrying amounts. There was no impairment of goodwill recognized for the year ended December 31, 2015.

Intangible assets acquired in a business combination are recognized separately from goodwill and are initially recognized at their fair value at the acquisition date (which is regarded as their cost). Intangible assets related to in-process research and development (“IPR&D”) are treated as indefinite-lived intangible assets and not amortized until they become definite lived assets upon certain regulatory approval in specified markets in the case of X-Body, and in the case of Stage, when the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgment. At that time, we will determine the useful life of the asset, reclassify the asset out of IPR&D and begin amortization. Intangible assets are reviewed for impairment at least annually or if indicators of potential impairment exist. There were no impairments of intangible assets recognized for the year ended December 31, 2015.

Build-to-Suit Lease Accounting

In February 2015, we entered into a lease for a manufacturing facility, which commenced in March 2015. We were responsible for the leasehold improvements required to remodel the facility and we bore the majority of the construction risk. ASC 840-40, Leases – Sale-Leaseback Transactions (Subsection 05-5), required us to be considered the owner of the building solely for accounting purposes, even though we were not the legal owner. As a result, we recorded an asset and build-to-suit lease obligation on our balance sheet as of December 31, 2015 equal to the fair value of the building at the inception of the lease.

Construction was completed in the first quarter of 2016 and we considered the requirements for sale-leaseback accounting treatment, including evaluating whether all risks of ownership have transferred back to the landlord,

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as evidenced by a lack of continuing involvement in the leased property. We determined that the arrangement does not qualify for sale-leaseback accounting treatment, and the building asset will remain on our balance sheet at its historical cost, and such asset will be depreciated over its estimated useful life. We bifurcate our lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the statements of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

The interest rate used for the build-to-suit lease obligation represents our estimated incremental borrowing rate, adjusted to reduce any built in loss.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development services. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. This process involves reviewing open contracts and purchase orders and communicating with our applicable internal personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual cost. In addition, we periodically confirm the accuracy of our estimates with selected service providers and make adjustments, if necessary.

Examples of estimated research and development expenses that we accrue include:

- clinical trial costs;
- external research and development expenses incurred under arrangements with third parties, such as CROs, CMOs, academic and non-profit institutions and consultants; and
- costs incurred in connection with preclinical development activities.

We base our expense accruals related to clinical trials on patient enrollment and our estimates of the services received and efforts expended pursuant to contracts with multiple research institutions that conduct and manage clinical trials on our behalf. The financial terms of these agreements vary from contract to contract and may result in uneven payment flows. Payments under some of these contracts depend on several factors, such as the successful enrollment of patients and the manufacturing of the associated product candidates, and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If we do not identify costs that we have begun to incur or if we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates. For service contracts entered into that include a nonrefundable prepayment for service the upfront payment is deferred and recognized in the statement of operations as the services are rendered.

To date, we have not experienced significant changes in our estimates of accrued research and development expenses after a reporting period. However, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical trials and other research activities.

Stock-Based Compensation

Under the Financial Accounting Standards Board's ("FASB") ASC 718, Compensation—Stock Compensation, we measure and recognize compensation expense for restricted stock, restricted stock units ("RSUs"), and stock options granted to our employees and directors based on the fair value of the awards on the date of grant. The fair

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value of stock options is estimated at the date of grant using the Black-Scholes option pricing model that requires management to apply judgment and make estimates, including:

- the expected term of the stock option award, which we calculate using the simplified method, as permitted by the SEC Staff Accounting Bulletin No. 110, Share-Based Payment, as we have insufficient historical information regarding our stock options to provide a basis for an estimate;
- the expected volatility of our underlying common stock, which we estimate based on the historical volatility of a representative group of publicly traded biopharmaceutical companies with similar characteristics to us, and our own historical and implied future volatility;
- the risk-free interest rate, which we based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued;
- the expected dividend yield, which we estimate to be zero based on the fact that we have never paid cash dividends and have no present intention to pay cash dividends; and
- the fair value of our common stock on the date of grant.

Stock-based compensation expense for restricted stock, RSUs, and stock options is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective award. We are required to estimate a forfeiture rate to calculate the stock-based compensation expense for our awards. Our forfeiture rate is based on an analysis of our actual forfeitures since the adoption of our equity award plan. Since inception our estimated forfeiture rate has been de minimis. We routinely evaluate the appropriateness of the forfeiture rate based on actual forfeiture experience, analysis of employee turnover, and expectations of future option exercise behavior.

We have also granted restricted stock awards that vest in conjunction with certain performance conditions to certain key employees, scientific founders, and directors. At each reporting date, we are required to evaluate whether the achievement of the performance condition is probable. Compensation expense is recorded over the appropriate service period based on our assessment of the probability of achieving each performance provision or the occurrence of other events that may cause the awards to accelerate and vest.

We periodically grant stock-based awards to certain service providers who are not employees, scientific founders, or directors. We account for these stock-based awards to non-employees in accordance with FASB ASC 505-50, Equity-Based Payments to Non-Employees, which requires the fair value of such awards to be re measured at each reporting period until services required under the arrangement are completed, which is the vesting date. We have made a few stock-based awards to consultants that are accounted for in this manner, but the most significant such award is a 2013 restricted stock award made to a former co-founding director who became a consultant upon his departure from the board of directors in 2014.

Determination of the fair value of our common stock on grant dates prior to our initial public offering ("IPO")

Prior to becoming a public company, the fair value of the common stock underlying our stock-based awards was determined on each grant date by our board of directors, taking into account input from management and independent third-party valuation analyses. Our board of directors is comprised of a majority of non-employee directors with significant experience investing in and operating companies in the biotechnology industry. All stock-based awards were intended to be granted at a price no less than the fair value per share of our common stock based on information known to us on the date of grant. In the absence of a public trading market for our common stock on each grant date we determined the fair value of our common stock using methodologies, approaches, and assumptions consistent with the American Institute of Certified Public Accountants Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation (the "AICPA Guide").

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Because our common stock was not publicly traded, the board of directors exercised significant judgment in determining the fair value of our common stock. Changes in judgments could have had a material impact on our results of operations.

For stock-based awards made prior to September 2014, our board of directors considered various objective and subjective factors, with input from management, to determine the value of our common stock, including:

- the hiring of key personnel;
- our financial condition as of such date;
- the status of our research and development efforts;
- the status of strategic transactions, including the acquisition of intellectual property and technology;
- the public trading price or private sale price of comparable companies;
- the lack of marketability of our common stock as a private company;
- risk factors relevant to our business;
- capital market conditions generally; and
- the prices of shares of our preferred stock sold to investors in arm's length transactions, and the rights, preferences and privileges of our preferred stock relative to our common stock.

For financial reporting purposes for the periods ending December 31, 2013 and December 31, 2014 on a retrospective basis, our management also considered estimated fair values determined on a retrospective basis by an independent third party valuation firm in accordance with the guidance provided by the AICPA Guide. For stock-based grants beginning in September 2014 until the date we became a public company, the fair value of our common stock was determined in connection with such grants by our board of directors based upon the factors described above and with consideration given to contemporaneous valuations of our common stock prepared by the same independent third party valuation firm in accordance with the guidance provided by the AICPA Guide.

The methods used by the independent third party valuation firm were:

- Option Pricing Method ("OPM"). The OPM treats the rights of the holders of preferred and common stock as equivalent to call options on the value of the enterprise above certain break points of value based upon the liquidation preferences of the holders of preferred stock, as well as their rights to participation and conversion. Under this method, the common stock has value only if the funds available for distribution to the stockholders exceed the value of the liquidation preference(s) at the time of the liquidity event. The OPM uses the Black-Scholes option pricing model. This model defines securities' fair values as functions of the current fair value of a company and uses assumptions, such as the anticipated timing of a potential liquidity event, the estimated applicable risk-free rate, and the estimated volatility of the equity securities.
- Probability-weighted Expected Return Method ("PWERM"). The PWERM considers various potential liquidity outcomes, including in our case an initial public offering, the sale of our company, dissolution and staying private, and assigns probabilities to each outcome to arrive at a weighted equity value.

The valuation of our common stock in 2013 was based on the OPM and subsequent valuations were based on the hybrid method of the OPM and the PWERM consistent with how such hybrid method is described in the AICPA Guide.

We recorded stock-based compensation expense of $31.9 million, $6.5 million and $0.1 million for the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013, respectively. As of December 31, 2015, there was $107.2 million of unrecognized stock-based compensation expense, of

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which $20.3 million is related to restricted stock grants and RSUs and $86.9 million is related to stock options. We expect to recognize these costs over a remaining weighted average period of 2.39 and 3.06 years, respectively. In future periods, we expect stock-based compensation expense related to employees, scientific founders, and director grants to increase, due in part to our existing unrecognized stock-based compensation expense, and as we grant additional stock-based awards to continue to attract and retain our employees and directors. We expect stock-based compensation expense related to grants to non-employee service providers to fluctuate, sometimes significantly, based on the fair value of our common stock at each reporting period. We expect the most significant such fluctuation through the third quarter of 2017 will be related to the grant to the former co-founding director who became a consultant upon his departure from the board of directors in 2014, due to the size of such grant, which was made at the founding of the company in 2013.

Success Payments

Fred Hutchinson Cancer Research Center

Under the terms of our collaboration agreement with FHCRC, we granted FHCRC the right to receive certain share-based success payments, payable in cash or publicly-traded equity at our discretion. These success payments are based on increases in the estimated fair value of our common stock, with such payments determined upon, and payable following, certain events (valuation measurement dates) during the term of the success payment agreement, in each case as described in more detail in the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” of this report. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending from $20.00 per share to $160.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending from $10 million at $20.00 per share to $375 million at $160.00 per share, payable if such threshold is reached. Any previous success payments made to FHCRC are credited against the success payment owed as of any valuation measurement date, so that FHCRC does not receive multiple success payments in connection with the same threshold. The success payments to FHCRC are not to exceed, in aggregate, $375 million, which would only be owed when the value of the common stock reaches $160.00 per share. In June 2014, we entered into an agreement with FHCRC in which certain indirect costs related to the collaboration projects conducted by FHCRC are creditable against any success payments, and we amended this agreement in December 2015. See Note 4 to our audited consolidated financial statements included in this report for a summary of the value of success payments required to be made at different price levels.

The success payment liability is initially accounted for under ASC 505-50, Equity-Based Payments to Non-Employees. The success payment liability is estimated at fair value at inception and at each subsequent balance sheet date and the expense is amortized using the accelerated attribution method over the term of the related collaboration agreement, which is initially six years. The success payment expense is classified as research and development because it is directly associated with our collaboration agreement with FHCRC. To determine the estimated fair value of the success payments we use a Monte Carlo simulation methodology which models the future movement of stock prices based on several key parameters combined with empirical knowledge of the process governing the behavior of the stock price. The following variables were incorporated in the calculation of the estimated fair value of the success payment liability as of December 31, 2015: estimated term of the success payments, stock price, expected volatility, risk-free interest rate, estimated number and timing of valuation measurement dates, and estimated indirect costs related to the collaboration projects conducted by FHCRC that are creditable against the success payments. Once the service period ends, which we expect will occur in 2019, the success payment liability will be accounted for under ASC 815, Derivatives and Hedging.

In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million. We elected to make the payment in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015.

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The estimated fair value of the total success payment obligation to FHCRC after giving effect to the success payments achieved in December 2015 was approximately $67.3 million as of December 31, 2015. With respect to the FHCRC success payment obligations, we recognized research and development expense of $44.3 million and $61.2 million in the years ended December 31, 2015 and 2014, respectively. The expense recorded in both periods represents the change in the estimated FHCRC success payment liability during such periods, twelve months of accrued expense, and the success payments achieved in 2015. The FHCRC success payment liabilities on the consolidated balance sheets as of December 31, 2015 and 2014 were $33.8 million and $61.2 million, respectively.

The assumptions used to calculate the fair value of the success payments are subject to a significant amount of judgment including the expected volatility, estimated term, and estimated number and timing of valuation measurement dates. A small change in the assumptions may have a relatively large change in the estimated valuation and associated liability and expense. For example, keeping all other variables constant, a hypothetical 10% increase in the stock price at December 31, 2015 from $43.97 per share to $48.37 per share would have increased the expense recorded in 2015 associated with the success payment liability by $4.9 million. A hypothetical 10% decrease in the stock price from $43.97 per share to $39.57 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $4.8 million. Further, keeping all other variables constant, a hypothetical 35% increase in the stock price at December 31, 2015 from $43.97 per share to $59.36 per share would have increased the expense recorded in 2015 associated with the success payment liability by $17.5 million. A hypothetical 35% decrease in the stock price from $43.97 per share to $28.58 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $16.0 million.

Memorial Sloan Kettering Cancer Center

Under the terms of our collaboration agreement with MSK we granted MSK the right to receive certain share-based success payments, payable in cash or publicly-traded equity at our discretion. These success payments are based on increases in the per share fair market value of our common stock, with such payments determined upon, and payable following, certain events (valuation measurement dates) during the term of the success payment agreement, in each case as described in more detail in the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” of this report. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending from $10 million at $40.00 per share to $150 million at $120.00 per share, payable if such threshold is reached. Any previous success payments made to MSK are credited against the success payment owed as of any valuation measurement date, so that MSK does not receive multiple success payments in connection with the same threshold. The success payments paid to MSK will not exceed, in aggregate, $150 million, which would only be owed when the value of the common stock reaches $120.00 per share. In October 2015, we entered into an agreement with MSK in which certain indirect costs related to certain clinical studies and research projects conducted by MSK are creditable against any success payments, and we amended this agreement in December 2015. See Note 4 to our audited consolidated financial statements included in this report for a summary of the value of success payments required to be made at different price levels.

The success payment liability is initially accounted for under ASC 505-50, Equity-Based Payments to Non-Employees. The success payment liability is estimated at fair value at inception and at each subsequent balance sheet date and the expense is amortized using the accelerated attribution method over the term of the related collaboration agreement, which is initially five years. The success payment expense is classified as research and development because it is directly associated with our collaboration agreement with MSK. To determine the estimated fair value of the success payments we use a Monte Carlo simulation methodology which models the future movement of stock prices based on several key parameters combined with empirical knowledge of the process governing the behavior of the stock price. The following variables were incorporated in the calculation of

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the estimated fair value of the success payment liability as of December 31, 2015: estimated term of the success payments, stock price, expected volatility, risk-free interest rate, estimated number and timing of valuation measurement dates, and estimated indirect costs related to certain clinical studies conducted by MSK that are creditable against the success payments. Once the service period ends, which we expect will occur in 2018, the success payment liability will be accounted for under ASC 815, Derivatives and Hedging.

In December 2015, a success payments to MSK was triggered in the amount of $10.0 million, less indirect cost offsets that will be determined at the time of payment in March 2016. The success payment obligation to MSK is required to be paid, in cash or shares of our common stock at our election, on March 18, 2016.

As of December 31, 2015 and 2014, the estimated fair value of the total success payment obligation to MSK after giving effect to the success payment achieved in December 2015, was approximately $48.9 million and $56.8 million, respectively. With respect to the MSK success payment obligations, we recognized research and development expense of $7.3 million and $23.7 million in the years ended December 31, 2015 and 2014, respectively. The expense recorded in both periods represents the change in the estimated MSK success payment liability during such periods, twelve months of accrued expense, and the success payment achieved in 2015. The MSK success payment liabilities on the consolidated balance sheets as of December 31, 2015 and 2014 were $31.0 million and $23.7 million, respectively.

The assumptions used to estimate the fair value of the success payment liability are subject to a significant amount of judgment including the expected volatility of our common stock, estimated term, and estimated number and timing of valuation measurement dates. A small change in our stock price or other assumptions may have a relatively large change in the estimated fair value of the success payment liability and associated expense. For example, keeping all other variables constant, a hypothetical 10% increase in our stock price at December 31, 2015 from $43.97 per share to $48.37 per share, would have increased the expense recorded in 2015 associated with the success payment liability by $2.8 million. A hypothetical 10% decrease in our stock price from $43.97 per share to $39.57 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $2.8 million. Further, keeping all other variables constant, a hypothetical 35% increase in our stock price at December 31, 2015 from $43.97 per share to $59.36 per share would have increased the expense recorded in 2015 associated with the success payment liability by $9.8 million. A hypothetical 35% decrease in our stock price from $43.97 per share to $28.58 per share would have decreased the expense recorded in 2015 associated with the success payment liability to zero resulting in a gain of $2.4 million.

Convertible Preferred Stock Option

We have raised capital through several rounds of private preferred stock financings, each of which included multiple closings. The Series A and Series A-2 convertible preferred stock purchase agreements each included subsequent closings under our control, as well as potential obligations to sell such shares upon the occurrence of certain events. We assessed our rights to control subsequent closings and our potential obligations under each agreement and determined that the financial instruments should be treated as a single unit of accounting under each of the Series A and Series A-2 agreements. These financial instruments were recognized at inception at fair value and classified outside of equity in accordance with ASC 480, Distinguishing Liabilities from Equity. The preferred stock options were revalued at each subsequent balance sheet date, with fair value changes recognized as increases or reductions to other income (expense), net in the statements of operations. We estimated the fair value of these instruments based on commonly used methods recommended by the AICPA and other accounting guidance. As of each valuation date, the fair value was estimated using the Black-Scholes option pricing model and assumptions that were based on the individual characteristics of the option on the valuation date, as well as assumptions for expected volatility, expected term, and risk-free interest rate. Determining the appropriate fair value model and calculating the fair value of the convertible preferred stock options required considerable judgment, and a small change in certain estimates used may lead to a relatively large change in the estimated fair value. Other expense of $10.7 million was recorded in the year ended December 31, 2014 related to changes in the fair value of the convertible preferred stock options. All of the Series A and Series A-2 convertible preferred stock converted to common stock in connection with our initial public offering.

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Deemed Dividends Upon Issuance of Convertible Preferred Stock, Non-Cash

We have raised capital through several rounds of private preferred stock financings, each of which included multiple closings. As of the dates of certain of the subsequent closings of the Series A and Series A-2 convertible preferred stock financings, the estimated fair value of the Series A and A-2 convertible preferred stock was greater than the issuance price per share of $4.00. For financial reporting purposes, the estimated fair value of the Series A and Series A-2 convertible preferred stock at these closing dates was derived taking into account numerous valuation factors, including, but not limited to, retrospective valuations performed by independent third party valuation firms, our stage of development, capital resources, current business plans, likelihood of achieving a liquidity event, and the rights, preferences, and privileges of our Series A and Series A-2 convertible preferred stock compared to the rights, preferences and privileges of our other outstanding equity securities. The differences between the estimated fair value of the Series A and Series A-2 convertible preferred stock shares as of the respective closing dates and the issuance prices of the shares were deemed to be equivalent to preferred stock dividends. As a result, we recorded deemed dividends of $67.5 million in the year ended December 31, 2014. The deemed dividends were recorded as an increase in convertible preferred stock of $67.5 million, a decrease in additional paid-in capital of $16.4 million, and an increase in accumulated deficit of $51.1 million. The deemed dividends increased the net loss attributable to common stockholders by $67.5 million in the calculation of basic and diluted net loss per common share for the year ended December 31, 2014. All of the Series A and Series A-2 convertible preferred stock converted to common stock in connection with our initial public offering.

Components of Operating Results

Revenue

Our revenues have been primarily derived from collaboration and license agreements.

Ongoing collaboration revenue is generated from our collaboration with Celgene. The terms of this arrangement contain multiple deliverables, which include (1) access to certain of our technology through a non-exclusive, worldwide, royalty-free right and license to conduct certain activities under the collaboration and (2) participation on various collaboration committees. We recognize revenue from upfront payments ratably over the term of our estimated period of performance under the arrangement. In addition to receiving upfront payments, we may also be entitled to option exercise fees.

We expect that any revenue we generate will fluctuate from period to period as a result of the timing and amount of opt-in payments and other payments from our collaboration and license agreements.

Research and Development Expenses

Research and development expenses represent costs incurred by us for the discovery, development, and manufacture of our product candidates and include costs to acquire technology complimentary to our own, external research and development expenses incurred under arrangements with third parties, such as contract research organizations, CMOs, academic and non- profit institutions and consultants, salaries and personnel-related costs, including non-cash stock-based compensation, the estimated fair value of the liability attributable to the elapsed service period as of the balance sheet date associated with our success payments to FHCRC and MSK, changes in the estimated fair value of our contingent consideration liabilities, and other expenses, which include direct and allocated expenses for laboratory, facilities, and other costs.

We use our employee and infrastructure resources across multiple research and development programs directed toward developing our cell-based platform and for identifying and developing product candidates. We manage certain activities such as contract research, clinical trial operations, and manufacture of product candidates through our partner institutions or other third-party vendors. We track our significant external costs by product

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candidate. Due to the number of ongoing projects and our ability to use resources across several projects, we do not record or maintain information regarding the indirect operating costs incurred for our research and development programs on a program-specific basis.

Our research and development expenses by project were as follows for the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013 (in thousands):

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
Project-specific external costs:			
JCAR015	$ 11,271	$ 4,237	$ 7,706
JCAR014	5,343	4,364	3,857
JCAR017	4,485	225	—
Platform development	6,088	3,310	—
CD19 general	1,799	1,131	—
Early development	12,955	5,546	—
Success payment expense related to FHCRC collaboration agreement	44,262	61,362	
Success payment expense related to MSK collaboration agreement	7,296	23,702	
Upfront costs to acquire technology	30,810	84,087	33,400
Unallocated internal and external research and development costs (1)	80,851	16,547	1,282
Total research and development expenses	$205,160	$204,511	$ 46,245

(1) Unallocated internal and external research and development costs include salaries and personnel-related costs, including non-cash stock-based compensation, for our personnel in research, clinical development, process development and manufacturing, regulatory and other research and development functions, allocated facilities and other overhead costs, lab supplies and other research and development costs not specific to a project.

Research and development activities account for a significant portion of our operating expenses. Excluding amounts attributable to changes in the estimated fair value of the success payment and contingent consideration liabilities and upfront fees to acquire technology, we expect our research and development expenses to increase over the next several years as we implement our business strategy which includes conducting existing and new clinical trials, manufacturing clinical trial and preclinical study materials, expanding our research and development and process development efforts, seeking regulatory approvals for our product candidates that successfully complete clinical trials, and costs associated with hiring additional personnel to support our research and development efforts. Research and development expense related to our success payments is unpredictable and may vary significantly from quarter to quarter and year to year due to changes in our stock price or other assumptions used in the calculation. A significant decline in the estimated value of the success payment liability may result in a gain and possibly net income during the period. Amounts associated with the change in the estimated fair value of the contingent consideration liabilities also may vary significantly from quarter to quarter and year to year due to changes in our assumptions used in the calculation. In addition, we expect to incur research and development expense for acquisition of technology in the future, but the timing and amount of those expenses cannot be estimated with reliability and may also fluctuate from quarter to quarter and year to year.

General and Administrative Expenses

General and administrative expenses consist of salaries and personnel-related costs, including non-cash stock-based compensation, for our personnel in executive, legal, finance and accounting, and other administrative functions, legal costs other than litigation costs associated with the Penn litigation, transaction costs associated

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with acquisitions and collaboration and licensing agreements, as well as fees paid for accounting and tax services, consulting fees and facility costs not otherwise included in research and development expenses. Legal costs include general corporate legal fees and patent costs, and legal expense associated with inter partes review proceedings at the USPTO.

We anticipate that our general and administrative expenses will increase in the future to support our continued research and development activities, potential commercialization of our product candidates, future business development opportunities, and the increased costs of operating as a public company. These increases will likely include costs related to outside consultants, attorneys, and accountants, among other expenses.

Litigation Expense

Litigation expense includes legal expense we have directly incurred with respect to the Penn litigation, as well as expenses we were required to reimburse to St. Jude with respect to such litigation. In April 2015 the Penn litigation was settled, in connection with which Novartis paid us an initial license fee of $12.3 million. Under a separate agreement with St. Jude, we incurred litigation expense of $5.3 million associated with the reimbursement of litigation expenses to St. Jude. See Note 4, Collaboration and License Agreements, in the notes to the consolidated financial statements included elsewhere in this report.

Results of Operations

Comparison of the years ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014 (in thousands):

	Year Ended December 31,	
	2015	2014
Revenue	$ 18,215	$ —
Operating expenses:		
Research and development	205,160	204,511
General and administrative	51,130	19,529
Litigation	6,025	8,718
Total operating expenses	262,315	232,758
Loss from operations	(244,100)	(232,758)
Interest income, net	1,730	69
Other income (expenses), net	234	(10,718)
Loss before income taxes	(242,136)	(243,407)
Benefit for income taxes	2,760	—
Net loss	$(239,376)	$(243,407)
Net loss attributable to common stockholders:		
Net loss	(239,376)	(243,407)
Deemed dividends upon issuance of convertible preferred stock, non-cash	—	(67,464)
Net loss attributable to common stockholders	$(239,376)	$(310,871)

Revenue

Revenue was $18.2 million in the year ended December 31, 2015, which includes $5.1 million in revenue related to the Celgene collaboration. Also included in revenue in the year ended December 31, 2015 is $12.3 million received in connection with the Novartis sublicense agreement.

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Operating Expenses

Research and Development Expenses. Research and development expenses were $205.2 million for the year ended December 31, 2015, compared to $204.5 million for the year ended December 31, 2014. Excluding expense related to our success payment liability, research and development expenses were $153.6 million and $119.6 million for the years ended December 31, 2015 and 2014, respectively. The increase of $34.0 million was primarily due to an increase of $71.9 million in expenses attributable to efforts to expand the company's overall research and development capabilities and advance programs at our founding institutions, which expenses include personnel costs, manufacturing costs in support of our clinical trials, lab supplies, clinical and research costs under our collaboration agreements and in support of our company-sponsored clinical trials, costs incurred by our German subsidiary, consulting, and facilities and allocated overhead costs and an increase of $14.2 million in non-cash stock-based compensation, of which $4.6 million is related to a former co-founding director who became a consultant upon his departure from the board of directors. These increases were partially offset by lower costs to acquire technology of $51.0 million. In 2015 we incurred upfront fees of $30.8 million in connection with technology acquired from the Editas and Fate Therapeutics transactions, and in 2014 we incurred a non-cash upfront fee of $64.1 million and a cash upfront fee of $20.0 million to acquire technology related to JCAR018.

Expense related to our success payment liability for the years ended December 31, 2015 and 2014 was $51.6 million and $84.9 million, respectively. The decline was primarily due to a decrease in our stock price at December 31, 2015 compared to December 31, 2014.

General and Administrative Expenses. General and administrative expenses were $51.1 million for the year ended December 31, 2015, compared to $19.5 million for the year ended December 31, 2014. The increase of $31.6 million was primarily due to an increase of $11.3 million in non-cash stock-based compensation expense, expenses related to the Celgene, Stage, X-Body, and other business development transactions of $9.7 million, increased costs of $4.9 million incurred to support the business including patent and corporate legal fees, a $3.6 million increase in personnel expenses primarily related to increased headcount, and an increase of $2.1 million associated with expenses incurred related to being a public company.

Litigation Expense. Litigation expense was $6.0 million for the year ended December 31, 2015, compared to $8.7 million for the year ended December 31, 2014. Litigation costs in both periods consisted of costs we incurred directly in connection with the Penn litigation and costs we were required to reimburse to St. Jude in connection with such litigation. In April 2015 the Penn litigation was settled. See Note 4, Collaboration and License Agreements, to the consolidated financial statements included elsewhere in this report.

Interest Income, Net. Interest income, net for the year ended December 31, 2015 was $1.7 million compared to $0.1 million for the year ended December 31, 2014. The increase of $1.6 million was due to our increased marketable securities balance and the associated interest earned, that was offset by interest expense associated with the accounting for the build-to-suit lease of our manufacturing facility.

Other Income (Expense). Other income was $0.2 million for the year ended December 31, 2015 and consisted of the gain on our original investment in Stage recorded in connection with the acquisition of Stage in May 2015. Other expense was $10.7 million for the year ended December 31, 2014 and consisted of changes in the fair value of our Series A and Series A-2 convertible preferred stock option, which were exercised during 2014.

Benefit for Income Taxes. The benefit for income taxes was $2.8 million for the year ended December 31, 2015 compared to zero for the year ended December 31, 2014. Of the $2.8 million income tax benefit recognized for the year ended December 31, 2015, $1.7 million relates to our Germany subsidiary's net loss incurred in the period from May 11, 2015 to December 31, 2015. The remaining $1.1 million of income tax benefit relates to the release of valuation allowance on the U.S. deferred tax assets as a result of the acquisition of X-Body.

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Deemed Dividends Upon Issuance of Convertible Preferred Stock, Non-Cash. We recorded deemed dividends of $67.5 million in the year ended December 31, 2014 related to the amount by which the fair value of the convertible preferred stock we issued during the period exceeded the actual cash proceeds from the sale and issuance of such convertible preferred stock. The deemed dividends increased convertible preferred stock by $67.5 million, reduced additional paid-in capital by $16.4 million, and increased accumulated deficit by $51.1 million. The deemed dividends increased the net loss attributable to common stockholders by $67.5 million in the calculation of basic and diluted net loss per common share for the year ended December 31, 2014.

Comparison of the year ended December 31, 2014 to the period from August 5, 2013 to December 31, 2013

The following table summarizes our results of operations for the year ended December 31, 2014 and the period from August 5, 2013 to December 31, 2013 (in thousands):

	Year Ended December 31, 2014	Period From August 5, 2013 to December 31, 2013
Revenue	$ —	$ —
Operating expenses:		
Research and development	204,511	46,245
General and administrative	19,529	4,238
Litigation	8,718	1,195
Total operating expenses	232,758	51,678
Loss from operations	(232,758)	(51,678)
Interest income, net	69	—
Other (expense)	(10,718)	(142)
Net loss	$ (243,407)	$ (51,820)
Net loss attributable to common stockholders:		
Net loss	(243,407)	(51,820)
Deemed dividends upon issuance of convertible preferred stock, non-cash	(67,464)	—
Net loss attributable to common stockholders	$ (310,871)	$ (51,820)

Operating Expenses

Research and Development Expenses. Research and development expenses in the year ended December 31, 2014 were $204.5 million consisting primarily of:

- $84.9 million associated with the portion of the estimated success payment liability to FHCRC and MSK attributable to the elapsed service period;
- $84.1 million in upfront fees to acquire technology related to JCAR018, a CD22-directed product candidate, $64.1 million of which was paid through the issuance of stock (calculated by multiplying the number of shares issued, or 1,602,564 shares, by the fair value of our common stock on the date of issuance of December 24, 2014), and $20 million was paid in cash;
- $30.1 million of costs to expand the company's overall research and development capabilities and advance programs at our founding institutions including clinical and research costs under our collaboration agreements, personnel costs, contract research, manufacturing costs in support of our clinical trials, initial fees under a development agreement with a third party, facilities and allocated overhead costs, consulting costs, and lab supplies; and

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- $2.9 million of non-cash stock-based compensation, of which $2.5 million is related to a former co-founding director who became a consultant upon his departure from the board of directors.

Research and development expenses in the period from August 5, 2013 to December 31, 2013 were $46.2 million consisting primarily of $44.5 million in upfront fees to acquire technology, $0.5 million in clinical development costs, and $0.5 million in personnel-related costs. Included in the $44.5 million in upfront fees to acquire technology is $25.0 million, $0.3 million and $6.9 million in cash payments to St. Jude, FHCRC, and MSK, respectively, $9.8 million of non-cash stock-based expense associated with stock issuances to ZetaRx, FHCRC, and MSK, and $2.5 million in other expenses in connection with the ZetaRx transaction. The cash payment to St. Jude and the cash payment and non-cash stock-based expense associated with the stock issuance to FHCRC were made in connection with our JCAR014 program and the cash payments and non-cash stock-based expense associated with the stock issuance to MSK were related to our JCAR015 program.

General and Administrative Expenses. General and administrative expenses in the year ended December 31, 2014 were $19.5 million consisting primarily of personnel related costs of $10.2 million, including $3.5 million of non-cash stock-based compensation, $4.3 million of general corporate legal fees and patent costs, $2.8 million of consulting fees to support our operations, and $0.9 million of facilities and allocated overhead costs.

General and administrative expense for the period from August 5, 2013 to December 31, 2013 consisted primarily of $2.8 million in patent and corporate legal costs, $0.4 million of personnel-related costs, and $0.4 million of non-cash stock-based compensation expense.

Litigation Expense. Litigation expense was $8.7 million for the year ended December 31, 2014, compared to $1.2 million for the period from August 5, 2013 to December 31, 2013. Litigation costs in both periods consisted of costs we incurred directly in connection with the Penn litigation and costs we were required to reimburse to St. Jude in connection with such litigation. In April 2015 the Penn litigation was settled. See Note 4, Collaboration and License Agreements, to the consolidated financial statements included elsewhere in this report.

Other Income (Expense). Other expense was $10.7 million for the year ended December 31, 2014 and consists of changes in the fair value of our Series A and Series A-2 convertible preferred stock options.

Deemed Dividends Upon Issuance of Convertible Preferred Stock, Non-Cash. We recorded deemed dividends of $67.5 million in the year ended December 31, 2014 related to the amount by which the fair value of the convertible preferred stock we issued during the period exceeded the actual cash proceeds from the sale and issuance of such convertible preferred stock. The deemed dividends increased convertible preferred stock by $67.5 million, reduced additional paid-in capital by $16.4 million, and increased accumulated deficit by $51.1 million. The deemed dividends increased the net loss attributable to common stockholders by $67.5 million in the calculation of basic and diluted net loss per common share for the year ended December 31, 2014.

Liquidity and Capital Resources

Sources and Uses of Liquidity

As of December 31, 2015, we had $1.2 billion in cash, cash equivalents, and marketable securities. Prior to our entry into the Celgene collaboration, we raised an aggregate of approximately $618.0 million in gross proceeds, through our IPO and private placements of our convertible preferred stock which we have used to fund our operations. As a result of our entry into the collaboration with Celgene and our initial sale of stock to Celgene, we received $1.0 billion in cash from Celgene in August 2015. Celgene also has the right to purchase additional shares of our common stock, including annual “top-up” rights as described under “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” elsewhere in this report. If exercised, these purchases will provide us with additional funding for our operations. This funding decreases our need for additional near term funding, although we may still need to raise additional capital in the future. We believe that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our operations for at least the next 12 months.

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We expect to continue to incur substantial additional losses in the future as we expand our research and development activities and build our commercial infrastructure. Until such time, if ever, as we can generate substantial product revenue, and if funding from Celgene is not sufficient for our operations, we may be required to finance our cash needs through a combination of equity or debt financings. We currently have no credit facility or committed sources of capital. To the extent that we raise additional capital through the future sale of equity or debt, the ownership interests of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through the issuance of debt securities, these securities could contain covenants that would restrict our operations. We may require additional capital beyond our currently anticipated amounts. Additional capital may not be available on reasonable terms, or at all. If we raise additional funds through additional collaboration arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Cash Flows

The following table summarizes our cash flows for the periods set forth below (in thousands):

	Year Ended December 31,		Period from August 5, 2013 to December 31,
	2015	2014	2013
Net cash provided by (used in):			
Operating activities	$ 7,325	$ (82,545)	$ (30,510)
Investing activities	(962,066)	(124,785)	(42)
Financing activities	851,238	527,332	66,518
Effect of exchange rate changes on cash and cash equivalents	(67)	—	—
Net (decrease) increae in cash and cash equivalents	$(103,570)	$ 320,002	$ 35,966

Operating Activities

The increase in cash provided by operating activities for the year ended December 31, 2015 of $89.9 million compared to the year ended December 31, 2014 was primarily due to cash received from Celgene in connection with the Celgene collaboration agreement of $150.2 million, offset by an increase in cash payments to expand our overall research and development capabilities and acquire technology.

Net cash used in operating activities for the years ended December 31, 2015 and 2014 included payments of $30.8 million and $26.9 million, respectively, to acquire technology. Net cash used in operating activities for the period from August 5, 2013 to December 31, 2013 included a $25.0 million payment to acquire technology.

Investing Activities

The increase in cash used in investing activities for the year ended December 31, 2015 of $837.3 million compared to the year ended December 31, 2014 was primarily due to the purchase of marketable securities of $730.6 million; cash paid, net of cash acquired, to acquire Stage and X-Body of $77.7 million; an investment in Fate Therapeutics of $7.2 million; and an increase in property and equipment purchases primarily related to the build out of our manufacturing facility and purchase of lab equipment of $25.2 million. The increase in cash used in investing activities for the year ended December 31, 2015 was offset by the investment in Stage of $3.5 million in 2014.

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Financing Activities

The increase in net cash provided by financing activities in the year ended December 31, 2015 of $323.9 million compared to the year ended December 31, 2014 was primarily due to cash received in connection with the sale of 9,137,672 shares of our common stock to Celgene, resulting in proceeds of $849.8 million, and proceeds from the exercise of stock options, offset by net proceeds of $527.3 million in 2014 from our IPO and from the issuance of our convertible preferred stock.

Net cash provided by financing activities in the period from August 5, 2013 to December 31, 2013 of $66.5 million was the result of net proceeds from the issuance of our convertible preferred stock.

Off-Balance Sheet Arrangements

As of December 31, 2015, we did not have any off-balance sheet arrangements or any holdings in variable interest entities.

Contractual Obligations

Our contractual obligations as of December 31, 2015 were as follows:

	Total	Less Than 1 Year	1-3 Years	4-5 Years	More Than 5 Years
Operating lease obligations (1)	$ 83,613	$ 3,890	$26,536	$22,571	$ 30,616
Collaboration funding (2)	26,479	12,838	12,328	1,313	—
Total contractual obligations	$110,092	$ 16,728	$38,864	$23,884	$ 30,616

(1) Represents future minimum lease payments under our operating leases as of December 31, 2015. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

(2) Represents non-cancellable fees due in connection with our collaboration agreements as of December 31, 2015.

Other than as disclosed in the table above, the payment obligations under our license and collaboration agreements as of December 31, 2015 are contingent upon future events such as our achievement of specified development, regulatory, and commercial milestones, or royalties on net product sales. See the section captioned “Licenses and Third-Party Collaborations” in Part I—Item 1—“Business” of this report for more information about these payment obligations. As described above under the caption “Critical Accounting Policies and Significant Judgments and Estimates—Success Payments,” we are also obligated to make up to $300.0 million in success payments to FHCRC and up to $140.0 million in success payments to MSK based on increases in the estimated fair value of our common stock. Both of these obligations are payable in cash or stock, at our election. In December 2015, success payment obligations to FHCRC were triggered in the amount of $75.0 million less indirect cost offsets of $3.3 million and to MSK of $10.0 million less indirect cost offsets that will be determined at the time of payment in March 2016. We elected to make the payment to FHCRC in shares of our common stock, and thereby issued 1,601,085 shares of our common stock to FHCRC in December 2015. The success payment obligation to MSK is required to be paid, in cash or shares of our common stock at our election, on March 18, 2016. As of December 31, 2015, we were unable to estimate the timing or likelihood of achieving the milestones or generating future product sales and therefore, any related payments are not included in the table above.

Recent Accounting Pronouncements

In November 2015, the FASB issued Accounting Standards Update (“ASU”) No. 2015-17, Balance Sheet Classification of Deferred Taxes (Topic 740), intended to improve how deferred taxes are classified on

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organizations' balance sheets. The new guidance eliminates the current requirement to present deferred tax liabilities and assets as current and noncurrent in a classified balance sheet. Under the new guidance, companies are required to classify all deferred tax assets and liabilities as noncurrent. ASU No. 2015-17 is effective for periods beginning after December 15, 2015, and interim periods within those fiscal years, with early adoption permitted. We early adopted this standard for the year ended December 31, 2015. The adoption of this standard did not have a material impact on our financial position, results of operation or related financial statement disclosures.

In 2014, the FASB issued new accounting guidance related to revenue recognition. This new standard will replace all current GAAP guidance on this topic and establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. This guidance can be applied either retrospectively to each period presented or as a cumulative-effect adjustment as of the date of adoption. In July 2015, the FASB voted to defer the effective date to January 1, 2018 with early adoption permitted beginning January 1, 2017. We are evaluating the method we will use to adopt the new standard and the impact on our consolidated financial statements.

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ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business, primarily related to interest rate sensitivities and the volatility of our stock price.

Interest Rate Sensitivity

As of December 31, 2015, we had $963.9 million in marketable securities, largely composed of investment grade short- to intermediate-term fixed income securities. The primary objective of our investment activities is to preserve capital to fund our operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of investments in a variety of securities of high credit quality.

Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. The magnitude of this risk has increased over 2015 due to the increase in our marketable securities balance following our receipt of $1.0 billion in funding from Celgene in August 2015. A hypothetical 10% change in interest rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Stock Price Sensitivity

We agreed to make success payments to FHCRC and MSK based on increases in the per share fair market value of our common stock during the term of the agreements payable in cash or publicly-traded equity at our discretion.

As of December 31, 2015, the estimated fair value of the success payment obligations was approximately $116.2 million. The Company recognized research and development expense of $51.6 million in the year ended December 31, 2015, with respect to the success payment obligations. The success payment liabilities on the consolidated balance sheet as of December 31, 2015 were $64.8 million.

The assumptions used to calculate the fair value of the success payments are subject to a significant amount of judgment including the expected volatility, estimated term, and estimated number and timing of valuation measurement dates. A small change in the assumptions may have a relatively large change in the estimated valuation and associated liability and expense. For example, keeping all other variables constant, a hypothetical 10% increase in the stock price at December 31, 2015 from $43.97 per share to $48.37 per share would have increased the expense recorded in 2015 associated with the success payment liability by $7.7 million. A hypothetical 10% decrease in the stock price from $43.97 per share to $39.57 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $7.6 million. Further, keeping all other variables constant, a hypothetical 35% increase in the stock price at December 31, 2015 from $43.97 per share to $59.36 per share would have increased the expense recorded in 2015 associated with the success payment liability by $27.3 million. A hypothetical 35% decrease in the stock price from $43.97 per share to $28.58 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $25.7 million.

Foreign Currency Sensitivity

The majority of our transactions occur in U.S. dollars. However, we do have certain transactions and future potential milestones, including potential contingent consideration payments pursuant to the terms of our Stage acquisition, that are denominated in currencies other than the U.S. dollar, primarily the Euro, and we therefore are subject to foreign exchange risk. Additionally, our subsidiary Juno Therapeutics GmbH, which we acquired in May 2015, operates with the Euro as its functional currency. The fluctuation in the value of the U.S. dollar against the Euro affects the reported amounts of revenues, expenses, assets and liabilities. As we expand our international operations, our exposure to exchange rate fluctuations will increase. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

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ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

JUNO THERAPEUTICS, INC.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders
Juno Therapeutics, Inc.

We have audited the accompanying consolidated balance sheets of Juno Therapeutics, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for the years ended December 31, 2015 and 2014 and the period from August 5, 2013 to December 31, 2013. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Juno Therapeutics, Inc. at December 31, 2015 and 2014, and the consolidated results of its operations and its cash flows for the years ended December 31, 2015 and 2014 and the period from August 5, 2013 to December 31, 2013, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Juno Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 29, 2016 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Seattle Washington
February 29, 2016

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Juno Therapeutics, Inc.
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31, 2015	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 252,398	$ 355,968
Marketable securities	691,013	79,672
Prepaid expenses and other current assets	8,428	3,595
Total current assets	951,839	439,235
Property and equipment, net	42,086	4,018
Long-term marketable securities	272,888	38,411
Goodwill	122,092	—
Intangible assets	50,177	—
Other assets	6,046	7,499
Total assets	$1,445,128	$ 489,163
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,248	$ 1,096
Accrued liabilities and other current liabilities	33,376	14,577
Success payment liabilities	64,829	84,920
Contingent consideration	1,905	—
Deferred revenue	15,370	—
Total current liabilities	119,728	100,593
Build-to-suit lease obligation, less current portion	9,294	—
Contingent consideration obligations, less current portion	35,361	—
Deferred revenue, less current portion	129,831	—
Deferred tax liabilities	8,946	—
Other long-term liabilities	435	38
Commitments and contingencies (Note 14)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized at December 31, 2015 and December 31, 2014; 0 shares issued and outstanding at December 31, 2015 and December 31, 2014	—	—
Common stock, $0.0001 par value, 495,000,000 shares authorized at December 31, 2015 and December 31, 2014; 97,247,058 and 82,073,647 shares issued and outstanding at December 31, 2015 and December 31, 2014, respectively	10	8
Additional paid-in-capital	1,733,263	734,895
Accumulated other comprehensive loss	(6,083)	(90)
Accumulated deficit	(585,657)	(346,281)
Total stockholders' equity	1,141,533	388,532
Total liabilities and stockholders' equity	$1,445,128	$ 489,163

See accompanying notes.

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Juno Therapeutics, Inc.
Consolidated Statements of Operations
(In thousands, except share and per share amounts)

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
Revenue	$ 18,215	$ —	$ —
Operating expenses:			
Research and development	205,160	204,511	46,245
General and administrative	51,130	19,529	4,238
Litigation	6,025	8,718	1,195
Total operating expenses	262,315	232,758	51,678
Loss from operations	(244,100)	(232,758)	(51,678)
Interest income, net	1,730	69	—
Other income (expenses), net	234	(10,718)	(142)
Loss before income taxes	(242,136)	(243,407)	(51,820)
Benefit for income taxes	2,760	—	—
Net loss	$ (239,376)	$ (243,407)	$ (51,820)
Net loss attributable to common stockholders:			
Net loss	$ (239,376)	$ (243,407)	$ (51,820)
Deemed dividend upon issuance of convertible preferred stock, non-cash	—	(67,464)	—
Net loss attributable to common stockholders	$ (239,376)	$ (310,871)	$ (51,820)
Net loss per share attributable to common stockholders, basic and diluted	$ (2.72)	$ (36.82)	$ (14.16)
Weighted average common shares outstanding, basic and diluted	88,145,424	8,442,947	3,658,687

See accompanying notes.

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Juno Therapeutics, Inc.
Consolidated Statements of Comprehensive Loss
(In thousands)

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
Net loss	$(239,376)	$(243,407)	$ (51,820)
Other comprehensive loss:			
Unrealized loss on marketable securities	(5,388)	(90)	—
Foreign currency translation	(605)	—	—
Total other comprehensive loss	(5,993)	(90)	—
Comprehensive loss	$(245,369)	$(243,497)	$ (51,820)

See accompanying notes.

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Juno Therapeutics, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
OPERATING ACTIVITIES			
Net loss	$ (239,376)	$(243,407)	$ (51,820)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	6,041	395	2
Stock-based compensation	31,941	6,504	125
Non-cash expense in connection with equity issuance	—	64,086	10,235
Loss from remeasurement of fair value of convertible preferred stock options	—	10,718	142
Deferred income taxes	(1,660)	—	—
Deferred tax benefit recorded in connection with acquisition	(1,100)	—	—
Change in fair value of success payment liabilities	51,557	84,920	—
Change in fair value of contingent consideration obligation	78	—	—
Gain on initial investment in Stage	(227)	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(6,855)	(7,380)	(258)
Accounts payable, accrued liabilities and other liabilities	22,144	1,619	11,064
Deferred revenue	144,782	—	—
Net cash provided by (used in) operating activities	7,325	(82,545)	(30,510)
INVESTING ACTIVITIES			
Purchases of marketable securities	(1,315,597)	(118,372)	—
Sales and maturities of marketable securities	459,381	—	—
Acquisitions, net of cash acquired	(77,666)	—	—
Purchase of cost-method investment	—	(3,455)	—
Purchase of property and equipment	(28,184)	(2,958)	(42)
Net cash used in investing activities	(962,066)	(124,785)	(42)
FINANCING ACTIVITIES			
Proceeds from issuance of common stock, net of (payments) of issuance costs	(1,683)	281,383	12
Proceeds from issuance of convertible preferred stock	—	245,949	66,506
Proceeds from issuance of common stock to strategic partner	849,804	—	—
Proceeds from exercise of stock options	3,366	—	—
Payments of build-to-suit lease obligation	(249)	—	—
Net cash provided by financing activities	851,238	527,332	66,518
Effect of exchange rate changes on cash and cash equivalents	(67)	—	—
Net (decrease) increase in cash and cash equivalents	(103,570)	320,002	35,966
Cash and cash equivalents at beginning of period	355,968	35,966	—
Cash and cash equivalents at end of period	$ 252,398	$ 355,968	$ 35,966
SUPPLEMENTAL CASH FLOW INFORMATION			
Purchases of property and equipment included in accounts payable and accrued liabilities	$ 1,900	$ 1,216	$ —
Amounts capitalized under build-to-suit leases	$ 9,910	$ —	$ —
Issuance of common stock for acquisitions	$ 41,611	$ —	$ —
Issuance of common stock for success payments	$ 71,648	$ —	$ —
Fair value of convertible preferred stock option at issuance	$ —	$ (6,889)	$ (3,971)
Deferred offering costs incurred but unpaid	$ —	$ 1,683	$ —

See accompanying notes.

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Juno Therapeutics, Inc.
Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)
(In thousands, except share amounts)

	Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance as of August 5, 2013	—	$ —	—	$ —	$ —	$ —	$ —	$ —
Issuance of common stock	—	—	1,460,413	—	387	—	—	387
Issuance of Series A-1 convertible preferred stock as part of acquisition, non-cash	2,250,000	4,860	—	—	—	—	—	—
Issuance of Series A convertible preferred stock as part of acquisition, non-cash	263,747	1,055	—	—	—	—	—	—
Issuance of common stock as part of acquisition, non-cash	—	—	225,000	—	18	—	—	18
Issuance of Series A convertible preferred stock, net of $289 in issuance costs	16,666,917	66,668	—	—	(289)	—	—	(289)
Fair value of convertible preferred stock option at issuance	—	—	—	—	3,971	—	—	3,971
Issuance of common stock to strategic partners, non-cash	—	—	3,774,998	1	3,925	—	—	3,926
Stock-based compensation expense	—	—	918,859	—	125	—	—	125
Net loss	—	—	—	—	—	—	(51,820)	(51,820)
Balance as of December 31, 2013	19,180,664	72,583	6,379,270	1	8,137	—	(51,820)	(43,682)
Issuance of Series A-2 convertible preferred stock, net of $212 in issuance costs	23,484,072	93,936	—	—	(212)	—	—	(212)
Issuance of Series A convertible preferred stock	5,000,000	20,000	—	—	—	—	—	—
Issuance of Series B convertible preferred stock, net of $1,487 in issuance costs	12,244,661	133,712	—	—	(1,487)	—	—	(1,487)
Fair value of Series A-2 convertible preferred stock options at issuance	—	—	—	—	6,889	—	—	6,889
Deemed dividends on issuance of Series A-2 convertible preferred stock, non-cash	—	45,651	—	—	—	—	(45,651)	(45,651)
Deemed dividends on issuance of Series A convertible preferred stock, non-cash	—	21,813	—	—	(16,410)	—	(5,403)	(21,813)
Conversion of preferred stock into common stock	(59,909,397)	(387,695)	59,909,397	6	387,689	—	—	387,695
Issuance of stock in initial public offering, net of $24,533 in offering costs	—	—	12,676,354	1	279,699	—	—	279,700
Issuance of common stock to strategic partner, non-cash	—	—	1,602,564	—	64,086	—	—	64,086
Stock-based compensation expense	—	—	1,506,062		6,504	—	—	6,504
Other comprehensive loss, net	—	—	—	—	—	(90)	—	(90)
Net loss	—	—	—	—	—	—	(243,407)	(243,407)
Balance as of December 31, 2014	—	—	82,073,647	8	734,895	(90)	(346,281)	388,532
Issuance of common stock for acquisition, non-cash	—	—	852,713	—	41,611	—	—	41,611
Issuance of common stock to strategic partner	—	—	9,137,672	1	849,803	—	—	849,804
Issuance of common stock for success payments	—	—	1,601,085	—	71,648	—	—	71,648
Issuance of common stock in connection with the Company's equity award programs	—	—	3,581,941	—	3,366	—	—	3,366
Stock-based compensation expense	—	—	—	1	31,940	—	—	31,941
Other comprehensive loss, net	—	—	—	—	—	(5,993)	—	(5,993)
Net loss	—	—	—	—	—	—	(239,376)	(239,376)
Balance as of December 31, 2015	—	$ —	97,247,058	$ 10	$1,733,263	$ (6,083)	$ (585,657)	$ 1,141,533

See accompanying notes.

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Juno Therapeutics, Inc.
Notes to Consolidated Financial Statements

1. Organization

Juno Therapeutics, Inc. (the "Company") was incorporated in Delaware on August 5, 2013 as FC Therapeutics, Inc., and changed its name to Juno Therapeutics, Inc. on October 23, 2013. The Company is building a fully-integrated biopharmaceutical company focused on re-engaging the body's immune system to revolutionize the treatment of cancer. Founded on the vision that the use of human cells as therapeutic entities will drive one of the next important phases in medicine, the Company is developing cell-based cancer immunotherapies based on its chimeric antigen receptor ("CAR") and high-affinity T cell receptor ("TCR") technologies to genetically engineer T cells to recognize and kill cancer cells.

In May 2015, the Company acquired all the remaining ownership interests in Stage Cell Therapeutics GmbH ("Stage") not already held by it. See Note 3, Acquisitions. As a result of the acquisition, Stage has become a wholly owned subsidiary of the Company and the results of Stage have been consolidated with the Company's results since the date of the acquisition. Stage has operations in Göttingen and Munich, Germany and its operations are focused on developing technology platforms, including novel reagents and automation technologies that enable the development and production of cell therapeutics. Stage has been renamed as Juno Therapeutics GmbH ("Juno GmbH").

In June 2015, the Company acquired X-Body, Inc. ("X-Body"). See Note 3, Acquisitions. As a result of the acquisition, X-Body has become a wholly owned subsidiary of the Company and the results of X-Body have been consolidated with the Company's results since the date of the acquisition. X-Body has operations in Waltham, Massachusetts and its operations are focused on the discovery of human monoclonal antibodies and discovery of TCR binding domains.

The Company is subject to a number of risks similar to other biopharmaceutical companies in the early stage, including, but not limited to, possible failure of preclinical testing or clinical trials, the need to obtain marketing approval for its product candidates, competitors developing new technological innovations, the need to successfully commercialize and gain market acceptance of the Company's products, protection of proprietary technology, and the need to obtain adequate additional funding. If the Company, or any commercialization partner for the Company's product candidates, does not successfully commercialize any of the Company's product candidates, the Company will not be able to generate product revenue or achieve profitability. As of December 31, 2015, the Company had an accumulated deficit of $585.7 million.

2. Significant Accounting Policies

Basis of Presentation and Use of Estimates

The accompanying consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("GAAP"). The consolidated financial statements include the accounts of Juno Therapeutics, Inc. and its wholly-owned subsidiaries. All significant intercompany transactions and balances are eliminated in consolidation.

The preparation of the Company's consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from such estimates.

The Company utilizes significant estimates and assumptions in determining the estimated success payment and contingent consideration liabilities and associated expense at each balance sheet date. A small change in the Company's stock price may have a relatively large change in the estimated fair value of the success payment liability and associated expense. Changes in the probabilities and estimated timing of milestones used in the

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calculation of the contingent consideration liability may have a relatively large impact of the resulting liability and associated expense.

Prior to becoming a public company, the Company utilized significant estimates and assumptions in determining the fair value of its common stock for financial reporting purposes. The Company recorded expense for restricted stock grants at prices not less than the fair market value of its common stock as determined by the board of directors, taking into consideration input from management and independent third-party valuation analysis, and in accordance with the AICPA Accounting and Valuation Guide, Valuation of Privately-Held Company Equity Securities Issued as Compensation. The estimated fair value of the Company's common stock was based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which the Company sold shares of convertible preferred stock, and the superior rights and preferences of securities senior to the Company's common stock at the time.

Initial Public Offering

On December 23, 2014, the Company closed its initial public offering ("IPO") and issued and sold 12,676,354 shares of common stock (inclusive of 1,653,437 shares of common stock sold by the Company pursuant to the full exercise of the underwriters' option to purchase additional shares) at a price to the public of $24.00 per share. The shares began trading on The NASDAQ Global Select Market on December 19, 2014. The aggregate net proceeds received by the Company from the offering, net of underwriting discounts and commissions and offering expenses, were $279.7 million. Upon the closing of the IPO, all then-outstanding shares of Company convertible preferred stock converted into 59,909,397 shares of common stock. The related carrying value of $387.7 million was reclassified to common stock and additional paid-in capital. Additionally, the Company amended and restated its certificate of incorporation effective December 23, 2014 to, among other things, change the authorized number of shares of common stock to 495,000,000 shares and the authorized number of shares of preferred stock to 5,000,000 shares.

Comprehensive Loss

Comprehensive loss is comprised of net loss and other comprehensive income or loss. Other comprehensive income or loss consists of unrealized gains and losses on marketable securities and foreign currency translation adjustments.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at acquisition to be cash equivalents. Cash equivalents, which consist primarily of money market funds, are stated at fair value.

Marketable Securities

The Company generally invests its excess cash in investment grade short- to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents, marketable securities, or long-term marketable securities on the balance sheets, classified as available-for-sale, and reported at fair value with unrealized gains and losses included in accumulated other comprehensive income (loss). Realized gains and losses on the sale of these securities are recognized in net income or loss. The cost of marketable securities sold is based on the specific identification method.

The Company periodically evaluates whether declines in fair values of its investments below their book value are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as the Company's ability and intent to hold the investment until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the security or

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it is more likely than not it will be required to sell any investment before recovery of its amortized cost basis. Factors considered include quoted market prices, recent financial results and operating trends, implied values from any recent transactions or offers of investee securities, credit quality of debt instrument issuers, other publicly available information that may affect the value of the investments, duration and severity of the decline in value, and our strategy and intentions for holding the investment.

Property and Equipment, Net

Property and equipment primarily consists of laboratory equipment, computer equipment and software, leasehold improvements and build-to-suit property. Property and equipment is stated at cost, and depreciated using the straight-line method over the estimated useful lives of the respective assets.

Laboratory equipment	5 years
Computer equipment and software	3 years
Leasehold improvements	Shorter of asset's useful life or remaining term of lease

Build-to-Suit Lease Accounting

In February 2015, the Company entered into a lease for a manufacturing facility, which commenced in March 2015. The Company is responsible for the leasehold improvements required to remodel the facility and it bore the majority of the construction risk. Financial Accounting Standards Board ("FASB") Accounting Standard Codification ("ASC") 840-40, Leases—Sale-Leaseback Transactions (Subsection 05-5), required the Company to be considered the owner of the building solely for accounting purposes, even though it was not the legal owner. As a result, the Company recorded an asset and build-to-suit lease obligation on its balance sheet as of December 31, 2015 equal to the fair value of the building at the inception of the lease.

Construction was completed in the first quarter of 2016, and the Company considered the requirements for sale-leaseback accounting treatment, including evaluating whether all risks of ownership have transferred back to the landlord, as evidenced by a lack of continuing involvement in the leased property. The Company determined that the arrangement does not qualify for sale-leaseback accounting treatment and the building asset will remain on its balance sheet at its historical cost, and such asset will be depreciated over its estimated useful life. The Company bifurcates the lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the statements of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

The interest rate used for the build-to-suit lease obligation represents the Company's estimated incremental borrowing rate, adjusted to reduce any built in loss.

Other Assets

Prior to the acquisition of Stage in May 2015, the Company accounted for its minority interest investment in Stage using the cost method in accordance with ASC 325-20, Cost Method Investments, as the Company did not exercise significant influence. Under the cost method, an investment is carried at cost until it is sold or there is evidence that changes in the business environment or other facts and circumstances suggest it may be other than temporarily impaired. This investment totaled $3.5 million as of December 31, 2014 and was included in other assets on the consolidated balance sheets.

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Impairment of Long-Lived Assets

The Company regularly reviews the carrying value and estimated lives of its long-lived assets, including property and equipment, to determine whether indicators of impairment may exist which warrant adjustments to carrying values or estimated useful lives. The determinants used for this evaluation include management's estimate of the asset's ability to generate positive income from operations and positive cash flow in future periods as well as the strategic significance of the asset to the Company's business objectives. Should an impairment exist, the impairment loss would be measured based on the excess of the asset's carrying amount over its fair value. The Company has not recognized any impairment losses since inception on August 5, 2013.

Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the net amount of identifiable assets acquired and liabilities assumed in a business combination measured at fair value. The Company evaluates goodwill for impairment annually during the fourth quarter and upon the occurrence of triggering events or substantive changes in circumstances that could indicate a potential impairment by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that the fair value of the net assets are below their carrying amounts.

Intangible assets acquired in a business combination are recognized separately from goodwill and are initially recognized at their fair value at the acquisition date (which is regarded as their cost). Intangible assets related to in-process research and development ("IPR&D") are treated as indefinite-lived intangible assets and not amortized until they become definite lived assets upon certain regulatory approval in specified markets, typically either the U.S. or the EU in the case of X-Body, and in the case of Stage, when the acquired reagents or automation technology is accepted by the FDA as part of an Investigational New Drug ("IND") filing, subject to management judgment. At that time, the Company will determine the useful life of the asset, reclassify the asset out of IPR&D and begin amortization. Intangible assets are reviewed for impairment at least annually or if indicators of potential impairment exist.

Contingent Consideration from Business Combinations

At and subsequent to the acquisition date of a business combination, contingent consideration obligations are remeasured to fair value at each balance sheet date with changes in fair value recognized in research and development expense in the consolidated statements of operations. Changes in fair values reflect changes to the Company's assumptions regarding probabilities of successful achievement of related milestones, the timing in which the milestones are expected to be achieved, and the discount rate used to estimate the fair value of the obligation, as well as the foreign currency impact of the contingent consideration for the Stage acquisition as it is denominated in Euro.

Fair Value of Financial Instruments

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1—Quoted prices in active markets for identical assets or liabilities

Level 2—Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly

Level 3—Unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability

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The Company's financial instruments, in addition to those presented in Note 6, Fair Value Measurements, include cash and cash equivalents, accounts payable, and accrued liabilities. The carrying amount of cash and cash equivalents, accounts payable and accrued liabilities approximate fair value because of the short-term nature of these instruments.

Convertible Preferred Stock Option

Pursuant to certain 2013 and 2014 convertible preferred stock purchase agreements, the Company had the right to sell, or "put," additional shares of Series A and A-2 convertible preferred stock in subsequent closings as well as potential obligations to issue additional shares upon the occurrence of certain events. The Company assessed its rights and potential obligations to sell additional shares and determined them to be a single unit of accounting, with classification outside of equity in accordance with ASC 480, Distinguishing Liabilities from Equity. As of each balance sheet date, the fair value of these combined instruments was estimated using the option pricing model and assumptions that are based on the individual characteristics of the option on the valuation date, as well as assumptions for expected volatility, expected term, and risk-free interest rate.

The Company recorded these combined instruments as convertible preferred stock options as of the date of the initial closings of the Series A convertible preferred stock financing and Series A-2 convertible preferred stock financing. The options were revalued to fair value at each subsequent balance sheet date, with fair value changes recognized as increases or reductions to other income (expense), net in the consolidated statements of operations. The Company estimated the fair value of these instruments based on the Black-Scholes option pricing model. These options were exercised during 2014. For the year ended December 31, 2014, $10.7 million was recognized in other expense related to the changes in fair value of these options.

Deemed Dividends upon Issuance of Convertible Preferred Stock, Non-Cash

As of the dates of the second tranche closing and third tranche closing of the Series A-2 convertible preferred stock financing in June and July 2014, the estimated fair value of the Series A-2 convertible preferred stock was $5.96 and $7.88 per share, respectively, compared with the purchase price per share of $4.00. As of the date of the final closing of the Series A convertible preferred stock financing in July 2014, the estimated fair value of the Series A convertible preferred stock was $8.36 per share compared with the purchase price per share of $4.00. The differences between the estimated fair value as of the closing dates and the purchase prices were deemed to be equivalent to a preferred stock dividend. As a result, the Company recorded deemed dividends of $15.4 million, $30.3 million, and $21.8 million for the Series A-2 second tranche closing, Series A-2 third tranche closing, and Series A final closing, respectively, in the year ended December 31, 2014. The deemed dividends increased convertible preferred stock by $67.5 million, reduced additional paid-in capital by $16.4 million, and increased accumulated deficit by $51.1 million. The deemed dividends increased the net loss attributable to common stockholders by $67.5 million in the calculation of basic and diluted net loss per common share for the year ended December 31, 2014.

Success Payments

The Company granted rights to share-based success payments to the Fred Hutchinson Cancer Research Center ("FHCRC") and the Memorial Sloan Kettering Cancer Center ("MSK") pursuant to the terms of its collaboration agreements with each of those entities. Pursuant to the terms of these arrangements, the Company may be required to make success payments based on increases in the per share fair market value of the Company's common stock, payable in cash or publicly-traded equity at the Company's discretion. See Note 4, Collaboration and License Agreements. The success payments are accounted for under ASC 505-50, Equity-Based Payments to Non-Employees. Once the service period is complete, the instruments will be accounted for under ASC 815, Derivatives and Hedging, and continue to be marked to market with all changes in value recognized immediately in other income or expense.

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Success payment liabilities are estimated at fair value at inception and at each subsequent balance sheet date and the expense is amortized using the accelerated attribution method over the remaining term (service period) of the related collaboration agreement or related possible payment due date (whichever is sooner). To determine the estimated fair value of the success payments the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the estimated fair value of the success payment liability: estimated term of the success payments, fair value of common stock, expected volatility, risk-free interest rate, estimated number and timing of valuation measurement dates on the basis of which payments may be triggered, and certain estimated indirect costs creditable against the success payments are also included in the calculation. The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and its historical and projected volatility. In addition, prior to the Company becoming publicly traded there was one valuation measurement date on the basis of which payments may be triggered. There are several valuation measurement dates subsequent to the IPO on the basis of which payments may be triggered.

In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million. The Company elected to make the payment in shares of the Company's common stock, and thereby issued 1,601,085 shares of common stock to FHCRC in December 2015. In December 2015, a success payment to MSK was triggered in the amount of $10.0 million, which is required to be paid, less indirect cost offsets that will be determined at the time of payment, in March 2016.

As of December 31, 2015 and 2014, the estimated fair value of the success payment obligation after giving effect to the success payments achieved by FHCRC and MSK was approximately $116.2 million and $195.9 million, respectively. The Company recognized research and development expense of $51.6 million and $84.9 million in the year ended December 31, 2015 and 2014, respectively, with respect to the success payment obligations. The success payment liabilities on the consolidated balance sheets as of December 31, 2015 and 2014 were $64.8 million and $84.9 million, respectively.

The assumptions used to calculate the fair value of the success payments are subject to a significant amount of judgment including the expected volatility, estimated term, and estimated number and timing of valuation measurement dates. A small change in the assumptions may have a relatively large change in the estimated valuation and associated liability and expense. For example, keeping all other variables constant, a hypothetical 10% increase in the stock price at December 31, 2015 from $43.97 per share to $48.37 per share would have increased the expense recorded in 2015 associated with the success payment liability by $7.7 million. A hypothetical 10% decrease in the stock price from $43.97 per share to $39.57 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $7.6 million. Further, keeping all other variables constant, a hypothetical 35% increase in the stock price at December 31, 2015 from $43.97 per share to $59.36 per share would have increased the expense recorded in 2015 associated with the success payment liability by $27.3 million. A hypothetical 35% decrease in the stock price from $43.97 per share to $28.58 per share would have decreased the expense recorded in 2015 associated with the success payment liability by $25.7 million.

Concentrations of Credit Risk and Off-Balance Sheet Risk

The Company maintains its cash, cash equivalents, and marketable securities with high quality, accredited financial institutions. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to significant risk on these funds. The Company has no off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

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Revenue

The Company recognizes revenue for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue in the Company's consolidated balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue in current liabilities. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, less current portion.

The Company analyzes agreements with more than one element, or deliverable, based on the guidance in ASC 605-25, Revenue Recognition-Multiple-Element Arrangements ("ASC 605-25"). The Company identifies the deliverables within the agreement and evaluates which deliverables represent separate units of accounting. Analyzing the agreement to identify deliverables requires the use of judgment. A deliverable is considered a separate unit of accounting when the deliverable has value to the collaborator or licensee on a standalone basis based on the consideration of the relevant facts and circumstances for each agreement.

In assessing whether an item has standalone value, the Company considers factors such as the research, manufacturing, and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the other deliverable(s) can be used for their intended purpose without the receipt of the remaining element(s), whether the value of the deliverable is dependent on the undelivered item(s) and whether there are other vendors that can provide the undelivered element(s).

Consideration received is allocated at the inception of the agreement to all identified units of accounting based on the relative selling prices. The relative selling price for each deliverable is estimated using objective evidence if it is available. If objective evidence is not available, the Company uses its best estimate of the selling price for the deliverable. Management may be required to exercise considerable judgment in estimating the selling prices of identified units of accounting under its agreements.

Options for future deliverables are considered substantive if, at the inception of the arrangement, the Company is at risk as to whether the collaboration partner will choose to exercise the option. Factors that the Company considers in evaluating whether an option is substantive include the overall objective of the arrangement, the benefit the collaborator might obtain from the arrangement without exercising the option, the cost to exercise the option and the likelihood that the option will be exercised. For arrangements under which an option is considered substantive, the Company does not consider the item underlying the option to be a deliverable at the inception of the arrangement and the associated option fees are not included in the initial consideration, assuming the option is not priced at a significant and incremental discount. Conversely, for arrangements under which an option is not considered substantive or if an option is priced at a significant and incremental discount, the Company would consider the item underlying the option to be a deliverable at the inception of the arrangement and a corresponding amount would be included in the initial consideration.

The consideration received is allocated among the separate units of accounting, and the applicable revenue recognition criteria are applied to each of the separate units. The Company recognizes the revenue allocated to each unit of accounting over the period of performance. Revenue is recognized using either a proportional performance or straight-line method, depending on whether the Company can reasonably estimate the level of effort required to complete its performance obligations under an arrangement.

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Research and Development Expense

The Company records expense for research and development costs to operations as incurred. For service contracts entered into that include a nonrefundable prepayment for service, the upfront payment is deferred and recognized in the statement of operations as the services are rendered. Research and development expenses consist of costs incurred by the Company for the discovery and development of the Company's product candidates and include:

- Clinical trial costs;
- external research and development expenses incurred under arrangements with third parties, such as contract research organizations, contract manufacturing organizations, academic and non-profit institutions and consultants;
- costs incurred in connection with preclinical development activities;
- costs to acquire complimentary technology;
- personnel-related expenses, including non-cash stock-based compensation expense;
- changes in the estimated fair value of the liability attributable to the elapsed service period as of the balance sheet date associated with the Company's success payments to FHCRC and MSK;
- changes in the estimated fair value of the contingent consideration liabilities;
- license fees; and
- other expenses, which include direct and allocated expenses for laboratory, facilities, and other costs.

General and Administrative Expense

General and administrative costs are expensed as incurred and include personnel-related expenses including non-cash stock-based compensation for our personnel in executive, legal, finance and accounting, and other administrative functions, legal costs other than litigation expense associated with Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn), transaction costs related to acquisitions and collaboration and licensing agreements, as well as fees paid for accounting and tax services, consulting fees, and facilities costs not otherwise included in research and development expenses. Legal costs include general corporate legal fees, patent costs, and legal expense associated with inter partes review proceedings at the USPTO.

Litigation Expense

Litigation expense includes legal expense the Company incurred with respect to Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn), as well as expenses the Company was required to reimburse to St. Jude Children's Research Hospital ("St. Jude") with respect to such litigation. See Note 4, Collaboration and License Agreements.

Stock-Based Compensation

Under ASC 718, Compensation—Stock Compensation, the Company measures and recognizes expense for restricted stock awards, restricted stock unit ("RSU") awards, and stock options granted to employees and directors based on the fair value of the awards on the date of grant. The fair value of stock options is estimated at the date of grant using the Black-Scholes option pricing model that requires management to apply judgment and make estimates, including:

- the expected term of the option, which is calculated using the simplified method, as permitted by the Securities and Exchange Commission ("SEC") Staff Accounting Bulletin No. 110, Share-Based Payment, as the Company has insufficient historical information regarding its stock options to provide a basis for an estimate;

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- the expected volatility of the underlying common stock, which the Company estimates based on the historical volatility of a representative group of publicly traded biopharmaceutical companies with similar characteristics, and the Company's own historical and implied future volatility;
- the risk-free interest rate, which is based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued;
- the expected dividend yield, which the Company estimates to be zero based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends; and
- the fair value of the Company's common stock on the date of grant.

Stock-based compensation expense for restricted stock, RSUs, and stock options is recognized on a straight-line basis over the requisite service period, which is generally the vesting period of the respective award. The Company is required to estimate a forfeiture rate to calculate the stock-based compensation expense for its awards. The Company's forfeiture rate is based on an analysis of its actual forfeitures since the adoption of its equity award plan. Since inception the Company's estimated forfeiture rate has been de minimis. The Company routinely evaluates the appropriateness of the forfeiture rate based on actual forfeiture experience, analysis of employee turnover and expectations of future option exercise behavior.

The Company also granted restricted stock awards that vest in conjunction with certain performance conditions to certain key employees, scientific founders, and directors. At each reporting date, the Company is required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon the Company's assessment of accomplishing each performance provision. Compensation expense is measured using the fair value of the award at the grant date, net of forfeitures, and is adjusted annually to reflect actual forfeitures.

The Company also grants stock-based awards to certain service providers who are not employees, scientific founders, or directors. Stock-based awards issued to such persons, or to directors for non-board related services, are accounted for based on the fair value of such services received or of the equity instruments issued, whichever is more reliably measured. The fair value of such awards is subject to remeasurement at each reporting period until services required under the arrangement are completed, which is the vesting date.

Patent Costs

The costs related to acquiring patents and to prosecuting and maintaining intellectual property rights are expensed as incurred to general and administrative due to the uncertainty surrounding the drug development process and the uncertainty of future benefits.

Income Taxes

The Company determines its deferred tax assets and liabilities based on the differences between the financial reporting and tax basis of assets and liabilities. The deferred tax assets and liabilities are measured using the enacted tax rates that will be in effect when the differences are expected to reverse. A valuation allowance is recorded when it is more likely than not that the deferred tax asset will not be recovered. The Company applies judgment in the determination of the consolidated financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. The Company recognizes any material interest and penalties related to unrecognized tax benefits in income tax expense.

The Company is required to file income tax returns in the U.S. federal jurisdiction and various state and foreign jurisdictions. The Company currently is not under examination by the Internal Revenue Service or other jurisdictions for any tax years.

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Foreign Currency Translation

Assets and liabilities denominated in foreign currencies were translated into U.S. dollars, the reporting currency, at the exchange rate prevailing at the balance sheet date. Revenue and expenses denominated in foreign currencies were translated into U.S. dollars at the monthly average exchange rate for the period and the translation adjustments are reported as an element of accumulated other comprehensive income or loss on the consolidated balance sheets.

Net Loss per Share Attributable to Common Stockholders

Basic and diluted net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period, without consideration for common stock equivalents. The Company's potentially dilutive shares, which include unvested restricted stock, unvested RSUs, options to purchase common stock, and potential shares issued for success payments, are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive. The following table reconciles net loss to net loss attributable to common stockholders (in thousands, except share and per share data):

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
Net loss	$ (239,376)	$ (243,407)	$ (51,820)
Deemed dividend upon issuance of convertible preferred stock	—	(67,464)	—
Net loss attributable to common stockholders	$ (239,376)	$ (310,871)	$ (51,820)
Weighted average number of common shares used in net loss per share attributable to common stockholders—basic and diluted	88,145,424	8,442,947	3,658,687
Net loss per share attributable to common stockholders—basic and diluted	$ (2.72)	$ (36.82)	$ (14.16)

The amounts in the table below were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated due to their anti-dilutive effect:

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
Series A convertible preferred stock	—	—	16,930,664
Series A-1 convertible preferred stock	—	—	2,250,000
Unvested restricted common stock and restricted stock units	5,476,600	8,352,714	5,789,123
Options to purchase common stock	5,218,939	2,720,351	—
Estimated number of shares issued for success payments	204,527[1]	1,627,729[2]	—
Total	10,900,066	12,700,794	24,969,787

(1) In December 2015 a success payment to MSK was triggered in the amount of $10.0 million, less certain indirect cost offsets that will be determined at the time of payment in March 2016. This represents the number of shares that would have been issued if the success payment to MSK had been made on December 31, 2015 had we chosen to pay this obligation by issuing stock. The number of shares issued for purposes of this presentation is calculated by dividing the success payment by the closing stock price per share on December 31, 2015. The actual number of shares to be issued, if we choose to pay the obligation by issuing stock, will be calculated by dividing the success payment achieved by the volume weighted average trading price of the Company's common stock on March 17, 2016.

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(2) Represents the number of shares that would have been issued if the success payment valuation date had been December 31, 2014. The Company's common stock closing price per share was $52.22 at December 31, 2014 which value if used for purposes of determining what success payments were triggered would have resulted in a success payment of $85.0 million ($75.0 million for FHCRC and $10.0 million for MSK). The number of shares issued for purposes of this presentation is calculated by dividing the success payment by the closing stock price per share at December 31, 2014.

Segments

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business in one operating segment and one reportable segment.

Recent Accounting Pronouncements

In November 2015, the FASB issued Accounting Standards Update ("ASU") No. 2015-17, Balance Sheet Classification of Deferred Taxes (Topic 740), intended to improve how deferred taxes are classified on organizations' balance sheets. The new guidance eliminates the current requirement to present deferred tax liabilities and assets as current and noncurrent in a classified balance sheet. Under the new guidance, companies are required to classify all deferred tax assets and liabilities as noncurrent. ASU No. 2015-17 is effective for periods beginning after December 15, 2015, and interim periods within those fiscal years, with early adoption permitted. The Company early adopted this standard for the year ended December 31, 2015. The adoption of this standard did not have a material impact on its financial position, results of operation or related financial statement disclosures.

In 2014, the FASB issued new accounting guidance related to revenue recognition. This new standard will replace all current GAAP guidance on this topic and establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. This guidance can be applied either retrospectively to each period presented or as a cumulative-effect adjustment as of the date of adoption. In July 2015, the FASB voted to defer the effective date to January 1, 2018 with early adoption permitted beginning January 1, 2017. The Company is evaluating the impact of adopting the new accounting guidance on its consolidated financial statements.

3. Acquisitions

Acquisition of Stage

On May 11, 2015, the Company completed the acquisition of all the outstanding ownership interests in Stage not already held by it. Prior to the acquisition, the Company held a 4.76% equity interest in Stage. As a result of the acquisition, Stage became a wholly owned subsidiary of the Company. The Company paid €52.5 million, or $58.5 million, in cash and issued an aggregate of 486,279 shares of common stock, valued at $22.2 million based on the closing stock price on May 11, 2015 of $45.58 per share, to the selling shareholders.

The Company also agreed to pay additional amounts of up to an aggregate of €135.0 million in cash based on the achievement of certain technical, clinical, regulatory, and commercial milestones related to novel reagents (€40.0 million), advanced automation technology (€65.0 million), and Stage's existing clinical pipeline (€30.0 million). The fair value of this contingent consideration was estimated to be $28.2 million at the date of acquisition. Payments could vary based on milestones that are reached.

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The elements of the purchase consideration are as follows (in thousands):

Cash paid (1)	$ 58,496
Common stock issued (2)	22,165
Fair value of contingent consideration (3)	28,244
Total consideration for 95.24% equity	108,905
Fair value of 4.76% initial investment in Stage (4)	3,682
Implied purchase price consideration for 100% equity	$ 112,587

(1) The cash consideration represents the consideration paid in cash amounting to €52.5 million which is translated based on an exchange rate on May 11, 2015.
(2) Based on the share purchase agreement, the purchase consideration included 486,279 shares of the Company's common stock. The closing stock price on the transaction date was $45.58 per share.
(3) The fair value of the contingent consideration was determined by calculating the probability-weighted milestone payments based on the assessment of the likelihood and estimated timing that certain milestones would be achieved. The fair value of the contingent consideration was estimated using a discount rate of 14.6%. The discount rate captures the credit risk associated with the payment of the contingent consideration when earned and due.
(4) The fair value of the initial investment is calculated as the implied per share fair value of the stock based upon the acquisition purchase price reduced by a lack of control discount associated with the 4.76% holding. Upon acquiring the remaining outstanding ownership interests in Stage, the Company remeasured its original equity interest to its fair value and recognized a $0.2 million gain during the year ended December 31, 2015, which was recorded in other income (expense) on the consolidated statements of operations.

The Company accounted for the Stage acquisition using the acquisition method. The acquisition method of accounting requires, among other things, that the assets acquired and liabilities assumed in a business combination be measured at their fair values as of the closing date of the acquisition. The allocation of the purchase price is based on estimates of the fair value of assets acquired and liabilities assumed as of the date of acquisition. The components of the purchase price allocation are as follows (in thousands):

Net working capital	$ 1,863
Property and equipment	651
Net assets acquired	2,514
Deferred tax liabilities	(10,801)
Acquired in-process research and development	34,457
Goodwill	86,417
Total consideration transferred	$112,587

The fair value of the acquired in-process research and development has been estimated using the replacement cost method. Under this method, the Company estimated the cost of recreating the technology and derived an estimated value to develop the technology. In-process research and development are required to be classified as indefinite-lived assets until they become definite lived assets upon the successful completion or the abandonment of the associated research and development effort. Accordingly, during the development period after the date of acquisition, these assets will not be amortized until the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgment. At that time, the Company will determine the useful life of the asset and begin amortization. If the associated research and development effort is abandoned, the related in-process research and development assets will be written-off and an impairment charge recorded.

The excess of the purchase price over the estimated fair value of the tangible net assets and identifiable intangible assets acquired was recorded as goodwill. The factors contributing to the recognition of the amount of goodwill

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are based on several strategic and synergistic benefits that are expected to be realized from the Stage acquisition. The acquisition of Stage is intended to provide the Company access to transformative cell selection and activation capabilities, next generation manufacturing automation technologies, enhanced control of its supply chain, and lower expected long-term cost of goods. None of the goodwill is expected to be deductible for income tax purposes. The Company made a Section 338(g) election under the Internal Revenue Code with respect to this acquisition, resulting in the acquired entity being treated for U.S. tax purposes as a newly incorporated company. Under such election, the U.S. tax basis of the assets and liabilities of Stage were stepped up to fair value as of the closing date of the acquisition to reflect the consequences of the Section 338(g) election.

Acquisition of X-Body

On June 1, 2015, the Company completed the acquisition of 100% of the outstanding equity in X-Body. The Company paid $21.3 million in cash and issued an aggregate of 366,434 shares of common stock, valued at $19.4 million based on the closing stock price on June 1, 2015 of $53.07 per share, to the former X-Body stockholders. Further, an additional 72,831 shares of common stock were issued to two former X-Body stockholders in the transaction, which shares are subject to monthly vesting over the three years following the closing of the transaction, contingent on such former X-Body stockholders providing consulting services to the Company through each such vesting date. These will be accounted for as post-acquisition compensation expenses.

The Company also agreed to pay additional amounts in cash upon the realization of specified milestones substantially as follows, with respect to products generated using the X-Body technology: $5.0 million per target upon the achievement, during a specified period, of a certain regulatory milestone for products that utilize a certain type of binding mechanism; up to $30.0 million upon the achievement, during a specified period, of regulatory and clinical milestones for the first product using another type of binding mechanism (any product using such type of binding mechanism, a “Type X Product”); $5.0 million per product upon the achievement, during a specified period, of a certain regulatory milestone for a certain number of subsequent Type X Products; $50.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain specified binding properties (a “Type Y Product”); and $20.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain other specified binding properties. If a Type X Product or a Type Y Product is commercialized, Juno can choose either to make a commercialization milestone payment for such a product or to pay a low single-digit royalty on net sales of such a product. The fair value of this contingent consideration was estimated to be $8.9 million at the date of acquisition. Payments could vary based on milestones that are reached. The elements of the purchase consideration are as follows (in thousands):

Cash paid	$21,331
Common stock issued (1)	19,447
Fair value of contingent consideration (2)	8,944
Settlement of preexisting obligation (3)	1,123
Total consideration	$50,845

(1) Based on the share purchase agreement, the purchase consideration included 366,434 shares of the Company’s common stock. The closing stock price on the transaction date was $53.07 per share.

(2) The fair value of the contingent consideration was determined by calculating the probability-weighted milestone based on the assessment of the likelihood and estimated timing that certain milestones would be achieved. The fair value of the contingent consideration was estimated using a discount rate of 15.2%. The discount rate captures the credit risk associated with the payment of the contingent consideration when earned and due.

(3) The settlement of preexisting obligation reflects the effective settlement of the Company’s preexisting prepaid contract research agreement with X-Body. No gain or loss was recognized by the Company on the effective settlement of this prepaid expense as of the acquisition date.

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The allocation of the purchase price is based on estimates of the fair value of assets acquired and liabilities assumed as of the acquisition date. The components of the purchase price allocation are as follows (in thousands):

Net liabilities assumed	$ (181)
Deferred tax liabilities	(1,099)
Acquired in-process research and development	16,450
Goodwill	35,675
Total consideration transferred	$50,845

The fair value of the acquired in-process research and development has been estimated using the replacement cost method. Under this method, the Company estimated the cost to recreate the technology and derived an estimated value to develop the technology. In-process research and development are required to be classified as indefinite-lived assets until they become definite lived assets upon the successful completion or the abandonment of the associated research and development effort. Accordingly, during the development period after the date of acquisition, these assets will not be amortized until regulatory approval is obtained in a major market, typically either the United States or the EU, subject to management judgment. At that time, the Company will determine the useful life of the asset and begin amortization. If the associated research and development effort is abandoned, the related in-process research and development assets will be written-off and an impairment charge recorded.

The excess of the purchase price over the estimated fair value of the tangible net assets and identifiable intangible assets acquired was recorded as goodwill. The goodwill recognized as a result of the X-Body acquisition is primarily attributable to the fact that the acquisition furthers the Company's strategy of investing in technologies that augment the Company's capabilities to create best-in-class engineered T cells against a broad array of cancer targets. The acquisition brings in-house to the Company an innovative discovery platform that interrogates the human antibody repertoire, rapidly selecting fully human antibodies with desired characteristics, even against difficult targets. None of the goodwill is expected to be deductible for income tax purposes.

Post-Acquisition and Pro Forma Consolidated Financial Information

The Stage and X-Body acquisitions did not have a material impact on the Company's consolidated statements of operations, and therefore actual and pro forma disclosures have not been presented. The intangible assets acquired in the Stage and X-Body acquisitions are in-process research and development assets, and as such, there would be no pro forma adjustment needed for the amortization of intangible assets.

Goodwill and Intangible Assets

The following table summarizes the changes in the carrying amount of goodwill (in thousands):

Balance at December 31, 2014	$ —
Goodwill acquired	122,092
Balance at December 31, 2015	$122,092

Goodwill represents the excess of the purchase price over the net amount of identifiable assets acquired and liabilities assumed in a business combination measured at fair value. We evaluate goodwill for impairment annually during the fourth quarter and upon the occurrence of triggering events or substantive changes in circumstances that could indicate a potential impairment by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that the fair value of net assets are below their carrying amounts. There was no impairment of goodwill for the year ended December 31, 2015.

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The following table summarizes the gross carrying amount, accumulated amortization and the net carrying amount of intangible assets (in thousands):

	December 31, 2015		
	Gross Carrying Amount	Accumulated Amortization	Intangible Assets, Net
Acquired in-process research and development	$ 50,177	$ —	$ 50,177
Total intangible assets	$ 50,177	$ —	$ 50,177

Intangible assets acquired in a business combination are recognized separately from goodwill and are initially recognized at their fair value at the acquisition date (which is regarded as their cost). Intangible assets related to IPR&D are treated as indefinite-lived intangible assets and not amortized until they become definite lived assets upon obtaining certain regulatory approval in specified markets in the case of X-Body, and in the case of Stage, when the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgment. At that time, the Company will determine the useful life of the asset, reclassify the asset out of IPR&D and begin amortization. Intangible assets are reviewed for impairment at least annually or if indicators of potential impairment exist. There was no impairment of intangible assets for the year ended December 31, 2015.

Transaction Costs

The Company incurred approximately $4.5 million of direct transaction costs related to the Stage and X-Body acquisitions for the year ended December 31, 2015. These costs are included in general and administrative expenses in the consolidated statements of operations.

4. Collaboration and License Agreements

Celgene

In June 2015, the Company entered into a Master Research and Collaboration Agreement (“Celgene Collaboration Agreement”) with Celgene Corporation and one of its wholly owned subsidiaries (collectively, “Celgene”) pursuant to which the Company and Celgene agreed to collaborate on researching, developing, and commercializing novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. The Celgene Collaboration Agreement was amended and restated in August 2015. Pursuant to the collaboration, prior to the exercise of an option for a program, each of the Company and Celgene will conduct independent programs to research, develop, and commercialize such product candidates (including, in the case of the Company, its CD19 and CD22 programs). Each party has certain options to obtain either an exclusive license to develop and commercialize specified product candidates arising from specified types of programs conducted by the other party within the scope of the collaboration, or the right to participate in the co-development and co-commercialization of specified product candidates arising from such programs, in each case in specified territories. Further, following the exercise of an option, Celgene has the right to exercise an option for a specified number of such programs, excluding the CD19 program and the CD22 program, to co-develop and co-commercialize products arising out of such programs in certain countries, and each of Celgene and Company has the right to elect to participate in certain commercialization activities for products in such programs in territories where it is not leading commercialization of such product. The parties may exercise their options with respect to specified product candidates arising under programs within the scope of the collaboration until the tenth anniversary of the effective date of the Celgene Collaboration Agreement (the “Research Collaboration Term”), subject to a tail period applicable to certain programs, for which options have not yet been exercised as of the expiration of the Research Collaboration Term.

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For Company-originated programs (which may include the CD19 program and the CD22 program) under the collaboration for which Celgene exercises its option to obtain an exclusive license:

- The Company would be responsible for research and development in the United States, Canada, and Mexico, and, for cellular therapy product candidates, China, and would retain commercialization rights and would lead commercialization activities and book sales of products in those countries (the "Juno Territory"), subject to Celgene's option, for a specified number of programs, to elect to co-develop and co-commercialize product candidates arising from such programs, or for other programs, to elect to participate in certain commercialization activities in the Juno Territory, as further described below. Under all such license agreements, the Company has the right to participate in specified commercialization activities arising from such programs in certain major European markets;
- On a program-by-program basis, Celgene would receive an exclusive license, and pursuant to such license would be responsible for, development and commercialization outside of the Juno Territory (the "Celgene Territory"), including by leading commercialization activities and booking sales of products in the Celgene Territory. Celgene would be required to pay the Company a royalty on sales of products arising from such program in the Celgene Territory as further described below; and
- For Company-originated programs, excluding CD19 and CD22, Celgene would have the right to exercise an option for a specified number of such programs, to obtain the right to co-develop and co-commercialize products arising from such program worldwide, except for China. For each such program, following Celgene's exercise of such option, the parties would enter into an agreed form of co-development and co-commercialization agreement, pursuant to which:
    - Celgene would have the right to co-develop and co-commercialize product candidates arising from such programs, with the parties each entitled to bear and receive an equal share of the profits and losses arising from development and commercialization activities in such programs worldwide (other than China); and
    - The Company would remain the lead party for development and commercialization activities for such product candidates in the Juno Territory, and Celgene would remain the lead party for development and commercialization activities for such product candidates in the Celgene Territory, subject to the Company's right to participate in certain commercialization activities in certain major European countries, and Celgene's right to elect to participate in a specified percentage of commercialization activities in the Juno Territory.

For other Company originated programs for which Celgene does not exercise such a co-development and co-commercialization right, Celgene would also have the right to elect to participate in up to a specified percentage of certain commercialization activities for product candidates in such program in the Juno Territory, and the Company would have the right to elect to participate in up to a specified percentage of certain commercialization activities for such product candidates in certain major European markets.

For Celgene-originated programs under the collaboration for which the Company exercises its option to obtain an exclusive license, the parties will enter into a co-development and co-commercialization agreement and:

- The parties will share global profits and losses from development and commercialization activities with 70% allocated to Celgene and 30% allocated to the Company; and
- Celgene will lead global development and commercialization activities, subject to the Company's right to elect to participate in up to a specified percentage of certain commercialization activities in the Juno Territory under certain circumstances and in certain major European countries.

Furthermore, each of Celgene and the Company will have the exclusive right to exercise options to co-develop and co-commercialize product candidates arising out of programs for which the other party in-licenses or acquires rights that are within the scope of their collaboration, where such rights are available to be granted, with

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the parties each bearing an equal share of the profits and losses arising out of such programs following the exercise of such option. In general, for such programs where the rights are in-licensed or acquired by the Company and for which Celgene exercises its options, the Company will be the lead party for development and commercialization of product candidates arising from such programs in the Juno Territory, subject to Celgene's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory, and Celgene will be the lead party for development and commercialization of product candidates arising in such programs in the Celgene Territory, subject to the Company's right to elect to participate in certain commercialization activities for such product candidates in certain major European markets. Conversely, for such programs where the rights are in-licensed or acquired by Celgene and for which the Company exercises its options, Celgene will be the lead party for development and commercialization activities for product candidates arising from such programs on a worldwide basis, subject to the Company's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory and in certain major European markets. The party exercising an option for these in-licensed or acquired programs is generally required to pay to the other party an upfront payment equal to one half of the costs incurred by other party in connection with the acquisition of rights to such programs.

In addition to an upfront cash payment of approximately $150.2 million under the Celgene Collaboration Agreement, Celgene is required to pay to the Company an additional fee if it exercises its option for each of the CD19 Program and the CD22 Program, totaling, if the options are exercised for both programs during the initial opt-in window, $100.0 million. Upon a party's exercise of the option for any other program (other than certain in-licensed or acquired programs where a party exercises its option at the time such program is acquired), the party exercising the option is required to pay to the other party a payment at the time of exercise of its option, calculated as a multiple of the costs incurred by the other party in relation to the development activities for such program prior to the exercise of the option, with such multiple based on the point in development of such product at which such party exercises such option. For programs for which the parties have entered into a license agreement, the Company will also receive royalties from Celgene, for product candidates arising from the CD19 and CD22 programs, at a percentage in the mid-teens of net sales of such product candidates in the Celgene Territory, and for product candidates arising from other Company programs that are subject to a license agreement, tiered royalties on net sales of such product candidates in the Celgene Territory, at percentages ranging from the high single digits to the mid-teens, calculated based on the stage of development at which Celgene exercises its option for such program.

In June 2015, the Company also entered into a Share Purchase Agreement (the "Purchase Agreement") with Celgene. Pursuant to the Purchase Agreement, the Company agreed to sell 9,137,672 shares of the Company's common stock to Celgene at an aggregate cash price of approximately $849.8 million, or $93.00 per share of common stock, at an initial closing (the "Initial Closing"). Beyond the Initial Closing, the Purchase Agreement provides for potential future sales of shares by the Company to Celgene as follows:

- First Period Top-Up Rights. After the Initial Closing and until June 29, 2020, Celgene has the annual right, following the filing of each Annual Report on Form 10-K filed by the Company, to purchase additional shares from the Company at a market average price, allowing it to "top up" to an ownership interest equal to 10% of the then-outstanding shares (after giving effect to such purchase), subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise).
- First Acquisition Right. During the period beginning on June 29, 2019 and ending on June 28, 2020, subject to Celgene opting in to a certain number of Company programs under the Celgene Collaboration Agreement, Celgene will have the right (the "First Acquisition Right") to purchase up to such number of shares that will allow Celgene to have ownership of 19.99% of the then-outstanding shares of the Company's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market (currently The NASDAQ Global Select Market) on the

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date of exercise (the "FAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.

- Second Period Top-Up Rights. After the closing of the purchase of shares upon the exercise of the First Acquisition Right until the SAR Termination Date (as defined below), in the event that Celgene has been diluted after exercising the First Acquisition Right, the Company will, following the filing of each Annual Report on Form 10-K filed by the Company, offer Celgene the right to purchase additional shares from the Company at 105% of market average price, allowing Celgene to "top up" to an ownership interest (after giving effect to such purchase) equal to the percentage ownership of shares that Celgene obtained upon exercise of the First Acquisition Right, subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any year in which it is offered such right by the Company, then the percentage of ownership targeted for a top-up stock purchase for the next year it is offered such top-up right will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). The "SAR Termination Date" is the later of (a) June 29, 2025, and (b) the earlier of (x) the date that is 6 months following the date that the conditions to the exercise of the Second Acquisition Right (as defined herein) are satisfied and (y) December 29, 2025.
- Second Acquisition Right. During the period beginning on June 29, 2024 and ending on the SAR Termination Date, subject to each of Celgene and the Company opting into a certain number of programs under the Celgene Collaboration Agreement, and provided that Celgene exercised the First Acquisition Right so as to obtain an aggregate percentage ownership of at least 17% of the Company, Celgene will have the right (the "Second Acquisition Right") to purchase up to such number of shares that will allow Celgene to have ownership of 30% of the then-outstanding shares of the Company's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market on the date of exercise (the "SAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.
- Final Top-Up Rights. Following the closing of the purchase of shares upon the exercise of the Second Acquisition Right and until the Celgene Collaboration Agreement expires or is terminated, Celgene would have the annual right, in the event that Celgene has been diluted after exercising the Second Acquisition Right, following the filing of each Annual Report on Form 10-K filed by the Company, to purchase additional shares from the Company at a price equal to 105% of market average price, allowing it to "top up" to the percentage ownership it had attained upon exercising the Second Acquisition Right, less 250 basis points, subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). These rights and the other described top-up rights, as well as the First Acquisition Right and Second Acquisition Right, may be limited or eliminated in certain circumstances when and if Celgene disposes of any of its shares.

The First Period Top-Up Rights, Second Period Top-Up Rights and Third Period Top-Up Rights are collectively referred to herein as the "Top-Up Rights". The First Acquisition Right and Second Acquisition Right are collectively referred to herein as the "Acquisition Rights."

Each closing of the sale of shares to Celgene is subject to customary closing conditions, including termination or expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended. The Purchase Agreement also limits the aggregate number of shares that may be issued thereunder to 19.99% of the Company's common stock outstanding immediately prior to the entry into the Purchase Agreement, unless stockholder approval is obtained for additional issuances of Company stock in accordance with NASDAQ rules. The Company has agreed to submit the additional equity issuances for approval by its stockholders at the Company's 2016 annual meeting of stockholders.

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The Celgene Collaboration Agreement became effective on July 31, 2015, in connection with which the Company received an upfront cash payment of $150.2 million. On August 4, 2015 the Initial Closing under the Purchase Agreement occurred, and the Company sold 9,137,672 shares of the Company's common stock to Celgene for an aggregate cash purchase price of approximately $849.8 million.

Accounting Analysis

The Celgene Collaboration Agreement contains the following deliverables: (1) access to certain of the Company's technology through a non-exclusive, worldwide, royalty-free right and license to conduct certain activities under the collaboration, and (2) participation on various collaboration committees. The Company considered the provisions of the multiple-element arrangement guidance in determining how to recognize the revenue associated with the two deliverables. The Company has accounted for access to certain of the Company's technology and participation on various collaboration committees as a single unit of accounting because the two deliverables do not have standalone value and both obligations will be delivered throughout the estimated period of performance.

Under the terms of the Celgene Collaboration Agreement, the Company received an upfront cash payment of $150.2 million. The Company has identified the initial consideration for the Celgene Collaboration Agreement, which is the best estimated selling price, as the $150.2 million upfront payment under the Celgene Collaboration Agreement. The Company determined that each of the identified deliverables have the same period of performance (the ten year research collaboration term) and have the same pattern of revenue recognition, ratably over the period of performance. As a result, the $150.2 million in arrangement consideration was recorded in deferred revenue and will be recognized over the ten year research collaboration term. The Company recognized revenue of $5.1 million for the year ended December 31, 2015 in connection with the Celgene Collaboration Agreement.

The Company also evaluated its own options pertaining to Celgene's programs. If the Company exercises any of its options, it is required to make a payment equal to a percentage of the costs incurred by Celgene prior to the exercise of the option in connection with the research and development activities and regulatory activities for such development candidate. The percentage of costs to be paid varies based on the point in development of such product at the time the Company exercises its option. The Company will account for the payments as research and development expense upon the exercise of the related option. The Company determined that payments related to licenses that will be used in future research and development activities with no proven alternative future use at the time of acquisition by the Company should be expensed when incurred in accordance with the Company's accounting policy.

In addition, Celgene purchased 9,137,672 shares of the Company's common stock at a price of $93.00 per share, resulting in gross proceeds of $849.8 million. The Company determined that this initial purchase of common stock combined with the embedded future stock purchase rights had a fair value of $849.8 million and this amount was recorded in equity.

The Company evaluated and determined that the Top-Up Rights and Acquisition Rights granted to Celgene under the Purchase Agreement are not freestanding instruments as these rights are not legally detachable and separately exercisable from the Company's common stock. In addition, the Company has further assessed whether the Top-Up Rights and Acquisition Rights should be accounted for as derivative instruments and determined that derivative accounting does not apply. The Company determined that the Top-Up Rights and Acquisition Rights are embedded and inseparable from the initial stock purchase and no subsequent remeasurement is necessary.

Fred Hutchinson Cancer Research Center

In October 2013, the Company entered into a collaboration agreement with FHCRC, focused on research and development of cancer immunotherapy products. The agreement has a six year term and can be extended if mutually agreed upon. The research is conducted under project orders containing plans and budgets approved by

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the parties. The Company recognized $10.3 million, $6.9 million, and $3.4 million of research and development expenses in connection with its collaboration agreement with FHCRC for the years ended December 31, 2015 and 2014, and for the period from August 5, 2013 to December 31, 2013, respectively.

The Company granted FHCRC rights to certain share-based success payments. Under the terms of this arrangement, the Company may be required to make success payments to FHCRC based on increases in the estimated fair value of the Company's common stock. The potential payments are based on multiples of increased value ranging from 5x to 40x based on a comparison of the fair value of the common stock relative to its original $4.00 issuance price. The payments are based on whether the value of the Company's common stock meets or exceeds certain specified threshold values ascending from $20.00 per share to $160.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. The aggregate success payments to FHCRC are not to exceed $375 million which would only occur at a stock valuation of $160.00 per share. In June 2014, the Company entered into an agreement with FHCRC in which it can offset certain indirect costs related to the collaboration projects conducted by FHCRC against any success payments. The term of the success payment agreement ranges from eight to eleven years depending upon when or if the company receives FDA approval of certain of its product candidates as specified in the agreement.

The following table summarizes all possible FHCRC success payments, which are payable in cash or publicly-traded equity at the Company's discretion:

Multiple of Initial Equity Value at issuance	5.0x	7.5x	10.0x	15.0x	20.0x	25.0x	30.0x	35.0x	40.0x
Per share common stock price required for payment	$20.00	$30.00	$40.00	$60.00	$80.00	$100.00	$120.00	$140.00	$160.00
Success payment(s) (in millions)	$ 10	$ 25	$ 40	$ 50	$ 50	$ 50	$ 50	$ 50	$ 50

The success payments will be owed if the value of the Company's common stock on the contractually specified valuation measurement dates during the term of the success payment agreement equals or exceeds the above outlined multiples. The valuation measurement dates are triggered by events which include an initial public offering of the Company's stock, a merger, an asset sale, or the sale of the majority of the shares held by certain of the Company's stockholders or the last day of the term of the success payment agreement. If a higher success payment tier is first met at the same time a lower tier is first met, both tiers will be owed. Any previous success payments made to FHCRC are credited against the success payment owed as of any valuation measurement date, so that FHCRC does not receive multiple success payments in connection with the same threshold. A payment may be triggered on the first anniversary of the closing of the IPO (or the date that is 90 days following such anniversary, at the Company's option, if the Company is contemplating a capital market transaction during such 90 day period). The value of any such success payment will be determined by the average trading price of a share of the Company's common stock over the consecutive 90-day period preceding such determination date.

In December 2015, success payments to FHCRC were triggered in the aggregate amount of $75.0 million, less indirect cost offsets of $3.3 million. These success payments represent the success payments identified on the table above for the 5.0x, 7.5x, and 10.0x Multiple of Initial Equity Value triggers. The Company elected to make the payment in shares of its common stock, and thereby issued 1,601,085 shares of its common stock to FHCRC in December 2015. In the future, the outstanding potential success payments to FHCRC are owed only if the criteria are met with the equity value at the 15.0x Multiple of Initial Equity Value or higher.

The estimated fair value of the success payment obligation to FHCRC after giving effect to the success payments achieved in December 2015 was approximately $67.3 million and $139.1 million as of December 31, 2015 and 2014, respectively. With respect to the FHCRC success payment obligations, the Company recognized research and development expense of $44.3 million and $61.2 million in the years ended December 31, 2015 and 2014, respectively. The expense recorded in both periods represents the change in the FHCRC success payment liability during such periods, the success payment amounts achieved in 2015, and twelve months of accrued expense. The FHCRC success payment liabilities on the consolidated balance sheets as of December 31, 2015 and December 31, 2014 were $33.8 million and $61.2 million, respectively.

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The Company's liability for share-based success payments under the FHCRC collaboration is carried at fair value and recognized as expense over the term of the six-year collaboration agreement. To determine the estimated fair value of the success payment liability the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the calculation of the estimated fair value of the success payment liability as of the following balance sheet dates:

	December 31,	
Assumptions	2015	2014
Fair value of common stock	$ 43.97	$ 52.22
Risk free interest rate	1.89% – 2.20%	1.94% – 2.16%
Expected volatility	70%	75%
Expected term (years)	5.79 – 8.79	6.79 – 9.79

The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and our historical and implied future volatility. The risk free interest rate and expected term assumptions depend on the estimated timing of FDA approval. In addition, the Company incorporated the estimated number and timing of valuation measurement dates in the calculation of the success payment liability.

In October 2013, the Company entered into a license agreement with FHCRC, pursuant to which the Company acquired an exclusive, worldwide, sublicensable license under certain patent rights, and a non-exclusive, worldwide, sublicensable license under certain technology, to research, develop, manufacture, improve, and commercialize products and processes covered by such patent rights or incorporating such technology for all therapeutic uses for the treatment of human cancer. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including target specific constructs and customized spacer regions, TCR constructs, and their use for immunotherapy. The Company classifies on the consolidated statement of operations payments accrued or made under its licensing arrangements based on the underlying nature of the expense. Expenses related to the reimbursement of legal and patent costs are classified as general and administrative because the nature of the expense is not related to the research or development of the technologies the Company is licensing.

The Company also agreed to pay FHCRC annual maintenance fees, milestone payments, and royalties as a percentage of net sales of licensed products. After five years the Company is obligated to pay a $0.1 million minimum annual royalty, with such payments creditable against royalties.

Milestone payments to FHCRC of up to an aggregate of $6.8 million per licensed product, including JCAR014 and JCAR017, are triggered upon the achievement of specified clinical and regulatory milestones and are not creditable against royalties. The Company may terminate the license agreement at any time with advance written notice.

Memorial Sloan Kettering Cancer Center

In November 2013, the Company entered into a sponsored research agreement with MSK, focused on research and development relating to chimeric antigen receptor T cell technology. The research is conducted under project orders containing plans and budgets approved by the parties. The Company also entered into a master clinical study agreement with MSK for clinical studies to be conducted at MSK on the Company's behalf. Each such study will be conducted in accordance with a written plan and budget and protocol, or separate clinical trial agreement, approved by the parties. The Company recognized $4.7 million, $2.5 million, and $0.5 million of research and development expenses in connection with its research and clinical agreements with MSK for the years ended December 31, 2015 and 2014, and for the period from August 5, 2013 to December 31, 2013, respectively.

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The Company granted MSK rights to certain share-based success payments. Under the terms of this arrangement, the Company may be required to make success payments to MSK based on the increases in the estimated fair value of the Company's common stock. The potential payments are based on multiples of increased value ranging from 10x to 30x based on a comparison of the fair value of the common stock relative to its original $4.00 issuance price. The payments are based on whether the value of the Company's common stock meets or exceeds certain specified threshold values ascending from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. The aggregate success payments to MSK are not to exceed $150 million, which would only occur at a stock valuation of $120.00 per share. In October 2015, the Company entered into an agreement with MSK in which certain indirect costs related to certain clinical studies and research projects conducted by MSK are creditable against any success payments, and the Company amended this agreement in December 2015. The term of the success payment agreement ranges from eight to eleven years depending upon when or if the company receives FDA approval of certain of its product candidates as specified in the agreement.

The following table summarizes all possible MSK success payments, which are payable in cash or publicly-traded equity at the Company's discretion:

Multiple of Initial Equity Value at issuance	10.0x	15.0x	30.0x
Per share common stock price required for payment	$40.00	$60.00	$120.00
Success payment(s) (in millions)	$ 10	$ 70	$ 70

The success payments will be owed, if the value of the Company's common stock on contractually specified valuation measurement dates equals or exceeds the above outlined multiples. The valuation measurement dates are triggered by events which include an initial public offering of the Company's stock, a merger, an asset sale, or the sale of the majority of the shares held by certain of the Company's stockholders or the last day of the term of the success payment agreement. If a higher success payment tier is met at the same time a lower tier is met, both tiers will be owed. Any previous success payments made to MSK are credited against the success payment owed as of any valuation measurement date, so that MSK does not receive multiple success payments in connection with the same threshold. A payment may be triggered on the first anniversary of the closing of the IPO (or the date that is 90 days following such anniversary, at the Company's option, if the Company is contemplating a capital market transaction during such 90 day period). The value of any such success payment will be determined by the average trading price of a share of the Company's common stock over the consecutive 90-day period preceding such determination date.

In December 2015, a success payment to MSK was triggered in the amount of $10.0 million, less indirect cost offsets that will be determined at the time of payment in March 2016. This success payment represents the success payment identified on the table above for the 10.0x Multiple of Initial Equity Value trigger. Going forward, the only potential remaining success payment obligations relate to the 15.0x and 30.0x Multiple of Initial Equity Value.

As of December 31, 2015 and 2014, the estimated fair value of the success payment obligation to MSK after giving effect to the success payment achieved in December 2015, was approximately $48.9 million and $56.8 million, respectively. With respect to the MSK success payment obligations, the Company recognized research and development expense of $7.3 million and $23.7 million in the years ended December 31, 2015 and 2014, respectively. The expense recorded in both periods represents the change in the MSK success payment liability during such periods, the success payment amount achieved in 2015, and twelve months of accrued expense. The MSK success payment liabilities on the consolidated balance sheets as of December 31, 2015 and December 31, 2014 were $31.0 million and $23.7 million, respectively.

The Company's liability for share-based success payments under the MSK collaboration is carried at fair value and recognized as expense over the term of the five-year collaboration agreement. To determine the estimated

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fair value of the success payment liability the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the calculation of the estimated fair value of the success payment liability as of the following balance sheet dates:

	December 31,	
Assumptions	2015	2014
Fair value of common stock	$ 43.97	$ 52.22
Risk free interest rate	1.91% – 2.20%	1.95% – 2.16%
Expected volatility	70%	75%
Expected term (years)	5.89 – 8.89	6.89 – 9.89

The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and our historical volatility. The risk free interest rate and expected term assumptions depend on the estimated timing of FDA approval. In addition, the Company incorporated the estimated number and timing of valuation measurement dates in the calculation of the success payment liability.

In November 2013, the Company entered into a license agreement with MSK, pursuant to which the Company acquired a worldwide, sublicensable license to specified patent rights and intellectual property rights related to certain know-how to develop, make, and commercialize licensed products and to perform services for all therapeutic and diagnostic uses, which license is exclusive with respect to such patent rights and tangible materials within such know-how, and non-exclusive with respect to such know-how and related intellectual property rights. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including bispecific and armored CARs, and their use for immunotherapy. The Company recorded $6.9 million in the period from August 5, 2013 to December 31, 2013 for the upfront license fee, which was recorded as research and development expense.

The Company also agreed to pay MSK milestone payments and royalties as a percentage of net sales of licensed products and services by us or our affiliates and sublicensees. After five years the Company is obligated to pay a $0.1 million minimum annual royalty, with such payments credible against royalties.

Milestone payments to MSK of up to an aggregate of $6.8 million per licensed product, including JCAR015, are triggered upon the achievement of specified clinical and regulatory milestones and are not creditable against royalties. The Company may terminate the license agreement at any time with advance written notice, but if the Company has commenced the commercialization of licensed products, the Company can only terminate at will if it ceases all development and commercialization of licensed products.

St. Jude Children's Research Hospital/Novartis

In December 2013, the Company entered into an agreement with St. Jude ("St. Jude License Agreement"), pursuant to which the Company (1) obtained control over, and the obligation to pursue and defend, St. Jude's causes of action in Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn.), which concerned both U.S. Patent No. 8,399,645 (the "'645 Patent") and a contractual dispute between St. Jude and the Trustees of the University of Pennsylvania ("Penn") and (2) acquired an exclusive, worldwide, royalty-bearing license under certain patent rights owned by St. Jude, including the '645 Patent, to develop, make, and commercialize licensed products and services for all therapeutic, diagnostic, preventative, and palliative uses. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs capable of signaling both a primary and a costimulatory pathway. Together with St. Jude, the Company was a party in, and was adverse to Penn and Novartis Pharmaceutical Corporation ("Novartis") in, that litigation (the "Penn litigation"), which was settled by the parties in April 2015.

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The Company paid $25.0 million in the period from August 5, 2013 to December 31, 2013, as a license fee, which was recorded as research and development expense. The Company also agreed to pay to St. Jude milestone payments and royalties as a percentage of net sales of licensed products and services, and a percentage of St. Jude's reasonable legal fees incurred in connection with the Penn litigation. For the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013, $5.5 million, $3.6 million and $0.2 million, respectively, has been recorded as litigation expense for legal reimbursements. The Company is obligated to pay a $0.1 million minimum annual royalty for the first two years of the agreement and a $0.5 million minimum annual royalty thereafter.

Milestone payments to St. Jude of up to an aggregate of $62.5 million are triggered upon the achievement of specified clinical, regulatory, and commercialization milestones for licensed products, including JCAR014 or JCAR017, and are not creditable against royalties. The Company can terminate the agreement for any reason upon advance written notice.

In April 2015, the Company and St. Jude agreed to settle the Penn litigation with Penn and Novartis. In connection with such settlement, in April 2015, the Company entered into a sublicense agreement (the "Penn/Novartis Sublicense Agreement") with Penn and an affiliate of Novartis pursuant to which the Company granted to Novartis a non-exclusive, royalty-bearing sublicense under certain patent rights, including the '645 Patent, to develop, make, and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative, and palliative uses. This sublicense is not sublicensable without the Company's prior written consent, although Novartis may authorize third parties to act on its behalf with respect to the manufacture, development, or commercialization of Novartis' licensed products and licensed services. Under the Penn/Novartis Sublicense Agreement, Novartis paid the Company an initial license fee of $12.3 million, which was recorded as revenue for the year ended December 31, 2015. In addition, Novartis is also required to pay mid-single digit royalties on the U.S. net sales of products and services related to the disputed contract and patent claims (the "Royalty Payments"), a low double digit percentage of the royalties Novartis pays to Penn for global net sales of those products (the "Penn Royalty Payments"), and milestone payments upon the achievement of specified clinical, regulatory, and commercialization milestones for licensed products (the "Milestone Payments"). If the Company achieves any of the milestones with respect to its own products leveraging the same patents, prior to Novartis, the related Milestone Payment will be reduced by 50%. In addition, if the Company achieves any milestone after Novartis, the Company will reimburse Novartis 50% of any Milestone Payment previously paid by Novartis to the Company in respect of such milestone. These milestones largely overlap with the milestones for which the Company may owe a payment to St. Jude under the St. Jude License Agreement and the Milestone Payments would in effect serve to partially offset the Company's obligations to St. Jude with respect to such milestones.

Novartis may terminate the Penn/Novartis Sublicense Agreement at will upon advance written notice to the Company.

Under a separate agreement with St. Jude, the Company agreed to pay St. Jude $5.3 million as reimbursement of litigation expenses. The Company and St. Jude also amended the St. Jude License Agreement to provide the terms by which the Penn/Novartis Sublicense Agreement would be treated under the St. Jude License Agreement.

Seattle Children's Research Institute

In February 2014, the Company entered into a sponsored research agreement with Seattle Children's Research Institute ("SCRI") pursuant to which the Company committed to provide research funding to SCRI totaling not less than $2.1 million over a period of five years. Effective April 1, 2015, the sponsored research agreement was amended to extend the term of the agreement through April 2020, thereby increasing the minimum funding obligations by an additional $0.3 million. The research is conducted under project orders containing plans and budgets approved by the parties. The Company has also entered into clinical support and manufacturing services

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agreements with SCRI related to the Company's JCAR017 trials. The clinical support agreement includes a commitment by the Company to provide funding to SCRI totaling not less than $3.8 million over a period of five years. The Company recognized $2.5 million and $0.4 million of research and development expenses in connection with its sponsored research, clinical support and manufacturing services agreements with SCRI for the years ended December 31, 2015 and 2014, respectively.

In February 2014, the Company entered into a license agreement with SCRI that grants the Company an exclusive, worldwide, royalty-bearing sublicensable license to certain patent rights to develop, make and commercialize licensed products and to perform licensed services for all therapeutic, prophylactic, and diagnostic uses. Effective June 2015, the license agreement was amended to include additional patent rights. The Company paid $0.2 million to SCRI in the year ended December 31, 2014 for the upfront license fee, which was recorded as research and development expense.

The Company is required to pay to SCRI annual license maintenance fees, creditable against royalties and milestone payments due to SCRI, of $50,000 per year for the first five years and $0.2 million per year thereafter.

The Company also agreed to pay SCRI milestone payments and royalties as a percentage of net sales of licensed products and licensed services. Milestone payments to SCRI related to licensed products, including JCAR014 and JCAR017, are triggered upon the achievement of specified clinical, regulatory, and commercialization milestones and are not creditable against future royalties. The Company may terminate the license agreement for any reason with advance written notice.

Opus Bio

In December 2014, the Company entered into a license agreement with Opus Bio, Inc. pursuant to which the Company was granted an exclusive, worldwide, sublicensable license under certain patent rights and data to research, develop, make, have made, use, have used, sell, have sold, offer to sell, import and otherwise exploit products that incorporate or use engineered T cells directed against CD22 and that are covered by such patent rights or use or incorporate such data. Certain of the licensed patent rights are in-licensed by Opus Bio from the National Institutes of Health ("NIH"). Under the agreement, the Company is required to use commercially reasonable efforts to research, develop, and commercialize licensed products. Such development must be in accordance with the timelines provided in the license agreement for achievement of certain clinical, regulatory, and commercial benchmarks, and with the development plans set forth in Opus Bio's agreements with the NIH.

During the year ended December 31, 2014, the Company made an upfront payment to Opus Bio of $20.0 million, which was recorded as research and development expense. Additionally, the Company issued to Opus Bio 1,602,564 shares of its common stock, and recognized $64.1 million in research and development expense based on the fair value of the stock on the issuance date of December 24, 2014.

Upon achievement of certain clinical, regulatory, and commercial milestones set forth in the license agreement, the Company will be obligated to pay Opus Bio additional consideration. The consideration due upon achievement of the first three clinical milestones would consist of additional shares of our common stock in an amount equal to the dollar value specified for the applicable milestone, which is $52.5 million in the aggregate for the three milestones, divided by the greater of $10.92 and the arithmetic average of the daily volume- weighted average price of our common stock on The NASDAQ Global Select Market over the 30 trading days preceding the achievement of the milestone, up to a maximum of 4,807,692 shares in the aggregate (this minimum per share value and maximum number of shares subject, in each case, to adjustment for any stock dividend, stock split, combination of shares, or other similar events). As disclosed in Note 18, Subsequent Events, the first of these milestones was achieved in January 2016 and the Company issued 408,068 shares of its common stock as payment. Upon achievement of any subsequent milestones beyond the first three, the Company will be obligated to pay Opus Bio cash consideration, which potential milestone payments total $215.0 million in

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the aggregate. Once certain milestones have been achieved, the Company will be required to spend at least $2.5 million per year on development and commercialization of licensed products.

The license agreement further provides that the Company is required to pay to Opus Bio tiered royalties based on annual net sales of licensed products by us and by sublicensees. The Company will also be required to make certain pass-through payments owed by Opus Bio to NIH under its NIH license agreements, including certain patent costs, development and commercial milestones of up to $2.8 million in the aggregate, royalties based on annual net sales. The Company may terminate the agreement at will upon advance written notice.

Fate Therapeutics

In May 2015, the Company entered into a collaboration and license agreement with Fate Therapeutics, Inc. (“Fate Therapeutics”), to identify and utilize small molecules to modulate the Company’s genetically-engineered T cell product candidates to improve their therapeutic potential for cancer patients. The Company paid an upfront fee of $5.0 million in cash and purchased 1,000,000 shares in Fate Therapeutics common stock at a purchase price of $8.00 per share, representing an approximately 5% ownership interest in Fate Therapeutics. The $5.0 million upfront fee and the premium paid for the common stock of $0.8 million were recorded as research and development expense for the year ended December 31, 2015. The investment in Fate Therapeutics is classified as available-for-sale, and reported at fair value with unrealized gains and losses included in accumulated other comprehensive income (loss). The Company also agreed to provide Fate Therapeutics with research funding of $2.0 million per year during the initial four year research term. The Company has an option to extend the collaboration for two additional years, subject to payment of an extension fee and additional annual research funding. Under the collaboration and license agreement, for each product developed by the Company that incorporates modulators identified through the collaboration, the Company will also be required to pay Fate Therapeutics target selection fees and milestone payments upon achievement of clinical, regulatory, and commercial milestones, as well as low single-digit royalties on net sales. The Company can terminate the agreement at will upon advance written notice, but such termination may not be effective any earlier than May 2017. In addition to the upfront fee of $5.0 million and the premium paid for the common stock of $0.8 million, the Company recognized $1.3 million of research and development expenses in connection with its collaboration agreement with Fate Therapeutics for the year ended December 31, 2015.

Editas Medicine

In May 2015, the Company entered into a collaboration and license agreement with Editas Medicine, Inc. (“Editas”), to pursue research programs utilizing Editas’ genome editing technologies with Juno’s CAR and TCR technologies. The Company paid an upfront fee of $25.0 million in cash, which was recorded as research and development expense for the year ended December 31, 2015. The Company also agreed to provide Editas with research funding of up to $22.0 million over the initial five year research term. The Company and Editas may mutually agree to extend the collaboration for two additional years, subject to payment of extension fees. Editas is also eligible to receive future research, regulatory, and commercial sales milestones for each program. Following the approval of any products resulting from the alliance, Editas is also eligible to receive tiered royalties. The Company can terminate the agreement at will upon advance written notice. In addition to the upfront fee of $25.0 million, the Company recognized $1.9 million of research and development expenses in connection with its collaboration agreement with Editas for the year ended December 31, 2015.

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5. Cash Equivalents and Marketable Securities

The following tables summarize the estimated fair value of our cash equivalents and marketable securities and the gross unrealized holding gains and losses (in thousands):

	December 31, 2015			
	Amortized Cost	Gross Unrealized Holding Gains	Gross Unrealized Holding Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$177,164	$ —	$ —	$ 177,164
Commercial paper	45,352	—	—	45,352
U.S. government and agency securities	2,000	—	—	2,000
Corporate debt securities	5,040	—	—	5,040
Total cash equivalents	229,556	—	—	229,556
Marketable securities:				
Commercial paper	73,078	—	—	73,078
U.S. government and agency securities	470,519	2	(485)	470,036
Corporate debt securities	148,143	1	(245)	147,899
Total marketable securities	691,740	3	(730)	691,013
Long-term marketable securities:				
U.S. government and agency securities	204,551	1	(770)	203,782
Corporate debt securities	65,898	33	(195)	65,736
Equity securities	7,190	—	(3,820)	3,370
Total long-term marketable securities	$277,639	$ 34	$ (4,785)	$ 272,888

	December 31, 2014			
	Amortized Cost	Gross Unrealized Holding Gains	Gross Unrealized Holding Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$223,745	$ —	$ —	$ 223,745
Commercial paper	13,294	—	—	13,294
U.S. government and agency securities	7,582	—	—	7,582
Corporate debt securities	1,702	—	—	1,702
Total cash equivalents	246,323	—	—	246,323
Marketable securities:				
Commercial paper	1,999	—	—	1,999
U.S. government and agency securities	47,868	—	(21)	47,847
Corporate debt securities	29,863	—	(37)	29,826
Total marketable securities	79,730	—	(58)	79,672
Long-term marketable securities:				
U.S. government and agency securities	34,898	—	(25)	34,873
Corporate debt securities	3,544	1	(7)	3,538
Total long-term marketable securities	$ 38,442	$ 1	$ (32)	$ 38,411

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The following tables summarize the gross unrealized holding losses and fair value for investments in an unrealized loss position, and the length of time that individual securities have been in a continuous loss position (in thousands):

	December 31, 2015					
	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Marketable securities:						
U.S. government and agency securities	$457,641	$ (485)	$ —	$ —	$457,641	$ (485)
Corporate debt securities	144,499	(245)	—	—	144,499	(245)
Total marketable securities	602,140	(730)	—	—	602,140	(730)
Long-term marketable securities:						
U.S. government and agency securities	190,767	(770)	—	—	190,767	(770)
Corporate debt securities	50,591	(195)	—	—	50,591	(195)
Equity securities	3,370	(3,820)	—	—	3,370	(3,820)
Total long-term marketable securities	$244,728	$ (4,785)	$ —	$ —	$244,728	$ (4,785)

	December 31, 2014					
	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Marketable securities:						
U.S. government and agency securities	$ 43,332	$ (21)	$ —	$ —	$ 43,332	$ (21)
Corporate debt securities	26,611	(37)	—	—	26,611	(37)
Total marketable securities	69,943	(58)	—	—	69,943	(58)
Long-term marketable securities:						
U.S. government and agency securities	33,873	(25)	—	—	33,873	(25)
Corporate debt securities	2,003	(7)	—	—	2,003	(7)
Total long-term marketable securities	$ 35,876	$ (32)	$ —	$ —	$ 35,876	$ (32)

The Company evaluated its securities for other-than-temporary impairment and considers the decline in market value for the securities to be primarily attributable to current economic and market conditions. For the debt securities, it is not more likely than not that the Company will be required to sell the securities, and the Company does not intend to do so prior to the recovery of the amortized cost basis. The unrealized loss for equity securities is related to the Company's investment in Fate Therapeutics. The Company has evaluated the near-term prospects of the Fate Therapeutics investment in relation to the severity and duration of the impairment and based on that evaluation, the Company has the ability and intent to hold this investment until a recovery of fair value. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of December 31, 2015 and 2014.

All of our marketable securities have an effective maturity date of three years or less and are available for use and therefore classified as available-for-sale.

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6. Fair Value Measurements

The following tables set forth the fair value of the Company's financial assets and liabilities measured at fair value on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	December 31, 2015			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$177,164	$ —	$ —	$ 177,164
Commercial paper	—	118,430	—	118,430
U.S. government and agency securities	—	675,818	—	675,818
Corporate debt securities	—	218,675	—	218,675
Equity securities	3,370	—	—	3,370
Total financial assets	$180,534	$1,012,923	$ —	$1,193,457
Financial Liabilities:				
Success payment liabilities	$ —	$ —	$ 64,829	$ 64,829
Contingent consideration	—	—	37,266	37,266
Total financial liabilities	$ —	$ —	$102,095	$ 102,095

	December 31, 2014			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$223,745	$ —	$ —	$ 223,745
Commercial paper	—	15,293	—	15,293
U.S. government and agency securities	—	90,302	—	90,302
Corporate debt securities	—	35,066	—	35,066
Total financial assets	$223,745	$ 140,661	$ —	$ 364,406
Financial Liabilities:				
Success payment liabilities	$ —	$ —	$ 84,920	$ 84,920
Total financial liabilities	$ —	$ —	$ 84,920	$ 84,920

The Company measures the fair value of money market funds based on quoted prices in active markets for identical assets or liabilities. The Level 2 marketable securities include U.S. government and agency securities, corporate debt securities, and commercial paper and are valued either based on recent trades of securities in inactive markets or based on quoted market prices of similar instruments and other significant inputs derived from or corroborated by observable market data.

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The following table sets forth a summary of the changes in the fair value of the Company's Level 3 financial liabilities (in thousands):

	Success Payment Liabilities	Contingent Consideration	Total
Balance at December 31, 2013	$ —	$ —	$ —
Additions	—	—	—
Changes in fair value (1)	84,920	—	84,920
Balance at December 31, 2014	84,920	—	84,920
Additions	—	37,188	37,188
Payments	(71,648)	—	(71,648)
Changes in fair value (1)	51,557	78	51,635
Balance at December 31, 2015	$ 64,829	$ 37,266	$102,095

(1) The amount of success payments achieved and changes in fair value for success payment liabilities and contingent consideration are recorded in research and development expense in the consolidated statements of operations.

As of December 31, 2015 and 2014, the estimated fair value of the success payment obligations after giving effect to the success payments achieved by FHCRC and MSK was approximately $116.2 million and $195.9 million, respectively. Included in research and development expense for the years ended December 31, 2015 and 2014 were success payment expenses of $51.6 million and $84.9 million, respectively. There was no expense in 2013 related to the success payments. See Note 4, Collaboration and License Agreements, for additional discussion of estimated fair value of the success payment obligations.

The Company utilizes significant estimates and assumptions in determining the estimated success payment and contingent consideration liabilities and associated expense at each balance sheet date. A small change in the Company's stock price may have a relatively large change in the estimated fair value of the success payment liability and associated expense.

In connection with the acquisitions of Stage and X-Body, the Company also agreed to pay additional amounts based on the achievement of certain milestones. This contingent consideration is measured at fair value and is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The valuation of contingent consideration uses assumptions the Company believes would be made by a market participant. The Company assesses these estimates on an on-going basis as additional data impacting the assumptions is obtained.

Contingent consideration may change significantly as development progresses and additional data are obtained, impacting the Company's assumptions regarding probabilities of successful achievement of related milestones used to estimate the fair value of the liability and the timing in which they are expected to be achieved. In evaluating the fair value information, judgment is required to interpret the market data used to develop the estimates. The estimates of fair value may not be indicative of the amounts that could be realized in a current market exchange. Accordingly, the use of different market assumptions and/or different valuation techniques could result in materially different fair value estimates.

The significant unobservable inputs used in the measurement of fair value of the Company's contingent consideration are probabilities of successful achievement of the milestones, the period in which these milestones are expected to be achieved ranging from 2016 to 2043, and a discount rate of 17.0%. Significant increases or decreases in any of the probabilities of success would result in a significantly higher or lower fair value measurement, respectively. Significant increases or decreases in these other inputs would result in a significantly lower or higher fair value measurement, respectively.

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As of December 31, 2015, the estimated fair value of the contingent consideration associated with the Stage acquisition was $28.3 million. As of December 31, 2015, the estimated fair value of the contingent consideration associated with the X-Body acquisition was $9.0 million. The Company recognized an expense of $0.1 million in research and development expense in the year ended December 31, 2015 related to the change in fair value of the contingent consideration.

7. Property and Equipment, Net

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2015	2014
Construction in progress	$23,214	$ —
Build-to-suit asset	9,910	—
Laboratory equipment	9,706	3,921
Computer equipment, software and other	773	198
Leasehold improvements	300	98
Property and equipment, at cost	43,903	4,217
Less: Accumulated depreciation	(1,817)	(199)
Property and equipment, net	$42,086	$4,018

Depreciation expense related to property and equipment was $1.6 million and $0.2 million for the years ended December 31, 2015 and 2014, respectively. Depreciation expense was immaterial in 2013.

8. Accrued Liabilities and Other Current Liabilities

Accrued liabilities and other current liabilities consisted of the following (in thousands):

	December 31,	
	2015	2014
Accrued clinical expenses	$ 7,174	$ 564
Accrued research and development expenses	7,132	2,724
Accrued bonus expense	7,054	3,106
Accrued employee expenses	3,281	531
Accrued milestones	2,827	—
Accrued legal expenses	1,987	4,309
Accrued offering costs	—	1,456
Other	3,921	1,887
Total accrued liabilities and other current liabilities	$33,376	$14,577

9. Build-to-Suit Lease Obligation

In February 2015, the Company entered into a lease for an approximately 68,000 square foot manufacturing facility in Bothell, Washington, which commenced in March 2015. The Company is responsible for the leasehold improvements required to remodel the facility and bears the majority of the construction risk. ASC 840-40, Leases—Sale-Leaseback Transactions, requires the Company to be considered the owner of the building solely for accounting purposes during the construction period, even though it is not the legal owner. In connection with the accounting for this transaction, the Company capitalized $9.9 million as a build-to-suit property within property and equipment, net and recognized a corresponding build-to-suit lease obligation for the same amount.

The Company bifurcates its lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is

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treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the consolidated statements of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

At December 31, 2015, $0.4 million of the build-to-suit lease obligation, representing the expected reduction in the liability over the next twelve months, is classified as a current liability and $9.3 million is classified as a non-current liability on the consolidated balance sheets.

10. Common Stock

As of December 31, 2015 and 2014, there were 97,247,058 shares and 82,073,647 shares of common stock outstanding, excluding 5,153,445 shares and 8,352,714 shares, respectively, of restricted stock outstanding that are subject to vesting requirements.

As of December 31, 2015 and 2014, the Company had reserved 5,614,926 shares and 2,720,351 shares of common stock for future issuance upon the exercise of outstanding stock options and vesting of outstanding RSUs.

Each share of common stock is entitled to one vote, subject to any special voting rights of preferred stock, none of which was outstanding as of December 31, 2015 and 2014.

11. Stock-Based Compensation

Equity Incentive Plans

Until the IPO, the Company maintained and granted restricted stock awards and option awards under the 2013 Stock Incentive Plan (the “2013 Plan”) for employees, directors, consultants, and advisors to the Company. The 2013 Plan terminated as of the IPO as to future awards, but will continue to govern restricted stock awards and option awards previously granted thereunder. Upon termination of the 2013 Plan, the 453,547 shares that were then unissued and available for future award under the 2013 Plan became available under the 2014 Equity Incentive Plan (the “2014 Plan”), described below.

In December 2014, the Company’s board of directors adopted the 2014 Plan. The 2014 Plan became effective the day prior to the effective date of the registration statement for the Company’s IPO, and enables the grant of incentive and non-qualified stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights, and other stock-based awards to employees, directors, consultants, and advisors to the Company. Terms of the awards, including vesting requirements, are determined by the Company’s board of directors or by a committee appointed by our board of directors. The 2014 Plan provides for an initial reserve of 6,200,000 shares, plus the 453,547 shares initially transferred from the 2013 Plan, and any share awards that subsequently are forfeited or lapse unexercised under the 2013 Plan.

The 2014 Plan provides for an annual increase in the shares available for issuance thereunder, to be added on the first day of each fiscal year, beginning with the year ending December 31, 2015 and continuing until the expiration of the 2014 Plan, equal to the lesser of (i) four percent (4%) of the outstanding shares of the Company’s common stock on the last day of the immediately preceding fiscal year or (ii) such number of shares determined by the board of director or an authorized committee of the board of directors; provided, however, that such determination under clause (ii) will be made no later than the last day of the immediately preceding fiscal year. As of December 31, 2015, the total number of shares available for issuance pursuant to future awards under the 2014 Plan was 7,021,850. As a result of the operation of this provision, on January 1, 2016, an additional 4,096,020 shares became available for issuance under the 2014 Plan.

Generally, awards granted by the Company under the 2013 Plan and 2014 Plan vest over four years.

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2014 Employee Stock Purchase Plan

In December 2014, the Company's board of directors adopted the 2014 employee stock purchase plan (the "ESPP"). The ESPP is administered by the Company's board of directors or by a committee appointed by the board of directors. The ESPP allows eligible employees to purchase shares of the Company's common stock at a discount through payroll deductions of up to 15% of their eligible compensation, subject to any plan limitations. The initial offering period under the ESPP began on December 19, 2014 and ended on November 16, 2015, on which date participating employees purchased shares at $20.40 per share, which is 85% of the price to the public of a share of the Company's common stock in its IPO. Following the initial offering period, the ESPP provides for consecutive six-month offering periods beginning on the first trading day on or after November 15 and May 15 of each year, and at the end of each offering period, employees are able to purchase shares at 85% of the lower of the fair market value of the Company's common stock on the first trading day of the offering period or on the last day of the offering period.

The Company initially reserved 1,500,000 shares of common stock for issuance under the ESPP. As of December, 31, 2015, 67,664 shares had been issued under the ESPP. As of December 31, 2014, no shares had been issued under the ESPP.

The ESPP also provides for an annual share increase, to be added on the first day of each fiscal year, beginning with the year ending December 31, 2015 and continuing until the expiration of the ESPP, equal to the lesser of (i) one and a half percent (1.5%) of the outstanding shares of the Company's common stock on the last day of the immediately preceding fiscal year or (ii) such number of shares determined by the board of directors or authorized committee of the board of directors. As of December 31, 2015, the total number of shares available for future issuance pursuant to the ESPP was 2,788,731. As a result of the operation of this provision, on January 1, 2016, an additional 1,536,008 shares became available for issuance under the ESPP.

Stock-Based Compensation

Stock-based compensation expense is recognized in our consolidated statements of operations as follows (in thousands):

	Year Ended December 31,		Period from August 5, 2013
	2015	2014	December 31, 2013
Research and development	$ 17,089	$ 2,908	$ 125
General and administrative	14,852	3,596	—
Total stock-based compensation expense (1)	$ 31,941	$ 6,504	$ 125

(1) Included in stock-based compensation expense recognized for the years ended December 31, 2015 and 2014, is $8.1 million and $2.8 million, respectively, related to service providers other than our employees, scientific founders, and directors, including $6.2 million and $2.5 million, respectively, for a former co-founding director who became a consultant upon his departure from the board of directors.

As of December 31, 2015, there was $107.2 million of total unrecognized stock-based compensation cost related to employees. Of the $107.2 million in unrecognized stock-based compensation costs, $20.3 million is related to restricted stock and RSUs, and $86.9 million is related to stock options. As of December 31, 2015, the Company expects to recognize these costs over a remaining weighted average period of 2.39 years for restricted stock and RSUs, and 3.06 years for stock options.

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Restricted Stock and RSUs

A summary of the Company's restricted stock and RSU activity is as follows:

	Shares	Weighted Average Fair Value at Date of Grant per Share
Unvested shares as of December 31, 2014	8,352,714	$ 1.46
Granted	395,987	49.51
Vested	(3,245,512)	0.51
Forfeited	(26,589)	0.60
Unvested shares as of December 31, 2015	5,476,600	$ 3.72

Management estimates expected forfeitures and recognizes compensation costs only for those equity awards expected to vest. The fair value of awards vested during the years ended December 31, 2015 and 2014 and for the period from August 5, 2013 to December 31, 2013 was $158.5 million, $21.4 million, and $0.4 million, respectively.

Stock Options

A summary of the Company's stock option activity is as follows:

	Number of Stock Options	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2014	2,720,351	$ 7.23		
Granted	2,914,406	49.08		
Exercised	(268,765)	7.39		
Cancelled	(147,053)	19.20		
Outstanding as of December 31, 2015	5,218,939	$ 30.25	9.13	$ 86,609
Exercisable as of December 31, 2015	806,477	$ 16.17	8.70	$ 23,160

The fair value of each stock option granted has been determined using the Black-Scholes option pricing model. The material factors incorporated in the Black-Scholes model in estimating the fair value of the options granted to employees, directors, and consultants included the following:

	December 31,	
Assumptions	2015	2014
Risk free interest rate	1.53% – 2.35%	1.59% – 2.17%
Expected volatility	70% – 80%	75%
Expected life (years)	6.02 – 10	6.25 – 10
Expected dividend yield	0%	0%

For employees, scientific founders, and directors, the expected life was calculated based on the simplified method as permitted by the SEC Staff Accounting Bulletin No. 110, Share-Based Payment. For other service providers, the expected life was calculated using the contractual term of the award. Management's estimate of expected volatility was based on available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and its own historical and implied future

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volatility. The risk-free interest rate is based on a U.S. Treasury instrument whose term is consistent with the expected life of the stock options. In addition to the assumptions above, management made an estimate of expected forfeitures and is recognizing compensation costs only for those equity awards expected to vest. The weighted average grant date fair value of options granted for the years ended December 31, 2015 and 2014 was $32.51 per share and $4.86 per share, respectively. The intrinsic value of options exercised during the year ended December 31, 2015 was $10.9 million. No options were exercised as of December 31, 2014.

12. Accumulated Other Comprehensive Income (Loss)

The components of accumulated other comprehensive income (loss) and the adjustments to other comprehensive income (loss) are as follows (in thousands):

	Foreign Currency Translation Adjustments	Net Unrealized Gains (Losses) On Available-For-Sale Investments	Accumulated Other Comprehensive Income (Loss)
Balance at December 31, 2013	$ —	$ —	$ —
Other comprehensive loss	—	(90)	(90)
Balance at December 31, 2014	—	(90)	(90)
Other comprehensive loss	(605)	(5,388)	(5,993)
Balance at December 31, 2015	$ (605)	$ (5,478)	$ (6,083)

13. Income Taxes

The Company recorded an income tax benefit of $2.8 million on a pre-tax loss of $242.1 million for year ended December 31, 2015. Of the $2.8 million total tax benefit, $1.7 million relates to our Germany subsidiary's net loss incurred in the period from the acquisition date to December 31, 2015. The remaining $1.1 million of income tax benefit relates to the release of valuation allowance on the U.S. deferred tax assets as a result of the deferred tax liabilities established for definite lived intangible assets from the acquisition of X-Body.

The Celgene Collaboration Agreement became effective on July 31, 2015. In addition, on August 4, 2015 the Initial Closing under the Purchase Agreement with Celgene occurred. The Company does not expect that the $849.8 million in consideration allocable to the sale of the Company's shares and future rights to purchase shares of common stock of the Company under the Purchase Agreement will result in gain or loss in accordance with the Internal Revenue Code. The Company has determined that the $150.2 million consideration allocable to the upfront payment for the Celgene Collaboration Agreement is fully taxable, partially in 2015, with the remainder in 2016.

Loss before income taxes is attributable to the following tax jurisdictions (in thousands):

	Year Ended December 31,		Period from August 5, 2013 to December 31, 2013
	2015	2014	
United States	$236,028	$243,407	$ 51,820
Foreign	6,108	—	—
Loss before income taxes	$242,136	$243,407	$ 51,820

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The components of the benefit for income taxes are as follows (in thousands):

	Year Ended December 31, 2015	Year Ended December 31, 2014	Period from August 5, 2013 to December 31, 2013
Deferred:			
United States	$ 1,100	$ —	$ —
Foreign	1,660	—	—
Total deferred	2,760	—	—
Provision for income taxes	$ 2,760	$ —	$ —

As of December 31, 2015 and 2014, the Company had U.S. federal net operating loss ("NOL") carryforwards of approximately $167.3 million and $51.1 million, respectively, which are available to reduce future taxable income. Of these NOL carryforwards, a $3.5 million benefit will be recorded to equity when utilized. The Company also had U.S. federal and state tax credits of $14.6 million and $1.8 million as of December 31, 2015 and 2014, respectively, which may be used to offset future tax liabilities. The NOL and tax credit carryforwards will begin to expire in 2033. The NOL and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders over a three year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code of 1986 ("IRC"). This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. Subsequent ownership changes may further affect the limitation in future years. The Company also has German NOL carryforwards of $4.9 million, which have an indefinite carryforward period.

A reconciliation of income taxes computed using the U.S. federal statutory rate to that reflected in operations follows:

	Year Ended December 31, 2015	Year Ended December 31, 2014	Period from August 5, 2013 to December 31, 2013
Federal statutory tax	35.0%	34.0%	34.0%
Foreign tax rate differential	(0.1)	—	—
Valuation allowance	(36.2)	(32.4)	(30.0)
Tax credits	3.8	0.7	0.2
Other	(1.4)	(2.3)	(4.2)
Total	1.1%	0.0%	0.0%

The effective tax rate for the years ended December 31, 2015 and 2014, and the period from August 5, 2013 to December 31, 2013, is different from the federal statutory tax rate primarily due to a valuation allowance against deferred tax assets as a result of insufficient sources of income.

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The principal components of the Company's net deferred tax liabilities are as follows (in thousands):

	December 31, 2015	December 31, 2014
Deferred tax assets:		
Net operating loss carryforwards	$ 56,862	$ 17,391
Tax credit carryforwards	14,561	1,799
Acquired technology	57,369	45,534
Success payments	47,745	28,872
Stock compensation	4,342	115
Other	5,019	1,430
Gross deferred tax assets	185,898	95,141
Valuation allowance	(183,597)	(94,368)
Deferred tax assets, net of valuation allowance	2,301	773
Deferred tax liabilities:		
Acquired technology	(10,540)	—
Other	(707)	(773)
Deferred tax liabilities	(11,247)	(773)
Net deferred tax liabilities	$ (8,946)	$ —

The valuation allowance relates primarily to net U.S. deferred tax assets from operating losses, research and development tax credit carryforwards, amounts paid and accrued to enter into various agreements for which the tax treatment requires capitalization and amortization, and success-based payments that are accrued but not yet paid for tax purposes. The Company's deferred tax liability relates primarily to technology acquired in the acquisition of Stage.

The Company will continue to maintain a full valuation allowance on its net U.S. deferred tax assets. The assessment regarding whether a valuation allowance is required considers both positive and negative evidence when determining whether it is more-likely-than-not that deferred tax assets are recoverable. In making this assessment, significant weight is given to evidence that can be objectively verified. In its evaluation, the Company considered its cumulative loss in recent years and its forecasted losses in the near-term as significant negative evidence. Based upon a review of the four sources of income identified within ASC 740, the Company determined that the negative evidence outweighed the positive evidence and a full valuation allowance on its U.S. net deferred tax assets will be maintained. The Company will continue to assess the realizability of its deferred tax assets going forward and will adjust the valuation allowance as needed. Increases in the valuation allowance were $89.2 million and $78.8 million for the years ended December 31, 2015 and 2014, respectively. The Company has determined that it is more-likely-than-not that it will realize the benefit of the losses for its Germany subsidiary and has not recorded a valuation allowance against the German deferred tax assets.

The Company follows the provisions of ASC 740, Accounting for Income Taxes, and the accounting guidance related to accounting for uncertainty in income taxes. The Company determines its uncertain tax positions based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is more likely than not to be sustained upon examination by the relevant income tax authorities. As of December 31, 2015 and 2014, the Company has no uncertain tax positions. The Company has not, as yet, conducted a study of tax credit carryforwards. Such a study, if undertaken by the Company, would not result in a material adjustment to the Company's tax credit carryforwards. The Company will recognize both accrued interest and penalties related to unrecognized benefits in income tax expense. The Company is generally subject to examination by the U.S. federal and local income tax authorities for all tax years in which a loss carryforward is available and is subject to examination in Germany for four years.

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14. Commitments and Contingencies

Leases

The Company has entered into various non-cancelable lease agreements for its office, laboratory, and manufacturing spaces with original lease periods expiring between 2016 and 2026. In addition to minimum rent, certain leases require payment of real estate taxes, insurance, common area maintenance charges and other executory costs. These executory costs are not included in the table below. Certain of these arrangements have free or escalating rent payment provisions. The Company recognizes rent expense under such arrangements on a straight-line basis over the effective term of each lease.

The following table summarizes the Company's future minimum lease commitments as of December 31, 2015 (in thousands):

Year ending December 31:	
2016	$ 3,890
2017	4,983
2018	10,652
2019	10,901
2020	11,156
Thereafter	42,031
Total minimum lease payments	$83,613

Rent expense for the years ended December 31, 2015 and 2014, and for the period from August 5, 2013 to December 31, 2013 was $2.3 million, $0.9 million, and $0.1 million, respectively.

Litigation

From time to time, the Company may become involved in litigation or proceedings relating to claims arising from the ordinary course of business.

In connection with the entry by the Company into its exclusive license agreement with St. Jude in December 2013, the Company acquired control of St. Jude's causes of action in the Penn litigation, which concerns both a patent exclusively licensed to the Company by St. Jude and a contractual dispute between St. Jude and Penn. Together with St. Jude, the Company was a party in, and was adverse to Penn and Novartis Pharmaceutical Corporation in, that litigation, which was settled by the parties in April 2015. Under a separate agreement with St. Jude, the Company agreed to reimburse a percentage of St. Jude's reasonable legal fees incurred in connection with the litigation. For the years ended December 31, 2015 and 2014, and for the period from August 5, 2013 to December 31, 2013, the Company recorded litigation expense of $5.5 million, $3.6 million, and $0.2 million, respectively, in the statements of operations for such legal reimbursements.

15. Related-Party Transactions

The Company is party to the Celgene Collaboration Agreement, the Purchase Agreement, a voting agreement, and a registration rights agreement with Celgene, who is a holder of more than 5% of the Company's common stock. See Note 4, Collaboration and License Agreements.

16. Employee Benefit Plan

In January 2014, the Company adopted a 401(k) retirement and savings plan (the "401(k) Plan") covering all employees. The 401(k) Plan allows employees to make pre- and post-tax contributions up to the maximum allowable amount set by the IRS. The Company does not make matching contributions to the 401(k) Plan on behalf of participants.

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17. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for the years ended December 31, 2015 and 2014. The unaudited quarterly information has been prepared on a basis consistent with the audited consolidated financial statements and includes all adjustments that the Company considers necessary for a fair presentation of the information shown. The operating results for any fiscal quarter are not necessarily indicative of the operating results for a full fiscal year or for any future period and there can be no assurances that any trend reflected in such results will continue in the future.

Year Ended December 31, 2015	First Quarter	Second Quarter (2)	Third Quarter	Fourth Quarter
	(In thousands, except per share data)			
Loss from operations (1)	(65,160)	(67,965)	(23,533)	(87,442)
Net loss	(64,965)	(65,958)	(23,240)	(85,213)
Net loss per share attributable to common stockholders, basic and diluted	(0.79)	(0.79)	(0.26)	(0.89)

Year Ended December 31, 2014	First Quarter	Second Quarter	Third Quarter	Fourth Quarter (3)
	(In thousands, except per share data)			
Loss from operations	(8,320)	(12,680)	(19,818)	(191,940)
Net loss	(8,949)	(22,769)	(19,818)	(191,871)
Deemed dividends upon issuance of convertible preferred stock	—	(15,357)	(52,107)	—
Net loss attributable to common stockholders	(8,949)	(38,126)	(71,925)	(191,871)
Net loss per share attributable to common stockholders, basic and diluted	(1.41)	(5.80)	(10.50)	(13.68)

(1) Included in loss from operations is non-cash expense associated with the success payment liabilities to FHCRC and MSK attributable to the change in value and elapsed service period as follows:

Year Ended December 31, 2015	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
	(In thousands)			
Non-cash succes payment expense (gain) included in loss from operations	38,911	3,961	(25,586)	34,273

(2) Included in loss from operations in the second quarter of 2015 is $30.8 million in upfront fees associated with the Editas and Fate collaborations.

(3) Included in loss from operations in the fourth quarter of 2014 is $83.4 million associated with the portion of the success payment liability to FHCRC and MSK attributable to the elapsed service period and $84.1 million in upfront fees to acquire technology related to JCAR018, $20.0 million of which was paid in cash and $64.1 million was paid through the issuance of common stock.

18. Subsequent Events

In January 2016, the Company acquired AbVitro Inc., a company with a leading next-generation single cell sequencing platform. As consideration for the AbVitro Inc. acquisition, the Company paid approximately $78 million in cash and issued 1,289,188 shares of its common stock. There are no contingent consideration obligations under the terms of the AbVitro Inc. acquisition. The Company has not yet completed the initial accounting for this business combination.

In January 2016, the first clinical milestone of $20.0 million was achieved under the Company's license agreement with Opus Bio, and the Company issued 408,068 shares of its common stock as payment.

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ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

As of December 31, 2015, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2015, the design and operation of our disclosure controls and procedures were effective to provide reasonable assurance that information we are required to disclose in reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and to provide reasonable assurance that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate to allow timely decisions regarding required disclosure.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rule 13a-15(f) of the Exchange Act.

Our management, with the participation of the Chief Executive Officer and Chief Financial Officer, has assessed the effectiveness of our internal control over financial reporting as of December 31, 2015. Management's assessment was based on criteria described in the Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this assessment, management concluded that, as of December 31, 2015, our internal control over financial reporting was effective in providing reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Management reviewed the results of this assessment with our audit committee.

Our assessment of, and conclusion on, the effectiveness of internal control over financial reporting did not include the internal controls of Stage Cell Therapeutics GmbH, acquired on May 11, 2015, which is included in our 2015 consolidated financial statements and represents approximately 3% of our total assets as of December 31, 2015, and 2% of our total operating expenses for the year ended December 31, 2015.

The effectiveness of our internal control over financial reporting as of December 31, 2015 has been audited by Ernst & Young LLP, our independent registered public accounting firm, as stated in its report, which is included below.

Changes in Internal Control over Financial Reporting

There has been no change in our internal control over financial reporting during the quarter ended December 31, 2015 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating the disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply its judgment in evaluating the benefits of possible controls and procedures relative to their costs.

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Shareholders
Juno Therapeutics, Inc.

We have audited Juno Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2015, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). Juno Therapeutics, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

As indicated in the accompanying Management's Annual Report on Internal Control over Financial Reporting, management's assessment of and conclusion on the effectiveness of internal control over financial reporting did not include the internal controls of Stage Cell Therapeutics GmbH, which is included in the 2015 consolidated financial statements of Juno Therapeutics, Inc. and constituted $37.2 million and $2.7 million of total and net assets, respectively, as of December 31, 2015 and $0.6 million and $3.9 million of revenues and net loss, respectively, for the year then ended. Our audit of internal control over financial reporting of Juno Therapeutics, Inc. also did not include an evaluation of the internal control over financial reporting of Stage Cell Therapeutics GmbH.

In our opinion, Juno Therapeutics, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2015, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Juno Therapeutics, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit), and cash flows for the years ended December 31, 2015 and 2014 and the period from August 5, 2013 to December 31, 2013 of Juno Therapeutics, Inc. and our report dated February 29, 2016 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Seattle, Washington
February 29, 2016

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ITEM 9B. OTHER INFORMATION

None.

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PART III

ITEM 10. DIRECTORS, EXECUTIVES OFFICERS AND CORPORATE GOVERANCE

Information required by this item will be contained in our definitive proxy statement to be filed with the SEC on Schedule 14A in connection with our 2016 Annual Meeting of Stockholders (the "Proxy Statement"), which is expected to be filed not later than 120 days after December 31, 2015, under the headings "Executive Officers," "Election of Directors," "Corporate Governance," and "Section 16(a) Beneficial Ownership Reporting Compliance," and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors, and employees which is available on the Investor Relations section of our website at www.junotherapeutics.com. The Code of Business Conduct and Ethics is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (1) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (2) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

ITEM 11. EXECUTIVE COMPENSATION

Information required by this item will be contained in the Proxy Statement under the headings "Compensation Discussion & Analysis" and "Director Compensation," and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

Information required by this item will be contained in the Proxy Statement under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information," and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS, RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

Information required by this item will be contained in the Proxy Statement under the headings "Certain Relationships and Related Party Transactions" and "Corporate Governance," and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Information required by this item will be contained in the Proxy Statement under the heading "Principal Accountant Fees and Services," and is incorporated herein by reference.

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PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) The following documents are filed as part of this report:

1. Consolidated Financial Statements

See Index to Consolidated Financial Statements at Item 8 herein.

2. Consolidated Financial Statement Schedules

All schedules are omitted because they are not applicable or the required information is shown in the consolidated financial statements or notes thereto.

3. Exhibits

See the Exhibit Index immediately following the signature page of this report.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

JUNO THERAPEUTICS, INC.

By: /s/ Hans E. Bishop
Hans E. Bishop
President and Chief Executive Officer

Date: February 29, 2016

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Hans E. Bishop, Steven D. Harr, and Bernard J. Cassidy, and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this Annual Report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Hans E. Bishop Hans E. Bishop	President, Chief Executive Officer and Director (Principal Executive Officer)	February 29, 2016
/s/ Steven D. Harr Steven D. Harr	Chief Financial Officer and Head of Corporate Development (Principal Accounting and Financial Officer)	February 29, 2016
/s/ Howard H. Pien Howard H. Pien	Chairman of the Board	February 29, 2016
/s/ Hal V. Barron Hal V. Barron	Director	February 29, 2016
/s/ Thomas O. Daniel Thomas O. Daniel	Director	February 29, 2016
/s/ Anthony B. Evnin Anthony B. Evnin	Director	February 29, 2016
/s/ Richard Klausner Richard Klausner	Director	February 29, 2016

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Signature	Title	Date
/s/ Robert T. Nelsen Robert T. Nelsen	Director	February 29, 2016
/s/ Marc Tessier-Lavigne Marc Tessier-Lavigne	Director	February 29, 2016
/s/ Mary Agnes Wilderotter Mary Agnes Wilderotter	Director	February 29, 2016

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EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
1.1	Form of Underwriting Agreement	S-1/A	12/09/2014	1.1	
2.1†γΔ	Share Purchase Agreement, dated May 11, 2015, by and among Dr. Herbert Stadler, Dr. Lothar Germeroth, Prof. Dr. Dirk Busch, and the registrant	8-K	05/11/2015	2.1	
2.2†γΔ	Agreement and Plan of Merger, dated June 1, 2015, by and among X Acquisition Corporation, XBody, Inc., Brant Binder as stockholder representative, certain principal stockholders of X-Body, Inc., and the registrant	8-K	06/05/2015	2.1	
2.3+γΔ	Agreement and Plan of Reorganization, dated January 11, 2016, by and among registrant, P. Acquisition Corporation, P Acquisition LLC, AbVitro, Inc., Fortis Advisors LLC, as securityholders' representative, and those AbVitro stockholders made party thereto by joinder	8-K	01/11/2016	2.1	
3.1	Amended and Restated Certificate of Incorporation	8-K	12/29/2014	3.1	
3.2	Amended and Restated Bylaws	S-1/A	12/09/2014	3.2	
4.1	Fourth Amended and Restated Investors' Rights Agreement, dated December 5, 2014, by and among the registrant and the investors named therein	S-1/A	12/09/2014	4.1	
4.2	Amendment and Waiver of Fourth Amended and Restated Investors' Rights Agreement, dated July 27, 2015	10-Q	08/14/2015	4.2	
4.3	Second Amendment to Fourth Amended and Restated Investors' Rights Agreement, dated January 29, 2016				X
4.4	Form of Common Stock Certificate	S-1/A	12/09/2014	4.2	
10.1†	Exclusive License Agreement, dated November 1, 2009, by and between City of Hope and ZetaRx, LLC, predecessor to the registrant	S-1	11/17/2014	10.1	
10.2†	Amended and Restated Patent and Technology License Agreement, effective November 1, 2009, by and between Fred Hutchinson Cancer Research Center and ZetaRx, LLC, predecessor to the registrant	S-1/A	11/24/2014	10.2	
10.3†	Amended and Restated Patent and Technology License Agreement, effective January 2, 2012, by and between Fred Hutchinson Cancer Research Center and ZetaRx BioSciences, Inc., predecessor to the registrant	S-1/A	11/24/2014	10.3	
10.4(A)†	Collaboration Agreement, dated October 16, 2013, by and between Fred Hutchinson Cancer Research Center and the registrant	S-1/A	11/24/2014	10.4(A)	
10.4(B)†	Amendment No. 1 to Collaboration Agreement, dated November 19, 2014, by and between Fred Hutchinson Cancer Research Center and the registrant	S-1/A	11/24/2014	10.4(B)	

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Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.4(C)	Amendment No. 2 to Collaboration Agreement, dated February 17, 2016, by and between Fred Hutchinson Cancer Research Center and the registrant				X
10.5(A)	Letter Agreement, dated October 16, 2013, by and between Fred Hutchinson Cancer Research Center and the registrant	S-1	11/17/2014	10.5	
10.5(B)+	Amendment to Letter Agreement, dated December 21, 2015, by and between Fred Hutchinson Cancer Research Center and the registrant				X
10.6†	Amended and Restated Patent and Technology License Agreement, effective October 16, 2013, by and between Fred Hutchinson Cancer Research Center and the registrant	S-1/A	11/24/2014	10.6	
10.7(A)†	Exclusive License Agreement, dated November 21, 2013, by and between Memorial Sloan Kettering Cancer Center and the registrant	S-1	11/17/2014	10.7(A)	
10.7(B)†	Amendment No. 1 to Exclusive License Agreement, dated September 8, 2014, by and between Memorial Sloan Kettering Cancer Center and the registrant	S-1	11/17/2014	10.7(B)	
10.8†	Master Sponsored Research Agreement, dated November 21, 2013, by and between Memorial Sloan Kettering Cancer Center and the registrant	S-1	11/17/2014	10.8	
10.9†	Master Clinical Study Agreement, dated November 21, 2013, by and between Memorial Sloan Kettering Cancer Center and the registrant	S-1/A	12/16/2014	10.9	
10.10(A)†	Letter Agreement, dated November 21, 2013, by and between Memorial Sloan Kettering Cancer Center and the registrant	S-1	11/17/2014	10.10	
10.10(B)+	Amendment to Letter Agreement, dated December 14, 2015, by and between Memorial Sloan Kettering Cancer Center and the registrant				X
10.11(A)†	Exclusive License Agreement, dated December 3, 2013, by and between St. Jude Children's Research Hospital, Inc. and the registrant	S-1	11/17/2014	10.11	
10.11(B)†	Amendment #2 to License Agreement, dated April 4, 2015, by and between St. Jude Children's Research Hospital, Inc. and the registrant	10-Q	08/14/2015	10.1	
10.12(A)†	Exclusive License Agreement, dated February 13, 2014, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	S-1	11/17/2014	10.12(A)	
10.12(B)†	Amendment No. 1 to Exclusive License Agreement, dated August 4, 2014, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	S-1	11/17/2014	10.12(B)	

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Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.12(C)†	Amendment No. 2 to Exclusive License Agreement, dated June 15, 2015, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	10-Q/A	11/23/2015	10.7	
10.13(A)†	Sponsored Research Agreement, dated February 13, 2014, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	S-1	11/17/2014	10.13	
10.13(B)	Amendment No. 1 to Sponsored Research Agreement, effective April 1, 2015, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	10-Q	05/12/2015	10.4	
10.14#	Offer Letter Agreement, dated September 5, 2013, by and between Hans E. Bishop and the registrant, as amended by the Side Letter Agreement dated September 16, 2013	S-1	11/17/2014	10.14	
10.15#	Offer Letter Agreement, dated January 1, 2014, by and between Bernard J. Cassidy and the registrant	S-1	11/17/2014	10.15	
10.16#	Offer Letter Agreement, dated January 13, 2014, by and between Mark Frohlich, M.D. and the registrant	S-1	11/17/2014	10.16	
10.17#	Offer Letter Agreement, dated March 20, 2014, by and between Steven D. Harr, M.D. and the registrant	S-1	11/17/2014	10.17	
10.18#	Form of Director and Executive Officer Indemnification Agreement	S-1	11/17/2014	10.18	
10.19#	2013 Equity Incentive Plan, as amended	S-1	11/17/2014	10.19	
10.20#	Form of Restricted Stock Purchase Agreement under the 2013 Equity Incentive Plan	S-1	11/17/2014	10.20	
10.21#	Form of Stock Option Grant Notice and Option Agreement under the 2013 Equity Incentive Plan	S-1	11/17/2014	10.21	
10.22#	2014 Equity Incentive Plan	S-1/A	12/09/2014	10.22	
10.23(A)#	Form of Restricted Stock Unit Agreement under the 2014 Equity Incentive Plan	S-1	12/09/2014	10.23	
10.23(B)#	Form of Restricted Stock Unit Agreement under the 2014 Equity Incentive Plan (with accelerated vesting)				X
10.24(A)#	Form of Stock Option Grant Notice and Option Agreement under the 2014 Equity Incentive Plan	S-1	12/09/2014	10.24	
10.24(B)#	Form of Stock Option Grant Notice and Option Agreement under the 2014 Equity Incentive Plan (with accelerated vesting)				X
10.25#	2014 Employee Stock Purchase Plan	S-1	12/09/2014	10.25	
10.26	Sublease Agreement, dated November 22, 2013, by and between Seattle Biomedical Research Institute and the registrant	S-1	11/17/2014	10.26	

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Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
10.27	Sublease Agreement, dated November 20, 2014, by and between Seattle Biomedical Research Institute and the registrant	S-1/A	11/24/2014	10.27	
10.28#	Executive Incentive Compensation Plan	S-1/A	12/09/2014	10.28	
10.29(A)†	Exclusive License Agreement, dated December 3, 2014, by and between Opus Bio, Inc. and the registrant	S-1/A	12/09/2014	10.29	
10.29(B)+	Amendment No. 1 to Exclusive License Agreement, effective November 9, 2015, by and between Opus Bio, Inc. and the registrant				X
10.30(A)	Lease, dated as of February 2, 2015, by and between BMR-217th Place LLC and the registrant	8-K	02/09/2015	10.1	
10.30(B)	First Amendment to Lease, dated July 31, 2015, by and between BMR-217th Place LLC and the registrant	10-Q	08/14/2015	10.13	
10.31(A)	Lease Agreement, dated as of April 6, 2015, by and between ARE-Seattle No. 16, LLC and the registrant	8-K	04/07/2015	10.1	
10.31(B)	First Amendment to Lease Agreement, dated May 21, 2015, by and between ARE-Seattle No. 16, LLC and the registrant	10-Q	08/14/2015	10.4	
10.31(C)	Second Amendment to Lease Agreement, effective September 30, 2015, by and between ARE-Seattle No. 16, LLC and the registrant	10-Q	11/12/2015	10.1	
10.32(A)#	2015 Non-Employee Director Compensation Program, adopted April 3, 2015 (effective for 2015)	10-Q	05/12/2015	10.3	
10.32(B)#	Non-Employee Director Compensation Policy, adopted December 7, 2015 (effective beginning January 1, 2016) and Restricted Stock Unit Election Form thereunder				X
10.33†	Non-Exclusive Sublicense Agreement, effective April 7, 2015, by and among Novartis Institutes for Biomedical Research, Inc., The Trustees of the University of Pennsylvania, and the registrant	10-Q	08/14/2015	10.2	
10.34†	Amended and Restated Master Research and Collaboration Agreement, dated August 13, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	10-Q	08/14/2015	10.12	
10.35†	Share Purchase Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.1	
10.36	Voting and Standstill Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.2	
10.37	Registration Rights Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.3	

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Exhibit Number	Exhibit Description	Incorporated by Reference Form	Date	Number	Filed Herewith
10.38#	Offer Letter with Hyam Levitsky, dated May 27, 2015	10-Q	08/14/2015	10.8	
10.39#	Offer Letter with Robert Azelby, dated September 28, 2015	10-Q	11/12/2015	10.2	
10.40#	Change in Control and Severance Plan				X
21	Subsidiaries of the registrant				X
23.1	Consent of independent registered public accounting firm				X
24.1	Power of Attorney (included on signature page to this Annual Report on Form 10-K)				X
31.1	Certification of Principal Executive Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended				X
31.2	Certification of Principal Financial Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended				X
32.1*	Certification of Principal Executive Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. §1350				X
32.2*	Certification of Principal Financial Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. §1350				X
101	The following materials from the registrant's Annual Report on Form 10-K for the fiscal year ended December 31, 2015, formatted in eXtensible Business Reporting Language (XBRL): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Loss, (iii) Consolidated Statements of Cash Flows, (iv) Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit), and (v) Notes to the Consolidated Financial Statements.				X

† Confidential treatment has been granted for certain information contained in this exhibit. Such information has been omitted and filed separately with the Securities and Exchange Commission.

# Indicates management contract or compensatory plan.

+ Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been filed separately with the Securities and Exchange Commission.

γ The representations and warranties contained in this agreement were made only for purposes of the transactions contemplated by the agreement as of specific dates and may have been qualified by certain disclosures between the parties and a contractual standard of materiality different from those generally applicable under securities laws, among other limitations. The representations and warranties were made for purposes of allocating contractual risk between the parties to the agreement and should not be relied upon as a disclosure of factual information about the registrant or the transactions contemplated thereby.

Δ The exhibits and schedules to this agreement have been omitted in reliance on Item 601(b)(2) of Regulation S-K promulgated by the Securities and Exchange Commission, and a copy thereof will be furnished supplementally to the Securities and Exchange Commission upon its request.

* The certifications attached as Exhibits 32.1 and 32.2 that accompany this Annual Report on Form 10-K are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Juno Therapeutics, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

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UNITED ST ATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

(Mark One)

☒ QUARTERL Y REPOR T PURSUANT T O SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the quarterly period ended June 30, 2015

OR

☐ TRANSITION REPOR T PURSUANT T O SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission File Number: 001-36781

Juno Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Delaware	46-3656275
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
307 Westlake Avenue North, Suite 300 Seattle, WA (Address of principal executive offices)	98109 (Zip Code)

(206) 582-1600
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common stock, par value $0.0001 per share	The NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of “large accelerated filer,” “accelerated filer” and “smaller reporting company” in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐	Accelerated filer ☐
Non-accelerated filer ☒ (Do not check if a smaller reporting company)	Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act). Yes ☐ No ☒

The number of shares outstanding of the registrant’s common stock as of August 7, 2015 was 100,556,371.

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Juno Therapeutics, Inc.

Quarterly Report on Form 10-Q
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Juno Therapeutics, Inc.
Condensed Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	June 30, 2015 (unaudited)	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 39,518	$ 355,968
Marketable securities	264,055	79,672
Prepaid expenses and other current assets	4,182	3,595
Total current assets	307,755	439,235
Property and equipment, net	28,689	4,018
Long-term marketable securities	9,839	38,411
Goodwill	122,092	—
Intangible assets	50,758	—
Other assets	5,036	7,499
Total assets	$ 524,169	$ 489,163
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 1,902	$ 1,096
Accrued liabilities and other current liabilities	26,341	14,577
Success payment liabilities	127,791	84,920
Contingent consideration obligations	4,422	—
Total current liabilities	160,456	100,593
Build-to-suit lease obligation, less current portion	9,483	—
Contingent consideration obligations, less current portion	32,686	—
Deferred tax liabilities	10,240	—
Other long-term liabilities	—	38
Commitments and Contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized at June 30, 2015 and December 31, 2014; 0 shares issued and outstanding at June 30, 2015 and December 31, 2014	—	—
Common stock, $0.0001 par value, 495,000,000 shares authorized at June 30, 2015 and December 31, 2014; 84,625,858 and 82,073,647 shares issued and outstanding at June 30, 2015 and December 31, 2014, respectively	9	8
Additional paid-in-capital	789,348	734,895
Accumulated other comprehensive loss	(849)	(90)
Accumulated deficit	(477,204)	(346,281)
Total stockholders' equity	311,304	388,532
Total liabilities and stockholders' equity	$ 524,169	$ 489,163

See accompanying notes.

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Juno Therapeutics, Inc.
Condensed Consolidated Statements of Operations
(In thousands, except share and per share amounts)
(unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Revenue	$ 12,461	$ —	$ 12,461	$ —
Operating expenses:				
Research and development	60,235	6,479	118,034	9,418
General and administrative	14,857	4,568	21,527	7,959
Litigation	5,334	1,633	6,025	3,623
Total operating expenses	80,426	12,680	145,586	21,000
Loss from operations	(67,965)	(12,680)	(133,125)	(21,000)
Interest income, net	158	—	353	—
Other income (expenses), net	233	(10,089)	233	(10,718)
Loss before income taxes	(67,574)	(22,769)	(132,539)	(31,718)
Benefit from income taxes	1,616	—	1,616	—
Net loss	$ (65,958)	$ (22,769)	$ (130,923)	$ (31,718)
Net loss attributable to common stockholders:				
Net loss	$ (65,958)	$ (22,769)	$ (130,923)	$ (31,718)
Deemed dividend upon issuance of convertible preferred stock, non-cash	—	(15,357)	—	(15,357)
Net loss attributable to common stockholders	$ (65,958)	$ (38,126)	$ (130,923)	$ (47,075)
Net loss per share attributable to common stockholders, basic and diluted	$ (0.79)	$ (5.80)	$ (1.58)	$ (7.06)
Weighted average common shares outstanding, basic and diluted	83,716,681	6,576,466	83,116,743	6,664,013

See accompanying notes.

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Juno Therapeutics, Inc.
Condensed Consolidated Statements of Comprehensive Loss
(In thousands)
(unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Net loss	$ (65,958)	$ (22,769)	$ (130,923)	$ (31,718)
Other comprehensive loss:				
Unrealized loss on marketable securities	(706)	—	(634)	—
Foreign currency translation	(125)	—	(125)	—
Other comprehensive loss	(831)	—	(759)	—
Comprehensive loss	$ (66,789)	$ (22,769)	$ (131,682)	$ (31,718)

See accompanying notes.

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Juno Therapeutics, Inc.
Condensed Consolidated Statements of Cash Flows
(In thousands)
(unaudited)

	Six Months Ended June 30,	
	2015	2014
OPERATING ACTIVITIES		
Net loss	$ (130,923)	$ (31,718)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,210	9
Stock-based compensation	12,475	1,588
Loss from remeasurement of fair value of convertible preferred stock options	—	10,718
Deferred income taxes	(519)	—
Deferred tax benefit recorded in connection with acquisition	(1,100)	—
Change in fair value of success payment liabilities	42,871	386
Change in fair value of contingent consideration obligation	(80)	—
Gain on initial investment in Stage	(227)	—
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(1,588)	(1,869)
Accounts payable, accrued liabilities and other liabilities	6,723	(2,479)
Net cash used in operating activities	(70,158)	(23,365)
INVESTING ACTIVITIES		
Purchases of marketable securities	(222,178)	—
Sales and maturities of marketable securities	64,115	—
Acquisitions, net of cash acquired	(77,666)	—
Purchase of cost-method investment	—	(3,455)
Purchase of property and equipment	(9,154)	(715)
Net cash used in investing activities	(244,883)	(4,170)
FINANCING ACTIVITIES		
Payment of issuance costs related to issuance of common stock	(1,683)	—
Proceeds from issuance of convertible preferred stock	—	62,614
Proceeds from exercise of stock options	368	—
Payments of build-to-suit lease obligation	(82)	—
Net cash (used in)/provided by financing activities	(1,397)	62,614
Effect of exchange rate changes on cash and cash equivalents	(12)	—
Net (decrease)/increase in cash and cash equivalents	(316,450)	35,079
Cash and cash equivalents at beginning of period	355,968	35,966
Cash and cash equivalents at end of period	$ 39,518	$ 71,045
SUPPLEMENTAL CASH FLOW INFORMATION		
Purchases of property and equipment included in accounts payable and accrued liabilities	$ 6,675	$ —
Amounts capitalized under build-to-suit leases	$ 9,910	$ —
Issuance of common stock for acquisitions	$ 41,611	$ —
Fair value of convertible preferred stock option at issuance	$ —	$ (6,889)
Convertible preferred stock issuance costs incurred but unpaid	$ —	$ 187

See accompanying notes.

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Juno Therapeutics, Inc.
Notes to Condensed Consolidated Financial Statements

1. Significant Accounting Policies

Organization and Basis of Presentation

Juno Therapeutics, Inc. (the "Company") was incorporated in Delaware on August 5, 2013 as FC Therapeutics, Inc., and changed its name to Juno Therapeutics, Inc. on October 23, 2013. The Company is building a fully-integrated biopharmaceutical company focused on revolutionizing medicine by re-engaging the body's immune system to treat cancer. Founded on the vision that the next important phase of medicine will be driven by the use of human cells as therapeutic entities, the Company is developing cell-based cancer immunotherapies based on its chimeric antigen receptor ("CAR") and high-affinity T cell receptor ("TCR") technologies to genetically engineer T cells to recognize and kill cancer cells.

In May 2015, the Company acquired all the remaining ownership interests in Stage Cell Therapeutics GmbH ("Stage") not already held by it. See Note 2, Acquisitions. As a result of the acquisition, Stage has become a wholly owned subsidiary of the Company and the results of Stage have been consolidated with the Company's results since the date of the acquisition. Stage has operations in Göttingen and Munich, Germany and its operations are focused on developing technology platforms, including novel reagents and automation technologies, that enable the development and production of cell therapeutics. Stage has been renamed as Juno Therapeutics GmbH ("Juno GmbH").

In June 2015, the Company acquired X-Body, Inc. ("X-Body"). See Note 2, Acquisitions. As a result of the acquisition, X-Body has become a wholly owned subsidiary of the Company and the results of X-Body have been consolidated with the Company's results since the date of the acquisition. X-Body has operations in Waltham, Massachusetts and its operations are focused on the discovery of human monoclonal antibodies and discovery of TCR binding domains.

The Company is subject to a number of risks similar to other biopharmaceutical companies in the early stage, including, but not limited to, possible failure of preclinical testing or clinical trials, the need to obtain marketing approval for its product candidates, competitors developing new technological innovations, the need to successfully commercialize and gain market acceptance of the Company's products, protection of proprietary technology, and the need to obtain adequate additional funding, If the Company does not successfully commercialize or partner any of its product candidates, it will be unable to generate product revenue or achieve profitability. As of June 30, 2015, the Company had an accumulated deficit of $477.2 million.

The financial data as of December 31, 2014 is derived from audited financial statements, which are included in our Annual Report on Form 10-K, which was filed with the Securities and Exchange Commission on March 19, 2015 (the "2014 Annual Report"), and should be read in conjunction with the audited financial statements and notes thereto.

Use of Estimates

The preparation of the Company's consolidated financial statements in conformity with U.S. generally accepted accounting principles ("GAAP") requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from such estimates.

The Company utilizes significant estimates and assumptions in determining the estimated success payment and contingent consideration liabilities and associated expense at each balance sheet date. A small change in the Company's stock price may have a relatively large change in the estimated fair value of the success payment liability and associated expense. Changes in the probabilities and estimated timing used in the calculation of the contingent consideration liability may have a relatively large impact of the resulting liability and associated expense.

Prior to becoming a public company, the Company utilized significant estimates and assumptions in determining the fair value of its common stock for financial reporting purposes. The Company recorded expense for restricted stock

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grants at prices not less than the fair market value of its common stock as determined by the board of directors, taking into consideration input from management and independent third-party valuation analysis, and in accordance with the AICPA Accounting and Valuation Guide, Valuation of Privately-Held Company Equity Securities Issued as Compensation. The estimated fair value of the Company's common stock was based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which the Company sold shares of convertible preferred stock, and the superior rights and preferences of securities senior to the Company's common stock at the time.

Unaudited Interim Financial Information

The accompanying interim balance sheet as of June 30, 2015, the statements of operations and comprehensive loss for the three and six months ended June 30, 2015 and 2014, and statements of cash flows for the six months ended June 30, 2015 and 2014 and the related footnote disclosures are unaudited. These unaudited interim condensed consolidated financial statements have been prepared in accordance with GAAP. In management's opinion, the unaudited interim condensed consolidated financial statements have been prepared on the same basis as the audited financial statements and include all adjustments, which include only normal recurring adjustments, necessary for the fair presentation of the Company's financial position as of June 30, 2015 and its results of operations and comprehensive loss for the three and six months ended June 30, 2015 and 2014, and its cash flows for the six months ended June 30, 2015 and 2014. The results for the three and six months ended June 30, 2015 and 2014 are not necessarily indicative of the results expected for the full fiscal year or any other interim period.

Initial Public Offering

On December 23, 2014, the Company closed its initial public offering ("IPO") and issued and sold 12,676,354 shares of common stock (inclusive of 1,653,437 shares of common stock sold by the Company pursuant to the full exercise of the underwriters' option to purchase additional shares) at a price to the public of $24.00 per share. The shares began trading on The NASDAQ Global Select Market on December 19, 2014. The aggregate net proceeds received by the Company from the offering, net of underwriting discounts and commissions and offering expenses, were $279.7 million. Upon the closing of the IPO, all then-outstanding shares of Company convertible preferred stock converted into 59,909,397 shares of common stock. The related carrying value of $387.7 million was reclassified to common stock and additional paid-in capital. Additionally, the Company amended and restated its certificate of incorporation effective December 23, 2014 to, among other things, change the authorized number of shares of common stock to 495,000,000 shares and the authorized number of shares of preferred stock to 5,000,000 shares.

Comprehensive Loss

Comprehensive loss is comprised of net loss and other comprehensive income or loss. Other comprehensive income or loss consists of unrealized gains and losses on marketable securities and foreign currency translation adjustments.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of three months or less at acquisition to be cash equivalents. Cash equivalents, which consist primarily of money market funds, are stated at fair value.

Marketable Securities

The Company generally invests its excess cash in investment grade short- to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents, marketable securities, or long-term marketable securities on the balance sheets, classified as available-for-sale, and reported at fair value with unrealized gains and losses included in accumulated other comprehensive income (loss). Realized gains and losses on the sale of these securities are recognized in net income or loss. The cost of marketable securities sold is based on the specific identification method.

The Company periodically evaluates whether declines in fair values of its investments below their book value are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as the Company's ability and intent to hold the investment until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the security or it is more likely than not it will be required to sell any investment before recovery of its amortized cost basis. Factors

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considered include quoted market prices, recent financial results and operating trends, implied values from any recent transactions or offers of investee securities, credit quality of debt instrument issuers, other publicly available information that may affect the value of our investments, duration and severity of the decline in value, and our strategy and intentions for holding the investment.

Property and Equipment, Net

Property and equipment consist of laboratory equipment, computer equipment and software, leasehold improvements and build-to suit property. Property and equipment is stated at cost, and depreciated using the straight-line method over the estimated useful lives of the respective assets.

Laboratory equipment	5 years
Computer equipment and software	3 years
Leasehold improvements	Shorter of asset's useful life or remaining term of lease
Build-to-suit property	10 years

Build-to-Suit Lease Accounting

In certain lease arrangements, the Company is involved in the construction of a building. To the extent the Company is involved with structural improvements of the construction project or takes construction risk prior to the commencement of a lease, the Financial Accounting Standards Board ("FASB") Accounting Standards Codification ("ASC") 840-40, Leases – Sale-Leaseback Transactions (Subsection 05-5), requires the Company to be considered the owner solely for accounting purposes, even though the Company is not the legal owner. In these instances, the Company will record an asset and build-to-suit lease obligation on its balance sheet equal to the fair value of the building.

Once construction is complete, the Company will consider the requirements for sale-leaseback accounting treatment, including evaluating whether all risks of ownership have transferred back to the landlord, as evidenced by a lack of continuing involvement in the leased property. If the arrangement does not qualify for sale-leaseback accounting treatment, the building asset remains on the Company's balance sheet at its historical cost, and such asset is depreciated over its estimated useful life. The Company bifurcates its lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the condensed consolidated statements of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

The interest rate used for the build-to-suit lease obligation represents our estimated incremental borrowing rate, adjusted to reduce any built in loss.

Other Assets

The Company accounted for its investment in a minority interest of Stage, which minority interest the Company acquired in 2014, over which the Company as of December 31, 2014 had not exercised significant influence, using the cost method in accordance with ASC 325-20, Cost Method Investments. Under the cost method, an investment is carried at cost until it is sold or there is evidence that changes in the business environment or other facts and circumstances suggest it may be other than temporarily impaired. This investment totaled $3.5 million as of December 31, 2014 and was included in other assets on the balance sheet. In May 2015, the Company acquired the remaining ownership interests in Stage. See Note 2, Acquisitions.

Impairment of Long-Lived Assets

The Company regularly reviews the carrying value and estimated lives of all of its long-lived assets, including property and equipment, to determine whether indicators of impairment may exist which warrant adjustments to carrying values or estimated useful lives. The determinants used for this evaluation include management's estimate of the asset's ability to generate positive income from operations and positive cash flow in future periods as well as the strategic significance of the assets to the Company's business objective. Should an impairment exist, the impairment loss would be measured based on the excess of the carrying amount of the asset's fair value. The Company has not recognized any impairment losses since inception.

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Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the net amount of identifiable assets acquired and liabilities assumed in a business combination measured at fair value. The Company evaluates goodwill for impairment annually during the fourth quarter and upon the occurrence of triggering events or substantive changes in circumstances that could indicate a potential impairment by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that the fair value of the net assets are below their carrying amounts.

Intangible assets acquired in a business combination are recognized separately from goodwill and are initially recognized at their fair value at the acquisition date (which is regarded as their cost). Intangible assets related to in-process research and development ("IPR&D") are treated as indefinite-lived intangible assets and not amortized until certain regulatory approval is obtained in a major market, typically either the U.S. or the EU in the case of X-Body, and in the case of Stage, when the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgment. At that time, the Company will determine the useful life of the asset, reclassify the asset out of IPR&D and begin amortization. Intangible assets are reviewed for impairment at least annually or if indicators of potential impairment exist. There were no impairments as of June 30, 2015.

Contingent Consideration from Business Combinations

At and subsequent to the acquisition date of a business combination, contingent consideration obligations are remeasured to fair value at each balance sheet date with changes in fair value recognized in research and development expense in the condensed consolidated statements of operations. Changes in fair values reflect changes to the Company's assumptions regarding probabilities of successful achievement of related milestones, the timing in which the milestones are expected to be achieved, and the discount rate used to estimate the fair value of the obligation, as well as the foreign currency impact of the contingent consideration for the Stage acquisition as it is denominated in Euro.

Fair Value of Financial Instruments

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy prioritizes valuation inputs based on the observable nature of those inputs. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1 – Quoted prices in active markets for identical assets or liabilities

Level 2 – Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly

Level 3 – Unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability

Our financial instruments, in addition to those presented in Note 5, Fair Value Measurements, include cash and cash equivalents, accounts payable and accrued liabilities. The carrying amount of cash and cash equivalents, accounts payable and accrued liabilities approximate fair value because of the short-term nature of these instruments.

Convertible Preferred Stock

Prior to its IPO, the Company had several series of convertible preferred stock outstanding. The carrying value of the Company's convertible preferred stock is adjusted to reflect dividends when and if declared by the board of directors. No dividends have been declared by the board of directors since inception. The Company classified its convertible preferred stock outside of permanent equity as the redemption of such stock was not solely under the control of the Company. Upon the occurrence of the IPO in December 2014, the carrying value of the convertible preferred stock was reclassified to common stock and additional paid-in capital.

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Convertible Preferred Stock Option

Pursuant to certain 2013 and 2014 convertible preferred stock purchase agreements, the Company had the right to sell, or "put," additional shares of Series A and A-2 convertible preferred stock in subsequent closings as well as potential obligations to issue additional shares upon the occurrence of certain events. The Company assessed its rights and potential obligations to sell additional shares and determined them to be a single unit of accounting, with classification outside of equity in accordance with ASC 480, Distinguishing Liabilities from Equity. As of each balance sheet date, the fair value of these combined instruments was estimated using the option pricing model and assumptions that are based on the individual characteristics of the option on the valuation date, as well as assumptions for expected volatility, expected term, and risk-free interest rate.

The Company recorded these combined instruments as convertible preferred stock options as of the date of the initial closings of the Series A convertible preferred stock financing and Series A-2 convertible preferred stock financing. The options were revalued to fair value at each subsequent balance sheet date, with fair value changes recognized as increases or reductions to other income (expense), net in the condensed consolidated statements of operations. The Company estimated the fair value of these instruments based on the Black-Scholes option pricing model. These options were exercised during 2014. For the three and six months ended June 30, 2014, $10.1 million and $10.7 million was recognized in other expense, respectively, related to the changes in fair value of these options.

Success Payments

The Company granted rights to share-based success payments to the Fred Hutchinson Cancer Research Center ("FHCRC") and the Memorial Sloan Kettering Cancer Center ("MSK") pursuant to the terms of its collaboration agreements with each of those entities. Pursuant to the terms of these arrangements, the Company may be required to make success payments based on increases in the per share fair market value of the Company's common stock, payable in cash or publicly-traded equity at the Company's discretion. See Note 3, Collaboration and License Agreements. The success payments are accounted for under ASC 505-50, Equity-Based Payments to Non-Employees. Once the service period is complete, the instruments will be accounted for under ASC 815, Derivatives and Hedging, and continue to be marked to market with all changes in value recognized immediately in other income or expense.

Success payment liabilities are estimated at fair value at inception and at each subsequent balance sheet date and the expense is amortized using the accelerated attribution method over the remaining term (service period) of the related collaboration agreement or related possible payment due date (whichever is sooner). To determine the estimated fair value of the success payments the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the estimated fair value of the success payment liability: estimated term of the success payments, fair value of common stock, expected volatility, risk-free interest rate, and estimated number and timing of valuation measurement dates on the basis of which payments may be triggered. For FHCRC success payments, estimated indirect costs related to the collaboration projects conducted by FHCRC that are creditable against the success payments are also included in the calculation. The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and our historical volatility. In addition, prior to the Company becoming publicly traded there was one valuation measurement date on the basis of which payments may be triggered. There are several valuation measurement dates subsequent to the IPO on the basis of which payments may be triggered.

As of June 30, 2015 and December 31, 2014, the estimated fair value of the total success payment obligation was approximately $211.4 million and $195.9 million, respectively. The Company recognized research and development expense of $4.0 million and $0.2 million in the three months ended June 30, 2015 and 2014, respectively, with respect to the success payment obligations. The Company recognized research and development expense of $42.9 million and $0.4 million in the six months ended June 30, 2015 and 2014, respectively, with respect to the success payment obligations. The expense recorded for the three and six months ended June 30, 2015 and 2014 represents the change in the success payment liability during such periods and reflects an additional three or six months of accrued expense, respectively. The success payment liabilities on the condensed consolidated balance sheets as of June 30, 2015 and December 31, 2014 were $127.8 million and $84.9 million, respectively.

The assumptions used to calculate the fair value of the success payments are subject to a significant amount of judgment including the expected volatility, estimated term, and estimated number and timing of valuation measurement dates. A small change in the assumptions may have a relatively large change in the estimated

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valuation and associated liability and expense. For example, keeping all other variables constant, a hypothetical 10% increase in the stock price at June 30, 2015 from $53.33 per share to $58.66 per share would have increased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $15.5 million. A hypothetical 10% decrease in the stock price from $53.33 per share to $48.00 per share would have decreased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $15.7 million, resulting in a gain of $11.7 million. Further, keeping all other variables constant, a hypothetical 35% increase in the stock price at June 30, 2015 from $53.33 per share to $72.00 per share would have increased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $147.2 million. A hypothetical 35% decrease in the stock price from $53.33 per share to $34.66 per share would have decreased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $56.3 million, resulting in a gain of $52.3 million. If the fair value of the Company's common stock at the first valuation measurement date in December 2015 remains at its June 30, 2015 value of $53.33, the Company will be required to make a $75 million payment to FHCRC and a $10 million payment to MSK, payable in cash or stock at the Company's discretion.

Concentrations of Credit Risk and Off-Balance Sheet Risk

The Company maintains its cash, cash equivalents, and marketable securities with high quality, accredited financial institutions. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to significant risk on these funds. The Company has no off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

Revenue

The Company recognizes revenue in accordance with ASC 605, Revenue Recognition. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Revenue is primarily related to an initial license fee received in the three and six months ended June 30, 2015. See Note 3, Collaboration and License Agreements, under the heading "St. Jude Children's Research Hospital/Novartis" for additional information.

Research and Development Expense

The Company records expense for research and development costs to operations as incurred. The Company accounts for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the goods have been received or when the service has been performed rather than when the payment is made. Research and development expenses consist of costs incurred by the Company for the discovery and development of the Company's product candidates and include:

- personnel-related expenses, including non-cash stock-based compensation expense;
- external research and development expenses incurred under arrangements with third parties, such as contract research organizations, contract manufacturing organizations, academic and non-profit institutions and consultants;
- the estimated fair value of the liability attributable to the elapsed service period as of the balance sheet date associated with the Company's success payments to FHCRC and MSK;
- changes in the estimated fair value of the contingent consideration liabilities;

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- license fees; and
- other expenses, which include direct and allocated expenses for laboratory, facilities, and other costs.

General and Administrative Expense

General and administrative costs are expensed as incurred and include personnel-related expenses including non-cash stock-based compensation for our personnel in executive, legal, finance and accounting, and other administrative functions, non-litigation legal costs, as well as fees paid for accounting and tax services, consulting fees, and facilities costs not otherwise included in research and development expenses. Non-litigation legal costs include general corporate legal fees and patent costs.

Litigation Expense

Litigation expense includes legal expense the Company incurred with respect to Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn), as well as expenses the Company is required to reimburse to St. Jude Children's Research Hospital ("St. Jude") with respect to such litigation. See Note 3, Collaboration and License Agreements.

Stock-Based Compensation

Under ASC 718, Compensation—Stock Compensation, the Company measures and recognizes expense for restricted stock awards, restricted stock unit ("RSU") awards, and stock options granted to employees and directors based on the fair value of the awards on the date of grant. The fair value of stock options is estimated at the date of grant using the Black-Scholes option pricing model that requires management to apply judgment and make estimates, including:

- the expected term of the option, which is calculated using the simplified method, as permitted by the Securities and Exchange Commission ("SEC") Staff Accounting Bulletin No. 110, Share-Based Payment, as the Company has insufficient historical information regarding its stock options to provide a basis for an estimate;
- the expected volatility of the underlying common stock, which the Company estimates based on the historical volatility of a representative group of publicly traded biopharmaceutical companies with similar characteristics;
- the risk-free interest rate, which is based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued;
- the expected dividend yield, which the Company estimates to be zero based on the fact that the Company has never paid cash dividends and has no present intention to pay cash dividends; and
- the fair value of the Company's common stock on the date of grant.

Stock-based compensation expense for restricted stock, RSUs, and stock options is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company is required to estimate a forfeiture rate to calculate the stock-based compensation expense for its awards. The Company's forfeiture rate is based on an analysis of its actual forfeitures since the adoption of its equity award plan. Since inception, the Company's estimated forfeiture rate has been de minimis. The Company routinely evaluates the appropriateness of the forfeiture rate based on actual forfeiture experience, analysis of employee turnover and expectations of future option exercise behavior.

The Company also granted restricted stock awards that vest in conjunction with certain performance conditions to certain key employees, scientific founders, and directors. At each reporting date, the Company is required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon the Company's assessment of accomplishing each performance provision. Compensation expense is measured using the fair value of the award at the grant date, net of forfeitures, and is adjusted annually to reflect actual forfeitures.

The Company also grants stock-based awards to certain service providers who are not employees, scientific founders, or directors. Stock-based awards issued to such persons, or to directors for non-board related services, are

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accounted for based on the fair value of such services received or of the equity instruments issued, whichever is more reliably measured. The fair value of such awards is subject to remeasurement at each reporting period until services required under the arrangement are completed, which is the vesting date.

Patent Costs

The costs related to acquiring patents and to prosecuting and maintaining intellectual property rights are expensed as incurred to general and administrative due to the uncertainty surrounding the drug development process and the uncertainty of future benefits.

Income Taxes

The Company determines its deferred tax assets and liabilities based on the differences between the financial reporting and tax bases of assets and liabilities. The deferred tax assets and liabilities are measured using the enacted tax rates that will be in effect when the differences are expected to reverse. A valuation allowance is recorded when it is more likely than not that the deferred tax asset will not be recovered. The Company applies judgment in the determination of the consolidated financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. The Company recognizes any material interest and penalties related to unrecognized tax benefits in income tax expense.

The Company is required to file income tax returns in the U.S. federal jurisdiction and various state and foreign jurisdictions. The Company currently is not under examination by the Internal Revenue Service or other jurisdictions for any tax years.

Foreign Currency Translation

Assets and liabilities denominated in foreign currencies were translated into U.S. dollars, the reporting currency, at the exchange rate prevailing at the balance sheet date. Revenue and expenses denominated in foreign currencies were translated into U.S. dollars at the monthly average exchange rate for the period and the translation adjustments are reported as an element of accumulated other comprehensive income or loss on the condensed consolidated balance sheets.

Net Loss per Share Attributable to Common Stockholders

Basic and diluted net loss per share attributable to common stockholders is calculated by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period, without consideration for common stock equivalents. The Company's potentially dilutive shares, which include unvested restricted stock, unvested RSUs, options to purchase common stock, and potential shares issued for success payments, are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive. The following table reconciles net loss to net loss attributable to common stockholders (in thousands, except share and per share data):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Net loss	$ (65,958)	$ (22,769)	$ (130,923)	$ (31,718)
Deemed dividend upon issuance of convertible preferred stock	—	(15,357)	—	(15,357)
Net loss attributable to common stockholders	$ (65,958)	$ (38,126)	$ (130,923)	$ (47,075)
Weighted average number of common shares used in net loss per share attributable to common stockholders – basic and diluted	83,716,681	6,576,466	83,116,743	6,664,013
Net loss per share attributable to common stockholders – basic and diluted	$ (0.79)	$ (5.80)	$ (1.58)	$ (7.06)

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The amounts in the table below were excluded from the calculation of diluted net loss per share attributable to common stockholders for the periods indicated due to their anti-dilutive effect:

	As of June 30,	
	2015	2014
Series A convertible preferred stock	—	16,930,668
Series A-1 convertible preferred stock	—	2,250,000
Series A-2 convertible preferred stock	—	15,656,049
Unvested restricted common stock and restricted stock units	6,837,535	9,478,601
Options to purchase common stock	4,453,101	—
Estimated shares issued if success payment valuation occurred at June 30, 2015 (1)	1,593,850	—
Total	12,884,486	44,315,318

(1) Represents the number of shares that would be issued if the success payment valuation date had been June 30, 2015. The Company's common stock price per share was $53.33 at June 30, 2015 which would have resulted in a success payment of $85 million ($75 million for FHCRC and $10 million for MSK). The number of shares issued is calculated by dividing the $85 million success payment by the stock price per share of $53.33 at June 30, 2015. At June 30, 2014 the stock price was below the threshold that would require a payment to FHCRC or MSK, therefore no shares are included.

Recent Accounting Pronouncements

In 2014, the FASB issued new accounting guidance related to revenue recognition. This new standard will replace all current GAAP guidance on this topic and establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. This guidance can be applied either retrospectively to each period presented or as a cumulative-effect adjustment as of the date of adoption. In July 2015, the FASB voted to defer the effective date to January 1, 2018 with early adoption permitted beginning January 1, 2017. The Company is evaluating the impact of adopting the new accounting guidance on its financial statements.

2. Acquisitions

Acquisition of Stage

On May 11, 2015, the Company completed the acquisition of all the outstanding ownership interests in Stage not already held by it. Prior to the acquisition, the Company held a 4.76% equity interest in Stage. As a result of the acquisition, Stage became a wholly owned subsidiary of the Company. The Company paid €52.5 million, or $58.5 million, in cash and issued an aggregate of 486,279 shares of common stock, valued at $22.2 million based on the closing stock price on May 11, 2015 of $45.58 per share, to the selling shareholders.

The Company also agreed to pay additional amounts of up to an aggregate of €135.0 million in cash based on the achievement of certain technical, clinical, regulatory, and commercial milestones related to novel reagents (€40.0 million), advanced automation technology (€65.0 million), and Stage's existing clinical pipeline (€30.0 million). The fair value of this contingent consideration was estimated to be $28.2 million at the date of acquisition. Payments could vary based on milestones that are reached.

The elements of the purchase consideration are as follows (in thousands):

Cash paid (1)	$ 58,496
Common stock issued (2)	22,165
Fair value of contingent consideration (3)	28,244
Total consideration for 95.24% equity	108,905
Fair value of 4.76% initial investment in Stage (4)	3,682
Implied purchase price consideration for 100% equity	$ 112,587

(1) The cash consideration represents the consideration paid in cash amounting to €52.5 million which is translated based on an exchange rate of 1.1142 EUR/USD on May 11, 2015.
(2) Based on the share purchase agreement, the purchase consideration included 486,279 shares of the Company's common stock. The closing stock price on the transaction date was $45.58 per share.

(3) The fair value of the contingent consideration was determined by calculating the probability-weighted

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milestone payments based on the assessment of the likelihood and estimated timing that certain milestones would be achieved. The fair value of the contingent consideration is estimated using a discount rate of 14.6%. The discount rate captures the credit risk associated with the payment of the contingent consideration when earned and due.

(4) The fair value of the initial investment is calculated as the implied per share fair value of the stock based upon the acquisition purchase price reduced by a lack of control discount associated with the 4.76% holding. Upon acquiring the remaining outstanding ownership interests in Stage, the Company re-measured its original equity interest to its fair value and recognized a $0.2 million gain during the six months ended June 30, 2015, which was recorded in other income (expense) on the condensed consolidated statements of operations.

The Company accounted for the Stage acquisition using the acquisition method. The acquisition method of accounting requires, among other things, that the assets acquired and liabilities assumed in a business combination be measured at their fair values as of the closing date of the acquisition. The allocation of the purchase price is based on estimates of the fair value of assets acquired and liabilities assumed as of the date of acquisition. The components of the purchase price allocation are as follows (in thousands):

Net working capital	$ 1,863
Property and equipment	651
Net assets acquired	2,514
Deferred tax liabilities	(10,801)
Acquired in-process research and development	34,457
Goodwill	86,417
Total consideration transferred	$112,587

The fair value of the acquired in-process research and development has been estimated using the replacement cost method. Under this method, the Company estimated the cost of recreating the technology and derived an estimated value to develop the technology. In-process research and development are required to be classified as indefinite-lived assets until the successful completion or the abandonment of the associated research and development effort. Accordingly, during the development period after the date of acquisition, these assets will not be amortized until the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgement. At that time, the Company will determine the useful life of the asset and begin amortization. If the associated research and development effort is abandoned, the related in-process research and development assets will be written-off and an impairment charge recorded.

The excess of the purchase price over the estimated fair value of the tangible net assets and identifiable intangible assets acquired was recorded as goodwill. The factors contributing to the recognition of the amount of goodwill are based on several strategic and synergistic benefits that are expected to be realized from the Stage acquisition. The acquisition of Stage is intended to provide the Company access to transformative cell selection and activation capabilities, next generation manufacturing automation technologies, enhanced control of its supply chain, and lower expected long-term cost of goods. None of the goodwill is expected to be deductible for income tax purposes.

Acquisition of X-Body

On June 1, 2015, the Company completed the acquisition of 100% of the outstanding equity in X-Body. The Company paid $21.3 million in cash and issued an aggregate of 366,434 shares of common stock, valued at $19.4 million based on the closing stock price on June 1, 2015 of $53.07 per share, to the former X-Body stockholders. Further, an additional 72,831 shares of common stock were issued to two former X-Body stockholders in the transaction, which shares are subject to monthly vesting over the three years following the closing of the transaction, contingent on such former X-Body stockholders providing consulting services to the Company through each such vesting date. These will be accounted for as post-acquisition compensation expenses.

The Company also agreed to pay additional amounts in cash upon the realization of specified milestones substantially as follows, with respect to products generated using the X-Body technology: $5.0 million per target upon the achievement, during a specified period, of a certain regulatory milestone for products that utilize a certain type of binding mechanism; up to $30.0 million upon the achievement, during a specified period, of regulatory and clinical milestones for the first product using another type of binding mechanism (any product using such type of binding mechanism, a “Type X Product”); $5.0 million per product upon the achievement, during a specified period,

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of a certain regulatory milestone for a certain number of subsequent Type X Products; $50.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain specified binding properties (a "Type Y Product"); and $20.0 million upon the achievement, during a specified period, of a clinical milestone related to the first product with certain other specified binding properties. If a Type X Product or a Type Y Product is commercialized, Juno can choose either to make a commercialization milestone payment for such a product or to pay a low single-digit royalty on net sales of such a product. The fair value of this contingent consideration was estimated to be $8.9 million at the date of acquisition. Payments could vary based on milestones that are reached.

Cash paid	$21,331
Common stock issued (1)	19,447
Fair value of contingent consideration (2)	8,944
Settlement of preexisting obligation (3)	1,123
Total consideration	$50,845

(1) Based on the share purchase agreement, the purchase consideration included 366,434 shares of the Company's common stock. The closing stock price on the transaction date was $53.07 per share.
(2) The fair value of the contingent consideration was determined by calculating the probability-weighted milestone based on the assessment of the likelihood and estimated timing that certain milestones would be achieved. The fair value of the contingent consideration is estimated using a discount rate of 15.2%. The discount rate captures the credit risk associated with the payment of the contingent consideration when earned and due.
(3) The settlement of preexisting obligation reflects the effective settlement of the Company's preexisting prepaid contract research agreement with X-Body. No gain or loss was recognized by the Company on the effective settlement of this prepaid expense as of the acquisition date.

The allocation of the purchase price is based on estimates of the fair value of assets acquired and liabilities assumed as of the acquisition date. The components of the purchase price allocation are as follows (in thousands):

Net liabilities assumed	$ (181)
Deferred tax liabilities	(1,099)
Acquired in-process research and development	16,450
Goodwill	35,675
Total consideration transferred	$50,845

The fair value of the acquired in-process research and development has been estimated using the replacement cost method. Under this method, the Company estimated the cost to recreate the technology and derived an estimated value to develop the technology. In-process research and development are required to be classified as indefinite-lived assets until the successful completion or the abandonment of the associated research and development effort. Accordingly, during the development period after the date of acquisition, these assets will not be amortized until regulatory approval is obtained in a major market, typically either the United States or the EU, subject to management judgment. At that time, the Company will determine the useful life of the asset and begin amortization. If the associated research and development effort is abandoned, the related in-process research and development assets will be written-off and an impairment charge recorded.

The excess of the purchase price over the estimated fair value of the tangible net assets and identifiable intangible assets acquired was recorded as goodwill. The goodwill recognized as a result of the X-Body acquisition is primarily attributable to the fact that the acquisition furthers the Company's strategy of investing in technologies that augment the company's capabilities to create best-in-class engineered T cells against a broad array of cancer targets. The acquisition brings in-house to the Company an innovative discovery platform that interrogates the human antibody repertoire, rapidly selecting fully human antibodies with desired characteristics, even against difficult targets. None of the goodwill is expected to be deductible for income tax purposes.

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Post-Acquisition and Pro Forma Consolidated Financial Information

The Stage and X-Body acquisitions did not have a material impact on the Company's condensed consolidated statements of operations, and therefore actual and pro forma disclosures have not been presented. The intangible assets acquired in the Stage and X-Body acquisitions are in-process research and development assets, and as such, there would be no pro forma adjustment needed for the amortization of intangible assets.

Transaction Costs

The Company incurred approximately $4.2 million of direct transaction costs related to the Stage and X-Body acquisitions for the three and six months ended June 30, 2015. These costs are included in general and administrative expenses in the condensed consolidated statements of operations.

3. Collaboration and License Agreements

Celgene

In June 2015, the Company entered into a Master Research and Collaboration Agreement (the "Collaboration Agreement") with Celgene Corporation and Celgene RIVOT Ltd. (collectively, "Celgene") pursuant to which the Company and Celgene agreed to collaborate on researching, developing, and commercializing novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. Pursuant to the collaboration, prior to the exercise of an option for a program, each of the Company and Celgene will conduct independent programs to research, develop, and commercialize such product candidates (including, in the case of the Company, its CD19 and CD22 programs). Each party has certain options to obtain either an exclusive license to develop and commercialize specified product candidates arising from specified types of programs conducted by the other party within the scope of the collaboration, or the right to participate in the co-development and co-commercialization of specified product candidates arising from such programs, in each case in specified territories. Further, following the exercise of an option, Celgene has the right to exercise an option for a specified number of such programs, excluding the CD19 program and the CD22 program, to co-develop and co-commercialize products arising out of such programs in certain countries, and each of Celgene and Company has the right to elect to participate in certain commercialization activities for products in such programs in territories where it is not leading commercialization of such product. The parties may exercise their options with respect to specified product candidates arising under programs within the scope of the collaboration until the tenth anniversary of the effective date of the Collaboration Agreement (the "Research Collaboration Term"), subject to a tail period applicable to certain programs, for which options have not yet been exercised as of the expiration of the Research Collaboration Term.

For Company-originated programs (which may include the CD19 program and the CD22 program) under the collaboration for which Celgene exercises its option to obtain an exclusive license:

- The Company would be responsible for research and development in the United States, Canada, and Mexico, and, for cellular therapy product candidates, China, and would retain commercialization rights and would lead commercialization activities and book sales of products in those countries (the "Juno Territory"), subject to Celgene's option, for a specified number of programs, to elect to co-develop and co-commercialize product candidates arising from such programs, or for other programs, to elect to participate in certain commercialization activities in the Juno Territory, as further described below. Under all such license agreements, the Company has the right to participate in specified commercialization activities arising from such programs in certain major European markets;
- On a program-by-program basis, Celgene would receive an exclusive license, and pursuant to such license would be responsible for, development and commercialization outside of the Juno Territory (the "Celgene Territory"), including by leading commercialization activities and booking sales of products in the Celgene Territory. Celgene would be required to pay the Company a royalty on sales of products arising from such program in the Celgene Territory as further described below; and
- For Company-originated programs, excluding CD19 and CD22, Celgene would have the right to exercise an option for a specified number of such programs, to obtain the right to co-develop and co-commercialize products arising from such program worldwide, except for China. For each such program, following Celgene's exercise of such option, the parties would enter into an agreed form of co-development and co-commercialization agreement, pursuant to which:
    - Celgene would have the right to co-develop and co-commercialize product candidates arising from such programs, with the parties each entitled to bear and receive an equal share of the profits and losses arising from development and commercialization activities in such programs worldwide (other than China);
    - The Company would remain the lead party for development and commercialization activities for such product candidates in the Juno Territory, and Celgene would remain the lead party for development and commercialization activities for such

product candidates in the Celgene Territory, subject to the Company's right to participate in certain commercialization activities in certain major European countries, and Celgene's right to elect to participate in a specified percentage of commercialization activities in the Juno Territory;

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For other Company originated programs for which Celgene does not exercise such a co-development and co-commercialization right, Celgene would also have the right to elect to participate in up to a specified percentage of certain commercialization activities for product candidates in such program in the Juno Territory, and the Company would have the right to elect to participate in up to a specified percentage of certain commercialization activities for such product candidates in certain major European markets.

For Celgene-originated programs under the collaboration for which the Company exercises its option to obtain an exclusive license, the parties will enter into a co-development and co-commercialization agreement and:

- The parties will share global profits and losses from development and commercialization activities with 70% allocated to Celgene and 30% allocated to the Company; and
- Celgene will lead global development and commercialization activities, subject to the Company's right to elect to participate in up to a specified percentage of certain commercialization activities in the Juno Territory under certain circumstances and in certain major European countries.

Furthermore, each of Celgene and the Company will have the exclusive right to exercise options to co-develop and co-commercialize product candidates arising out of programs for which the other party in-licenses or acquires rights that are within the scope of their collaboration, where such rights are available to be granted, with the parties each bearing an equal share of the profits and losses arising out of such programs following the exercise of such option. In general, for such programs where the rights are in-licensed or acquired by the Company and for which Celgene exercises its options, the Company will be the lead party for development and commercialization of product candidates arising from such programs in the Juno Territory, subject to Celgene's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory, and Celgene will be the lead party for development and commercialization of product candidates arising in such programs in the Celgene Territory, subject to the Company's right to elect to participate in certain commercialization activities for such product candidates in certain major European markets. Conversely, for such programs where the rights are in-licensed or acquired by Celgene and for which the Company exercises its options, Celgene will be the lead party for development and commercialization activities for product candidates arising from such programs on a worldwide basis, subject to the Company's right to elect to participate in certain commercialization activities for such product candidates in the Juno Territory and in certain major European markets. The party exercising an option for these in-licensed or acquired programs is generally required to pay to the other party an upfront payment equal to one half of the costs incurred by other party in connection with the acquisition of rights to such programs.

In addition to an upfront cash payment of approximately $150.2 million under the Collaboration Agreement, Celgene is required to pay to the Company an additional upfront fee if it exercises its option for each of the CD19 Program and the CD22 Program, totaling, if the options are exercised for both programs during the initial opt-in window, $100.0 million. Upon a party's exercise of the option for any other program (other than certain in-licensed or acquired programs where a party exercises its option at the time such program is acquired), the party exercising the option is required to pay to the other party an upfront payment at the time of exercise of its option, calculated as a multiple of the costs incurred by the other party in relation to the development activities for such program prior to the exercise of the option, with such multiple based on the point in development of such product at which such party exercises such option. For programs for which the parties have entered into a license agreement, the Company will also receive royalties from Celgene, for product candidates arising from the CD19 and CD22 programs, at a percentage in the mid-teens of net sales of such product candidates in the Celgene Territory, and for product candidates arising from other Company programs that are subject to a license agreement, tiered royalties on net sales of such product candidates in the Celgene Territory, at percentages ranging from the high single digits to the mid-teens, calculated based on the stage of development at which Celgene exercises its option for such program.

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In June 2015, the Company also entered into a Share Purchase Agreement (the "Purchase Agreement") with Celgene. Pursuant to the Purchase Agreement, the Company agreed to sell 9,137,672 shares of the Company's common stock to Celgene at an aggregate cash price of approximately $849.8 million, or $93.00 per share of common stock, at an initial closing (the "Initial Closing"). Beyond the Initial Closing, the Purchase Agreement provides for potential future sales of shares by the Company to Celgene as follows:

- First Period Top-Up Rights. After the Initial Closing and until June 29, 2020, Celgene has the annual right, following the filing of each Annual Report on Form 10-K filed by the Company, to purchase additional shares from the Company at a market average price, allowing it to "top up" to an ownership interest equal to 10% of the then-outstanding shares (after giving effect to such purchase), subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise).
- First Acquisition Right. During the period beginning on June 29, 2019 and ending on June 28, 2020, subject to Celgene opting in to a certain number of Company programs under the Collaboration Agreement, Celgene will have the right (the "First Acquisition Right") to purchase up to such number of shares that will allow Celgene to have ownership of 19.99% of the then-outstanding shares of the Company's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market (currently The NASDAQ Global Select Market) on the date of exercise (the "FAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.
- Second Period Top-Up Rights. After the closing of the purchase of shares upon the exercise of the First Acquisition Right until the SAR Termination Date (as defined below), in the event that Celgene has been diluted after exercising the First Acquisition Right, the Company will, following the filing of each Annual Report on Form 10-K filed by the Company, offer Celgene the right to purchase additional shares from the Company at 105% of market average price, allowing Celgene to "top up" to an ownership interest (after giving effect to such purchase) equal to the percentage ownership of shares that Celgene obtained upon exercise of the First Acquisition Right, subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any year in which it is offered such right by the Company, then the percentage of ownership targeted for a top-up stock purchase for the next year it is offered such top-up right will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). The "SAR Termination Date" is the later of (a) June 29, 2025, and (b) the earlier of (x) the date that is 6 months following the date that the conditions to the exercise of the Second Acquisition Right (as defined herein) are satisfied and (y) December 29, 2025.
- Second Acquisition Right. During the period beginning on June 29, 2024 and ending on the SAR Termination Date, subject to each of Celgene and the Company opting into a certain number of programs under the Collaboration Agreement, and provided that Celgene exercised the First Acquisition Right so as to obtain a percentage ownership of 17% of the Company, Celgene will have the right (the "Second Acquisition Right") to purchase up to such number of shares that will allow Celgene to have ownership of 30% of the then-outstanding shares of the Company's common stock (after giving effect to such purchase) at the closing price of the common stock on the principal trading market on the date of exercise (the "SAR Base Price"), plus a premium on all shares in excess of the number of shares for which Celgene would then be able to purchase if it then had a top-up right as described in the preceding paragraph.
- Final Top-Up Rights. Following the closing of the purchase of shares upon the exercise of the Second Acquisition Right and until the Collaboration Agreement expires or is terminated, Celgene would have the annual right, in the event that Celgene has been diluted after exercising the Second Acquisition Right, following the filing of each Annual Report on Form 10-K filed by the Company, to purchase additional shares from the Company at a price equal to 105% of market average price, allowing it to "top up" to the percentage ownership it had attained upon exercising the Second Acquisition Right, less 250 basis points, subject to adjustment downward in certain circumstances. If Celgene does not exercise its top-up right in full in any given year, then the percentage of ownership targeted for a top-up stock purchase for the next year will be reduced to Celgene's percentage ownership at the time of such non-exercise or partial exercise (after giving effect to the issuance of shares in any partial exercise). These rights and the other described top-up rights, as well as the First Acquisition Right and Second Acquisition Right, may be limited or eliminated in certain circumstances when and if Celgene disposes of any of its shares.

Each closing of the sale of shares to Celgene is subject to customary closing conditions, including termination or expiration of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended. The Purchase Agreement also limits the aggregate number of shares that may be issued thereunder to 19.99% of the Company's common stock outstanding immediately prior to the entry into the Purchase Agreement, unless

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stockholder approval is obtained for additional issuances of Company stock in accordance with NASDAQ rules. The Company has agreed to submit the additional equity issuances for approval by its stockholders at the Company's 2016 annual meeting of stockholders.

The Collaboration Agreement became effective on July 31, 2015, in connection with which the Company received an upfront cash payment of $150.2 million. On August 4, 2015 the Initial Closing under the Purchase Agreement occurred, and the Company sold 9,137,672 shares of the Company's common stock to Celgene for an aggregate cash purchase price of approximately $849.8 million.

Fred Hutchinson Cancer Research Center

In October 2013, the Company entered into a collaboration agreement with FHCRC, focused on research and development of cancer immunotherapy products. The agreement has a six year term and can be extended if mutually agreed upon. The research will be conducted in accordance with a research plan and budget approved by the parties. The Company is committed to aggregate research funding of $9.3 million over a period of six years relating to the research and development of cellular immunology products. The Company recognized $2.4 million and $1.7 million of research and development expenses in connection with its collaboration agreement with FHCRC for the three months ended June 30, 2015 and 2014, respectively, and $4.4 million and $2.2 million for the six months ended June 30, 2015 and 2014, respectively.

The Company granted FHCRC rights to certain share-based success payments. Under the terms of this arrangement, the Company may be required to make success payments to FHCRC based on increases in the estimated fair value of the Company's common stock. The potential payments are based on multiples of increased value ranging from 5x to 40x based on a comparison of the fair value of the common stock relative to its original $4.00 issuance price. The payments are based on whether the value of the Company's common stock meets or exceeds certain specified threshold values ascending from $20.00 per share to $160.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. In June 2014, the Company entered into an agreement with FHCRC in which it can offset certain indirect costs related to the collaboration projects conducted by FHCRC against any success payments. The aggregate success payments to FHCRC are not to exceed $375 million which would only occur upon a 40x increase in value. The term of the success payment agreement ranges from eight to eleven years depending upon when or if the company receives FDA approval of certain of its product candidates as specified in the agreement.

The following table summarizes the potential success payments, which are payable in cash or publicly-traded equity at the Company's discretion:

Multiple of Equity Value at issuance	5.0x	7.5x	10.0x	15.0x	20.0x	25.0x	30.0x	35.0x	40.0x
Per share common stock price required for payment	$20.00	$30.00	$40.00	$60.00	$80.00	$100.00	$120.00	$140.00	$160.00
Success payment(s) (in millions)	$ 10	$ 25	$ 40	$ 50	$ 50	$ 50	$ 50	$ 50	$ 50

The success payments will be owed if the value of our common stock on the contractually specified valuation measurement dates during the term of the success payment agreement equals or exceeds the above outlined multiples. The valuation measurement dates are triggered by events which include an initial public offering of the Company's stock, a merger, an asset sale, or the sale of the majority of the shares held by certain of the Company's stockholders or the last day of the term of the success payment agreement. If a higher success payment tier is first met at the same time a lower tier is first met, both tiers will be owed. Any previous success payments made to FHCRC are credited against the success payment owed as of any valuation measurement date, so that FHCRC does not receive multiple success payments in connection with the same threshold. A payment may be triggered on the first anniversary of the closing of the IPO (or the date that is 90 days following such anniversary, at the Company's option, if the Company is contemplating a capital market transaction during such 90 day period). The value of any such success payment will be determined by the average trading price of a share of the Company's common stock over the consecutive 90-day period preceding such determination date.

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The Company's liability for share-based success payments under the FHCRC collaboration is carried at fair value and recognized as expense over the term of the six-year collaboration agreement. To determine the estimated fair value of the success payment liability the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the calculation of the estimated fair value of the success payment liability as of June 30, 2015:

Assumptions	June 30, 2015	December 31, 2014
Fair value of common stock	$ 53.33	$ 52.22
Risk free interest rate	1.92%-2.28%	1.94%-2.16%
Expected volatility	75%	75%
Expected term (years)	6.30-9.30	6.79-9.79

The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and our historical volatility. The risk free interest rate and expected term assumptions ranged from 1.92% to 2.28% and 6.30 to 9.30 years, respectively, depending on the estimated timing of FDA approval. In addition, the Company incorporated the estimated number and timing of valuation measurement dates in the calculation of the success payment liability. As of June 30, 2015 and December 31, 2014, the estimated fair value of the total success payment obligation to FHCRC was approximately $149.4 million and $139.1 million, respectively. The Company recognized research and development expense of $2.8 million and $0.2 million in the three months ended June 30, 2015 and 2014, respectively, and $29.9 million and $0.3 million in the six months ended June 30, 2015 and 2014, respectively. The expense associated with the success payment obligation is amortized to research and development expense using the accelerated attribution method over the service period. The success payment liabilities as of June 30, 2015 and December 31, 2014 was $91.2 million and $61.2 million, respectively. If the fair value of the Company's common stock at the first valuation measurement date in December 2015 remains at its June 30, 2015 value of $53.33, the Company will be required to make a $75 million payment to FHCRC, payable in cash or stock at the Company's discretion.

In October 2013, the Company entered into a license agreement with FHCRC, pursuant to which the Company acquired an exclusive, worldwide, sublicensable license under certain patent rights, and a non- exclusive, worldwide, sublicensable license under certain technology, to research, develop, manufacture, improve, and commercialize products and processes covered by such patent rights or incorporating such technology for all therapeutic uses for the treatment of human cancer. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including target specific constructs and customized spacer regions, TCR constructs, and their use for immunotherapy. The Company classifies on the condensed consolidated statement of operations payments accrued or made under its licensing arrangements based on the underlying nature of the expense. Expenses related to the reimbursement of legal and patent costs are classified as general and administrative because the nature of the expense is not related to the research or development of the technologies the Company is licensing.

The Company also agreed to pay FHCRC annual maintenance fees, milestone payments, and royalties as a percentage of net sales of licensed products. After five years the Company is obligated to pay a $0.1 million minimum annual royalty, with such payments creditable against royalties.

Milestone payments to FHCRC of up to an aggregate of $6.8 million per licensed product, including JCAR014 and JCAR017, are triggered upon the achievement of specified clinical and regulatory milestones and are not creditable against royalties. The Company may terminate the license agreement at any time with advance written notice.

Memorial Sloan Kettering Cancer Center

In November 2013, the Company entered into a sponsored research agreement with MSK, focused on research and development relating to chimeric antigen receptor T cell technology. The research will be conducted in accordance with a research plan and budget approved by the parties. The Company is committed to aggregate research funding of $2.2 million over a period of five years. The Company also entered into a master clinical study agreement, with MSK, pursuant to which the Company committed to provide aggregate funding to MSK of up to $7.2 million for six clinical studies to be conducted at MSK on the Company's behalf. Each such study will be conducted in accordance with a written plan and budget and protocol approved by the parties. The Company recognized $1.8 million and $0.3 million of research and development expenses in connection with its collaboration agreement with MSK for the three months ended June 30, 2015 and 2014, respectively, and $2.8 million and $0.6 million for the six months ended June 30, 2015 and 2014, respectively.

The Company granted MSK rights to certain share-based success payments. Under the terms of this arrangement, the Company may be required to make success payments to MSK based on the increases in the estimated fair value of the Company's common stock. The potential payments are based on multiples of increased value ranging from

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10x to 30x based on a comparison of the fair value of the common stock relative to its original $4.00 issuance price. The payments are based on whether the value of the Company's common stock meets or exceeds certain specified threshold values ascending from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. The aggregate success payments to MSK are not to exceed $150 million, which would only occur upon a 30x increase in value. The term of the success payment agreement ranges from eight to eleven years depending upon when or if the company receives FDA approval of certain of its product candidates as specified in the agreement.

The following table summarizes the potential success payments, which are payable in cash or publicly-traded equity at the Company's discretion:

Multiple of Equity Value at issuance	10.0x	15.0x	30.0x
Per share common stock price required for payment	$40.00	$60.00	$120.00
Success payment(s) (in millions)	$ 10	$ 70	$ 70

The success payments will be owed, if the value of our common stock on contractually specified valuation measurement dates equals or exceeds the above outlined multiples. The valuation measurement dates are triggered by events which include an initial public offering of the Company's stock, a merger, an asset sale, or the sale of the majority of the shares held by certain of the Company's stockholders or the last day of the term of the success payment agreement. If a higher success payment tier is met at the same time a lower tier is met, both tiers will be owed. Any previous success payments made to MSK are credited against the success payment owed as of any valuation measurement date, so that MSK does not receive multiple success payments in connection with the same threshold. A payment may be triggered on the first anniversary of the closing of the IPO (or the date that is 90 days following such anniversary, at the Company's option, if the Company is contemplating a capital market transaction during such 90 day period). The value of any such success payment will be determined by the average trading price of a share of the Company's common stock over the consecutive 90-day period preceding such determination date.

The Company's liability for share-based success payments under the MSK collaboration is carried at fair value and recognized as expense over the term of the five-year collaboration agreement. To determine the estimated fair value of the success payment liability the Company uses a Monte Carlo simulation methodology which models the future movement of stock prices based on several key variables. The following variables were incorporated in the calculation of the estimated fair value of the success payment liability as of June 30, 2015:

Assumptions	June 30, 2015	December 31, 2014
Fair value of common stock	$ 53.33	$ 52.22
Risk free interest rate	1.94%-2.29%	1.95%-2.16%
Expected volatility	75%	75%
Expected term (years)	6.40-9.40	6.89-9.89

The computation of expected volatility was estimated using a combination of available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption and our historical volatility. The risk free interest rate and expected term assumptions ranged from 1.94% to 2.29% and 6.40 to 9.40 years, respectively, depending on the estimated timing of FDA approval. In addition, the Company incorporated the estimated number and timing of valuation measurement dates in the calculation of the success payment liability. As of June 30, 2015 and December 31, 2014, the estimated fair value of the total success payment obligation to MSK was approximately $62.0 million and $56.8 million, respectively. The Company recognized research and development expense of $1.2 million and $0.1 million in the three months ended June 30, 2015 and 2014, respectively, and $12.9 million and $0.1 million in the six months ended June 30, 2015 and 2014, respectively. The expense associated with the success payment obligation is amortized to research and development expense using the accelerated attribution method over the service period. The success payment liabilities as of June 30, 2015 and December 31, 2014 was $36.6 million and $23.7 million, respectively. If the fair value of the Company's common stock at the first valuation measurement date in December 2015 remains at its June 30, 2015 value of $53.33, the Company will be required to make a $10 million payment to MSK, payable in cash or stock at the Company's discretion.

In November 2013, the Company entered into a license agreement with MSK, pursuant to which the Company acquired a worldwide, sublicensable license to specified patent rights and intellectual property rights related to certain know-how to develop, make, and commercialize licensed products and to perform services for all therapeutic

and diagnostic uses, which license is exclusive with respect to such patent rights and tangible materials within such know-how, and non-exclusive with respect to such know-how and related intellectual property rights. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs, including bispecific and armored CARs, and their use for immunotherapy.

The Company also agreed to pay MSK milestone payments and royalties as a percentage of net sales of licensed products and services by us or our affiliates and sublicensees. After five years the Company is obligated to pay a $0.1 million minimum annual royalty, with such payments credible against royalties.

Milestone payments to MSK of up to an aggregate of $6.8 million per licensed product, including JCAR015, are triggered upon the achievement of specified clinical and regulatory milestones and are not creditable against royalties. The Company may terminate the license agreement at any time with advance written notice, but if the Company has commenced the commercialization of licensed products, the Company can only terminate at will if it ceases all development and commercialization of licensed products.

St. Jude Children's Research Hospital/Novartis

In December 2013, the Company entered into an agreement with St. Jude ("St. Jude License Agreement"), pursuant to which the Company (1) obtained control over, and the obligation to pursue and defend, St. Jude's causes of action in Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn.), which concerned both U.S. Patent No. 8,399,645 (the "'645 Patent") and a contractual dispute between St. Jude and the Trustees of the University of Pennsylvania ("Penn") and (2) acquired an exclusive, worldwide, royalty-bearing license under certain patent rights owned by St. Jude, including the '645 Patent, to develop, make, and commercialize licensed products and services for all therapeutic, diagnostic, preventative, and palliative uses. The patents and patent applications covered by this agreement are directed, in part, to CAR constructs capable of signaling both a primary and a costimulatory pathway. Together with St. Jude, the Company was a party in, and was adverse to, Penn and Novartis Pharmaceutical Corporation ("Novartis") in that litigation (the "Penn litigation"), which was settled by the parties in April 2015.

The Company also agreed to pay to St. Jude milestone payments and royalties as a percentage of net sales of licensed products and services, and a percentage of St. Jude's reasonable legal fees incurred in connection with the Penn litigation. The Company is obligated to pay a $0.1 million minimum annual royalty for the first two years of the agreement and a $0.5 million minimum annual royalty thereafter.

Milestone payments to St. Jude of up to an aggregate of $62.5 million are triggered upon the achievement of specified clinical, regulatory, and commercialization milestones for licensed products, including JCAR014 or JCAR017, and are not creditable against royalties. The Company can terminate the agreement for any reason upon advance written notice.

In April 2015, the Company and St. Jude agreed to settle the Penn litigation with Penn and Novartis. In connection with such settlement, in April 2015, the Company entered into a sublicense agreement (the "Penn/Novartis Sublicense Agreement") with Penn and an affiliate of Novartis pursuant to which the Company granted to Novartis a non-exclusive, royalty-bearing sublicense under certain patent rights, including the '645 Patent, to develop, make, and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative, and palliative uses. This sublicense is not sublicensable without the Company's prior written consent, although Novartis may authorize third parties to act on its behalf with respect to the manufacture, development, or commercialization of Novartis' licensed products and licensed services. Under the Penn/Novartis Sublicense Agreement, Novartis paid the Company an initial license fee of $12.3 million, which was recorded as revenue for the three and six months ended June 30, 2015. In addition, Novartis is also required to pay mid-single digit royalties on the U.S. net sales of products and services related to the disputed contract and patent claims (the "Royalty Payments"), a low double digit percentage of the royalties Novartis pays to Penn for global net sales of those products (the "Penn Royalty Payments"), and milestone payments upon the achievement of specified clinical, regulatory, and commercialization milestones for licensed products (the "Milestone Payments"). If the Company achieves any of the milestones with respect to its own products leveraging the same patents, prior to Novartis, the related Milestone Payment will be reduced by 50%. In addition, if the Company achieves any milestone after Novartis, the Company will reimburse Novartis 50% of any Milestone Payment previously paid by Novartis to the Company in respect of such milestone. These milestones largely overlap with the milestones for which the Company may owe a payment to St. Jude under the St. Jude License Agreement and the Milestone Payments would in effect serve to partially offset the Company's obligations to St. Jude with respect to such milestones.

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Novartis may terminate the Penn/Novartis Sublicense Agreement at will upon advance written notice to the Company.

Under a separate agreement with St. Jude, the Company agreed to pay St. Jude $5.3 million as reimbursement of litigation expenses. The Company and St. Jude also amended the St. Jude License Agreement to provide the terms by which the Penn/Novartis Sublicense Agreement would be treated under the St. Jude License Agreement.

Seattle Children's Research Institute

In February 2014, the Company entered into a sponsored research agreement with Seattle Children's Research Institute ("SCRI") pursuant to which the Company committed to provide research funding to SCRI totaling not less than $2.1 million over a period of five years. Effective April 1, 2015, the sponsored research agreement was amended to extend the term of the agreement through April 2020, thereby increasing the minimum funding obligations by an additional $0.3 million. The research will be conducted in accordance with a written plan and budget approved by the parties. In November 2014, the Company entered into a Letter of Intent with SCRI pursuant to which the Company committed to provide clinical trial funding to SCRI totaling not less than $4.1 million over a period of five years. The Company recognized $0.2 million of research and development expenses in connection with its sponsored research agreement with SCRI for the three months ended June 30, 2015 and $0.3 million for the six months ended June 30, 2015. The Company recognized expense of $0.1 million in connection with its sponsored research agreement with SCRI for the six months ended June 30, 2014.

In February 2014, the Company entered into a license agreement with SCRI that grants the Company an exclusive, worldwide, royalty-bearing sublicensable license to certain patent rights to develop, make and commercialize licensed products and to perform licensed services for all therapeutic, prophylactic, and diagnostic uses. Effective June 2015, the license agreement was amended to include additional patent rights. The Company paid $0.2 million in the six months ended June 30, 2014 for the upfront license fee, which was recorded as research and development expense.

The Company is required to pay to SCRI annual license maintenance fees, creditable against royalties and milestone payments due to SCRI, of $50,000 per year for the first five years and $0.2 million per year thereafter.

The Company also agreed to pay SCRI milestone payments and royalties as a percentage of net sales of licensed products and licensed services. Milestone payments to SCRI of up to an aggregate of $16.3 million per licensed product, including JCAR014 and JCAR017, are triggered upon the achievement of specified clinical, regulatory, and commercialization milestones and are not creditable against future royalties. The Company may terminate the license agreement for any reason with advance written notice.

Opus Bio

In December 2014, the Company entered into a license agreement with Opus Bio, Inc. pursuant to which the Company was granted an exclusive, worldwide, sublicensable license under certain patent rights and data to research, develop, make, have made, use, have used, sell, have sold, offer to sell, import and otherwise exploit products that incorporate or use engineered T cells directed against CD22 and that are covered by such patent rights or use or incorporate such data. Certain of the licensed patent rights are in-licensed by Opus Bio from the National Institutes of Health ("NIH"). Under the agreement, the Company is required to use commercially reasonable efforts to research, develop, and commercialize licensed products. Such development must be in accordance with the timelines provided in the license agreement for achievement of certain clinical, regulatory, and commercial benchmarks, and with the development plans set forth in Opus Bio's agreements with the NIH.

Upon achievement of certain clinical, regulatory, and commercial milestones set forth in the license agreement, the Company will be obligated to pay Opus Bio additional consideration. The consideration due upon achievement of the first three clinical milestones would consist of additional shares of our common stock in an amount equal to the dollar value specified for the applicable milestone, which is $52.5 million in the aggregate for the three milestones, divided by the greater of $10.92 and the arithmetic average of the daily volume- weighted average price of our common stock on The NASDAQ Global Select Market over the 30 trading days preceding the achievement of the milestone, up to a maximum of 4,807,692 shares in the aggregate (this minimum per share value and maximum number of shares subject, in each case, to adjustment for any stock dividend, stock split, combination of shares, or other similar events). Upon achievement of any subsequent milestones, the Company will be obligated to pay Opus Bio cash consideration, which potential milestone payments total $215.0 million in the aggregate. Once certain milestones have been achieved, the Company will be required to spend at least $2.5 million per year on development and commercialization of licensed products.

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The license agreement further provides that the Company is required to pay to Opus Bio tiered royalties based on annual net sales of licensed products by us and by sublicensees. The Company will also be required to make certain pass-through payments owed by Opus Bio to NIH under its NIH license agreements, including certain patent costs, development and commercial milestones of up to $2.8 million in the aggregate, royalties based on annual net sales. The Company may terminate the agreement at will upon advance written notice.

Fate Therapeutics

In May 2015, the Company entered into a collaboration and license agreement with Fate Therapeutics, Inc. (“Fate Therapeutics”), to identify and utilize small molecules to modulate the Company’s genetically-engineered T cell product candidates to improve their therapeutic potential for cancer patients. The Company paid an upfront fee of $5.0 million in cash and purchased 1,000,000 shares in Fate Therapeutics common stock at a purchase price of $8.00 per share, representing an approximately 5% ownership interest in Fate Therapeutics. The $5.0 million upfront fee and the premium paid for the common stock of $0.8 million were recorded as research and development expense in the three and six months ended June 30, 2015. The investment in Fate Therapeutics is classified as available-for-sale, and reported at fair value with unrealized gains and losses included in accumulated other comprehensive income (loss). The Company also agreed to provide Fate Therapeutics with research funding of $2.0 million per year during the initial four year research term. The Company has an option to extend the collaboration for two additional years, subject to payment of an extension fee and additional annual research funding. Under the collaboration and license agreement, for each product developed by the Company that incorporates modulators identified through the collaboration, the Company will also be required to pay Fate Therapeutics target selection fees and milestone payments upon achievement of clinical, regulatory, and commercial milestones, as well as low single-digit royalties on net sales. The Company can terminate the agreement at will upon advance written notice, but such termination may not be effective any earlier than May 2017. In addition to the upfront fee of $5.0 million and the premium paid for the common stock of $0.8 million, the Company recognized $0.3 million of research and development expenses in connection with its collaboration agreement with Fate Therapeutics for the three and six months ended June 30, 2015.

Editas Medicine

In May 2015, the Company entered into a collaboration and license agreement with Editas Medicine, Inc. (“Editas”), to pursue research programs utilizing Editas’ genome editing technologies with Juno’s CAR and TCR technologies. The Company paid an upfront fee of $25.0 million in cash, which was recorded as research and development expense in the three and six months ended June 30, 2015. The Company also agreed to provide Editas with research funding of up to $22.0 million over the initial five year research term. The Company and Editas may mutually agree to extend the collaboration for two additional years, subject to payment of extension fees. Editas is also eligible to receive future research, regulatory, and commercial sales milestones for each program. Following the approval of any products resulting from the alliance, Editas is also eligible to receive tiered royalties. The Company can terminate the agreement at will upon advance written notice. In addition to the upfront fee of $25.0 million, the Company recognized $0.2 million of research and development expenses in connection with its collaboration agreement with Editas for the three and six months ended June 30, 2015.

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4. Cash Equivalents and Marketable Securities

The following tables summarize the estimated fair value of our cash equivalents and marketable securities and the gross unrealized holding gains and losses (in thousands):

	June 30, 2015			
	Amortized Cost	Gross Unrealized Holding Gains	Gross Unrealized Holding Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 7,651	$ —	$ —	$ 7,651
Commercial paper	6,499	—	—	6,499
U.S. government and agency securities	8,039	—	(1)	8,038
Corporate debt securities	3,402	—	(1)	3,401
Total cash equivalents	25,591	—	(2)	25,589
Marketable securities:				
U.S. government and agency securities	201,234	39	(9)	201,264
Corporate debt securities	62,821	1	(31)	62,791
Total marketable securities	264,055	40	(40)	264,055
Long-term marketable securities:				
U.S. government and agency securities	1,356	—	—	1,356
Corporate debt securities	2,015	—	(2)	2,013
Equity securities	7,190	—	(720)	6,470
Total long-term marketable securities	$ 10,561	$ —	$ (722)	$ 9,839

	December 31, 2014			
	Amortized Cost	Gross Unrealized Holding Gains	Gross Unrealized Holding Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 223,745	$ —	$ —	$ 223,745
Commercial paper	13,294	—	—	13,294
U.S. government and agency securities	7,582	—	—	7,582
Corporate debt securities	1,702	—	—	1,702
Total cash equivalents	246,323	—	—	246,323
Marketable securities:				
Commercial paper	1,999	—	—	1,999
U.S. government and agency securities	47,868	—	(21)	47,847
Corporate debt securities	29,863	—	(37)	29,826
Total marketable securities	79,730	—	(58)	79,672
Long-term marketable securities:				
U.S. government and agency securities	34,898	—	(25)	34,873
Corporate debt securities	3,544	1	(7)	3,538
Total long-term marketable securities	$ 38,442	$ 1	$ (32)	$ 38,411

The following table summarizes the gross unrealized holding losses and fair value for investments in an unrealized loss position, and the length of time that individual securities have been in a continuous loss position (in thousands):

	June 30, 2015					
	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Marketable securities:						
U.S. government and agency securities	$ 78,510	$ (9)	$ —	$ —	$ 78,510	$ (9)
Corporate debt securities	51,252	(31)	—	—	51,252	(31)
Total marketable securities	129,762	(40)	—	—	129,762	(40)
Long-term marketable securities:						
Corporate debt securities	2,013	(2)	—	—	2,013	(2)
Equity securities	6,470	(720)	—	—	6,470	(720)

Total long-term marketable securities	$ 8,483	$ (722)	$ —	$ —	$ 8,483	$ (722)

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	December 31, 2014					
	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Marketable securities:						
U.S. government and agency securities	$ 43,332	$ (21)	$ —	$ —	$ 43,332	$ (21)
Corporate debt securities	26,611	(37)	—	—	26,611	(37)
Total marketable securities	69,943	(58)	—	—	69,943	(58)
Long-term marketable securities:						
U.S. government and agency securities	33,873	(25)	—	—	33,873	(25)
Corporate debt securities	2,003	(7)	—	—	2,003	(7)
Total long-term marketable securities	$ 35,876	$ (32)	$ —	$ —	$ 35,876	$ (32)

The Company evaluated its securities for other-than-temporary impairment and considers the decline in market value for the securities to be primarily attributable to current economic and market conditions. For the debt securities, it is not more likely than not that the Company will be required to sell the securities, and the Company does not intend to do so prior to the recovery of the amortized cost basis. The unrealized loss for equity securities is related to the Company's investment in Fate Therapeutics. The Company has evaluated the near-term prospects of the Fate Therapeutics investment in relation to the severity and duration of the impairment and based on that evaluation, the Company has the ability and intent to hold this investment until a recovery of fair value. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of June 30, 2015 and December 31, 2014.

All of our marketable securities have an effective maturity date of two years or less and are available for use and therefore classified as available-for-sale.

5. Fair Value Measurements

The following table sets forth the fair value of the Company's financial assets and liabilities measured at fair value on a recurring basis based on the three-tier fair value hierarchy (in thousands):

	June 30, 2015			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$ 7,651	$ —	$ —	$ 7,651
Commercial paper	—	6,499	—	6,499
U.S. government and agency securities	—	210,658	—	210,658
Corporate debt securities	—	68,205	—	68,205
Equity securities	6,470	—	—	6,470
Total financial assets	$14,121	$285,362	$ —	$299,483
Financial Liabilities:				
Fair value of success payments liabilities attributable to the elapsed service period	$ —	$ —	$127,791	$127,791
Contingent consideration	—	—	32,686	32,686
Total financial liabilities	$ —	$ —	$160,477	$160,477

	December 31, 2014			
	Level 1	Level 2	Level 3	Total
Financial Assets:				
Money market funds	$223,745	$ —	$ —	$223,745
Commercial paper	—	15,293	—	15,293
U.S. government and agency securities	—	90,302	—	90,302
Corporate debt securities	—	35,066	—	35,066
Total financial assets	$223,745	$140,661	$ —	$364,406
Financial Liabilities:				
Fair value of success payments liabilities attributable to the elapsed service period	$ —	$ —	$84,920	$ 84,920
Total financial liabilities	$ —	$ —	$84,920	$ 84,920

The Company measures the fair value of money market funds based on quoted prices in active markets for identical assets or liabilities. The Level 2 marketable securities include U.S. government and agency securities, corporate debt securities, and commercial paper and are valued either based on recent trades of securities in inactive markets or based on quoted market prices of similar instruments and other significant inputs derived from or corroborated by observable market data.

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The following table sets forth a summary of the changes in the fair value of the Company's Level 3 financial liabilities (in thousands):

	Success Payments Liabilities	Contingent Consideration	Total
Balance at December 31, 2014	$ 84,920	$ —	$ 84,920
Additions	—	37,188	37,188
Changes in fair value (1)	42,871	(80)	42,791
Balance at June 30, 2015	$ 127,791	$ 37,108	$164,899

(1) Changes in fair value for success payments liabilities and contingent consideration is recorded in research and development expense in the condensed consolidated statements of operations.

As of June 30, 2015, the estimated fair value of the success payment obligations was approximately $211.4 million, of which $127.8 million represents the portion attributable to the valuation measurement dates and the associated elapsed service period. See Note 3, Collaboration and License Agreements, for additional discussion of estimated fair value of the success payment obligations.

In connection with the acquisitions of Stage and X-Body, the Company also agreed to pay additional amounts based on the achievement of certain milestones. This contingent consideration is measured at fair value and is based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The valuation of contingent consideration uses assumptions the Company believes would be made by a market participant. The Company assesses these estimates on an on-going basis as additional data impacting the assumptions is obtained.

Contingent consideration may change significantly as development progresses and additional data are obtained, impacting the Company's assumptions regarding probabilities of successful achievement of related milestones used to estimate the fair value of the liability and the timing in which they are expected to be achieved. In evaluating the fair value information, judgment is required to interpret the market data used to develop the estimates. The estimates of fair value may not be indicative of the amounts that could be realized in a current market exchange. Accordingly, the use of different market assumptions and/or different valuation techniques could result in materially different fair value estimates.

The significant unobservable inputs used in the measurement of fair value of the Company's contingent consideration are probabilities of successful achievement of the milestones, the period in which these milestones are expected to be achieved ranging from 2015 to 2035, and a discount rate of 15.4%. Significant increases or decreases in any of the probabilities of success would result in a significantly higher or lower fair value measurement, respectively. Significant increases or decreases in these other inputs would result in a significantly lower or higher fair value measurement, respectively.

As of June 30, 2015, the estimated fair value of the contingent consideration associated with the Stage acquisition was $28.1 million. The Company recognized a gain of $0.1 million in research and development expense in the six months ended June 30, 2015 related to the change in fair value of the contingent consideration. As of June 30, 2015, the estimated fair value of the contingent consideration associated with the X-Body acquisition was $8.9 million. As the value was unchanged from the acquisition date, the Company did not recognize an expense in the six months ended June 30, 2015 related to the change in fair value of the contingent consideration.

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6. Accrued Liabilities

Accrued liabilities consisted of the following (in thousands):

	June 30, 2015	December 31, 2014
Accrued construction in progress	$ 6,031	$ —
Accrued legal expenses	5,562	4,309
Accrued research and development expenses	3,895	2,724
Accrued clinical expenses	3,301	564
Accrued bonus expense	1,982	3,106
Accrued employee expenses	1,227	531
Accrued offering costs	—	1,456
Other	4,343	1,887
Total accrued liabilities	$ 26,341	$ 14,577

7. Build-to-Suit Lease Obligation

In February 2015, the Company entered into a lease for an approximately 68,000 square foot manufacturing facility in Bothell, Washington, which lease commenced in March 2015. The Company is responsible for the leasehold improvements required to remodel the facility and bears the majority of the construction risk. ASC 840-40, Leases – Sale-Leaseback Transactions, requires the Company to be considered the owner of the building solely for accounting purposes during the construction period, even though it is not the legal owner. In connection with the accounting for this transaction, the Company capitalized $9.9 million as a build-to-suit property within property and equipment, net and recognized a corresponding build-to-suit lease obligation for the same amount.

The Company bifurcates its lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the condensed consolidated statement of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

At June 30, 2015, $0.3 million of the build-to-suit lease obligation, representing the expected reduction in the liability over the next twelve months, is classified as a current liability and the remaining $9.5 million is classified as a non-current liability on the balance sheet.

8. Stock-Based Compensation

Restricted Stock and RSUs

A summary of the Company's restricted stock and RSU activity for the six months ended June 30, 2015 is as follows:

	Shares	Weighted Average Fair Value at Date of Grant per Share
Unvested shares as of December 31, 2014	8,352,714	$ 1.46
Granted	158,516	50.98
Vested	(1,647,445)	0.33
Forfeited	(26,250)	0.60
Unvested shares as of June 30, 2015	6,837,535	$ 1.45

Management estimates expected forfeitures and recognizes compensation costs only for those equity awards expected to vest.

For the three months ended June 30, 2015 and 2014, the Company recognized $2.9 million and $1.2 million, respectively, in compensation cost related to vested restricted stock, of which $1.9 million and $0.5 million, respectively, was related to service providers other than our employees, scientific founders, and directors, including $1.7 million and $0.4 million, respectively, for a former co-founding director who became a consultant upon his

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departure from the board of directors. Of the compensation cost for the three months ended June 30, 2015 and 2014 related to vested restricted stock, $2.1 million and $0.2 million, respectively, was classified as research and development expense and $0.8 million and $1.0 million, respectively, was classified as general and administrative expense.

For the six months ended June 30, 2015 and 2014, the Company recognized $6.2 million and $1.6 million, respectively, in compensation cost related to vested restricted stock, of which $3.9 million and $0.5 million, respectively, was related to service providers other than our employees, scientific founders, and directors, including $3.6 million and $0.5 million, respectively, for a former co-founding director who became a consultant upon his departure from the board of directors. Of the compensation cost for the six months ended June 30, 2015 and 2014 related to vested restricted stock, $4.8 million and $0.3 million, respectively, was classified as research and development expense and $1.4 million and $1.3 million, respectively, was classified as general and administrative expense.

As of June 30, 2015, there was $16.0 million of total unrecognized compensation cost related to non-vested restricted stock and RSUs held by employees, scientific founders, and directors. As of June 30, 2015, the Company expects to recognize these costs over a remaining weighted average period of 2.77 years.

Stock Options

A summary of the Company's stock option activity for the six months ended June 30, 2015 is as follows:

	Number of Stock Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life	Aggregate Intrinsic Value (in thousands)
Oustanding as of December 31, 2014	2,720,351	$ 7.23	9.75	122,390
Granted	1,788,303	49.92		
Exercised	(52,053)	7.07		
Cancelled	(3,500)	59.50		
Oustanding as of June 30, 2015	4,453,101	$ 24.34	9.46	$ 130,398
Exercisable as of June 30, 2015	407,581	$ 12.92	9.31	$ 16,471

The fair value of each stock option granted has been determined using the Black-Scholes option pricing model. The material factors incorporated in the Black-Scholes model in estimating the fair value of the options granted to employees and consultants during the six months ended June 30, 2015 included the following:

Assumptions	Six Months Ended June 30, 2015
Risk free interest rate	1.53%-2.35%
Expected volatility	75%-80%
Expected life	6.02-10 years
Expected dividend yield	0%

For employees, scientific founders, and directors, the expected life was calculated based on the simplified method as permitted by the SEC Staff Accounting Bulletin No. 110, Share-Based Payment. For other service providers, the expected life was calculated using the contractual term of the award. Management's estimate of expected volatility was based on available information about the historical volatility of stocks of similar publicly-traded companies for a period matching the expected term assumption. The risk-free interest rate is based on a U.S. Treasury instrument whose term is consistent with the expected life of the stock options. In addition to the assumptions above, management made an estimate of expected forfeitures and is recognizing compensation costs only for those equity awards expected to vest. The weighted average grant date fair value of options granted for the six months ended June 30, 2015 was $49.93 per share.

For the three months ended June 30, 2015, the Company recognized $4.2 million in compensation expense related to stock options, of which $0.3 million was related to service providers other than our employees, scientific founders, and directors. Of the compensation costs related to stock options, for the three months ended June 30, 2015, $2.0 million was classified as research and development expense and $2.2 million was classified as general and administrative expense.

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For the six months ended June 30, 2015, the Company recognized $6.4 million in compensation expense related to stock options, of which $0.5 million was related to service providers other than our employees, scientific founders, and directors. Of the compensation costs related to stock options, for the six months ended June 30, 2015, $2.9 million was classified as research and development expense and $3.5 million was classified as general and administrative expense.

As of June 30, 2015, there was $66.1 million of total unrecognized compensation costs related to employees' and directors' stock options, which costs the Company expects to recognize over a remaining weighted average period of 3.29 years.

9. Accumulated Other Comprehensive Income (Loss)

The components of accumulated other comprehensive income (loss) and the adjustments to other comprehensive income (loss) are as follows (in thousands):

	Foreign currency translation adjustments	Net unrealized gains (losses) on available-for-sale investments	Accumulated other comprehensive income (loss)
Balance at December 31, 2014	$ —	$ (90)	$ (90)
Other comprehensive income (loss)	(125)	(634)	(759)
Balance at June 30, 2015	$ (125)	$ (724)	$ (849)

10. Income Taxes

The Company recorded an income tax benefit of $1.6 million on a pre-tax loss of $132.5 million for the six months ended June 30, 2015. Of the $1.6 million total tax benefit, $0.5 million relates to the Juno GmbH net loss incurred in the period from May 11, 2015 to June 30, 2015, as the Company has determined that it is more-likely-than-not that it will realize the benefit of these losses. The remaining $1.1 million of income tax benefit relates to the release of valuation allowance on the U.S. deferred tax assets as a result of the deferred tax liabilities established for definite lived intangible assets from the acquisition of X-Body.

After consideration of the X-Body acquisition impact, the Company will continue to maintain a full valuation allowance on its net U.S. deferred tax assets. The assessment regarding whether a valuation allowance is required considers both positive and negative evidence when determining whether it is more-likely-than-not that deferred tax assets are recoverable. In making this assessment, significant weight is given to evidence that can be objectively verified. In its evaluation, the Company considered its cumulative loss in recent years and its forecasted losses in the near-term as significant negative evidence. The Company determined that the negative evidence outweighed the positive evidence and a full valuation allowance on its net deferred tax assets will be maintained. The Company will continue to assess the realizability of its deferred tax assets going forward and will adjust the valuation allowance as needed.

The Company applies judgment in the determination of the consolidated financial statement recognition and measurement of tax positions taken or expected to be taken in a tax return. As of June 30, 2015 and December 31, 2014, the Company had no material unrecognized tax benefits.

The Collaboration Agreement with Celgene became effective on July 31, 2015. The Company is currently in the process of evaluating the impact on its income tax accounts (including the valuation allowance) of the cash consideration received from Celgene.

11. Commitments and Contingencies

Leases

The Company has an operating lease for 23,191 square feet of office and laboratory space located in Seattle, Washington, which expires on June 27, 2017. The Company may terminate the lease agreement with 120 days' notice after March 31, 2016. In November 2014, the Company entered into an operating lease for an additional 17,841 square feet of office and laboratory space located in the same building in Seattle, Washington as the Company's existing leased space. The lease began in December 2014 and expires June 29, 2017. The Company may terminate the lease agreement with 120 days' notice after March 31, 2016.

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In February 2015, the Company entered into a lease for an approximately 68,000 square foot manufacturing facility located in Bothell, Washington. The lease commenced in March 2015 and has an initial term of ten years. The Company has the right to terminate the lease effective as of any date after the second and on or before the seventh anniversary of the commencement of the lease term, with 12-months' advance written notice and payment of an early termination fee equal to two years of rent and any unamortized leasing commissions paid by the landlord to any broker with respect to the initial term of the lease. The Company will also have two options to extend the term of the lease by five years each option, subject to a market-based rent escalation provision.

In April 2015, the Company entered into a lease agreement for approximately 90,000 square feet of office and laboratory space in a to-be-constructed building to be located in Seattle, Washington. The Company will also have three opportunities at certain points during the initial term to elect to expand the new premises to include additional space in the new building, subject to certain limitations. The anticipated commencement date of the lease is on or about February 1, 2017. The initial term of the lease continues for 84 months from the first day of the first full month following the commencement date.

The Company has an operating lease for 11,560 square feet of office and laboratory space located in Munich, Germany. The lease expires on December 31, 2016, with an option to extend the term for one approximately three-year period. The Company has an operating lease for 1,857 square feet of office and laboratory space located in Göttingen, Germany. The lease is cancellable by either party upon six weeks written notice.

The Company has an operating lease for 3,529 square feet of office and laboratory space located in Waltham, Massachusetts. The lease is cancellable by either party upon four months written notice.

The Company records rent expense on a straight-line basis over the effective term of the lease, including any free rent periods. Rent expense for the three months ended June 30, 2015 and 2014 was $0.5 million and $0.2 million, respectively. Rent expense for the six months ended June 30, 2015 and 2014 was $0.9 million and $0.4 million, respectively. The Company's lease agreements also require payment of common area maintenance charges and other executory costs.

The following table summarizes the Company's future minimum lease commitments as of June 30, 2015 (in thousands):

Year ending December 31:	
2015	$ 1,465
2016	2,992
2017	4,096
2018	5,964
2019	6,113
Thereafter	28,650
Total minimum lease payments	$49,280

12. Related-Party Transactions

The Company has collaboration and license agreements with FHCRC and MSK, who are also common stockholders. See Note 3, Collaboration and License Agreements.

13. Subsequent Events

The Collaboration Agreement with Celgene became effective on July 31, 2015, in connection with which the Company received an upfront cash payment of $150.2 million. On August 4, 2015, the Initial Closing under the Purchase Agreement with Celgene occurred, and the Company sold 9,137,672 shares of the Company's common stock to Celgene for an aggregate cash purchase price of approximately $849.8 million.

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ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion in conjunction with our condensed consolidated financial statements (unaudited) and related notes included elsewhere in this report. This Quarterly Report on Form 10-Q contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. All statements other than statements of historical facts contained in this report are forward-looking statements. In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "aim," "potential," "continue," "ongoing," "goal," or the negative of these terms or other similar expressions, although not all forward-looking statements contain these words. These forward-looking statements, include, but are not limited to, statements regarding: the success, cost and timing of our product development activities and clinical trials; our ability and the potential to successfully advance our technology platform to improve the safety and effectiveness of our existing product candidates; the potential for our identified research priorities to advance our CAR and TCR technologies; the potential of our collaboration with Celgene and the ability and willingness of Celgene to be our commercialization partner outside of North America; the ability and willingness of our third-party research institution collaborators to continue research and development activities relating to our product candidates; our ability to obtain orphan drug designation or breakthrough status for our CD19 product candidates and any other product candidates, or to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate; our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates; our ability to commercialize our products in light of the intellectual property rights of others; our ability to obtain funding for our operations, including funding necessary to complete further development and commercialization of our product candidates; our plans to research, develop, and commercialize our product candidates; the size and growth potential of the markets for our product candidates, and our ability to serve those markets; regulatory developments in the United States and foreign countries; our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately; our plans to develop our own manufacturing facilities; the success of competing therapies that are or may become available; our ability to attract and retain key scientific or management personnel; the accuracy of our estimates regarding expenses, success payments, future revenue, capital requirements, profitability, and needs for additional financing; fluctuations in the trading price of our common stock; the anticipated benefits of our recent litigation settlement; our plans regarding our corporate headquarters; and our use of the proceeds from our IPO. These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under "Risk Factors" in this Quarterly Report on Form 10-Q. These forward-looking statements speak only as of the date hereof. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future. Unless the context requires otherwise, in this Quarterly Report on Form 10-Q, the terms "Juno," "Company," "we," "us" and "our" refer to Juno Therapeutics, Inc., a Delaware corporation, unless otherwise noted.

Overview

We are building a fully-integrated biopharmaceutical company focused on developing cell-based cancer immunotherapies based on our CAR and high-affinity TCR technologies to genetically engineer T cells to recognize and kill cancer cells.

We have shown compelling evidence of tumor shrinkage in clinical trials with multiple cell-based product candidates to address refractory B cell lymphomas and leukemias. Before the end of 2015, we plan to have begun a Phase II trial that could support accelerated U.S. regulatory approval in relapsed/refractory B cell acute lymphoblastic leukemia ("ALL"), a Phase I trial in relapsed/refractory B cell non-Hodgkin lymphoma ("NHL"), and Phase I trials for at least five additional product candidates that target different cancer-associated proteins in hematological and solid organ cancers. Patient enrollment has begun in three of these Phase I trials as of the date of this report.

We have assembled a talented group of scientists, engineers, clinicians, directors, and other advisers who consolidate and develop technologies and intellectual property from some of the world's leading research institutions, including FHCRC, MSK, SCRI, and the National Cancer Institute.

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We have agreed to make success payments to each of FHCRC and MSK pursuant to the terms of our collaboration agreements with each of those entities. For additional information regarding these success payments, see the section captioned "Critical Accounting Polices and Significant Judgments and Estimates— Success Payments" in Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations" in our 2014 Annual Report.

We are devoting significant resources to process development and manufacturing in order to optimize the safety and efficacy of our product candidates, as well as our cost of goods and time to market. To date, we have leveraged our relationships with our founding institutions for manufacturing for our clinical trials; however, we are in the process of both establishing our own manufacturing facility and bringing a contract manufacturing organization ("CMO") on-line to support current Good Manufacturing Practices ("cGMP") manufacturing to meet the expected demand needs of clinical supply and commercial launch.

Our goal is to carefully manage our fixed cost structure, maximize optionality, and drive long-term cost of goods as low as possible. The use of one or more CMOs with established cGMP infrastructure will increase the speed with which capacity can be brought on-line. We plan to complement the use of one or more CMOs by establishing our own cGMP manufacturing facility to be brought on-line after the first CMO. As described in Part I—Item 2—"Properties" of our 2014 Annual Report, we have entered into a ten-year lease for a facility that we plan to remodel to support our clinical and commercial manufacturing activities. We believe that operating our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and the commercial market, will enable the more rapid implementation of process changes, and will allow for better long-term margins.

As of June 30, 2015, the only revenue we had generated is from an upfront license payment in connection with the Penn/Novartis Sublicense Agreement entered into in April 2015 and limited grant and product revenue from our newly acquired subsidiary in Germany. We will also recognize revenue in the third quarter of 2015 related to our entry into the Collaboration Agreement with Celgene. In the future, we may generate revenue from product sales, collaboration agreements, strategic alliances and licensing arrangements, or a combination of these. We expect that any revenue we generate will fluctuate from quarter to quarter and year to year as a result of the timing and amount of license fees, milestones, reimbursement of costs incurred and other payments and product sales, to the extent any are successfully commercialized. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval of them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

As of June 30, 2015, we had cash, cash equivalents, and marketable securities of $313.4 million compared with $474.1 million as of December 31, 2014. Cash used in operations for the six months ended June 30, 2015 was $70.2 million compared with cash used in operations of $23.4 million for the six months ended June 30, 2014. Included in cash used in operations in the six months ended June 30, 2015 is $30.8 million in costs to acquire technology in the Editas and Fate Therapeutics collaborations. Included in net cash used in investing activities is $77.7 million of net cash used to acquire Stage and X-Body, offset by cash acquired, and $7.2 million used to acquire the investment in Fate Therapeutics.

Recent Developments

During the second quarter of 2015, we had a number of corporate developments:

- In April 2015, we entered into a lease agreement for approximately 90,000 square feet of office and laboratory space in a to-be-constructed building to be located in Seattle, Washington, with an estimated commencement date of February 1, 2017. We will also have opportunities to expand the new premises to include additional space in the new building. See Note 11, Commitments and Contingencies, in the notes to the condensed consolidated financial statements included elsewhere in this report for additional information.
- In April 2015, we and St. Jude agreed to settle the Penn litigation with Penn and Novartis. In connection with such settlement, we entered into the Penn/Novartis Sublicense Agreement with Penn and an affiliate of Novartis. As described in more detail in Note 3, Collaboration and License Agreements, in the notes to the condensed consolidated financial statements included elsewhere in this report, Novartis paid us an initial license fee of $12.3 million, and will be required to pay us royalties on the U.S. net sales of products and services related to the disputed contract and patent claims, a percentage of the royalties Novartis pays to Penn for global net sales of those products, and milestone payments.

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- In April 2015, we entered into a clinical study collaboration agreement with MedImmune, Inc. ("MedImmune") to conduct combination clinical trials in immuno-oncology with one of our investigational CD19-directed CAR product candidates and MedImmune's investigational programmed cell death ligand 1 ("PD-L1") immune checkpoint inhibitor, MEDI4736. Under the initial development plan, both companies will explore the safety, tolerability and preliminary efficacy of the combination therapy as a potential treatment for patients with NHL. MedImmune and Juno will jointly co-fund the initial Phase Ib trial, which is expected to begin later in 2015. The companies will also explore the combination of MEDI4736 with a next-generation, Juno-developed fully human CD19-directed CAR product candidate.
- In May 2015, we entered into a collaboration and license agreement with Fate Therapeutics to identify and utilize small molecules to modulate our genetically-engineered T cell product candidates to improve their therapeutic potential for cancer patients. As described in Note 3, Collaboration and License Agreements, in the notes to the condensed consolidated financial statements included elsewhere in this report, we made an upfront payment, including the purchase of common stock of Fate Therapeutics, we will be required to provide research funding to Fate Therapeutics, and we may be obligated to make milestone and royalty payments on Juno products that result from such collaboration.
- In May 2015, we entered into a collaboration and license agreement with Editas, to pursue research programs utilizing Editas' genome editing technologies with our CAR and TCR technologies. As described in Note 3, Collaboration and License Agreements, in the notes to the condensed consolidated financial statements included elsewhere in this report, we made an upfront payment to Editas, will be required to provide research funding to Editas, and may be obligated to make milestone and royalty payments on Juno products that result from such collaboration.
- In May 2015, we acquired all the remaining ownership interests in Stage not already held by us. See Note 2, Acquisitions, in the notes to the condensed consolidated financial statements included elsewhere in this report for additional information. The acquisition furthers our strategy of being a world leader in process development and the manufacturing of cellular therapies. The acquisition provides Juno access to transformative cell selection and activation capabilities, next generation manufacturing automation technologies, enhanced control of its supply chain, and lower expected long-term cost of goods. We are operating the acquired company as a wholly-owned German subsidiary under the name Juno Therapeutics GmbH and the results of Juno GmbH have been consolidated with our results since the date of the acquisition.
- In June 2015, we acquired X-Body. See Note 2, Acquisitions, in the notes to the condensed consolidated financial statements included elsewhere in this report for additional information. The acquisition furthers our strategy of investing in technologies that augment our capabilities to create best-in-class engineered T cells against a broad array of cancer targets. The acquisition brings in-house an innovative discovery platform that interrogates the human antibody repertoire, rapidly selecting fully human antibodies with desired characteristics, even against difficult targets. As a result of the acquisition, X-Body has become a wholly owned subsidiary and the results of X-Body have been consolidated with our results since the date of the acquisition.
- In June 2015, we entered into the Collaboration Agreement with Celgene pursuant to which we and Celgene agreed to collaborate on researching, developing, and commercializing novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. We also entered into the Purchase Agreement with Celgene for the sale of shares of our common stock to Celgene at an initial closing and multiple potential future closings. See Note 3, Collaboration and License Agreements, for additional information about this broad-reaching collaboration. On July 31, 2015, the Collaboration Agreement became effective, in connection with which we received an upfront cash payment of $150.2 million from Celgene. On August 4, 2015, we sold 9,137,672 shares of Juno's common stock to Celgene for an aggregate cash purchase price of approximately $849.8 million.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in accordance with GAAP. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenue generated and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

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Goodwill and Intangible Assets

Goodwill represents the excess of the purchase price over the net amount of identifiable assets acquired and liabilities assumed in a business combination measured at fair value. We evaluate goodwill for impairment annually during the fourth quarter and upon the occurrence of triggering events or substantive changes in circumstances that could indicate a potential impairment by assessing qualitative factors or performing a quantitative analysis in determining whether it is more likely than not that the fair value of net asset are below their carrying amounts.

Intangible assets acquired in a business combination are recognized separately from goodwill and are initially recognized at their fair value at the acquisition date (which is regarded as their cost). Intangible assets related to in-process research and development ("IPR&D") are treated as indefinite-lived intangible assets and not amortized until certain regulatory approval in specified markets is obtained in the case of X-Body, and in the case of Stage, when the acquired reagents or automation technology is accepted by the FDA as part of an IND, subject to management judgment. At that time, we will determine the useful life of the asset, reclassify the asset out of IPR&D and begin amortization. Intangible assets are reviewed for impairment at least annually or if indicators of potential impairment exist. There were no impairments as of June 30, 2015.

Contingent Consideration from Business Combinations

At and subsequent to the acquisition date of a business combination, contingent consideration obligations are remeasured to fair value at each balance sheet date with changes in fair value recognized in research and development expense in the condensed consolidated statements of operations. Changes in fair values reflect changes to our assumptions regarding probabilities of successful achievement of related milestones, the timing in which the milestones are expected to be achieved, and the discount rate used to estimate the fair value of the obligation, as well as the foreign currency impact of the contingent consideration for the Stage acquisition as it is denominated in Euro.

Build-to-Suit Lease Accounting

In February 2015, we entered into the Bothell Lease for a manufacturing facility, which lease commenced in March 2015. We are responsible for the leasehold improvements required to remodel the facility and we bear the majority of the construction risk. ASC 840-40, Leases – Sale-Leaseback Transactions (Subsection 05-5), requires us to be considered the owner of the building solely for accounting purposes, even though we are not the legal owner. As a result, we recorded an asset and build-to-suit lease obligation on our balance sheet as of June 30, 2015 equal to the fair value of the building.

Once construction is complete, we will consider the requirements for sale-leaseback accounting treatment, including evaluating whether all risks of ownership have transferred back to the landlord, as evidenced by a lack of continuing involvement in the leased property. If the arrangement does not qualify for sale-leaseback accounting treatment, the building asset remains on our balance sheet at its historical cost, and such asset is depreciated over its estimated useful life. We bifurcate our lease payments into a portion allocated to the building and a portion allocated to the parcel of land on which the building has been built. The portion of the lease payments allocated to the land is treated for accounting purposes as operating lease payments, and therefore is recorded as rent expense in the statements of operations. The portion of the lease payments allocated to the building is further bifurcated into a portion allocated to interest expense and a portion allocated to reduce the build-to-suit lease obligation.

The interest rate used for the build-to-suit lease obligation represents our estimated incremental borrowing rate, adjusted to reduce any built in loss.

There have been no other materials changes to our critical accounting policies from those described in Part II—Item 7—"Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our 2014 Annual Report.

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Components of Operating Results

Research and Development

Research and development expenses represent costs incurred by us for the discovery, development, and manufacture of our product candidates and include: costs to acquire technology complimentary to our own, license fees to acquire technology, external research and development expenses incurred under arrangements with third parties, such as contract research organizations, CMOs, academic and non- profit institutions and consultants, salaries and personnel-related costs, including non-cash stock-based compensation, the estimated fair value of the liability attributable to the elapsed service period as of the balance sheet date associated with our success payments to FHCRC and MSK, changes in the estimated fair value of our contingent consideration liabilities, and other expenses, which include direct and allocated expenses for laboratory, facilities, and other costs.

We use our employee and infrastructure resources across multiple research and development programs directed toward developing our cell-based platform and for identifying and developing product candidates. We manage certain activities such as contract research, clinical trial operations, and manufacture of product candidates through our partner institutions or other third-party vendors. We track our significant external costs by product candidate. Due to the number of ongoing projects and our ability to use resources across several projects, we do not record or maintain information regarding the indirect operating costs incurred for our research and development programs on a program-specific basis.

Research and development activities account for a significant portion of our operating expenses. Excluding amounts attributable to changes in the estimated fair value of the success payment liability and upfront fees to acquire technology, we expect our research and development expenses to increase over the next several years as we implement our business strategy which includes conducting existing and new clinical trials, manufacturing clinical trial and preclinical study materials, expanding our research and development and process development efforts, seeking regulatory approvals for our product candidates that successfully complete clinical trials, and costs associated with hiring additional personnel to support our research and development efforts. Research and development expense related to our success payments is unpredictable and may vary significantly from quarter to quarter and year to year due to changes in our stock price or other assumptions used in the calculation. A significant decline in the estimated value of the success payment liability may result in negative expense and possibly net income during the period. In addition, we expect to incur expense for acquisition of technology in the future, but the timing and amount of those expenses cannot be estimated with reliability and may also fluctuate from quarter to quarter and year to year.

General and Administrative

General and administrative expenses consist of salaries and personnel-related costs, including non-cash stock-based compensation, for our personnel in executive, legal, finance and accounting, and other administrative functions, non-litigation legal costs, as well as fees paid for accounting and tax services, consulting fees and facility costs not otherwise included in research and development expenses. Non-litigation legal costs include general corporate legal fees and patent costs.

We anticipate that our general and administrative expenses will increase in the future to support our continued research and development activities, potential commercialization of our product candidates, and the increased costs of operating as a public company. These increases will likely include costs related to outside consultants, attorneys, and accountants, among other expenses.

Litigation

Litigation expense includes legal expense we have directly incurred with respect to the Penn litigation, as well as expenses we are required to reimburse to St. Jude with respect to such litigation. In April 2015 the Penn litigation was settled, in connection with which Novartis paid us an initial license fee of $12.3 million. In connection with the settlement, we incurred litigation expense of $5.3 million associated with the reimbursement of litigation expenses to St. Jude. See Note 3, Collaboration and License Agreements, in the notes to the condensed consolidated financial statements included elsewhere in this report.

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Results of Operations

Comparison of the three and six months ended June 30, 2015 and June 30, 2014

The following table summarizes our results of operations for the three and six months ended June 30, 2015 and 2014 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Revenue	$ 12,461	$ —	$ 12,461	$ —
Operating expenses:				
Research and development	60,235	6,479	118,034	9,418
General and administrative	14,857	4,568	21,527	7,959
Litigation	5,334	1,633	6,025	3,623
Total operating expenses	80,426	12,680	145,586	21,000
Loss from operations	(67,965)	(12,680)	(133,125)	(21,000)
Interest income, net	158	—	353	
Other income (expenses)	233	(10,089)	233	(10,718)
Loss before income taxes	(67,574)	(22,769)	(132,539)	(31,718)
Benefit from income taxes	1,616	—	1,616	—
Net loss	$ (65,958)	$ (22,769)	$ (130,923)	$ (31,718)

Revenue

Revenue was $12.5 million in the three and six months ended June 30, 2015 which consisted of $12.3 million received in connection to the Novartis sublicense agreement and $0.2 million related to grant and product revenue earned by Juno GmbH, our German subsidiary.

Operating Expenses

Research and Development Expenses. Research and development expenses were $60.2 million for the three months ended June 30, 2015, compared to $6.5 million for the three months ended June 30, 2014, and $118.0 million for the six months ended June 30, 2015, compared to $9.4 million for the six months ended June 30, 2014. The increase of $53.7 million in the three months ended June 30, 2015 was primarily due to increased expenses of:

- $30.8 million in costs to acquire technology;
- $12.9 million of costs to expand the company's overall research and development capabilities and advance programs at our founding institutions including personnel costs, manufacturing costs in support of our clinical trials, clinical and research costs under our collaboration agreements and in support of our company-sponsored clinical trials, lab supplies, consulting, and facilities and allocated overhead costs;
- $3.8 million of non-cash stock-based compensation, of which $1.7 million is related to a former co-founding director who became a consultant upon his departure from the board of directors; and
- $3.8 million associated with the portion of the estimated success payment liability to FHCRC and MSK attributable to the elapsed service period and driven by the increase in our stock price compared to the prior year.

The increase of $108.6 million in the six months ended June 30, 2015 was primarily due to increased expenses of:

- $42.5 million associated with the portion of the estimated success payment liability to FHCRC and MSK attributable to the elapsed service period and driven by the increase in our stock price compared to the prior year;
- $30.8 million in costs to acquire technology;
- $24.6 million of costs to expand the company's overall research and development capabilities and advance programs at our founding institutions including personnel costs, manufacturing costs in support of our clinical trials, clinical and research costs under our collaboration agreements and in support of our company-sponsored clinical trials, lab supplies, consulting, and facilities and allocated overhead costs; and
- $7.3 million of non-cash stock-based compensation, of which $3.6 million is related to a former co-founding director who became a consultant upon his departure from the board of directors.

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Our research and development expenses by project were as follows for the three and six months ended June 30, 2015 and 2014 (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2015	2014	2015	2014
Project-specific external costs:				
JCAR015	$ 2,667	$ 644	$ 4,833	$ 929
JCAR014	1,283	881	2,021	1,275
JCAR017	847	—	1,605	—
Platform development	5	130	741	255
CD19 general	315	286	1,301	517
Early development	2,706	1,705	4,582	1,931
Success payment expense related to FHCRC collaboration agreement	2,764	143	29,935	265
Success payment expense related to MSK collaboration agreement	1,198	66	12,937	121
Upfront costs to acquire technology	30,800	—	30,800	—
Unallocated internal and external research and development costs	17,650	2,624	29,279	4,125
Total research and development expenses	$ 60,235	$ 6,479	$ 118,034	$ 9,418

General and Administrative Expenses. General and administrative expenses were $14.9 million for the three months ended June 30, 2015 compared to $4.6 million for the three months ended June 30, 2014, and $21.5 million for the six months ended June 30, 2015, compared to $8.0 million for the six months ended June 30, 2014. The increase of $10.3 million in the three months ended June 30, 2015 was primarily due to transaction costs associated with the Stage and X-Body acquisitions of $4.2 million, higher personnel expenses of $2.7 million largely related to increased headcount, $1.7 million of which was non-cash stock-based compensation, and an increase in patent and corporate legal fees of $2.5 million primarily due to business development activities. The increase of $13.5 million in the six months ended June 30, 2015 was primarily due to higher personnel expenses of $4.6 million largely related to increased headcount, $3.0 million of which was non-cash stock-based compensation, costs associated with the Stage and X-Body acquisitions of $4.3 million, and an increase in patent and corporate legal fees of $3.0 million primarily due to business development activities.

Litigation Expense. Litigation expense was $5.3 million for the three months ended June 30, 2015 compared to $1.6 million for the three months ended June 30, 2014, and $6.0 million for the six months ended June 30, 2015 compared to $3.6 million for the six months ended June 30, 2014. Litigation costs in both periods consisted of costs we incurred directly in connection with the Penn litigation and costs we were required to reimburse to St. Jude in connection with such litigation. In April 2015 the Penn litigation was settled. See Note 3, Collaboration and License Agreements, to the condensed consolidated financial statements included elsewhere in this report.

Interest Income, Net. Interest income, net for the three and six months ended June 30, 2015 of $0.2 million and $0.4 million, respectively, consisted of interest income earned on our marketable securities offset by interest expense associated with the accounting for the build-to-suit lease of our manufacturing facility.

Other Income (Expense). Other income was $0.2 million for both the three and six months ended June 30, 2015 which consisted of the gain on our original investment in Stage recorded in connection with the acquisition of Stage in May 2015. Other expense was $10.1 million and $10.7 million for the three and six months ended June 30, 2014, respectively, which consisted of changes in the fair value of our Series A convertible preferred stock option, which was exercised during 2014.

Benefit from Income Taxes. Benefit from income taxes was $1.6 million for both the three and six months ended June 30, 2015. The Company recorded an income tax benefit of $1.6 million on a pre-tax loss of $132.5 million for 2015. No income tax benefit is recognized for the U.S. pre-tax loss generated during the quarter as it was subject to a full valuation allowance. Of the $1.6 million income tax benefit, $0.5 million of the income tax benefit relates to Juno GmbH net loss incurred in the period from May 11, 2015 to June 30, 2015, and the Company has determined that it is more-likely-than-not that it will realize the benefit of these losses. The remaining $1.1 million of income tax benefit relates to the release of valuation allowance on the U.S. deferred tax assets as a result of the acquisition of X-Body. In the future we may be required to pay tax on revenue generated from the Celgene collaboration.

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Liquidity and Capital Resources

Sources of Liquidity

To date we have raised an aggregate of approximately $618 million in gross proceeds, through our IPO and private placements of our convertible preferred stock which we have used to fund our operations. As of June 30, 2015, we had $313.4 million in cash, cash equivalents and marketable securities.

See “Liquidity and Capital Resources—Plan of Operation and Future Funding Requirements” in Part II—Item 7—“Management’s Discussion and Analysis of Financial Condition and Results of Operations” of the 2014 Annual Report for a description of potential future funding requirements. As a result of our entry into the collaboration with Celgene and our initial sale of stock to Celgene, we received $1.0 billion in cash from Celgene in August 2015. This funding decreases our need for additional near term funding, although we may still need to raise additional capital in the future.

We believe that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our operations for at least the next 12 months.

Cash Flows

The following table summarizes our cash flows for the six months ended June 30, 2015 and 2014 (in thousands):

	Six Months Ended June 30, 2015	2014
Net cash (used in) provided by:		
Operating activities	$ (70,158)	$ (23,365)
Investing activities	(244,883)	(4,170)
Financing activities	(1,397)	62,614
Effect of exchange rate changes on cash and cash equivalents	(12)	—
Net (decrease) increase in cash and cash equivalents	$ (316,450)	$ 35,079

Operating Activities

The increase in cash used in operating activities for the six months ended June 30, 2015 of $46.8 million compared to the six months ended June 30, 2014 was primarily due to the $30.8 million in upfront cash payments made in connection with the Editas and Fate collaborations as well as the overall growth of the business which included expanding the workforce, manufacturing in support of our clinical trials, and clinical and research costs. This was offset by the cash received in connection with the Penn/Novartis Sublicense Agreement of $12.3 million.

Investing Activities

The increase in cash used in investing activities for the six months ended June 30, 2015 of $240.7 million compared to the six months ended June 30, 2014 was primarily due to net purchases of marketable securities of $150.9 million in 2015, cash paid, net of cash acquired, to acquire Stage and X-Body of $77.7 million, an investment in Fate of $7.2 million, and an increase in property and equipment purchases of $8.4 million, offset by the investment in Stage of $3.5 million in 2014.

Financing Activities

Net cash used in financing activities for the six months ended June 30, 2015 consisted primarily of cash payments for costs associated with our IPO and proceeds from the exercise of stock options. Net cash provided by financing activities for the six months ended June 30, 2014 consisted of cash proceed from the issuance of our convertible preferred stock.

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Off-Balance Sheet Arrangements

As of June 30, 2015, we did not have any off-balance sheet arrangements or any holdings in variable interest entities.

JOBS Act

As an "emerging growth company," the Jumpstart our Business Startups Act allows us to delay adoption of new or revised accounting standards applicable to public companies until such standards are made applicable to private companies. However, we have irrevocably elected not to avail ourselves of this extended transition period for complying with new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business, primarily related to interest rate sensitivities and the volatility of our stock price.

Interest Rate Sensitivity

As of June 30, 2015, we had $273.9 million in marketable securities, largely composed of investment grade short- to intermediate-term fixed income securities. The primary objective of our investment activities is to preserve capital to fund our operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of investments in a variety of securities of high credit quality.

Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. A hypothetical 10% change in interest rates during any of the periods presented would not have had a material impact on our financial statements.

Stock Price Sensitivity

We agreed to make success payments to FHCRC and MSK based on increases in the per share fair market value of our common stock during the term of the agreements payable in cash or publicly-traded equity at our discretion. A small change in our stock price may have a relatively large change in the estimated fair value of the success payment liability and associated expense.

As of June 30, 2015, the estimated fair value of the success payment obligations was approximately $211.4 million. We recognized research and development expense of $4.0 million and $42.9 million in the three and six months ended June 30, 2015, respectively, related to the success payment obligations. The expense recorded for the three and six months ended June 30, 2015 represents the change in the success payment liability during such period and reflects an additional three months of accrued expense. The success payment liabilities on the balance sheet as of June 30, 2015 were $127.8 million.

The assumptions used to calculate the fair value of the success payments are subject to a significant amount of judgment including the expected volatility, estimated term, and estimated number and timing of valuation measurement dates. A small change in the assumptions may have a relatively large change in the estimated valuation and associated liability and expense. For example, keeping all other variables constant, a hypothetical 10% increase in the stock price at June 30, 2015 from $53.33 per share to $58.66 per share would have increased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $15.5 million. A hypothetical 10% decrease in the stock price from $53.33 per share to $48.00 per share would have decreased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $15.7 million, resulting in a gain of $11.7 million. Further, keeping all other variables constant, a hypothetical 35% increase in the stock price at June 30, 2015 from $53.33 per share to $72.00 per share would have increased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $147.2 million. A hypothetical 35% decrease in the stock price from $53.33 per share to $34.66 per share would have decreased the expense recorded in the three months ended June 30, 2015 associated with the success payment liability by $56.3 million, resulting in a gain of $52.3 million.

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ITEM 4. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

As required by Rule 13a-15(b) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), our management, under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of the design and operation of our disclosure controls and procedures as of June 30, 2015. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of June 30, 2015, our Chief Executive Officer and Chief Financial Officer have concluded that, as of June 30, 2015, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

There has been no change in our internal control over financial reporting during the quarter ended June 30, 2015, that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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PART II. OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

From time to time, we may become involved in litigation relating to claims arising from the ordinary course of business. Our management believes that there are currently no claims or actions pending against us, the ultimate disposition of which could have a material adverse effect on our results of operations, financial condition or cash flows.

On April 4, 2015, Juno and St. Jude agreed to settle the Penn litigation with Penn and Novartis, and the case was dismissed on April 7, 2015. In connection with such settlement, we entered into the Penn/Novartis Sublicense Agreement and an amendment to the St. Jude License Agreement. See Note 3, Collaboration and License Agreements, in the notes to the condensed consolidated financial statements included elsewhere in this report for more information about the settlement and these agreements.

ITEM 1A. RISK FACTORS

The following section includes the most significant factors that may adversely affect our business and operations. You should carefully consider the risks and uncertainties described below and all information contained in this report, including our financial statements and the related notes and Part I—Item 2—"Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations.

Risks Related to Our Business and Industry

We are a clinical-stage company and have a very limited operating history, which may make it difficult to evaluate our current business and predict our future performance.

We are a clinical-stage biopharmaceutical company that was recently formed in August 2013. We have no cell-therapy products approved for commercial sale and as of June 30, 2015 had not generated any revenue from such products. We are focused on developing products that use human cells as therapeutic entities and, although there have been significant advances in cell- based immunotherapy, our T cell technologies are new and largely unproven. Our limited operating history, particularly in light of the rapidly evolving cancer immunotherapy field, may make it difficult to evaluate our current business and predict our future performance. Our very short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage companies in rapidly evolving fields. If we do not address these risks successfully, our business will suffer.

We have incurred net losses in each period since our inception and anticipate that we will continue to incur net losses in the future.

We are not profitable and have incurred losses in each period since our inception. For the three and six months ended June 30, 2015, we reported a net loss of $66.0 million and $130.9 million, respectively. For the year ended December 31, 2014, we reported a net loss of $243.4 million. As of June 30, 2015, we had an accumulated deficit of $477.2 million, of which $127.8 million represents the portion of the estimated success payment liability attributable to the elapsed service period; $51.1 million of deemed dividends on our convertible preferred stock; and $10.7 million of expense associated with our convertible preferred stock options. We expect these losses to increase as we continue to incur significant research and development and other expenses related to our ongoing operations, seek regulatory approvals for our product candidates, scale-up manufacturing capabilities and hire additional personnel to support the development of our product candidates and to enhance our operational, financial and information management systems.

A critical aspect of our strategy is to invest significantly in our technology platform to improve the efficacy and safety of our product candidates. Even if we succeed in commercializing one or more of these product candidates, we will continue to incur losses for the foreseeable future relating to our substantial research and development expenditures to develop our technologies. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. The size of our future net losses will

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depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital. Further, the net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period to period comparison of our results of operations may not be a good indication of our future performance.

We expect to continue to incur significant losses for the foreseeable future. We expect these losses and our cash utilization to increase in the near term as we continue to conduct clinical trials, file additional Investigational New Drug ("IND") filings for additional product candidates, and conduct research and development of our other product candidates.

We are collaborating with Celgene pursuant to a collaboration agreement, under which we and Celgene will research, develop and commercialize novel cellular therapy product candidates and other immuno-oncology and immunology therapeutics, including, in particular, CAR and TCR product candidates. Contingent upon the payment of certain upfront payments, Celgene may exercise options to acquire exclusive licenses to certain therapeutics we develop and each party may exercise certain options to co-develop and co-commercialize product candidates developed, or acquired or in-licensed, by the other party. If Celgene does not exercise its options, or if our collaboration with Celgene terminates, we will be responsible for funding further development of the relevant product candidates, which would cause our expenses to increase, unless we enter into another collaboration for such product candidates, which may not be possible within and acceptable timeframe, or on suitable terms. Similarly, our expenses would increase if we exercise an option to co-develop and co-commercialize any product candidate developed, or in-licensed or acquired, by Celgene. If any of these were to occur, our losses could increase.

We have never generated any revenue from sales of cell-therapy products and our ability to generate revenue from cell-therapy product sales and become profitable depends significantly on our success in a number of factors.

We have no products approved for commercial sale, have not generated any revenue from product sales, and do not anticipate generating any revenue from product sales until some time after we have received regulatory approval for the commercial sale of a product candidate. Our ability to generate revenue and achieve profitability depends significantly on our success in many factors, including:

- completing research regarding, and nonclinical and clinical development of, our product candidates;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we complete clinical studies;
- developing a sustainable and scalable manufacturing process for our product candidates, including establishing and maintaining commercially viable supply relationships with third parties and establishing our own manufacturing capabilities and infrastructure;
- launching and commercializing product candidates for which we obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor;
- obtaining market acceptance of our product candidates as viable treatment options, and obtaining adequate coverage, reimbursement, and pricing by third-party payors and government authorities;
- addressing any competing technological and market developments;
- Celgene exercising any of its options under our collaboration agreement with Celgene, and Celgene's efforts to further develop and commercialize the associated product candidates;
- identifying, assessing, acquiring and/or developing new product candidates;
- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

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Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the U.S. Food & Drug Administration ("FDA"), or other regulatory agencies, domestic or foreign, to change our manufacturing processes or assays, or to perform clinical, nonclinical, or other types of studies in addition to those that we currently anticipate. If we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. If we are not able to generate revenue from the sale of any approved products, we may never become profitable.

Our technology platform, including our CAR and high-affinity TCR technologies are new approaches to cancer treatment that present significant challenges.

We have concentrated our research and development efforts on T cell immunotherapy technology, and our future success is highly dependent on the successful development of T cell immunotherapies in general and our CAR and TCR technologies and product candidates in particular. Our approach to cancer treatment aims to alter T cells ex vivo through genetic modification using certain viruses designed to reengineer the T cells to recognize specific proteins on the surface or inside cancer cells. Because this is a new approach to cancer immunotherapy and cancer treatment generally, developing and commercializing our product candidates subjects us to a number of challenges, including:

- obtaining regulatory approval from the FDA and other regulatory authorities that have very limited experience with the commercial development of genetically modified T cell therapies for cancer;
- developing and deploying consistent and reliable processes for engineering a patient's T cells ex vivo and infusing the engineered T cells back into the patient;
- conditioning patients with chemotherapy in conjunction with delivering each of our products, which may increase the risk of adverse side effects of our products;
- educating medical personnel regarding the potential side effect profile of each of our products, such as the potential adverse side effects related to cytokine release;
- developing processes for the safe administration of these products, including long-term follow-up for all patients who receive our product candidates;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a manufacturing process and distribution network with a cost of goods that allows for an attractive return on investment;
- establishing sales and marketing capabilities after obtaining any regulatory approval to gain market acceptance, and obtaining adequate coverage, reimbursement, and pricing by third-party payors and government authorities; and
- developing therapies for types of cancers beyond those addressed by our current product candidates.

We cannot be sure that our T cell immunotherapy technologies will yield satisfactory products that are safe and effective, scalable, or profitable.

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Additionally, because our technology involves the genetic modification of patient cells ex vivo using a virus, we are subject to many of the challenges and risks that gene therapies face, including:

- Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. To date, no products that involve the genetic modification of patient cells have been approved in the United States and only one has been approved in the European Union ("EU").
- Genetically modified products in the event of improper insertion of a gene sequence into a patient's chromosome could lead to lymphoma, leukemia or other cancers, or other aberrantly functioning cells.
- Although our viral vectors are not able to replicate, there is a risk with the use of retroviral or lentiviral vectors that they could lead to new or reactivated pathogenic strains of virus or other infectious diseases.
- The FDA recommends a 15 year follow-up observation period for all patients who receive treatment using gene therapies, and we may need to adopt such an observation period for our product candidates.
- Clinical trials using genetically modified cells conducted at institutions that receive funding for recombinant DNA research from the NIH, are subject to review by the Recombinant DNA Advisory Committee ("RAC"). Although the FDA decides whether individual protocols may proceed, the RAC review process can impede the initiation of a clinical trial, even if the FDA has reviewed the study and approved its initiation.

Moreover, public perception of therapy safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to subscribe to the novel treatment mechanics. Physicians, hospitals and third-party payors often are slow to adopt new products, technologies and treatment practices that require additional upfront costs and training. Physicians may not be willing to undergo training to adopt this novel and personalized therapy, may decide the therapy is too complex to adopt without appropriate training and may choose not to administer the therapy. Based on these and other factors, hospitals and payors may decide that the benefits of this new therapy do not or will not outweigh its costs.

Our near term ability to generate product revenue is dependent on the success of one or more of our CD19 product candidates, each of which are at an early-stage of development and will require significant additional clinical testing before we can seek regulatory approval and begin commercial sales.

Our near term ability to generate product revenue is highly dependent on our ability to obtain regulatory approval of and successfully commercialize one or more of our CD19 product candidates. Our most advanced product candidates, JCAR015, JCAR017, and JCAR014, are in the early stages of development, have been tested in a relatively small number of patients, and will require additional clinical and nonclinical development, regulatory review and approval in each jurisdiction in which we intend to market the products, substantial investment, access to sufficient commercial manufacturing capacity, and significant marketing efforts before we can generate any revenue from product sales. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical studies to demonstrate the safety, purity, and potency of the product candidates in humans. We cannot be certain that any of our product candidates will be successful in clinical studies and they may not receive regulatory approval even if they are successful in clinical studies.

In addition, because JCAR015, JCAR017, and JCAR014 are our most advanced product candidates, and because our other product candidates are based on similar technology, if JCAR015, JCAR017, or JCAR014 encounter safety or efficacy problems, developmental delays, regulatory issues, reagent supply issues, or other problems, our development plans and business could be significantly harmed. Further, competitors who are developing products with similar technology may experience problems with their products that could identify problems that would potentially harm our business.

Prior to the Juno-sponsored Phase I trial of JCAR017 and the Phase II clinical trial of JCAR015 that are expected to commence in the near term, third parties had sponsored and conducted all clinical trials of our CD19 product candidates and other product candidates, and our ability to influence the design and conduct of such trials has been limited. We have assumed control over the future clinical and regulatory development of JCAR015 and, for NHL, JCAR017, and may do so for other product candidates, which will entail additional expenses and may be subject to delay. Any failure by a third party to meet its obligations with respect to the clinical and regulatory development of our product candidates may delay or impair our ability to obtain regulatory approval for our products and result in liability for our company.

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Prior to the Juno-sponsored Phase I clinical trial of JCAR017 and the Phase II clinical trial of JCAR015, both of which are planned to start in the near term, we had not sponsored any clinical trials relating to our CD19 product candidates or other product candidates. Instead, faculty members at our third-party research institution collaborators, or those institutions themselves, sponsored all clinical trials relating to these product candidates, in each case under their own INDs. We have now assumed control of the overall clinical and regulatory development of JCAR015 and, for NHL, JCAR017 for future clinical trials, and the FDA has cleared Juno-sponsored INDs for the Phase I clinical trial of JCAR017 in r/r NHL and Phase II clinical trial of JCAR015 in adult r/r ALL. We may determine to assume control over the clinical and regulatory development of other product candidates in the future, in which case we will need to obtain sponsorship of the INDs or file new Juno-sponsored INDs. Failure to obtain, or delays in obtaining, sponsorship of INDs or in filing new Juno-sponsored INDs for these or any other product candidates we determine to advance could negatively affect the timing of our potential future clinical trials. Additionally, although MSK received breakthrough therapy designation for JCAR015 from the FDA, we will separately need to request breakthrough therapy designation from the FDA under our own IND, which we may not be successful in obtaining, which could adversely affect the timing of future clinical trials and regulatory review and approval. Any such impacts on timing could increase research and development costs and could delay or prevent obtaining regulatory approval for our most advanced product candidates, either of which could have a material adverse effect on our business.

Further, even in the event that the IND sponsorship is or has been obtained for existing and new INDs, we did not control the design or conduct of the previous trials. It is possible that the FDA will not accept these previous trials as providing adequate support for future clinical trials, whether controlled by us or third parties, for any of one or more reasons, including the safety, purity, and potency of the product candidate, the degree of product characterization, elements of the design or execution of the previous trials or safety concerns, or other trial results. We may also be subject to liabilities arising from any treatment-related injuries or adverse effects in patients enrolled in these previous trials. As a result, we may be subject to unforeseen third-party claims and delays in our potential future clinical trials. We may also be required to repeat in whole or in part clinical trials previously conducted by our third-party research institution collaborators, which will be expensive and delay the submission and licensure or other regulatory approvals with respect to any of our product candidates. Any such delay or liability could have a material adverse effect on our business.

Although we have assumed control of the overall clinical and regulatory development of JCAR015 and, for NHL, JCAR017 going forward, we expect to be dependent on our contractual arrangements with third-party research institution collaborators for ongoing and planned trials for our other product candidates, and for JCAR017 other than in NHL, until we determine to assume control of the clinical and regulatory development of those candidates. Such arrangements provide us certain information rights with respect to certain previous, planned, or ongoing trials with respect to our product candidates, including access to and the ability to use and reference the data, including for our own regulatory filings, resulting from such trials. If these obligations are breached by our third-party research institution collaborators, or if the data, or our data rights, prove to be inadequate compared to the first-hand knowledge we might have gained had the completed trials been Juno-sponsored trials, then our ability to design and conduct our planned corporate-sponsored clinical trials may be adversely affected. Additionally, the FDA may disagree with the sufficiency of our right to reference the preclinical, manufacturing, or clinical data generated by these prior investigator-sponsored trials, or our interpretation of preclinical, manufacturing, or clinical data from these clinical trials. If so, the FDA may require us to obtain and submit additional preclinical, manufacturing, or clinical data before we may begin our planned trials and/or may not accept such additional data as adequate to begin our planned trials.

We may encounter substantial delays in our clinical trials, or may not be able to conduct our trials on the timelines we expect.

Clinical testing is expensive, time consuming, and subject to uncertainty. We cannot guarantee that any clinical studies will be conducted as planned or completed on schedule, if at all. We expect that the early clinical work performed by our third-party research institution collaborators will help support the filing with the FDA of multiple INDs for product candidates in the next five years. However, we cannot be sure that we will be able to submit INDs at this rate, and we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin. Moreover, even if these trials begin, issues may arise that could suspend or terminate such clinical trials. A failure of one or more clinical studies can occur at any stage of testing, and our future clinical studies may not be successful. Events that may prevent successful or timely completion of clinical development include:

- inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation of clinical studies;

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- delays in sufficiently developing, characterizing, or controlling a manufacturing process suitable for advanced clinical trials;
- delays in reaching a consensus with regulatory agencies on study design;
- the FDA may not allow us to use the clinical trial data from a research institution to support an IND if we cannot demonstrate the comparability of our product candidates with the product candidate used by the relevant research institution in its clinical studies;
- delays in reaching agreement on acceptable terms with prospective contract research organizations ("CROs") and clinical study sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical study sites;
- delays in obtaining required IRB approval at each clinical study site;
- imposition of a temporary or permanent clinical hold by regulatory agencies for a number of reasons, including after review of an IND application or amendment, or equivalent application or amendment; as a result of a new safety finding that presents unreasonable risk to clinical trial participants; a negative finding from an inspection of our clinical study operations or study sites; developments on trials conducted by competitors for related technology that raises FDA concerns about risk to patients of the technology broadly; or if FDA finds that the investigational protocol or plan is clearly deficient to meet its stated objectives;
- delays in recruiting suitable patients to participate in our clinical studies;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties, or us to adhere to clinical study requirements;
- failure to perform in accordance with the FDA's cGCP requirements, or applicable regulatory guidelines in other countries;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- patients dropping out of a study;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- the cost of clinical studies of our product candidates being greater than we anticipate;
- clinical studies of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical studies or abandon product development programs;

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- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by either a CMO or by us, and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process;
- delays or failure to secure supply agreements with suitable reagent suppliers, or any failures by suppliers to meet our quantity or quality requirements for necessary reagents; and
- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical studies or the inability to do any of the foregoing.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates, we may be required to or we may elect to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical study delays could also shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

We have entered into collaborations, including our Celgene collaboration, and may form or seek collaborations or strategic alliances or enter into additional licensing arrangements in the future, and we may not realize the benefits of such alliances or licensing arrangements.

We have entered into a number of research and development collaborations, including with Celgene, Fate Therapeutics, Editas Medicine, and MedImmune, and these collaborations are subject to numerous risks, which may include the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to a collaboration;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in their strategic focus due to the acquisition of competitive products, availability of funding, or other external factors, such as a business combination that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to their marketing and distribution;
- collaborators may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- disputes may arise between us and a collaborator that cause the delay or termination of the research, development or commercialization of our product candidates, or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates; and
- collaborators may own or co-own intellectual property covering our products that results from our collaborating with them, and in such cases, we would not have the exclusive right to commercialize such intellectual property.

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In particular, if Celgene opts to exercise its options to license any product candidates under the collaboration agreement with us, we may have limited influence or control over their approaches to development and commercialization in the territories in which they lead development and commercialization. Although we will still lead development and commercialization activities in North America for our product candidates arising from programs for which Celgene has exercised an option, Celgene's development and commercialization activities in the territories where it is the lead party may adversely impact our own efforts in North America. Failure by Celgene to meet its obligations under the collaboration agreement and any co-development or co-commercialization agreement we enter into, or failure by Celgene to apply sufficient efforts at developing and commercializing collaboration products, may materially adversely affect our business and our results of operations. Additionally, Celgene's exercise of an option for a program that includes a given product candidate may also lead to changes to clinical and regulatory development strategy for such product candidate that may impact previously announce development timelines for such product candidate, which may or may not adversely affect our stock price.

We may form or seek further strategic alliances, create joint ventures or collaborations, or enter into additional licensing arrangements with third parties that we believe will complement or augment our development and commercialization efforts with respect to our product candidates and any future product candidates that we may develop. Such alliances will be subject to many of the risks set forth above. Moreover, any of these relationships may require us to incur non-recurring and other charges, increase our near and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex.

As a result of these risks, we may not be able to realize the benefit of our existing collaborations or any future collaborations or licensing agreements we may enter into. Any delays in entering into new collaborations or strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates in certain geographies for certain indications, which would harm our business prospects, financial condition, and results of operations.

The FDA or comparable foreign regulatory authorities may disagree with our regulatory plans, including our plans to seek accelerated approval, and we may fail to obtain regulatory approval of our product candidates.

We plan to begin a trial in adult relapsed/refractory ALL in the near term with JCAR015 that could support accelerated U.S. regulatory approval. We also plan to begin a Phase I/II trial in adult relapsed/refractory NHL in the near term with JCAR017, with the potential to move to a registration trial in late 2016 or early 2017. We intend to conduct each of these clinical trials in the United States. If the results of these trials are sufficiently compelling, we intend to discuss with the FDA filing BLAs for accelerated approval of such CD19 product candidates as a treatment for patients who are refractory to currently approved treatments in these indications.

The FDA standard for regular approval of a biologic generally requires two adequate and well-controlled Phase III studies or one large and robust, well-controlled Phase III study in the patient population being studied that provides substantial evidence that a biologic is safe, pure and potent. Phase III clinical studies typically involve hundreds of patients, have significant costs and take years to complete. However, product candidates studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval and may be approved on the basis of adequate and well-controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA may require a sponsor of a drug or biologic receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug or biologic may be subject to withdrawal procedures by the FDA that are more accelerated than those available for regular approvals. We believe our accelerated approval strategy is warranted given the currently limited alternative therapies for patients with relapsed/refractory ALL and relapsed/refractory NHL, but the FDA may not agree. The FDA may ultimately require one or multiple Phase III clinical trials prior to approval, particularly because our product candidates are novel and personalized treatments.

As part of its marketing authorization process, the European Medicines Agency ("EMA") may grant marketing authorizations on the basis of less complete data than is normally required, when, for certain categories of medicinal

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products, doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use ("CHMP") to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating diseases or life-threatening diseases and those designated as orphan medicinal products.

A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete nonclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public-health threats.

Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a conditional marketing authorization will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product are generated, submitted, assessed and acted upon. Although we may seek a conditional marketing authorization for one or more of our product candidates by the EMA, the EMA or CHMP may ultimately not agree that the requirements for such conditional marketing authorization have been satisfied.

Our clinical trial results may also not support approval, whether accelerated approval, conditional marketing authorizations, or regular approval. The results of preclinical and clinical studies may not be predictive of the results of later-stage clinical trials, and product candidates in later stages of clinical trials may fail to show the desired safety and efficacy despite having progressed through preclinical studies and initial clinical trials. In addition, our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- we may be unable to demonstrate that our product candidates' risk-benefit ratios for their proposed indications are acceptable;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- we may be unable to demonstrate that the clinical and other benefits of our product candidates outweigh their safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;

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- the data collected from clinical trials of our product candidates may not be sufficient to the satisfaction of the FDA or comparable foreign regulatory authorities to support the submission of a BLA or other comparable submission in foreign jurisdictions or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, our own manufacturing facilities, or a third-party manufacturer's facilities with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Further, failure to obtain approval for any of the above reasons may be made more likely by the fact that the FDA and other regulatory authorities have very limited experience with commercial development of genetically engineered T cell therapies for cancer. Failure to obtain regulatory approval to market any of our product candidates would significantly harm our business, results of operations, and prospects.

Our clinical trials may fail to demonstrate adequately the safety and efficacy of our product candidates, which would prevent or delay regulatory approval and commercialization.

The clinical trials of our product candidates are, and the manufacturing and marketing of our products will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and market our product candidates. Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. In particular, because our product candidates are subject to regulation as biological drug products, we will need to demonstrate that they are safe, pure, and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use. The risk/benefit profile required for product licensure will vary depending on these factors and may include not only the ability to show tumor shrinkage, but also adequate duration of response, a delay in the progression of the disease, and/or an improvement in survival. For example, response rates from the use of our product candidates may not be sufficient to obtain regulatory approval unless we can also show an adequate duration of response. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. The results of studies in one set of patients or line of treatment may not be predictive of those obtained in another. We expect there may be greater variability in results for products processed and administered on a patient-by-patient basis, as anticipated for our product candidates, than for "off-the-shelf" products, like many other drugs. There is typically an extremely high rate of attrition from the failure of product candidates proceeding through clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising results in earlier trials. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization.

Data from studies conducted by the third-party research institutions that are our collaboration partners, FHCRC, MSK, and SCRI, should not be relied upon as evidence that later or larger-scale clinical trials will succeed. Some future trials may have different patient populations than current studies and will test our product candidates in different indications, among other differences. In addition, our proposed manufacturing processes for our CD19 product candidates include what we believe will be process improvements that are not part of the production processes that are currently being used in the clinical trials being conducted by the research institutions. Accordingly, our results with our CD19 product candidates may not be consistent with the results of the clinical trials being conducted by our research institute collaborators.

In addition, even if such trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we submit our product candidates for approval. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates.

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Our product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences.

As with most biological drug products, use of our product candidates could be associated with side effects or adverse events which can vary in severity from minor reactions to death and in frequency from infrequent to prevalent. Undesirable side effects or unacceptable toxicities caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical trials. We have seen severe neurotoxicity or severe cytokine release syndrome ("sCRS"), in some cases leading to death, in a number of patients with ALL using each of JCAR015, JCAR017, and JCAR014. sCRS is a condition that, by convention, and for our JCAR015 and JCAR017 trials, is currently defined clinically by certain side effects, which can include hypotension, or low blood pressure, and confusion or other central nervous system side effects, related to the release of inflammatory proteins in the body as the CAR T cells rapidly multiply in the presence of the target tumor protein, when such side effects are serious enough to lead to intensive care unit care with mechanical ventilation or significant vasopressor support. For the JCAR014 trial, sCRS is defined as certain side effects, which can include hypotension, confusion, or other central nervous system side effects, when such side effects are CTCAE grade 3 or higher. In early 2014, two patient deaths in the JCAR015 trial, which we believe were either directly or indirectly related to sCRS, resulted in the FDA placing the trial on clinical hold. Several JCAR015 protocol changes were made after those deaths, the most important of which include using a lower dose in patients with morphologic relapsed/refractory ALL, excluding patients with Class III or IV congestive heart failure as defined by the New York Heart Association, excluding patients with active central nervous system leukemia or symptomatic central nervous system leukemia within 28 days, adding sCRS as a dose limiting toxicity, and restricting a patient from receiving a second treatment of JCAR015 if the patient experienced any non-hematologic grade 4 toxicities, including sCRS, with the prior JCAR015 treatment. The protocol changes resulted in the FDA removing the clinical hold. However, these protocol changes may reduce efficacy and may not result in a better tolerability profile. The FDA or comparable foreign regulatory authorities could delay or deny approval of our product candidates for any or all targeted indications and negative side effects could result in a more restrictive label for any product that is approved. Side effects such as toxicity or other safety issues associated with the use of our product candidates could also require us or our collaborators to perform additional studies or halt development or sale of these product candidates.

Treatment-related side effects could also affect patient recruitment or the ability of enrolled subjects to complete the trial, or could result in potential product liability claims. In addition, these side effects may not be appropriately or timely recognized or managed by the treating medical staff, particularly outside of the research institutions that collaborate with us, as toxicities resulting from personalized T cell therapy are not normally encountered in the general patient population and by medical personnel. We expect to have to train medical personnel using our product candidates to understand their side effect profiles, both for our planned clinical trials and upon any commercialization of any product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in adverse effects to patients, including death. Any of these occurrences may materially and adversely harm our business, financial condition and prospects.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, including during any long-term follow-up observation period recommended or required for patients who receive treatment using our products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a REMS plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, and/or other elements to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of the foregoing could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations, and prospects.

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If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol;
- the size of the study population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials for similar therapies or other new therapeutics not involving T cell based immunotherapy;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will not complete a clinical trial.

In addition, our clinical trials will compete with other clinical trials for product candidates that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Because the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. Moreover, because our product candidates represent a departure from more commonly used methods for cancer treatment, potential patients and their doctors may be inclined to use conventional therapies, such as chemotherapy and hematopoietic cell transplantation, rather than enroll patients in any future clinical trial.

Even if we are able to enroll a sufficient number of patients in our clinical trials, delays in patient enrollment may result in increased costs or may affect the timing or outcome of the planned clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of our product candidates.

Clinical trials are expensive, time-consuming and difficult to design and implement, and our clinical trial costs may be higher than for more conventional therapeutic technologies or drug products.

Clinical trials are expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. Because our product candidates are based on new technologies and manufactured on a patient-by-patient basis, we expect that they will require extensive research and development and have substantial manufacturing costs. In addition, costs to treat patients with relapsed/refractory cancer and to treat potential side effects that may result from our product candidates can be significant. Some clinical trial sites may not bill, or obtain coverage from, Medicare, Medicaid, or other third-party payors for some or all of these costs for patients enrolled in our clinical trials, and we may be required by those trial sites to pay such costs. Accordingly, our clinical trial costs are likely to be significantly higher per patient than those of more conventional therapeutic technologies or drug products. In addition, our proposed personalized product candidates involve several complex and costly manufacturing and processing steps, the costs of which will be borne by us. Depending on the number of patients we ultimately enroll in our trials, and the number of trials we may need to conduct, our overall clinical trial costs may be higher than for more conventional treatments.

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Research and development of biopharmaceutical products is inherently risky. We may not be successful in our efforts to use and enhance our technology platform and CAR and TCR technologies to create a pipeline of product candidates and develop commercially successful products, or we may expend our limited resources on programs that do not yield a successful product candidate and fail to capitalize on product candidates or diseases that may be more profitable or for which there is a greater likelihood of success. If we fail to develop additional product candidates, our commercial opportunity will be limited.

Although our most advanced product candidates are JCAR015, JCAR017, and JCAR014, we and our collaborators are simultaneously pursuing clinical development of additional product candidates developed employing our CAR and TCR technologies. We are at an early stage of development and our technology platform has not yet led, and may never lead, to approved or commercially successful products.

Even if we are successful in continuing to build our pipeline, obtaining regulatory approvals and commercializing additional product candidates may require substantial additional funding and are prone to the risks of failure inherent in medical product development.

Investment in biopharmaceutical product development involves significant risk that any potential product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval, and become commercially viable. We cannot provide you any assurance that we will be able to successfully advance any of these additional product candidates through the development process. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development or commercialization for many reasons, including the following:

- our platform may not be successful in identifying additional product candidates;
- we may not be able or willing to assemble sufficient resources to acquire or discover additional product candidates;
- our product candidates may not succeed in preclinical or clinical testing;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- the market for a product candidate may change during our program so that the continued development of that product candidate is no longer reasonable;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, or we may not be able to identify, discover, develop, or commercialize additional product candidates, which would have a material adverse effect on our business and could potentially cause us to cease operations.

Even if we receive FDA approval to market additional product candidates, whether for the treatment of cancers or other diseases, we cannot assure you that any such product candidates will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives. Further, because of our limited financial and managerial resources, we are required to focus our research programs on certain product candidates and on specific diseases. As a result, we may fail to capitalize on viable commercial products or

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profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases that may later prove to have greater commercial potential, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to retain sole development and commercialization rights. For additional information regarding the factors that will affect our ability to achieve revenue from product sales, see the risk factor above "—We have never generated any revenue from product sales and our ability to generate revenue from product sales and become profitable depends significantly on our success in a number of factors."

Our product candidates are biologics and the manufacture of our product candidates is complex and we may encounter difficulties in production, particularly with respect to process development or scaling-out of our manufacturing capabilities. If we or any of our third-party manufacturers encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

Our product candidates are biologics and the process of manufacturing our products is complex, highly-regulated and subject to multiple risks. The manufacture of our product candidates involves complex processes, including harvesting T cells from patients, genetically modifying the T cells ex vivo, multiplying the T cells to obtain the desired dose, and ultimately infusing the T cells back into a patient's body. As a result of the complexities, the cost to manufacture biologics in general, and our genetically modified cell product candidates in particular, is generally higher than traditional small molecule chemical compounds, and the manufacturing process is less reliable and is more difficult to reproduce. Our manufacturing process will be susceptible to product loss or failure due to logistical issues associated with the collection of white blood cells, or starting material, from the patient, shipping such material to the manufacturing site, shipping the final product back to the patient, and infusing the patient with the product, manufacturing issues associated with the differences in patient starting materials, interruptions in the manufacturing process, contamination, equipment or reagent failure, improper installation or operation of equipment, vendor or operator error, inconsistency in cell growth, and variability in product characteristics. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects, and other supply disruptions. If for any reason we lose a patient's starting material or later-developed product at any point in the process, the manufacturing process for that patient will need to be restarted and the resulting delay may adversely affect that patient's outcome. If microbial, viral, or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. Because our product candidates are manufactured for each particular patient, we will be required to maintain a chain of identity with respect to materials as they move from the patient to the manufacturing facility, through the manufacturing process, and back to the patient. Maintaining such a chain of identity is difficult and complex, and failure to do so could result in adverse patient outcomes, loss of product, or regulatory action including withdrawal of our products from the market. Further, as product candidates are developed through preclinical to late stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

Historically, our product candidates have been manufactured using unoptimized processes by our third-party research institution collaborators that we do not intend to use for more advanced clinical trials or commercialization. Although we are working to develop commercially viable processes, doing so is a difficult and uncertain task, and there are risks associated with scaling to the level required for advanced clinical trials or commercialization, including, among others, cost overruns, potential problems with process scale-out, process reproducibility, stability issues, lot consistency, and timely availability of reagents or raw materials. As a result of these challenges, we may experience delays in our clinical development and/or commercialization plans. We may ultimately be unable to reduce the cost of goods for our product candidates to levels that will allow for an attractive return on investment if and when those product candidates are commercialized.

In some circumstances, changes in the manufacturing process may require us to perform both ex vivo comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials. For instance, changes we are making to the manufacturing process, including changes in reagents and in the viral vector, in preparation for our Phase II trial for JCAR015 will require us to show the comparability of the Phase II product to Phase I product. We plan to provide the FDA with comparability evidence from ex vivo experimental studies comparing Phase I product to Phase II product, as well as clinical comparability data from our planned Phase II trial. We also plan to make further changes to our manufacturing process prior to commercialization, and such changes

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will also require us to show the comparability of the resulting product to the product used in the clinical trials using the earlier process. We may be required to collect additional clinical data from the modified process prior to obtaining marketing approval for the product candidate produced with the modified process. If clinical data is not ultimately comparable to that seen in the earlier trials in terms of safety or efficacy, we may be required to make further changes to our process and/or undertake additional clinical testing, either of which could significantly delay the clinical development of JCAR015.

We expect our manufacturing strategy will involve the use of one or more CMOs as well as establishing our own capabilities and infrastructure, including a manufacturing facility to manufacture our product candidates. We also plan to manufacture certain of the reagents used for making our product candidates ourselves. We expect that development of our own manufacturing facility, as well as manufacturing some of our own reagents, will provide us with enhanced control of material supply for both clinical trials and the commercial market, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility or in manufacturing reagents and may never be successful in developing our own manufacturing facility or capability or in manufacturing reagents in sufficient quantities or with sufficient quality for clinical or commercial use. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

In addition, the manufacturing process for any products that we may develop is subject to FDA and foreign regulatory authority approval process, and we will need to contract with manufacturers who can meet all applicable FDA and foreign regulatory authority requirements on an ongoing basis. If we or our CMOs are unable to reliably produce products to specifications acceptable to the FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

We expect to rely on third parties to manufacture our clinical product supplies, and we intend to rely on third parties for at least a portion of the manufacturing process of our product candidates, if approved. Our business could be harmed if those third parties fail to provide us with sufficient quantities of product or fail to do so at acceptable quality levels or prices.

We currently rely on outside vendors to manufacture supplies and process our product candidates, which is and will need to be done on a patient-by-patient basis. We have not yet caused our product candidates to be manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates. Although our manufacturing and processing approach is based upon the current approach undertaken by our third-party research institution collaborators, we have limited experience in managing the T cell engineering process, and our process may be more difficult or expensive than the approaches currently in use. We will make changes as we work to optimize the manufacturing process, and we cannot be sure that even minor changes in the process will not result in significantly different T cells that may not be as safe and effective as any T cell therapy deployed by our third-party research institution collaborators.

Although we do intend to develop our own manufacturing facility, and we have leased a facility that we intend to build out to support our clinical and commercial manufacturing activities, we also intend to continue to use third parties as part of our manufacturing process and may, in any event, never be successful in developing our own manufacturing facility. Our anticipated reliance on a limited number of third-party manufacturers exposes us to the following risks:

- We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and the FDA must approve any manufacturers. This approval would require new testing and good manufacturing practices compliance inspections by FDA. In addition, a new manufacturer would have to be educated in, or develop substantially equivalent processes for, production of our products.

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- Our manufacturers may have little or no experience with autologous cell products, which are products made from a patient's own cells, and therefore may require a significant amount of support from us in order to implement and maintain the infrastructure and processes required to manufacture our product candidates.
- Our third-party manufacturers might be unable to timely manufacture our product or produce the quantity and quality required to meet our clinical and commercial needs, if any.
- Contract manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately.
- Our future contract manufacturers may not perform as agreed, may not devote sufficient resources to our products, or may not remain in the contract manufacturing business for the time required to supply our clinical trials or to successfully produce, store, and distribute our products.
- Manufacturers are subject to ongoing periodic unannounced inspection by the FDA and corresponding state agencies to ensure strict compliance with cGMPs and other government regulations and corresponding foreign standards. We do not have control over third-party manufacturers' compliance with these regulations and standards.
- We may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our products.
- Our third-party manufacturers could breach or terminate their agreement with us.
- Raw materials and components used in the manufacturing process, particularly those for which we have no other source or supplier, may not be available or may not be suitable or acceptable for use due to material or component defects.
- Our contract manufacturers and critical reagent suppliers may be subject to inclement weather, as well as natural or man-made disasters.
- Our contract manufacturers may have unacceptable or inconsistent product quality success rates and yields.

Each of these risks could delay or prevent the completion of our clinical trials or the approval of any of our product candidates by the FDA, result in higher costs or adversely impact commercialization of our product candidates. In addition, we will rely on third parties to perform certain specification tests on our product candidates prior to delivery to patients. If these tests are not appropriately done and test data are not reliable, patients could be put at risk of serious harm and the FDA could require additional clinical trials or place significant restrictions on our company until deficiencies are remedied.

The manufacture of biological drug products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls.

Manufacturers of biologic products often encounter difficulties in production, particularly in scaling up or out, validating the production process, and assuring high reliability of the manufacturing process (including the absence of contamination). These problems include logistics and shipping, difficulties with production costs and yields, quality control, including stability of the product, product testing, operator error, availability of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Furthermore, if contaminants are discovered in our supply of our product candidates or in the manufacturing facilities, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that any stability failures or other issues relating to the manufacture of our product candidates will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to provide our product candidate to patients in clinical trials would be jeopardized. Any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to begin new clinical trials at additional expense or terminate clinical trials completely.

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Cell-based therapies rely on the availability of reagents, specialized equipment, and other specialty materials, which may not be available to us on acceptable terms or at all. For some of these reagents, equipment, and materials, we rely or may rely on sole source vendors or a limited number of vendors, which could impair our ability to manufacture and supply our products.

Manufacturing our product candidates will require many reagents, which are substances used in our manufacturing processes to bring about chemical or biological reactions, and other specialty materials and equipment, some of which are manufactured or supplied by small companies with limited resources and experience to support commercial biologics production. We currently depend on a limited number of vendors for certain materials and equipment used in the manufacture of our product candidates. Some of these suppliers may not have the capacity to support commercial products manufactured under cGMP by biopharmaceutical firms or may otherwise be ill-equipped to support our needs. We also do not have supply contracts with many of these suppliers and may not be able to obtain supply contracts with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key materials and equipment to support clinical or commercial manufacturing.

For some of these reagents, equipment, and materials, we rely and may in the future rely on sole source vendors or a limited number of vendors. An inability to continue to source product from any of these suppliers, which could be due to regulatory actions or requirements affecting the supplier, adverse financial or other strategic developments experienced by a supplier, labor disputes or shortages, unexpected demands, or quality issues, could adversely affect our ability to satisfy demand for our product candidates, which could adversely and materially affect our product sales and operating results or our ability to conduct clinical trials, either of which could significantly harm our business.

As we continue to develop and scale our manufacturing process, we expect that we will need to obtain rights to and supplies of certain materials and equipment to be used as part of that process. We may not be able to obtain rights to such materials on commercially reasonable terms, or at all, and if we are unable to alter our process in a commercially viable manner to avoid the use of such materials or find a suitable substitute, it would have a material adverse effect on our business. Even if we are able to alter our process so as to use other materials or equipment, such a change may lead to a delay in our clinical development and/or commercialization plans. If such a change occurs for product candidate that is already in clinical testing, the change may require us to perform both ex vivo comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials.

We are and will continue to rely in significant part on outside scientists and their third-party research institutions for research and development and early clinical testing of our product candidates. These scientists and institutions may have other commitments or conflicts of interest, which could limit our access to their expertise and harm our ability to leverage our technology platform.

We rely to a large extent at present on our third-party research institution collaborators for research and development capabilities. Currently, MSK is conducting Phase I clinical trials using JCAR015 to address adult ALL and pediatric ALL; SCRI is conducting a Phase I/II clinical trial using JCAR017 to address pediatric ALL; and FHCRC is conducting a Phase I/II clinical trial using JCAR014 to address ALL, NHL, and CLL. Each of these clinical trials addresses a limited number of patients. We expect to use the results of these trials to help support the filing with the FDA of INDs to conduct more advanced clinical trials with one or more of our CD19 product candidates. To date, we have filed, and the FDA has cleared, a Juno-sponsored IND for the Phase I clinical trial of JCAR017 and a Juno-sponsored IND for the Phase II clinical trial of JCAR015, and these Juno-sponsored trials are expected to commence in the near term.

With respect to our CD22 product candidate, JCAR018, the NCI is conducting a clinical trial of the product candidate for the treatment of pediatric relapsed/refractory ALL and relapsed/refractory NHL. If the results of this trial are compelling, we expect to use the results of the NCI's clinical trial to support the filing with the FDA of a Juno-sponsored IND to conduct more advanced clinical trials of JCAR018.

We also fund research and development under agreements with FHCRC, MSK, and SCRI. However, the research we are funding constitutes only a small portion of the overall research of each research institution. Other research being conducted by these institutions may at times receive higher priority than research on the programs we are funding.

The outside scientists who conduct the clinical testing of our current product candidates, and who conduct the research and development upon which our product candidate pipeline depends, are not our employees; rather they

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serve as either independent contractors or the primary investigators under research collaboration agreements that we have with their sponsoring academic or research institution. Such scientists and collaborators may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if an actual or potential conflict of interest between their work for us and their work for another entity arises, we may lose their services. These factors could adversely affect the timing of the clinical trials, the timing of receipt and reporting of clinical data, the timing of Juno-sponsored IND filings, and our ability to conduct future planned clinical trials. It is also possible that some of our valuable proprietary knowledge may become publicly known through these scientific advisors if they breach their confidentiality agreements with us, which would cause competitive harm to, and have a material adverse effect on, our business.

Our existing agreements with our collaboration partners may be subject to termination by the counterparty upon the occurrence of certain circumstances as described in more detail under the caption "Licenses and Third-Party Research Collaborations" in Part I—Item 1—"Business" of our 2014 Annual Report. If any of our collaboration partners terminates their collaboration agreement, the research and development of the relevant product candidate would be suspended, and we may be unable to research, develop, and license future product candidates. We may be required to devote additional resources to the development of our product candidates or seek a new collaboration partner, and the terms of any additional collaborations or other arrangements that we establish may not be favorable to us. In addition, there is a natural transition period when a new third-party begins work. In addition, switching or adding third parties to conduct our clinical trials involves substantial cost and requires extensive management time and focus. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines.

We will be highly dependent on the NCI for early clinical testing of JCAR018.

In December 2014, we entered into an exclusive license agreement with Opus Bio pursuant to which Opus Bio has granted us an exclusive, worldwide, sublicenseable license under certain patent rights related to a CD22-directed CAR product candidate, JCAR018. In connection therewith, the National Cancer Institute ("NCI") agreed to separate the activities that are exclusively related to CD22 under its agreement with Opus Bio and to enter into a separate agreement with us (the "Juno CRADA"), on the same terms as such agreement and incorporate such activities into its agreement with us.

The NCI has commenced a Phase I clinical trial of JCAR018 for the treatment of pediatric relapsed/refractory ALL and relapsed/refractory NHL. If the results of this trial are compelling, we expect to use the results of the NCI's clinical trial to support the filing with the FDA of a Juno-sponsored IND to conduct more advanced clinical trials of JCAR018. However, we will have limited control over the nature or timing of the NCI's clinical trial and limited visibility into their day-to-day activities. For example, the clinical trial will constitute only a small portion of the NCI's overall research and the research of the principal investigators. Other research being conducted by the principal investigators may at times receive higher priority than research on JCAR018. We will also be dependent on the NCI to provide us with data, include batch records, to support the filing of our IND. These factors could adversely affect the timing of our IND filing.

The NCI may unilaterally terminate our rights under the Juno CRADA at any time for any reason or for no reason upon at least 60 days prior written notice. If the NCI unilaterally terminates the Juno CRADA, the research and development under the Juno CRADA would be suspended and we may lose certain of our data rights, which may impair our ability to obtain regulatory approval of JCAR018.

If we fail to obtain additional financing, we may be unable to complete the development and commercialization of our product candidates.

Our operations have required substantial amounts of cash since inception. We expect to continue to spend substantial amounts to continue the clinical development of our product candidates, including our planned clinical trials for our CD19 product candidates. If approved, we will require significant additional amounts in order to launch and commercialize our product candidates.

As of June 30, 2015, we had $313.4 million in cash, cash equivalents, and marketable securities. In August 2015, we received $1.0 billion from Celgene from the sale of common stock to Celgene and from the initial payment under our collaboration agreement. We believe that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our operations for at least the next 12 months. However, changing circumstances

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may cause us to increase our spending significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. We may require additional capital for the further development and commercialization of our product candidates and may need to raise additional funds sooner if we choose to expand more rapidly than we presently anticipate.

We cannot be certain that additional funding will be available on acceptable terms, or at all. We have no committed source of additional capital and if we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of our product candidates or other research and development initiatives. Our license and collaboration agreements may also be terminated if we are unable to meet the payment obligations under the agreements. We could be required to seek additional collaborators for our product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available or relinquish or license on unfavorable terms our rights to our product candidates in markets where we otherwise would seek to pursue development or commercialization ourselves.

If Celgene declines to exercise its option with respect to one or more product candidates covered by our collaboration agreement with Celgene, or terminates the collaboration agreement with us, we will need to secure funding to advance development of those programs on our own or secure relationships with collaborators that have the necessary capital and expertise. In addition, we may need additional funding to advance product candidates prior to Celgene's decisions regarding option exercise with respect to such product candidate if development of that program is not discontinued. In addition, if we exercise our option to any of Celgene's in-licensed programs to co-develop and co-commercialize products, then we may need to secure additional funding to support our obligations to pay one-half of the acquisition costs of any such in-licensed program.

If we are unable to obtain sufficient financing when needed, it could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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Any future revenue from the license agreement with Penn and Novartis is highly dependent upon milestone and contingent royalty payments generated from the efforts of Penn and Novartis, over which we have no control, and we may not realize the intended benefits of this agreement.

On April 4, 2015, the parties to Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Civil Action No. 2:13-cv-01502-SD (E.D. Penn.), agreed to settle the case, which was dismissed on April 7, 2015. In connection with this settlement we entered into a sublicense agreement with Penn and an affiliate of Novartis pursuant to which we granted Novartis a non-exclusive, royalty-bearing sublicense under certain patent rights, including U.S. Patent No. 8,399,645, to develop, make and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative and palliative uses. In exchange for this sublicense, Novartis is obligated to pay us mid-single digit royalties on the U.S. net sales of products and services related to the disputed contract and patent claims, a low double digit percentage of the royalties Novartis pays to Penn for global net sales of those products, and milestone payments upon the achievement of specified clinical, regulatory and commercialization milestones for licensed products. The sublicense agreement with Novartis and Penn is terminable by Novartis at will without notice to us and without our consent.

Our receipt of royalty and milestone payments from Novartis is subject to many risks and uncertainties. In particular, these payments are dependent upon Novartis' ability to make U.S. and global sales of its products and services, and its ability to achieve clinical, regulatory and commercialization milestones for the licensed products. We will have no control over the nature or timing of Novartis' efforts towards making these sales or achieving these milestones. Furthermore, in the course of developing and commercializing its products, Novartis and Penn will likely be subject to many risks and uncertainties similar to those faced by our company and our product candidates as described in this section, and may be subject to other risks specific to Novartis and Penn. Additionally, if Novartis or Penn breaches our sublicense agreement, we may determine to terminate the agreement, or may be required to do so by St. Jude pursuant to the terms of our license agreement with St. Jude. To the extent Novartis fails, for any of the reasons outlined above or any other reason, to remit royalty payments or milestone payments under our sublicense agreement, or fails to remit these payments in the amount anticipated, or to the extent that our sublicense agreement with Novartis and Penn is terminated, we may not realize the potential benefits of the sublicense agreement with Penn and Novartis.

We will rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines or comply with regulatory requirements, we may not be able to obtain regulatory approval of or commercialize our product candidates.

We will depend upon independent investigators to conduct our clinical trials under agreements with universities, medical institutions, CROs, strategic partners, and others. We expect to have to negotiate budgets and contracts with CROs and trial sites, which may result in delays to our development timelines and increased costs.

We will rely heavily on third parties over the course of our clinical trials, and as a result will have limited control over the clinical investigators and limited visibility into their day-to-day activities, including with respect to how they are providing and administering T cell therapy. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol and legal, regulatory, and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with cGCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for product candidates in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of trial sponsors, principal investigators, and trial sites. If we or any of these third parties fail to comply with applicable cGCP regulations, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional nonclinical or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the cGCP regulations. In addition, our clinical trials must be conducted with biologic product produced under cGMP regulations and will require a large number of test patients. Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any third parties conducting our clinical trials are not and will not be our employees and, except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing preclinical, clinical, and nonclinical programs. These third parties may also have

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relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical studies or other drug development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed, or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed. We have disclosed in our 2014 Annual Report certain third party investigator-reported interim data from some of our trials, including interim data for which we have not yet independently reviewed the source data. We also sometimes rely on such investigator-reported interim data in making business decisions. Independent review of the data could fail to confirm the investigator- reported interim data, which may lead to revisions in disclosed clinical trial results in the future. Any such revisions that reveal more negative data than previously disclosed investigator-reported interim data could have an adverse impact on our business prospects and the trading price of our common stock. Such revisions could also reduce investor confidence in investigator-reported interim data that we disclose in the future.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition, and prospects.

The market opportunities for our product candidates may be limited to those patients who are ineligible for or have failed prior treatments and may be small.

Cancer therapies are sometimes characterized as first line, second line, or third line, and the FDA often approves new therapies initially only for third line use. When cancer is detected early enough, first line therapy is sometimes adequate to cure the cancer or prolong life without a cure. Whenever first line therapy, usually chemotherapy, hormone therapy, surgery, or a combination of these, proves unsuccessful, second line therapy may be administered. Second line therapies often consist of more chemotherapy, radiation, antibody drugs, tumor targeted small molecules, or a combination of these. Third line therapies can include bone marrow transplantation, antibody and small molecule targeted therapies, more invasive forms of surgery, and new technologies. We expect to initially seek approval of our product candidates as a third line therapy for patients who have failed other approved treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval as a second line therapy and potentially as a first line therapy, but there is no guarantee that our product candidates, even if approved, would be approved for second line or first line therapy. In addition, we may have to conduct additional clinical trials prior to gaining approval for second line or first line therapy.

Our projections of both the number of people who have the cancers we are targeting, as well as the subset of people with these cancers in a position to receive third line therapy and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations, or market research and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these cancers. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. For instance, with our CD19 product candidates we expect to initially target a small patient population that suffers from ALL and certain types of aggressive NHL. Even if we obtain significant market share for our product candidates, because the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications, including use as a first or second line therapy.

Our market opportunities may also be limited by competitor treatments that may enter the market. See the risk factor below "—We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively."

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We plan to seek orphan drug status for some or all of our CD19 product candidates, but we may be unable to obtain such designations or to maintain the benefits associated with orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, including a BLA, to market the same biologic for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan drug exclusivity or if FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. As a result, even if one of our drug candidates receives orphan exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

We plan to seek orphan drug designation for some or all of our CD19 product candidates in specific orphan indications in which there is a medically plausible basis for the use of these products, including relapsed/ refractory ALL and relapsed/refractory NHL indications. We have obtained orphan drug designation for each of JCAR015 and JCAR014 for the treatment of ALL. Even when we obtain orphan drug designation, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan designated indication and may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. In addition, although we intend to seek orphan drug designation for other product candidates, we may never receive such designations.

We plan to seek but may fail to obtain breakthrough therapy designation for some or all of our CD19 product candidates.

In 2012, the FDA established a breakthrough therapy designation which is intended to expedite the development and review of products that treat serious or life-threatening diseases when “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.” The designation of a product candidate as a breakthrough therapy provides potential benefits that include more frequent meetings with FDA to discuss the development plan for the product candidate and ensure collection of appropriate data needed to support approval; more frequent written correspondence from FDA about such things as the design of the proposed clinical trials and use of biomarkers; intensive guidance on an efficient drug development program, beginning as early as Phase I; organizational commitment involving senior managers; and eligibility for rolling review and priority review.

Breakthrough therapy designation does not change the standards for product approval. We intend to seek breakthrough therapy designation for some or all of our CD19 product candidates that may qualify for such designation. Our collaborator MSK obtained breakthrough therapy designation for JCAR015 for relapsed/refractory ALL, but we will have to seek such designation separately under our own IND, which we may not receive. In addition, although we intend to seek breakthrough therapy designation for other product candidates, we may never receive such designations.

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We currently have no marketing and sales organization and have no experience in marketing products. If we are unable to establish marketing and sales capabilities on our own or through our collaboration with Celgene or enter into agreements with third parties to market and sell our product candidates, we may not be able to generate product revenue.

We currently have no sales, marketing, or commercial product distribution capabilities and have no experience as a company in marketing products. We intend to develop an in-house marketing organization and sales force, which will require significant capital expenditures, management resources, and time. We will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, and retain marketing and sales personnel.

Under our collaboration with Celgene, for Juno-developed programs that Celgene opts into, Celgene will lead development and commercialization activities outside of North America and, for cellular therapy product candidates, China, but we will still be responsible for leading such activities in North America and, for cellular therapy product candidates, China. If Celgene does not opt into a program for one of our product candidates that we move to commercialization, we will alone be responsible for commercialization activities worldwide, unless we find another collaborator to assist with the sales and marketing of our products.

If we are unable or decide not to establish internal sales, marketing and commercial distribution capabilities for any or all products we develop, we will likely pursue further collaborative arrangements regarding the sales and marketing of our products. However, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend upon the efforts of such third parties, which may not be successful. We may have little or no control over the marketing and sales efforts of such third parties, and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates.

There can be no assurance that we will be able to develop in-house sales and commercial distribution capabilities or establish or maintain relationships with third-party collaborators to successfully commercialize any product in the United States or overseas, and as a result, we may not be able to generate product revenue.

A variety of risks associated with operating our business internationally could materially adversely affect our business.

As a result of the Stage acquisition, we acquired a German subsidiary with employees in Germany. We also plan to seek regulatory approval of our product candidates outside of the United States. Accordingly, we expect that we, and any potential collaborators that have operations in foreign jurisdictions, will be subject to additional risks related to operating in foreign countries, including:

- differing regulatory requirements in foreign countries;
- unexpected changes in tariffs, trade barriers, price and exchange controls, and other regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with applicable tax, employment, immigration, data privacy, and labor laws for employees living or traveling abroad, including for our German employees;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign laws;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;

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- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism.

These and other risks associated with our planned international operations may materially adversely affect our ability to attain or maintain profitable operations.

We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry, and the rapidly evolving market for developing genetically engineered T cells in particular, is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, universities, and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations as well as established sales forces. Smaller or early- stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaborative partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized, or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products.

Specifically, genetically engineering T cells faces significant competition in both the CAR and TCR technology space from multiple companies and their collaborators, such as Novartis/University of Pennsylvania, bluebird bio, Kite Pharma/NCI, Unum Therapeutics, Bellicum, Celyad, NantKwest, Johnson & Johnson/Transposagen Biopharmaceuticals, Autolus, Cellectis/Pfizer, Adaptimmune/GSK, and Intrexon/Ziopharm/MD Anderson Cancer Center. We face competition from non-cell based treatments offered by other companies such as Amgen, AstraZeneca, Bristol-Myers, Incyte, Merck, and Roche. For instance, the FDA recently granted accelerated approval to Amgen's blinotumomab for the treatment of relapsed/refractory ALL, and that product has demonstrated a complete remission rate of approximately 40% in clinical trials. Even if we obtain regulatory approval of our product candidates, we may not be the first to market and that may affect the price or demand for our product candidates. Additionally, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances. Additionally, a competitor could obtain orphan product exclusivity from the FDA with respect to such competitor's product. If such competitor product is determined to be the same product as one of our product candidates, that may prevent us from obtaining approval from the FDA for such product candidate for the same indication for seven years, except in limited circumstances.

For additional information regarding our competition, see the section captioned "Competition" in Part I—Item 1—"Business" of our 2014 Annual Report.

We are highly dependent on our key personnel, and if we are not successful in attracting, motivating and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, particularly our chief executive officer, Hans Bishop, and our scientific and medical personnel. The loss of the services of any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements, could result in delays in product development and harm our business.

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We conduct most of our operations at our facility in Seattle, Washington, in a region that is headquarters to many other biopharmaceutical companies and many academic and research institutions. As a result of our acquisition of X-Body and Stage, we have also expanded our operations into Massachusetts and Germany and currently have employees in both geographies. Competition for skilled personnel is intense in all of these geographies and the turnover rate can be high, which may limit our ability to hire and retain highly qualified personnel on acceptable terms or at all. We expect that we will need to recruit talent from outside of the regions in which we currently operate, and doing so may be costly and difficult. Further expansion into additional states or countries could also increase our regulatory and legal risks.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided restricted stock and stock option grants that vest over time. The value to employees of these equity grants that vest over time may be significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. Although we have employment agreements with our key employees, these employment agreements provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice. We do not maintain “key man” insurance policies on the lives of all of these individuals or the lives of any of our other employees.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

As of June 30, 2015, we had 206 employees worldwide, most of whom are full time. As our development and commercialization plans and strategies develop, and as we transition into operating as a public company, we must add a significant number of additional research and development, managerial, operational, sales, marketing, financial, and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining, and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for our product candidates, while complying with our contractual obligations to contractors and other third parties; and
- improving our operational, financial and management controls, reporting systems, and procedures.

Our future financial performance and our ability to commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities. Our efforts to manage our growth are complicated by the fact that all of our executive officers other than our chief executive officer have joined us since January 2014. This lack of long-term experience working together may adversely impact our senior management team’s ability to effectively manage our business and growth.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services. There can be no assurance that the services of these independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, if at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development, and commercialization goals.

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We have engaged in and may in the future engage in acquisitions or strategic partnerships, which could divert management's attention, increase our capital requirements, dilute our stockholders, be difficult to integrate, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We have made or entered into several acquisitions or strategic partnerships, and we may continue to evaluate various acquisitions and strategic partnerships, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. For instance, in May 2015, we acquired all the outstanding equity interests in Stage, in connection with which we paid €52.5 million in cash and issued 486,279 shares of common stock as an upfront payment, with potential earn out payments of up to €135.0 million in cash based on the achievement of certain technical, clinical, regulatory, and commercial milestones.

Any acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- the issuance of our equity securities;
- assimilation of operations, intellectual property and products of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing product programs and initiatives in pursuing such a strategic merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- expense or diversion of efforts related to the development of acquired technology under any diligence obligation required of us with respect to earn out milestones for an acquisition transaction, where we may not undertake such expense or efforts absent such diligence obligations;
- risk that the other party or parties to an acquisition transaction may claim that we have not satisfied any earn out diligence obligation and seek damages or other legal or equitable relief;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we undertake additional acquisitions, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. We also cannot be certain that, following a strategic transaction or license, we will achieve the revenue or specific net income that justifies such transaction. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business.

Our success payment obligations to FHCRC and MSK may result in dilution to our stockholders, may be a drain on our cash resources, or may cause us to incur debt obligations to satisfy the payment obligations.

We have agreed to make success payments to each of FHCRC and MSK pursuant to the terms of our agreements with each of those entities. These success payments will be based on increases in the estimated fair value of our common stock, payable in cash or publicly-traded equity at our discretion. The term of these obligations may last up to 11 years. Success payments will be owed (if applicable) after measurement of the value of our common stock in connection with the following valuation measurement dates during the term of the success payment agreement: (1) the date on which we complete an initial public offering of our common stock, or our shares otherwise become publicly traded; (2) the date on which we sell, lease, transfer or exclusively license all or substantially all of our

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assets to another company; (3) the date on which we merge or consolidate with or into another entity (other than a merger in which our pre-merger stockholders own a majority of the shares of the surviving entity); (4) any date on which ARCH Venture Fund VII, L.P. or C.L. Alaska L.P. transfers a majority of its shares of company capital stock held by it on such date to a third party; (5) the bi-annual anniversary of any event described in the preceding clauses (1), (2), (3) or (4), but only upon a request by FHCRC made within 20 calendar days after receiving written notice from us of such event; and (6) the last day of the 11 year period. The amount of a success payment is determined based on whether the value of our common stock meets or exceeds certain specified threshold values ascending, in the case of FHCRC, from $20.00 per share to $160.00 per share and, in the case of MSK, from $40.00 per share to $120.00 per share, in each case subject to adjustment for any stock dividend, stock split, combination of shares, or other similar events. Each threshold is associated with a success payment, ascending, in the case of FHCRC, from $10 million at $20.00 per share to $375 million at $160.00 per share and, in the case of MSK, from $10 million at $40.00 per share to $150 million at $120.00 per share, payable if such threshold is reached. The maximum aggregate amount of success payments to FHCRC is $375 million and to MSK is $150 million. The amount of success payments payable to FHCRC will be reduced by certain indirect costs paid by us to FHCRC related to collaboration projects conducted by FHCRC. See the section captioned “Licenses and Third-Party Research Collaborations” in Part I—Item 1—“Business” in our 2014 Annual Report for further discussion of these success payments.

Our initial public offering triggered a possible success payment to each of FHCRC and MSK. However, we will not be able to determine until the first anniversary of the completion of our initial public offering (subject to a 90-day grace period following such anniversary, at our option if we are contemplating a capital market transaction during such grace period), whether any such payment is required to be made and the amount of such payment. The value of any such initial public offering success payment will be determined by the average trading price of a share of our common stock over the consecutive 90-day period preceding such determination date. For example, the first payment due to FHCRC and MSK would be due if the average trading price of the share of our common stock over the consecutive 90-day period preceding the determination is at least $20.00 per share in the case of FHCRC or at least $40.00 in the case of MSK, subject to adjustment for any stock dividend, stock split, combination of shares, and other similar events. See Note 2, Acquisitions, to our unaudited financial statements included in this report for a summary of the value of success payments required to be made at different price levels.

In order to satisfy our obligations to make these success payments, if and when they are triggered, we may issue equity securities that may cause dilution to our stockholders, or we may use our existing cash or incur debt obligations to satisfy the success payment obligation in cash, which may adversely affect our financial position.

The success payment obligations to FHCRC and MSK may cause GAAP operating results to fluctuate significantly from quarter to quarter, which may reduce the usefulness of our GAAP financial statements.

Our success payment obligations to FHCRC and MSK are recorded as a liability on our balance sheet. Under generally accepted accounting principles in the United States (“GAAP”), we are required to estimate the fair value of this liability as of each quarter end and changes in estimated fair value are amortized to expense using the accelerated attribution method over the remaining term of the collaboration agreement. Factors that may lead to increases or decreases in the estimated fair value of this liability include, among others, changes in the value of the common stock, change in volatility, changes in the applicable term of the success payments, changes in the risk free rate, and changes in the estimated indirect costs related to the collaboration projects conducted by FHCRC that are creditable against FHCRC success payments. As a result, our operating results and financial condition as reported by GAAP may fluctuate significantly from quarter to quarter and from year to year and may reduce the usefulness of our GAAP financial statements. As of June 30, 2015 the estimated fair values of the liabilities associated with the success payments were $149.4 million and $62.0 million related to FHCRC and MSK, respectively.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships, and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. The incurrence of indebtedness would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

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If we, our CROs or our CMOs use hazardous and biological materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of potentially hazardous substances, including chemical and biological materials, by us or third parties, such as CROs and CMOs. We and such third parties are subject to federal, state, and local laws and regulations in the United States governing the use, manufacture, storage, handling, and disposal of medical and hazardous materials. Although we believe that our and such third parties' procedures for using, handling, storing, and disposing of these materials comply with legally prescribed standards, we cannot completely eliminate the risk of contamination or injury resulting from medical or hazardous materials. As a result of any such contamination or injury, we may incur liability or local, city, state, or federal authorities may curtail the use of these materials and interrupt our business operations. In the event of an accident, we could be held liable for damages or penalized with fines, and the liability could exceed our resources. We do not have any insurance for liabilities arising from medical or hazardous materials. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, prospects, financial condition, or results of operations.

Our internal computer systems, or those used by our third-party research institution collaborators, CROs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs and other contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. Although to our knowledge we have not experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on our third-party research institution collaborators for research and development of our product candidates and other third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our third-party research institution collaborators, CROs, CMOs, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. In addition, we rely on our third-party research institution collaborators for conducting research and development of our product candidates, and they may be affected by government shutdowns or withdrawn funding. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce and process our product candidates on a patient-by-patient basis. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption. Damage or extended periods of interruption to our corporate, development or research facilities due to fire, natural disaster, power loss, communications failure, unauthorized entry or other events could cause us to cease or delay development of some or all of our product candidates. Although we maintain property damage and business interruption insurance coverage, our insurance might not cover all losses under such circumstances and our business may be seriously harmed by such delays and interruption.

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If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- a decline in our share price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaborators. Although we currently carry $10.0 million of clinical trial insurance, the amount of such insurance coverage may not be adequate, we may be unable to maintain such insurance, or we may not be able to obtain additional or replacement insurance at a reasonable cost, if at all. Our insurance policies may also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

As of December 31, 2014, we had federal net operating loss carryforwards of approximately $51.1 million, which will begin to expire in 2033. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change" (generally defined as a greater than 50-percentage- point cumulative change (by value) in the equity ownership of certain stockholders over a rolling three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income or taxes may be limited. As a result of our transactions that have occurred since our incorporation in August 2013, including our initial public offering, we may have experienced such an "ownership change." We may also experience ownership changes in the future as a result of subsequent shifts in our stock

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ownership, some of which changes are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

Risks Related to Government Regulation

The FDA regulatory approval process is lengthy, time-consuming, and inherently unpredictable, and we may experience significant delays in the clinical development and regulatory approval, if any, of our product candidates.

The research, testing, manufacturing, labeling, approval, selling, import, export, marketing, and distribution of drug products, including biologics, are subject to extensive regulation by the FDA and other regulatory authorities in the United States. We are not permitted to market any biological drug product in the United States until we receive a Biologics License from the FDA. We have not previously submitted a BLA to the FDA, or similar approval filings to comparable foreign authorities. A BLA must include extensive preclinical and clinical data and supporting information to establish that the product candidate is safe, pure, and potent for each desired indication. The BLA must also include significant information regarding the chemistry, manufacturing, and controls for the product, and the manufacturing facilities must complete a successful pre- license inspection. We expect the novel nature of our product candidates to create further challenges in obtaining regulatory approval. For example, the FDA has limited experience with commercial development of genetically modified T cell therapies for cancer. The FDA may also require a panel of experts, referred to as an Advisory Committee, to deliberate on the adequacy of the safety and efficacy data to support licensure. The opinion of the Advisory Committee, although not binding, may have a significant impact on our ability to obtain licensure of the product candidates based on the completed clinical trials. Accordingly, the regulatory approval pathway for our product candidates may be uncertain, complex, expensive, and lengthy, and approval may not be obtained.

In addition, clinical trials can be delayed or terminated for a variety of reasons, including delays or failures related to:

- obtaining regulatory approval to begin a trial, if applicable;
- the availability of financial resources to begin and complete the planned trials;
- reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining approval at each clinical trial site by an independent IRB;
- recruiting suitable patients to participate in a trial in a timely manner;
- having patients complete a trial or return for post-treatment follow-up;
- clinical trial sites deviating from trial protocol, not complying with cGCPs, or dropping out of a trial;
- addressing any patient safety concerns that arise during the course of a trial;
- addressing any conflicts with new or existing laws or regulations;
- adding new clinical trial sites; or
- manufacturing qualified materials under cGMPs for use in clinical trials.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors. See the risk factor above "—If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected" for additional information on risks related to patient enrollment. Further, a clinical trial may be suspended or terminated by us, the IRBs for the institutions in which such trials are being conducted, the Data Monitoring Committee for such trial, or the FDA or other regulatory authorities due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements

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or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience termination of, or delays in the completion of, any clinical trial of our product candidates, the commercial prospects for our product candidates will be harmed, and our ability to generate product revenue will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product development and approval process and jeopardize our ability to commence product sales and generate revenue.

Our third-party research institution collaborators may also experience similar difficulties in completing ongoing clinical trials and conducting future clinical trials of product candidates. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical trials as clinical studies conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we receive regulatory approval of our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post- marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to cGMP, and in certain cases Good Tissue Practices regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, other marketing application, and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient

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registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, we will have to comply with requirements including submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and cGCPs for any clinical trials that we conduct post-approval.

The FDA may impose consent decrees or withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters, or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention, or refusal to permit the import or export of our product candidates; and
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. The policies of the FDA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

In addition, if we were able to obtain accelerated approval of any of our CD19 product candidates, the FDA would require us to conduct a confirmatory study to verify the predicted clinical benefit and additional safety studies. The results from the confirmatory study may not support the clinical benefit, which would result in the approval being withdrawn. While operating under accelerated approval, we will be subject to certain restrictions that we would not be subject to upon receiving regular approval.

Even if we obtain regulatory approval of our product candidates, the products may not gain market acceptance among physicians, patients, hospitals, cancer treatment centers, and others in the medical community.

The use of engineered T cells as a potential cancer treatment is a recent development and may not become broadly accepted by physicians, patients, hospitals, cancer treatment centers, and others in the medical community. We expect physicians in the large bone marrow transplant centers to be particularly influential, and we may not be able to convince them to use our product candidates for many reasons. For example, certain of the product candidates that we will be developing target a cell surface marker that may be present on cancer cells as well as non-cancerous cells. It is possible that our product candidates may kill these non-cancerous cells, which may result in unacceptable side effects, including death. Additional factors will influence whether our product candidates are accepted in the market, including:

- the clinical indications for which our product candidates are approved;

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- physicians, hospitals, cancer treatment centers, and patients considering our product candidates as a safe and effective treatment;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA or other regulatory authorities;
- limitations or warnings contained in the labeling approved by the FDA;
- the timing of market introduction of our product candidates as well as competitive products;
- the cost of treatment in relation to alternative treatments;
- the amount of upfront costs or training required for physicians to administer our product candidates;
- the availability of adequate coverage, reimbursement, and pricing by third-party payors and government authorities;
- the willingness of patients to pay out-of-pocket in the absence of coverage and reimbursement by third-party payors and government authorities;
- relative convenience and ease of administration, including as compared to alternative treatments and competitive therapies; and
- the effectiveness of our sales and marketing efforts.

In addition, although we are not utilizing embryonic stem cells or replication competent vectors, adverse publicity due to the ethical and social controversies surrounding the therapeutic use of such technologies, and reported side effects from any clinical trials using these technologies or the failure of such trials to demonstrate that these therapies are safe and effective may limit market acceptance our product candidates. If our product candidates are approved but fail to achieve market acceptance among physicians, patients, hospitals, cancer treatment centers or others in the medical community, we will not be able to generate significant revenue.

Even if our products achieve market acceptance, we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our products, are more cost effective or render our products obsolete.

Coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates profitably.

Successful sales of our product candidates, if approved, depend on the availability of adequate coverage and reimbursement from third-party payors. In addition, because our product candidates represent new approaches to the treatment of cancer, we cannot accurately estimate the potential revenue from our product candidates.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors are critical to new product acceptance.

Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs and treatments they will cover and the amount of reimbursement. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a product is:

- a covered benefit under its health plan;

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- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

In the United States, no uniform policy of coverage and reimbursement for products exists among third- party payors. As a result, obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our products on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given product, the resulting reimbursement payment rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our genetically modified products. Patients are unlikely to use our product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our product candidates. Because our product candidates have a higher cost of goods than conventional therapies, and may require long- term follow up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater.

We intend to seek approval to market our product candidates in both the United States and in selected foreign jurisdictions. If we obtain approval in one or more foreign jurisdictions for our product candidates, we will be subject to rules and regulations in those jurisdictions. In some foreign countries, particularly those in the EU, the pricing of biologics is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after obtaining marketing approval of a product candidate. In addition, market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for our product candidates and may be affected by existing and future health care reform measures.

Healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government’s comparative effectiveness research.

In addition, other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation’s automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

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There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud, misconduct or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and negligent conduct that fails to: comply with the laws of the FDA and other similar foreign regulatory bodies; provide true, complete and accurate information to the FDA and other similar foreign regulatory bodies; comply with manufacturing standards we have established; comply with healthcare fraud and abuse laws in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research patients, as well as proposed and future sales, marketing and education programs. In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices.

These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, physician payment transparency laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations may be directly, or indirectly through our customers, subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs;

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- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other third-party payors that are false or fraudulent or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- the federal Physician Payment Sunshine Act, created under the Affordable Care Act, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply regardless of the payor.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. In addition, recent health care reform legislation has strengthened these laws. For example, the Affordable Care Act, among other things, amends the intent requirement of the federal Anti-Kickback and criminal healthcare fraud statutes. As a result of such amendment, a person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation. Moreover, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

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Risks Related to Intellectual Property

We depend on intellectual property licensed from third parties and termination of any of these licenses could result in the loss of significant rights, which would harm our business.

We are dependent on patents, know-how, and proprietary technology, both our own and licensed from others. Any termination of these licenses could result in the loss of significant rights and could harm our ability to commercialize our product candidates. See the section captioned “Licenses and Third-Party Research Collaborations” in Part I—Item 1—“Business” of our 2014 Annual Report for additional information regarding our license agreements.

Disputes may also arise between us and our licensors regarding intellectual property subject to a license agreement, including those relating to:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the license agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- whether we are complying with our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates; and
- the allocation of ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and by us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. We are generally also subject to all of the same risks with respect to protection of intellectual property that we license as we are for intellectual property that we own, which are described below. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

We depend, in part, on our licensors to file, prosecute, maintain, defend, and enforce patents and patent applications that are material to our business.

Patents relating to our product candidates are controlled by certain of our licensors. Each of our licensors generally has rights to file, prosecute, maintain, and defend the patents we have licensed from such licensor. We generally have the first right to enforce our patent rights, although our ability to settle such claims often requires the consent of the licensor. If our licensors or any future licensees having rights to file, prosecute, maintain, and defend our patent rights fail to conduct these activities for patents or patent applications covering any of our product candidates, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using, or selling competing products. We cannot be certain that such activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents or other intellectual property rights. Pursuant to the terms of the license agreements with some of our licensors, the licensors may have the right to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents and, even if we are permitted to pursue such enforcement or defense, we cannot ensure the cooperation of our licensors. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. Even if we are not a party to these legal actions, an adverse outcome could harm our business because it might prevent us from continuing to license intellectual property that we may need to operate our business. In addition, even when we have the right to control patent prosecution of licensed patents and patent applications, enforcement of licensed patents, or defense of claims asserting the invalidity of those patents, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to or after our assuming control.

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We may not be successful in obtaining or maintaining necessary rights to product components and processes for our product development pipeline.

We own or license from third parties certain intellectual property rights necessary to develop our product candidates. The growth of our business will likely depend in part on our ability to acquire or in-license additional proprietary rights. For example, our programs may involve additional product candidates that may require the use of additional proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently. These formulations may be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all, which would harm our business. We may need to cease use of the compositions or methods covered by such third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on such intellectual property rights which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license under such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us.

Additionally, we sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

The licensing and acquisition of third-party intellectual property rights is a competitive practice, and companies that may be more established, or have greater resources than we do, may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their larger size and cash resources or greater clinical development and commercialization capabilities. There can be no assurance that we will be able to successfully complete such negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to acquire.

We are dependent on intellectual property sublicensed to us by Opus Bio from the NIH for development of JCAR018. Failure to meet our own obligations to Opus Bio and the NIH may result in the loss of our rights to such intellectual property, which could harm our business.

Under our license agreement with Opus Bio, we are obligated to make certain pass-through payments to the NIH as well as to meet certain development benchmarks within certain time periods. We may be unable to make these payments or meet these benchmarks or may breach our other obligations under this license agreement, which could lead to the termination of the license agreement.

In addition, the NIH has the right to require us to grant mandatory sublicenses to the intellectual property licensed from the NIH under certain specified circumstances, including if it is necessary to meet health and safety needs that we are not reasonably satisfying or if it is necessary to meet requirements for public use specified by federal regulations. Any required sublicense of these licenses could result in the loss of significant rights and could harm our ability to commercialize licensed products.

We could be unsuccessful in obtaining or maintaining adequate patent protection for one or more of our products or product candidates.

We anticipate that we will file additional patent applications both in the United States and in other countries, as appropriate. However, we cannot predict:

- if and when any patents will issue;
- the degree and range of protection any issued patents will afford us against competitors, including whether third parties will find ways to invalidate or otherwise circumvent our patents;

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- whether others will apply for or obtain patents claiming aspects similar to those covered by our patents and patent applications; or
- whether we will need to initiate litigation or administrative proceedings to defend our patent rights, which may be costly whether we win or lose.

Composition of matter patents for biological and pharmaceutical products such as CAR or TCR product candidates are generally considered to be the strongest form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of use. We cannot be certain, however, that the claims in our pending patent applications covering the composition of matter of our product candidates will be considered patentable by the United States Patent and Trademark Office ("USPTO"), or by patent offices in foreign countries, or that the claims in any of our issued patents will be considered valid and enforceable by courts in the United States or foreign countries. Method of use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label" for those uses that are covered by our method of use patents. Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The strength of patents in the biotechnology and pharmaceutical field can be uncertain, and evaluating the scope of such patents involves complex legal and scientific analyses. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates or uses thereof in the United States or in other foreign countries. Even if the patents do successfully issue, third parties may challenge the validity, enforceability, or scope thereof, which may result in such patents being narrowed, invalidated, or held unenforceable. For example, on August 13, 2015, Kite Pharma filed a petition with the USPTO for inter partes review of U.S. Patent No. 7,446,190, a patent that we have exclusively licensed from MSK. If Kite Pharma is successful in its petition and resulting proceedings at the USPTO, the patent could be narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property or prevent others from designing their products to avoid being covered by our claims. If the breadth or strength of protection provided by the patent applications we hold with respect to our product candidates is threatened, this could dissuade companies from collaborating with us to develop, and could threaten our ability to commercialize, our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market our product candidates under patent protection would be reduced. Because patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Furthermore, for U.S. applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third party or instituted by the USPTO to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. For U.S. applications containing a claim not entitled to priority before March 16, 2013, there is a greater level of uncertainty in the patent law in view of the passage of the America Invents Act, which brought into effect significant changes to the U.S. patent laws, including new procedures for challenging pending patent applications and issued patents.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce, and any other elements of our product discovery and development processes that involve proprietary know-how, information, or technology that is not covered by patents. Trade secrets, however, may be difficult to protect. We seek to protect our proprietary processes, in part, by entering into confidentiality agreements with our employees, consultants, outside scientific advisors, contractors, and collaborators. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, outside scientific advisors, contractors, and collaborators might intentionally or inadvertently disclose our trade secret information to competitors. In addition, competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, or misappropriation of our intellectual property by third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results, and financial condition.

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Third-party claims of intellectual property infringement against us or our collaborators may prevent or delay our product discovery and development efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. Recently, due to changes in U.S. law referred to as patent reform, new procedures including inter partes review and post-grant review have been implemented. As stated above, this reform adds uncertainty to the possibility of challenge to our patents in the future.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may give rise to claims of infringement of the patent rights of others.

Although we have conducted analyses of the patent landscape with respect to our CD19 product candidates, and based on these analyses, we believe that we will be able to commercialize our CD19 product candidates, third parties may nonetheless assert that we infringe their patents, or that we are otherwise employing their proprietary technology without authorization, and may sue us. For instance, Novartis Pharmaceutical Corporation has asserted in writing its belief that we infringe the following patents controlled by Novartis Pharmaceutical Corporation: U.S. Patent Nos. 7,408,053, 7,205,101, 7,527,925, and 7,442,525. There may be third-party patents of which we are currently unaware with claims to compositions, formulations, methods of manufacture, or methods of use or treatment that cover our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies or the manufacture, use, or sale of our product candidates infringes upon these patents. If any such third-party patents were held by a court of competent jurisdiction to cover our technologies or product candidates, the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, our ability to commercialize our product candidates may be impaired or delayed, which could in turn significantly harm our business.

Third parties asserting their patent rights against us may seek and obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties, or redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our product candidates, which could harm our business significantly.

We have limited foreign intellectual property rights and may not be able to protect our intellectual property rights throughout the world.

We have limited intellectual property rights outside the United States, and, in particular, some of our patents directed to CAR constructs do not extend outside of the United States. Filing, prosecuting, maintaining and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can have a different scope and strength than do those in the United States. In addition, the laws of some foreign countries, such as China, Brazil, Russia, India, and South Africa, do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or adequate to prevent them from competing.

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Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, such as China, Brazil, Russia, India, and South Africa, do not favor the enforcement of patents, trade secrets and other intellectual property, particularly those relating to biopharmaceutical products, which could make it difficult in those jurisdictions for us to stop the infringement or misappropriation of our patents or other intellectual property rights, or the marketing of competing products in violation of our proprietary rights. Proceedings to enforce our patent and other intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Furthermore such proceedings could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims of infringement or misappropriation against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To cease such infringement or unauthorized use, we may be required to file patent infringement claims, which can be expensive and time- consuming. In addition, in an infringement proceeding or a declaratory judgment action against us, a court may decide that one or more of our patents is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceeding could put one or more of our patents at risk of being invalidated, held unenforceable, or interpreted narrowly and could put our patent applications at risk of not issuing. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business.

Interference or derivation proceedings provoked by third parties or brought by the USPTO may be necessary to determine the priority of inventions with respect to, or the correct inventorship of, our patents or patent applications or those of our licensors. An unfavorable outcome could result in a loss of our current patent rights and could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Litigation, interference, or derivation proceedings may result in a decision adverse to our interests and, even if we are successful, may result in substantial costs and distract our management and other employees.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court or before the USPTO or comparable foreign authority.

If we or one of our licensing partners initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, inter partes review, post-grant review, and equivalent proceedings in foreign jurisdictions, such as opposition or derivation proceedings. Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have a material adverse impact on our business.

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Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves, both technological and legal complexity, and is therefore costly, time-consuming, and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on decisions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, in Assoc. for Molecular Pathology v. Myriad Genetics, Inc., the U.S. Supreme Court held that certain claims to naturally-occurring substances are not patentable. Although we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress, or the USPTO may impact the value of our patents.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties.

We have received confidential and proprietary information from third parties. In addition, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies. We may be subject to claims that we or our employees, consultants, or independent contractors have inadvertently or otherwise used or disclosed confidential information of these third parties or our employees' former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial cost and be a distraction to our management and employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent application process. Although an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In any such event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

The lives of our patents may not be sufficient to effectively protect our products and business.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after its first effective filing date. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from biosimilar or generic medications. Our issued patents will expire on dates ranging from 2015 to 2031, subject to any patent extensions that may be available for such patents. If patents are issued on our pending patent applications, the resulting patents are projected to expire on dates ranging from 2022 to 2036. In addition, although upon issuance in the United States a patent's life can be increased based on certain delays caused by the USPTO, this increase can be reduced or eliminated based on certain delays caused by the patent applicant during patent prosecution. If we do not have sufficient patent life to protect our products, our business and results of operations will be adversely affected.

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We may face competition from biosimilars, which may have a material adverse impact on the future commercial prospects of our product candidates.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This new pathway could allow competitors to reference data from innovative biological products 12 years after the time of approval of the innovative biological product. This data exclusivity does not prevent another company from developing a product that is highly similar to the innovative product, generating its own data, and seeking approval. Data exclusivity only assures that another company cannot rely upon the data within the innovator's application to support the biosimilar product's approval. In his proposed budget for fiscal year 2014, President Obama proposed to cut this 12-year period of exclusivity down to seven years. He also proposed to prohibit additional periods of exclusivity due to minor changes in product formulations, a practice often referred to as "evergreening." It is possible that Congress may take these or other measures to reduce or eliminate periods of exclusivity. The Biologics Price Competition and Innovation Act of 2009 is complex and only beginning to be interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning is subject to uncertainty. Although it is uncertain when any such processes may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our product candidates.

In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to get it on the market until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products.

If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators, or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Risks Related to Our Common Stock

We expect that our stock price will fluctuate significantly.

The trading price of our common stock may be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- adverse results or delays in the planned clinical trials of our product candidates or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- any delay in our regulatory filings for our product candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;

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- regulatory or legal developments in the United States and other countries, especially changes in laws or regulations applicable to our products, including clinical trial requirements for approvals;
- our inability to obtain or delays in obtaining adequate product supply for any approved product or inability to do so at acceptable prices;
- any failure to commercialize our product candidates or if the size and growth of the markets we intend to target fail to meet expectations;
- additions or departures of key scientific or management personnel;
- unanticipated serious safety concerns related to cancer immunology or the use of our product candidates;
- introductions or announcements of new products offered by us or significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our collaborators or our competitors and the timing of such introductions or announcements;
- announcements relating to future collaborations or our existing collaboration with Celgene, including decisions regarding the exercise by Celgene or us of any of our or their options thereunder, or any exercise or non-exercise by Celgene of a right to purchase shares of our common stock;
- our ability to effectively manage our growth;
- our ability to successfully treat additional types of cancers or at different stages;
- changes in the structure of healthcare payment systems;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- publication of research reports about us or our industry, or immunotherapy in particular, or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- market conditions in the pharmaceutical and biotechnology sectors or the economy generally;
- our ability or inability to raise additional capital through the issuance of equity or debt or collaboration arrangements and the terms on which we raise it;
- trading volume of our common stock;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies; and
- significant lawsuits, including patent or stockholder litigation.

The stock market in general, and market prices for the securities of biopharmaceutical companies like ours in particular, have from time to time experienced volatility that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common stock, regardless of our operating performance. In several recent situations when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results.

An active trading market for our common stock may not be sustained.

Prior to our initial public offering in December 2014, there was no public market for our common stock. Although our common stock is listed on The NASDAQ Global Select Market, the market for our shares has demonstrated

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varying levels of trading activity. Furthermore, an active trading market may not be sustained in the future. The lack of an active market may impair investors' ability to sell their shares at the time they wish to sell them or at a price that they consider reasonable, may reduce the market value of their shares and may impair our ability to raise capital.

If securities or industry analysts do not publish research reports about our business, or if they issue an adverse opinion about our business, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us issues an adverse opinion about our company, our stock price would likely decline. If one or more of these analysts ceases research coverage of us or fails to regularly publish reports on us, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Future sales of our common stock in the public market could cause our stock price to fall.

Our stock price could decline as a result of sales of a large number of shares of our common stock or the perception that these sales could occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

As of June 30, 2015, we had 91,376,720 shares of common stock outstanding, including 6,751,850 shares of restricted stock that remained subject to vesting requirements. In connection with the sale of shares to Celgene, all 9,137,672 shares acquired by Celgene on August 4, 2015, representing 9.1% of our common stock outstanding as of the date of issuance (after giving effect to such issuance), are subject to a market standoff agreement for 364 days from the date of acquisition. Any subsequent acquisitions of shares of our common stock by Celgene will commence another 364 day market standoff period, subject to certain exceptions.

We have also registered the offer and sale of all shares of common stock that we may issue under our equity compensation plans, including upon the exercise of stock options. These shares can be freely sold in the public market upon issuance.

As of August 20, 2015, the holders of as many as 37,295,209 shares, or 40.8% of our common stock outstanding as of June 30, 2015, will have rights, subject to some conditions, under the investor rights agreement with such holders to require us to file registration statements covering the sale of their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. Once we register the offer and sale of shares for the holders of registration rights, they can be freely sold in the public market. In connection with the collaboration agreement with Celgene, we have also entered into a registration rights agreement, pursuant to which upon the written request of Celgene at certain times and subject to the satisfaction of certain conditions, we have agreed to prepare and file with the SEC a registration statement on Form S-3 for purposes of registering the resale of the shares specified in Celgene's written request or, if we are not at such time eligible for the use of Form S-3, use commercially reasonable efforts to prepare and file a registration statement on a Form S-1 or alternative form that permits the resale of the shares.

In addition, in the future, we may issue additional shares of common stock or other equity or debt securities convertible into common stock in connection with a financing, acquisition, litigation settlement, employee arrangements or otherwise, including up to 30% of shares of our outstanding common stock to Celgene. Any such issuance could result in substantial dilution to our existing stockholders and could cause our stock price to decline.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

Our executive officers, directors and our 10% or greater stockholders, together with their respective affiliates, beneficially owned approximately 48.4% of our capital stock as of June 30, 2015, excluding shares underlying outstanding options. Accordingly, such persons and entities, if they acted together, would be able to determine the composition of the board of directors, retain the voting power to approve many matters requiring stockholder approval, including mergers and other business combinations, and continue to have significant influence over our operations. In addition, other than in connection with a change of control, in any vote or action by written consent of our stockholders, including, without limitation, with respect to the election of directors, Celgene has agreed to vote or execute a written consent with respect to all of our voting securities held by Celgene in accordance with the

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recommendation of our board of directors, limiting the ability of Celgene to contrary to our board of directors that you otherwise may believe is in your best interest as our stockholder. This concentration of ownership amongst our significant holders, including Celgene, could have the effect of delaying or preventing a change in our control or otherwise discouraging a potential acquirer from attempting to obtain control of us that you may believe are in your best interests as one of our stockholders. This in turn could have a material adverse effect on our stock price and may prevent attempts by our stockholders to replace or remove the board of directors or management.

In connection with the entry into the Celgene collaboration agreement, Celgene acquired 9.1% of our outstanding shares of common stock and subject to certain conditions, may purchase additional shares annually to obtain and maintain a 10% ownership percentage through June 29, 2020. Furthermore, between June 29, 2019 and June 29, 2025 and between June 29, 2024 and the expiration of the collaboration agreement, subject to certain conditions, Celgene has the option to acquire and maintain an ownership of up to 19.99% and up to 30%, respectively, of our then outstanding shares of common stock. We have also entered into a voting and standstill agreement with Celgene, pursuant to which we have agreed to give Celgene certain board designation rights until at least June 29, 2020, and thereafter for as long as Celgene and its affiliates beneficially own at least 7.5% of the voting power of our outstanding shares. As a result of the concentration of ownership, Celgene could have the ability to delay or prevent a change in our control or otherwise discourage a potential acquirer from attempting to obtain control of us that you may believe are in your best interests as our stockholder.

Anti-takeover provisions in our charter documents and under Delaware or Washington law could make an acquisition of us difficult, limit attempts by our stockholders to replace or remove our current management and adversely affect our stock price.

Provisions of our certificate of incorporation and bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares, or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our stock. Among other things, the certificate of incorporation and bylaws will:

- permit the board of directors to issue up to 5,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate;
- provide that the authorized number of directors may be changed only by resolution of the board of directors;
- provide that all vacancies, including newly-created directorships, may, except as otherwise required by law, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum;
- divide the board of directors into three classes;
- provide that a director may only be removed from the board of directors by the stockholders for cause;
- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and may not be taken by written consent;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner, and meet specific requirements as to the form and content of a stockholder’s notice;
- prevent cumulative voting rights (therefore allowing the holders of a plurality of the shares of common stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose);
- require that, to the fullest extent permitted by law, a stockholder reimburse us for all fees, costs and expenses incurred by us in connection with a proceeding initiated by such stockholder in which such stockholder does not obtain a judgment on the merits that substantially achieves the full remedy sought;
- provide that special meetings of our stockholders may be called only by the chairman of the board, our chief executive officer (or president, in the absence of a chief executive officer) or by the board of directors; and
- provide that stockholders will be permitted to amend the bylaws only upon receiving at least two- thirds of the total votes entitled to be cast by holders of all outstanding shares then entitled to vote generally in the election of directors, voting together as a single class.

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Furthermore, pursuant to the voting and standstill agreement with Celgene, until the later of the fifth anniversary of the date of such agreement and the expiration or earlier termination of our collaboration agreement with Celgene, it will be bound by certain "standstill" provisions which generally will prevent it from purchasing outstanding shares of our common stock, making a tender offer or encouraging or supporting a third party tender offer, nominating a director whose nomination has not been approved by our board of directors, soliciting proxies in opposition to the recommendation of our board of directors or assisting a third party in taking such actions, entering into discussions with a third party as to such actions, or requesting or proposing in writing to our board of directors or any member thereof that we amend or waive any of these limitations. As a result, the ability of Celgene to act in contrary to our board of directors is severely limited and any attempts by Celgene to acquire us or encourage a third party to acquire us are prohibited by this voting and standstill agreement. In addition, subject to certain exceptions—including a vote in connection with a change in control of our company—Celgene has agreed to vote or execute a written consent with respect to all of our voting securities held by Celgene in accordance with the recommendation of our board of directors, limiting the ability of Celgene to contrary to our board of directors that you otherwise may believe is in your best interest as our stockholder.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which generally prohibits a Delaware corporation from engaging in any of a broad range of business combinations with any "interested" stockholder for a period of three years following the date on which the stockholder became an "interested" stockholder. Likewise, because our principal executive offices are located in Washington, the anti-takeover provisions of the Washington Business Corporation Act may apply to us under certain circumstances now or in the future. These provisions prohibit a "target corporation" from engaging in any of a broad range of business combinations with any stockholder constituting an "acquiring person" for a period of five years following the date on which the stockholder became an "acquiring person."

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our bylaws, any action to interpret, apply, enforce, or determine the validity of our certificate of incorporation or bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees. Alternatively, if a court were to find the choice of forum provision contained in our certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

Complying with the laws and regulations affecting public companies has increased and will increase our costs and the demands on management and could harm our operating results.

As a public company, we will continue to incur significant legal, accounting and other expenses that we did not incur as a private company, including costs associated with public company reporting requirements. We also anticipate that we will incur costs associated with relatively recently adopted corporate governance requirements, including requirements of the SEC and NASDAQ. We expect these rules and regulations to increase our legal and financial compliance costs and to make some activities more time-consuming and costly. We also expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified individuals to serve on our board of directors or as executive officers. We are currently evaluating and monitoring developments with respect to these rules, and we cannot predict or estimate the amount of additional costs we may incur or the timing of such costs.

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Starting January 1, 2016, we will no longer be an "emerging growth company" and after that date we will no longer be able to avail ourselves of exemptions from various reporting requirements applicable to other public companies but not to "emerging growth companies." For example, the Sarbanes-Oxley Act requires, among other things, that we assess the effectiveness of our internal control over financial reporting annually and the effectiveness of our disclosure controls and procedures quarterly. Section 404 of the Sarbanes-Oxley Act ("Section 404") requires us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm potentially to attest to, the effectiveness of our internal control over financial reporting. We are currently an "emerging growth company," and have availed ourselves of the exemption from the requirement that our independent registered public accounting firm attest to the effectiveness of our internal control over financial reporting under Section 404. However, beginning on January 1, 2016, we will no longer avail ourselves of this exemption when we cease to be an "emerging growth company." When our independent registered public accounting firm is required to undertake an assessment of our internal control over financial reporting, the cost of our compliance with Section 404 will correspondingly increase. Our compliance with applicable provisions of Section 404 will require that we incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Moreover, if we are not able to comply with the requirements of Section 404 applicable to us in a timely manner, or if we or our independent registered public accounting firm identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources. Furthermore, investor perceptions of our company may suffer if deficiencies are found, and this could cause a decline in the market price of our stock. Irrespective of compliance with Section 404, any failure of our internal control over financial reporting could have a material adverse effect on our stated operating results and harm our reputation. If we are unable to implement these requirements effectively or efficiently, it could harm our operations, financial reporting, or financial results and could result in an adverse opinion on our internal control over financial reporting from our independent registered public accounting firm.

Our management team has broad discretion to use the net proceeds from the initial payments to us under our collaboration agreement with Celgene and from the sale of our shares to Celgene and its investment of these proceeds may not yield a favorable return. We may invest the proceeds of the Celgene transaction and any remaining proceeds from our initial public offering in December 2014 in ways with which investors disagree.

Our management has broad discretion over the use of proceeds from the initial payments to us under our collaboration agreement with Celgene and from the sale of our shares to Celgene, as well as any remaining proceeds from our December 2014 initial public offering, and we could spend the proceeds from these transactions in ways our stockholders may not agree with or that do not yield a favorable return, if at all. In addition, until the proceeds are used, they may be placed in investments that do not produce significant income or that may lose value. If we do not invest or apply the proceeds in ways that improve our operating results, we may fail to achieve expected financial results, which could cause our stock price to decline.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

(a)

Not applicable.

(b)

On December 23, 2014, we closed our IPO, in which we sold an aggregate of 12,676,354 shares of common stock at a price to the public of $24.00 per share. The offer and sale of all of the shares in the initial public offering were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-200293), which was declared effective by the SEC on December 18, 2014 (the "Registration Statement"), and a registration statement on Form S-1 (File No. 333-201062), which became effective immediately upon filing with the SEC on December 18, 2014.

There has been no material change in the planned use of proceeds from our IPO as described in the Registration Statement. We invested the funds received in short-term, interest-bearing investment-grade securities and government securities. As of June 30, 2015, we have used approximately $155.4 million of the net proceeds from the IPO primarily to fund the costs to advance JCAR015 through a Phase II clinical trial and the filing of a Biologics

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License Application for the treatment of relapsed/refractory ALL, to advance JCAR017 through a Phase I/II clinical trial and into a potential registration trial in relapsed/refractory NHL, to further develop additional product candidates, to expand our internal research and development capabilities, to establish manufacturing capabilities, to acquire, license and invest in complementary products, technologies and businesses, and other general corporate purposes. None of the offering proceeds were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates.

(c)

Not applicable.

ITEM 3. DEFAULTS UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

ITEM 5. OTHER INFORMATION

(a)

Not applicable.

(b)

Not applicable.

ITEM 6. EXHIBITS

See the Exhibit Index on the page immediately following the signature page to this Quarterly Report on Form 10-Q for a list of the exhibits filed as part of this Quarterly Report, which Exhibit Index is incorporated herein by reference.

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SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Juno Therapeutics, Inc.

Date: August 14, 2015

By: /s/ Steven D. Harr

Steven D. Harr
Chief Financial Officer &
Head of Corporate Development
(principal financial and accounting officer)

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EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
2.1#‡Δ	Share Purchase Agreement, dated May 11, 2015, by and among Dr. Herbert Stadler, Dr. Lothar Germeroth, Prof. Dr. Dirk Busch, and the registrant	8-K	05/11/2015	2.1	
2.2#‡Δ	Agreement and Plan of Merger, dated June 1, 2015, by and among X Acquisition Corporation, X-Body, Inc., Brant Binder as stockholder representative, certain principal stockholders of X-Body, Inc., and the registrant	8-K	06/05/2015	2.1	
3.1	Amended and Restated Certificate of Incorporation	8-K	12/29/2014	3.1	
3.2	Amended and Restated Bylaws	S-1/A	12/09/2014	3.2	
4.1	Fourth Amended and Restated Investors' Rights Agreement, dated December 5, 2014, by and among the registrant and the investors named therein	S-1/A	12/09/2014	4.1	
4.2	Amendment and Waiver of Fourth Amended and Restated Investors' Rights Agreement, dated July 27, 2015				X
4.3	Form of Common Stock Certificate	S-1/A	12/09/2014	4.2	
10.1+	Amendment #2 to License Agreement, dated April 4, 2015, by and between St. Jude Children's Research Hospital, Inc. and the registrant				X
10.2+	Non-Exclusive Sublicense Agreement, effective April 7, 2015, by and among Novartis Institutes for Biomedical Research, Inc., The Trustees of the University of Pennsylvania, and the registrant				X
10.3	Lease Agreement, dated as of April 6, 2015, by and between ARE-Seattle No. 16, LLC and the registrant	8-K	04/07/2015	10.1	
10.4	First Amendment to Lease Agreement, dated May 21, 2015, by and between ARE-Seattle No. 16, LLC and the registrant				X
10.5	2015 Non-Employee Director Compensation Program, adopted April 3, 2015	10-Q	05/12/2015	10.3	
10.6	Amendment No. 1 to Sponsored Research Agreement, effective April 1, 2015, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant	10-Q	05/12/2015	10.4	
10.7+	Amendment No. 2 to Exclusive License Agreement, dated June 15, 2015, by and between Seattle Children's Hospital d/b/a Seattle Children's Research Institute and the registrant				X
10.8	Offer Letter with Hyam Levitsky, dated May 27, 2015				X
10.9+‡	Share Purchase Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.1	
10.10	Voting and Standstill Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.2	
10.11	Registration Rights Agreement, dated June 29, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	8-K	06/29/2015	10.3	

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10.12+	Amended and Restated Master Research and Collaboration Agreement, dated August 13, 2015, by and among Celgene Corporation, Celgene RIVOT Ltd., and the registrant	X
10.13	First Amendment to Lease, dated July 31, 2015, by and between BMR-217th Place LLC and the registrant	X
31.1	Certification of Principal Executive Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended	X
31.2	Certification of Principal Financial Officer Required Under Rule 13a-14(a) and 15d-14(a) of the Securities Exchange Act of 1934, as amended	X
32.1*	Certification of Principal Executive Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. §1350	X
32.2*	Certification of Principal Financial Officer Required Under Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, and 18 U.S.C. §1350	X
101†	The following materials from Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, formatted in eXtensible Business Reporting Language (XBRL) includes: (i) Condensed Consolidated Balance Sheets at June 30, 2015 (unaudited) and December 31, 2014, (ii) Condensed Consolidated Statements of Operations and Comprehensive Loss (unaudited) for the three and six months ended June 30, 2015 and 2014, (iii) Condensed Consolidated Statements of Cash Flows (unaudited) for the six months ended June 30, 2015 and 2014, and (iv) Notes to the Condensed Consolidated Financial Statements.	X

* The certifications attached as Exhibits 32.1 and 32.2 that accompany this Quarterly Report on Form 10-Q are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Juno Therapeutics, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

† XBRL information is furnished and not filed or a part of a registration statement or prospectus for purposes of sections 11 or 12 of the Securities Exchange Act of 1933, as amended, is deemed not filed for purposes of section 18 of the Securities Exchange Act of 1934, as amended, and otherwise is not subject to liability under these sections.

\+ Portions of this exhibit (indicated by asterisks) have been omitted pursuant to a request for confidential treatment and this exhibit has been filed separately with the Securities and Exchange Commission.

\# Confidential treatment has been granted for certain information contained in this exhibit. Such information has been omitted and filed separately with the Securities and Exchange Commission.

‡ The representations and warranties contained in this agreement were made only for purposes of the transactions contemplated by the agreement as of specific dates and may have been qualified by certain disclosures between the parties and a contractual standard of materiality different from those generally applicable under securities laws, among other limitations. The representations and warranties were made for purposes of allocating contractual risk between the parties to the agreement and should not be relied upon as a disclosure of factual information about the registrant or the transactions contemplated thereby.

Δ The exhibits and schedules to this agreement have been omitted in reliance on Item 601(b)(2) of Regulation S-K promulgated by the Securities and Exchange Commission, and a copy thereof will be furnished supplementally to the Securities and Exchange Commission upon its request.

Reference II

Material Transfer Agreements:

1. NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice
2. Uniform Biological Material Transfer Agreement ("UBMTA")
3. First St. Jude – U. Pennsylvania MTA
4. Second St. Jude – U. Pennsylvania MTA
5. November 22, 2011 letter from U. Pennsylvania to St. Jude

The meeting is closed to the public.

Dated: December 16, 1999.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 99–33295 Filed 12–22–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice

AGENCY: National Institutes of Health (NIH), Public Health Service, DHHS.

SUMMARY: On May 25, 1999 the National Institutes of Health (NIH) published for public comment in the **Federal Register** a proposed policy entitled SHARING BIOMEDICAL RESEARCH RESOURCES: Principles and Guideline for Recipients of NIH Research Grants and Contracts [64 FR 28205]. This policy is designed to provide recipients of NIH funding with guidance concerning appropriate terms for disseminating and acquiring unique research resources developed with federal funds and is intended to assist recipients in complying with their obligations under the Bayh-Dole Act and NIH funding policy. Comments on the Principles and Guidelines were requested by August 23, 1999. This Notice presents the final Principles and Guidelines together with NIH's response to the public comments received.

Background

The Present policy represents part of the overall implementation of recommendations made by the Advisory Committee to the Director (ACD) to Dr. Harlod Varmus, Director, NIH. Dr. Varmus requested that a Working Group of the ACD look into problems encountered in the dissemination and use of proprietary research tools, the competing interests of intellectual property owners and research users underlying these problems, and possible NIH responses. One of the recommendations in the Report was that NIH issue guidance to the recipients of NIH funding.

Purpose

The present policy is a two-part document, consisting of Principles setting forth the fundamental concepts and Guidelines providing specific information to patent and license professionals and sponsored research administrators for implementation. The purpose of these Principles and Guidelines is to assist NIH funding recipients in determining. (1) Reasonable terms and conditions for making NIH-funded research resources available to scientists in other institutions in the public and private sectors (disseminating research tools): and (2) restrictions to accept as a condition of receiving access to research tools for use in NIH-funded research (acquiring research tools). The intent is to help Recipients ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act and NIH funding agreements. It is also hoped that these Principles and Guidelines will be adopted by the wider research community so that all biomedical research and development can be synergistic and accelerated.

Comments and Agency Response

The National Institutes of Health (NIH) recognizes the importance of public involvement in the development of policy and sought widespread comment and participation by the various stakeholders in the biomedical research and development communities regarding the proposed policy. To this end, NIH sought comment not only from NIH grantees, but also from academic, not-for-profit, government, and private sector participants in biomedical research and development. In order to involve as many stakeholders as possible in the comment process, the proposed policy was advertised and comments solicited in a wide variety of venues. In addition to its publication on May 25, 1999, in the **Federal Register,** the proposed policy was made available on several different websites including the Federal Register Online, numerous NIH websites (Edison, NIH Office of Technology Transfer, NIH Office of Extramural Research and the NIH Director's Policy Forum), the Association of University Technology Managers (AUTM) website and Recombinant Capital's Signals Magazine. The proposed policy was also advertised on a variety of e-mail lists (including Techno-L) as well as in direct letters and e-mail to various stakeholders. In addition, the proposed policy was profiled in articles appearing in a variety of journals and magazines, including Science, Nature and Nature Biotechnology.

In response to the May 25 proposal, NIH received 45 letters, each of which contained one or more comments. Comments were received from academic institutions, scientific foundations, pharmaceutical companies, biotechnology companies (including providers of research instruments, biological reagents and genomic data), an industry trade association, professional societies, individual researchers and other individual commenters. Below is NIH's response to comments offered, organized by the section of the proposed policy to which they pertain.

Introduction

Several commenters suggested that sponsored research administrators be included within the target audience to which this policy is addressed. This suggestion has been adopted in the final policy.

Several commenters suggested that the policy is a de facto regulation and should either be promulgated in accordance with regulatory process or withdrawn. Several other commenters suggested that as a policy the Principles/Guidelines are not enforceable as law and that NIH should issue them as a regulation to ensure compliance. The NIH does not believe that a regulation, enforceable as law, is required at this time to facilitate sharing and access to research tools for its Recipients. Although the final policy is issued as a grants policy, to be incorporated into the NIH Grants Policy Statement, the NIH has not precluded the possibility of engaging in the regulatory process if widespread problems continue in access to NIH-funded research tools by NIH Recipients. In addition, on a case-by-case basis, the expectations set forth in the Principles and Guidelines may be imposed as specific requirements of NIH funding awards where the Recipient has failed to demonstrate sufficient progress in implementing the Principles and Guidelines.

Some commenters suggested that the policy should not be applicable to all projects that include NIH grant funds, but that NIH should set a minimum level of NIH funding that would trigger application of the policy. NIH has determined that the establishment of such a threshold would not be consistent with NIH's objective of ensuring that broad availability of research tools.

One commenter expressed concern that the proposed policy, if applied to recipients of Small Business Innovation Research (SBIR) grants, would place SBIR recipients under conflicting directives. The commenter suggests that because SBIR recipients are required, as a condition of their grant, to focus on the commercialization of technology, they would be unable to disseminate

research tools with the minimal intellectual property encumbrances advocated by the proposed policy. SBIR Recipients, like other NIH grantees, are subject to the dual obligations of disseminating unique research resources while promoting utilization, commercialization and public availability of their inventions. The NIH does not see a conflict between these obligations. The NIH invites its SBIR grantees to consult with their project officer in the event they encounter difficulty in the interpretation or implementation of this policy, either in general or with respect to particular unique research resources developed under their grant.

Principles

1. Ensure Academic Freedom and Publication

Several commenters suggested that language be added to the guidelines to prohibit recipients from making coauthorship a condition of providing research tools. There appears to be general consensus within the research community that authorship is properly based upon significant intellectual contribution to the published paper. In most cases, simply making available research materials will not, in the absence of other contributions, justify coauthorship. (See *e.g.,* Responsible Science, Volume I: Ensuring the Integrity of the Research Process, Panel on Scientific Responsibility and the Conduct of Research, National Academy Press, 1992, p. 52). The final policy has been amended to reflect this view.

Several commenters expressed concern that the definition of ''Recipient'' in the proposed policy might not include individuals or entities receiving NIH funds through ''cooperative agreements.'' The policy is applicable to cooperative agreements and this has been clarified in the Principles and Guidelines.

2. Ensure Appropriate Implementation of the Bayh-Dole Act

Virtually all commenters requested clarification on how this policy would preserve incentives for the development and production of research tools that are ultimately sold as products to the research community. The policy has been clarified to ensure that where patent protection is necessary for development of a research tool as a potential product for sale and distribution to the research community. Recipients are not discouraged from seeking such protection, but should license the intellectual property in a manner that maximizes the potential for broad distribution of the research tool. The policy is not intended to require Recipient scientists to develop of maintain tools for widespread distribution, to discourage development of research tool products, nor to set or influence the price for research tools that are commercial products.

3. Minimize Administrative Impediments to Academic Research

One commenter suggested that reach-through rights should not be discouraged because they are sometimes helpful to Recipients by allowing them to obtain materials and equipment at reduced or nominal upfront cost. NIH is aware of this rationale for a Recipient agreeing to reach-through but finds that such practices contribute not only to specific restriction of access to subsequent tools arising out of the NIH-funded work, but also to the general proliferation of multiple ties and competing interests that is the source of the current access problems. NIH does not support the coupling of procurement with intellectual property rights and restrictions and expects Recipients to ensure that NIH-funded tools are not restricted as a result of such agreements. Therefore, Recipients should engage in such interactions on an infrequent, case-by-case, and highly controlled and monitored basis.

4. Ensure Dissemination of Research Resources Developed with NIH Funds

Numerous comments were received concerning the conditions under which research tools developed by recipients of NIH funds are to be transferred to for-profit entities. The comments received reflected the wide range of opinions present within the life sciences community on this point. On the one hand, some commenters urged that transfer of research tools to for-profit entities be carried out under the same terms as transfers to nonprofits/academic institutions. These commenters argue that because of the increasingly important role research tools play in the discovery and development of new therapeutic compounds, it is critical that these tools be made available to for-profit entities free of onerous contractual provisions. They argue that by adopting a transfer policy similar to that proposed for transfers to academic laboratories, NIH will ensure that the public will reap the benefit of its investment in government research in the form of new and improved pharmaceuticals. Other commenters opposed the general idea that the terms for transferring tools to for-profit entities should be identical to those for transfers of tools to academic and non-profit organizations. They argue that the fundamental differences in mission between for-profit entities and academic institutions justify different treatment with respect to the terms under which each obtains and uses tools.

In the final policy, the NIH has left considerable discretion to Recipients in determining how to achieve the principle of ensuring appropriate distribution of NIH-funded tools. As articulated by the policy, imposing reach-through royalty terms as a condition of use of a research tool is inconsistent with this principle. When transferring an NIH-funded research tool to a for-profit entity that intends to use the tool for its own internal purposes, Recipients are entitled to capture the value of their invention. Arrangements such as execution or annual fees are an appropriate way for Recipients to do so. Royalties on the sale of a final product that does not embody the tool, or other reach-through rights directed to a final product that does not embody the tool, discourage use of tools and are not appropriate in these circumstances. Royalties on the sale of final products are more appropriate to situations where a for-profit entity seeks to commercialize the tool, *e.g.,* by developing a marketable product or service, or incorporating the tool into a marketable product or service.

Appendix A Guidelines for Implementation

The final policy has been clarified with regard to NIH intent in attaching the more specific Guidelines to the general Principles. The Principles set forth the policy that NIH is issuing to its funding Recipients to assist them in fulfilling the dual obligations imposed by NIH grants policy with respect to the dissemination of unique research resources, and the Bayh-Dole Act with respect to utilization, commercialization and public availability of government funded inventions. These dual obligations must be thoughtfully managed. The Guidelines provide further information, model language, and suggested strategies for implementing the principles. The model language and strategies provided by the Guidelines are not intended as the sole means by which Recipients may implement the articulated Principles. It is the nature of advancing science and technology to present unique factual circumstances, and NIH expects that Recipients will determine the most appropriate means to achieve the Principles for unique technologies when the Guidelines do not provide a workable strategy.

Several commenters suggested that research tools be better defined and that more examples be used to assist in determining whether the policy should be applied and if so, what licensing strategy is appropriate. For example, one commenter suggested that the policy draw a distinction between ''broad platform technologies'' and ''product-specific technologies'' when determining whether an exclusive license is appropriate. The final policy provides clarification of the criteria that Recipients might apply in determining how to handle a particular technology.

One commenter requested that the definition of research tools be expanded to include diagnostic genetic tests performed with ''home-brew'' reagents. The commenter suggested that the patenting and exclusive licensing of such tests is having a deleterious effect on clinical education, clinical research, and patient care. NIH declines to expand the definition of research tools to include diagnostic genetic tests. Where such tests are patented and licensed to for-profit entities, academic medical centers wishing to use such licensed tests in their clinical programs should negotiate terms of use with the commercial licensee.

Many commenters were of the opinion that the thirty-day time limit for disclosure of research findings was too short. The final policy has been amended to state that a delay of 30–60 days is generally viewed as reasonable. This amendment is in accord with previous NIH guidance on sponsored research agreements, Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts, 59 FR 55674.

Comments were received in favor of adopting the Simple Letter Agreement as a free-standing, one page, uniform material transfer agreement. If used by the NIH intramural program and NIH grantees, commenters believe that the majority of transfers among and between not-for-profits and government laboratories would be greatly simplified. In response to specific comments, the Simple Letter Agreement has been significantly edited and updated. Recipients are encouraged to adopt the Simple Letter Agreement as their institution's model Material Transfer Agreement (MTA), and are expected to use the terms of the Simple Letter Agreement, or no more restrictive terms, for transfers of unpatented materials developed with NIH funding to other NIH grantees.

FOR FURTHER INFORMATION CONTACT: Ms. Barbara McGarey, J.D., NIH Office of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852–3804; Fax: (301) 402–3257; E-mail: NIHOTT@od.nih.gov.

Dated: December 14, 1999.

Maria C. Freire,

Director, Office of Technology Transfer, National Institutes of Health.

Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts

Introduction

The National Institutes of Health is dedicated to the advancement of health through science. As a public sponsor of biomedical research, NIH has a dual interest in accelerating scientific discovery and facilitating product development. In 1997, Dr. Harold Varmus, Director, NIH requested that a Working Group of the Advisory Committee to the Director look into problems encountered in the dissemination and use of unique research resources, the competing interests of intellectual property owners and research tool users, and possible NIH responses.[1] The Working Group found that intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development. One of the recommendations of the Working Group was that NIH issue guidance to its funding recipients to help them achieve the appropriate balance. That guidance is provided in this two-part document, consisting of Principles setting forth the fundamental concepts and Guidelines that provide specific information to patent and license professionals and sponsored research administrators for implementation. A copy of the full Report of the Working Group, with more detailed background information, is available at the NIH web site, www.nih.gov/welcome/forum, or from the NIH Office of the Director.

[1] The term ''unique research resource'' is used in its broadest sense to embrace the full range of tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines. The terms ''research tools'' and ''materials'' are used throughout this document interchangeably with ''unique research resources.'' Databases and materials subject to copyright, such as software, are also research tools in many contexts. Although the information provided here may be applicable to such resources, the NIH recognizes that databases and software present unique questions which cannot be fully explored in this document.

Principles

1. Ensure Academic Freedom and Publication

Academic research freedom based upon collaboration, and the scrutiny of research findings within the scientific community, are at the heart of the scientific enterprise. Institutions that receive NIH research funding through grants, cooperative agreements or contracts (''Recipients'') have an obligation to preserve research freedom, safeguard appropriate authorship, and ensure timely disclosure of their scientists' research findings through, for example, publications and presentations at scientific meetings. Recipients are expected to avoid signing agreements that unduly limit the freedom of investigators to collaborate and publish, or that automatically grant co-authorship or copyright to the provider of a material.

Reasonable restrictions on collaboration by academic researchers involved in sponsored research agreements with an industrial partner that avoid conflicting obligations to other industrial partners, are understood and accepted. Similarly, brief delays in publication may be appropriate to permit the filing of patent applications and to ensure that confidential information obtained from a sponsor or the provider of a research tool is not inadvertently disclosed. However, excessive publication delays or requirements for editorial control, approval of publications, or withholding of data all undermine the credibility of research results and are unacceptable.

2. Ensure Appropriate Implementation of the Bayh-Dole Act

When a Recipient's research work is funded by NIH, the activity is subject to various laws and regulations, including the Bayh-Dole Act (35 U.S.C. 200 *et seq.*). Generally, Recipients are expected to maximize the use of their research findings by making them available to the research community and the public, and through their timely transfer to industry for commercialization.

The right of Recipients to retain title to inventions made with NIH funds comes with the corresponding obligations to promote utilization, commercialization, and public availability of these inventions. The Bayh-Dole Act encourages Recipients to patent and license subject inventions as one means of fulfilling these obligations.

However, the use of patents and exclusive licenses is not the only, nor in some cases the most appropriate, means of implementing the Act. Where the subject invention is useful primarily as a research tool, inappropriate licensing practices are likely to thwart rather than promote utilization, commercialization and public availability of the invention.

In determining an intellectual property strategy for an NIH-funded invention useful primarily as a research tool, Recipients should analyze whether further research, development and private investment are needed to realize this primary usefulness. If it is not, the goals of the Act can be met through publication, deposit in an appropriate databank or repository, widespread non-exclusive licensing or any other number of dissemination techniques. Restrictive licensing of such an invention, such as to a for-profit sponsor for exclusive internal use, is antithetical to the goals of the Bayh-Dole Act.

Where private sector involvement is desirable to assist with maintenance, reproduction, and/or distribution of the tool, or because further research and development are needed to realize the invention's usefulness as a research tool, licenses should be crafted to fit the circumstances, with the goal of ensuring widespread and appropriate distribution of the final tool product. Exclusive licensing of such an invention, such as to a distributor that will sell the tool or to a company that will invest in the development of a tool from the nascent invention, can be consistent with the goals of the Bayh-Dole Act.

3. Minimize Administrative Impediments to Academic Research

Each iteration in a negotiation over the terms of a license agreement or materials transfer agreement delays the moment when a research tool may be put to use in the laboratory. Recipients should take every reasonable step to streamline the process of transferring their own research tools freely to other academic research institutions using either no formal agreement, a cover letter, the Simple Letter Agreement of the Uniform Biological Materials Transfer Agreement (UBMTA), or the UBMTA itself. The Appendix contains an updated free-standing version of the Simple Letter Agreement that is strongly encouraged for transfers of unpatented research materials among Recipients.

Where they have not already done so, Recipients should develop and implement clear policies which articulate acceptable conditions for acquiring resources, and refuse to yield on unacceptable conditions. NIH acknowledges the concern of some for-profit organizations that the concept of purely academic research may be diluted by the close ties of some not-for-profit organizations with for-profit entities, such as research sponsors and spin-off companies in which such organizations take equity. Of concern to would-be providers is the loss of control over a proprietary research tool that, once shared with a not-for-profit Recipient for academic research, results in commercialization gains to the providers' for-profit competitors. Recipients must be sensitive to this legitimate concern if for-profit organizations are expected to share tools freely.

For-profit organizations, in turn, must minimize the encumbrances they seek to impose upon not-for-profit organizations for the academic use of their tools. Reach-through royalty or product rights, unreasonable restraints on publication and academic freedom, and improper valuation of tools impede the scientific process whether imposed by a not-for-profit or for-profit provider of research tools. While these Principles are directly applicable only to recipients of NIH funding, it is hoped that other not-for-profit and for-profit organizations will adopt similar policies and refrain from seeking unreasonable restrictions or conditions when sharing materials.

4. Ensure Dissemination of Research Resources Developed With NIH Funds

Progress in science depends upon prompt access to the unique research resources that arise from biomedical research laboratories throughout government, academia, and industry. Ideally, these new resources flow to others who advance science by conducting further research. Prompt access can be accomplished in a number of ways, depending on the type of resource that has been developed, whether it has broad or specific uses, and whether it is immediately useful or private sector investment is needed to realize its usefulness. The goal is widespread, timely distribution of tools for further discovery. When research tools are used only within one or a small number of institutions, there is a great risk that fruitful avenues of research will be neglected.

Unique research resources arising from NIH-funded research are to be made available to the scientific research community. Recipients are expected to manage interactions with third parties that have the potential to restrict Recipients' ability to disseminate research tools developed with NIH funds.[2] For example, a Recipient might use NIH funds with funds from one or more third party sponsors, or acquire a research tool from a third party provider for use in an NIH-funded research project. Either situation may result in a Recipient incurring obligations to a third party that conflict with Recipient's obligations to the NIH. To avoid inconsistent obligations, Recipients are encouraged to share these Principles with potential co-sponsors of research projects and third party providers of materials.

Recipients should also examine and, where appropriate, simplify the transfer of materials developed with NIH funds to for-profit institutions for internal use by those institutions. NIH endorses distinguishing internal use by for-profit institutions from the right to commercial development and sale or provision of services. In instances where the for-profit institution is seeking access for internal use purposes, Recipients are encouraged to transfer research tools developed with NIH funding to such institutions without seeking option rights or royalties on the final product.

Summary

Access to research tools is a prerequisite to continuing scientific advancement. Ensuring broad access while preserving opportunities for product development requires thoughtful, strategic implementation of the Bayh-Dole act. The NIH urges Recipients to develop patent, license, and material sharing policies with this goal in mind, realizing both product development as well as the continuing availability of new research tools to the scientific community.

Appendix—Guidelines for Implementation

The following Guidelines provide specific information, strategies, and model language for patent and license professionals and sponsored research administrators at Recipient institutions to assist in implementing the Principles on Obtaining and Disseminating Biomedical Resources. Recipients are encouraged to use the strategies below, other strategies developed at their own institutions, or any other appropriate means of achieving the Principles.

[2] Research tools obtained or derived from human tissues constitute a special case. Certain restrictions on the use and further dissemination of such tools may be appropriate to ensure consistency with donor consent and human subjects protection. See 45 CFR Part 46.

Guidelines for Disseminating Research Resources Arising Out of NIH-Funded Research

Definition of Research Tools

The definition of research tools is necessarily broad, and it is acknowledged that the same material can have different uses, being a research tool in some contexts and a product in others. In determining how an NIH-funded resource that falls within the definition should be handled, Recipients should determine whether: (1) The Primary usefulness of the resource is as a tool for discovery rather than an FDA-approved product or integral component of such a product; (2) the resource is a broad, enabling invention that will be useful to many scientists (or multiple companies in developing multiple products), rather than a project or product-specific resource; and (3) the resource is readily useable or distributable as a tool rather than the situation where private sector involvement is necessary or the most expedient means for developing or distributing the resource. Recipients should ensure that their intellectual property strategy for resources fitting one or more of the above criteria enhances rather than restricts the ultimate availability of the resource. If Recipient believes private sector involvement is desirable to achieve this goal, Recipient should strategically license the invention under terms commensurate with the goal.

Use of Simple Letter Agreement

Recipients are expected to ensure that unique research resources arising from NIH-funded research are made available to the scientific research community. The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the UBMTA. In particular, Recipients are expected to use the Simple Letter Agreement provided below, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other Recipients for use in NIH-funded projects. If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercialization option rights, royalty reach-through, or product reach-through rights back to the provider are inappropriate.

Similarly, when for-profit entities are seeking access to NIH-funded tools for internal use purposes, Recipients should ensure that the tools are transferred with the fewest encumbrances possible. The Simple Letter Agreement may be expanded for use in transferring tools to for-profit entities, or simple internal use license agreements with execution or annual use fees may be appropriate.

Simple Letter Agreement for the Transfer of Materials

In response to RECIPIENT's request for the MATERIAL [insert description] _____ the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

1. The above MATERIAL is the property of the PROVIDER and is made available as a service to the research community.

2. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS.

3. The MATERIAL will be used for teaching or not-for-profit research purposes only.

4. The MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agree to make the MATERIAL available, under a separate Simple Letter Agreement to other scientists for teaching or not-for-profit research purposes only.

5. The RECIPIENT agrees to acknowledge the source of the MATERIAL in any publications reporting use of it.

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, Recipient assumes all liability for claims for damages against it by third parties which may arise from the use, storage or disposal of the Material except that, to the extent permitted by law, the Provider shall be liable to the Recipient when the damage is caused by the gross negligence or willful misconduct of the Provider.

7. The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations.

8. The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here: _____

The PROVIDER, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER will then send the MATERIAL.

Provider Information and Authorized Signature

Provider Scientist: _____
Provider Organization: _____
Address: _____
Name of Authorized Official: _____
Title of Authorized Official: _____
Certification of Authorized Official: This Simple Letter Agreement ____ has ____ has not [check one] been modified. If modified, the modification are attached.

_____
(Signature of Authorized Official) (Date)

Recipient Information and Authorized Signature

Recipient Scientist: _____
Recipient Organization: _____
Address: _____
Name of Authorized Official: _____
Title of Authorized Official: _____
Signature of Authorized Official: _____
Date: _____
Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

_____
(Recipient Scientist) (Date)

Ensuring Consistent Obligations

Recipients must ensure that obligations to other sources of funding of projects in which NIH funds are used are consistent with the Bayh-Dole Act and NIH funding requirements. Unique research resources generated under such projects are expected to be made available to the research community. Recipients are encouraged to share these Guidelines with potential co-sponsors. Any agreements covering projects in which NIH funds will be used along with other funds are expected to contain language to address the issue of dissemination of unique research resources. Examples of possible language follow. The paragraphs are presented in a ''mix and match'' format:

''The project covered by this agreement is supported with funding from the National Institutes of Health. Provider agrees that upon publication, unpatented unique research resources arising out of this project may be freely distributed.''

''In the event an invention is primarily useful as a research tool, any option granted shall either be limited to a non-exclusive license or the terms of any resulting exclusive license shall include provisions that ensure that the research tool will be

available to the academic research community on reasonable terms.''

''Provider agrees that Recipient shall have the right to make any materials and inventions developed by Recipient in the course of the collaboration (including materials and inventions developed jointly with Provider, but not including any Provider materials (or parts thereof) or Provider sole inventions available to other scientists at not-for-profit organizations for use in research, subject to Provider's independent intellectual property rights.''

''Subject to Recipient's obligations to the U.S. government, including 37 CFR Part 401, the NIH Grants Policy Statement, and the NIH Guidelines for Obtaining and Disseminating Biomedical Research Resources, Recipient grants to Sponsor the following rights: * * *''

Limiting Exclusive Licenses to Appropriate Field of Use

Exclusive licenses for research tools (where no further research and development is needed to realize the invention's usefulness as a tool) should generally be avoided except in cases where the licensee undertakes to make the research tool widely available to researchers through unrestricted sale, or the licensor retains rights to make the research tool widely available. When an exclusive license is necessary to promote investment in commercial applications of a subject invention that is also a research tool, the Recipient should ordinarily limit the exclusive license to the commercial field of use, retaining rights regarding use and distribution as a research tool. Examples of possible language include:

''Research License'' means a nontransferable, nonexclusive license to make and to use the Licensed Products or Licensed Processes as defined by the Licensed Patent Rights for purposes of research and not for purposes of commercial manufacture, distribution, or provision of services, or in lieu of purchase, or for developing a directly related secondary product that can be sold. Licensor reserves the right to grant such nonexclusive Research Licenses directly or to require Licenses on reasonable terms. The purpose of this Research License is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however, Licensor shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of the materials.''

''Licensor reserves the right to provide the Biological Materials and to grant licenses under Patent Rights to not-for-profit and governmental institutions for their internal research and scholarly use.''

''Notwithstanding anything to the contrary in this agreement, Licensor shall retain a paid-up, nonexclusive, irrevocable license to practice, and to sublicense other not-for-profit research organizations to practice, the Patent Rights for internal research use.''

''The grant of rights provided herein is subject to the rights of the United States government pursuant to the Bayh-Dole Act and is limited by the right of the Licensor to use Patent Rights for its own research and educational purposes and to freely distribute Materials to not-for-profit entities for internal research purposes.''

''Licensor reserves the right to supply any or all of the Biological materials to academic research scientists, subject to limitation of use by such scientists for research purposes and restriction from further distribution.''

''Licensor reserves the right to practice under the Patent Rights and to use and distribute to third parties the Tangible Property for Licensor's own internal research purposes.''

Guidelines for Acquiring Research Resources for Use in NIH-Funded Research

Prompt Publication

Agreements to acquire materials for use in NIH-funded research are expected to address the timely dissemination of research results. Recipients should not agree to significant publication delays, any interference with the full disclosure of research findings, or any undue influence on the objective reporting of research results. A delay of 30–60 days to allow for patent filing or review for confidential proprietary information is generally viewed as reasonable.

Definition of Materials

Under the Bayh-Dole Act and its implementing regulations, agreements to acquire materials for use in NIH-funded projects cannot require that title to resulting inventions be assigned to the provider. For this reason, definitions of ''materials'' that include all derivatives or modifications are unacceptable. Other unacceptable variations include definitions of ''materials'' that include any improvements, or any other materials that could not have been made without the provided material. Conversely, it is important for providers of materials to be aware that a Recipient does not gain any ownership or interest in a provider's material by virtue of the Recipient using the material in an NIH-funded activity. Examples of acceptable definitions for ''materials'' include:

'' 'Materials' means the materials provided as specified in this document.''

'' 'Materials' means the materials provided as specified in this document. Materials may also include Unmodified Derivatives of the materials provided, defined as substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original materials, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line.''

'' 'Materials' means the materials provided as specified in this document. Materials may also include Progeny and Unmodified Derivatives of the materials provided. Progeny is an unmodified descendant from the original material, such as virus from virus, cell from cell, or organism from organism. Unmodified Derivatives are substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original material, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line.''

'' 'Materials' means the materials being transferred as specified in this document. Materials shall not include: (a) Modifications, or (b) other substances created by the recipient through the use of the Material which are not Modifications, Progeny, or Unmodified Derivatives. Progeny is an unmodified descendant from the Material, such as virus from virus, cell from cell, or organism from organism. Unmodified Derivatives are substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original Material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original Material, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line.'' [Source: Uniform Biological Materials Transfer Agreement; terms defined therein]

Ensuring Consistent Obligations

Recipients are expected to avoid signing agreements to acquire research tools that are likely to restrict Recipients' ability to promote broad dissemination of additional tools that may arise from the research. This might occur when an agreement gives a provider an exclusive license option to any new intellectual property arising out of the project. A new transgenic mouse developed during the project could fall under this license option and become unavailable to third party scientists as a result. Examples of agreements to examine include material transfer agreements (MTAs), memoranda of understanding (MOU), research or collaboration agreements, and sponsored research agreements. Recipients should consider adopting standard language to place in such agreements to address this issue. The following are examples of possible language to include in MTAs, sponsored research agreements, and other agreements that either acquire materials from or co-mingle funds with non-government sources. The paragraphs are presented in a ''mix and match'' format:

''The project covered by this agreement is supported with funding from the National Institutes of Health. Provider agrees that after publication, unpatented unique research resources arising out of this project may be freely distributed.''

''In the event an invention is primarily useful as a research tool, any option granted shall either be limited to a non-exclusive license or the terms of any resulting exclusive license shall include provisions which insure that the research tool will be available to the academic research community on reasonable terms.''

''Provider agrees that Recipient shall have the right to make any materials and inventions developed by Recipient in the course of the collaboration (including materials and inventions developed jointly with Provider, but not including any Provider materials (or parts thereof) or Provider sole inventions available to other scientists at not-for-profit organizations for use in research, subject to Provider's independent intellectual property rights.''

''Subject to Recipient's obligations to the U.S. government, including 37 CFR Part 401, the NIH Grants Policy Statement, and the NIH Guidelines for Obtaining and Disseminating Biomedical Research Resources, Recipient grants to Sponsor the following rights: * * *''

Grantbacks and Option Rights

• Agreements to acquire materials from for-profit entities for use in NIH-funded research may provide a grant back of non-exclusive, royalty-free rights to the provider to use improvements and new uses of the material that, if patented, would infringe any patent claims held by the provider. They may also provide an option for an exclusive or non-exclusive commercialization license to new inventions arising directly from use of the material. These should be limited to circumstances where the material sought to be acquired is unique, such as a patented proprietary material, and not reasonably available from any other source. A non-exclusive ''grant-back'' might be used, for example, to protect a for-profit entity that provides a proprietary compound from being blocked from using new uses or improvements of that compound discovered during the NIH-funded project. In providing license options, Recipients must ensure that licenses granted to providers under such options are consistent with Bayh-Dole requirements, including the preference for U.S. industry requirements and reservation of government rights under 47 CFR part 401.

• In determining the scope of license or option rights that are granted in advance to a provider of materials, Recipient should balance the relative value of the provider's contributions against the value of the rights granted, cost of the research, and importance of the research results. The rights granted to providers should be limited to inventions that have been made directly through the use of the materials provided. In addition, Recipients should reserve the right to negotiate license terms that will ensure: (1) continuing availability to the research community if the new invention is a unique research resource; (2) that the provider has the technical and financial capability and commitment to bring all potential applications to the marketplace in a timely manner; and (3) that if an exclusive license is granted, the provider will provide a commercial development plan and agree to benchmarks and milestones for any fields of use granted.

• It is expected that agreements to acquire NIH-funded materials from not-for-profit entities for use in NIH-funded research will not include commercialization option rights, royalty reach-through, or product reach-through rights back to the provider. Such materials should be acquired under the Simple Letter Agreement or UBMTA, or, if the materials are patented,a simple license agreement that does not request reach-through to either future products or royalties. If the providing not-for-profit organization is constrained in sharing the material due to a pre-existing sponsored research agreement or license, NIH expects that not-for-profit provider to negotiate a suitable resolution with the private research sponsor or licensee. The co-mingling of NIH and sponsored research funds is allowed, however, Recipient is responsible for ensuring that conditions on the use of the sponsored funds do not interfere with the open dissemination of research tools.

[FR Doc. 99–33292 Filed12–22–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Center for Substance Abuse Prevention; Notice of Meeting

Pursuant to Public Law 92–463, notice is hereby given of the meeting of the Center for Substance Abuse Prevention (CSAP) National Advisory Council in January 2000.

The meeting will be open. The agenda will include presentations and updates on CSAP's programs, the SAMHSA Administrator's Report, a CSAP budget update, and discussions of administrative matters and announcements. If anyone needs special accommodations for persons with disabilities, please notify the contact listed below.

A summary of this meeting, a roster of committee members, and substantive program information may be obtained from the contact listed below.

Committee Name: Center for Substance Abuse Prevention National Advisory Council

Meeting Dates: January 10, 2000, 9 a.m.–5 p.m. (Open)

Place: Bethesda Marriott Hotel, 5151 Pooks Hill Road, Bethesda, Maryland 20841.

Contact: Yuth Nimit, Ph.D., 5600 Fishers Lane, Rockwall II Building, Suite 901, Rockville, Maryland 20857, Telephone: (301) 443–8455.

Dated: December 17, 1999.

Sandra Stephens,

Acting Committee Management Officer, Substance Abuse and Mental Health Services Administration.

[FR Doc. 99–33306 Filed 12–22–99; 8:45 am]

BILLING CODE 4162–20–P

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

[Docket No. FR–4432–N–51]

Federal Property Suitable as Facilities to Assist the Homeless

AGENCY: Office of the Assistant Secretary for Community Planning and Development, HUD.

ACTION: Notice.

SUMMARY: This Notice identifies unutilized, underutilized, excess, and surplus Federal property reviewed by HUD for suitability for possible use to assist the homeless.

FOR FURTHER INFORMATION CONTACT: Clifford Taffet, room 7266, Department of Housing and Urban Development, 451 Seventh Street SW, Washington, DC 20410; telephone (202) 708–1234; TTY number for the hearing- and speech-impaired (202) 708–2565 (these telephone numbers are not toll-free), or call the toll-free Title V information line at 1–800–927–7588.

SUPPLEMENTARY INFORMATION: In accordance with 24 CFR Part 581 and section 501 of the Stewart B. McKinney Homeless Assistance Act (42 U.S.C. 11411), as amended, HUD is publishing this Notice to identify Federal buildings and other real property that HUD has reviewed for suitability for use to assist the homeless. The properties were reviewed using information provided to HUD by Federal landholding agencies regarding unutilized and underutilized buildings and real property controlled

UNIFORM BIOLOGICAL MATERIAL TRANSFER AGREEMENT FINALIZED

NIH GUIDE, Volume 24, Number 14, April 14, 1995

P.T.

Keywords:

Public Health Service

National Institutes of Health

After consideration of public comments, the NIH, as designated lead PHS agency for technology transfer activities, has issued the final version of the Uniform Biological Material Agreement ("UBMTA") to be used by participating public and nonprofit organizations, an implementing letter to memorialize individual exchanges of materials under the UBMTA, and a simple letter agreement for transferring nonproprietary biological materials among public and nonprofit organizations. For-profit organizations may also choose to adopt these agreements as well. The PHS recommends that the UBMTA be considered for general use in the exchange of materials for research purposes among public and nonprofit entities. Background, discussion of public comments received, and the final agreement were published in the Federal Register on March 8, 1995 (FR 60 12771). The complete text of this notice is also available on the electronic edition of the NIH Guide to Grants and Contracts available via anonymous ftp from ftp.cu.nih.gov.

INQUIRIES

If you would like a copy of the Master Agreement for execution, an Implementing Letter, or a Simple Letter Agreement for Transfer of Non-Proprietary Biological Material, please contact:

Penny Dalziel
AUTM
71 East Avenue, Suite S
Norwalk, CT 06851-4903
Telephone: 203/852-7168
Fax: 203/838-5714
Email: autm@ao1.com

Technical questions may be addressed to:

Carol Lavrich
Technology Licensing Specialist
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard, Suite 325
Rockville, MD 20852-3804
Telephone: 301/496-7735 ext 287
Fax: 301/402-0220
Email: lavrichc@od6100m1.od.nih.gov

Full Text N2

UNIFORM BIOLOGICAL MATERIAL TRANSFER AGREEMENT: DISCUSSION OF PUBLIC COMMENTS RECEIVED; PUBLICATION OF THE FINAL FORMAT OF THE AGREEMENT

(as published in the Federal Register, March 8, 1995)

NIH GUIDE, Volume 24, Number 14, April 14, 1995

P.T.

Keywords:

AGENCY: National Institutes of Health (NIH), Public Health Service (PHS), DHHS

ACTION: Notice

SUMMARY: Following consideration of public comments, the NIH, as designated lead PHS agency for technology transfer activities, is issuing the final version of the Uniform Biological Materials Agreement ("UBMTA") to be used by participating public and nonprofit organizations, an implementing letter to memorialize individual exchanges of materials under the UBMTA, and a simple letter agreement for transferring nonproprietary biological materials among public and nonprofit organizations. For-profit organizations may also choose to adopt these agreements as well. The PHS recommends that the UBMTA be considered for general use in the exchange of materials for research purposes among public and nonprofit entities.

FOR FURTHER INFORMATION CONTACT: Carol C. Lavrich, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852-3804, phone: 301-496-7735 ext. 287, fax: 301-402-0220

BACKGROUND: Open access to the results of federally-funded research is a cornerstone of PHS's research policy. In the case of many research projects, this includes not only access to information provided through publications, but also access to biological research materials necessary to replicate or build on the initial results. Frequently, the exchange of research materials between scientists in separate organizations involves case-by-case negotiation of material transfer agreements ("MTAs"). In order to guide and facilitate the increasing number of such transfers, PHS issued in 1988, a "Policy Relating to Distribution of Unique Research Resources Produced with PHS Funding" (NIH Guide for Grants and Contracts, Vol. 17, No. 29, September 16, 1988: pg. 1; also published at pp. 8-25-8-26 of the PHS Grants Policy Statement, DHHS Publication No. (OASH) 94- 50,000 (Rev.) April 1, 1994. This was followed in 1989 by adoption of a standard Material Transfer Agreement form for use by PHS scientists. MTAs are important because they require the recipient to exercise care in the handling of the materials, to maintain control over the distribution of the materials, to acknowledge the provider in publications, and to follow relevant PHS guidelines relating to recombinant DNA, protection of human subjects in research, and the use of animals. However, while most other organizations have adopted some standard material transfer agreement form, they are not all consistent.

ISSUE: Several issues have affected the sharing of research materials. These include delays in sharing of materials while conducting unnecessarily extensive negotiations on individual MTAs, required grants of invention rights to improvements to the materials or to inventions made using the materials, and required approval for publication. The negotiation of these complex issues has resulted in significant delays in sharing materials, undue administrative barriers to sharing, and in some cases, lack of availability of materials for further research by federal grantees. (For reports and discussion of these issues, please refer to The New Biologist, Vol. 2, No. 6, June 1990: pp 495- 497; and SCIENCE, Vol. 248, 25 May, 1990: pp 952-957).

PROPOSAL: The PHS, in conjunction with representatives of academia and industry, has coordinated the development of a proposed uniform biological material transfer agreement ("UBMTA") to address concerns about contractual obligations imposed by some MTAs and to simplify the process of sharing proprietary materials among public and nonprofit organizations. Since 1990, the Association of University Technology Managers ("AUTM"), and many individuals representing universities, law firms, and industry, have played leadership roles in furthering the development of common materials sharing practices. The consistent use of the UBMTA by public and nonprofit organizations could reduce the administrative burden of sharing materials as investigators come to rely on common acceptance of its terms by cooperating organizations.

The PHS recommends that the UBMTA be considered for general use in the exchange of materials for research purposes among public and nonprofit organizations. For-profit organizations may also choose to adopt this agreement as well. While use of the UBMTA may not be appropriate for every material transfer, if used for the majority of transfers, it could set standards for materials sharing that would be of long-term benefit to the research enterprise and to the public health.

As a further suggestion to simplify the process of materials sharing, it is proposed that the UBMTA be approved at the organizational level, and handled in a master agreement or treaty format, so that individual transfers could be made with reference to the UBMTA, without the need for separate negotiation of an individual document to cover each transfer. As a result, transfers of biological materials would be accomplished by an Implementing Letter (see sample) containing a description of the material and a statement indicating that the material was being transferred in accordance with the terms of the UBMTA. The Implementing Letter would be executed by the provider scientist, the recipient scientist, and any other authorized official(s) of the provider or recipient organization who might be required to sign on behalf of the organization. Thus, sharing of materials between organizations, each of which had executed the UBMTA, would be significantly simplified. At the same time, any organization would retain the option to handle specific material with unusual commercial or research value on a customized basis. Thus, the use of the UBMTA would not be mandatory, even for signatory organizations. Administration of the signatory process also may be organization-specific. For example, organizational policies may require additional, or fewer, signatures.

For non-proprietary materials, a Simple Letter Agreement also has been developed, which incorporates many of the same principles as the UBMTA. This Simple Letter Agreement also could be used where the organizations have not agreed to the UBMTA.

On behalf of PHS, NIH published the full text of the proposed version of the UBMTA, the draft Implementing Letter, and the draft Simple Letter Agreement in the Federal Register on June 21, 1994, and invited public comment. NIH received thirteen written comments from universities, research organizations, and various associations. The primary concerns raised by respondents and the NIH response to these comments are described in the comment section below.

COMMENTS: The vast majority of the respondents were extremely supportive of the UBMTA concept as a means of simplifying and expediting biological material transfers among public and nonprofit organizations. Several respondents suggested that a comparable agreement be developed for transfers between for- profit and nonprofit organizations. The PHS fully supports this idea and

recognizes the importance of streamlining this type of agreement with industry. The NIH, in conjunction with the working group listed above, developed a proposed model for UBMTA transfers from industry to nonprofit organizations which was circulated to AUTM membership on December 31, 1992. This was an adaptation of the original UBMTA format which grants the industrial provider an option to negotiate a license agreement to inventions made through the use of the provided material. It should be noted that government agencies will not be able to use this format unless a Cooperative Research and Development Agreement ("CRADA") is negotiated because of limitations in statutory authority to provide licenses or options to license intellectual property in other types of agreements. No format was ultimately created by the working group for the transfer of material from nonprofit organizations to industry because it was viewed as being essentially a license negotiation. Most organizations have license agreement formats for internal use of biological materials by commercial organizations, as well as for commercial sale of biological materials. The PHS will be soliciting further public commentary on the proposed model for UBMTA transfers from industry to nonprofit organizations.

Several respondents indicated that some of the UBMTA definitions were confusing. As appropriate, clarifications have been made. In particular, the definition relating to "Modifications" has been refined so that it is clear that Modifications are developed by the Recipient and contain or incorporate the Material. While the Modifications are owned by the Recipient who can license them for commercial use, this new use also may require a second commercial license or other evidence of agreement from the Provider since the Modifications incorporate the Material. The UBMTA also acknowledges that there may be other substances created by the Recipient through the use of the Material which are not Modifications, Progeny, or Unmodified Derivatives of the Material, and are owned by the Recipient, who is free to license them. The UBMTA does not provide for any type of "reach-through" rights for the Provider of the Material, i.e. property rights in products developed by the Recipient through the use of the transferred material. Several definitions of "nonprofit organization" were proposed, and the final definition used was taken directly from the implementing regulations to the Bayh-Dole Act (37 CFR Part 401). We have also instituted a definition of Commercial Purposes to provide a clear distinction between academic research and activities which are considered commercial.

Other issues raised by respondents fell into two areas: issues regarding confidentiality with respect to protection of intellectual property rights, and issues regarding organizational policy variance on signature requirements from the suggested UBMTA signature requirements:

1) Confidentiality Issues

Some respondents were concerned that the requirement for the Provider to provide the Recipient with specific information regarding patent status of the Material might impair an organization's ability to obtain patent protection and questioned the necessity for the Recipient to obtain such information. The PHS agrees that the provision of such information is not necessary and would create an additional administrative burden that would be inconsistent with the primary purpose of the UBMTA. We also agree that any commercial use or improper disclosure on the part of the Recipient could impair the Provider~s ability to obtain suitable patent protection. Therefore, we have removed the requirement for the Provider to inform the Recipient about patent status and have included a provision that the Material may be the subject of a patent application. However, the Recipient is bound to inform the Provider upon filing patent

applications which claim Modifications or method(s) of manufacture or use(s) of the Material so that the Provider may determine whether it believes joint inventorship is appropriate. The requirement to divulge the Provider's prior grant of rights to a third party (other than the customary rights granted to the federal government), that would substantially affect Recipient, has been eliminated since the agreement specifies that this transfer is for teaching and academic research purposes and that the Provider is under no obligation to widen the rights granted.

2) Signature Requirement Issues

Some respondents were concerned that their organizational polices with respect to signing MTAs are different than those suggested in the UBMTA Implementing Letter. An organization may require an additional signature of an authorized official of the Recipient organization if the signatory scientist is not legally authorized to bind the organization. In this case, the legally binding signature of the authorized official of the Recipient organization would provide assurance to the Provider organization that the Recipient organization is a signatory to the UBMTA. This assurance is critical because if the Recipient organization is not a party to the UBMTA, it may not be bound by the terms of the UBMTA. The signatures of the scientists provide a necessary record for both organizations of the transfer of the Material. Of course, organizations are free to develop their own signatory policies regarding the UBMTA.

We hope to get practical guidance and constructive feedback from scientists and technology transfer professionals as they begin to use the UBMTA. It is anticipated that the UBMTA will be a "living" document which will be further refined and streamlined over time. Many of the definitions were intensively debated throughout the course of drafting the UBMTA and it is expected that they will be sharpened over time through use. We attempted to emphasize a fair allocation of rights between the Provider and the Recipient and had to draw lines especially in the definitions of Modifications and Commercial Purposes. The use of the UBMTA over time will ultimately determine whether the right decisions were made.

The Association of University Technology Managers ("AUTM") will be providing assistance in implementation of the UBMTA among its members and nonprofit organizations by notifying members of its availability in its newsletter, providing signature copies of the agreement at its annual meeting, assisting with training regarding material transfers, and maintaining a master list of signatories to the UBMTA. We anticipate that the master list of signatories will be published in the Federal Register annually. In order for AUTM to compile a master list of signatories, organizations should return an executed copy of the UBMTA Master Agreement to: The UBMTA Project, AUTM Headquarters, 71 East Avenue, Suite S, Norwalk, CT 06851-4903. A read only version of the signatory list will be made available on the Internet. A copy of this announcement also will be appearing in the NIH Guide For Grants and Contracts.

Complete texts of the final version of the UBMTA, the Implementing Letter, and the Simple Letter Agreement follow in the Appendix.

MASTER AGREEMENT REGARDING USE OF THE UNIFORM BIOLOGICAL MATERIAL TRANSFER AGREEMENT (dated March 8, 1995)

Upon execution of an Implementing Letter in the form attached which specifies the materials to be transferred, this organization agrees

to be bound by the terms of the attached Uniform Biological Material Transfer Agreement ("UBMTA") published in the Federal Register on March 8, 1995.

Attachments: UBMTA Implementing Letter
Organization:_____
Address: _____
_____ Authorized
Official:_____ Title:
_____ Signature:
_____ Date: _____

Please return an executed copy of this Master Agreement to: The UBMTA Project, Association of University Technology Managers (AUTM), 71 East Avenue, Suite S, Norwalk, CT 06851-4903. AUTM will be maintaining signed originals and the official list of signatory organizations.

THE UNIFORM BIOLOGICAL MATERIAL TRANSFER AGREEMENT
(dated March 8, 1995)

I.Definitions:

1.PROVIDER: Organization providing the ORIGINAL MATERIAL. The name and address of this party will be specified in an implementing letter.

2.PROVIDER SCIENTIST: The name and address of this party will be specified in an implementing letter.

3.RECIPIENT: Organization receiving the ORIGINAL MATERIAL. The name and address of this party will be specified in an implementing letter.

4.RECIPIENT SCIENTIST: The name and address of this party will be specified in an implementing letter.

5.ORIGINAL MATERIAL: The description of the material being transferred will be specified in an implementing letter.

6.MATERIAL: ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES. The MATERIAL shall not include: (a) MODIFICATIONS, or (b) other substances created by the RECIPIENT through the use of the MATERIAL which are not MODIFICATIONS, PROGENY, or UNMODIFIED DERIVATIVES.

7.PROGENY: Unmodified descendant from the MATERIAL, such as virus from virus, cell from cell, or organism from organism.

8.UNMODIFIED DERIVATIVES: Substances created by the RECIPIENT which constitute an unmodified functional subunit or product expressed by the ORIGINAL MATERIAL. Some examples include: subclones of unmodified cell lines, purified or fractionated subsets of the ORIGINAL MATERIAL, proteins expressed by DNA/RNA supplied by the PROVIDER, or monoclonal antibodies secreted by a hybridoma cell line.

9.MODIFICATIONS: Substances created by the RECIPIENT which contain/incorporate the MATERIAL.

10.COMMERCIAL PURPOSES: The sale, lease, license, or other transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. COMMERCIAL PURPOSES shall also include uses of the MATERIAL or MODIFICATIONS by any organization, including RECIPIENT, to perform contract research, to screen compound libraries, to produce or manufacture products for general sale, or to conduct research

activities that result in any sale, lease, license, or transfer of the MATERIAL or MODIFICATIONS to a for-profit organization. However, industrially sponsored academic research shall not be considered a use of the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES per se, unless any of the above conditions of this definition are met.

11.NONPROFIT ORGANIZATION(S): A university or other institution of higher education or an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1954 (26 U.S.C. 501(c)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)) or any nonprofit scientific or educational organization qualified under a state nonprofit organization statute. As used herein, the term also includes government agencies.

II.Terms and Conditions of this Agreement:

1.The PROVIDER retains ownership of the MATERIAL, including any MATERIAL contained or incorporated in MODIFICATIONS.

2.The RECIPIENT retains ownership of: (a) MODIFICATIONS (except that, the PROVIDER retains ownership rights to the MATERIAL included therein), and (b) those substances created through the use of the MATERIAL or MODIFICATIONS, but which are not PROGENY, UNMODIFIED DERIVATIVES or MODIFICATIONS (i.e., do not contain the ORIGINAL MATERIAL, PROGENY, UNMODIFIED DERIVATIVES). If either 2 (a) or 2 (b) results from the collaborative efforts of the PROVIDER and the RECIPIENT, joint ownership may be negotiated.

3.The RECIPIENT and the RECIPIENT SCIENTIST agree that the MATERIAL:
(a)is to be used solely for teaching and academic research purposes;
(b)will not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects without the written consent of the PROVIDER;
(c)is to be used only at the RECIPIENT organization and only in the RECIPIENT SCIENTIST's laboratory under the direction of the RECIPIENT SCIENTIST or others working under his/her direct supervision; and
(d)will not be transferred to anyone else within the RECIPIENT organization without the prior written consent of the PROVIDER.

4.The RECIPIENT and the RECIPIENT SCIENTIST agree to refer to the PROVIDER any request for the MATERIAL from anyone other than those persons working under the RECIPIENT SCIENTIST's direct supervision. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agrees to make the MATERIAL available, under a separate implementing letter to this Agreement or other agreement having terms consistent with the terms of this Agreement, to other scientists (at least those at NONPROFIT ORGANIZATION(S)) who wish to replicate the RECIPIENT SCIENTIST's research; provided that such other scientists reimburse the PROVIDER for any costs relating to the preparation and distribution of the MATERIAL.

5.(a)The RECIPIENT and/or the RECIPIENT SCIENTIST shall have the right, without restriction, to distribute substances created by the RECIPIENT through the use of the ORIGINAL MATERIAL only if those substances are not PROGENY, UNMODIFIED DERIVATIVES, or MODIFICATIONS.

(b)Under a separate implementing letter to this Agreement (or an agreement at least as protective of the PROVIDER's rights), the RECIPIENT may distribute MODIFICATIONS to NONPROFIT ORGANIZATION(S) for research and teaching purposes only.

(c)Without written consent from the PROVIDER, the RECIPIENT and/or the RECIPIENT SCIENTIST may NOT provide MODIFICATIONS for COMMERCIAL PURPOSES. It is recognized by the RECIPIENT that such COMMERCIAL PURPOSES may require a commercial license from the PROVIDER and the

PROVIDER has no obligation to grant a commercial license to its ownership interest in the MATERIAL incorporated in the MODIFICATIONS. Nothing in this paragraph, however, shall prevent the RECIPIENT from granting commercial licenses under the RECIPIENT's intellectual property rights claiming such MODIFICATIONS, or methods of their manufacture or their use.

6.The RECIPIENT acknowledges that the MATERIAL is or may be the subject of a patent application. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the RECIPIENT under any patents, patent applications, trade secrets or other proprietary rights of the PROVIDER, including any altered forms of the MATERIAL made by the PROVIDER. In particular, no express or implied licenses or other rights are provided to use the MATERIAL, MODIFICATIONS, or any related patents of the PROVIDER for COMMERCIAL PURPOSES.

7.If the RECIPIENT desires to use or license the MATERIAL or MODIFICATIONS for COMMERCIAL PURPOSES, the RECIPIENT agrees, in advance of such use, to negotiate in good faith with the PROVIDER to establish the terms of a commercial license. It is understood by the RECIPIENT that the PROVIDER shall have no obligation to grant such a license to the RECIPIENT, and may grant exclusive or non-exclusive commercial licenses to others, or sell or assign all or part of the rights in the MATERIAL to any third party(ies), subject to any pre-existing rights held by others and obligations to the Federal Government.

8.The RECIPIENT is free to file patent application(s) claiming inventions made by the RECIPIENT through the use of the MATERIAL but agrees to notify the PROVIDER upon filing a patent application claiming MODIFICATIONS or method(s) of manufacture or use(s) of the MATERIAL.

9.Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. The PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

10.Except to the extent prohibited by law, the RECIPIENT assumes all liability for damages which may arise from its use, storage or disposal of the MATERIAL. The PROVIDER will not be liable to the RECIPIENT for any loss, claim or demand made by the RECIPIENT, or made against the RECIPIENT by any other party, due to or arising from the use of the MATERIAL by the RECIPIENT, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the PROVIDER.

11.This agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the MATERIAL or the MODIFICATIONS. The RECIPIENT SCIENTIST agrees to provide appropriate acknowledgement of the source of the MATERIAL in all publications.

12.The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations, including Public Health Service and National Institutes of Health regulations and guidelines such as, for example, those relating to research involving the use of animals or recombinant DNA.

13.This Agreement will terminate on the earliest of the following dates: (a) when the MATERIAL becomes generally available from third

parties, for example, through reagent catalogs or public depositories, or (b) on completion of the RECIPIENT's current research with the MATERIAL, or (c) on thirty (30) days written notice by either party to the other, or (d) on the date specified in an implementing letter, provided that:

(i)if termination should occur under 13(a), the RECIPIENT shall be bound to the PROVIDER by the least restrictive terms applicable to the MATERIAL obtained from the then-available sources; and

(ii)if termination should occur under 13(b) or (d) above, the RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVIDER, return or destroy any remaining MATERIAL. The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as they apply to MODIFICATIONS; and

(iii)in the event the PROVIDER terminates this Agreement under 13(c) other than for breach of this Agreement or for cause such as an imminent health risk or patent infringement, the PROVIDER will defer the effective date of termination for a period of up to one year, upon request from the RECIPIENT, to permit completion of research in progress. Upon the effective date of termination, or if requested, the deferred effective date of termination, RECIPIENT will discontinue its use of the MATERIAL and will, upon direction of the PROVIDER, return or destroy any remaining MATERIAL. The RECIPIENT, at its discretion, will also either destroy the MODIFICATIONS or remain bound by the terms of this agreement as they apply to MODIFICATIONS.

14.Paragraphs 6, 9, and 10 shall survive termination.

15.The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested by the PROVIDER, the amount will be indicated in an implementing letter.

IMPLEMENTING LETTER

The purpose of this letter is to provide a record of the biological material transfer, to memorialize the agreement between the PROVIDER SCIENTIST (identified below) and the RECIPIENT SCIENTIST (identified below) to abide by all terms and conditions of the Uniform Biological Material Transfer Agreement ("UBMTA") (dated March 8, 1995), and to certify that the RECIPIENT (identified below) organization has accepted and signed an unmodified copy of the UBMTA. The RECIPIENT organization's Authorized Official also will sign this letter if the RECIPIENT SCIENTIST is not authorized to certify on behalf of the RECIPIENT organization. The RECIPIENT SCIENTIST (and the Authorized Official of RECIPIENT, if necessary) should sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER SCIENTIST will forward the material to the RECIPIENT SCIENTIST upon receipt of the signed copy from the RECIPIENT organization.

Please fill in all of the blank lines below:

1.PROVIDER: Organization providing the ORIGINAL MATERIAL:

Organization:_____
Address: _____
_____

2.RECIPIENT: Organization receiving the ORIGINAL MATERIAL:
Organization:_____

Address: _____
_____

3.ORIGINAL MATERIAL (Enter description):
_____
_____
_____
_____
_____
_____

4. Termination date for this letter (optional):
_____

5.Transmittal Fee to reimburse the PROVIDER for preparation and distribution costs (optional). Amount:_____

This Implementing Letter is effective when signed by all parties. The parties executing this Implementing Letter certify that their respective organizations have accepted and signed an unmodified copy of the UBMTA, and further agree to be bound by its terms, for the transfer specified above.

PROVIDER SCIENTIST

Name:_____
Title:_____
Address:_____
_____
Signature:_____ Date: _____

RECIPIENT SCIENTIST

Name:_____
Title:_____
Address:_____
_____
Signature:_____ Date: _____

RECIPIENT ORGANIZATION CERTIFICATION

Certification: I hereby certify that the RECIPIENT organization has accepted and signed an unmodified copy of the UBMTA (May be the RECIPIENT SCIENTIST if authorized by the RECIPIENT organization):
Authorized Official:
_____
Title:
_____
Address:
_____
_____
Signature: _____
Date: _____

SIMPLE LETTER AGREEMENT FOR TRANSFER OF NON-PROPRIETARY BIOLOGICAL MATERIAL

PROVIDER:

Authorized Official: _____
Organization:_____
Address:_____
_____

RECIPIENT:

Authorized Official: ____

Organization:
____
Address:____
____

In response to the RECIPIENT's request for the BIOLOGICAL MATERIAL identified as
____
____
____
____
____
____
____
____
________,
the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the BIOLOGICAL MATERIAL:

1. The above BIOLOGICAL MATERIAL is the property of the PROVIDER and is made available as a service to the research community.

2. The BIOLOGICAL MATERIAL will be used for teaching and academic research purposes only.

3. The BIOLOGICAL MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the BIOLOGICAL MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agrees to make the BIOLOGICAL MATERIAL available, under a separate Simple Letter Agreement, to other scientists (at least those at nonprofit organizations or government agencies) who wish to replicate the RECIPIENT SCIENTIST's research.

4. The RECIPIENT agrees to acknowledge the source of the BIOLOGICAL MATERIAL in any publications reporting use of it.

5. Any BIOLOGICAL MATERIAL delivered pursuant to this Simple Letter Agreement is understood to be experimental in nature and may have hazardous properties. The PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE BIOLOGICAL MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Except to the extent prohibited by law, the RECIPIENT assumes all liability for damages which may arise from its use, storage or disposal of the BIOLOGICAL MATERIAL. The PROVIDER will not be liable to the RECIPIENT for any loss, claim or demand made by the RECIPIENT, or made against the RECIPIENT by any other party, due to or arising from the use of the MATERIAL by the RECIPIENT, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the PROVIDER.

6. The RECIPIENT agrees to use the BIOLOGICAL MATERIAL in compliance with all applicable statutes and regulations, including, for example, those relating to research involving the use of human and animal subjects or recombinant DNA.

7. The BIOLOGICAL MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here:_____

The RECIPIENT and the RECIPIENT SCIENTIST should sign both copies of this letter and return one signed copy to the PROVIDER SCIENTIST. The PROVIDER will then forward the BIOLOGICAL MATERIAL.

PROVIDER SCIENTIST

Organization:_____
Address:_____
_____
Name:_____
Title:_____
Signature:_____ Date: _____

RECIPIENT SCIENTIST

Organization:_____
Address:_____
_____
Name:_____
Title:_____
Signature:_____ Date: _____

RECIPIENT ORGANIZATION APPROVAL

Authorized Official:
_____
Title:_____
Address:_____
_____
Signature:_____ Date: _____

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Office of Extramural Research (OER)
National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892
Department of Health and Human Services (HHS)

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder

December 10, 2003

Collaboration and Materials Transfer Agreement

Dr. Carl June
Professor of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Room 554 BRB II/III
421 Curie Boulevard
Philadelphia, PA 19104-6160

Dear Dr. June:

This Agreement, effective upon signing, governs an arrangement whereby Dr. Dario Campana of St. Jude Children's Research Hospital, Inc., ("St. Jude") agrees to provide biological material that is proprietary to St. Jude, for use in a collaborative research study with Dr. Carl June ("Recipient Scientist") of the University of Pennsylvania ("Recipient"), subject to the terms and conditions set forth below. Trustees of the University of Pennsylvania

1. The biological material to be provided to Recipient Scientist is the anti-CD19-BB-ζ chimeric T-cell receptor construct, including any progeny, portions, unmodified derivatives and any accompanying know-how or data ("Material"). Legal title to the Material shall remain with St. Jude. The Recipient acknowledges that the Material is or may be the subject of a patent application. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the Recipient under any patents, patent applications, trade secrets or other proprietary rights of St. Jude, including any altered forms of the Material made by St. Jude.

2. The Material is for use by Recipient Scientist or persons directly supervised by Recipient Scientist. The Material may not be transferred or taken to any other laboratory or made available to any other person or third party, but is to remain under the immediate and direct control of Recipient Scientist.

3. Recipient Scientist agrees that the Material will only be used to create a lentiviral chimeric T-cell receptor construct to be used in pre-clinical studies.

4. The Material may not be used in humans and will be stored, used, and disposed of in accordance with applicable law and regulations. The Material will not be used for any commercial purpose.

5. St. Jude retains the unrestricted right to distribute the Material to other commercial or noncommercial entities.

6. Recipient agrees that any publications that result from the collaborative research study between St. Jude and Recipient Scientist using the Material will be jointly published in accordance with academic standards.

7. The transfer of the Material grants to Recipient no rights in the Material other than those specifically set forth in the Agreement. This agreement may be terminated upon thirty (30) days written notice by either party to the other. Upon termination of

the agreement, Recipient shall destroy all unused Materials.

8. Recipient shall not commercialize any product that contains Material without the prior written approval of St. Jude. The Recipient is free to file patent application(s) claiming inventions made by Recipient through use of the Material but agrees to notify St. Jude within sixty (60) days of filing any patent application which claims subject matter that contains or incorporates the Material or which claims a method of manufacture or use of the Material. Recipient grants to St. Jude a non-exclusive, royalty-free license to use for non-commercial purposes any inventions that arise from the use of the Materials. INVENTORSHIP WILL BE DETERMINED ACCORDING TO US PATENT LAW TJR 12/17/03

9. The Material provided is experimental in nature, and it is provided WITHOUT ANY WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE. St. Jude MAKES NO REPRESENTATION AND PROVIDES NO WARRANTY THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT. 12/16/03

10. Except to the extent prohibited by law, the Recipient assumes all liability for damages that may arise from its use, storage or disposal of the Materials. St. Jude and corporate affiliates of St. Jude and their respective Boards of Governors, Directors, officers, staff, representatives and agents will not be liable to the Recipient for any damages, expenses (including without limitation legal expenses), losses, claims, demands, suit or other actions (collectively hereinafter "Claims") made by the Recipient, or made against the Recipient by any other party, due to or arising from the use, storage or disposal of the Materials by the Recipient, except to the extent such Claims are solely caused by the gross negligence or willful misconduct of St. Jude.

If Recipient Scientist and Recipient agree to the above, please sign and have an authorized official of Recipient sign and return a copy of this letter to Esther Allay in the Office of Technology Licensing.

Sincerely,

J. Scott Elmer
Director
Office of Technology Licensing

Agreed and Accepted

Dr. Carl June
12/16/2003
Date

Institution Official

Name: Timothy J. Raynor
Director, Intellectual Property
Center for Technology Transfer
University of Pennsylvania

Title

12/17/03
Date

St. Jude Children's Research Hospital

October 2, 2007

Materials Transfer Agreement

Dr. Carl June
Professor of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Room 554 BRB II/III
421 Curie Boulevard
Philadelphia, PA 19104-6160

Dear Dr. June:

St. Jude Children's Research Hospital ("St. Jude") agrees to provide you and your institute, the Trustees of the University of Pennsylvania (collectively referred to herein as "Recipient"), with materials developed at St. Jude. Before receiving the materials, we ask that you and your institute agree to the following terms and conditions:

1. The biological materials to be provided to Recipient are the anti-CD19-BBζ chimeric receptor construct, including any progeny, portions, unmodified derivatives and any accompanying know-how or data ("Materials"). The Recipient acknowledges that the Materials are or may be the subject of patent(s), pending patent application(s) or other proprietary right of St. Jude. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the Recipient under any patents, patent applications, trade secrets or other proprietary rights of St. Jude, including any altered forms of the Materials made by St. Jude.

2. Recipient accepts sole responsibility for any and all receipt, storage, handling, disposition, transfer and uses of the Materials in compliance with all applicable Federal, State and local laws, rules, regulations and guidelines including, but not limited to Federal and State laws relating to the protection of human research subjects.

3. The Recipient further agrees that the Materials are provided for the sole purpose of allowing Recipient to use Materials to produce a molecular lentiviral vector clone incorporating Materials in compliance with GMP for application in ex vivo autologous cell modification in quantities sufficient to complete a Phase I clinical trial to be conducted at the Recipient's clinical facilities. Without limiting the foregoing, Recipient acknowledges and agrees that (i) the Materials may not be taken or sent to another institution without written permission from St. Jude and (ii) the Materials may not be provided to a commercial entity, and may not be used in research that is subject to consulting or licensing obligations to another party (other than those obligations imposed upon grantee institutions of the U.S. government) without express written consent by St. Jude.

4. Recipient agrees to provide St. Jude with a copy of any publication that contains experimental results obtained from the use of the Materials, and will acknowledge St.

Jude as the source of the Materials.

5. Recipient acknowledges St. Jude's ownership of the Materials and any progeny thereof. If Recipient files a patent application or commercializes a product which contains a portion of the Materials, is derived from the Materials, or which could not have been produced but for the use of the Materials, Recipient agrees to contact St. Jude to determine ownership interests, if any, St. Jude may have in such patent application or commercial product. Ownership shall follow inventorship according to US patent law. Further, Recipient shall not publish or disclose the results of such research using the Materials without submitting the proposed publication or disclosure to St. Jude at least thirty (30) days prior to the submission for publication or disclosure to allow St. Jude to review such publication or disclosure for the disclosure of St. Jude proprietary information.

6. The Materials provided are experimental in nature, and are provided WITHOUT ANY WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE. ST. JUDE MAKES NO REPRESENTATION AND PROVIDE NO WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT. IN NO EVENT SHALL ST. JUDE BE LIABLE FOR ANY INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES, EVEN IF ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

7. Recipient agrees to indemnify, defend and hold harmless St. Jude and the American Lebanese Syrian Associated Charities (ALSAC) and their respective corporate affiliates and Boards of Governors, trustees, directors, officers, medical and professional staff, employees, representatives and agents and their respective successors, heirs and assigns against any and all liability, claims, demands or legal causes of action of any nature whatsoever (including without limitation legal expenses), arising out of or related to Recipient's acceptance, use and disposal of the Materials and their progeny or derivatives, including but not limited to any and all claims for personal injury or death.

8. Recipient shall maintain liability insurance on an occurrence basis, or if claims made including tail coverage, in the amount of not less than One Million ($1,000,000) dollars per claim and Three Million ($3,000,000) dollars aggregate.

9. Recipient shall provide St. Jude, upon request, with a Certificate of Insurance from its insurer (i) stating that the insurance coverage set forth in section 8 is in full force and effect, and (ii) promising to provide St. Jude with thirty (30) days prior written notice of cancellation or reduction in coverage.

10. St. Jude may terminate this MTA if Recipient breaches any term and fails to cure such breach within thirty (30) days after written notice thereof. Upon such termination, Recipient will immediately cease use of the Materials and all progeny thereof, and return all Materials and progeny to St. Jude. Sections 5, 6 and 7 shall survive termination or expiration of this MTA.

11. This MTA may only be modified in writing signed by an authorized representative of each party. No express or implied waiver by a party of any breach hereunder shall in any way be, or be construed as, a waiver of any subsequent breach. In the event that any provision of this MTA is held by a court of competent jurisdiction to be invalid or unenforceable, such provision will be stricken from this MTA and the remaining provisions shall remain in full force and effect to the extent permitted by law.

Penn
University of Pennsylvania
Center for Technology Transfer

215.898.9467
katann@ctt.upenn.edu

November 22, 2011

McGehee V. Marsh, Ph.D.
Associate General Counsel
St. Jude Children's
Research Hospital
262 Danny Thomas Place MS 280
Memphis, Tennessee 38105

RE: Compliance with Oct. 2, 2007 MTA terms for receipt and use of an anti-CD19BBζ chimeric receptor construct from Dr. Dario Campana

Dear Dr. Marsh:

We are in receipt of your letter dated October 25, 2011. We disagree with many of the statements you make in your letter. We feel that numerous statements in the letter do not accurately reflect the terms and conditions of the 2007 MTA, nor do they accurately reflect the actions that Penn has taken to comply with the MTA. Specific points raised in your letter are addressed below.

Acknowledgment

Contrary to the statements made in your letter, Dr. June has acknowledged Dr. Campana's contributions to the discoveries made by Penn researchers. Dr. Campana was a co-author of the original work reported in the Milone Molecular Therapy paper in 2009. In addition, in the NEJM paper in 2011, as is detailed in my e-mail to you dated September 22, 2011, Dr. Campana and St. Jude were clearly acknowledged as the source of the original CART-19scFv plasmid. To suggest otherwise is incorrect. The NEJM paper unambiguously states that "The CART-19 scFv plasmid was previously reported[31] and was generously provided by Dr. Dario Campana (St. Jude)." We note that reference 31 is the Milone paper on which Dr. Campana was included as co-author. You indicate dissatisfaction with the level of acknowledgment, but the 2007 MTA does not require Penn to satisfy St. Jude's subjective standard of what is "appropriate" acknowledgement. Penn therefore believes that Dr. Campana and St. Jude as the source of the original construct were acknowledged and that the acknowledgement requirement of the MTA has been satisfied. Contrary to the suggestion in your October 25 letter, there was and is no intent on the part of Penn or Dr. June to minimize Dr. Campana's contribution. However, Dr. June would be happy, as a courtesy to Dr. Campana and to St. Jude, to write a letter to the editor of the NEJM to both reiterate and highlight the fact that Dr. Campana contributed the original construct. We do not know whether the editors of the NEJM would publish such reiteration of the St. Jude contribution.

3160 Chestnut Street Suite 200 Philadelphia, PA 19104-6283
Tel 215.573.4500 Fax 215.898.9519 www.ctt.upenn.edu

Penn
University of Pennsylvania
Center for Technology Transfer

Transfer of Dr. Campana's Construct

St. Jude has alleged in 2007 and again in your recent letters that Dr. June has transferred Dr. Campana's construct to third parties. Dr. June has confirmed his previous statements, which we relayed to St. Jude in 2007 that he has not sent Dr. Campana's original construct to any third party. Further, Dr. June has confirmed with us that Dr. Campana's construct remains in a freezer at Penn and is readily identifiable. Dr. June has sent his modified construct to researchers and collaborators. However, the MTA does not give St. Jude the right to the information you requested concerning any party to whom Dr. June sent his modified construct. Further, the MTA does not give St. Jude the right to require that researchers obtain St. Jude's permission in order to use Dr. June's construct.

Patent Applications

St. Jude has requested copies of Penn patent applications. This demand exceeds the requirements of the MTA. Dr. Campana's construct was published by him many years ago and is prior art to any Penn or third party invention. Moreover, there has never been a research collaboration between Dr. Campana and Dr. June. There is thus no basis for Dr. Campana/St. Jude to claim any inventorship/ownership of patents filed by Penn.

Drafts of Dr. June's publications

Your demand that Penn send to St. Jude manuscripts at least 30 days prior to publication exceeds the scope and requirements of the 2007 MTA, which governs the current relationship. As a first matter, Dr. Campana was a co-author on the original paper reporting Dr. June's construct. As such, it is impossible for St. Jude to allege that they did not have a copy of this manuscript. As for the NEJM paper, we view this paper as reporting findings on Dr. June's construct, not Dr. Campana's construct.

Termination of the MTA

Dr. June has a sincere appreciation of Dr. Campana's contribution of the original construct in 2003. However, Dr. June has spent over eight years and significant research dollars developing the Penn construct, without the further involvement of Dr. Campana or St. Jude. Dr. June's construct has been significantly modified from that provided by Dr. Campana and is currently in use in clinical trials. Yet, Dr. June has continued to acknowledge Dr. Campana and St. Jude in the NEJM paper reporting his landmark clinical results in cancer treatment.

You have indicated that you may contact editors to "inform" them that the publication of Dr. June's papers "involve a legal breach of a signed MTA" or a "serious breach of standard scientific behavior." Such statements would be intentionally false and misleading. I have made multiple attempts to contact you by phone and e-mail both before and after I sent you our response dated September 22, 2011 to your letter dated August 29 and e-mail dated September 7. In lieu of a phone call, you instead chose to write a formal letter with demands which exceed the scope of the MTA. Moreover, you have threatened to make false statements about Dr. June and Penn if we do not comply with these demands "without qualification". We have therefore concluded that the best way to move forward is to simply

3160 Chestnut Street Suite 200 Philadelphia, PA 19104-6283
Tel 215.573.4500 Fax 215.898.9519 www.ctt.upenn.edu

Penn
University of Pennsylvania

Center for Technology Transfer

part ways. Please let this letter serve as written notice that Penn wishes to terminate the MTA. Penn will either return or destroy the remaining portion of Dr. Campana's construct at St. Jude's election. In conclusion, please confirm the termination of the MTA. Please provide me with your instructions as to St. Jude's preferred disposition of the vial containing the original Campana construct, and indicate whether or not St. Jude would like Dr. June to write to the editors of NEJM and request publication of an enhanced additional acknowledgment of receipt of Dr. Campana's original construct. We would appreciate your written response within fifteen days from the date of this letter.

Very truly yours,

Kathryn A. Donohue
Director, Legal Affairs,
Center for Technology Transfer and
Associate General Counsel

cc: Michael J. Cleare, PhD

3160 Chestnut Street Suite 200 Philadelphia, PA 19104-6283
Tel 215.573.4500 Fax 215.898.9519 www.ctt.upenn.edu

Reference I

Selected Patent Statutes

EFFECTIVE DATE OF 2013 AMENDMENT

Amendment by Pub. L. 112–274 effective Jan. 14, 2013, and applicable to proceedings commenced on or after such date, see section 1(n) of Pub. L. 112–274, set out as a note under section 5 of this title.

EFFECTIVE DATE OF 2011 AMENDMENT

Pub. L. 112–29, § 22(b), Sept. 16, 2011, 125 Stat. 336, provided that: "The amendments made by this section [amending this section] shall take effect on October 1, 2011."

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, § 4732(a)(10)(A)] of Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, § 4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

EFFECTIVE DATE OF 1998 AMENDMENT

Amendment by Pub. L. 105–358 effective Oct. 1, 1998, see section 5 of Pub. L. 105–358, set out as a note under section 41 of this title.

EFFECTIVE DATE OF 1982 AMENDMENT

Amendment by Pub. L. 97–247 effective Oct. 1, 1982, see section 17(a) of Pub. L. 97–247, set out as a note under section 41 of this title.

EFFECTIVE DATE OF 1980 AMENDMENT

Amendment by Pub. L. 96–517 effective on first day of first fiscal year beginning on or after one calendar year after Dec. 12, 1980, subject to authorization of appropriation account credits from collected reexamination fees prior to the effective date, made available for payment of reexamination proceedings costs, see section 8(c) of Pub. L. 96–517, set out as a note under section 41 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

AUTHORIZATION OF AMOUNTS AVAILABLE TO THE PATENT AND TRADEMARK OFFICE

Pub. L. 107–273, div. C, title III, § 13102, Nov. 2, 2002, 116 Stat. 1899, provided that:

"(a) IN GENERAL.—There are authorized to be appropriated to the United States Patent and Trademark Office for salaries and necessary expenses for each of the fiscal years 2003 through 2008 an amount equal to the fees estimated by the Secretary of Commerce to be collected in each such fiscal year, respectively, under—

"(1) title 35, United States Code; and

"(2) the Act entitled 'An Act to provide for the registration and protection of trademarks used in commerce, to carry out the provisions of certain international conventions, and for other purposes', approved July 5, 1946 (15 U.S.C. 1051 et seq.) (commonly referred to as the Trademark Act of 1946).

"(b) ESTIMATES.—Not later than February 15, of each fiscal year, the Undersecretary of Commerce for Intellectual Property and the Director of the Patent and Trademark Office (in this subtitle [subtitle A (§§ 13101–13106) of title III of div. C of Pub. L. 107–273, amending sections 134, 141, 303, 312, and 315 of this title and enacting provisions set out as notes under sections 2, 134, and 303 of this title] referred to as the Director) shall submit an estimate of all fees referred to under subsection (a) to be collected in the next fiscal year to the chairman and ranking member of—

"(1) the Committees on Appropriations and Judiciary of the Senate; and

"(2) the Committees on Appropriations and Judiciary of the House of Representatives."

APPROPRIATIONS AUTHORIZED TO BE CARRIED OVER

Pub. L. 100–703, title I, § 102, Nov. 19, 1988, 102 Stat. 4674, provided that: "Amounts appropriated under this Act and such fees as may be collected under title 35, United States Code, and the Trademark Act of 1946 (15 U.S.C. 1051 and following) may remain available until expended."

Similar provisions were contained in the following prior authorization act:

Pub. L. 99–607, § 2, Nov. 6, 1986, 100 Stat. 3470.

PART II—PATENTABILITY OF INVENTIONS AND GRANT OF PATENTS

AMENDMENTS

2002—Pub. L. 107–273, div. C, title III, § 13206(a)(6), Nov. 2, 2002, 116 Stat. 1904, substituted "Examination of Application" for "Examination of Applications" in heading of chapter 12.

1982—Pub. L. 97–256, title I, § 101(6), Sept. 8, 1982, 96 Stat. 816, added item for chapter 18.

1975—Pub. L. 93–596, § 1, Jan. 2, 1975, 88 Stat. 1949, substituted "Patent and Trademark Office" for "Patent Office" in heading of chapter 13.

CHAPTER 10—PATENTABILITY OF INVENTIONS

AMENDMENTS

2011—Pub. L. 112–29, § 3(b)(3), (d), Sept. 16, 2011, 125 Stat. 287, substituted in item 102 "Conditions for patentability; novelty" for "Conditions for patentability; novelty and loss of right to patent" and struck out item 104 "Invention made abroad".

1990—Pub. L. 101–580, § 1(b), Nov. 15, 1990, 104 Stat. 2863, added item 105.

§ 100. Definitions

When used in this title unless the context otherwise indicates—

(a) The term "invention" means invention or discovery.

(b) The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

(c) The terms "United States" and "this country" mean the United States of America, its territories and possessions.

(d) The word "patentee" includes not only the patentee to whom the patent was issued but also the successors in title to the patentee.

[1] So in original. Does not conform to chapter heading.

(e) The term "third-party requester" means a person requesting ex parte reexamination under section 302 who is not the patent owner.

(f) The term "inventor" means the individual or, if a joint invention, the individuals collectively who invented or discovered the subject matter of the invention.

(g) The terms "joint inventor" and "coinventor" mean any 1 of the individuals who invented or discovered the subject matter of a joint invention.

(h) The term "joint research agreement" means a written contract, grant, or cooperative agreement entered into by 2 or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.

(i)(1) The term "effective filing date" for a claimed invention in a patent or application for patent means—

(A) if subparagraph (B) does not apply, the actual filing date of the patent or the application for the patent containing a claim to the invention; or

(B) the filing date of the earliest application for which the patent or application is entitled, as to such invention, to a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c).

(2) The effective filing date for a claimed invention in an application for reissue or reissued patent shall be determined by deeming the claim to the invention to have been contained in the patent for which reissue was sought.

(j) The term "claimed invention" means the subject matter defined by a claim in a patent or an application for a patent.

(July 19, 1952, ch. 950, 66 Stat. 797; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4603], Nov. 29, 1999, 113 Stat. 1536, 1501A–567; Pub. L. 112–29, § 3(a), Sept. 16, 2011, 125 Stat. 285; Pub. L. 112–211, title I, § 102(1), Dec. 18, 2012, 126 Stat. 1531.)

HISTORICAL AND REVISION NOTES

Paragraph (a) is added only to avoid repetition of the phrase "invention or discovery" and its derivatives throughout the revised title. The present statutes use the phrase "invention or discovery" and derivatives.

Paragraph (b) is noted under section 101.

Paragraphs (c) and (d) are added to avoid the use of long expressions in various parts of the revised title.

AMENDMENTS

2012—Subsec. (i)(1)(B). Pub. L. 112–211 substituted "right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c)" for "right of priority under section 119, 365(a), or 365(b) or to the benefit of an earlier filing date under section 120, 121, or 365(c)".

2011—Subsec. (e). Pub. L. 112–29, § 3(a)(1), struck out "or inter partes reexamination under section 311" after "302".

Subsecs. (f) to (j). Pub. L. 112–29, § 3(a)(2), added subsecs. (f) to (j).

1999—Subsec. (e). Pub. L. 106–113 added subsec. (e).

EFFECTIVE DATE OF 2012 AMENDMENT

Pub. L. 112–211, title I, § 103, Dec. 18, 2012, 126 Stat. 1532, provided that:

"(a) IN GENERAL.—The amendments made by this title [enacting part V of this title and amending this section and sections 102, 111, 115, 120, 154, 173, 365, and 366 of this title] shall take effect on the later of—

"(1) the date that is 1 year after the date of the enactment of this Act [Dec. 18, 2012]; or

"(2) the date of entry into force of the treaty with respect to the United States [May 13, 2015].

"(b) APPLICABILITY OF AMENDMENTS.—

"(1) IN GENERAL.—Subject to paragraph (2), the amendments made by this title shall apply only to international design applications, international applications, and national applications filed on and after the effective date set forth in subsection (a), and patents issuing thereon.

"(2) EXCEPTION.—Sections 100(i) and 102(d) of title 35, United States Code, as amended by this title, shall not apply to an application, or any patent issuing thereon, unless it is described in section 3(n)(1) of the Leahy-Smith America Invents Act [Pub. L. 112–29] (35 U.S.C. 100 note).

"(c) DEFINITIONS.—For purposes of this section—

"(1) the terms 'treaty' and 'international design application' have the meanings given those terms in section 381 of title 35, United States Code, as added by this title;

"(2) the term 'international application' has the meaning given that term in section 351(c) of title 35, United States Code; and

"(3) the term 'national application' means 'national application' within the meaning of chapter 38 of title 35, United States Code, as added by this title."

EFFECTIVE DATE OF 2011 AMENDMENT; SAVINGS PROVISIONS

Pub. L. 112–29, § 3(n), Sept. 16, 2011, 125 Stat. 293, provided that:

"(1) IN GENERAL.—Except as otherwise provided in this section [amending this section and sections 32, 102, 103, 111, 119, 120, 134, 135, 145, 146, 154, 172, 202, 287, 291, 305, 363, 374, and 375 of this title, repealing sections 104 and 157 of this title, and enacting provisions set out as notes under sections 32, 102, and 111 of this title], the amendments made by this section shall take effect upon the expiration of the 18-month period beginning on the date of the enactment of this Act [Sept. 16, 2011], and shall apply to any application for patent, and to any patent issuing thereon, that contains or contained at any time—

"(A) a claim to a claimed invention that has an effective filing date as defined in section 100(i) of title 35, United States Code, that is on or after the effective date described in this paragraph; or

"(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim.

"(2) INTERFERING PATENTS.—The provisions of sections 102(g), 135, and 291 of title 35, United States Code, as in effect on the day before the effective date set forth in paragraph (1) of this subsection, shall apply to each claim of an application for patent, and any patent issued thereon, for which the amendments made by this section also apply, if such application or patent contains or contained at any time—

"(A) a claim to an invention having an effective filing date as defined in section 100(i) of title 35, United States Code, that occurs before the effective date set forth in paragraph (1) of this subsection; or

"(B) a specific reference under section 120, 121, or 365(c) of title 35, United States Code, to any patent or application that contains or contained at any time such a claim."

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective Nov. 29, 1999, and applicable to any patent issuing from an original application filed in the United States on or after that date, see section 1000(a)(9) [title IV, § 4608(a)] of Pub. L. 106–113, set out as a note under section 41 of this title.

§ 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composi-

tion of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(July 19, 1952, ch. 950, 66 Stat. 797.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., §31 (R.S. 4886, amended (1) Mar. 3, 1897, ch. 391, §1, 29 Stat. 692, (2) May 23, 1930, ch. 312, §1, 46 Stat. 376, (3) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212).

The corresponding section of existing statute is split into two sections, section 101 relating to the subject matter for which patents may be obtained, and section 102 defining statutory novelty and stating other conditions for patentability.

Section 101 follows the wording of the existing statute as to the subject matter for patents, except that reference to plant patents has been omitted for incorporation in section 301 and the word "art" has been replaced by "process", which is defined in section 100. The word "art" in the corresponding section of the existing statute has a different meaning than the same word as used in other places in the statute; it has been interpreted by the courts as being practically synonymous with process or method. "Process" has been used as its meaning is more readily grasped than "art" as interpreted, and the definition in section 100(b) makes it clear that "process or method" is meant. The remainder of the definition clarifies the status of processes or methods which involve merely the new use of a known process, machine, manufacture, composition of matter, or material; they are processes or methods under the statute and may be patented provided the conditions for patentability are satisfied.

LIMITATION ON ISSUANCE OF PATENTS

Pub. L. 112–29, §33, Sept. 16, 2011, 125 Stat. 340, provided that:

"(a) LIMITATION.—Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism.

"(b) EFFECTIVE DATE.—

"(1) IN GENERAL.—Subsection (a) shall apply to any application for patent that is pending on, or filed on or after, the date of the enactment of this Act [Sept. 16, 2011].

"(2) PRIOR APPLICATIONS.—Subsection (a) shall not affect the validity of any patent issued on an application to which paragraph (1) does not apply."

§ 102. Conditions for patentability; novelty

(a) NOVELTY; PRIOR ART.—A person shall be entitled to a patent unless—

(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or

(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

(b) EXCEPTIONS.—

(1) DISCLOSURES MADE 1 YEAR OR LESS BEFORE THE EFFECTIVE FILING DATE OF THE CLAIMED INVENTION.—A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if—

(A) the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(B) the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

(2) DISCLOSURES APPEARING IN APPLICATIONS AND PATENTS.—A disclosure shall not be prior art to a claimed invention under subsection (a)(2) if—

(A) the subject matter disclosed was obtained directly or indirectly from the inventor or a joint inventor;

(B) the subject matter disclosed had, before such subject matter was effectively filed under subsection (a)(2), been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(C) the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person.

(c) COMMON OWNERSHIP UNDER JOINT RESEARCH AGREEMENTS.—Subject matter disclosed and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person in applying the provisions of subsection (b)(2)(C) if—

(1) the subject matter disclosed was developed and the claimed invention was made by, or on behalf of, 1 or more parties to a joint research agreement that was in effect on or before the effective filing date of the claimed invention;

(2) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(3) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(d) PATENTS AND PUBLISHED APPLICATIONS EFFECTIVE AS PRIOR ART.—For purposes of determining whether a patent or application for patent is prior art to a claimed invention under subsection (a)(2), such patent or application shall be considered to have been effectively filed, with respect to any subject matter described in the patent or application—

(1) if paragraph (2) does not apply, as of the actual filing date of the patent or the application for patent; or

(2) if the patent or application for patent is entitled to claim a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b), or to claim the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c), based upon 1 or more prior filed applications for patent, as of the filing date of the earliest such application that describes the subject matter.

(July 19, 1952, ch. 950, 66 Stat. 797; Pub. L. 92–358, §2, July 28, 1972, 86 Stat. 502; Pub. L. 94–131, §5,

Nov. 14, 1975, 89 Stat. 691; Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §§4505, 4806], Nov. 29, 1999, 113 Stat. 1536, 1501A–565, 1501A–590; Pub. L. 107–273, div. C, title III, §13205(1), Nov. 2, 2002, 116 Stat. 1902; Pub. L. 112–29, §3(b)(1), Sept. 16, 2011, 125 Stat. 285; Pub. L. 112–211, title I, §102(2), Dec. 18, 2012, 126 Stat. 1531.)

HISTORICAL AND REVISION NOTES

Paragraphs (a), (b), and (c) are based on Title 35, U.S.C., 1946 ed., §31 (R.S. 4886, amended (1) Mar. 3, 1897, ch. 391, §1, 29 Stat. 692, (2) May 23, 1930, ch. 312, §1, 46 Stat. 376, (3) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212).

No change is made in these paragraphs other than that due to division into lettered paragraphs. The interpretation by the courts of paragraph (a) as being more restricted than the actual language would suggest (for example, "known" has been held to mean "publicly known") is recognized but no change in the language is made at this time. Paragraph (a) together with section 104 contains the substance of Title 35, U.S.C., 1946 ed., §72 (R.S. 4923).

Paragraph (d) is based on Title 35, U.S.C., 1946 ed., §32, first paragraph (R.S. 4887 (first paragraph), amended (1) Mar. 3, 1897, ch. 391, §3, 29 Stat. 692, 693, (2) Mar. 3, 1903, ch. 1019, §1, 32 Stat. 1225, 1226, (3) June 19, 1936, ch. 594, 49 Stat. 1529).

The section has been changed so that the prior foreign patent is not a bar unless it was granted before the filing of the application in the United States.

Paragraph (e) is new and enacts the rule of *Milburn* v. *Davis-Bournonville*, 270 U.S. 390, by reason of which a United States patent disclosing an invention dates from the date of filing the application for the purpose of anticipating a subsequent inventor.

Paragraph (f) indicates the necessity for the inventor as the party applying for patent. Subsequent sections permit certain persons to apply in place of the inventor under special circumstances.

Paragraph (g) is derived from Title 35, U.S.C., 1946 ed., §69 (R.S. 4920, amended (1) Mar. 3, 1897, ch. 391, §2, 29 Stat. 692, (2) Aug. 5, 1939, ch. 450, §1, 53 Stat. 1212), the second defense recited in this section. This paragraph retains the present rules of law governing the determination of priority of invention.

Language relating specifically to designs is omitted for inclusion in subsequent sections.

AMENDMENTS

2012—Subsec. (d)(2). Pub. L. 112–211 substituted "to claim a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b), or to claim the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c)" for "to claim a right of priority under section 119, 365(a), or 365(b), or to claim the benefit of an earlier filing date under section 120, 121, or 365(c)".

2011—Pub. L. 112–29 amended section generally. Prior to amendment, section related to conditions for patentability; novelty and loss of right to patent.

2002—Subsec. (e). Pub. L. 107–273, amended Pub. L. 106–113, §1000(a)(9) [title IV, §4505]. See 1999 Amendment note below. Prior to being amended by Pub. L. 107–273, Pub. L. 106–113, §1000(a)(9) [title IV, §4505], had amended subsec. (e) to read as follows: "The invention was described in—

"(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

"(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a); or".

1999—Subsec. (e). Pub. L. 106–113, §1000(a)(9) [title IV, §4505], as amended by Pub. L. 107–273, amended subsec. (e) generally. Prior to amendment, subsec. (e) read as follows: "the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent, or".

Subsec. (g). Pub. L. 106–113, §1000(a)(9) [title IV, §4806], amended subsec. (g) generally. Prior to amendment, subsec. (g) read as follows: "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other."

1975—Par. (e). Pub. L. 94–131 inserted provision for nonentitlement to a patent where the invention was described in a patent granted on an international application by another who has fulfilled the requirements of pars. (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

1972—Subsec. (d). Pub. L. 92–358 inserted reference to inventions that were the subject of an inventors' certificate.

EFFECTIVE DATE OF 2012 AMENDMENT

Amendment by Pub. L. 112–211 effective on the later of the date that is 1 year after Dec. 18, 2012, or the date that the Geneva Act of the Hague Agreement Concerning the International Registration of Industrial Designs enters into force with respect to the United States (May 13, 2015), and applicable only to certain applications filed on and after that effective date and patents issuing thereon, with certain exceptions, see section 103 of Pub. L. 112–211, set out as a note under section 100 of this title.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by Pub. L. 112–29 effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, §4505] of Pub. L. 106–113 effective Nov. 29, 2000 and applicable to all patents and all applications for patents pending on or filed after Nov. 29, 2000, see section 1000(a)(9) [title IV, §4508] of Pub. L. 106–113, as amended, set out as a note under section 10 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

EFFECTIVE DATE OF 1972 AMENDMENT

Pub. L. 92–358, §3(b), July 28, 1972, 86 Stat. 502, provided that: "Section 2 of this Act [amending this section] shall take effect six months from the date when Articles 1 to 12 of the Paris Convention of March 20, 1883, for the Protection of Industrial Property, as re-

vised at Stockholm, July 14, 1967, come into force with respect to the United States [Aug. 25, 1973] and shall apply to applications thereafter filed in the United States."

SAVINGS PROVISIONS

Provisions of former subsec. (g) of this section, as in effect on the day before the expiration of the 18-month period beginning on Sept. 16, 2011, apply to each claim of certain applications for patent, and certain patents issued thereon, for which the amendments made by section 3 of Pub. L. 112–29 also apply, see section 3(n)(2) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

CONTINUITY OF INTENT UNDER THE CREATE ACT

Pub. L. 112–29, §3(b)(2), Sept. 16, 2011, 125 Stat. 287, provided that: "The enactment of section 102(c) of title 35, United States Code, under paragraph (1) of this subsection is done with the same intent to promote joint research activities that was expressed, including in the legislative history, through the enactment of the Cooperative Research and Technology Enhancement Act of 2004 (Public Law 108–453; the 'CREATE Act') [see Short Title of 2004 Amendment note set out under section 1 of this title], the amendments of which are stricken by subsection (c) of this section [amending section 103 of this title]. The United States Patent and Trademark Office shall administer section 102(c) of title 35, United States Code, in a manner consistent with the legislative history of the CREATE Act that was relevant to its administration by the United States Patent and Trademark Office."

TAX STRATEGIES DEEMED WITHIN THE PRIOR ART

Pub. L. 112–29, §14, Sept. 16, 2011, 125 Stat. 327, provided that:

"(a) IN GENERAL.—For purposes of evaluating an invention under section 102 or 103 of title 35, United States Code, any strategy for reducing, avoiding, or deferring tax liability, whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.

"(b) DEFINITION.—For purposes of this section, the term 'tax liability' refers to any liability for a tax under any Federal, State, or local law, or the law of any foreign jurisdiction, including any statute, rule, regulation, or ordinance that levies, imposes, or assesses such tax liability.

"(c) EXCLUSIONS.—This section does not apply to that part of an invention that—

"(1) is a method, apparatus, technology, computer program product, or system, that is used solely for preparing a tax or information return or other tax filing, including one that records, transmits, transfers, or organizes data related to such filing; or

"(2) is a method, apparatus, technology, computer program product, or system used solely for financial management, to the extent that it is severable from any tax strategy or does not limit the use of any tax strategy by any taxpayer or tax advisor.

"(d) RULE OF CONSTRUCTION.—Nothing in this section shall be construed to imply that other business methods are patentable or that other business method patents are valid.

"(e) EFFECTIVE DATE; APPLICABILITY.—This section shall take effect on the date of the enactment of this Act [Sept. 16, 2011] and shall apply to any patent application that is pending on, or filed on or after, that date, and to any patent that is issued on or after that date."

EMERGENCY RELIEF FROM POSTAL SITUATION AFFECTING PATENT CASES

Relief as to filing date of patent application or patent affected by postal situation beginning on Mar. 18, 1970, and ending on or about Mar. 30, 1970, but patents issued with earlier filing dates not effective as prior art under subsec. (e) of this section as of such earlier filing dates, see section 1(a) of Pub. L. 92–34, formerly set out in a note under section 111 of this title.

§103. Conditions for patentability; non-obvious subject matter

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 98–622, title I, §103, Nov. 8, 1984, 98 Stat. 3384; Pub. L. 104–41, §1, Nov. 1, 1995, 109 Stat. 351; Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §4807(a)], Nov. 29, 1999, 113 Stat. 1536, 1501A–591; Pub. L. 108–453, §2, Dec. 10, 2004, 118 Stat. 3596; Pub. L. 112–29, §§3(c), 20(j), Sept. 16, 2011, 125 Stat. 287, 335.)

HISTORICAL AND REVISION NOTES

There is no provision corresponding to the first sentence explicitly stated in the present statutes, but the refusal of patents by the Patent Office, and the holding of patents invalid by the courts, on the ground of lack of invention or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.

The second sentence states that patentability as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius.

AMENDMENTS

2011—Pub. L. 112–29, §3(c), amended section generally. Prior to amendment, section consisted of subsecs. (a) to (c) and related to conditions for patentability; non-obvious subject matter.

Subsecs. (a), (c)(1). Pub. L. 112–29, §20(j), struck out "of this title" after "102".

2004—Subsec. (c). Pub. L. 108–453 amended subsec. (c) generally. Prior to amendment, subsec. (c) read as follows: "Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

1999—Subsec. (c). Pub. L. 106–113 substituted "one or more of subsections (e), (f), and (g)" for "subsection (f) or (g)".

1995—Pub. L. 104–41 designated first and second pars. as subsecs. (a) and (c), respectively, and added subsec. (b).

1984—Pub. L. 98–622 inserted "Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by section 3(c) of Pub. L. 112–29 effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

Amendment by section 20(j) of Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, see section 20(*l*) of Pub. L. 112–29, set out as a note under section 2 of this title.

EFFECTIVE DATE OF 2004 AMENDMENT

Pub. L. 108–453, § 3, Dec. 10, 2004, 118 Stat. 3596, provided that:

"(a) IN GENERAL.—The amendments made by this Act [amending this section] shall apply to any patent granted on or after the date of the enactment of this Act [Dec. 10, 2004].

"(b) SPECIAL RULE.—The amendments made by this Act shall not affect any final decision of a court or the United States Patent and Trademark Office rendered before the date of the enactment of this Act, and shall not affect the right of any party in any action pending before the United States Patent and Trademark Office or a court on the date of the enactment of this Act to have that party's rights determined on the basis of the provisions of title 35, United States Code, in effect on the day before the date of the enactment of this Act."

EFFECTIVE DATE OF 1999 AMENDMENT

Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4807(b)], Nov. 29, 1999, 113 Stat. 1536, 1501A–591, provided that: "The amendment made by this section [amending this section] shall apply to any application for patent filed on or after the date of the enactment of this Act [Nov. 29, 1999]."

EFFECTIVE DATE OF 1995 AMENDMENT

Pub. L. 104–41, § 3, Nov. 1, 1995, 109 Stat. 352, provided that: "The amendments made by section 1 [amending this section] shall apply to any application for patent filed on or after the date of enactment of this Act [Nov. 1, 1995] and to any application for patent pending on such date of enactment, including (in either case) an application for the reissuance of a patent."

EFFECTIVE DATE OF 1984 AMENDMENT

Pub. L. 98–622, title I, § 106, Nov. 8, 1984, 98 Stat. 3385, provided that:

"(a) Subject to subsections (b), (c), (d), and (e) of this section, the amendments made by this Act [probably should be "this title", meaning title I of Pub. L. 98–622, enacting section 157 of this title, amending this section and sections 116, 120, 135, and 271 of this title, and enacting a provision set out as a note under section 157 of this title] shall apply to all United States patents granted before, on, or after the date of enactment of this Act [Nov. 8, 1984], and to all applications for United States patents pending on or filed after the date of enactment.

"(b) The amendments made by this Act shall not affect any final decision made by the court or the Patent and Trademark Office before the date of enactment of this Act [Nov. 8, 1984], with respect to a patent or application for patent, if no appeal from such decision is pending and the time for filing an appeal has expired.

"(c) Section 271(f) of title 35, United States Code, added by section 101 of this Act shall apply only to the supplying, or causing to be supplied, of any component or components of a patented invention after the date of enactment of this Act [Nov. 8, 1984].

"(d) No United States patent granted before the date of enactment of this Act [Nov. 8, 1984] shall abridge or affect the right of any person or his successors in business who made, purchased, or used prior to such effective date anything protected by the patent, to continue the use of, or to sell to others to be used or sold, the specific thing so made, purchased, or used, if the patent claims were invalid or otherwise unenforceable on a ground obviated by section 103 or 104 of this Act [amending this section and sections 116 and 120 of this title] and the person made, purchased, or used the specific thing in reasonable reliance on such invalidity or unenforceability. If a person reasonably relied on such invalidity or unenforceability, the court before which such matter is in question may provide for the continued manufacture, use, or sale of the thing made, purchased, or used as specified, or for the manufacture, use, or sale of which substantial preparation was made before the date of enactment of this Act, and it may also provide for the continued practice of any process practiced, or for the practice of which substantial preparation was made, prior to the date of enactment, to the extent and under such terms as the court deems equitable for the protection of investments made or business commenced before the date of enactment.

"(e) The amendments made by this Act shall not affect the right of any party in any case pending in court on the date of enactment [Nov. 8, 1984] to have their rights determined on the basis of the substantive law in effect prior to the date of enactment."

[§ 104. Repealed. Pub. L. 112–29, § 3(d), Sept. 16, 2011, 125 Stat. 287]

Section, act July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 93–596, § 1, Jan. 2, 1975, 88 Stat. 1949; Pub. L. 94–131, § 6, Nov. 14, 1975, 89 Stat. 691; Pub. L. 98–622, title IV, § 403(a), Nov. 8, 1984, 98 Stat. 3392; Pub. L. 103–182, title III, § 331, Dec. 8, 1993, 107 Stat. 2113; Pub. L. 103–465, title V, § 531(a), Dec. 8, 1994, 108 Stat. 4982; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906; Pub. L. 112–29, § 20(j), Sept. 16, 2011, 125 Stat. 335, related to inventions made abroad.

EFFECTIVE DATE OF REPEAL

Repeal effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

§ 105. Inventions in outer space

(a) Any invention made, used or sold in outer space on a space object or component thereof under the jurisdiction or control of the United States shall be considered to be made, used or sold within the United States for the purposes of this title, except with respect to any space object or component thereof that is specifically identified and otherwise provided for by an international agreement to which the United States is a party, or with respect to any space object or component thereof that is carried on the registry of a foreign state in accordance with the Convention on Registration of Objects Launched into Outer Space.

(b) Any invention made, used or sold in outer space on a space object or component thereof that is carried on the registry of a foreign state in accordance with the Convention on Registration of Objects Launched into Outer Space, shall be considered to be made, used or sold within the United States for the purposes of this title if specifically so agreed in an international agreement between the United States and the state of registry.

(Added Pub. L. 101–580, § 1(a), Nov. 15, 1990, 104 Stat. 2863.)

EFFECTIVE DATE: SPECIAL RULES

Pub. L. 101–580, §2, Nov. 15, 1990, 104 Stat. 2863, provided that:

"(a) EFFECTIVE DATE.—Subject to subsections (b), (c), and (d) of this section, the amendments made by the first section of this Act [enacting this section] shall apply to all United States patents granted before, on, or after the date of enactment of this Act [Nov. 15, 1990], and to all applications for United States patents pending on or filed on or after such date of enactment.

"(b) FINAL DECISIONS.—The amendments made by the first section of this Act [enacting this section] shall not affect any final decision made by a court or the Patent and Trademark Office before the date of enactment of this Act [Nov. 15, 1990] with respect to a patent or an application for a patent, if no appeal from such decision is pending and the time for filing an appeal has expired.

"(c) PENDING CASES.—The amendments made by the first section of this Act [enacting this section] shall not affect the right of any party in any case pending in a court on the date of enactment of this Act [Nov. 15, 1990] to have the party's rights determined on the basis of the substantive law in effect before such date of enactment.

"(d) NON-APPLICABILITY.—The amendments made by the first section of this Act [enacting this section] shall not apply to any process, machine, article of manufacture, or composition of matter, an embodiment of which was launched prior to the date of enactment of this Act [Nov. 15, 1990]."

CHAPTER 11—APPLICATION FOR PATENT

AMENDMENTS

2011—Pub. L. 112–29, §10(g)(2), Sept. 16, 2011, 125 Stat. 319, which directed adding item 123 at the end of this chapter, was executed by adding the item at the end of the table of sections of this chapter, to reflect the probable intent of Congress.

Pub. L. 112–29, §4(a)(4), Sept. 16, 2011, 125 Stat. 296, amended item 115 generally, substituting "Inventor's oath or declaration" for "Oath of applicant".

2002—Pub. L. 107–273, div. C, title III, §13206(a)(7), Nov. 2, 2002, 116 Stat. 1904, substituted "Inventors" for "Joint inventors" in item 116.

1999—Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §4507(5)], Nov. 29, 1999, 113 Stat. 1536, 1501A–566, inserted "; publication of patent applications" after "applications" in item 122.

1994—Pub. L. 103–465, title V, §532(c)(6), Dec. 8, 1994, 108 Stat. 4987, substituted "Application" for "Application for patent" in item 111 and "Benefit of earlier filing date; right of priority" for "Benefit of earlier filing date in foreign country; right of priority" in item 119.

§ 111. Application

(a) IN GENERAL.—

(1) WRITTEN APPLICATION.—An application for patent shall be made, or authorized to be made, by the inventor, except as otherwise provided in this title, in writing to the Director.

(2) CONTENTS.—Such application shall include—

(A) a specification as prescribed by section 112;

(B) a drawing as prescribed by section 113; and

(C) an oath or declaration as prescribed by section 115.

(3) FEE, OATH OR DECLARATION, AND CLAIMS.—The application shall be accompanied by the fee required by law. The fee, oath or declaration, and 1 or more claims may be submitted after the filing date of the application, within such period and under such conditions, including the payment of a surcharge, as may be prescribed by the Director. Upon failure to submit the fee, oath or declaration, and 1 or more claims within such prescribed period, the application shall be regarded as abandoned.

(4) FILING DATE.—The filing date of an application shall be the date on which a specification, with or without claims, is received in the United States Patent and Trademark Office.

(b) PROVISIONAL APPLICATION.—

(1) AUTHORIZATION.—A provisional application for patent shall be made or authorized to be made by the inventor, except as otherwise provided in this title, in writing to the Director. Such application shall include—

(A) a specification as prescribed by section 112(a); and

(B) a drawing as prescribed by section 113.

(2) CLAIM.—A claim, as required by subsections (b) through (e) of section 112, shall not be required in a provisional application.

(3) FEE.—The application shall be accompanied by the fee required by law. The fee may be submitted after the filing date of the application, within such period and under such conditions, including the payment of a surcharge, as may be prescribed by the Director. Upon failure to submit the fee within such prescribed period, the application shall be regarded as abandoned.

(4) FILING DATE.—The filing date of a provisional application shall be the date on which a specification, with or without claims, is received in the United States Patent and Trademark Office.

(5) ABANDONMENT.—Notwithstanding the absence of a claim, upon timely request and as prescribed by the Director, a provisional application may be treated as an application filed under subsection (a). Subject to section 119(e)(3), if no such request is made, the provisional application shall be regarded as abandoned 12 months after the filing date of such application and shall not be subject to revival after such 12-month period.

(6) OTHER BASIS FOR PROVISIONAL APPLICATION.—Subject to all the conditions in this subsection and section 119(e), and as prescribed by the Director, an application for patent filed under subsection (a) may be treated as a provisional application for patent.

(7) NO RIGHT OF PRIORITY OR BENEFIT OF EARLIEST FILING DATE.—A provisional application shall not be entitled to the right of priority of

any other application under section 119, 365(a), or 386(a) or to the benefit of an earlier filing date in the United States under section 120, 121, 365(c), or 386(c).

(8) APPLICABLE PROVISIONS.—The provisions of this title relating to applications for patent shall apply to provisional applications for patent, except as otherwise provided, and except that provisional applications for patent shall not be subject to sections 131 and 135.

(c) PRIOR FILED APPLICATION.—Notwithstanding the provisions of subsection (a), the Director may prescribe the conditions, including the payment of a surcharge, under which a reference made upon the filing of an application under subsection (a) to a previously filed application, specifying the previously filed application by application number and the intellectual property authority or country in which the application was filed, shall constitute the specification and any drawings of the subsequent application for purposes of a filing date. A copy of the specification and any drawings of the previously filed application shall be submitted within such period and under such conditions as may be prescribed by the Director. A failure to submit the copy of the specification and any drawings of the previously filed application within the prescribed period shall result in the application being regarded as abandoned. Such application shall be treated as having never been filed, unless—

(1) the application is revived under section 27; and

(2) a copy of the specification and any drawings of the previously filed application are submitted to the Director.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 97–247, § 5, Aug. 27, 1982, 96 Stat. 319; Pub. L. 103–465, title V, § 532(b)(3), Dec. 8, 1994, 108 Stat. 4986; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, §§ 4732(a)(10)(A), 4801(a)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582, 1501A–588; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906; Pub. L. 112–29, §§ 3(e)(2), 4(a)(3), (d), 20(j), Sept. 16, 2011, 125 Stat. 287, 295, 296, 335; Pub. L. 112–211, title I, § 102(3), title II, § 201(a), Dec. 18, 2012, 126 Stat. 1531, 1533.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 33 (R.S. 4888, amended (1) Mar. 3, 1915, ch. 94, § 1, 38 Stat. 958; (2) May 23, 1930, ch. 312, § 2, 46 Stat. 376).

The corresponding section of existing statute is divided into an introductory section relating to the application generally (this section) and a section on the specification (sec. 112).

The parts of the application are specified and the requirement for signature is placed in this general section so as to insure that only one signature will suffice.

AMENDMENTS

2012—Subsec. (a)(3), (4). Pub. L. 112–211, § 201(a)(1), added pars. (3) and (4) and struck out former pars. (3) and (4) which related to fee and oath or declaration and failure to submit.

Subsec. (b)(3), (4). Pub. L. 112–211, § 201(a)(2), added pars. (3) and (4) and struck out former pars. (3) and (4) which related to fee and filing date of a provisional application.

Subsec. (b)(7). Pub. L. 112–211, § 102(3), substituted "section 119, 365(a), or 386(a)" for "section 119 or 365(a)" and "section 120, 121, 365(c), or 386(c)" for "section 120, 121, or 365(c)".

Subsec. (c). Pub. L. 112–211, § 201(a)(3), added subsec. (c).

2011—Subsec. (a)(2)(A). Pub. L. 112–29, § 20(j), struck out "of this title" after "112".

Subsec. (a)(2)(B). Pub. L. 112–29, § 20(j), struck out "of this title" after "113".

Subsec. (a)(2)(C). Pub. L. 112–29, § 20(j), struck out "of this title" after "115".

Pub. L. 112–29, § 4(a)(3)(A), substituted "or declaration" for "by the applicant".

Subsec. (a)(3). Pub. L. 112–29, § 4(a)(3)(B), (C), inserted "or declaration" after "and oath" in heading and text.

Subsec. (a)(4). Pub. L. 112–29, § 4(a)(3)(C), inserted "or declaration" after "and oath" in two places.

Subsec. (b)(1)(A). Pub. L. 112–29, § 4(d)(1), substituted "section 112(a)" for "the first paragraph of section 112 of this title".

Subsec. (b)(1)(B). Pub. L. 112–29, § 20(j), struck out "of this title" after "113".

Subsec. (b)(2). Pub. L. 112–29, § 4(d)(2), substituted "subsections (b) through (e) of section 112," for "the second through fifth paragraphs of section 112,".

Subsec. (b)(5). Pub. L. 112–29, § 20(j), struck out "of this title" after "119(e)(3)".

Subsec. (b)(6). Pub. L. 112–29, § 20(j), struck out "of this title" after "119(e)".

Subsec. (b)(7). Pub. L. 112–29, § 20(j), struck out "of this title" after "365(a)" and after "365(c)".

Subsec. (b)(8). Pub. L. 112–29, § 20(j), struck out "of this title" before period at end.

Pub. L. 112–29, § 3(e)(2), substituted "sections 131 and 135" for "sections 115, 131, 135, and 157".

2002—Subsecs. (a)(1), (3), (4), (b)(1), (3)(B), (C), (6). Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113, § 1000(a)(9) [title IV, § 4732(a)(10)(A)]. See 1999 Amendment notes below.

1999—Subsecs. (a)(1), (3), (4), (b)(1), (3)(B), (C). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], as amended by Pub. L. 107–273, substituted "Director" for "Commissioner".

Subsec. (b)(5). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4801(a)], amended heading and text of par. (5) generally. Prior to amendment, text read as follows: "The provisional application shall be regarded as abandoned 12 months after the filing date of such application and shall not be subject to revival thereafter."

Subsec. (b)(6). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], as amended by Pub. L. 107–273, substituted "Director" for "Commissioner".

1994—Pub. L. 103–465 amended section generally. Prior to amendment, section read as follows: "Application for patent shall be made, or authorized to be made, by the inventor, except as otherwise provided in this title, in writing to the Commissioner. Such application shall include (1) a specification as prescribed by section 112 of this title; (2) a drawing as prescribed by section 113 of this title; and (3) an oath by the applicant as prescribed by section 115 of this title. The application must be accompanied by the fee required by law. The fee and oath may be submitted after the specification and any required drawing are submitted, within such period and under such conditions, including the payment of a surcharge, as may be prescribed by the Commissioner. Upon failure to submit the fee and oath within such prescribed period, the application shall be regarded as abandoned, unless it is shown to the satisfaction of the Commissioner that the delay in submitting the fee and oath was unavoidable. The filing date of an application shall be the date on which the specification and any required drawing are received in the Patent and Trademark Office."

1982—Pub. L. 97–247 inserted ", or authorized to be made," after "shall be made", struck out the colon after "shall include", struck out "signed by the applicant and" after "The application", and inserted provisions that the fee and oath may be submitted after the specification and any required drawing are submitted, within such period and under such conditions, includ-

ing the payment of a surcharge, as may be prescribed by the Commissioner, that upon failure to submit the fee and oath within such prescribed period, the application shall be regarded as abandoned, unless it is shown to the satisfaction of the Commissioner that the delay in submitting the fee and oath was unavoidable, and that the filing date of an application shall be the date on which the specification and any required drawing are received in the Patent and Trademark Office.

EFFECTIVE DATE OF 2012 AMENDMENT

Amendment by section 102(3) of Pub. L. 112–211 effective on the later of the date that is 1 year after Dec. 18, 2012, or the date that the Geneva Act of the Hague Agreement Concerning the International Registration of Industrial Designs enters into force with respect to the United States (May 13, 2015), and applicable only to certain applications filed on and after that effective date and patents issuing thereon, see section 103 of Pub. L. 112–211, set out as a note under section 100 of this title.

Amendment by section 201(a) of Pub. L. 112–211 effective on the date that is 1 year after Dec. 18, 2012, applicable to certain patents and applications for patent, and not effective with respect to patents in litigation commenced before the effective date, see section 203 of Pub. L. 112–211, set out as an Effective Date note under section 27 of this title.

EFFECTIVE DATE OF 2011 AMENDMENT

Pub. L. 112–29, § 3(e)(3), Sept. 16, 2011, 125 Stat. 288, provided that: "The amendments made by this subsection [amending this section and repealing section 157 of this title] shall take effect upon the expiration of the 18-month period beginning on the date of the enactment of this Act [Sept. 16, 2011], and shall apply to any request for a statutory invention registration filed on or after that effective date."

Pub. L. 112–29, § 4(e), Sept. 16, 2011, 125 Stat. 297, provided that: "The amendments made by this section [amending this section and sections 112, 115, 118, 121, and 251 of this title] shall take effect upon the expiration of the 1-year period beginning on the date of the enactment of this Act [Sept. 16, 2011] and shall apply to any patent application that is filed on or after that effective date."

Amendment by section 20(j) of Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, see section 20(*j*) of Pub. L. 112–29, set out as a note under section 2 of this title.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, § 4732(a)(10)(A)] of Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, § 4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

Amendment by section 1000(a)(9) [title IV, § 4801(a)] of Pub. L. 106–113 effective Nov. 29, 1999, and applicable to any provisional application filed on or after June 8, 1995, see section 1000(a)(9) [title IV, § 4801(d)] of Pub. L. 106–113, set out as a note under section 119 of this title.

EFFECTIVE DATE OF 1994 AMENDMENT

Amendment by Pub. L. 103–465 effective 6 months after Dec. 8, 1994, and applicable to all patent applications filed in the United States on or after that effective date, with provisions relating to earliest filed patent application, see section 534(b)(1), (3) of Pub. L. 103–465, set out as a note under section 154 of this title.

EFFECTIVE DATE OF 1982 AMENDMENT

Amendment by Pub. L. 97–247 effective six months after Aug. 27, 1982, see section 17(c) of Pub. L. 97–247, set out as an Effective Date note under section 294 of this title.

EMERGENCY RELIEF FROM POSTAL SITUATION AFFECTING PATENT, TRADEMARK, AND OTHER FEDERAL CASES

Pub. L. 92–34, June 30, 1971, 85 Stat. 87, provided that a patent or trademark application would be considered filed in the United States Patent Office on the date that it would have been received by the Patent Office except for the delay caused by emergency situation affecting postal service from Mar. 18, 1970 to Mar. 30, 1970, if a claim was made.

§ 112. Specification

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

(c) FORM.—A claim may be written in independent or, if the nature of the case admits, in dependent or multiple dependent form.

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

(e) REFERENCE IN MULTIPLE DEPENDENT FORM.—A claim in multiple dependent form shall contain a reference, in the alternative only, to more than one claim previously set forth and then specify a further limitation of the subject matter claimed. A multiple dependent claim shall not serve as a basis for any other multiple dependent claim. A multiple dependent claim shall be construed to incorporate by reference all the limitations of the particular claim in relation to which it is being considered.

(f) ELEMENT IN CLAIM FOR A COMBINATION.—An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

(July 19, 1952, ch. 950, 66 Stat. 798; Pub. L. 89–83, § 9, July 24, 1965, 79 Stat. 261; Pub. L. 94–131, § 7, Nov. 14, 1975, 89 Stat. 691; Pub. L. 112–29, § 4(c), Sept. 16, 2011, 125 Stat. 296.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 33 (R.S. 4888, amended (1) Mar. 3, 1915, ch. 94, § 1, 38 Stat. 958; (2) May 23, 1930, ch. 312, § 2, 46 Stat. 376).

The sentence relating to signature of the specification is omitted in view of the general requirement for a signature in section 111.

The last sentence is omitted for inclusion in the chapter relating to plant patents.

The clause relating to machines is omitted as unnecessary and the requirement for disclosing the best mode of carrying out the invention is stated as generally applicable to all types of invention (derived from Title 35, U.S.C., 1946 ed., § 69, first defense).

The clause relating to the claim is made a separate paragraph to emphasize the distinction between the description and the claim or definition, and the language is modified.

A new paragraph relating to functional claims is added.

AMENDMENTS

2011—Pub. L. 112–29 designated first to sixth pars. as subsecs. (a) to (f), respectively, inserted headings, in subsec. (a), substituted "or joint inventor of carrying out the invention" for "of carrying out his invention", in subsec. (b), substituted "inventor or a joint inventor regards as the invention" for "applicant regards as his invention", and, in subsec. (d), substituted "Subject to subsection (e)," for "Subject to the following paragraph,".

1975—Pub. L. 94–131 substituted provision authorizing the writing of claims, if the nature of the case admits, in dependent or multiple dependent form for prior provision for writing claims in dependent form, required claims in dependent form to contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed, substituted text respecting construction of a claim in dependent form so as to incorporate by reference all the limitations of the claim to which it refers for prior text for construction of a dependent claim to include all the limitations of the claim incorporated by reference into the dependent claim, and inserted paragraph respecting certain requirements for claims in multiple dependent form.

1965—Pub. L. 89–83 permitted a claim to be written in independent or dependent form, and if in dependent form, required it to be construed to include all the limitations of the claim incorporated by reference into the dependent claim.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to any patent application that is filed on or after that effective date, see section 4(e) of Pub. L. 112–29, set out as a note under section 111 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

EFFECTIVE DATE OF 1965 AMENDMENT

Amendment by Pub. L. 89–83 effective three months after July 24, 1965, see section 7(a) of Pub. L. 89–83, set out as a note under section 41 of this title.

§ 113. Drawings

The applicant shall furnish a drawing where necessary for the understanding of the subject matter sought to be patented. When the nature of such subject matter admits of illustration by a drawing and the applicant has not furnished such a drawing, the Director may require its submission within a time period of not less than two months from the sending of a notice thereof. Drawings submitted after the filing date of the application may not be used (1) to overcome any insufficiency of the specification due to lack of an enabling disclosure or otherwise inadequate disclosure therein, or (11) to supplement the original disclosure thereof for the purpose of interpretation of the scope of any claim.

(July 19, 1952, ch. 950, 66 Stat. 799; Pub. L. 94–131, § 8, Nov. 14, 1975, 89 Stat. 691; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 34, part (R.S. 4889, amended Mar. 3, 1915, ch. 94, § 2, 38 Stat. 958).

The requirement for signature in the corresponding section of existing statute is omitted; regulations of the Patent Office can take care of any substitute. A redundant clause is omitted.

AMENDMENTS

2002—Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

1999—Pub. L. 106–113, as amended by Pub. L. 107–273, substituted "Director" for "Commissioner".

1975—Pub. L. 94–131 substituted provisions respecting drawings requiring necessary-for-understanding drawings and submission of drawings within prescribed time period and limiting use of drawings submitted after filing date of application for prior provision requiring the applicant to furnish a drawing when the nature of the case admitted it.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, § 4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 94–131 effective Jan. 24, 1978, and applicable on and after that date to patent applications filed in the United States and to international applications, where applicable, see section 11 of Pub. L. 94–131, set out as an Effective Date note under section 351 of this title.

§ 114. Models, specimens

The Director may require the applicant to furnish a model of convenient size to exhibit advantageously the several parts of his invention.

When the invention relates to a composition of matter, the Director may require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment.

(July 19, 1952, ch. 950, 66 Stat. 799; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 34, part (R.S. 4890 and 4891).

The change in language in the second paragraph broadens the requirement for specimens.

AMENDMENTS

2002—Pub. L. 107–273 made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

1999—Pub. L. 106–113, as amended by Pub. L. 107–273, substituted "Director" for "Commissioner" in two places.

Patent and Trademark Office, and shall be signed by the Director or have his signature placed thereon and shall be recorded in the Patent and Trademark Office.

(July 19, 1952, ch. 950, 66 Stat. 804; Pub. L. 93–596, §1, Jan. 2, 1975, 88 Stat. 1949; Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582; Pub. L. 107–273, div. C, title III, §§13203(c), 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1902, 1906.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., §39 (R.S. 4883, amended (1) Feb. 18, 1888, ch. 15, 25 Stat. 40, (2) April 11, 1903, ch. 417, 32 Stat. 95, (3) Feb. 18, 1922, ch. 58, §5, 42 Stat. 391).

The phrases referring to the attesting officers and to the recording of the patents are broadened.

AMENDMENTS

2002—Pub. L. 107–273, §13206(b)(1)(B), made technical correction to directory language of Pub. L. 106–113. See 1999 Amendment note below.

Pub. L. 107–273, §13203(c), struck out "and attested by an officer of the Patent and Trademark Office designated by the Director," after "signature placed thereon".

1999—Pub. L. 106–113, as amended by Pub. L. 107–273, §13206(b)(1)(B), substituted "Director" for "Commissioner" in two places.

1975—Pub. L. 93–596 substituted "Patent and Trademark Office" for "Patent Office" wherever appearing.

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, §4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

EFFECTIVE DATE OF 1975 AMENDMENT

Amendment by Pub. L. 93–596 effective Jan. 2, 1975, see section 4 of Pub. L. 93–596, set out as a note under section 1111 of Title 15, Commerce and Trade.

§154. Contents and term of patent; provisional rights

(a) IN GENERAL.—

(1) CONTENTS.—Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to exclude others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for the particulars thereof.

(2) TERM.—Subject to the payment of fees under this title, such grant shall be for a term beginning on the date on which the patent issues and ending 20 years from the date on which the application for the patent was filed in the United States or, if the application contains a specific reference to an earlier filed application or applications under section 120, 121, 365(c), or 386(c), from the date on which the earliest such application was filed.

(3) PRIORITY.—Priority under section 119, 365(a), 365(b), 386(a), or 386(b) shall not be taken into account in determining the term of a patent.

(4) SPECIFICATION AND DRAWING.—A copy of the specification and drawing shall be annexed to the patent and be a part of such patent.

(b) ADJUSTMENT OF PATENT TERM.—

(1) PATENT TERM GUARANTEES.—

(A) GUARANTEE OF PROMPT PATENT AND TRADEMARK OFFICE RESPONSES.—Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the Patent and Trademark Office to—

(i) provide at least one of the notifications under section 132 or a notice of allowance under section 151 not later than 14 months after—

(I) the date on which an application was filed under section 111(a); or

(II) the date of commencement of the national stage under section 371 in an international application;

(ii) respond to a reply under section 132, or to an appeal taken under section 134, within 4 months after the date on which the reply was filed or the appeal was taken;

(iii) act on an application within 4 months after the date of a decision by the Patent Trial and Appeal Board under section 134 or 135 or a decision by a Federal court under section 141, 145, or 146 in a case in which allowable claims remain in the application; or

(iv) issue a patent within 4 months after the date on which the issue fee was paid under section 151 and all outstanding requirements were satisfied,

the term of the patent shall be extended 1 day for each day after the end of the period specified in clause (i), (ii), (iii), or (iv), as the case may be, until the action described in such clause is taken.

(B) GUARANTEE OF NO MORE THAN 3-YEAR APPLICATION PENDENCY.—Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years after the actual filing date of the application under section 111(a) in the United States or, in the case of an international application, the date of commencement of the national stage under section 371 in the international application, not including—

(i) any time consumed by continued examination of the application requested by the applicant under section 132(b);

(ii) any time consumed by a proceeding under section 135(a), any time consumed by the imposition of an order under section 181, or any time consumed by appellate review by the Patent Trial and Appeal Board or by a Federal court; or

(iii) any delay in the processing of the application by the United States Patent and Trademark Office requested by the applicant except as permitted by paragraph (3)(C),

the term of the patent shall be extended 1 day for each day after the end of that 3-year period until the patent is issued.

(C) GUARANTEE OF ADJUSTMENTS FOR DELAYS DUE TO DERIVATION PROCEEDINGS, SECRECY ORDERS, AND APPEALS.—Subject to the limitations under paragraph (2), if the issue of an original patent is delayed due to—

(i) a proceeding under section 135(a);

(ii) the imposition of an order under section 181; or

(iii) appellate review by the Patent Trial and Appeal Board or by a Federal court in a case in which the patent was issued under a decision in the review reversing an adverse determination of patentability,

the term of the patent shall be extended 1 day for each day of the pendency of the proceeding, order, or review, as the case may be.

(2) LIMITATIONS.—

(A) IN GENERAL.—To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

(B) DISCLAIMED TERM.—No patent the term of which has been disclaimed beyond a specified date may be adjusted under this section beyond the expiration date specified in the disclaimer.

(C) REDUCTION OF PERIOD OF ADJUSTMENT.—

(i) The period of adjustment of the term of a patent under paragraph (1) shall be reduced by a period equal to the period of time during which the applicant failed to engage in reasonable efforts to conclude prosecution of the application.

(ii) With respect to adjustments to patent term made under the authority of paragraph (1)(B), an applicant shall be deemed to have failed to engage in reasonable efforts to conclude processing or examination of an application for the cumulative total of any periods of time in excess of 3 months that are taken to respond to a notice from the Office making any rejection, objection, argument, or other request, measuring such 3-month period from the date the notice was given or mailed to the applicant.

(iii) The Director shall prescribe regulations establishing the circumstances that constitute a failure of an applicant to engage in reasonable efforts to conclude processing or examination of an application.

(3) PROCEDURES FOR PATENT TERM ADJUSTMENT DETERMINATION.—

(A) The Director shall prescribe regulations establishing procedures for the application for and determination of patent term adjustments under this subsection.

(B) Under the procedures established under subparagraph (A), the Director shall—

(i) make a determination of the period of any patent term adjustment under this subsection, and shall transmit a notice of that determination no later than the date of issuance of the patent; and

(ii) provide the applicant one opportunity to request reconsideration of any patent term adjustment determination made by the Director.

(C) The Director shall reinstate all or part of the cumulative period of time of an adjustment under paragraph (2)(C) if the applicant, prior to the issuance of the patent, makes a showing that, in spite of all due care, the applicant was unable to respond within the 3-month period, but in no case shall more than three additional months for each such response beyond the original 3-month period be reinstated.

(D) The Director shall proceed to grant the patent after completion of the Director's determination of a patent term adjustment under the procedures established under this subsection, notwithstanding any appeal taken by the applicant of such determination.

(4) APPEAL OF PATENT TERM ADJUSTMENT DETERMINATION.—

(A) An applicant dissatisfied with the Director's decision on the applicant's request for reconsideration under paragraph (3)(B)(ii) shall have exclusive remedy by a civil action against the Director filed in the United States District Court for the Eastern District of Virginia within 180 days after the date of the Director's decision on the applicant's request for reconsideration. Chapter 7 of title 5 shall apply to such action. Any final judgment resulting in a change to the period of adjustment of the patent term shall be served on the Director, and the Director shall thereafter alter the term of the patent to reflect such change.

(B) The determination of a patent term adjustment under this subsection shall not be subject to appeal or challenge by a third party prior to the grant of the patent.

(c) CONTINUATION.—

(1) DETERMINATION.—The term of a patent that is in force on or that results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act shall be the greater of the 20-year term as provided in subsection (a), or 17 years from grant, subject to any terminal disclaimers.

(2) REMEDIES.—The remedies of sections 283, 284, and 285 shall not apply to acts which—

(A) were commenced or for which substantial investment was made before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act; and

(B) became infringing by reason of paragraph (1).

(3) REMUNERATION.—The acts referred to in paragraph (2) may be continued only upon the payment of an equitable remuneration to the patentee that is determined in an action brought under chapter 28 and chapter 29 (other than those provisions excluded by paragraph (2)).

(d) PROVISIONAL RIGHTS.—

(1) IN GENERAL.—In addition to other rights provided by this section, a patent shall include the right to obtain a reasonable royalty from

any person who, during the period beginning on the date of publication of the application for such patent under section 122(b), or in the case of an international application filed under the treaty defined in section 351(a) designating the United States under Article 21(2)(a) of such treaty or an international design application filed under the treaty defined in section 381(a)(1) designating the United States under Article 5 of such treaty, the date of publication of the application, and ending on the date the patent is issued—

(A)(i) makes, uses, offers for sale, or sells in the United States the invention as claimed in the published patent application or imports such an invention into the United States; or

(ii) if the invention as claimed in the published patent application is a process, uses, offers for sale, or sells in the United States or imports into the United States products made by that process as claimed in the published patent application; and

(B) had actual notice of the published patent application and, in a case in which the right arising under this paragraph is based upon an international application designating the United States that is published in a language other than English, had a translation of the international application into the English language.

(2) RIGHT BASED ON SUBSTANTIALLY IDENTICAL INVENTIONS.—The right under paragraph (1) to obtain a reasonable royalty shall not be available under this subsection unless the invention as claimed in the patent is substantially identical to the invention as claimed in the published patent application.

(3) TIME LIMITATION ON OBTAINING A REASONABLE ROYALTY.—The right under paragraph (1) to obtain a reasonable royalty shall be available only in an action brought not later than 6 years after the patent is issued. The right under paragraph (1) to obtain a reasonable royalty shall not be affected by the duration of the period described in paragraph (1).

(4) REQUIREMENTS FOR INTERNATIONAL APPLICATIONS.—

(A) EFFECTIVE DATE.—The right under paragraph (1) to obtain a reasonable royalty based upon the publication under the treaty defined in section 351(a) of an international application designating the United States shall commence on the date of publication under the treaty of the international application, or, if the publication under the treaty of the international application is in a language other than English, on the date on which the Patent and Trademark Office receives a translation of the publication in the English language.

(B) COPIES.—The Director may require the applicant to provide a copy of the international application and a translation thereof.

(July 19, 1952, ch. 950, 66 Stat. 804; Pub. L. 89–83, § 5, July 24, 1965, 79 Stat. 261; Pub. L. 96–517, § 4, Dec. 12, 1980, 94 Stat. 3018; Pub. L. 100–418, title IX, § 9002, Aug. 23, 1988, 102 Stat. 1563; Pub. L. 103–465, title V, § 532(a)(1), Dec. 8, 1994, 108 Stat. 4983; Pub. L. 104–295, § 20(e)(1), Oct. 11, 1996, 110 Stat. 3529; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, §§ 4402(a), 4504], Nov. 29, 1999, 113 Stat. 1536, 1501A–557, 1501A–564; Pub. L. 107–273, div. C, title III, §§ 13204, 13206(a)(8), Nov. 2, 2002, 116 Stat. 1902, 1904; Pub. L. 112–29, §§ 3(j)(1), (2)(B), 9(a), 20(j), Sept. 16, 2011, 125 Stat. 290, 316, 335; Pub. L. 112–211, title I, § 102(6), Dec. 18, 2012, 126 Stat. 1531; Pub. L. 112–274, § 1(h), Jan. 14, 2013, 126 Stat. 2457.)

HISTORICAL AND REVISION NOTES

Based on Title 35, U.S.C., 1946 ed., § 40 (R.S. 4884, amended May 23, 1930, ch. 312, § 1, 46 Stat. 376).

The reference to plants is omitted for inclusion in another section and the reference to the title is shortened since the title is of no legal significance.

The wording of the granting clause is changed to "the right to exclude others from making, using, or selling", following language used by the Supreme Court, to render the meaning clearer.

"United States" is defined in section 100.

REFERENCES IN TEXT

The date of the enactment of the Uruguay Round Agreements Act, referred to in subsec. (c)(1), (2)(A), is the date of enactment of Pub. L. 103–465, which was approved Dec. 8, 1994.

AMENDMENTS

2013—Subsec. (b)(1)(A)(i)(II). Pub. L. 112–274, § 1(h)(1)(A), which directed substitution of "of commencement of the national stage under section 371 in an international application" for "on which an international application fulfilled the requirements of section 371 of this title", was executed by making the substitution for "on which an international application fulfilled the requirements of section 371", to reflect the probable intent of Congress and the intervening amendment by Pub. L. 112–29, § 20(j). See 2011 Amendment note below.

Subsec. (b)(1)(B). Pub. L. 112–274, § 1(h)(1)(B), substituted "the application under section 111(a) in the United States or, in the case of an international application, the date of commencement of the national stage under section 371 in the international application" for "the application in the United States" in introductory provisions.

Subsec. (b)(3)(B)(i). Pub. L. 112–274, § 1(h)(2), substituted "no later than the date of issuance of the patent" for "with the written notice of allowance of the application under section 151".

Subsec. (b)(4)(A). Pub. L. 112–274, § 1(h)(3), substituted "the Director's decision on the applicant's request for reconsideration under paragraph (3)(B)(ii) shall have exclusive remedy" for "a determination made by the Director under paragraph (3) shall have remedy" and "the date of the Director's decision on the applicant's request for reconsideration" for "the grant of the patent".

2012—Subsec. (a)(2). Pub. L. 112–211, § 102(6)(A)(i), substituted "section 120, 121, 365(c), or 386(c)" for "section 120, 121, or 365(c)".

Subsec. (a)(3). Pub. L. 112–211, § 102(6)(A)(ii), substituted "section 119, 365(a), 365(b), 386(a), or 386(b)" for "section 119, 365(a), or 365(b)".

Subsec. (d)(1). Pub. L. 112–211, § 102(6)(B), inserted "or an international design application filed under the treaty defined in section 381(a)(1) designating the United States under Article 5 of such treaty" after "Article 21(2)(a) of such treaty" in introductory provisions.

2011—Subsec. (a)(2). Pub. L. 112–29, § 20(j), struck out "of this title" after "365(c)".

Subsec. (a)(3). Pub. L. 112–29, § 20(j), struck out "of this title" after "365(b)".

Subsec. (b)(1)(A)(i). Pub. L. 112–29, § 20(j), in introductory provisions, struck out "of this title" after "132" and after "151".

Subsec. (b)(1)(A)(i)(I). Pub. L. 112–29, § 20(j), struck out "of this title" after "111(a)".

Subsec. (b)(1)(A)(i)(II). Pub. L. 112–29, § 20(j), struck out "of this title" after "371".

Subsec. (b)(1)(A)(iii), (B)(ii). Pub. L. 112–29, § 3(j)(1), substituted "Patent Trial and Appeal Board" for "Board of Patent Appeals and Interferences".

Subsec. (b)(1)(C). Pub. L. 112–29, § 3(j)(2)(B), amended heading generally. Prior to amendment, heading read as follows: "Guarantee or adjustments for delays due to interferences, secrecy orders, and appeals".

Subsec. (b)(1)(C)(iii). Pub. L. 112–29, § 3(j)(1), substituted "Patent Trial and Appeal Board" for "Board of Patent Appeals and Interferences".

Subsec. (b)(4)(A). Pub. L. 112–29, § 9(a), substituted "United States District Court for the Eastern District of Virginia" for "United States District Court for the District of Columbia".

Subsec. (c)(2). Pub. L. 112–29, § 20(j), in introductory provisions, struck out "of this title" after "285".

Subsec. (c)(3). Pub. L. 112–29, § 20(j), struck out "of this title" after "excluded by paragraph (2))".

2002—Subsec. (b)(4)(A). Pub. L. 107–273, § 13206(a)(8), struck out ", United States Code," after "title 5".

Subsec. (d)(4)(A). Pub. L. 107–273, § 13204, amended subsec. (d)(4)(A) as in effect on Nov. 29, 2000, by substituting "the date of" for "the date on which the Patent and Trademark Office receives a copy of the" and "publication in the English language" for "international application in the English language".

1999—Pub. L. 106–113, § 1000(a)(9) [title IV, § 4504(1)], inserted "; provisional rights" after "patent" in section catchline.

Subsec. (b). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4402(a)], amended heading and text of subsec. (b) generally. Prior to amendment, text provided for interference delay or secrecy orders, extensions for appellate review, a limitations period, and a maximum period of 5 years duration for all extensions.

Subsec. (d). Pub. L. 106–113, § 1000(a)(9) [title IV, § 4504(2)], added subsec. (d).

1996—Subsec. (c)(2). Pub. L. 104–295 substituted "acts" for "Acts" in introductory provisions.

1994—Pub. L. 103–465 amended section catchline and text generally. Prior to amendment, text read as follows: "Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, for the term of seventeen years, subject to the payment of fees as provided for in this title, of the right to exclude others from making, using, or selling the invention throughout the United States and, if the invention is a process, of the right to exclude others from using or selling throughout the United States, or importing into the United States, products made by that process,, referring to the specification for the particulars thereof. A copy of the specification and drawings shall be annexed to the patent and be a part thereof."

1988—Pub. L. 100–418 inserted "and, if the invention is a process, of the right to exclude others from using or selling throughout the United States, or importing into the United States, products made by that process," after "United States".

1980—Pub. L. 96–517 substituted "payment of fees" for "payment of issue fees".

1965—Pub. L. 89–83 added "subject to the payment of issue fees as provided for in this title".

EFFECTIVE DATE OF 2013 AMENDMENT

Amendment by Pub. L. 112–274 effective Jan. 14, 2013, and applicable to proceedings commenced on or after such date, see section 1(n) of Pub. L. 112–274, set out as a note under section 5 of this title.

EFFECTIVE DATE OF 2012 AMENDMENT

Amendment by Pub. L. 112–211 effective on the later of the date that is 1 year after Dec. 18, 2012, or the date that the Geneva Act of the Hague Agreement Concerning the International Registration of Industrial Designs enters into force with respect to the United States (May 13, 2015), and applicable only to certain applications filed on and after that effective date and patents issuing thereon, see section 103 of Pub. L. 112–211, set out as a note under section 100 of this title.

EFFECTIVE DATE OF 2011 AMENDMENT

Amendment by section 3(j)(1), (2)(B) of Pub. L. 112–29 effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to certain applications for patent and any patents issuing thereon, see section 3(n) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment; Savings Provisions note under section 100 of this title.

Amendment by section 9(a) of Pub. L. 112–29 effective Sept. 16, 2011, and applicable to any civil action commenced on or after that date, see section 9(b) of Pub. L. 112–29, set out as a note under section 1071 of Title 15, Commerce and Trade.

Amendment by section 20(j) of Pub. L. 112–29 effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, see section 20(*l*) of Pub. L. 112–29, set out as a note under section 2 of this title.

EFFECTIVE DATE OF 1999 AMENDMENT

Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, § 4405(a)], Nov. 29, 1999, 113 Stat. 1536, 1501A–560, provided that: "The amendments made by sections 4402 and 4404 [amending this section, sections 156 and 282 of this title, and section 1295 of Title 28, Judiciary and Judicial Procedure] shall take effect on the date that is 6 months after the date of the enactment of this Act [Nov. 29, 1999] and, except for a design patent application filed under chapter 16 of title 35, United States Code, shall apply to any application filed on or after the date that is 6 months after the date of the enactment of this Act."

Amendment by section 1000(a)(9) [title IV, § 4504] of Pub. L. 106–113 effective Nov. 29, 2000, applicable only to applications (including international applications designating the United States) filed on or after that date, and additionally applicable to any pending application filed before Nov. 29, 2000, if such pending application is published pursuant to a request of the applicant under such procedures as may be established by the Director, see section 1000(a)(9) [title IV, § 4508] of Pub. L. 106–113, as amended, set out as a note under section 10 of this title.

EFFECTIVE DATE OF 1994 AMENDMENT

Pub. L. 103–465, title V, § 534, Dec. 8, 1994, 108 Stat. 4990, provided that:

"(a) IN GENERAL.—Subject to subsection (b), the amendments made by this subtitle [subtitle C (§§ 531–534) of title V of Pub. L. 103–465, amending this section and sections 41, 104, 111, 119, 156, 172, 173, 252, 262, 271, 272, 287, 292, 295, 307, 365, and 373 of this title] take effect on the date that is one year after the date on which the WTO Agreement enters into force with respect to the United States [Jan. 1, 1995].

"(b) PATENT APPLICATIONS.—

"(1) IN GENERAL.—Subject to paragraph (2), the amendments made by section 532 [amending this section and sections 41, 111, 119, 156, 172, 173, 365, and 373 of this title] take effect on the date that is 6 months after the date of the enactment of this Act [Dec. 8, 1994] and shall apply to all patent applications filed in the United States on or after the effective date.

"(2) SECTION 154(a)(1).—Section 154(a)(1) of title 35, United States Code, as amended by section 532(a)(1) of this Act, shall take effect on the effective date described in subsection (a).

"(3) EARLIEST FILING.—The term of a patent granted on an application that is filed on or after the effective date described in subsection (a) and that contains a specific reference to an earlier application filed under the provisions of section 120, 121, or 365(c) of title 35, United States Code, shall be measured from the filing date of the earliest filed application."

EFFECTIVE DATE OF 1988 AMENDMENT

Amendment by Pub. L. 100-418 effective 6 months after Aug. 23, 1988, and, subject to enumerated exceptions, applicable only with respect to products made or imported after such effective date, see section 9006 of Pub. L. 100-418, set out as a note under section 271 of this title.

EFFECTIVE DATE OF 1980 AMENDMENT

Amendment by Pub. L. 96-517 effective Dec. 12, 1980, see section 8(a) of Pub. L. 96-517, set out as a note under section 41 of this title.

EFFECTIVE DATE OF 1965 AMENDMENT

Amendment by Pub. L. 89-83 effective three months after July 24, 1965, see section 7(a) of Pub. L. 89-83, set out as a note under section 41 of this title.

REGULATIONS

Pub. L. 103-465, title V, § 532(a)(2), Dec. 8, 1994, 108 Stat. 4985, authorized the Commissioner of Patents and Trademarks to prescribe regulations for further limited reexamination of applications pending 2 years or longer and for examination of more than 1 independent and distinct invention in applications pending 3 years or longer, as of the effective date of section 154(a)(2) of this title, and to establish appropriate related fees.

[§§ 155, 155A. Repealed. Pub. L. 112-29, § 20(k), Sept. 16, 2011, 125 Stat. 335]

Section 155, added Pub. L. 97-414, § 11(a), Jan. 4, 1983, 96 Stat. 2065; amended Pub. L. 106-113, div. B, § 1000(a)(9) [title IV, § 4732(a)(6), (10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A-582; Pub. L. 107-273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906, related to patent term extension.

Section 155A, added Pub. L. 98-127, § 4(a), Oct. 13, 1983, 97 Stat. 832; amended Pub. L. 106-113, div. B, § 1000(a)(9) [title IV, § 4732(a)(7), (10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A-582; Pub. L. 107-273, div. C, title III, § 13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906, related to patent term restoration.

EFFECTIVE DATE OF REPEAL

Repeal effective upon the expiration of the 1-year period beginning on Sept. 16, 2011, and applicable to proceedings commenced on or after that effective date, see section 20(*l*) of Pub. L. 112-29, set out as an Effective Date of 2011 Amendment note under section 2 of this title.

§ 156. Extension of patent term

(a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b), if—

(1) the term of the patent has not expired before an application is submitted under subsection (d)(1) for its extension;

(2) the term of the patent has never been extended under subsection (e)(1) of this section;

(3) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);

(4) the product has been subject to a regulatory review period before its commercial marketing or use;

(5)(A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;

(B) in the case of a patent which claims a method of manufacturing the product which primarily uses recombinant DNA technology in the manufacture of the product, the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of a product manufactured under the process claimed in the patent; or

(C) for purposes of subparagraph (A), in the case of a patent which—

(i) claims a new animal drug or a veterinary biological product which (I) is not covered by the claims in any other patent which has been extended, and (II) has received permission for the commercial marketing or use in non-food-producing animals and in food-producing animals, and

(ii) was not extended on the basis of the regulatory review period for use in non-food-producing animals,

the permission for the commercial marketing or use of the drug or product after the regulatory review period for use in food-producing animals is the first permitted commercial marketing or use of the drug or product for administration to a food-producing animal.

The product referred to in paragraphs (4) and (5) is hereinafter in this section referred to as the "approved product".

(b) Except as provided in subsection (d)(5)(F), the rights derived from any patent the term of which is extended under this section shall during the period during which the term of the patent is extended—

(1) in the case of a patent which claims a product, be limited to any use approved for the product—

(A) before the expiration of the term of the patent—

(i) under the provision of law under which the applicable regulatory review occurred, or

(ii) under the provision of law under which any regulatory review described in paragraph (1), (4), or (5) of subsection (g) occurred, and

(B) on or after the expiration of the regulatory review period upon which the extension of the patent was based;

(2) in the case of a patent which claims a method of using a product, be limited to any use claimed by the patent and approved for the product—

(A) before the expiration of the term of the patent—

(i) under any provision of law under which an applicable regulatory review occurred, and

(ii) under the provision of law under which any regulatory review described in paragraph (1), (4), or (5) of subsection (g) occurred, and

(B) on or after the expiration of the regulatory review period upon which the extension of the patent was based; and

(3) in the case of a patent which claims a method of manufacturing a product, be limited to the method of manufacturing as used to make—

(A) the approved product, or

(B) the product if it has been subject to a regulatory review period described in paragraph (1), (4), or (5) of subsection (g).

As used in this subsection, the term "product" includes an approved product.

(c) The term of a patent eligible for extension under subsection (a) shall be extended by the time equal to the regulatory review period for the approved product which period occurs after the date the patent is issued, except that—

(1) each period of the regulatory review period shall be reduced by any period determined under subsection (d)(2)(B) during which the applicant for the patent extension did not act with due diligence during such period of the regulatory review period;

(2) after any reduction required by paragraph (1), the period of extension shall include only one-half of the time remaining in the periods described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g);

(3) if the period remaining in the term of a patent after the date of the approval of the approved product under the provision of law under which such regulatory review occurred when added to the regulatory review period as revised under paragraphs (1) and (2) exceeds fourteen years, the period of extension shall be reduced so that the total of both such periods does not exceed fourteen years; and

(4) in no event shall more than one patent be extended under subsection (e)(1) for the same regulatory review period for any product.

(d)(1) To obtain an extension of the term of a patent under this section, the owner of record of the patent or its agent shall submit an application to the Director. Except as provided in paragraph (5), such an application may only be submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use, or in the case of a drug product described in subsection (1), within the sixty-day period beginning on the covered date (as defined in subsection (1)). The application shall contain—

(A) the identity of the approved product and the Federal statute under which regulatory review occurred;

(B) the identity of the patent for which an extension is being sought and the identity of each claim of such patent which claims the approved product or a method of using or manufacturing the approved product;

(C) information to enable the Director to determine under subsections (a) and (b) the eligibility of a patent for extension and the rights that will be derived from the extension and information to enable the Director and the Secretary of Health and Human Services or the Secretary of Agriculture to determine the period of the extension under subsection (g);

(D) a brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities; and

(E) such patent or other information as the Director may require.

For purposes of determining the date on which a product receives permission under the second sentence of this paragraph, if such permission is transmitted after 4:30 P.M., Eastern Time, on a business day, or is transmitted on a day that is not a business day, the product shall be deemed to receive such permission on the next business day. For purposes of the preceding sentence, the term "business day" means any Monday, Tuesday, Wednesday, Thursday, or Friday, excluding any legal holiday under section 6103 of title 5.

(2)(A) Within 60 days of the submittal of an application for extension of the term of a patent under paragraph (1), the Director shall notify—

(i) the Secretary of Agriculture if the patent claims a drug product or a method of using or manufacturing a drug product and the drug product is subject to the Virus-Serum-Toxin Act, and

(ii) the Secretary of Health and Human Services if the patent claims any other drug product, a medical device, or a food additive or color additive or a method of using or manufacturing such a product, device, or additive and if the product, device, and additive are subject to the Federal Food, Drug, and Cosmetic Act,

of the extension application and shall submit to the Secretary who is so notified a copy of the application. Not later than 30 days after the receipt of an application from the Director, the Secretary receiving the application shall review the dates contained in the application pursuant to paragraph (1)(C) and determine the applicable regulatory review period, shall notify the Director of the determination, and shall publish in the Federal Register a notice of such determination.

(B)(i) If a petition is submitted to the Secretary making the determination under subparagraph (A), not later than 180 days after the publication of the determination under subparagraph (A), upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary making the determination shall, in accordance with regulations promulgated by such Secretary, determine if the applicant acted with due diligence during the applicable regulatory review period. The Secretary making the determination shall make such determination not later than 90 days after the receipt of such a petition. For a drug product, device, or additive subject to the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, the Secretary may not delegate the authority to make the determination prescribed by this clause to an office below the Office of the Director[1] of Food and Drugs. For a product subject to the Virus-Serum-Toxin Act, the Secretary of Agriculture may not delegate the authority to make the determination prescribed by this clause to an office below the Of-

[1] So in original. Probably should be "Commissioner".

fice of the Assistant Secretary for Marketing and Inspection Services.

(ii) The Secretary making a determination under clause (i) shall notify the Director of the determination and shall publish in the Federal Register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary making the determination to hold an informal hearing on the determination. If such a request is made within such period, such Secretary shall hold such hearing not later than 30 days after the date of the request, or at the request of the person making the request, not later than 60 days after such date. The Secretary who is holding the hearing shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, such Secretary shall affirm or revise the determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register.

(3) For the purposes of paragraph (2)(B), the term "due diligence" means that degree of attention, continuous directed effort, and timeliness as may reasonably be expected from, and are ordinarily exercised by, a person during a regulatory review period.

(4) An application for the extension of the term of a patent is subject to the disclosure requirements prescribed by the Director.

(5)(A) If the owner of record of the patent or its agent reasonably expects that the applicable regulatory review period described in paragraph (1)(B)(ii), (2)(B)(ii), (3)(B)(ii), (4)(B)(ii), or (5)(B)(ii) of subsection (g) that began for a product that is the subject of such patent may extend beyond the expiration of the patent term in effect, the owner or its agent may submit an application to the Director for an interim extension during the period beginning 6 months, and ending 15 days, before such term is due to expire. The application shall contain—

(i) the identity of the product subject to regulatory review and the Federal statute under which such review is occurring;

(ii) the identity of the patent for which interim extension is being sought and the identity of each claim of such patent which claims the product under regulatory review or a method of using or manufacturing the product;

(iii) information to enable the Director to determine under subsection (a)(1), (2), and (3) the eligibility of a patent for extension;

(iv) a brief description of the activities undertaken by the applicant during the applicable regulatory review period to date with respect to the product under review and the significant dates applicable to such activities; and

(v) such patent or other information as the Director may require.

(B) If the Director determines that, except for permission to market or use the product commercially, the patent would be eligible for an extension of the patent term under this section, the Director shall publish in the Federal Register a notice of such determination, including the identity of the product under regulatory review, and shall issue to the applicant a certificate of interim extension for a period of not more than 1 year.

(C) The owner of record of a patent, or its agent, for which an interim extension has been granted under subparagraph (B), may apply for not more than 4 subsequent interim extensions under this paragraph, except that, in the case of a patent subject to subsection (g)(6)(C), the owner of record of the patent, or its agent, may apply for only 1 subsequent interim extension under this paragraph. Each such subsequent application shall be made during the period beginning 60 days before, and ending 30 days before, the expiration of the preceding interim extension.

(D) Each certificate of interim extension under this paragraph shall be recorded in the official file of the patent and shall be considered part of the original patent.

(E) Any interim extension granted under this paragraph shall terminate at the end of the 60-day period beginning on the date on which the product involved receives permission for commercial marketing or use, except that, if within that 60-day period the applicant notifies the Director of such permission and submits any additional information under paragraph (1) of this subsection not previously contained in the application for interim extension, the patent shall be further extended, in accordance with the provisions of this section—

(i) for not to exceed 5 years from the date of expiration of the original patent term; or

(ii) if the patent is subject to subsection (g)(6)(C), from the date on which the product involved receives approval for commercial marketing or use.

(F) The rights derived from any patent the term of which is extended under this paragraph shall, during the period of interim extension—

(i) in the case of a patent which claims a product, be limited to any use then under regulatory review;

(ii) in the case of a patent which claims a method of using a product, be limited to any use claimed by the patent then under regulatory review; and

(iii) in the case of a patent which claims a method of manufacturing a product, be limited to the method of manufacturing as used to make the product then under regulatory review.

(e)(1) A determination that a patent is eligible for extension may be made by the Director solely on the basis of the representations contained in the application for the extension. If the Director determines that a patent is eligible for extension under subsection (a) and that the requirements of paragraphs (1) through (4) of subsection (d) have been complied with, the Director shall issue to the applicant for the extension of the term of the patent a certificate of extension, under seal, for the period prescribed by subsection (c). Such certificate shall be recorded

in the official file of the patent and shall be considered as part of the original patent.

(2) If the term of a patent for which an application has been submitted under subsection (d)(1) would expire before a certificate of extension is issued or denied under paragraph (1) respecting the application, the Director shall extend, until such determination is made, the term of the patent for periods of up to one year if he determines that the patent is eligible for extension.

(f) For purposes of this section:

(1) The term "product" means:

(A) A drug product.

(B) Any medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act.

(2) The term "drug product" means the active ingredient of—

(A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act), or

(B) a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Virus-Serum-Toxin Act) which is not primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific genetic manipulation techniques,

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

(3) The term "major health or environmental effects test" means a test which is reasonably related to the evaluation of the health or environmental effects of a product, which requires at least six months to conduct, and the data from which is submitted to receive permission for commercial marketing or use. Periods of analysis or evaluation of test results are not to be included in determining if the conduct of a test required at least six months.

(4)(A) Any reference to section 351 is a reference to section 351 of the Public Health Service Act.

(B) Any reference to section 503, 505, 512, or 515 is a reference to section 503, 505, 512, or 515 of the Federal Food, Drug, and Cosmetic Act.

(C) Any reference to the Virus-Serum-Toxin Act is a reference to the Act of March 4, 1913 (21 U.S.C. 151–158).

(5) The term "informal hearing" has the meaning prescribed for such term by section 201(y)[2] of the Federal Food, Drug, and Cosmetic Act.

(6) The term "patent" means a patent issued by the United States Patent and Trademark Office.

(7) The term "date of enactment" as used in this section means September 24, 1984, for a human drug product, a medical device, food additive, or color additive.

(8) The term "date of enactment" as used in this section means the date of enactment of the Generic Animal Drug and Patent Term Restoration Act for an animal drug or a veterinary biological product.

(g) For purposes of this section, the term "regulatory review period" has the following meanings:

(1)(A) In the case of a product which is a new drug, antibiotic drug, or human biological product, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.

(B) The regulatory review period for a new drug, antibiotic drug, or human biological product is the sum of—

(i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507[2] became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507,[2] and

(ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507[2] and ending on the date such application was approved under such section.

(2)(A) In the case of a product which is a food additive or color additive, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.

(B) The regulatory review period for a food or color additive is the sum of—

(i) the period beginning on the date a major health or environmental effects test on the additive was initiated and ending on the date a petition was initially submitted with respect to the product under the Federal Food, Drug, and Cosmetic Act requesting the issuance of a regulation for use of the product, and

(ii) the period beginning on the date a petition was initially submitted with respect to the product under the Federal Food, Drug, and Cosmetic Act requesting the issuance of a regulation for use of the product, and ending on the date such regulation became effective or, if objections were filed to such regulation, ending on the date such objections were resolved and commercial marketing was permitted or, if commercial marketing was permitted and later revoked pending further proceedings as a result of such objections, ending on the date such proceedings were finally resolved and commercial marketing was permitted.

(3)(A) In the case of a product which is a medical device, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.

(B) The regulatory review period for a medical device is the sum of—

(i) the period beginning on the date a clinical investigation on humans involving the device was begun and ending on the date an application was initially submitted with respect to the device under section 515, and

(ii) the period beginning on the date an application was initially submitted with respect to the device under section 515 and

[2] See References in Text note below.

ending on the date such application was approved under such Act or the period beginning on the date a notice of completion of a product development protocol was initially submitted under section 515(f)(5) and ending on the date the protocol was declared completed under section 515(f)(6).

(4)(A) In the case of a product which is a new animal drug, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.

(B) The regulatory review period for a new animal drug product is the sum of—

(i) the period beginning on the earlier of the date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 became effective for the approved new animal drug product and ending on the date an application was initially submitted for such animal drug product under section 512, and

(ii) the period beginning on the date the application was initially submitted for the approved animal drug product under subsection (b) of section 512 and ending on the date such application was approved under such section.

(5)(A) In the case of a product which is a veterinary biological product, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.

(B) The regulatory period for a veterinary biological product is the sum of—

(i) the period beginning on the date the authority to prepare an experimental biological product under the Virus-Serum-Toxin Act became effective and ending on the date an application for a license was submitted under the Virus-Serum-Toxin Act, and

(ii) the period beginning on the date an application for a license was initially submitted for approval under the Virus-Serum-Toxin Act and ending on the date such license was issued.

(6) A period determined under any of the preceding paragraphs is subject to the following limitations:

(A) If the patent involved was issued after the date of the enactment of this section, the period of extension determined on the basis of the regulatory review period determined under any such paragraph may not exceed five years.

(B) If the patent involved was issued before the date of the enactment of this section and—

(i) no request for an exemption described in paragraph (1)(B) or (4)(B) was submitted and no request for the authority described in paragraph (5)(B) was submitted,

(ii) no major health or environmental effects test described in paragraph (2)(B) or (4)(B) was initiated and no petition for a regulation or application for registration described in such paragraph was submitted, or

(iii) no clinical investigation described in paragraph (3) was begun or product development protocol described in such paragraph was submitted,

before such date for the approved product the period of extension determined on the basis of the regulatory review period determined under any such paragraph may not exceed five years.

(C) If the patent involved was issued before the date of the enactment of this section and if an action described in subparagraph (B) was taken before the date of the enactment of this section with respect to the approved product and the commercial marketing or use of the product has not been approved before such date, the period of extension determined on the basis of the regulatory review period determined under such paragraph may not exceed two years or in the case of an approved product which is a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act), three years.

(h) The Director may establish such fees as the Director determines appropriate to cover the costs to the Office of receiving and acting upon applications under this section.

(i)(1) For purposes of this section, if the Secretary of Health and Human Services provides notice to the sponsor of an application or request for approval, conditional approval, or indexing of a drug product for which the Secretary intends to recommend controls under the Controlled Substances Act, beginning on the covered date, the drug product shall be considered to—

(A) have been approved or indexed under the relevant provision of the Public Health Service Act or Federal Food, Drug, and Cosmetic Act; and

(B) have permission for commercial marketing or use.

(2) In this subsection, the term "covered date" means the later of—

(A) the date an application is approved—

(i) under section 351(a)(2)(C) of the Public Health Service Act; or

(ii) under section 505(b) or 512(c) of the Federal Food, Drug, and Cosmetic Act;

(B) the date an application is conditionally approved under section 571(b) of the Federal Food, Drug, and Cosmetic Act;

(C) the date a request for indexing is granted under section 572(d) of the Federal Food, Drug, and Cosmetic Act; or

(D) the date of issuance of the interim final rule controlling the drug under section 201(j) of the Controlled Substances Act.

(Added Pub. L. 98–417, title II, § 201(a), Sept. 24, 1984, 98 Stat. 1598; amended Pub. L. 100–670, title II, § 201(a)–(h), Nov. 16, 1988, 102 Stat. 3984–3987; Pub. L. 103–179, §§ 5, 6, Dec. 3, 1993, 107 Stat. 2040, 2042; Pub. L. 103–465, title V, § 532(c)(1), Dec. 8, 1994, 108 Stat. 4987; Pub. L. 105–115, title I, § 125(b)(2)(P), Nov. 21, 1997, 111 Stat. 2326; Pub. L. 106–113, div. B, § 1000(a)(9) [title IV, §§ 4404, 4732(a)(10)(A)], Nov. 29, 1999, 113 Stat. 1536, 1501A–560, 1501A–582; Pub. L. 107–273, div. C, title III, § 13206(a)(9), (b)(1)(B), Nov. 2, 2002, 116 Stat.

1904, 1906; Pub. L. 112–29, §37(a), Sept. 16, 2011, 125 Stat. 341; Pub. L. 114–89, §2(c), Nov. 25, 2015, 129 Stat. 700.)

REFERENCES IN TEXT

The Virus-Serum-Toxin Act, referred to in subsecs. (d)(2)(A)(i), (B)(i), (f)(2)(B), (4)(C), and (g)(5)(B), (6)(C), is the eighth paragraph under the heading "Bureau of Animal Industry" of act Mar. 4, 1913, ch. 145, 37 Stat. 828, as amended, which is classified generally to chapter 5 (§151 et seq.) of Title 21, Food and Drugs. For complete classification of this Act to the Code, see Short Title note set out under section 151 of Title 21 and Tables.

The Federal Food, Drug, and Cosmetic Act, referred to in subsecs. (d)(2)(A)(ii), (B)(ii), (f), (g)(2)(B), (3)(B)(ii), (6)(C), and (i)(1)(A), is act June 25, 1938, ch. 675, 52 Stat. 1040, which is classified generally to chapter 9 (§301 et seq.) of Title 21, Food and Drugs. For complete classification of this Act to the Code, see section 301 of Title 21 and Tables.

The Public Health Service Act, referred to in subsecs. (d)(2)(B)(i), (f)(2)(A), and (i)(1)(A), is act July 1, 1944, ch. 373, 58 Stat. 682, which is classified generally to chapter 6A (§201 et seq.) of Title 42, The Public Health and Welfare. For complete classification of this Act to the Code, see Short Title note set out under section 201 of Title 42 and Tables.

Sections 503, 505, 512, 515, 571, and 572 of the Federal Food, Drug, and Cosmetic Act, referred to in subsecs. (f)(4)(B), (g)(1)(B), (3)(B), and (i)(2)(A)(ii), (B), (C), are classified, respectively, to sections 353, 355, 360b, 360e, 360ccc, and 360ccc–1 of Title 21, Food and Drugs. Section 507 of the Act, referred to in subsec. (g)(1)(B), was classified to section 357 of Title 21, prior to repeal by Pub. L. 105–115, title I, §125(b)(1), Nov. 21, 1997, 111 Stat. 2325.

Section 201 of the Federal Food, Drug, and Cosmetic Act, referred to in subsec. (f)(5), which is classified to section 321 of Title 21, was subsequently amended, and section 201(y) no longer defines the term "informal hearing". However, such term is defined elsewhere in that section.

Section 351 of the Public Health Service Act, referred to in subsecs. (f)(4)(A), (g)(1)(B)(i), (ii), and (i)(2)(A)(i), is classified to section 262 of Title 42, The Public Health and Welfare.

The date of enactment of the Generic Animal Drug and Patent Term Restoration Act, referred to in subsec. (f)(8), is the date of enactment of Pub. L. 100–670, which was approved Nov. 16, 1988.

The date of the enactment of this section, referred to in subsec. (g)(6), is the date of the enactment of Pub. L. 98–417, which was approved Sept. 24, 1984.

The Controlled Substances Act, referred to in subsec. (i)(1), is title II of Pub. L. 91–513, Oct. 27, 1970, 84 Stat. 1242, which is classified principally to subchapter I (§801 et seq.) of chapter 13 of Title 21, Food and Drugs. For complete classification of this Act to the Code, see Short Title note set out under section 801 of Title 21 and Tables.

Section 201 of the Controlled Substances Act, referred to in subsec. (i)(2)(D), is classified to section 811 of Title 21, Food and Drugs.

AMENDMENTS

2015—Subsec. (d)(1). Pub. L. 114–89, §2(c)(1), in introductory provisions, inserted ", or in the case of a drug product described in subsection (i), within the sixty-day period beginning on the covered date (as defined in subsection (i))" after "marketing or use".

Subsec. (i). Pub. L. 114–89, §2(c)(2), added subsec. (i).

2011—Subsec. (d)(1). Pub. L. 112–29 inserted concluding provisions.

2002—Subsec. (b)(3)(B). Pub. L. 107–273, §13206(a)(9)(A), substituted "paragraph" for "paragraphs".

Subsec. (d). Pub. L. 107–273, §13206(b)(1)(B), made technical correction to directory language of Pub. L. 106–113, §1000(a)(9) [title IV, §4732(a)(10)(A)]. See 1999 Amendment note below.

Subsec. (d)(2)(B)(i). Pub. L. 107–273, §13206(a)(9)(B), substituted "below the Office" for "below the office".

Subsec. (e). Pub. L. 107–273, §13206(b)(1)(B), made technical correction to directory language of Pub. L. 106–113, §1000(a)(9) [title IV, §4732(a)(10)(A)]. See 1999 Amendment note below.

Subsec. (g)(6)(B)(iii). Pub. L. 107–273, §13206(a)(9)(C), substituted "submitted" for "submittted".

Subsec. (h). Pub. L. 107–273, §13206(b)(1)(B), made technical correction to directory language of Pub. L. 106–113, §1000(a)(9) [title IV, §4732(a)(10)(A)]. See 1999 Amendment note below.

1999—Subsec. (a). Pub. L. 106–113, §1000(a)(9) [title IV, §4404], in introductory provisions, inserted ", which shall include any patent term adjustment granted under section 154(b)," after "the original expiration date of the patent".

Subsecs. (d), (e), (h). Pub. L. 106–113, §1000(a)(9) [title IV, §4732(a)(10)(A)], as amended by Pub. L. 107–273, §13206(b)(1)(B), substituted "Director" for "Commissioner" wherever appearing.

1997—Subsec. (f)(4)(B). Pub. L. 105–115, §125(b)(2)(P), struck out "507," after "505," in two places.

1994—Subsec. (a)(2). Pub. L. 103–465 inserted "under subsection (e)(1) of this section" after "extended".

1993—Subsec. (a)(1). Pub. L. 103–179, §6(1)(A), substituted "subsection (d)(1)" for "subsection (d)".

Subsec. (a)(3). Pub. L. 103–179, §6(1)(B), substituted "paragraphs (1) through (4) of subsection (d)" for "subsection (d)".

Subsec. (b). Pub. L. 103–179, §6(2), substituted "Except as provided in subsection (d)(5)(F), the rights" for "The rights" in introductory provisions.

Subsec. (c)(4). Pub. L. 103–179, §5(1), substituted "extended under subsection (e)(1)" for "extended".

Subsec. (d)(1). Pub. L. 103–179, §5(2), substituted "Except as provided in paragraph (5), such" for "Such" in second sentence.

Subsec. (d)(5). Pub. L. 103–179, §5(3), added par. (5).

Subsec. (e)(1). Pub. L. 103–179, §6(3)(A), substituted "paragraphs (1) through (4) of subsection (d)" for "subsection (d)".

Subsec. (e)(2). Pub. L. 103–179, §6(3)(B), substituted "subsection (d)(1)" for "subsection (d)".

1988—Subsec. (a)(5)(A). Pub. L. 100–670, §201(a)(1), inserted "or (C)" after "in subparagraph (B)".

Subsec. (a)(5)(C). Pub. L. 100–670, §201(a)(2), (3), added subpar. (C).

Subsec. (b). Pub. L. 100–670, §201(b), amended subsec. (b) generally. Prior to amendment, subsec. (b) read as follows: "The rights derived from any patent the term of which is extended under this section shall during the period during which the patent is extended—

"(1) in the case of a patent which claims a product, be limited to any use approved for the approved product before the expiration of the term of the patent under the provision of law under which the applicable regulatory review occurred;

"(2) in the case of a patent which claims a method of using a product, be limited to any use claimed by the patent and approved for the approved product before the expiration of the term of the patent under the provision of law under which the applicable regulatory review occurred; and

"(3) in the case of a patent which claims a method of manufacturing a product, be limited to the method of manufacturing as used to make the approved product."

Subsec. (c)(2). Pub. L. 100–670, §201(c), substituted "(3)(B)(i), (4)(B)(i), and (5)(B)(i)" for "and (3)(B)(i)".

Subsec. (d)(1)(C). Pub. L. 100–670, §201(d), inserted "or the Secretary of Agriculture" after "and Human Services".

Subsec. (d)(2)(A). Pub. L. 100–670, §201(e), amended subpar. (A) generally. Prior to amendment, subpar. (A) read as follows: "Within sixty days of the submittal of an application for extension of the term of a patent under paragraph (1), the Commissioner shall notify the Secretary of Health and Human Services if the patent claims any human drug product, a medical device, or a

food additive or color additive or a method of using or manufacturing such a product, device, or additive and if the product, device, and additive are subject to the Federal Food, Drug, and Cosmetic Act, of the extension application and shall submit to the Secretary a copy of the application. Not later than thirty days after the receipt of an application from the Commissioner, the Secretary shall review the dates contained in the application pursuant to paragraph (1)(C) and determine the applicable regulatory review period, shall notify the Commissioner of the determination, and shall publish in the Federal Register a notice of such determination."

Subsec. (d)(2)(B). Pub. L. 100–670, §201(f), amended subpar. (B) generally. Prior to amendment, subpar. (B) read as follows:

"(i) If a petition is submitted to the Secretary under subparagraph (A), not later than one hundred and eighty days after the publication of the determination under subparagraph (A), upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall, in accordance with regulations promulgated by the Secretary determine if the applicant acted with due diligence during the applicable regulatory review period. The Secretary shall make such determination not later than ninety days after the receipt of such a petition. The Secretary may not delegate the authority to make the determination prescribed by this subparagraph to an office below the Office of the Commissioner of Food and Drugs.

"(ii) The Secretary shall notify the Commissioner of the determination and shall publish in the Federal Register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the sixty-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such a request is made within such period, the Secretary shall hold such hearing not later than thirty days after the date of the request, or at the request of the person making the request, not later than sixty days after such date. The Secretary shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within thirty days after the completion of the hearing, the Secretary shall affirm or revise the determination which was the subject of the hearing and notify the Commissioner of any revision of the determination and shall publish any such revision in the Federal Register."

Subsec. (f)(1)(A). Pub. L. 100–670, §201(g)(1), struck out "human" before "drug product".

Subsec. (f)(2). Pub. L. 100–670, §201(g)(1), amended par. (2) generally. Prior to amendment, par. (2) read as follows: "The term 'human drug product' means the active ingredient of a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient."

Subsec. (f)(4)(B), (C). Pub. L. 100–670, §201(g)(2), which directed general amendment of subpars. (B) and (C) of par. (4), was executed by amending subpar. (B) generally, and adding subpar. (C) as probable intent of Congress in light of absence of subpar. (C) in par. (4). Prior to amendment, subpar. (B) read as follows: "Any reference to section 503, 505, 507, or 515 is a reference to section 503, 505, 507, or 515 of the Federal Food, Drug, and Cosmetic Act."

Subsec. (f)(7), (8). Pub. L. 100–670, §201(g)(3), added pars. (7) and (8).

Subsec. (g)(1)(A). Pub. L. 100–670, §201(h)(1)(A), (2), substituted "new drug, antibiotic drug, or human biological product" for "human drug product" and "paragraph (6)" for "paragraph (4)".

Subsec. (g)(1)(B). Pub. L. 100–670, §201(h)(1)(B), substituted "new drug, antibiotic drug, or human biological product" for "human drug product" in introductory provisions and "product" for "human drug product" in cls. (i) and (ii).

Subsec. (g)(2)(A), (3)(A). Pub. L. 100–670, §201(h)(3), substituted "paragraph (6)" for "paragraph (4)".

Subsec. (g)(4), (5). Pub. L. 100–670, §201(h)(4), added pars. (4) and (5). Former par. (4) redesignated (6).

Subsec. (g)(6). Pub. L. 100–670, §201(h)(4), redesignated former par. (4) as (6).

Subsec. (g)(6)(B)(i). Pub. L. 100–670, §201(h)(5)(A), substituted "paragraph (1)(B) or (4)(B) was submitted and no request for the authority described in paragraph (5)(B) was submitted" for "paragraph (1)(B) was submitted".

Subsec. (g)(6)(B)(ii). Pub. L. 100–670, §201(h)(5)(B), substituted "paragraph (2)(B) or (4)(B)" for "paragraph (2)".

Subsec. (g)(6)(C). Pub. L. 100–670, §201(h)(5)(C), inserted "or in the case of an approved product which is a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act or the Virus-Serum-Toxin Act), three years" after "exceed two years".

EFFECTIVE DATE OF 2011 AMENDMENT

Pub. L. 112–29, §37(b), Sept. 16, 2011, 125 Stat. 341, provided that: "The amendment made by subsection (a) [amending this section] shall apply to any application for extension of a patent term under section 156 of title 35, United States Code, that is pending on, that is filed after, or as to which a decision regarding the application is subject to judicial review on, the date of the enactment of this Act [Sept. 16, 2011]."

EFFECTIVE DATE OF 1999 AMENDMENT

Amendment by section 1000(a)(9) [title IV, §4404] of Pub. L. 106–113 effective on date that is 6 months after Nov. 29, 1999, and, except for design patent application filed under chapter 16 of this title, applicable to any application filed on or after such date, see section 1000(a)(9) [title IV, §4405(a)] of Pub. L. 106–113, set out as a note under section 154 of this title.

Amendment by section 1000(a)(9) [title IV, §4732(a)(10)(A)] of Pub. L. 106–113 effective 4 months after Nov. 29, 1999, see section 1000(a)(9) [title IV, §4731] of Pub. L. 106–113, set out as a note under section 1 of this title.

EFFECTIVE DATE OF 1994 AMENDMENT

Amendment by Pub. L. 103–465 effective 6 months after Dec. 8, 1994, and applicable to all patent applications filed in the United States on or after that effective date, with provisions relating to earliest filed patent application, see section 534(b)(1), (3) of Pub. L. 103–465, set out as a note under section 154 of this title.

[§ 157. Repealed. Pub. L. 112–29, § 3(e)(1), Sept. 16, 2011, 125 Stat. 287]

Section, added Pub. L. 98–622, title I, §102(a), Nov. 8, 1984, 98 Stat. 3383; amended Pub. L. 106–113, div. B, §1000(a)(9) [title IV, §4732(a)(10)(A), (11)], Nov. 29, 1999, 113 Stat. 1536, 1501A–582, 1501A–583; Pub. L. 107–273, div. C, title III, §13206(b)(1)(B), Nov. 2, 2002, 116 Stat. 1906; Pub. L. 112–29, §20(j), Sept. 16, 2011, 125 Stat. 335, related to statutory invention registration.

EFFECTIVE DATE OF REPEAL

Repeal effective upon the expiration of the 18-month period beginning on Sept. 16, 2011, and applicable to any request for a statutory invention registration filed on or after that effective date, see section 3(e)(3) of Pub. L. 112–29, set out as an Effective Date of 2011 Amendment note under section 111 of this title.

CHAPTER 15—PLANT PATENTS

Guidance for Industry

Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Office of Cellular, Tissues, and Gene Therapies at 301-827-5102.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2006

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry

Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides to you, sponsors of gene therapy studies, recommendations regarding the design of studies to include the collection of data on delayed adverse events in subjects who have been exposed to investigational gene therapy products. We, FDA, are providing: (1) recommended methods to assess the risk of gene therapy-related delayed adverse events following exposure to investigational gene therapy products, (2) recommended methods to determine the likelihood that long-term follow-up observations on study subjects will provide scientifically meaningful information, and (3) specific advice regarding the duration and design of long-term follow-up observations.[1] When a gene therapy clinical trial presents long-term risks to human subjects, a gene therapy clinical trial must provide for long-term follow-up observations in order to mitigate those risks. Without such long-term follow-up observations,

[1] This guidance does not cover the following topics:

- Inadvertent germline gene transfer. (The term "germline" is used to designate genetic material destined to be transferred to gametes). For a discussion of risks associated with inadvertent germline gene transfer for gene therapy products, we refer you to the following meeting transcripts:
  - December 15-16, 1997, Recombinant DNA Advisory Committee (RAC) meeting (http://www4.od.nih.gov/oba/rac/minutes/12151697.htm),
  - March 11-12, 1999, RAC meeting (http://www4.od.nih.gov/oba/rac/minutes/3-99RAC.htm), and
  - November 16-17, 2000, Biological Response Modifiers Advisory Committee (BRMAC) meeting (http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm. November 17, 2000, 3664t2_b.pdf).
- Vaccines used to prevent infectious diseases even if you use products analogous to those used for gene therapy (consult the Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER)).
- Post-marketing or licensure requirements for performing long-term follow-up studies of subjects. The specific information needed for a licensure or post-marketing study will vary, and therefore, will be addressed with individual sponsors.
- Replication-competent non-transgene-containing viruses used as agents to mediate oncolysis. Due to the diversity of the viral agents employed, we recommend that you discuss with the Office of Cellular, Tissues, and Gene Therapies (OCTGT, CBER) the potential for risks of delayed adverse events.
- Risks due to shedding of vector to close contacts, the public, or the environment. The specifics of how and whether to address these risks in your clinical trial design should be discussed with OCTGT, CBER. For general information, see "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, Revision 1" dated July 1998 (http://www.fda.gov/cber/gdlns/environ.pdf).

the study would expose the subjects to an unreasonable and significant risk of illness or injury (21 Code of Federal Regulations (CFR) 312.42(b)(1)(i) and (b)(2)(i)).

Exposure to gene transfer technology means any exposure to gene therapy products or to cells or tissue that has been transduced with gene therapy products ex vivo by any route of administration. Except as noted below, this guidance applies to all subjects in clinical studies using gene transfer technology. The recommendations in this guidance are limited to the performance of long-term observations for evidence of delayed adverse events, i.e., adverse events that occur more than one year after exposure to the investigational gene therapy product.

This guidance finalizes the draft guidance entitled "Guidance for Industry: Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events" dated August 2005. This guidance also supplements the recommendations for study subject long-term follow-up in the "Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors" (Retroviral Vector guidance), dated November 2006 (Ref. 1).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Potential Risks of Delayed Adverse Events Following Exposure to Gene Transfer Technology

Study subjects exposed to gene transfer technology may be at risk of delayed adverse events as a consequence of persistent biological activity of the genetic material or other components of the products used to carry the genetic material. The persistent biological activity may be necessary for the product to provide a continuing clinical benefit. However, persistent biological activity could have adverse effects upon normal cell function, placing subjects at risk for development of adverse events, some of which may be delayed by months or years.

Factors likely to increase the risk of delayed adverse events following exposure to gene transfer technology include persistence of the viral vector, integration of genetic material into the host genome, prolonged expression of the transgene, and altered expression of the host's genes. Persistence of the viral vector, sometimes associated with latency, could permit continued expression of the gene or delayed effects of viral infection. Integration of genetic material from a viral vector into the host cell genomic DNA raises the risk of malignant transformation (see Section V.F for a discussion of risks of malignancy associated with retroviral vectors). Prolonged expression of the transgene

may also be associated with long-term risks resulting from unregulated cell growth and malignant transformation, autoimmune-like reaction to self antigens, and unpredictable adverse events. Altered expression of the host genes could also result in unpredictable and undesirable biologic events.

B. Previous FDA Recommendations

We previously issued a guidance related to retroviral vector-mediated gene therapy (Ref. 1). We considered retroviruses to carry the highest known risk because of a reported case of new malignancy associated with a preclinical gene therapy study following exposure to cells transduced by a retroviral vector (Ref. 2), and therefore included in that guidance specific recommendations on performing long-term observations of subjects in trials of retroviral-mediated gene therapies.

We then sought additional information regarding gene-therapy related delayed adverse events following exposure to other gene-therapy products. We convened three separate meetings of our Biological Response Modifiers Advisory Committee (BRMAC) to solicit advice about long-term risks to subjects in gene therapy clinical trials exposed to other gene therapy products. The BRMAC meetings were held on November 17, 2000; April 6, 2001; and October 24, 2001.[2] Since 2001, and after reviewing BRMAC's recommendations, we have advised sponsors of studies involving gene transfer technology to submit to us their plans for long-term follow-up observations. We typically advised sponsors to observe subjects for potential gene therapy-related delayed adverse events for a 15 year period, and to include a minimum of five years of annual examinations, followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

C. Concerns Raised by the Gene Therapy Community

Members of the gene therapy community asked that the issue of long-term follow-up following exposure to gene transfer technology be discussed in a public forum. Accordingly, in June 2004 a public workshop was held in association with the annual meeting of the American Society of Gene Therapy (ASGT). The workshop was entitled "Long-Term Follow-Up of Participants in Human Gene Transfer Research" and was co-sponsored by the ASGT, Biotechnology Industry Organization (BIO), CBER, the NIH Office of Biotechnology Activities (OBA), and Pharmaceutical Research and Manufacturers of America (PhRMA). The workshop included a forum in which invited speakers discussed the challenges associated with long-term follow-up of subjects in gene therapy clinical studies. The workshop organizers published a summary of the discussion (Ref. 3).

[2] If you desire background information regarding prior recommendations from the BRMAC about gene therapy trials and long-term follow-up observations, we refer you to the transcripts for the November 17, 2000; April 6, 2001; and October 24, 2001, BRMAC meetings. The references can be located at http://www.fda.gov/cber/advisory/ctgt/ctgtmain.htm by searching under the year of the meeting.

Key issues identified by workshop participants include the following:

- Not all gene therapy products present the same risks of delayed adverse events. Uniform recommendations for long-term follow-up for all gene therapy products did not take product characteristics into account.
- Some study subjects appear unsuitable for meaningful long-term follow-up observations because of high short-term mortality, poor general health, or exposure to mutagenic agents.
- Our recommendations regarding the duration and design of long-term follow-up have not been sufficiently specific.

These issues are addressed in Sections IV and V of this guidance.

III. DEFINITIONS AND ABBREVIATIONS

The following definitions apply to this guidance:

Gene therapy products:
All products that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. The products may be used to modify cells in vivo or transferred to cells ex vivo prior to administration to the recipient.

Gene transfer:
The transfer of genetic material into a cell.

Gene transfer system:
The combination of the vector, regulating elements, vector formulation, and the route and method of vector delivery.

Gene transfer technology:
The use of genetic material either alone or in a suitable transfer medium, such as lipids, viruses, or other microorganisms, to mediate an effect by transcription, translation, or integration into the host genome or any combination of these processes. Exposure to gene transfer technology may result from direct administration of the product to a study subject or through use of cells or tissues exposed to such products ex vivo prior to administration to a study subject.

IND:
Investigational New Drug Application, as described in 21 CFR Part 312.

Integration (of DNA):
The process whereby exogenous DNA sequences become incorporated into a genome.

Latency (of a viral infection):
A period of time during which a virus is present in the host without producing overt clinical symptoms.

Long-term follow-up observations:
Long-term follow-up observations are extended assessments that continue some of the scheduled observations of a customary clinical trial. Long-term follow-up observations are an integral portion of the study of investigational products, such as gene therapy, that are considered to present a high risk of producing delayed adverse events.

Maximum feasible dose (MFD) (in preclinical studies):
The highest dose that can be administered to a non-human animal. Limitations may be due to animal size, administration site, or product characteristics. The MFD may not be equivalent to the clinically relevant dose.

Persistence:
With respect to transferred genetic material, the continued presence of genetic sequences in the host after acute exposure to a transfecting agent, whether due to integration of the genetic sequence into the host genome or to latent infection with the viral vector bearing the genetic sequence.

Preclinical Study:
An investigational study performed in non-human animals or in isolated cells or tissue from humans or other animals. Preclinical studies may be performed prior to or during clinical studies.

Reactivation (of a viral infection):
The re-emergence of a symptomatic or asymptomatic viral infection following a period of latency.

Transgene:
An exogenous gene that is introduced into a host cell.

Vector Sequences:
Refers to specific sequences of nucleotides, either DNA or RNA, that have been introduced into a gene therapy vector. The sequence includes all components of the gene therapy vector, the vector backbone, transgene(s), and regulatory elements.

Viral Vector:
A virus that has been modified to transfer genetic material.

IV. PRECLINICAL DATA USED FOR ASSESSMENT OF DELAYED RISKS IN GENE THERAPY CLINICAL TRIALS

A. Criteria to Assess Potential Delayed Risks of Gene Therapy

We generally will not require long-term follow-up observations following exposure to gene transfer technology when the risk of delayed adverse events is low. To assess the risk related to your product, we recommend that you use available preclinical and clinical evidence. To assess the risks of delayed adverse events, you may use current information about your product and similar products based on studies that you and others have performed. As more data accumulates, it is important to reassess the risk to your subjects and, if appropriate, revise your protocol as it relates to long-term follow-up observations.

We consider the assessment of risks to be a continuous process. New information may support the need for long-term follow-up observations or the revision of an existing study. For example, if recently reported evidence suggests a newly identified risk associated with your product or similar products, long-term follow-up observations may be necessary to mitigate long-term risks to subjects receiving these vectors. Similarly, if sufficient data accumulate to suggest that your product is not associated with delayed risks, it may be appropriate to reduce or eliminate provisions for long-term follow-up observations.

Pertinent previous preclinical and clinical experience with your product or similar products is highly relevant in the assessment of delayed adverse events. Experience with products in the same vector class, administered by a similar route, and given for the same clinical indication may contribute helpful information.

We recommend you refer to the series of questions in Figure 1, "Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events" to help you assess the level of risk. When the risk of delayed adverse events is low based on your answers to these questions, a plan for long-term follow-up observations may not be necessary to mitigate risks to subjects. Evidence from preclinical studies will help you answer questions 1 – 3. Include all of the primary data relevant to the assessment of the risk of delayed events when you submit your IND to FDA (see 21 CFR 312.23(a)(8), (10)(iv), (11)).

We suggest you use the framework in Figure 1 by answering the questions in sequence as follows:

- **Question 1:** "Is your gene therapy product used only for ex vivo modification of cells?"

  If the answer is "no," go to Question 2. If the answer is "yes," go to Questions 3 and 4.

- **Question 2:** "Do preclinical study results show persistence of vector sequences?" If the answer is "no," the risk of gene therapy-related delayed adverse events is low, and long-term follow-up observations may not be needed. If the answer is "yes," go to questions 3 and 4.

  If it is unknown whether your vector persists, for the purpose of assessing risk, we recommend that you either assume that it does persist, or perform a preclinical study to assay for vector persistence in a relevant animal species. Please refer to Section IV.B, "Considerations for Preclinical Study Design to Assess Vector Biodistribution and Persistence," for help with preclinical trial design and details on the use and expected sensitivity of polymerase chain reaction (PCR) assay for biodistribution studies. In assays performed after the final administration of vector, persistence is indicated by detectable levels of vector sequences above the threshold level in the PCR assay and absence of an apparent downward trend over several time points. In contrast, persistence is unlikely if you cannot detect vector sequences with a sensitive PCR assay or if the assay for vector sequences demonstrates a downward trend over time. We encourage you to consult with OCTGT, CBER for specific advice about determination of persistence and biodistribution in your test system.

- **Question 3:** "Are vector sequences integrated?"

  If the answer is "no," go to question 4. If the answer is "yes," we would require that clinical protocols with the product include clinical long-term follow-up observations.

- **Question 4:** "Does the vector have potential for latency and reactivation?"

  If the answer is "no," the risk is low that exposure to your gene transfer technology will be followed by gene therapy-related delayed adverse events. Long-term follow-up observations may not be needed. If the answer is "yes," we would require that all your clinical protocols with the product include clinical long-term follow-up observations.

Laboratory and preclinical evidence of the low risk of delayed adverse events following exposure to a similar product may show that long-term follow-up observations are not needed. If you provide data from a similar product, we can assess the relevance to your product if you provide a clear explanation.

We provide the following two examples:

- Your product is a plasmid and the similar product is also a plasmid, but has different coding sequences for the proposed therapeutic gene product. The similar product has been used in preclinical and clinical studies, administered by an identical route and in an identical final formulation to that proposed in the prospective studies. Reference to a published study demonstrating lack of persistence of the vector for the similar

product may adequately address concerns regarding the persistence of the proposed vector.

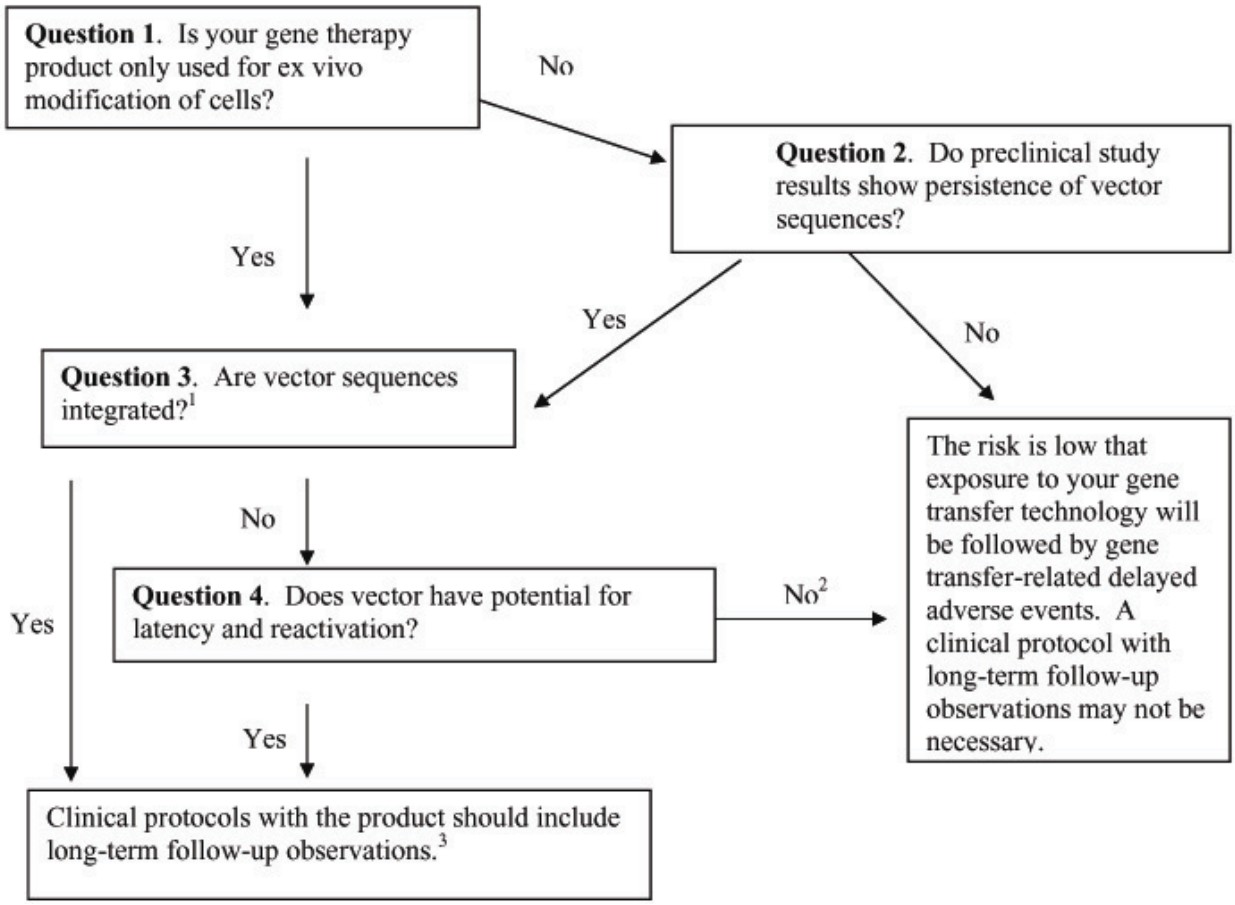
- Your proposed product and the similar product differ only with respect to route of administration. The similar product was administered into tumors (intratumorally). The proposed product is to be given intravenously. There is a published study demonstrating the lack of persistence of the vector when administered intratumorally. The data from the studies with the similar product are not sufficiently relevant, since there was no intended systemic exposure to the product. Thus, there is insufficient similarity to conclude that long-term follow-up observations are not necessary to mitigate long-term risks to subjects. In the absence of relevant data from a study involving a similar product, we recommend that you assess the risk of vector persistence in a preclinical study with the proposed product administered by the intravenous route.

If you believe you have evidence from studies on a similar product that is adequate to support conclusions that the vector is unlikely to persist in human hosts and that the vector's DNA does not integrate into the human genome, you may decide to submit a clinical protocol that does not provide for long-term follow-up observations. We will review such submissions and, if we disagree based upon our review of your submission or other additional information, we may conclude that long-term follow-up observations for delayed adverse events are necessary to mitigate long-term risks, and that without long-term follow-up observations, the study presents an unreasonable and significant risk to study subjects (21 CFR 312.42(b)(1)(i) and (b)(2)(i)).

We provide the following examples of evidence that might cause us to require you to perform long-term follow-up observations for delayed adverse events:

- A preclinical toxicology study indicates that expression of the transgene is associated with delayed toxicity.
- The transgene provides functional replacement of a host gene; the transgene product is potentially immunogenic.
- Data collected in your short-term clinical study indicate vector persistence, even though data from your preclinical studies suggested that the vector did not persist.

Figure 1. Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events.



[1] If you have evidence that suggests that the vector may integrate or if the vector was intentionally designed to facilitate integration (please refer to Table 1, Section IV.C), the answer is "yes." If you have no evidence regarding integration, we recommend that you include preclinical study in your development plan to address this question.

[2] If you or others identify an increased risk of delayed adverse events from persistent gene expression or from exposure to your product based on additional information reported after your protocol is accepted, you should plan to perform long-term follow-up observations even if the answer to these questions is "No". See Section IV.A of the text for examples.

[3] See Section V of the text for recommendations on how to perform clinical long-term follow-up observations.

B. Considerations for Preclinical Study Design to Assess Vector Biodistribution and Persistence

As discussed in Section IV.A, vector persistence heightens the risk of delayed adverse events following exposure to gene transfer technology. Indeed, the longer the vector persists, the greater the duration and degree of risk of delayed adverse events. We recommend that you perform preclinical biodistribution studies using methods that are shown to be sensitive and quantitative to detect vector sequences. Such studies would be designed to determine the distribution of your vector in nontarget tissues and the persistence of the vector in both nontarget and target tissues following direct in vivo administration of the vector product. If possible and applicable, we recommend that the studies employ an animal species that permits vector transduction and/or vector replication and that the animal species be biologically responsive to the specific transgene of interest (Ref. 4). The duration of the preclinical studies will vary, depending on the animal model employed. Projections of delayed adverse reactions in human subjects may be derived from assessment of data from appropriate long-term observational studies in animals, when possible.

A biodistribution study in animals can be performed either as a separate study or as a component of a toxicology study. Consider the following points in your animal study design to permit evaluation of vector localization and persistence (Ref. 5).

1. Animal Study Design

- Use the product in the final formulation proposed for the clinical study because changes in the final formulation may alter biodistribution patterns.
- Use both genders or justify the use of a single gender.
- Use at least 5 animals per gender per group per sacrifice time point for rodents, and between 3-5 animals per gender per group per sacrifice time point for nonrodents.
- Consider factors in the study design that might influence or compromise the vector distribution and/or persistence such as the animal's age and physiologic condition.
- Use the intended clinical route of vector administration if possible.
- Assess vector biodistribution in a vehicle control group and a group of animals that receives the MFD or clinically relevant dose (defined in Section III). Studies at additional dose levels might provide dose-dependent information.
- Include appropriate safety endpoints in your biodistribution study in order to assess any potential correlation between vector presence/persistence and adverse findings if safety endpoints have not been evaluated already in a separate toxicity study using the same animal model. These safety endpoints should include clinical observations, body weights, clinical pathology, gross organ pathology, and histopathology.

- Include several sacrifice intervals to characterize the kinetics of vector distribution and persistence. We recommend sacrifice at the expected time of peak vector detection and at several later time points to evaluate clearance of vector sequences from tissues.

2. Tissue Collection and Analysis

- Sample and analyze the following panel of tissues, at a minimum: blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen. Consider other tissues for evaluation, depending on the vector type and the transgene, as well as the route of administration (e.g., draining lymph nodes and contralateral sites for subcutaneous/intramuscular injection, bone marrow, eyes, etc.).
- Choose a method for tissue collection that avoids the potential for contamination among different tissue samples.
- Use a quantitative, sensitive PCR assay to analyze the samples for vector sequences. You should submit data to your IND to demonstrate that your assay methodology is capable of specifically detecting vector sequence in both animal and human tissues. We recognize that PCR technology is constantly changing, and encourage you to discuss the assay methology with us before initiating sample analysis. Current recommendations include the following:

  – The assay should have a demonstrated limit of quantitation of $\leq$50 copies of vector/1 μg genomic DNA, so that your assay can detect this limit with 95% confidence.
  – Use a minimum of three samples per tissue. One sample of each tissue should include a spike of control DNA, including a known amount of the vector sequences, in order to assess the adequacy of the PCR assay reaction. The spike control will determine the specified PCR assay sensitivity.
  – Provide a rationale for the number of replicates for testing per tissue, taking into account the size of the sample relative to the tissue you are testing.

3. Other Considerations

We encourage you to discuss with FDA your study design before starting the trial to ensure that the trial will adequately assess both biodistribution and vector persistence. There are many variables that will affect the outcome and interpretation of the in vivo assessment of each vector type.

C. Vector Integration Potential and Reactivation as Risks for Delayed Adverse Events

Three gene therapy vectors currently under study (i.e., Gammaretrovirus, Lentivirus, and Herpesvirus) possess characteristics that we consider to pose high

risks of delayed adverse events. Accordingly, we believe that clinical long-term follow-up observational studies would be necessary to mitigate long-term risks to subjects receiving these vectors. Gammaretrovirus and Lentivirus have a documented ability to integrate and Herpesvirus has a documented potential for latency and reactivation. In this section, we discuss those risks and the relatively low risks associated with gene transfer technology with vectors that lack those properties.

Most vectors used in gene therapy clinical trials can be categorized according to their propensity to integrate into host cell DNA. Please refer to Table 1, "Integration Properties of Current Commonly Used Gene Therapy Vectors in Clinical Trials." As shown in Table 1 and reflected in the answer to question 3 in Figure 1, "Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events," vectors that have a potential to integrate present sufficient risk that long-term follow-up observations are necessary to mitigate long-term risks to subjects receiving these vectors.

Because of its potential for latency and reactivation, a Herpes virus-based gene transfer vector also presents a risk of delayed adverse events related to its use as a vector in gene therapy products. During latency, the virus and its gene products remain inactive. Reactivation may be delayed for months or years following initial exposure.

We are aware that the potential of vectors to integrate may be modified to increase their utility as gene therapy agents. For example, an adenovirus vector can be modified to induce integration of its DNA (Refs. 5-9). Another example would be changes in the methods used to introduce plasmid DNA vectors into cells that result in higher integration frequencies (Ref. 10). In those cases where a modification of the gene therapy system may have altered the persistence or integration properties, we recommend that you take one of the following actions:

- Submit data to your IND from preclinical studies to assess vector persistence in an appropriate model. As stated in Section IV.B.3, we encourage you to discuss with FDA your study design before starting the trial.

    - If the vector is not persistent, the predicted risk of delayed adverse events would be low. Long-term follow-up observations would be at your discretion.
    - If the vector is persistent, we recommend that you perform preclinical studies to assess vector integration, as well as the potential for vector latency and reactivation.

        – If the studies show no evidence for persistence due to integration of the genetic material or development of latency, the predicted risk of delayed adverse events would be low. Long-term follow-up observations would be at your discretion.

  - If the studies show no evidence for integration of the genetic material but studies for latency and reactivation are inconclusive, cannot be performed, or show evidence of latency and/or reactivation, the predicted risk of delayed adverse events is indeterminate. We would require long-term follow-up observations.

- If preclinical studies of vector integration are not feasible, if the genetic material integrates, or if the vector is shown to persist in a latent state that may be reactivated, the risk of delayed adverse events is high or unknown, and long-term follow-up observations in study subjects are warranted.

- If vector integration studies are not performed, we recommend that you provide other evidence to support an assessment that your vector does not pose high risks of delayed adverse events, including the following:

  - A discussion of why vector integration studies were not performed.
  - The evidence supporting your assessment of the risk of delayed adverse events posed by your product.

Plasmids, poxvirus, adenovirus, and adeno-associated virus-based vectors (AAV) are vectors that do not have a propensity to integrate or reactivate following latency and, in the absence of evidence to the contrary, present a low risk of gene therapy-related delayed adverse events. However, even if your vector has a low propensity to integrate or reactivate, preclinical or clinical data showing persistence of the vector raise concerns about a risk of delayed adverse events, and follow-up observations would be necessary to mitigate long-term risks to subjects receiving these vectors. For example, if an AAV vector is shown to have persistent transgene expression, the risk of a delayed aberrant immune response should be considered because of the potential for autoimmune phenomena.

We also note that some vectors currently considered to pose delayed risks might be modified in order to reduce those risks. Therefore, data supporting claims of a decreased risk for delayed adverse events with novel vector types could provide the basis for reassessing the need for performing long-term follow-up observations in subjects exposed to those vectors.

Table 1. Integration Properties of Current Commonly Used Gene Therapy Vectors in Clinical Trials.

Vector Type	Propensity to Integrate[1]	Long-term Follow-up observations[2]
Plasmid	No	No
PoxVirus	No	No
Adenovirus	No	No
Adeno-associated virus[3]	No	No
Herpesvirus	No, but may undergo latency/reactivation	Yes
Gammaretrovirus	Yes	Yes
Lentivirus	Yes	Yes

[1]Based on vector design (i.e., lack of any known mechanism to facilitate integration), as well as cumulative preclinical and clinical evidence suggesting that vector does not integrate or integrates only at very low frequencies.
[2]Specific circumstances showing persistent expression of the transgene, in the absence of integration, may be the basis for a conclusion that long-term follow-up observations are necessary to mitigate long-term risks to subjects receiving these vectors. This would depend on additional criteria, such as the transgene expressed or clinical indication, as described in the text.
[3]*Rep*-negative vectors only.

V. RECOMMENDATIONS FOR PROTOCOLS FOR LONG-TERM FOLLOW-UP OBSERVATIONS: CLINICAL CONSIDERATIONS

In this section, we recommend elements appropriate to the design and conduct of long-term follow-up observations.

A. Decision to Conduct Long-term Follow-up Observations

The recommendations in this section apply to protocols for which long-term follow-up observations appear advisable. Long-term follow-up observations may be necessary to mitigate long-term risks to subjects receiving these vectors if:

- The answers to the questions posed in Section IV, Figure 1. "Framework to Assess the Risk of Gene Therapy-Related Delayed Adverse Events" lead you to decide that the risks associated with your product are high or uncertain.

- The information about your product, taken as a whole, shows that long-term follow-up observations would mitigate the risks to human subjects. For examples of such circumstances please refer to the final paragraphs in Section IV.A.

In selected instances where we would generally require long-term follow-up observations, you may determine that the observations would have no scientific value based on the suitability of your clinical trial population. If you make that determination and decide not to conduct long-term follow-up, you should include in your IND the justification for your decision not to continue to observe your subject population.

The sections below provide information on criteria you may choose to use to determine the suitability of monitoring your clinical trial population to collect scientifically informative data by the performance of long-term follow-up observations. We also discuss our recommendations for the minimum duration of follow-up observations and the minimum observations to be made during long-term follow-up.

B. Suitability of Clinical Trial Populations for Long-term Follow-up Observations

Long-term follow-up observations may have reduced utility in assessing and mitigating subject risk when the population selected for the trial has characteristics, such as short life expectancy, multiple morbidities, and exposure to other agents, that also could cause delayed adverse events. Thus, for example, long-term follow-up observations might have little impact if the subjects have widespread disease, or extensive exposure to agents with potential for delayed adverse events such as radiation or chemotherapy. In contrast, long-term follow-up observations could have greater value in assessing and mitigating the risks to subjects who have limited disease or are disease-free, and who have few co-morbidities and limited exposures to other agents with potential for delayed adverse events. In those cases where the gene therapy intervention alters life expectancy or co-morbidities, initial assessments regarding the suitability of long-term follow-up observations in a particular clinical trial may need to be reconsidered.

C. Recommended Duration of Follow-up Observations

The duration of long-term follow-up observations should be sufficient to observe the subjects for risks that may be due to the characteristics of the product, the nature of the exposure, and the anticipated time of occurrence of delayed adverse events. The BRMAC on November 17, 2000, April 6, 2001, and October 24, 2001, discussed several different time periods for the performance of long-term follow-up observations, including a 15 year period (See Section II.B for reference). Based on the BRMAC advice, we also recommend a minimum 15 year time period for follow-up observations. However, we recognize that shorter periods of observation may be appropriate in individual trials based on supporting evidence. Elements that will influence the determination of the duration of long-term follow-up observations include the following:

- The observed duration of in vivo vector persistence;
- The observed duration of in vivo transgene expression;
- The prior, concomitant, and post gene therapy exposures of the study population;
- The expected survival rates in the study population; and

- Other factors that may be relevant to the feasibility and scientific value of conducting long-term follow-up observations.

D. Elements of Follow-up Observations

Our recommendations on the nature of the follow-up observations are also based on the recommendations and discussions at the November 17, 2000, April 6, 2001, and October 24, 2001, BRMAC meetings (See Section II.B for references). As more clinical data accumulate, our recommendations regarding the duration of long-term follow-up observations may change.

It is important that the design of long-term follow-up observations be appropriate to detect potential gene therapy-related delayed adverse events in the study subjects enrolled in your clinical studies. In this document, we provide recommendations for general minimum elements for the long-term follow-up component of your study protocol.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject administered the investigational drug or employed as a control in the investigation (see 21 CFR 312.62(b)). These records would include a baseline history prior to exposure to the product in which all diseases, conditions and physical abnormalities are recorded. You are encouraged to develop a template for health care providers who are not investigators or subinvestigators (for example, the subject's physician, physician assistant, or nurse practitioner) to use in recording and reporting such observations to the investigator. Case histories should also include information from scheduled visits by a health care professional and test results for persistent vector sequences. The use of surrogate tests may be used to indicate vector persistence if direct sequence testing would require an invasive procedure for the subject.

In addition, for at least the first five years we recommend that you do the following:

- Implement methods for detection of gene therapy-related delayed adverse events;
- Assure that investigators maintain in the case history a detailed record of all exposures to mutagenic agents and other medicinal products and have ready access to information about their adverse event profiles;
- Design a plan for scheduled visits with a health care provider to elicit and record new findings for each study subject, including history, physical examination, or laboratory testing at minimum intervals of one year;
- Establish a method for investigators to record the emergence of new clinical conditions, including:
  - New malignancy(ies)
  - New incidence or exacerbation of a pre-existing neurologic disorder
  - New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
  - New incidence of a hematologic disorder; and

- Design a plan to elicit the cooperation of study subjects and their health care providers in reporting delayed adverse events, including unexpected illness and hospitalization.

For the subsequent ten years, at a minimum, we recommend that you ensure that your investigators:

- Contact subjects at a minimum of once a year. At your discretion, unless the long-term follow-up observation plan provides for additional, specific screening, you may arrange to contact subjects by telephone or written questionnaire rather than by office visits with a health care provider.

- Continue appropriate follow-up methods as indicated by previous test results. For example, it would be appropriate to monitor for vector sequences in subjects who had previous test results demonstrating vector persistence.

Perform all long-term follow-up observations according to FDA regulations governing clinical trials (See http://www.fda.gov/oc/gcp/regulations.html). We provide additional specific recommendations and requirements for data collection and reporting of adverse events for long-term follow-up clinical observations as follows:

1. Detection of Adverse Events: To facilitate detection of delayed adverse events, we recommend that the protocol identify suitable health care professionals whose observations would be used in the assessment of the occurrence of adverse events in the study population. Suitable health care professionals might include physicians, physician's assistants, and nurse practitioners who were not otherwise associated with the clinical trial. You may arrange to have such individuals notified to provide prompt reports of adverse events to the investigators.

   To increase subject compliance and improve the quality of data collection, we suggest that you encourage study subjects to monitor themselves and assist in reporting adverse events. Devices that study subjects could use to report events to the investigator include subject diaries of health-related events, informational brochures, and laminated, wallet-sized cards with investigator contact information.

2. IND Safety Reports: You must follow applicable reporting requirements outlined in 21 CFR 312.32 for adverse experiences associated with the use of the product. As the long-term follow-up observations proceed, you must also notify each participating investigator of any adverse experience associated with the use of the gene therapy product that is both serious and unexpected (21 CFR 312.32(c)(1)(i)(A)), as well as any new observations discovered by, or reported to, you (21 CFR 312.55(b)). In each IND Safety Report (required to be provided to investigators and FDA), you must identify all safety reports previously filed concerning a similar adverse experience, and analyze the significance of the adverse experience in light of the previous, similar reports (21 CFR

312.32(c)(1)(ii)). You must promptly investigate all safety information you receive (21 CFR 312.32(d)(1)). If the relationship of the adverse experience to the gene therapy product is uncertain, we may recommend that you perform additional investigations and revise your Informed Consent Document and Investigator Brochure to inform all study subjects of the risk of the adverse experiences. We may also request that investigators contact previously treated study subjects to inform them of the new risk.

3. Annual Reports to the IND/Summary Information: While the IND is in effect and until long-term follow-up observations are concluded, you must file an annual report. In that report, submit information obtained during the previous year's clinical and nonclinical investigations, including, among other things, a summary of all IND safety reports submitted during the past year, and a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system (21 CFR 312.33(b)(1) and (2)).

4. Amendments to Your Clinical Protocol: If clinical data suggest that your product is not associated with delayed risks, you may want to consider changing the clinical protocol regarding long-term follow-up of study subjects. However, before implementation of this change, you must submit to FDA a protocol amendment to your IND indicating the relevant changes (21 CFR 312.30(b)(1), (d), and (e)).

5. Scheduled Physical Examinations: We recommend that long-term follow-up observations include scheduled physical examinations performed by a health care professional at least once a year during the first five years, unless the assessed risks associated with your protocol indicate that they should be done more frequently. For example, if a subject exposed to your product or an analogous product develops a rapidly progressive, potentially reversible delayed adverse event, and there is a reasonable possibility that the event may have been caused by the product, it may then become advisable to perform observations on a semi-annual or quarterly basis. Such periodic evaluation should include a brief history and focused examination designed to determine whether there is any evidence of emergence of clinically important adverse events. Appropriate laboratory evaluations, such as a hematology profile, should be included with the periodic physical examination. Long-term follow-up observations are intended for study purposes only, not to provide evaluation and treatment of health care problems that are not associated with the use of the product.

6. Vector Sequences: During long-term follow-up, we recommend that you test study subjects at least annually for persistent vector sequences until they become undetectable. The assay should be sufficiently sensitive to detect vector sequences. We recommend that you sample the likely population of transduced cells without being overly invasive (e.g., peripheral blood is a suitable sample to test for presence of hematopoietic stem cells, rather than bone marrow biopsy). In those cases where the transduced cell population may require an invasive

procedure, we recommend that you consider, instead, measuring a surrogate that may indicate vector persistence (e.g., the level of transgene product or some clinical effect). Data demonstrating the lack of detectable vector may provide a rationale to revise the long-term follow-up elements of your study as an amendment to your IND. In any such protocol amendment, include an assessment of risks associated with your product and an evaluation of the impact of the waning persistence of the vector on those risks (21 CFR 312.30(b), (d)(2)).

E. Informed Consent in Trials Involving Long-term Follow-up Observations

The informed consent document must describe, among other things, the purposes of the research, the expected duration of the subject's participation and the procedures to be followed (21 CFR 50.25(a)(1)). Accordingly, the informed consent document must explain the purpose and duration of long-term follow-up observations, the time intervals and the locations at which you plan to request the subjects to have scheduled study visits or be contacted by other means, and details as to what those contacts will involve (21 CFR 50.25).

We provide additional informed consent recommendations for retroviral vectors in Section V.F.3 below.

F. Special Considerations Regarding Integrating Vectors

The recommendations in this section apply exclusively to subjects in clinical trials who received integrating vectors, such as retroviral vectors or cells modified ex vivo by retroviral vectors. In at least two preclinical studies performed in mice, integration of genetic material from a retroviral vector into mouse cell DNA was reported to cause malignant transformation (Refs. 11 and 12). In addition, in one clinical study, three out of a total of 11 human subjects with X-linked Severe Combined Immunodeficiency (X-SCID) have developed clonal T-cell proliferation after receiving hematopoietic cells that had been modified ex vivo with a retroviral vector (Refs. 13 and 14). One of the three subjects died (Ref. 14). These leukemias were the result of the retroviral vector-derived DNA integrating into the subjects' cellular DNA. The observation that children with X-SCID developed a malignancy after exposure to a retroviral vector (Ref. 13) has prompted us to provide additional recommendations for collection of data in studies in which subjects are exposed to integrating vectors, at this time best exemplified by retroviral vectors, including products derived from either gammaretroviruses or lentiviruses.

1. Data Collection

We recommend that you perform assays to assess the pattern of vector integration sites in relevant surrogate cells (e.g., determine whether cells carrying integrated vector sequences are polyclonal, oligoclonal, or monoclonal, with respect to vector integration patterns). We consider an assessment of the vector integration pattern to be relevant in subjects in gene therapy clinical trials involving

integrating vectors if: (1) the target cells are known to have a high replicative capacity and long survival, and (2) a suitable surrogate is accessible for assay. For example, hematopoietic stem cells have a high replicative capacity and long survival; peripheral blood could serve as a surrogate for testing for vector persistence if hematopoietic stem cells were the target of your gene therapy. In those cases where peripheral blood is the surrogate, analyses on purified subsets of hematopoietic cells (e.g., lymphocytes vs. granulocytes) may be performed, if deemed appropriate to the study by you or FDA. As an alternative example, if the integrating vector is used for in vivo transduction of liver hepatocytes, you may not need to perform this analysis, since terminally differentiated hepatocytes are non-dividing cells under normal circumstances, and there is no reasonable surrogate that allows for non-invasive testing of vector persistence. Please refer to the following recommendations for developing methods and plans for performing these analyses.

(a) The choice of method to assess the pattern of vector integration sites should be based upon data with appropriate positive and negative controls (i.e., target cells with a known number and sites of vector copies integrated vs. target cells with no vector integrants). Studies should be performed to provide information about the assay sensitivity, specificity, and reproducibility.

(b) We recommend that you perform an analysis to assess the pattern of vector integration sites if at least 1% cells in the surrogate sample are positive for vector sequences by PCR. As an alternative, you may base the decision to analyze for clonality of vector integration sites on an evaluation of the sensitivity of the assay system used to detect clonality.

(c) We recommend that you test for vector sequences by PCR in subject surrogate samples obtained at intervals of no greater than six months for the first five years and then no greater than yearly for the next ten years, or until such time that no vector sequences are detectable in the surrogate sample.

(d) We recommend that you perform an analysis to determine the site of vector integration if the analysis of a subject's surrogate cells suggests a predominant clone (e.g., oligoclonal pattern of vector insertions) or monoclonality. In addition, if you detect a predominant integration site, test for persistence by performing another analysis for clonality no more than three months later.

(e) When the nucleotide sequence adjacent to the site of the vector integration has been determined, we recommend that you compare the identified integration site sequence with known human sequences in the human genome database and other databases that document oncogenes to

determine whether the identified sequences are known to be associated with any human cancers.

(f) While we recognize that oligoclonality or even monoclonality itself will not a priori result in a malignancy (Refs. 15 and 16), we also recognize that these changes increase the risk of a malignancy, and therefore, we recommend that you institute a plan to monitor the subject closely for signs of malignancy if any of the following conditions pertain:

- Persistent monoclonality;
- Clonal expansion (e.g., the per cent cells positive for a particular vector integration site is shown to increase over multiple timepoints); or
- Evidence of vector integration near or within a locus known to have oncogenic activity.

(g) To screen for specific disease entities, we recommend that you use established methods and/or seek advice from clinicians with expertise in screening for the health care risks to which, according to your evidence, your subjects may be exposed.

2. Data Reporting

If no evidence of oligo- or monoclonality is observed, we recommend that you report a summary of all analyses for the pattern of vector integration sites in narrative or tabular form in the annual report to your IND (21 CFR 312.33(b)(5)). However, if evidence of oligo- or monoclonality is observed, submit this essential information in an information amendment to the IND (21 CFR 312.31(a)). We recommend that you submit this amendment within 30 days.

3. Informed Consent in Trials Involving Retroviral Vectors

Each subject in an investigation must be provided with a description of any reasonably foreseeable risks from participating in the investigation (21 CFR 50.25(a)(2)). Investigators must submit for Institutional Review Board approval the informed consent documents (21 CFR 56.109(b) and (c), 312.66). For all clinical trials in which subjects are exposed to retroviral vectors, the informed consent documents should include, in layman's language, a complete and accurate disclosure of the development of leukemia in the children with X-SCID. We recommend that you include the following information, where applicable, in language understandable to the study subjects, in the section describing the risks associated with the study agent:

- Description of study agent - The study involves giving a person some cells that have been changed by a retroviral vector. A retroviral vector is a virus that can insert genetic material into cells.

- Mechanism of action for retroviral vectors - When retroviral vectors enter a normal cell in the body, the deoxyribonucleic acid (DNA) of the vector inserts itself into the normal DNA in that cell. This process is called DNA integration.
- Effect of DNA integration - Most DNA integration is expected to cause no harm to the cell or to the patient. However, there is a chance that DNA integration might result in abnormal activity of other genes. In most cases, this effect will have no health consequences.
- Discussion of cancer occurring in animal studies - In some cases, abnormal activity of a normal gene may cause an uncontrolled growth of the cell that sometimes results in a cancer. This type of event has occurred in animal studies in which retroviral vector DNA integration appeared to cause cancers in mice and monkeys.
- Discussion of delayed adverse event, leukemia-like malignancy, occurring in human studies - It is important that you know about some cancers that occurred in another gene therapy research study. The study, conducted in France, involved a disease called X-linked Severe Combined Immunodeficiency (SCID). Years after receiving cells that were modified by a retroviral vector, a significant number of the children in this small study developed a leukemia-like malignant disease (cancer). At least one child died from the cancer. A group of experts in this field studied the results from tests performed on these children's blood cells. They concluded that the leukemia-like malignancy was caused by the retroviral vector DNA. However, most of the children with X-linked SCID who have received experimental gene therapy have not been found to have a leukemia-like disease at this time. Although they appear healthy, we still do not know whether they, too, will develop a malignant growth.
- Risk of malignancy for this study - We do not know if the retroviral vector used in this protocol might cause a new malignancy. However, you should be aware that the DNA contained in retroviral vectors will integrate into your DNA and that under some circumstances, this has been known to cause malignant (cancerous) growth months to years later.

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Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

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Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-7800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

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Guidance for Industry

This guidance represents the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance using the contact information on the title page of this guidance.

I. INTRODUCTION

The Center for Biologics Evaluation and Research (CBER)/Office of Cellular, Tissue, and Gene Therapies (OCTGT) is issuing this guidance to assist sponsors and investigators in designing early-phase clinical trials for cellular therapy (CT) and gene therapy (GT) products. CT and GT products will be referred to collectively as CGT products. This guidance provides OCTGT's current recommendations regarding clinical trials in which the primary objectives are the initial assessments of safety, tolerability, or feasibility of administration of investigational products. Such trials include most Phase 1 trials, including the initial introduction of an investigational new drug into humans, and some Phase 2 trials of CGT products.

The scope of this guidance is limited to products for which OCTGT has regulatory authority. CGT products within the scope of this guidance meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) and include CT and GT products that are used as therapeutic vaccines.[1] This guidance does not apply to those human cells, tissues, and cellular- and tissue-based products (HCT/Ps) regulated solely under section 361 of the PHS Act (42 U.S.C. 264), as described in Title 21 of the Code of Federal Regulations (CFR) Part 1271 (21 CFR Part 1271), or to products regulated as medical devices under the Federal Food, Drug, and Cosmetic Act, or to therapeutic biological products for which the Center for Drug Evaluation and Research (CDER) has regulatory responsibility.

There is increasing interest and activity in the development of CGT products because of their potential to address unmet medical needs. This guidance is intended to facilitate such development by providing recommendations regarding selected aspects of the design of early-phase clinical trials of these products. This guidance does not provide detailed information about the preclinical and chemistry, manufacturing, and controls (CMC) components of an

[1] Many of the principles in this guidance may apply to combination products involving a biological product under OCTGT's regulatory authority.

investigational new drug application (IND), as we have previously provided recommendations in connection with these components (Refs. 1, 2, and 3). This guidance is intended to complement the information in those guidances.

This guidance finalizes the draft guidance of the same title dated July 2013.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The design of early-phase clinical trials of CGT products often differs from the design of clinical trials for other types of pharmaceutical products. Differences in trial design are necessitated by the distinctive features of these products, and also may reflect previous clinical experience.

Early experiences with CGT products indicate that some CGT products may pose substantial risks to subjects. These experiences include multi-organ failure and death of a subject who received a GT product for ornithine transcarbamylase deficiency (Ref. 4), late-onset T-cell leukemia in subjects who received a GT product for X-linked severe combined immunodeficiency (X-SCID) (Ref. 5), and development of tumors in the brain and spinal cord of a patient who received intrathecal allogeneic stem cells for ataxia telangiectasia (Ref. 6). These events illustrate that the nature of the risks of CGT products can be different from those typically associated with other types of pharmaceuticals.

Features of some CGT products that may contribute to their risks include the potential for prolonged biological activity after a single administration, a high potential for immunogenicity, or the need for relatively invasive procedures to administer the product. Unlike many small molecule pharmaceuticals, the logistics and feasibility of manufacturing a CGT product sometimes influence the design of the clinical trials. In addition, the preclinical data generated for CGT products may not always be as informative as for small molecule pharmaceuticals, particularly since it usually is not feasible to conduct traditional preclinical pharmacokinetic (PK) studies with CGT products.

Thus, the design of early-phase clinical trials of CGT products often involves consideration of clinical safety issues, preclinical issues, and CMC issues that are encountered less commonly or not at all in the development of other pharmaceuticals. Section III of this guidance describes some distinctive features of CGT products and their development. Section IV discusses specific aspects of the design of early-phase trials of CGT products, based on consideration of the issues presented in Section III. Therefore, Section IV focuses on elements of trial design that may be different for CGT products than for other types of pharmaceuticals. Finally, Sections V and VI offer brief recommendations regarding IND submissions and meetings with OCTGT.

III. FEATURES OF CGT PRODUCTS THAT INFLUENCE CLINICAL TRIAL DESIGN

The design of early-phase clinical trials of CGT products is influenced by their many distinctive features. These features include product characteristics and manufacturing considerations, some of which are unique to CGT products, and can dictate critical elements of the clinical trial design. In addition, the preclinical studies conducted in support of the clinical trial design are often different from those for other types of products. This section describes some of these special features. Section IV describes how these special features influence the design of clinical trials for CGT products.

A. Product Characteristics

1. Characteristics of Both CT and GT Products

In contrast with some well-studied classes of small molecules, there is a relative lack of clinical experience with some CGT products. In the absence of substantial experience across a broad population, there can be considerable uncertainty about the nature and frequency of safety problems that might be associated with specific types of CGT products.

Also, some CGT products can persist in humans for an extended period after administration, or have an extended or permanent effect even after the product itself is no longer present. The effects of the product might evolve over time (e.g., stem cells that proliferate and differentiate). Therefore, evaluation of safety and pharmacologic activity might require observation of subjects for a substantial period of time to understand the safety profile. Additional information about duration of follow-up can be found in Section IV.F.3 of this guidance.

CGT products may require surgery or other invasive procedures for delivery to the target site. The risks added by the use of an invasive procedure might be a substantial component of the overall risk of treatment, particularly when the product is administered into a relatively sensitive site, such as the heart or central nervous system. In some cases, product delivery may require use of an investigational device. The use of an existing, legally marketed device for administering a CGT product also may be investigational. As indicated in Section V of this guidance, it is appropriate to discuss clinical issues related to such usage in the pre-IND meeting. Furthermore, when surgery or other invasive procedures are required, the training of those responsible for administering the product might affect the safety and reliability of the administration procedure (see Section IV.E.3).

Allogeneic CT products, GT vectors, and proteins that might be produced by CGT products have the potential to elicit immune responses (immunogenicity). The induction of an immune response may be the desired effect of some products, such as therapeutic vaccines. For other CGT products, immunogenicity may be a risk. For

example, pre-existing antibodies, or antibodies that develop after administration of the product, could reduce or extinguish a beneficial effect, cause an adverse reaction (e.g., an autoimmune syndrome), or influence safety or efficacy if there are any subsequent administrations. Also, in patients who have a condition that could be treated with a cellular, tissue, or organ transplant in the future, the development of antibodies to an allogeneic CGT product might jeopardize the success of the future transplant.

2. Characteristics of CT Products

CT products have unique complexities due to the dynamic nature of living cells. For example, cells may present a variety of molecules on their membranes and express a variety of factors. These molecules and factors may be affected by the microenvironment and change over time. Cells may differentiate in vivo into undesired cell types. Cells might also develop undesired autonomous functions, such as cells with the characteristics of cardiomyocytes forming a focus that generates electrical activity uncoordinated with the rest of the heart (Ref. 7). Stem cells, which have the potential to develop into a variety of mature tissue types, may undergo transformation and begin forming tumors (Ref. 6). In addition, a CGT product may include a variety of cell types, and it may be unclear which cell type or types are responsible for any specific toxic or therapeutic effect.

Another distinctive feature of cells is the ability to migrate. Systemic delivery of CT products may result in cells being distributed to a variety of tissues in the body; even cells delivered to a specific tissue or organ may migrate to unintended locations (Ref. 8).

The source (donor) of the cells or tissue may be the subject to be treated (autologous), or another individual (allogeneic). In some cases, the donor may receive a treatment prior to the harvest of source material. If the donor is also the trial subject, such pre-treatment may add to the overall risk to the subject.

Similarly, some CT products require pre-treatment of the recipient, e.g., with immune modification or myeloablative conditioning to facilitate cell survival. In such cases, the risks associated with the pre-treatment should be considered in the overall benefit-risk assessment.

3. Characteristics of GT Products

Several characteristics of GT products can influence trial design. For example, expression of a delivered gene may be uncontrolled and interfere with normal function of a critical enzyme, hormone, or biological process in the recipient. Some GT products are designed to integrate into the DNA of the recipient's cells to allow for long-term expression of the integrated genes. This genomic alteration could cause activation or inactivation of neighboring genes and give rise to benign or malignant

tumors (Ref. 5). In addition, GT products with a viral or bacterial vector present the possibility of shedding, i.e., excretion/secretion of viral particles or bacteria that could be transmitted to other individuals.

4. Characteristics of Gene-Modified Cellular Products

Gene-modified cells, or ex vivo GT products, are products in which a gene is introduced into cells ex vivo, and then the modified cells are administered to the subjects. Products of this type have features, and potential risks, of both GT and CT products. Therefore, clinical trial design considerations of both GT and CT products apply to gene-modified cells.

B. Manufacturing Considerations

The scientific or logistical complexities of manufacturing CGT products may impose practical limits on the dose of the product that can be produced, or may limit the concentration or volume of product that can be delivered. These factors might therefore restrict the range of doses that are feasible in an early-phase trial. The implications of these factors for trial design are discussed in Sections IV.A.1 and IV.D.

For autologous products or patient-specific allogeneic donor products, unique product lots are manufactured for each subject, and potentially for each dose a subject receives. For such products, the inability to control factors such as subject-to-subject variability can contribute to product complexity. Some CGT products may take several weeks to months to produce. A failure or delay in manufacturing could prevent a subject from being treated as intended. For other patient-specific products, cell viability and potency may decline rapidly from the time of formulation. Therefore, "fresh" cells that are not cryopreserved may require administration within hours of manufacturing. Trial design considerations for patient-specific products are discussed in Section IV.E.4.

C. Preclinical Considerations

Preclinical in vitro and in vivo proof-of-concept, pharmacology, and toxicology studies are conducted to establish feasibility and rationale for clinical use of the investigational CGT product, as well as characterize the product's safety profile. These studies also provide the scientific basis to support the conclusion that it is reasonably safe to conduct the proposed clinical investigations (21 CFR 312.23(a)(8)). Due to the diverse biology and scientific issues associated with CGT products, it is important to conduct a careful benefit-risk analysis, performed in the context of the particular clinical condition under study. Preclinical data generated from studies conducted in appropriate animal species and animal models of disease contribute to defining reasonable risk for the investigational CGT product.

Several issues can limit the ability of the preclinical data to guide various aspects of the design of the early-phase clinical trial. For example, the extrapolation of a potentially safe and possibly bioactive starting clinical dose from the animal data can depend on

various factors, such as the animal models used, the clinical route of product administration, the biodistribution profile, and any immune response to the administered CGT product. However, traditional PK study designs are generally not feasible for CGT products; thus, such data are not available to guide clinical trial design. Due to various issues, such as species specificity and immunogenicity, extrapolation from a CGT product dose administered in animals to a clinical dose can be less reliable than the customary allometric scaling typically used for small-molecule pharmaceuticals.

To provide additional information about preclinical program objectives, selection of suitable animal species and animal models of disease, and overall considerations for the design of preclinical studies to support early-phase clinical trials, FDA has published the guidance entitled "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products" dated November 2013 (Ref. 3).

IV. CLINICAL TRIAL DESIGN

This section describes specific elements of the design of an early-phase trial for a CGT product. For the most part, this guidance does not discuss elements of the trial design, such as efficacy endpoints and the analysis plan, that are generally the same for CGT products and other types of products. Instead, the discussion focuses on aspects of early-phase clinical trial design that are often different for CGT products than for other types of products. Due to the wide variety of CGT products and their potential applications, a case-by-case assessment is warranted for the design of each clinical trial. Therefore, OCTGT encourages prospective sponsors to meet with FDA review staff early in a development program (see Section V).

A. Early-Phase Trial Objectives

The IND regulations in 21 CFR Part 312 emphasize the importance of the assessment of trial risks and the safeguards for trial subjects. For early-phase clinical trials, especially first-in-human trials, the primary objective should be an evaluation of safety (21 CFR 312.21). Safety evaluation includes an assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose. For CGT products, these early-phase trials often assess not only safety of specific dose regimens and routes of administration, but also other issues, such as feasibility of administration and pharmacologic activity.

Sponsors should consider the design of early-phase studies in the context of the objectives of the overall development program. Therefore, sponsors might include design elements that could help foster further product development. For example, some Phase 1 studies include selected features of Phase 2 study design in order to gather preliminary evidence of effectiveness.

1. Dose Exploration

For some products and conditions, including many uses of CGT products for serious or life-threatening diseases, some toxicities may be expected and acceptable. In these situations, a major trial objective might be to identify the maximum tolerated dose (MTD), the highest dose that can be given with acceptable toxicity. To achieve this objective, some trials use a well-defined dose-escalation protocol.

For some CGT products, toxicity is not expected to be substantial in the predicted therapeutic range. In this situation, one objective of dose exploration may be to determine the range of biologically active or optimal effective doses. In some cases, indicators of potential benefit may appear to plateau above a certain dose, so that further dose escalation to reach an MTD may seem unnecessary. Although identifying an MTD may seem unnecessary or impractical, it is important to recognize that the effective clinical dose is difficult to estimate early in development. Failure to identify an MTD during early development may lead to subsequent clinical trials using sub-therapeutic dose levels. Therefore, dose exploration that includes identification of the MTD is generally recommended.

Alternatively, for many CGT products, there are significant practical limits on the dose of the product that can be produced or delivered. In such cases, the trial objectives may only be able to focus on achieving a specified target range of exposure or characterizing the safety profile of the feasible dose or doses, rather than finding the MTD.

For further discussion of considerations relating to dose, see Section IV.D.

2. Feasibility Assessments

CGT products sometimes require specialized devices or novel procedures for administration, customized preparation of products, special handling of products (e.g., very short expiration time), or adjunctive therapy. In these cases, sponsors should consider designing early-phase trials to identify and characterize any technical or logistic issues with manufacturing and administering the product. Such issues may need to be addressed before proceeding with further product development.

3. Activity Assessments

A common secondary objective of early-phase trials is to obtain preliminary assessments of product activity, using either short-term responses or longer-term outcomes that could suggest potential for efficacy. Such proof-of-concept data can support subsequent clinical development. For CGT products, activity assessments might include specialized measures such as gene expression, cell engraftment, or morphologic alterations, as well as more common measures such as changes in immune function, tumor shrinkage, or physiologic responses of various types.

B. Choosing a Study Population

Choice of the subjects to include in the trial depends on the expected risks and potential benefits, recognizing that there will be considerable uncertainty about those expectations in an early-phase trial. Expected risks may be estimated from the nonclinical data, an understanding of the biological mechanisms, and any previous relevant human experience, but the clinical significance of those risks can depend on the population that receives the product. Similarly, the potential for benefit might depend on the choice of study population. In addition, the choice of study population may affect the ability to detect the product's activity, either adverse or beneficial. For example, a biomarker that may be indicative of risk or benefit might be more sensitive, meaningful, or interpretable in one population versus another. Some populations may offer advantages (e.g., higher cell numbers or viability) as sources for autologous products. The objective is to select a trial population with an acceptable balance between the anticipated risks and potential benefits for the study subjects, while also achieving the study's scientific objectives. As discussed below in Section IV.E.4 of this guidance, there are special considerations regarding selection of the study population for patient-specific products.

1. Healthy Volunteers[2]

Study of healthy adult volunteers may be reasonable for an early-phase trial for products with short duration of action or in a class with a well understood safety profile. However, the risks of most CGT products include the possibility of extended or permanent effects, along with the risks of any invasive procedures necessary for product administration. Therefore, for most CGT trials, the benefit-risk profile is not acceptable for healthy volunteers.

2. Disease Stage or Severity

Selection of the most appropriate study population for an early-phase trial involves several considerations, including not only the potential risks, but also the potential benefits and the ability of the study population to provide interpretable data.

Subjects with more severe or advanced disease may be more willing to accept the risks of an investigational CGT product, or they may be in situations where the risks can be more readily justified. Therefore, sponsors sometimes propose to limit enrollment into early-phase trials to subjects with more severe or advanced disease. However, in some cases, selection of subjects with less advanced or more moderate disease may be appropriate.

Subjects with minimal reserve of physiological function due to severe or advanced disease may be less able than subjects with less severe disease to tolerate additional loss, which could leave them with no function. For example, the risk of a decrease in visual acuity might be more acceptable in a subject with some visual reserve than in a

[2] For the purposes of this guidance, the term *healthy volunteers* means individuals who do not have the disease or condition of interest.

subject for whom that same decrement might result in loss of all functional vision. Similarly, a risk of pulmonary or cardiovascular toxicity might be more acceptable in a subject with early lung disease than in a subject with more advanced disease and less pulmonary reserve. In addition, subjects with severe or advanced disease may not be able to tolerate invasive procedures needed for manufacture (e.g., cell harvest) or delivery of the product. Thus, the decision about the severity of disease to be studied in an early-phase trial should be made only after considering the estimated nature and magnitude of the risks to the subjects, and the implications of those risks, for various stages or severity of the disease.

In addition to considerations regarding risks, assessment of the overall benefit-risk profile should take into account any potential for individual subject benefit. In some situations, such as trials in children or trials that involve high-risk procedures, the prospect for individual clinical benefit may be an important factor in the overall benefit-risk assessment for the selected study population. The estimated prospect for benefit may depend on the severity or stage of disease. Although subjects with more severe or advanced disease may have the greatest need for benefit, there can be situations in which a greater potential for benefit might be expected for subjects who are less severely affected. Further, the ability to detect evidence of any benefit could depend on the severity or stage of disease in the study population, and the anticipated effects of the product might be more clearly discernible in subjects with milder disease. This could be a significant consideration if detecting evidence of treatment activity is important to the objectives of the study.

Also, the study population should be chosen with consideration of the potential interpretability of study outcomes. Subjects with severe or advanced disease might have confounding adverse events or be receiving concomitant treatment, related to underlying disease, that could make the safety or effectiveness data difficult to interpret. If the ultimate target population is patients with milder disease, a trial in severe or advanced disease could be essentially uninformative regarding relevant safety information and might also have a smaller prospect for benefit to offset risks.

Thus, while severely affected subjects are often included in early-phase CGT trials, they should not be an automatic choice. Several factors should be taken into account when selecting the appropriate subjects to include in the study for a specific condition. The study population should be chosen in light of the above considerations, and the choice should be discussed and justified in the IND submission.

3. Lack of Other Treatment Options

Early-phase studies of CGT products typically have significant risks and an uncertain potential for benefits. Therefore, early-phase CGT trials sometimes enroll only the subset of subjects who have not had an adequate response to available medical treatment or who have no acceptable treatment options. If a trial is designed to enroll only subjects for whom no other treatment options are available or acceptable, the

trial should include procedures to ensure that each subject's treatment options have been adequately evaluated, and it should be designed to capture the pertinent information regarding that evaluation.

4. Other Considerations

There are additional considerations for selecting the subject population for certain product types. For example, for cancer vaccines, it may be important to identify subjects whose tumors express a specific target antigen.[3] For certain gene therapies, pre-existing antibodies to either the vector or the transgene product may influence the safety or effectiveness of the product; therefore, the study might exclude subjects with such antibodies.[4] For products for indications (e.g., severe renal, hepatic, or cardiac disease) that might ultimately be amenable to organ transplantation, sponsors should consider whether exposure to the investigational agent would cause sensitization that could compromise the prospect for future transplant success. If so, early-phase trials might exclude subjects with the most imminent or predictable need for transplantation. The exclusion could be reconsidered for subsequent trials once the likelihood of sensitization is better understood.

5. Pediatric Subjects

Some CGT products are developed specifically for pediatric conditions. For example, GT products might be intended to correct childhood genetic diseases by replacing a missing gene or complementing a defective one. CT products might be intended as regenerative medicine to correct congenital deformities or as treatments for genetic diseases, such as hematologic or immunologic disorders, which result in abnormal cellular function.

Sponsors who are developing CGT products to treat pediatric diseases should consider how they will incorporate the additional safeguards for pediatric subjects in clinical investigations into the overall development program. Clinical development programs for pediatric indications usually obtain initial safety and tolerability data in adults before beginning studies in children (Ref. 9). Title 21 CFR Part 50 Subpart D (Subpart D) provides additional safeguards to children in clinical investigations. A detailed discussion of the individual provisions of Subpart D is beyond the scope of

[3] "Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines" dated October 2011, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf.

[4] In those cases where a special test, such as an antigen or antibody assay, could be critical to the safety or potential effectiveness of the product, the test might be regarded as a companion diagnostic product. If the specific use of the test is also investigational, then the Center for Devices and Radiological Health may need to evaluate the risk of that use. For additional information regarding companion diagnostics, please see the guidance document entitled "In Vitro Companion Diagnostic Devices – Guidance for Industry and Food and Drug Administration Staff" dated August 2014, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

this guidance, and the FDA has published other documents for that purpose (Refs. 9, 10). We highlight the following principles for sponsors and investigators who wish to conduct studies of CGT products in pediatric subjects.

Before a clinical trial that meets all other applicable requirements may proceed in children, Subpart D requires the Institutional Review Board (IRB) to determine that the trial meets additional requirements applicable to studies in pediatric subjects. The IRB must assess the level of risk that the interventions and procedures included in a clinical trial would present to pediatric subjects to determine whether they present minimal risk (21 CFR 50.51), greater than minimal risk (21 CFR 50.52), or a minor increase over minimal risk (21 CFR 50.53). Because of the special features of CGT products described earlier in this guidance, trials of CGT products usually present more than a minor increase over minimal risk, and therefore would need to meet the requirements of 21 CFR 50.52.

Clinical trials presenting greater than minimal risk may proceed only after the IRB finds either that the intervention or procedure presenting that risk holds out the prospect of direct benefit for the individual pediatric subjects, or that the monitoring procedure presenting that risk is likely to contribute to the subject's well-being. In addition, the IRB must find that:

- the risk is justified by the anticipated benefit to the subjects;
- the relation of the anticipated benefits to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (21 CFR 50.52 and 50.55).

When an IRB determines that existing data are inadequate to support the findings required under these regulations, it may not permit the study to proceed.[5]

IND submissions for pediatric trials must provide additional information related to plans for assessing pediatric safety and effectiveness (21 CFR 312.23(a)(10(iii)). The IND regulations also require the sponsor to submit to FDA an investigational plan, including the rationale for the drug or the research study (21 CFR 312.23(a)(3)(iv)(*a*)). Accordingly, the sponsor should provide a rationale for conducting the CGT study in children. To obtain the information necessary for a benefit-risk assessment under Subpart D, and because of considerations regarding informed consent, data to support the rationale are usually obtained in adults before

[5] If an IRB cannot conclude that a study meets the requirements of 21 CFR 50.51, 50.52, or 50.53, but finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB may refer the clinical protocol to FDA's Office of Pediatric Therapeutics for review under 21 CFR 50.54. For additional information on this issue, please refer to the FDA guidance entitled "Guidance for Clinical Investigators, Institutional Review Boards and Sponsors - Process for Handling Referrals to FDA Under 21 CFR 50.54 - Additional Safeguards for Children in Clinical Investigations" dated December 2006, http://www.fda.gov/RegulatoryInformation/Guidances/ucm127541.htm.

initiating pediatric studies. We recognize that in some situations, it may be appropriate to initiate clinical studies of CGT products in children based only on the results of preclinical studies. If the sponsor intends to conduct a pediatric trial when there has been no prior safety or efficacy study in adults, the rationale should explain why prior adult studies are unethical or infeasible. For example, the common childhood form of the disease may have severe manifestations or a rapidly deteriorating clinical course, whereas the adult-onset phenotype may be very mild and easily managed. In such a situation, if the intervention is highly invasive, the overall benefit-risk assessment for a study in adults might be so unfavorable that an adult trial to assess safety or efficacy is unethical. In other cases, the disease may occur so rarely in adults that a study in affected adults would not be feasible, and studies in healthy adults might have an unacceptable overall balance of benefits and risks (see Section IV.B.1).

FDA has a responsibility to assess the risks presented and determine whether the clinical trial presents an unreasonable risk to subjects (21 CFR 312.42(b)(1)(i), 312.42(b)(1)(iv) and 312.42(b)(2)(i)). When reviewing studies of CGT products proposed to be conducted in pediatric subjects, we intend to assess the reasonableness of the risks after full consideration of the information, including information relevant to the determinations that the IRB must make to comply with the Subpart D safeguards. The IND submission must provide adequate information to permit FDA to make this assessment (21 CFR 312.23(a)(10)(iii) and 312.23(a)(11)). For example, if the sponsor proposes that a study in pediatric subjects meets the criteria in 21 CFR 50.52 because, among other things, it presents a prospect of direct benefit to the subjects, the sponsor should include the available adult human and animal data relevant to this determination in the IND submission, and an analysis of the balance of anticipated benefit(s) and risks. In addition to providing the relevant animal or adult human data, the IND submission should include a discussion of how those data are sufficient to support an assessment that the pediatric study, taking into account the proposed starting dose, dosing regimen, and design, offers a prospect of direct benefit. FDA may place on clinical hold an IND that does not provide the information FDA needs to assess the risks presented to pediatric subjects (21 CFR 312.42(b)(1)(iv) and (b)(2)(i)).

Finally, in accordance with 21 CFR 312.23(a)(11), the sponsor also must provide the parent or guardian permission document and a child assent document required under 21 CFR 50.55.

C. Control Group and Blinding

The objectives of early-phase trials usually focus on safety, for which rigorous inference regarding comparison to a control (e.g., placebo) may not be necessary. Assessments of activity or efficacy, if any are to be made, are usually exploratory. Therefore, in early-phase trials, a concurrent control group and blinding are generally not as critical as for a

confirmatory efficacy trial. However, in early phases of clinical development, a control group can be useful to facilitate interpretation of the safety data and provide a comparator for any assessments of activity or efficacy.

For example, a concurrent control group may be particularly valuable for trials in diseases for which the natural history is not well-characterized or for trials that enroll subjects with a wide range of disease severity. The importance of concurrent controls and blinding in any specific trial depends on multiple factors, including not only the study objectives, but also the extent to which the study procedures and outcome assessments are subject to bias.

For some CGT products, use of an intra-subject control may be a useful and convenient way to control a trial. An example would be injection of the study agent into one limb and injection of the control agent into the contralateral limb. With intra-subject control, any systemic effects may confound the interpretation of the results, but comparisons of local effects can be facilitated by the elimination of inter-subject variation.

Standard-of-care and no-treatment controls allow evaluation of the risk of the overall investigational treatment, including the risks of both the study agent and the administration procedure. With this type of control, blinding of the subject and investigator may not be feasible, although it may be possible to maintain the blind for subjects for some kinds of standard-of-care controls.

For trials that do include a concurrent control group, blinding of subjects, investigators, and assessors can be useful to minimize the risk of bias in the study results. However, rigorous blinding in early-phase trials may not be desirable if it cannot be done simply and in a way that minimizes risk to control subjects. Some CGT products might require an invasive procedure for administration (e.g., cardiac catheterization) or for collection of tissue to use for starting materials. Use of the same invasive procedure in a control group could help to distinguish product-related from procedure-related adverse reactions. However, use of the invasive procedure in the control group solely to administer a placebo, or otherwise mimic the active treatment arm for purposes of blinding, could represent an unreasonable risk for an early-phase trial, even if it might be appropriate for a later confirmatory trial. For early-phase clinical trials involving children, the use of an invasive procedure in the control group should present no more than a minor increase over minimal risk, given the absence of a prospect of direct benefit from the control intervention.

Thus, the advantages and disadvantages of specific controls and blinding should be carefully considered in the context of the objectives and circumstances of the specific early-phase clinical trial.

D. Dose and Regimen

1. Role of Preclinical Data

If animal or in vitro data are available, there might be sufficient information to determine if a specific starting dose has an acceptable level of risk. However, conventional allometric scaling methods for CGT products may be less precise than for small-molecule drugs, and traditional PK and pharmacodynamic correlations might not be possible. Therefore, it may be difficult to establish an initial starting dose based on the considerations used for small-molecule drugs. If available, previous clinical experience with the CGT product or related products, even if by a different route of administration or for a different condition, might help to justify the clinical starting dose.

2. Considerations Regarding How Dose is Described

One of the objectives of early-phase trials should be the identification of the product attribute (or attributes) that is most relevant to characterizing dose. To that end, it is important to collect data on characteristics of the administered product and clinical outcomes that will enable correlative analyses to help in dose definition.

Selecting the study dose(s) of a CT product can be challenging. Dosing to target a therapeutic effect might be based on one cell type, but adverse reactions might depend more on a different cell type that is present in the same product. The active cell subset may not be known, so the dose is based on a specific subset that is thought to be the best representation of the desired activity. For example, for a CT product derived from cord blood or other hematopoietic tissues, the total number of nucleated cells might be used as the measure of dose, but the number of CD3+ cells could be an important aspect of the dose for consideration of certain safety outcomes, such as graft versus host disease (GVHD). In situations where there is uncertainty about the cell subset(s) responsible for the therapeutic or adverse effects, collecting data on various cell subsets in the final CT product, with a comparison of clinical outcomes associated with these different subsets, may help to identify the cell subsets most relevant to product safety and effectiveness.

For many GT products, dose is based on vector titer. However, some vector types may have specific properties that necessitate dosing using alternative units. For example, viral particles that do not contain the therapeutic gene are unlikely to have therapeutic activity. However, these particles themselves might produce adverse reactions, such as an allergic response. Therefore, if there are such safety considerations, the study dose(s) should be based on the total particle number, as is the case with adenoviral vectors. Other considerations for describing dosing may be related to the strengths and weaknesses of the methods available to accurately quantify specific attributes of the GT products. For example, adeno-associated viral

(AAV) vectors are typically dosed based on vector genomes, due to the strengths of the quantitative polymerase chain reaction (PCR) assay and the difficulties in quantitating transducing units.

For gene-modified cells, dosing should consider several factors, including transduction efficiency. For some products, transduction efficiency can vary from lot to lot. This variation might lead to substantial differences in the active dose administered to different subjects. Ideally, manufacturers should work to control variability in the transduction process. If variability in transduction is occurring, and if the transduced cell number can be identified prior to product administration, then transduced cell number might provide more consistent dosing among subjects. In addition to transduction efficiency, other factors that should be considered in determining the dose include the total number of cells administered to subjects, the mean number of copies of vector sequences integrated per cell, and cell viability.

3. Dose Escalation and Regimen

Clinical development of CGT products has often included dose escalation in half-log (approximately three-fold) increments. However, the dosing increments used for dose escalation should consider preclinical and any available clinical data regarding the risks and activity associated with changes in dose.

Many CGT products can persist in the subject or have an extended duration of activity, so that repeated dosing might not be an acceptable risk until there is a preliminary understanding of the product's toxicity and duration of activity. Therefore, most first-in-human CGT trials use a single administration or one-time dosing regimen. However, for some CGT products, such as therapeutic vaccines, multiple administrations may be appropriate for early-phase trials.

E. Treatment Plan

1. Staggering Administration

When there is no previous human experience with a specific CGT product or related product, treating several subjects simultaneously may represent an unreasonable risk. To address this issue, most first-in-human trials of CGT products include staggered treatment to limit the number of subjects who might be exposed to an unanticipated safety risk.

With staggered treatment, there is a specified follow-up interval between administration of the product to a subject, or small group of subjects, and administration to the next subject or group of subjects. For example, in a dose-escalation study, the first several individual subjects within the first cohort might be staggered, followed by staggering between cohorts. Depending on the degree of safety concern, staggered treatment of individual subjects within each new cohort

might be appropriate. When the dose of the CGT product is difficult to quantify precisely or is highly variable due to manufacturing issues, it may be necessary to stagger additional subjects.

The staggering interval, either within a cohort or between cohorts, is intended to be long enough to monitor for acute and subacute adverse events prior to treating additional subjects at the same dose, or prior to increasing the dose in subsequent subjects. The choice of staggering interval should consider the time course of acute and subacute adverse events that was observed in the animal studies and in any previous human experience with related products. The staggering interval should also consider the expected duration of product activity. However, the staggering interval should be practical in the context of overall development timelines.

2. Cohort Size

For trials that enroll sequential cohorts with dose-escalation between cohorts, the choice of cohort size should consider the amount of risk that is acceptable in the study population. Larger cohorts might be necessary to provide reasonable assurance of safety before escalating the dose of a product intended to treat a disease that is less serious and for which the tolerance for accepting risk might be lower. Smaller cohorts might be adequate for a product that is intended to treat a serious or life-threatening disease where a greater potential benefit may justify a higher risk. Standardized protocol designs, such as the 3+3 design, are often used for dose escalation of oncology products. However, the cohort size in such a design might not be appropriate for other therapeutic areas where there is less tolerance of risk, and a larger cohort might be needed to provide a greater assurance of safety prior to dose escalation. In addition, other study objectives, such as assessments of tolerability, feasibility, and pharmacologic activity may influence choice of cohort size.

For CGT products, manufacturing capacity is often limited, which might place a practical limit on cohort size, particularly early in clinical development. The prevalence of the proposed study population may also limit the cohort size. When considering the limitations due to manufacturing capacity and prevalence of the study population, sponsors should select a cohort size that is feasible, but still adequate to meet the study objectives.

3. Operator Training and Documentation of Procedures

For product delivery that involves a complex administration procedure or a device requiring special training, such as subretinal injection or use of specialized catheters for cardiac administration, the skill of the individual administering the product can impact the product's safety and efficacy. When individual skill in administering a product may affect its safety or effectiveness, the trial should specify minimum requirements for the operator's training, experience, or level of proficiency. In some cases (particularly, if there are multiple operators), training of operators on the specific administration procedures may reduce variability of administration and

thereby improve interpretability of the study results. Detailed, written standard operating procedures (SOPs) can also help ensure safety and consistency in product administration. Careful recording of steps and observations during the administration process can help identify the operator's compliance with the protocol. These records can also facilitate correlating procedure variations with clinical outcomes and identify modifications that may improve the administration process.

4. Considerations for Patient-Specific Products

As discussed earlier, some CT products or gene-modified cells are manufactured using cells or tissue from the intended recipient or from an allogeneic donor selected because of immunological matching to the recipient. In these cases, the product needs to be manufactured separately for each subject in a trial.

However, manufacturing of some CGT products may take many weeks or months. Although a subject might meet the study enrollment criteria when the tissue or cells are first collected, the subject might no longer meet those criteria at the time planned for product administration. For example, the subject's condition may have deteriorated so that the subject is no longer expected to tolerate the study procedures or survive for the study duration. To adjust for the possibility of a change in the subject's condition, the enrollment criteria may need to include selection for factors that would improve the likelihood that the recipient would still be suitable for product administration when the manufacturing process is complete. Alternatively, the trial might include separate criteria that need to be met at the time of product administration.

If a problem occurs in product manufacturing, there may be no product available to administer to an intended recipient. It is helpful to try to gain an understanding from early-phase trials of the likelihood of manufacturing failure and any subject factors that may relate to such failures (e.g., subject characteristics that might predict a poor cell harvest). This information can facilitate design of subsequent trials by suggesting subject selection criteria to reduce the chance of failure, or by prompting the development of a treatment protocol with a formalized manufacturing failure contingency plan.

In case of failure to administer the CGT product to a subject, the protocol should be designed so that the subject is not committed to any high-risk preparative procedures (e.g., myeloablation) until it is known that the product is available. The protocol should also clearly specify whether re-treatment will be attempted with another round of manufacturing and whether an untreated subject will be replaced by increasing enrollment. Failure-to-treat may be an important trial endpoint that is part of a feasibility evaluation, and there should be plans to analyze the proportion of failure-to-treat subjects to look for factors that may predict failure to administer the product and to evaluate the consequences to the subject if there is a failure to treat.

F. Monitoring and Follow-up

1. General Monitoring Considerations

Since a major objective of early-phase trials is evaluation of safety, early-phase trials should employ general tests and monitoring to look for both expected and unexpected safety issues. General safety monitoring typically includes recording of symptoms and common clinical measurements, such as physical examinations, chemistry profiles, complete blood counts, and possibly other examinations that are appropriate for the condition being investigated. Examples include continuous electrocardiographic monitoring if arrhythmogenicity is a concern, and antinuclear antibody (ANA) or other immunology testing if autoimmunity is a concern. The specific monitoring program will depend on multiple factors, such as the nature and mechanism of action of the product, the study population, the results of animal studies, and any related human experience.

Another objective of many early-phase trials is to provide preliminary evidence of efficacy or pharmacologic activity. Pharmacologic activity may develop slowly or be delayed relative to the traditional time course of activity of small molecules. Therefore, subjects should continue to be monitored for both safety and pharmacologic activity regardless of whether or not they receive the complete treatment regimen.

Attribution of individual adverse events to the product, study procedures, or other causes can be unreliable. Therefore, for early-phase trials, sponsors should capture all adverse events, even if the investigational product is an add-on to known toxic therapies, such as chemotherapy, radiation, or another toxic drug. Many early-phase CGT trials include a Data Monitoring Committee (DMC) to help ensure subject safety. Although use of a medical monitor may be sufficient, a DMC might be considered to enhance subject protection if the trial presents substantial risks to subjects.[6]

In addition to providing evidence of safety, many early-phase clinical trials have the secondary objective of obtaining preliminary efficacy or proof-of-concept data to support subsequent clinical development. Therefore, sponsors are encouraged to include a wide range of activity or efficacy outcome measures in early-phase clinical trials.

2. Special Monitoring Considerations for CGT Products

In addition to general tests and monitoring to look for unanticipated safety issues, evaluations may include assessments targeting specific safety issues that could be anticipated with CGT products. Such product-specific safety issues might include

[6] For additional information on DMCs, please see the guidance document entitled "Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees" dated March 2006, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf.

acute or delayed infusion reactions, autoimmunity, graft failure, GVHD, new malignancies, transmission of infectious agents from a donor, and viral reactivation. Monitoring procedures relevant to specific CGT products or study populations include the following:

- If immunogenicity is a concern (e.g., with viral capsids or allogeneic cellular products), then each subject's immune response to the product should be evaluated. This evaluation may include monitoring for evidence of both cellular and humoral immune responses. If adequate assays are not yet available, baseline and post-treatment blood and/or plasma, as appropriate, should be cryopreserved for later evaluation, once assays have been developed.

- Attempts should be made to determine the duration of persistence of the product and its activity. Product persistence is assessed by looking for evidence of the presence of cells, vector, or virus in biological fluids or tissues. Activity might be assessed by looking for physiologic effects, such as gene expression or changes in biomarkers. In some trials, these assessments of persistence or activity could be based on relevant tissue (e.g., from the site of administration or the site of intended activity) that becomes available in the course of subject management or is easily obtained by biopsy. In such trials, the protocol might include plans for tissue studies. If some deaths are expected to occur during the course of the trial, planning for possible postmortem studies to assess product persistence and activity may be useful.

- For CT products, if applicable, the potential for migration from the target site, ectopic tissue formation, or other abnormal cell activity should be addressed by performing evaluations appropriate to the nature of the concern (e.g., imaging studies for potential ectopic tissue, or cardiac rhythm monitoring for potential arrhythmogenic foci in cardiac disease).

- For GT products, the potential for viral shedding should be addressed early in product development.[7, 8]

- For GT products that integrate into the genome, monitoring for clonal outgrowths should be performed when technically feasible. Typically, this type of monitoring is done when hematopoietic stem cells are transduced with an integrating vector. Vector integration sites in patient peripheral blood

[7] "Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors" dated October 2006, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072961.htm.

[8] "Draft Guidance for Industry: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products" dated July 2014, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceregulatoryInformation/Guidances/CellularandGeneTherapy/ucm404050.htm. When finalized, this guidance will represent FDA's current thinking on this topic.

mononuclear cells (PMBCs) can be monitored for outgrowth of a predominant clone. Additional information can be found in the "Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" dated November 2006 (Ref. 11).

- CGT products may affect linear growth and maturation of developing organ systems in children. The systems that are most likely to be affected may vary by product, but concerns include potential reproductive, immunologic, neurologic, skeletal, or psychological effects. Therefore, monitoring and assessment of effects on these systems may be critical elements in the design of pediatric clinical trials.

3. Duration of Follow-up

In general, the duration of monitoring for adverse events should begin with any pretreatment and cover the time during which the product might reasonably be thought to present safety concerns. In addition, the expected time course of pharmacologic activity may influence the duration of monitoring. The appropriate duration of follow-up depends on the results of preclinical studies, experience with related products, knowledge of the disease process, and other scientific information. In case of failure to administer the CGT product to a subject, the protocol should stipulate any follow-up time needed to assess the risks of any harvesting procedure or other type of preparative treatments (e.g., immune modification) the subject received.

For most CGT products, a year or more of follow-up is appropriate for each subject in early-phase trials. For some CGT products, such as those with an indefinite duration of activity, additional long-term follow-up might be appropriate. For example, long-term safety monitoring can be useful if the product contains cells for which there is concern, either from the animal studies or other scientific information, that the cells might transform, migrate, or otherwise have the potential to develop ectopic tissue. The monitoring program should account for the duration of risks due to any concomitant medications, such as immunosuppressants. In addition, sponsors should consider the duration of follow-up that will provide preliminary evidence of efficacy and information on durability of activity.

With respect to extended follow-up, for certain GT products, we recommend following the recommendations in the FDA guidance document entitled "Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" dated November 2006 (Ref. 11). As stated in that guidance, if the product is a GT for which the vector is integrating, or if the vector has latency, such as herpes simplex virus, then sponsors should follow subjects for 15 years to identify any late safety issues. Long-term safety monitoring can also be useful if the product involves a gene that might predispose subjects to develop secondary malignancies.

Sponsors sometimes propose to have one protocol for a CGT study of safety or efficacy, and a separate protocol for long-term monitoring. However, long-term follow-up is sometimes necessary for the trial to have an acceptable balance of risks and benefits. In that case, long-term monitoring should be included as an integral part of the CGT trial, and not designed as a separate study. There may be logistical issues that influence the feasibility of including long-term monitoring in the initial protocol. When there is a separate protocol for long-term monitoring, subjects should be consented for all long-term monitoring prior to participation in the initial CGT trial.

Long-term monitoring does not need to be as detailed as the safety monitoring in the initial part of a trial. In general, long-term monitoring for CGT products focuses on subject survival and on serious adverse events that are hematologic, immunologic, neurologic, or oncologic. For some purposes, a telephone call to the subject, rather than a clinic visit, may be sufficient to obtain the necessary follow-up information. In addition, completion of long-term monitoring usually is not necessary prior to initiating subsequent trials or submitting a marketing application.

In the pediatric population, long-term monitoring following the administration of CGT products may need to characterize the effects of the intervention on growth and development as discussed in Section IV.F.2 of this guidance. Depending on the intervention, children also have the potential to be exposed for a longer time because of their younger age. Thus, clinical follow-up data over an extended period may be critical to assess safety and developmental outcomes, particularly when an intervention is tested in infants and young children. Therefore, monitoring the long-term safety and duration of effects may be more challenging in pediatric studies than in adult studies. Sponsors of all CGT early-phase trials, both adult and pediatric, should consider these issues in their proposals for long-term monitoring.

4. Study Stopping Rules

Because there can be considerable uncertainty about the frequency or severity of adverse reactions in trials of CGT products, most early-phase trials of these products should include study stopping rules. The purpose of these rules is to control the number of subjects put at risk, in the event that early experience uncovers important safety problems.

Study stopping rules typically specify a number or frequency of events, such as serious adverse events or deaths, that will result in temporary suspension of enrollment and dosing until the situation can be assessed. Based on the assessment, the clinical protocol might be revised to mitigate the risk to subjects. Such revisions could include changes in the enrollment criteria, for example, to exclude individuals who might be at relatively high risk for developing particular adverse reactions. Revisions might also include dose reduction, some other change in product preparation or administration, or changes in the monitoring plan. Following the implementation of such changes in the protocol, it may be safe for the trial to resume.

Therefore, study stopping rules do not necessarily terminate a trial. Well-designed stopping rules allow sponsors to assess and address risks identified as the trial proceeds, and to assure that risks to subjects remain reasonable.

V. MEETINGS WITH OCTGT

OCTGT encourages prospective sponsors to meet with FDA review staff. Meeting with OCTGT can be especially beneficial for sponsors who have little experience with the IND process, and for sponsors developing a product for the treatment of a rare disease. In such meetings, OCTGT can provide advice that may increase the likelihood that an IND submission will be sufficient to support a proposed trial, or that the overall development program will be sufficient to support a marketing application.

The FDA guidance document entitled "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants" dated May 2009 (Ref. 12), describes the process for requesting and preparing for a meeting. One type of formal meeting is the pre-IND meeting. A pre-IND meeting is intended to help ensure that appropriate work has or will be done to support a planned IND. The sponsor's pre-IND briefing package should include a clinical protocol or synopsis. In addition to discussions of preclinical studies and manufacturing issues, appropriate clinical topics for such a meeting could include the following:

- the adequacy of the available or planned safety and proof-of-concept information to justify the risks of the proposed trial;
- the choice of study population;
- the doses to be administered;
- the dosing schedule;
- clinical issues related to any invasive administration procedures;
- the treatment plan for the control group, if one is proposed;
- staggering plans;
- the safety monitoring plan, including long-term follow-up;
- any special safety assessments;
- stopping rules;
- selection of trial endpoints; and
- the overall clinical development program.

VI. GUIDANCE ON SUBMITTING AN IND

The requirements with respect to what needs to be submitted in support of an IND can be found in the FDA regulations, 21 CFR 312.23, and recommendations with respect to these submissions can be found in the FDA guidance document entitled, "Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products" dated November 1995 (Ref. 13). Information on the preparation of the CMC section of an IND for a CGT product can be found in the FDA guidances entitled "Guidance for FDA Reviewers and Sponsors:

Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)" dated April 2008 (Ref. 1) and "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" dated April 2008 (Ref. 2). As noted previously, information on the preparation of the preclinical section of an IND for a CGT product can be found in the FDA guidance entitled "Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products" dated November 2013 (Ref. 3).

The IND submission for an early-phase trial must include a summary of previous human experience known to the applicant with the investigational product, along with detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigator's rationale (21 CFR 312.23(a)(9)). The submission also should include a summary of previous human experience with similar or closely related products. OCTGT recommends that the submission include discussion of any of the issues raised in Sections III and IV of this guidance that are applicable to the proposed trial.

Sponsors also may find it prudent to develop an overall product development plan early in the course of development (prior to clinical trial initiation). Such a plan should be sufficiently flexible to accommodate adaptation based on data acquired through product development. One potential approach to planning development is known as a Target Product Profile (TPP). FDA has published a draft guidance for comment that discusses how this particular planning tool might be used (Ref. 14). When finalized, the TPP guidance will represent our current thinking on this topic.

FDA has developed additional resources that sponsors may find useful when preparing an IND for CGT products, including guidances relevant to the development of CGT products for selected specified conditions.[3,9,10,11] Likewise, information on manufacturing, preclinical, and clinical topics related to development of CGT products, including discussion of IND submissions and meeting requests, is available in the OCTGT Learn webinars on the OCTGT website: http://www.fda.gov/biologicsbloodvaccines/newsevents/ucm232821.htm.

[9] "Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products" dated September 2009, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm182440.htm.

[10] "Guidance for Industry: Cellular Therapy for Cardiac Disease" dated October 2010, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm.

[11] "Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage" dated December 2011, http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf.

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10. Final Rule: Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products. 78 FR 12937 (February 26, 2013).

11. Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events; dated November 2006, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm.

12. Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants; dated May 2009, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

13. Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products; dated November 1995, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071597.pdf.

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BLA 125643

YESCARTA™ (AXICABTAGENE CILOLEUCEL)

Suspension for Intravenous Infusion

Kite Pharma, Inc.

2225 Colorado Ave, Santa Monica, CA 90404

1-844-454-KITE

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1. GOAL

The goals of the YESCARTA REMS are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense YESCARTA are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer YESCARTA are aware of how to manage the risks of CRS and neurological toxicities.

2. REMS ELEMENTS

2.1 Elements to Assure Safe Use

2.1.1. Hospitals and their associated clinics that dispense YESCARTA must be certified

1. To become certified to dispense YESCARTA, hospitals and their associated clinics must:
    a. Designate an authorized representative to complete the certification process by submitting the completed *YESCARTA REMS Program Hospital Enrollment Form* on behalf of the hospital and their associated clinics.
    b. Ensure the authorized representative oversees implementation and compliance with the YESCARTA REMS Program requirements by doing the following:
        i. Complete the *YESCARTA REMS Program Live Training* and successfully complete a *YESCARTA REMS Program Knowledge Assessment*.

- Ensure all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA are trained on the *YESCARTA REMS Program Live Training* and *YESCARTA Adverse Reaction Management Guide* , successfully complete the YESCARTA REMS Program Knowledge Assessment, and maintain records of staff training.

ii. Put processes and procedures in place to ensure new staff involved in the prescribing, dispensing, or administering of YESCARTA are trained.

iii. Put processes and procedures in place to ensure staff involved in the prescribing, dispensing, or administering of YESCARTA are re-trained if YESCARTA has not been dispensed at least once annually from the date of certification in the YESCARTA REMS Program.

iv. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing YESCARTA:

1. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).

2. Provide patients and their guardians with the *Patient Wallet Card* to inform them of the following:

a. Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.

b. Importance of staying within 2 hours of the certified hospital and their associated clinics where the patient received YESCARTA for at least 4 weeks after receiving YESCARTA treatment, unless otherwise indicated by their doctor.

2. As a condition of certification, the certified hospital and their associated clinics must:

a. Recertify in the YESCARTA REMS Program if the hospital and their associated clinics designate a new authorized representative.

b. Report any adverse events suggestive of CRS or neurological toxicities.

c. Maintain documentation that all processes and procedures are in place and are being followed for the YESCARTA REMS Program and provide this documentation upon request to Kite Pharma, FDA, or a third party acting on behalf of Kite Pharma.

d. Comply with audits by Kite Pharma, FDA, or a third party acting on behalf of Kite Pharma to ensure that all training, processes, and procedures are in place and are being followed for the YESCARTA REMS Program.

e. Dispense YESCARTA only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient and ready for administration within 2 hours.

3. Kite Pharma must:

a. Ensure that hospitals and their associated clinics that dispense YESCARTA are certified, in accordance with the requirements described above.

b. Provide *YESCARTA REMS Program Live Training* for hospital staff who prescribe, dispense, or administer YESCARTA to ensure that the hospital and their associated clinics can complete the certification process for the YESCARTA REMS Program.

c. Provide *YESCARTA REMS Program Live Training* to hospitals and their associated clinics through the following mechanisms: in-person or live webcast.

d. Ensure that hospitals and their associated clinics can complete the certification process for the YESCARTA REMS Program using the following mechanisms: in-person, live webcast, email or fax.

e. Ensure that hospitals and their associated clinics are notified when they have been certified by the YESCARTA REMS Program.

f. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital and their associated clinics. If different, the hospital and their associated clinics must be required to re-certify with a new authorized representative.

The following materials are part of the REMS and are appended:

- *YESCARTA REMS Program Knowledge Assessment*
- *YESCARTA REMS Program Live Training*
- *YESCARTA REMS Program Hospital Enrollment Form*
- *YESCARTA Patient Wallet Card*
- *YESCARTA Adverse Reaction Management Guide*
- *YESCARTA REMS Program Website*

2.1.2. YESCARTA must be dispensed to patients only in certain healthcare settings, specifically certified hospitals and their associated clinics with on-site, immediate access to tocilizumab

1. Kite Pharma must ensure that YESCARTA will only be dispensed in certified hospitals and their associated clinics to ensure that a minimum of two doses of tocilizumab are available on-site for each patient for immediate administration (within 2 hours) for the treatment of CRS.

2.2 Implementation System

1. Kite Pharma must ensure that YESCARTA is distributed only to certified hospitals and their associated clinics.

2. Kite Pharma must maintain a validated secure database of hospitals and their associated clinics that are certified to administer YESCARTA in the YESCARTA REMS Program.

3. Kite Pharma must maintain records of YESCARTA distribution and dispensing to meet the REMS requirements.

4. Kite Pharma must maintain a YESCARTA REMS Customer Care Center (1-844-454-KITE) and YESCARTA REMS Program Website (www.YESCARTArems.com). The REMS Program Website must include the option to print the PI, Medication Guide, and YESCARTA REMS materials. The YESCARTA product website must include a prominent REMS-specific link to the YESCARTA REMS Program website.

5. Kite Pharma must ensure that the YESCARTA REMS Program website is fully operational and the REMS materials listed in or appended to the YESCARTA REMS document are available through the YESCARTA REMS program website and by calling the YESCARTA REMS Customer Care Center.

6. Kite Pharma must monitor on an ongoing basis the certified hospitals and their associated clinics to ensure the requirements of the YESCARTA REMS Program are being met. Kite Pharma must institute corrective action if noncompliance is identified and decertify hospitals that do not maintain compliance with the REMS requirements.

7. Kite Pharma must maintain an ongoing annual audit plan of hospitals and their associated clinics.

8. Kite Pharma must audit all certified hospitals within 180 calendar days after the hospital places its first order for YESCARTA to ensure that all processes and procedures are in place and functioning to support the requirements of the YESCARTA REMS Program. The certified hospital must also be included in the Kite Pharma ongoing annual audit plan. Kite Pharma must institute corrective action if noncompliance is identified.

9. Kite Pharma must take reasonable steps to improve implementation of and compliance with the requirements in the YESCARTA REMS Program based on the monitoring and evaluation of the YESCARTA REMS program.

3. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Kite Pharma must submit YESCARTA REMS Program assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS 10/18/2017. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Kite Pharma must submit each assessment so that it will be received by the FDA on or before the due date.

YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion

YESCARTA™ REMS Program Knowledge Assessment

To become an authorized representative for your hospital and its associated clinics in the YESCARTA™ REMS Program, you will need to answer all questions below correctly.

Responses to the YESCARTA™ REMS Program Knowledge Assessment questions and the YESCARTA™ REMS Program Hospital Enrollment Form must be emailed to **YESCARTAREMS@kitepharma.com** or faxed to **1-310-496-0397**.

Questions

1. What is the approved indication for YESCARTA™?

- **A.** Patients with relapsing multiple sclerosis
- **B.** Patients with lung cancer
- **C.** Patients with bladder cancer
- **D.** Adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

2. A YESCARTA™ Patient Wallet Card must be given to patients who have been infused with YESCARTA™.

True ____ False ____

3. Every certified hospital and its associated clinics are required to have a minimum of 2 doses of tocilizumab on-site for each patient and available for administration, for treatment of CRS, within 2 hours of YESCARTA™ infusion.

True ____ False ____

4. After YESCARTA™ infusion, patients should be advised to:

- **A.** Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA™ administration until at least 8 weeks after infusion
- **B.** Remain within close proximity (within 2 hours) of the certified treating hospital and its associated clinics for at least 4 weeks following infusion
- **C.** Seek immediate attention if they experience signs and symptoms of CRS and/or neurologic toxicities
- **D.** All of the above

5. Which of the following is true regarding the time to onset of CRS? It typically occurs:

- **A.** With a median time to onset of 7 days
- **B.** With a median time to onset of 5 days
- **C.** With a median time to onset of 2 days
- **D.** Rarely starts during the first week following YESCARTA™ infusion

Continued on Back

6. All of the following regarding neurologic toxicity related to YESCARTA™ are correct except:

- **A.** Neurologic toxicity always occurs concurrently with CRS
- **B.** Continuous cardiac telemetry and pulse oximetry are recommended for Grade 2 or higher neurologic toxicity
- **C.** The median time to onset of neurologic toxicity is 4 days
- **D.** The most common signs or symptoms of neurologic toxicity include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety

7. Four days after infusion with YESCARTA™, a 49-year-old woman with relapsed diffuse large B-cell lymphoma (DLBCL) fully recovers from a Grade 3 CRS that started the day after infusion of YESCARTA™. The next day, she develops a Grade 2 dysphasia. She has no signs or symptoms of CRS. Appropriate management for this patient would include:

- **A.** Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
- **B.** Start tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)
- **C.** Start dexamethasone at 10 mg IV every 6 hours
- **D.** A and C

8. One day after infusion of YESCARTA™, a 60-year-old man with relapsed diffuse large B-cell lymphoma (DLBCL) develops the following signs and symptoms of CRS: high fevers (39°C-40°C), hypoxia requiring < 40% FiO_2, and hypotension requiring IV fluids. This patient's CRS grade would be most consistent with:

- **A.** Grade 1 CRS
- **B.** Grade 2 CRS
- **C.** Grade 3 CRS
- **D.** Grade 4 CRS

Authorized Representative Name _____ Title _____

Credentials ____DO ____MD ____RPh ____NP/PA Other _____

Hospital/Associated Clinic Name _____

Address _____

City _____ State _____ ZIP Code _____

Signature _____ Date _____

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REMS Program Live Training

Kite
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This educational module contains information on selected YESCARTA™-associated adverse reactions observed in clinical trials for adult patients with relapsed/refractory large B-cell lymphoma after 2 or more lines of systemic therapy, cytokine release syndrome and neurologic toxicities. These are not all of the adverse reactions observed in these trials.

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Indication

YESCARTA™ is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

The full Prescribing Information includes **BOXED WARNINGS** for YESCARTA™.

Please see full Prescribing Information, including **BOXED WARNINGS** and Medication Guide.

YESCARTA™ REMS Program Overview

What Is the YESCARTA™ REMS (Risk Evaluation and Mitigation Strategy) Program?

A REMS Program is a strategy to manage known or potential risks associated with a drug and is required by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. YESCARTA™ is available only under a program called the YESCARTA™ REMS Program because of the serious risks of cytokine release syndrome (CRS) and neurologic toxicities.

The goals of the YESCARTA™ REMS Program are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and their associated clinics that dispense YESCARTA™ are specially certified and have on-site, immediate access to a minimum of 2 doses of tocilizumab
- Ensuring that those who prescribe, dispense, or administer YESCARTA™ are aware of how to manage the risks of CRS and neurologic toxicities

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion

Hospital Certification

To become certified to dispense YESCARTA™, hospitals and their associated clinics must:

1. Designate an authorized representative to complete the training program by completing and submitting the YESCARTA™ REMS Program Hospital Enrollment Form on behalf of the hospital and its associated clinics
2. Ensure that the authorized representative oversees implementation and compliance with the YESCARTA™ REMS Program requirements
3. Dispense YESCARTA™ only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for administration within 2 hours
4. Recertify in the YESCARTA™ REMS Program if a new authorized representative is designated

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Hospital Facility Certification (continued)

5. Maintain documentation that all processes and procedures are in place and are being followed for the YESCARTA™ REMS Program; provide this documentation upon request to Kite, FDA, or a third party acting on behalf of Kite or FDA
6. Comply with audits by Kite, FDA, or a third party acting on behalf of Kite or FDA, to ensure that all training, processes, and procedures are in place and are being followed for the YESCARTA™ REMS Program
7. Report any adverse events suggestive of CRS or neurologic toxicities

Who Can Be an Authorized Representative?

An authorized representative at the hospital and its associated clinics can be a:

- Physician
- Nurse
- Any responsible individual assigned by the hospital and its associated clinics

One representative (the “authorized representative”) must enroll for each hospital and its associated clinics and attest to the enrollment requirements as stated on the YESCARTA™ REMS Program Hospital Enrollment Form.

YESCARTA™ Authorized Representative Attestations

- ❑ Complete the YESCARTA™ REMS Program Live Training and successfully complete the YESCARTA™ REMS Program Knowledge Assessment
- ❑ Submit the completed YESCARTA™ REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com
- ❑ Submit the YESCARTA™ REMS Program Knowledge Assessment to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com
- ❑ Oversee implementation and compliance with the YESCARTA™ REMS Program

YESCARTA™ Authorized Representative Attestations (continued)

- Ensure that the healthcare hospital and its associated clinics will establish processes and procedures that are subject to monitoring by Kite or a third party acting on behalf of Kite to help ensure compliance with the requirements of the YESCARTA™ REMS Program, including the following, before administering YESCARTA™:
  - Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA™ are trained on the REMS Program requirements as described in the training materials, successfully complete the YESCARTA™ REMS Program Knowledge Assessment, and maintain training records for all staff
  - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing or administering of YESCARTA™ are retrained if YESCARTA™ has not been dispensed at least once annually from the date of certification in the YESCARTA™ REMS Program
  - Prior to dispensing YESCARTA™, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours)
  - Prior to dispensing YESCARTA™, provide patients/caregivers the Patient Wallet Card

Serious Risks of YESCARTA™

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Serious Risks Associated With YESCARTA™

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening, occurred in patients receiving YESCARTA™. Do not administer YESCARTA™ to patients with active infection. Treat severe CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurologic toxicities, including fatal or life-threatening, occurred in patients receiving YESCARTA™, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA™. Treat with corticosteriods and provide supportive care as needed.

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Cytokine Release Syndrome

- CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA™
- In a Kite clinical trial, CRS occurred in 94% (101/108) of patients receiving YESCARTA™, including Grade 3 or higher CRS in 13% (14/108) of patients
- The median time to onset was 2 days (range, 1-12 days)
- The median duration of CRS was 7 days (range, 2-58 days)
- 45% (49/108) of patients received tocilizumab after infusion of YESCARTA™
- Among patients who died after receiving YESCARTA™, 4 had CRS events at the time of death

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Neurologic Toxicities

- Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA™
- Neurologic toxicities occurred within 8 weeks of YESCARTA™ infusion in 85% of patients, including Grade 3 or higher neurologic toxicities in 31% of patients
- The median time to onset was 4 days (range, 1-43 days) following YESCARTA™ infusion
- The median duration was 17 days

Management of CRS and Neurologic Toxicities

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Patient Assessment of CRS Associated With YESCARTA™

Symptoms of CRS

CRS	
The following are signs and symptoms	
Capillary leak syndrome	Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS)
Cardiac arrest	Hypotension
Cardiac arrhythmias	Hypoxia
Cardiac failure	Renal insufficiency
Chills	Tachycardia
Fever	

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Guidance on Managing CRS

- Identify CRS based on clinical presentation
- Evaluate for and treat other causes of fever, hypoxia, and hypotension
- If CRS is suspected, manage according to the recommendations on slide 18
- Patients who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry
- For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function
- For severe or life-threatening CRS, consider intensive care supportive therapy

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Guidance on Managing CRS

Grading and Management of YESCARTA™-Related CRS

CRS Grade*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity	Tocilizumab† 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen Maximum of 3 doses in a 24-hour period Maximum total of 4 doses	If no improvement within 24 hours after starting tocilizumab, manage per Grade 3
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2	Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (eg, 10 mg IV every 6 hours) Continue corticosteroids use until the event is Grade 1 or less. Taper over 3 days
Grade 4 Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

*Modified Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to tocilizumab Prescribing Information for additional information.

Patient Assessment of Neurologic Toxicities Associated With YESCARTA™

Symptoms of Neurologic Toxicities

Neurologic Toxicities	
The following are common signs and symptoms	
Anxiety	Encephalopathy
Aphasia	Headache
Delirium	Insomnia
Dizziness	Tremor

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Guidance on Managing Neurologic Toxicities

- Monitor patients for signs and symptoms of neurologic toxicities
- Rule out other causes of neurologic symptoms
- Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry
- Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities
- Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities

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Guidance on Managing Neurologic Toxicities

Grading and Management of YESCARTA™-Related Neurologic Toxicities

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
Grade 2 Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab as per management of Grade 2 CRS (slide 18) If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg IV every 6 hours if not already taking other steroids Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Dexamethasone 10 mg IV every 6 hours Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days. Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis

Abbreviation: ADLs, activities of daily living.
*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

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Guidance on Managing Neurologic Toxicities

Grading and Management of YESCARTA™-Related Neurologic Toxicities (continued)

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab as per management of Grade 2 CRS (slide 18) In addition, administer dexamethasone 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Dexamethasone at 10 mg IV every 6 hours Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab as per management of Grade 2 CRS (slide 18) Administer methylprednisolone IV 1000 mg/day with first dose of tocilizumab and continue for methylprednisolone 100 mg/day for 2 more days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis

Abbreviation: ADLs, activities of daily living.
*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion

Adverse Reaction Reporting

Reporting suspected adverse reactions after administration of therapy is important. It allows continued monitoring of the risk/benefit balance of therapy. Healthcare providers are asked to report any suspected adverse reactions associated with YESCARTA™.

Please contact Kite at **1-844-454-KITE** or FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

Patient Counseling

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Patient Counseling

- Talk to the patient about the risk of CRS and neurologic toxicities. Tell them to contact their healthcare provider and/or seek immediate care if experiencing the signs and symptoms associated with CRS and neurologic toxicities:
  - Fever (100.4°F/38°C or higher)
  - Difficulty breathing
  - Chills/shaking chills
  - Confusion
  - Dizziness or lightheadedness
  - Severe nausea, vomiting, diarrhea
  - Fast/irregular heart beat
  - Severe fatigue or weakness
- Provide the YESCARTA™ Patient Wallet Card to the patient or the patient's caregiver. Tell the patient to carry the Patient Wallet Card at all times and to share the Patient Wallet Card with any healthcare provider involved in the patient's treatment
- Instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA™ infusion

YESCARTA™ REMS Program Resources

YESCARTA™ (axicabtagene ciloleucel) Suspension for IV infusion

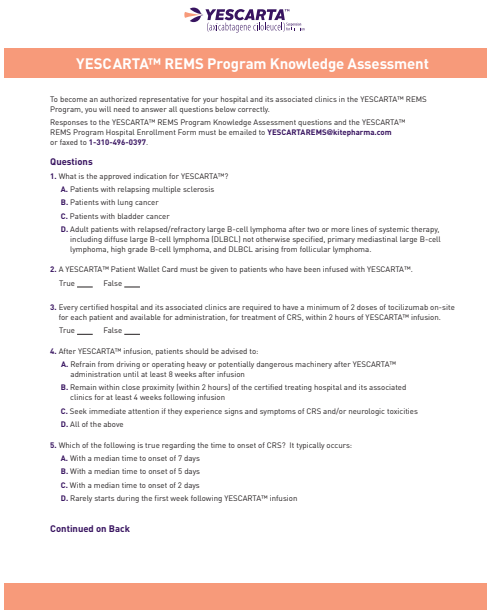
YESCARTA™ REMS Program Kit

Includes:

- YESCARTA™ full Prescribing Information and Medication Guide
- YESCARTA™ REMS Program Live Training
- YESCARTA™ REMS Program Knowledge Assessment
- YESCARTA™ REMS Program Hospital Enrollment Form
- YESCARTA™ Adverse Reaction Management Guide
- YESCARTA™ Patient Wallet Card

YESCARTA™ REMS Program Knowledge Assessment

- An authorized representative must enroll on behalf of the hospital and its associated clinics by answering all questions correctly
- Paper responses to the YESCARTA™ REMS Program Knowledge Assessment questions must be faxed to 1-310-496-0397 or emailed to YESCARTAREMS@kitepharma.com



YESCARTA™ (axicabtagene ciloleucel)

YESCARTA™ REMS Program Knowledge Assessment

To become an authorized representative for your hospital and its associated clinics in the YESCARTA™ REMS Program, you will need to answer all questions below correctly.

Responses to the YESCARTA™ REMS Program Knowledge Assessment questions and the YESCARTA™ REMS Program Hospital Enrollment Form must be emailed to **YESCARTAREMS@kitepharma.com** or faxed to **1-310-496-0397**.

Questions

1. What is the approved indication for YESCARTA™?
- **A.** Patients with relapsing multiple sclerosis
- **B.** Patients with lung cancer
- **C.** Patients with bladder cancer
- **D.** Adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

2. A YESCARTA™ Patient Wallet Card must be given to patients who have been infused with YESCARTA™.
True ___ False ___

3. Every certified hospital and its associated clinics are required to have a minimum of 2 doses of tocilizumab on-site for each patient and available for administration, for treatment of CRS, within 2 hours of YESCARTA™ infusion.
True ___ False ___

4. After YESCARTA™ infusion, patients should be advised to:
- **A.** Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA™ administration until at least 8 weeks after infusion
- **B.** Remain within close proximity (within 2 hours) of the certified treating hospital and its associated clinics for at least 4 weeks following infusion
- **C.** Seek immediate attention if they experience signs and symptoms of CRS and/or neurologic toxicities
- **D.** All of the above

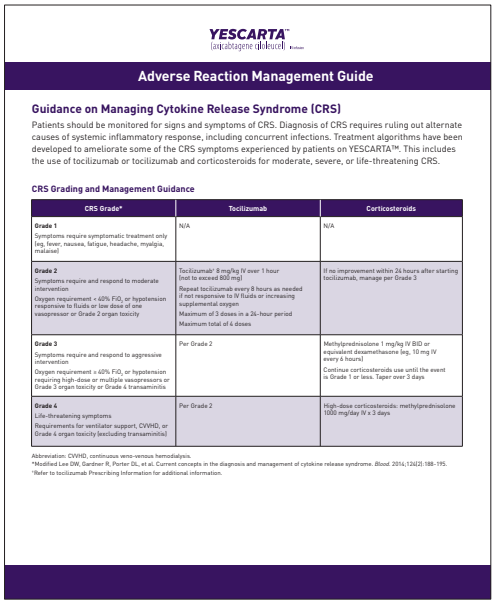
5. Which of the following is true regarding the time to onset of CRS? It typically occurs:
- **A.** With a median time to onset of 7 days
- **B.** With a median time to onset of 5 days
- **C.** With a median time to onset of 2 days
- **D.** Rarely starts during the first week following YESCARTA™ infusion

Continued on Back

YESCARTA™ Adverse Reaction Management Guide

This guide will help to:

- Identify patients with CRS or neurologic toxicities; rule out concurrent infection
- Grade the severity of CRS or neurologic toxicities
- Provide treatment of CRS or neurologic toxicities according to the severity grade, as shown in this guide



YESCARTA™ (axicabtagene ciloleucel)

Adverse Reaction Management Guide

Guidance on Managing Cytokine Release Syndrome (CRS)

Patients should be monitored for signs and symptoms of CRS. Diagnosis of CRS requires ruling out alternate causes of systemic inflammatory response, including concurrent infections. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA™. This includes the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS.

CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity	Tocilizumab† 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen Maximum of 3 doses in a 24-hour period Maximum total of 4 doses	If no improvement within 24 hours after starting tocilizumab, manage per Grade 3
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2	Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (eg, 10 mg IV every 6 hours) Continue corticosteroids use until the event is Grade 1 or less. Taper over 3 days
Grade 4 Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days

Abbreviation: CVVHD, continuous veno-venous hemodialysis.
*Modified Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188–195.
†Refer to tocilizumab Prescribing Information for additional information.

YESCARTA™ Patient Wallet Card

- Provide to all patients who receive YESCARTA™ and complete the treating oncologist contact information
- Patients should carry their wallet card to remind them
  - About the signs and symptoms of CRS and neurologic toxicities that require immediate attention
  - To remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following infusion
- Patients should show this card to all healthcare providers they see

Additional YESCARTA™ REMS Program Information and Resources

To enroll in the YESCARTA™ REMS Program or obtain information regarding enrollment in the program, call 1-844-454-KITE or visit the YESCARTA™ REMS Program website at www.YESCARTAREMS.com.

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YESCARTA™ REMS Program Hospital Enrollment Form

YESCARTA™ REMS Program Hospital Enrollment

YESCARTA™ is available only through the YESCARTA™ REMS Program. Only hospitals and their associated clinics certified in the YESCARTA™ REMS Program are permitted to dispense YESCARTA™.

YESCARTA™ Hospital Attestations

As a condition of certification, the certified hospital and its associated clinics must:

- ❑ Ensure that if the hospital and its associated clinics designate a new authorized representative, the new authorized representative must review the YESCARTA™ REMS Program Live Training, complete the YESCARTA™ REMS Program Knowledge Assessment, complete a new YESCARTA™ REMS Program Hospital Enrollment Form, and submit the forms via fax to **1-310-496-0397** or email at **YESCARTAREMS@kitepharma.com**.
- ❑ Report any adverse events suggestive of CRS, neurologic toxicities, or suspected, unexpected serious adverse reactions to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Kite at 1-844-454-KITE.
- ❑ Dispense YESCARTA™ to patients only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- ❑ Maintain documentation of all processes and procedures for the YESCARTA™ REMS Program and provide documentation upon request to Kite, FDA, or a third party acting on behalf of Kite or FDA.
- ❑ Comply with audits by Kite, FDA, or a third party acting on behalf of Kite or FDA.

YESCARTA™ REMS Program Hospital Registration Form

Please email the completed form to **YESCARTAREMS@kitepharma.com** or fax to **1-310-496-0397**.

Important Notice: Completion of the enrollment form and knowledge assessment does not guarantee that your hospital and its associated clinics will be certified to administer YESCARTA™. Please contact 1-844-454-KITE or visit the YESCARTA™ REMS Program website at www.YESCARTAREMS.com for more information.

YESCARTA™ REMS Program Hospital Enrollment Form

To finalize your registration in the YESCARTA™ REMS Program, please complete the form below in its entirety.

❑ **New Certification** ❑ **Recertification**

Authorized Representative Information:

First Name: _____ Last Name: _____

Title: _____ Credentials: ◯ DO ◯ MD ◯ RPh ◯ NP/PA Other: _____

Phone Number: _____ Fax Number: _____

Email Address: _____

Hospital/Associated Clinic Contact Information:

Hospital/Associated Clinic Name: _____

Street Address: _____

_____

City: _____ State: _____ ZIP Code: _____

Hospital/Associated Clinic Phone Number: _____ Hospital/Associated Clinic Fax Number: _____

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YESCARTA™ Authorized Representative Attestations

I am the authorized representative designated by my hospital and its associated clinics to coordinate the activities of the YESCARTA™ REMS Program.

By signing this form, I attest that I understand and agree to comply with the following REMS Program requirements:

- I must complete the YESCARTA™ REMS Program Live Training and successfully complete the YESCARTA™ REMS Program Knowledge Assessment.
- I must submit this completed YESCARTA™ REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com.
- I must submit the YESCARTA™ REMS Program Knowledge Assessment to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com.
- I will oversee implementation and compliance with the YESCARTA™ REMS Program.
- I will ensure that my hospital and its associated clinics will establish processes and procedures that are subject to monitoring by Kite or a third party acting on behalf of Kite to help ensure compliance with the requirements of the YESCARTA™ REMS Program, including the following, before administering YESCARTA™:
    - Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA™ are trained on the REMS Program requirements as described in the training materials, successfully complete the YESCARTA™ REMS Program Knowledge Assessment, and maintain training records for all staff.
    - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing or administering of YESCARTA™ are retrained if YESCARTA™ has not been dispensed at least once annually from the date of certification in the YESCARTA™ REMS Program.
    - Prior to dispensing YESCARTA™, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
    - Prior to dispensing YESCARTA™, provide patients/caregivers the Patient Wallet Card.

Authorized Representative Name _____ Title _____

Signature _____ Date _____

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Patient Information

YESCARTA™ can cause side effects that can lead to death.

Call or see your oncologist or get emergency help RIGHT AWAY if you have any of these symptoms:

- Fever (100.4˚F/38˚C or higher)
- Difficulty breathing
- Chills/shaking chills
- Confusion
- Dizziness/lightheadedness
- Severe nausea, vomiting, diarrhea
- Fast/irregular heartbeat
- Severe fatigue or weakness

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YESCARTA™
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Patient Wallet Card

Carry this card with you at all times. SHOW THIS CARD if you go to the emergency room or see any physician.

Tell any healthcare provider that sees you that you are being treated with YESCARTA™.

Stay within close proximity (within 2 hours) of the location where you received your treatment for at least 4 weeks after getting YESCARTA™.

Important Information for Healthcare Providers

Name of treating oncologist:

Office phone:

After-hours phone:

Date of YESCARTA™ (axicabtagene ciloleucel) infusion:

- This patient has received YESCARTA™, which is a CD19-directed genetically modified autologous T-cell immunotherapy
- **YESCARTA™ can cause cytokine release syndrome (CRS) and neurologic toxicities, which may be fatal or life threatening. CRS may involve any organ system**

- Contact the patient's oncologist immediately for further information

YESCARTA™
(axicabtagene ciloleucel) for IV infusion

Adverse Reaction Management Guide

Guidance on Managing Cytokine Release Syndrome (CRS)

Patients should be monitored for signs and symptoms of CRS. Diagnosis of CRS requires ruling out alternate causes of systemic inflammatory response, including concurrent infections. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA™. This includes the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS.

CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity	Tocilizumab† 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen Maximum of 3 doses in a 24-hour period Maximum total of 4 doses	If no improvement within 24 hours after starting tocilizumab, manage per Grade 3
Grade 3 Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2	Methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (eg, 10 mg IV every 6 hours) Continue corticosteroids use until the event is Grade 1 or less. Taper over 3 days
Grade 4 Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

*Modified Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2):188-195.

†Refer to tocilizumab Prescribing Information for additional information.

Guidance on Managing Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities. Treatment algorithms have been developed to ameliorate the neurologic toxicities experienced by patients on YESCARTA™. This includes the use of corticosteroids or corticosteroids and tocilizumab for moderate, severe, or life-threatening neurologic toxicities.

Neurologic Toxicity Grading and Management Guidance

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
Grade 2 Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on the other side for management of Grade 2 CRS If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg IV every 6 hours if not already taking other steroids Consider nonsedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Dexamethasone 10 mg IV every 6 hours Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days Consider nonsedating antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per the table on the other side for management of Grade 2 CRS In addition, administer dexamethasone 10 mg IV with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Dexamethasone 10 mg IV every 6 hours Continue dexamethasone use until the event is Grade 1 or less. Taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on the other side for management of Grade 2 CRS Administer methylprednisolone IV 1000 mg/day with first dose of tocilizumab and continue methylprednisolone 1000 mg/day for 2 more days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	High-dose corticosteroids: methylprednisolone 1000 mg/day IV x 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis

Abbreviation: ADLs, activities of daily living.

*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

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YESCARTA™ (axicabtagene ciloleucel) Suspension for IV Infusion

Risk Evaluation and Mitigation Strategy (REMS)

This website is intended for US healthcare professionals only.

What Is the YESCARTA™ REMS Program?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the United States (US) Food and Drug Administration (FDA). The FDA has determined that a REMS is necessary to ensure that the benefits of YESCARTA™ outweigh the risks of cytokine release syndrome and neurologic toxicities. YESCARTA™ is available only through the YESCARTA™ REMS Program.

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with YESCARTA™
- CRS occurred in 94% (101/108) of patients receiving YESCARTA™, including Grade 3 or higher CRS in 13% (14/108) of patients
- Among patients who died after receiving YESCARTA™, 4 had ongoing CRS events at the time of death
- The median time to onset was 2 days (range, 1-12 days), and the median duration of CRS was 7 days (range, 2-58 days)
- Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%)
- Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)

Neurologic Toxicities

- Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA™
- The median time to onset was 4 days (range, 1-43 days) following YESCARTA™ infusion
- Neurologic toxicities within 8 weeks of YESCARTA™ infusion occurred in 85% of patients with a median duration of 17 days
- Grade 3 or higher neurologic toxicities occurred in 31% of patients
- The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%), and anxiety (9%)
- Prolonged encephalopathy was noted up to 182 days post-infusion (maximum duration of 173 days)
- Serious events including leukoencephalopathy and seizures occurred with YESCARTA™
- Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA™

YESCARTA™ REMS Program Requirements

Hospitals and their associated clinics must be enrolled in the YESCARTA™ REMS Program to be able to dispense YESCARTA™.

All relevant staff involved in the prescribing, dispensing, or administering of YESCARTA™ are trained on the YESCARTA™ REMS Program requirements, and must successfully complete a YESCARTA™ REMS Program Knowledge Assessment.

Hospital Enrollment Instructions

An authorized representative must enroll on behalf of the hospital and its associated clinics. To be enrolled in the YESCARTA™ REMS Program, the representative must:

1. Complete the training program, which includes review of:
   - YESCARTA™ full Prescribing Information
   - YESCARTA™ REMS Program Live Training
   - YESCARTA™ Adverse Reaction Management Guide
2. Successfully complete the YESCARTA™ REMS Program Knowledge Assessment.
3. Complete the YESCARTA™ REMS Program Hospital Enrollment Form.
4. Oversee implementation and compliance with YESCARTA™ REMS Program requirements:
   - Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA™ are trained on the REMS Program requirements and successfully complete the YESCARTA™ REMS Program Knowledge Assessment
   - Maintain training records of staff
   - Ensure that the hospital and its associated clinics have a minimum of 2 doses of tocilizumab available on-site for each patient and are ready for immediate administration (within 2 hours)
   - Prior to dispensing YESCARTA™, provide patients/caregivers with the Patient Wallet Card
   - Put processes and procedures in place to ensure that new staff are trained and staff are retrained if YESCARTA™ has not been dispensed at least once annually from the date of certification in the YESCARTA™ REMS Program

Indication

YESCARTA™ is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA™ is not indicated for the treatment of patients with primary central nervous system lymphoma.

Where to Find YESCARTA™ REMS Program Information and Resources

To enroll in the YESCARTA™ REMS Program, call 1-844-454-KITE. For information related to enrollment in the YESCARTA™ REMS Program, call 1-844-454-KITE or visit the YESCARTA™ REMS Program website at www.YESCARTAREMS.com.

Reporting Adverse Reactions

You are encouraged to report suspected adverse reactions associated with YESCARTA™ to Kite at 1-844-454-KITE (1-844-454-5483) or the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.

Resources for Healthcare Professionals

- Download All Resources
- YESCARTA™ Prescribing Information and Medication Guide
- YESCARTA™ REMS Program Knowledge Assessment
- YESCARTA™ REMS Program Live Training
- YESCARTA™ REMS Program Hospital Enrollment Form
- YESCARTA™ Adverse Reaction Management Guide
- YESCARTA™ Patient Wallet Card

Adobe Reader is required to view PDFs. If you do not have it installed, download it here.

Kite, A GILEAD Company
2355 Utah Avenue, El Segundo, CA 90245

Initial REMS Approval: XX/2017

BLA 125646
KYMRIAH™ (tisagenlecleucel)
Suspension for Intravenous Infusion

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936
Telephone: 1-844-687-2278

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 Goal

The goals of the Kymriah™ REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities.

2 REMS Elements

2.1 Elements to Assure Safe Use

2.1.1 Hospitals and their associated clinics that dispense Kymriah must be certified

1. To become certified to dispense Kymriah, hospitals and their and associated clinics must:
    a. Designate an authorized representative to complete the certification process by submitting the completed *Kymriah REMS Program Hospital Enrollment Form* on behalf of the hospital and their associated clinics
    b. Ensure the authorized representative oversees implementation and compliance with Kymriah REMS Program requirements by doing the following:
        i. Complete the *Kymriah REMS Live Training Program* and successfully complete the *Kymriah REMS Program Knowledge Assessment*
        ii. Ensure all relevant staff involved in the prescribing, dispensing, or administering of Kymriah are trained on the Kymriah REMS Program requirements as described in the *Kymriah REMS Live Training Program* and successfully complete the *Kymriah REMS Program Knowledge Assessment*, and maintain records of staff training.
        iii. Put processes and procedures in place to ensure new staff involved in the prescribing, dispensing, or administering of Kymriah are trained.
        iv. Put processes and procedures in place to ensure staff involved in the prescribing dispensing or administering of Kymriah are re-trained if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
        v. Put processes and procedures in place to ensure the following requirements are completed prior to dispensing Kymriah:
            1. Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
            2. Provide patients and their guardians with the *Patient Wallet Card* to inform them of the following:

a. Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.

b. Importance of staying within 2 hours of the certified hospital and their associated clinics for at least 4 weeks after receiving Kymriah treatment, unless otherwise indicated by the doctor.

2. As a condition of certification each hospital and their associated clinics must:

   a. Recertify in the Kymriah REMS Program if the hospital and their associated clinics designate a new authorized representative.

   b. Report any adverse events suggestive of cytokine release syndrome or neurological toxicities.

   c. Maintain documentation that all processes and procedures are in place and are being followed for the Kymriah REMS Program and provide that documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis.

   d. Comply with audits by Novartis, FDA, or a third party acting on behalf of Novartis to ensure that all training, processes and procedures are in place and are being followed for the Kymriah REMS Program.

   e. Dispense Kymriah only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.

3. Novartis must:

   a. Ensure that hospitals and their associated clinics that dispense Kymriah are certified, in accordance with the requirements described above.

   b. Provide *Kymriah REMS Live Training Program* to hospital staff who prescribe, dispense, or administer Kymriah to ensure that the hospital and their associated clinics can complete the certification process for the Kymriah REMS Program.

   c. Provide *Kymriah REMS Live Training Program* for hospitals and their associated clinics through the following mechanisms: in-person or live webcast

   d. Ensure that hospitals and their associated clinics can complete the certification process for the Kymriah REMS Program using the following mechanisms: in-person, live webcast, online, fax, and phone

   e. Ensure that hospitals and their associated clinics are notified when they have been certified by the Kymriah REMS Program.

   f. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the certified hospital and their associated clinics. If different, the hospital and their associated clinics must be required to re-certify with a new authorized representative.

The following materials are part of the REMS and are appended:

- *Kymriah REMS Live Training Program Slides*
- *Kymriah REMS Program Knowledge Assessment*
- *Kymriah REMS Program Hospital Enrollment Form*
- *Kymriah REMS Program Website*
- *Kymriah REMS Program Patient Wallet Card*

2.1.2 Kymriah must be dispensed to patients only in certain healthcare settings, specifically certified hospitals and their associated clinics with on-site, immediate access to tocilizumab

1. Novartis must ensure that Kymriah will only be dispensed in certified hospitals and their associated clinics to ensure that a minimum of two doses of tocilizumab are available on-site for each patient for immediate administration (within 2 hours) for the treatment of cytokine release syndrome.

2.2 Implementation System

1. Novartis must ensure that Kymriah is only distributed to certified hospitals and their associated clinics.
2. Novartis must maintain a validated secure database of hospitals and their associated clinics that are certified to dispense Kymriah in the Kymriah REMS Program.
3. Novartis must maintain records of Kymriah distribution and dispensing to meet the REMS requirements.
4. Novartis must maintain a Kymriah REMS Program Call Center (844-4KYMRIAH) and Kymriah REMS Program Website (www.Kymriah-REMS.com). The REMS Program Website must include the option to print the PI, Medication Guide, and Kymriah REMS materials. The Kymriah product website must include a prominent REMS-specific link to the Kymriah REMS Program website.
5. Novartis must ensure the Kymriah REMS Program website is fully operational and the REMS materials listed in or appended to the Kymriah REMS document are available through the Kymriah REMS Program website and by calling the Kymriah REMS Program Call Center.
6. Novartis must monitor on an ongoing basis the certified hospital and their associated clinics to ensure the requirements of the Kymriah REMS Program are being met. Novartis must institute corrective action if noncompliance is identified and decertify hospitals that do not maintain compliance with the REMS requirements.
7. Novartis must maintain an ongoing annual audit plan of hospitals and their associated clinics.
8. Novartis must audit all certified hospitals within 180 calendar days after the hospital places its first order of Kymriah to ensure that all processes and procedures are in place and functioning to support the requirements of the Kymriah REMS Program. The

certified hospital must also be included in Novartis' ongoing annual audit plan. Novartis must institute corrective action if noncompliance is identified.

9. Novartis must take reasonable steps to improve implementation of and compliance with the requirements in the Kymriah REMS Program based on monitoring and evaluation of the Kymriah REMS Program.

3 Timetable for Submission of Assessments

Novartis must submit REMS assessments to the FDA at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS ([date of approval (mm/dd/yyyy format)]). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Novartis must submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1

Kymriah REMS Live Training Program Slides

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

Risk Evaluation and Mitigation Strategy (REMS): Cytokine release syndrome and neurological toxicities

A REMS is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of KYMRIAH outweigh its risks.

The purpose of the KYMRIAH REMS is to inform healthcare providers of the risks of cytokine release syndrome and neurological toxicities observed with KYMRIAH.

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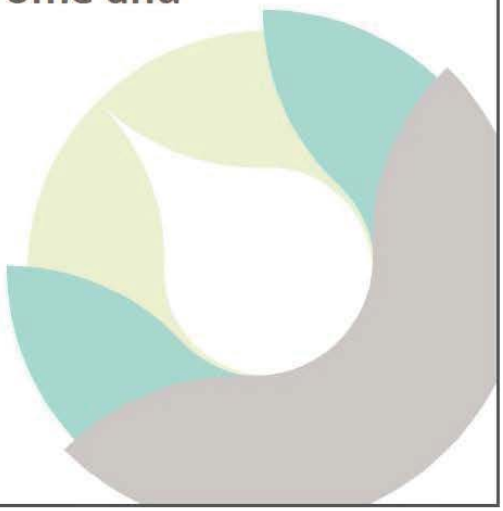
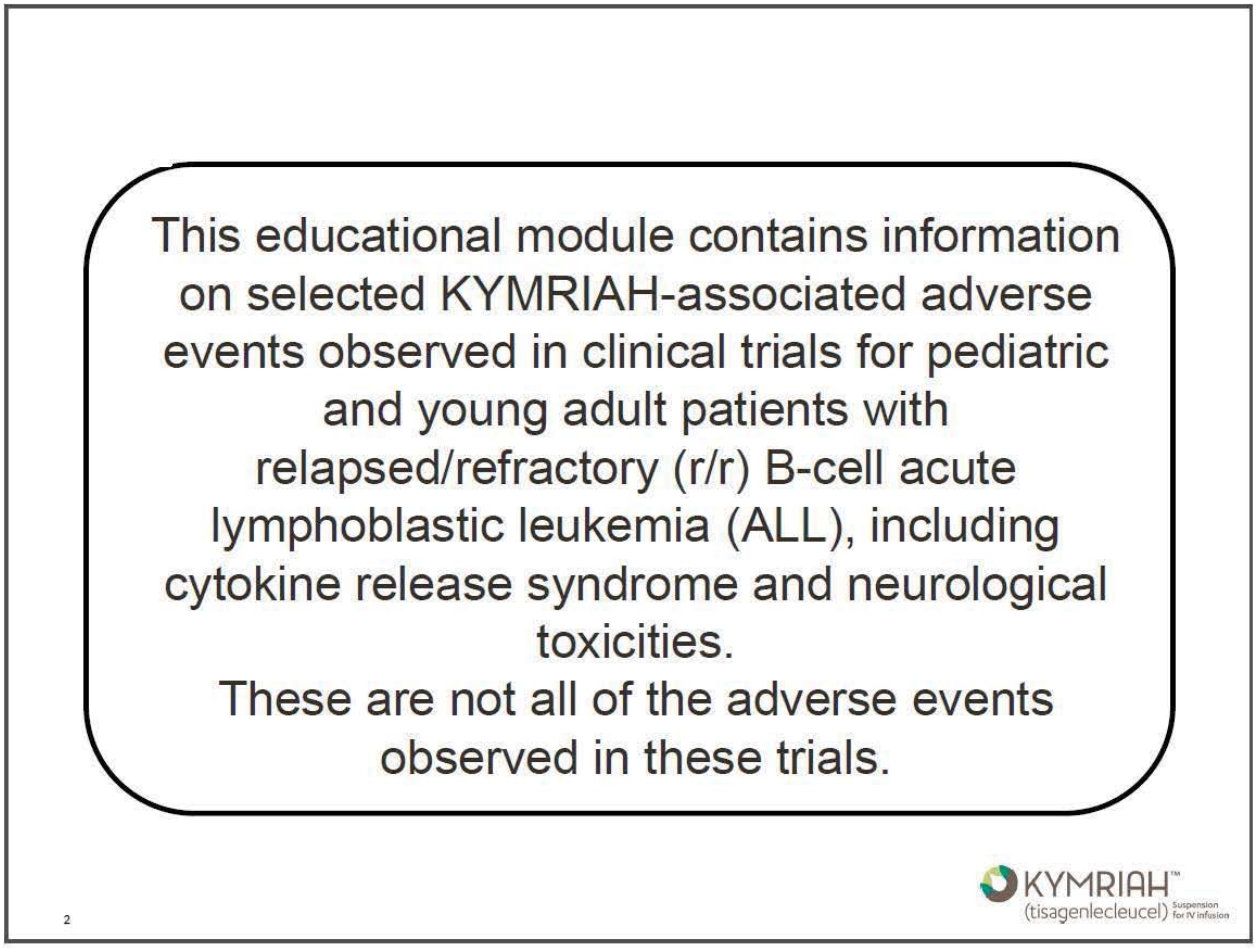



This educational module contains information on selected KYMRIAH-associated adverse events observed in clinical trials for pediatric and young adult patients with relapsed/refractory (r/r) B-cell acute lymphoblastic leukemia (ALL), including cytokine release syndrome and neurological toxicities.
These are not all of the adverse events observed in these trials.
2
KYMRIAH™
(tisagenlecleucel) Suspension for IV Infusion

KYMRIAH Indication

- KYMRIAH (tisagenlecleucel), previously known as CTL019, is a CD19-directed genetically modified autologous T cell immunotherapy

- Indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

3

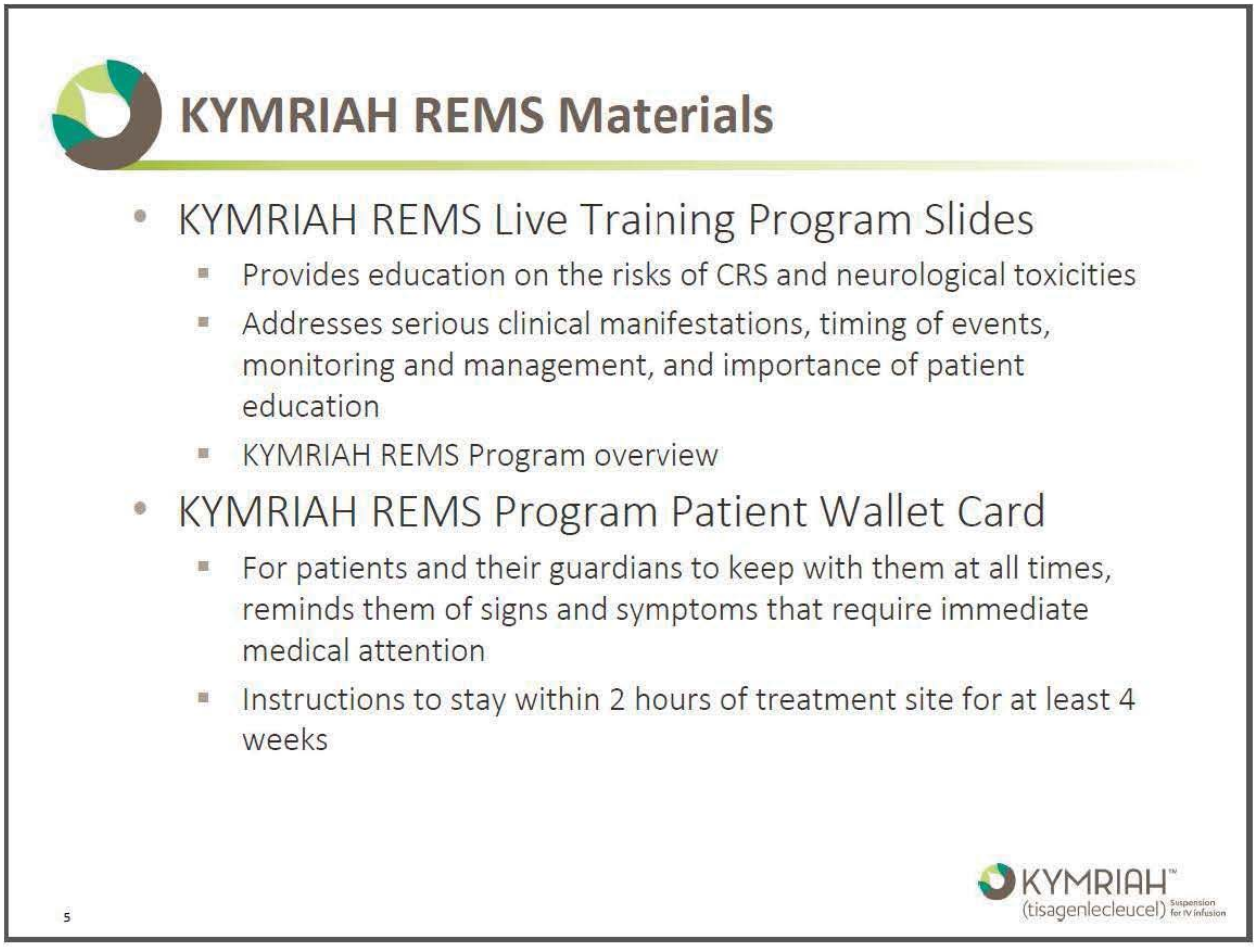
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion

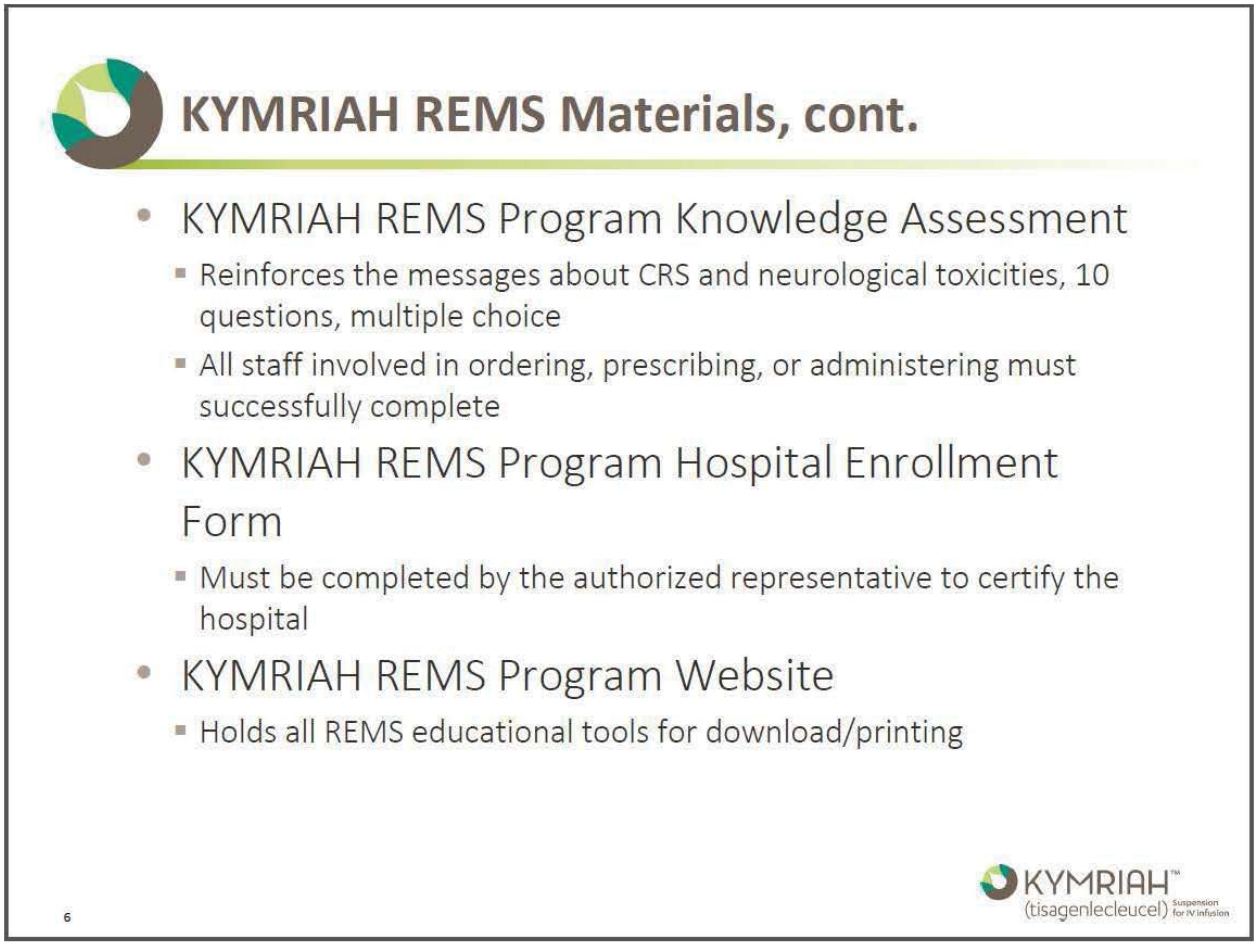
KYMRIAH REMS Goal

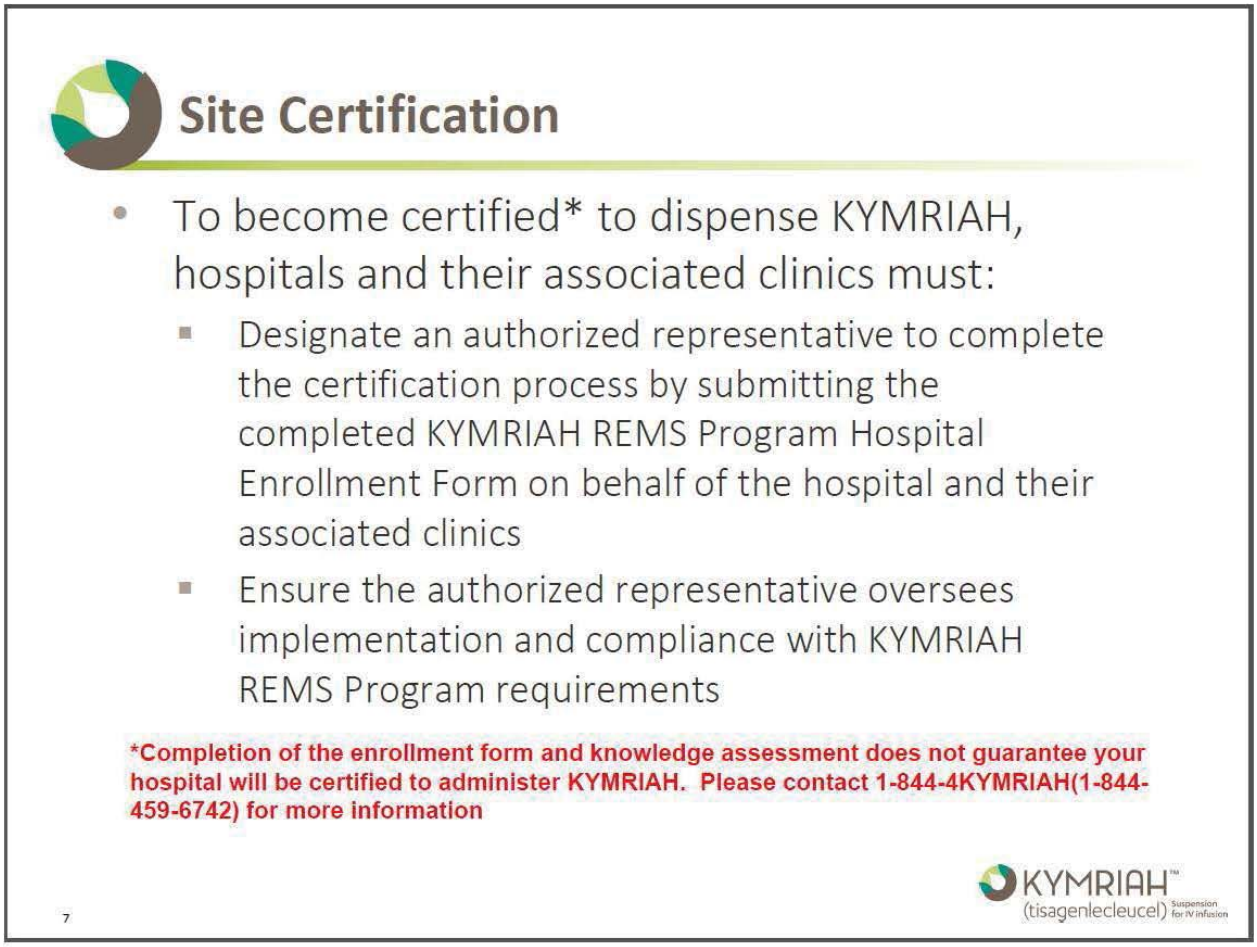
- The goals of the KYMRIAH REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:
  - Ensuring that hospitals and their associated clinics that dispense KYMRIAH are specially certified and have on-site, immediate access to tocilizumab.
  - Ensuring those who prescribe, dispense, or administer KYMRIAH are aware of how to manage the risks of CRS and neurological toxicities.

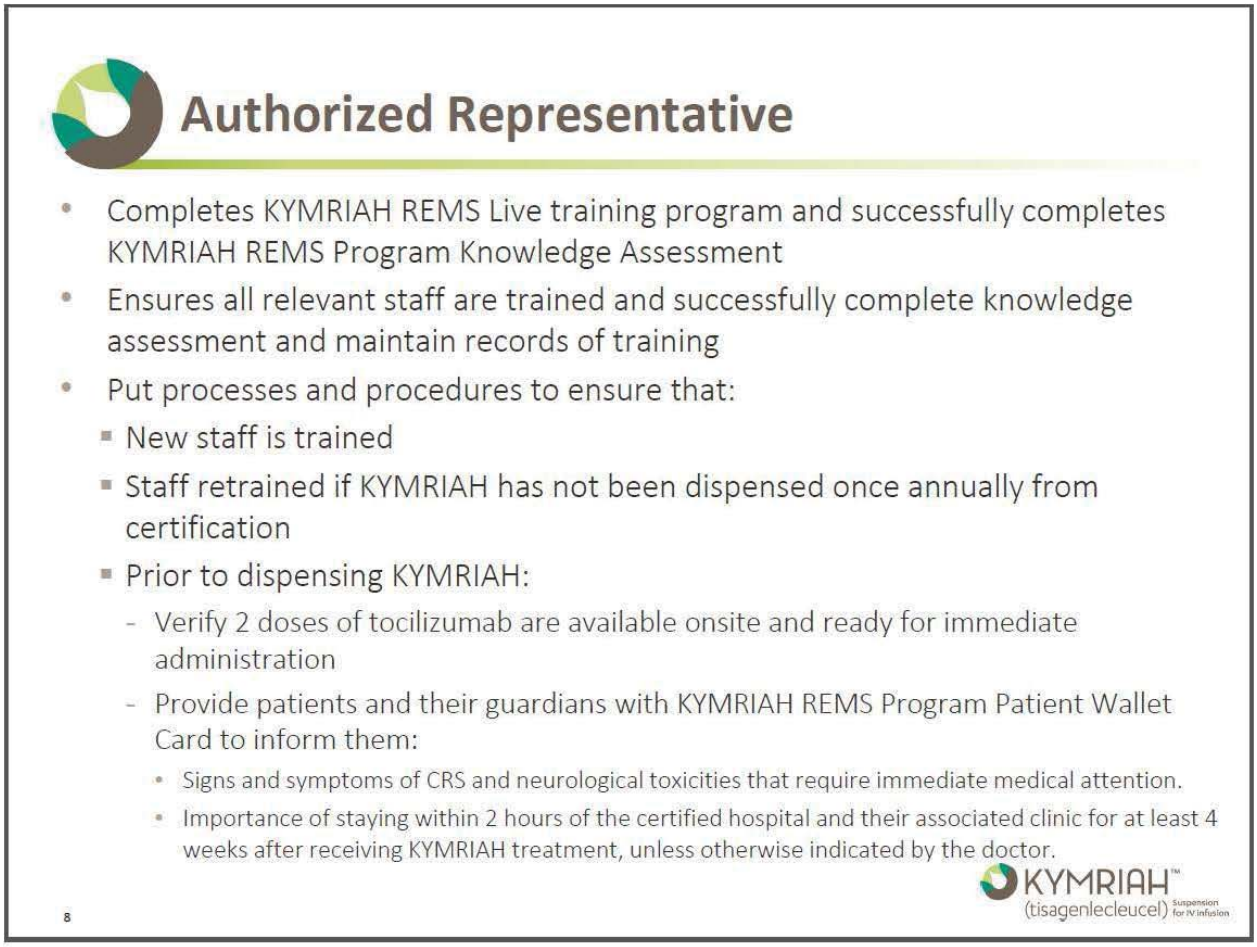
4

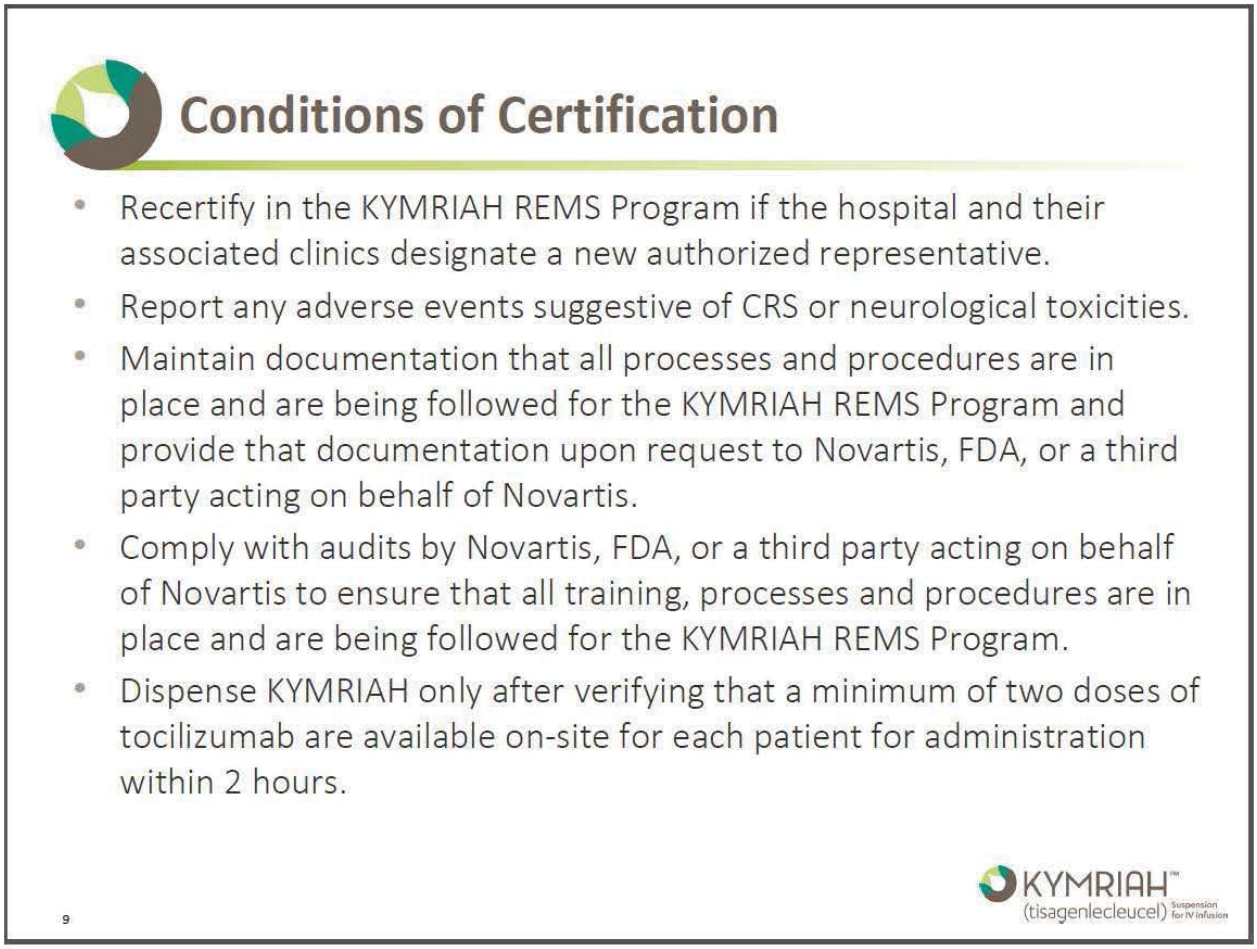
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion

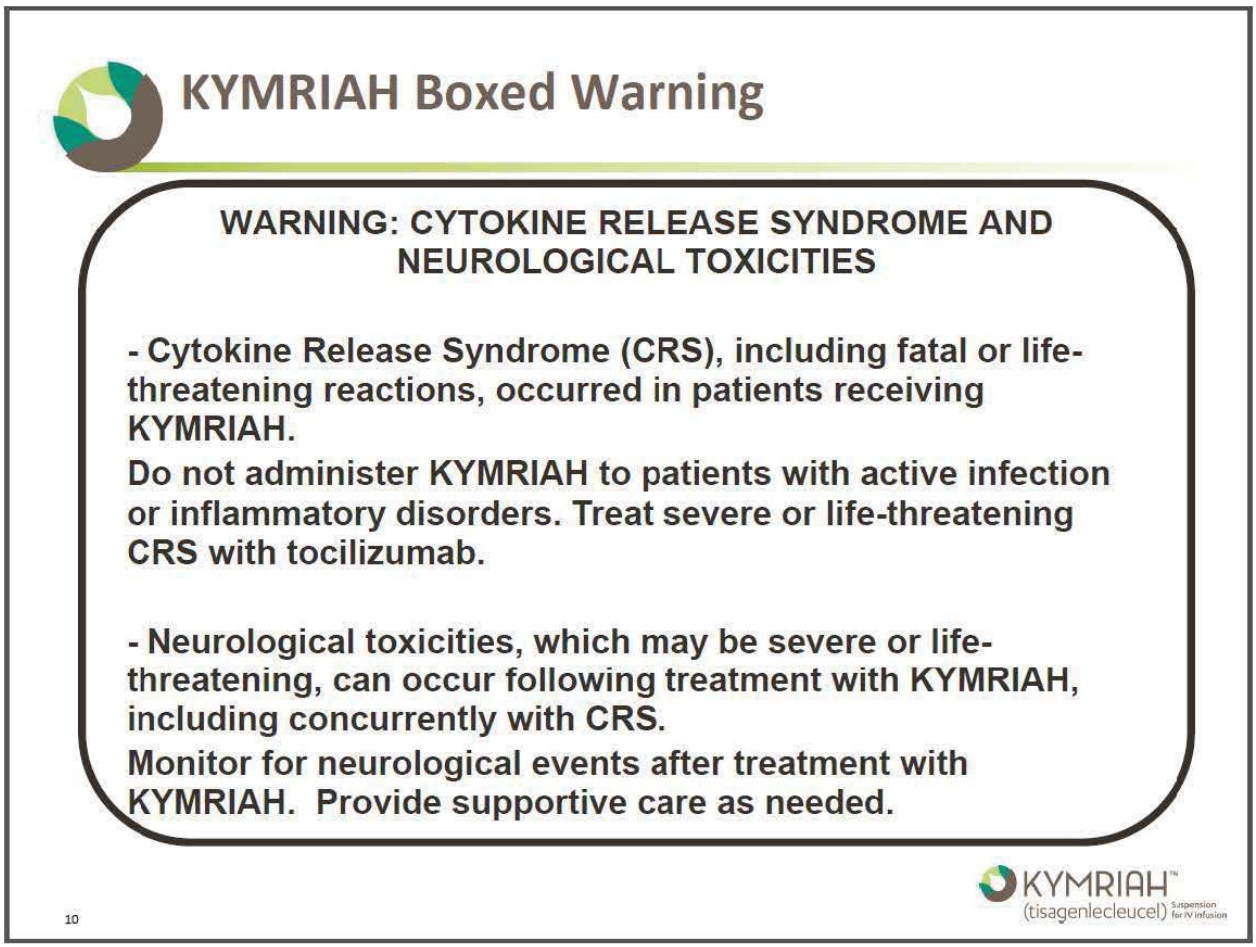

KYMRIAH REMS Materials
KYMRIAH REMS Live Training Program Slides
Provides education on the risks of CRS and neurological toxicities
Addresses serious clinical manifestations, timing of events, monitoring and management, and importance of patient education
KYMRIAH REMS Program overview
KYMRIAH REMS Program Patient Wallet Card
For patients and their guardians to keep with them at all times, reminds them of signs and symptoms that require immediate medical attention
Instructions to stay within 2 hours of treatment site for at least 4 weeks
5
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

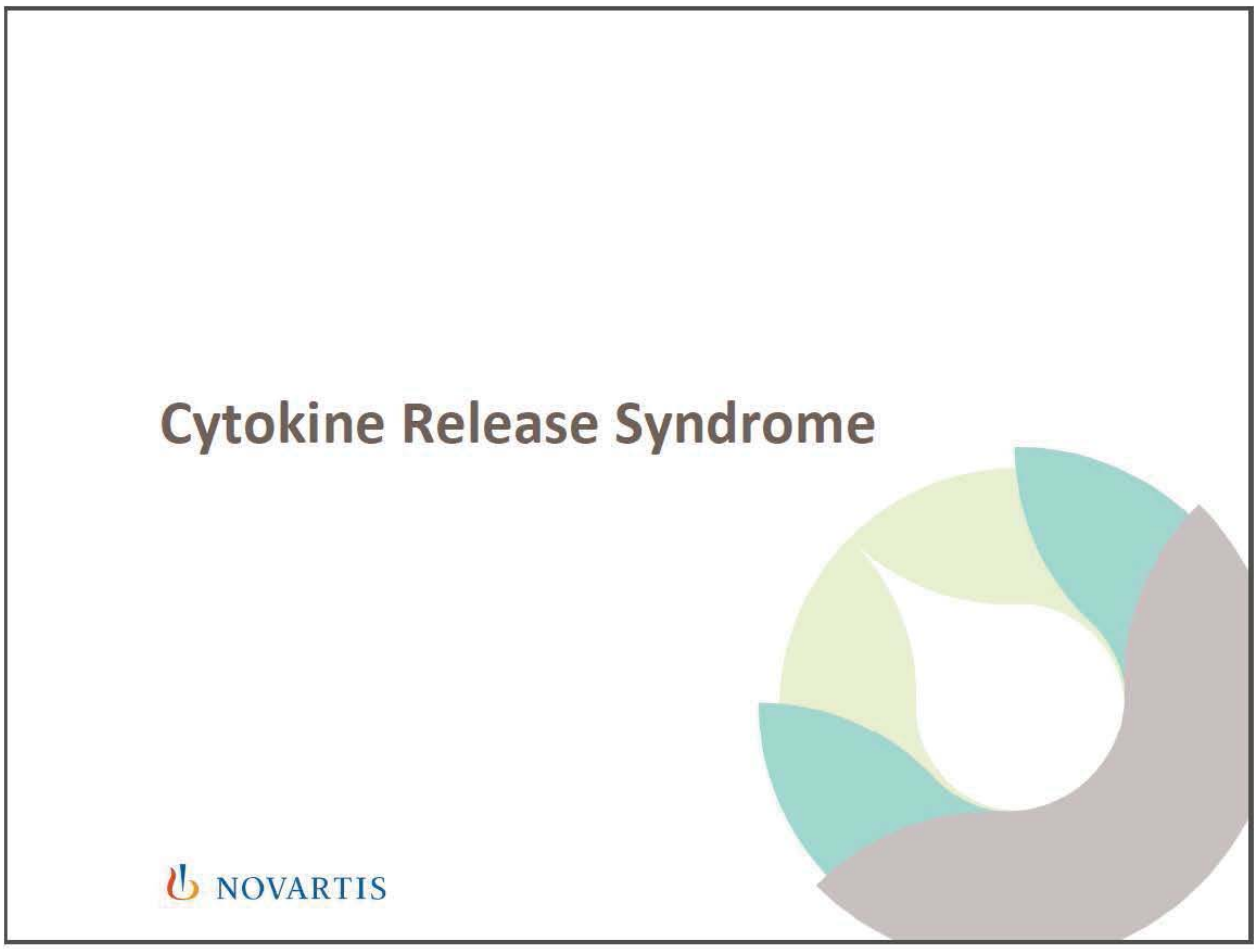

KYMRIAH REMS Materials, cont.
KYMRIAH REMS Program Knowledge Assessment
Reinforces the messages about CRS and neurological toxicities, 10 questions, multiple choice
All staff involved in ordering, prescribing, or administering must successfully complete
KYMRIAH REMS Program Hospital Enrollment Form
Must be completed by the authorized representative to certify the hospital
KYMRIAH REMS Program Website
Holds all REMS educational tools for download/printing
6
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion


Site Certification
To become certified* to dispense KYMRIAH, hospitals and their associated clinics must:
Designate an authorized representative to complete the certification process by submitting the completed KYMRIAH REMS Program Hospital Enrollment Form on behalf of the hospital and their associated clinics
Ensure the authorized representative oversees implementation and compliance with KYMRIAH REMS Program requirements
*Completion of the enrollment form and knowledge assessment does not guarantee your hospital will be certified to administer KYMRIAH. Please contact 1-844-4KYMRIAH(1-844-459-6742) for more information
7
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


Authorized Representative
Completes KYMRIAH REMS Live training program and successfully completes KYMRIAH REMS Program Knowledge Assessment
Ensures all relevant staff are trained and successfully complete knowledge assessment and maintain records of training
Put processes and procedures to ensure that:
New staff is trained
Staff retrained if KYMRIAH has not been dispensed once annually from certification
Prior to dispensing KYMRIAH:
Verify 2 doses of tocilizumab are available onsite and ready for immediate administration
Provide patients and their guardians with KYMRIAH REMS Program Patient Wallet Card to inform them:
Signs and symptoms of CRS and neurological toxicities that require immediate medical attention.
Importance of staying within 2 hours of the certified hospital and their associated clinic for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor.
8
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion


Conditions of Certification
• Recertify in the KYMRIAH REMS Program if the hospital and their associated clinics designate a new authorized representative.
• Report any adverse events suggestive of CRS or neurological toxicities.
• Maintain documentation that all processes and procedures are in place and are being followed for the KYMRIAH REMS Program and provide that documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis.
• Comply with audits by Novartis, FDA, or a third party acting on behalf of Novartis to ensure that all training, processes and procedures are in place and are being followed for the KYMRIAH REMS Program.
• Dispense KYMRIAH only after verifying that a minimum of two doses of tocilizumab are available on-site for each patient for administration within 2 hours.
9
KYMRIAH™
(tisagenlecleucel) Suspension for IV Infusion


KYMRIAH Boxed Warning
WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES
- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH.
Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS.
Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.
10
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion


Cytokine Release Syndrome
NOVARTIS

Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, was the most common adverse event associated with KYMRIAH pivotal clinical trial in pediatric and young adult patients with r/r ALL
  - 79% of patients developed CRS of any grade (Penn grading scale); 49% developed CRS grade 3 or grade 4
- The median time to onset of CRS was 3 days (range: 1-22 days) following KYMRIAH infusion
- The median time to resolution of CRS was 8 days (range: 1-36 days)
- In clinical trials, CRS was effectively managed in the majority of patients based on a CRS management algorithm
- Of the patients who developed CRS: 50% received tocilizumab; 13% received two doses of tocilizumab, 6% received three doses of tocilizumab, and 26% received addition of corticosteroids (e.g. methylprednisolone).

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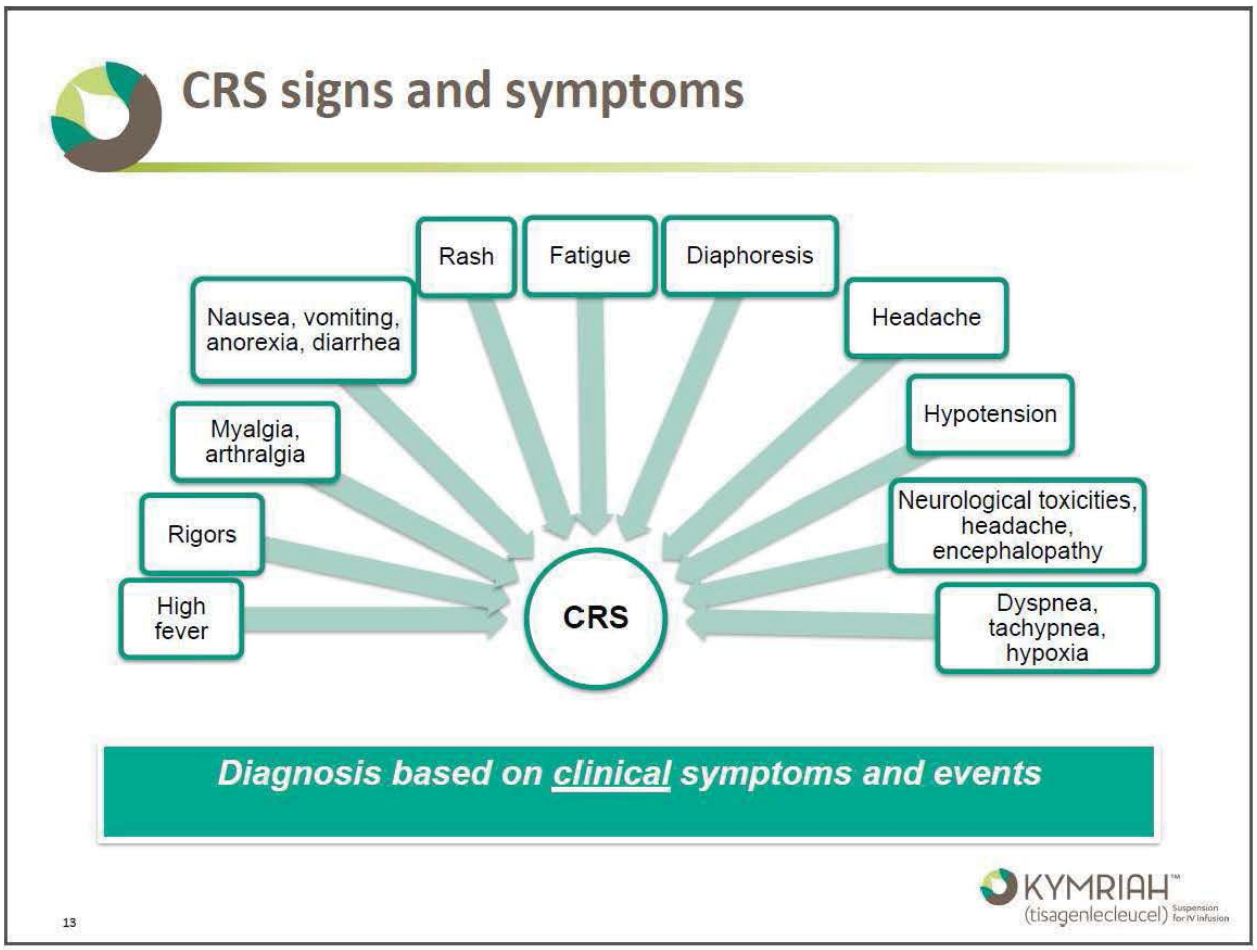
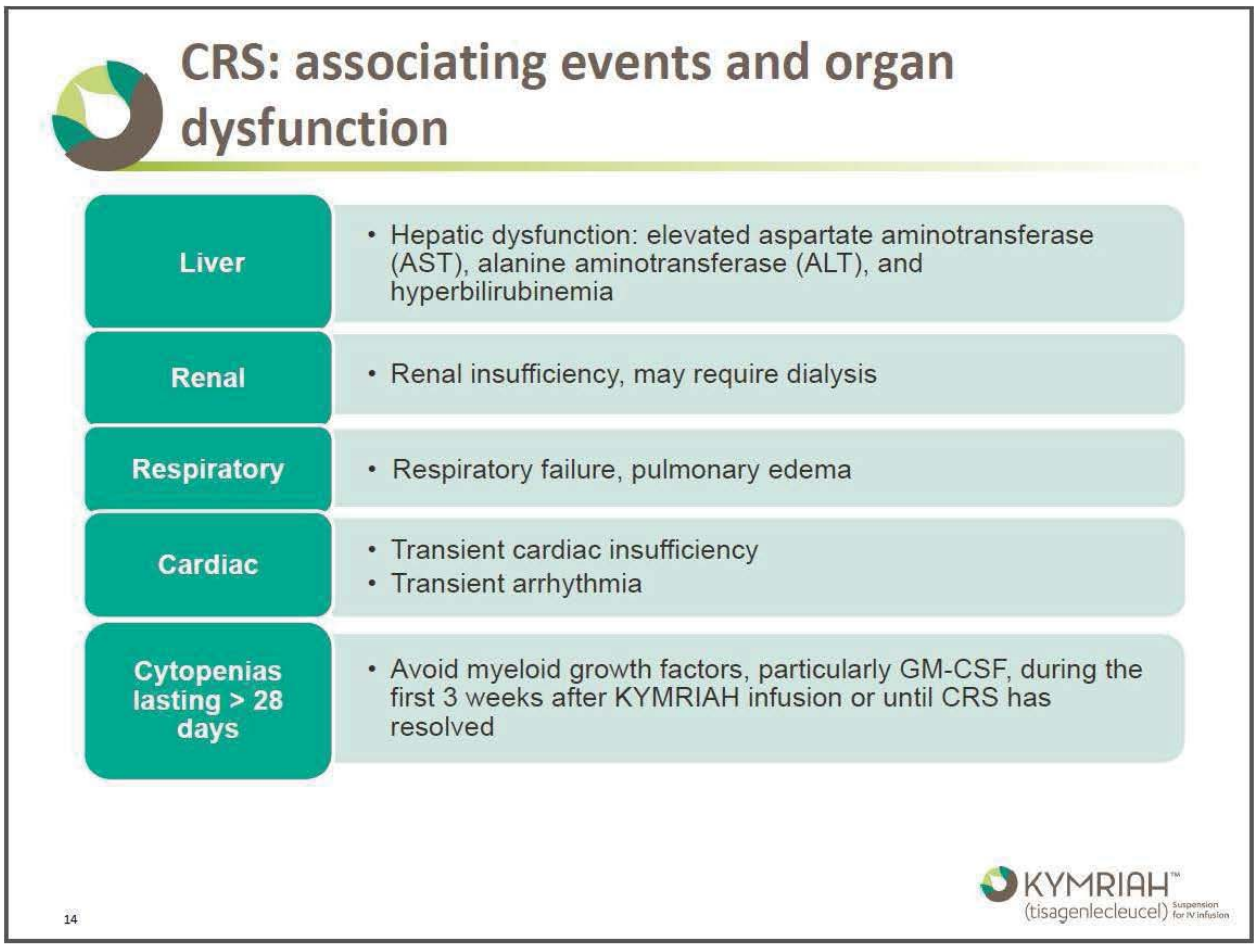
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


CRS signs and symptoms
Rash
Fatigue
Diaphoresis
Nausea, vomiting, anorexia, diarrhea
Headache
Myalgia, arthralgia
Hypotension
Rigors
Neurological toxicities, headache, encephalopathy
High fever
CRS
Dyspnea, tachypnea, hypoxia
Diagnosis based on clinical symptoms and events
13
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


CRS: associating events and organ dysfunction
Liver
• Hepatic dysfunction: elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hyperbilirubinemia
Renal
• Renal insufficiency, may require dialysis
Respiratory
• Respiratory failure, pulmonary edema
Cardiac
• Transient cardiac insufficiency
• Transient arrhythmia
Cytopenias lasting > 28 days
• Avoid myeloid growth factors, particularly GM-CSF, during the first 3 weeks after KYMRIAH infusion or until CRS has resolved
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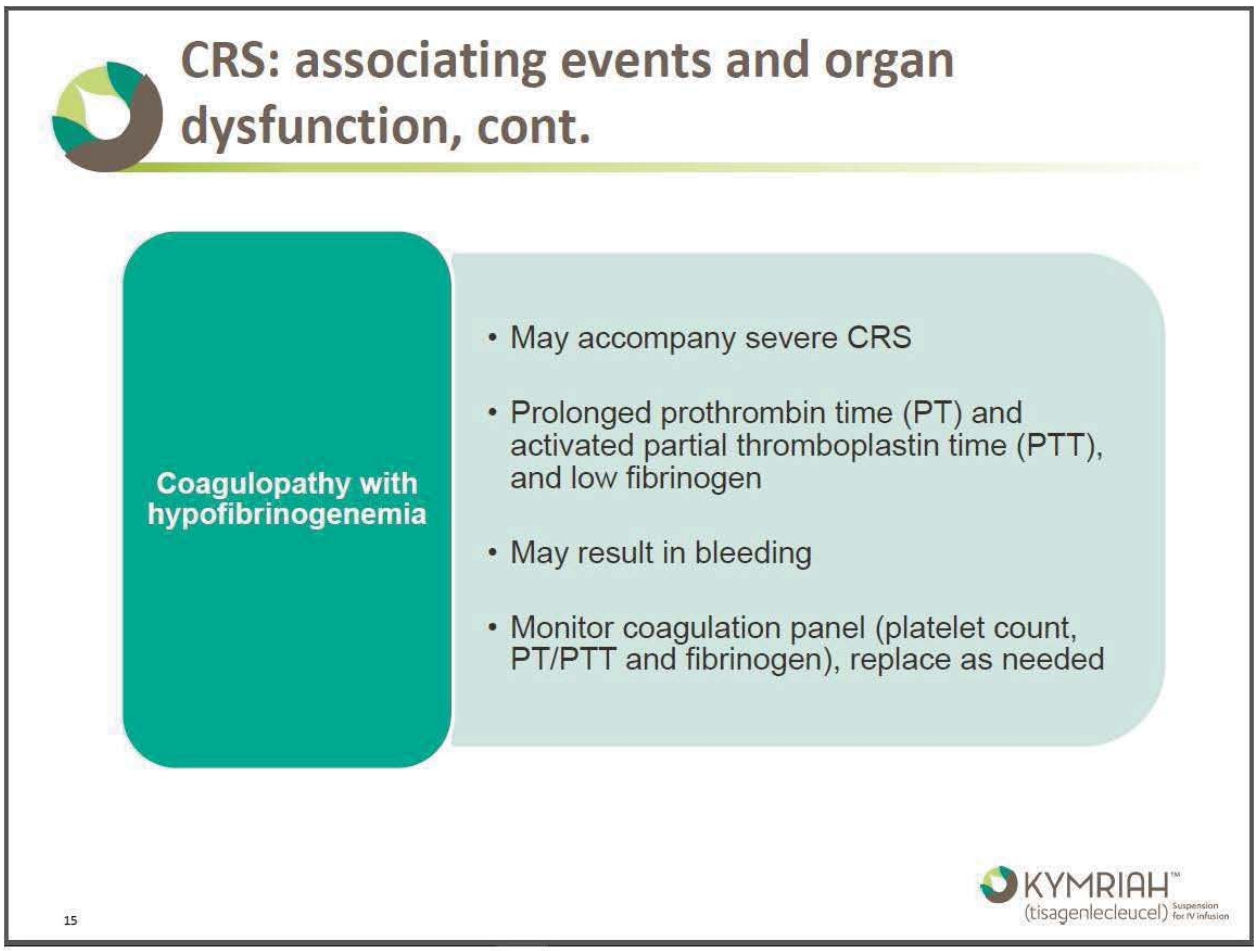
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion


CRS: associating events and organ dysfunction, cont.
Coagulopathy with hypofibrinogenemia
• May accompany severe CRS
• Prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT), and low fibrinogen
• May result in bleeding
• Monitor coagulation panel (platelet count, PT/PTT and fibrinogen), replace as needed
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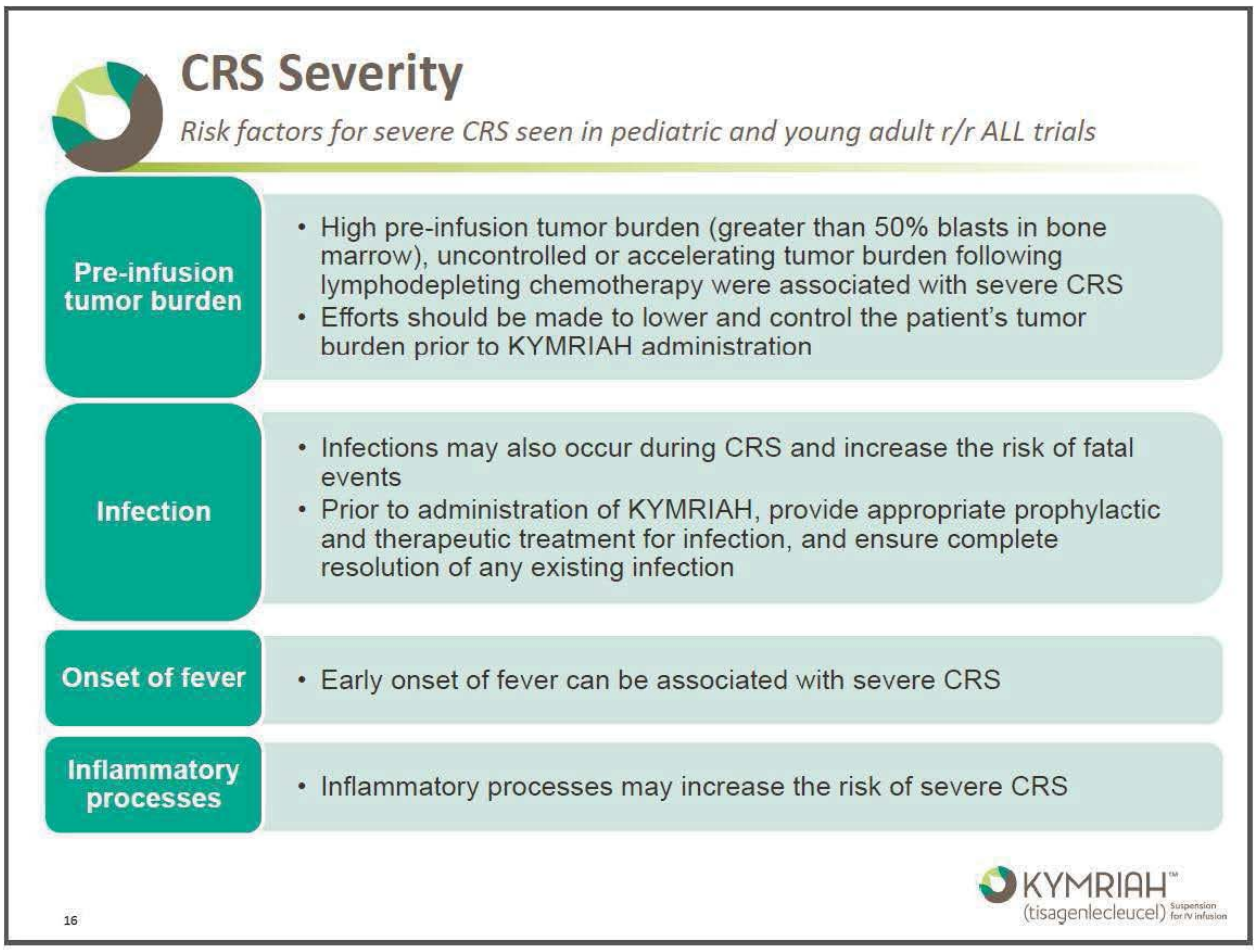
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


CRS Severity
Risk factors for severe CRS seen in pediatric and young adult r/r ALL trials
Pre-infusion tumor burden
• High pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy were associated with severe CRS
• Efforts should be made to lower and control the patient's tumor burden prior to KYMRIAH administration
Infection
• Infections may also occur during CRS and increase the risk of fatal events
• Prior to administration of KYMRIAH, provide appropriate prophylactic and therapeutic treatment for infection, and ensure complete resolution of any existing infection
Onset of fever
• Early onset of fever can be associated with severe CRS
Inflammatory processes
• Inflammatory processes may increase the risk of severe CRS
16
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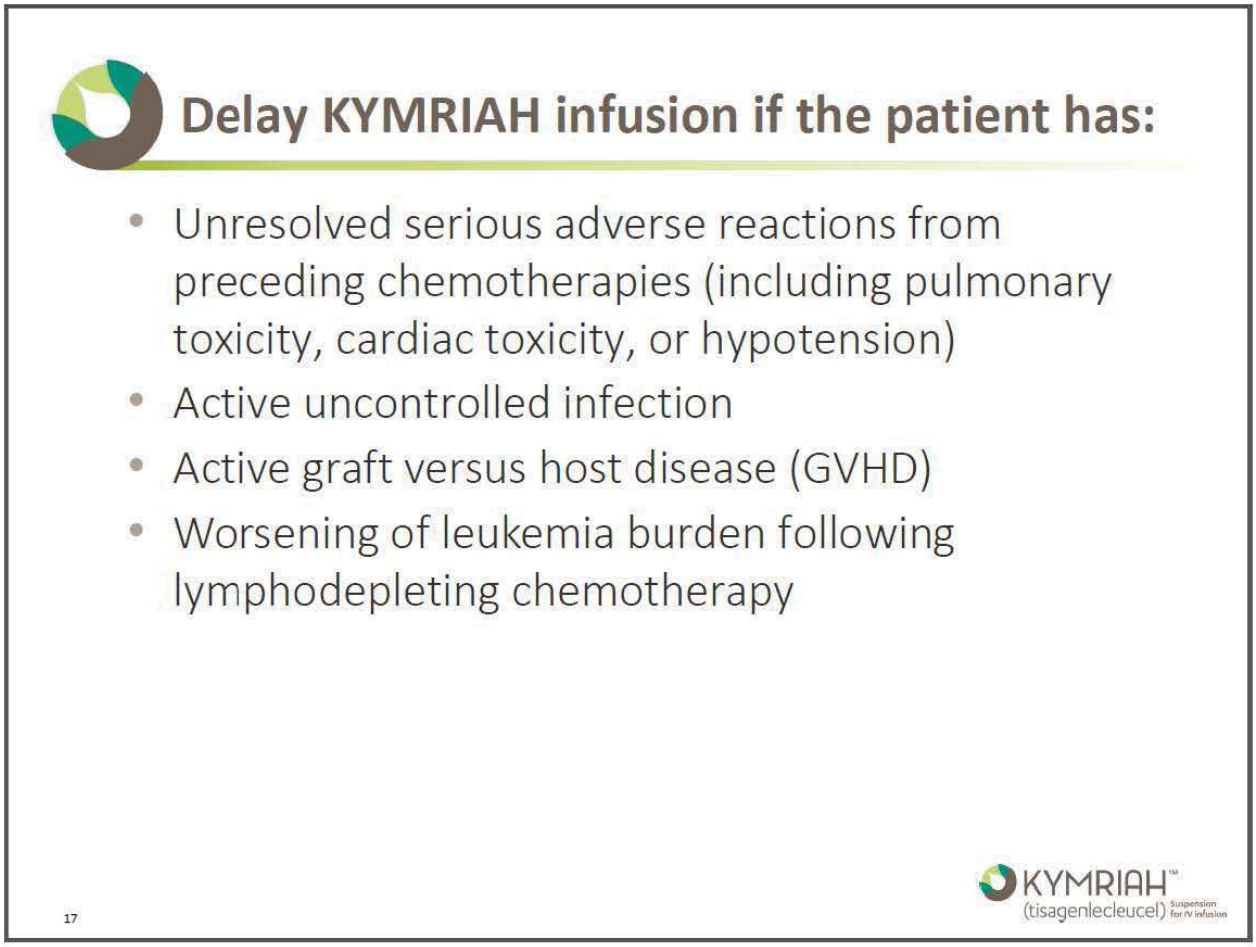
Delay KYMRIAH infusion if the patient has:
Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension)
Active uncontrolled infection
Active graft versus host disease (GVHD)
Worsening of leukemia burden following lymphodepleting chemotherapy
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CRS: Management

- Management of CRS is based solely upon clinical presentation
- Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with KYMRIAH
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
- At the first sign of CRS, immediately evaluate patient for hospitalization
- Evaluate for and treat other causes of fever, hypoxia, and hypotension
- CRS should be managed according to the KYMRIAH CRS management algorithm
- Interleukin-6 (IL-6) receptor antagonist, tocilizumab, has been administered for the management of moderate or severe CRS associated with KYMRIAH
- Verify two doses of tocilizumab are ordered and available on site for administration before KYMRIAH infusion

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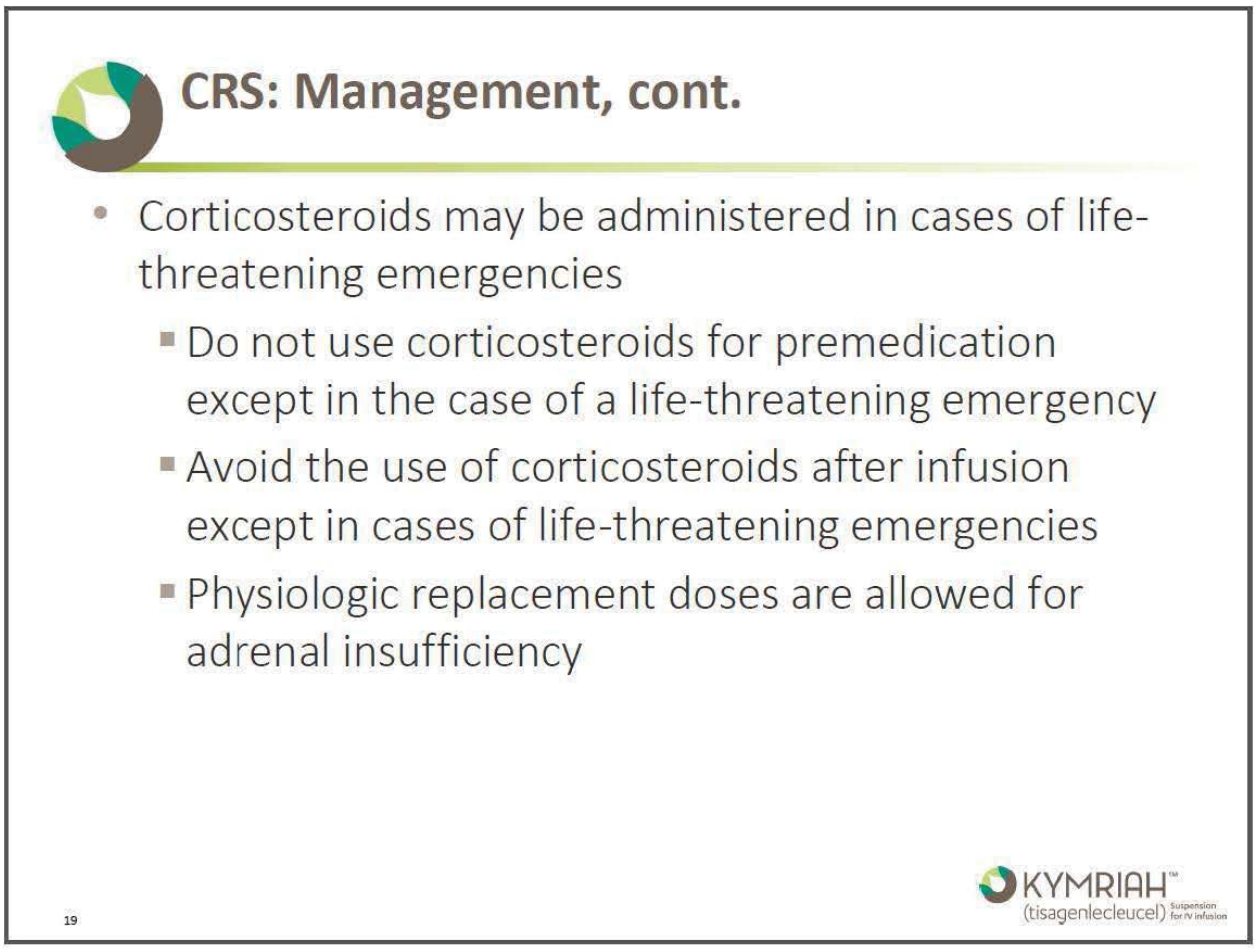
KYMRIAH™ (tisagenlecleucel) Suspension for IV Infusion


CRS: Management, cont.
Corticosteroids may be administered in cases of life-threatening emergencies
Do not use corticosteroids for premedication except in the case of a life-threatening emergency
Avoid the use of corticosteroids after infusion except in cases of life-threatening emergencies
Physiologic replacement doses are allowed for adrenal insufficiency
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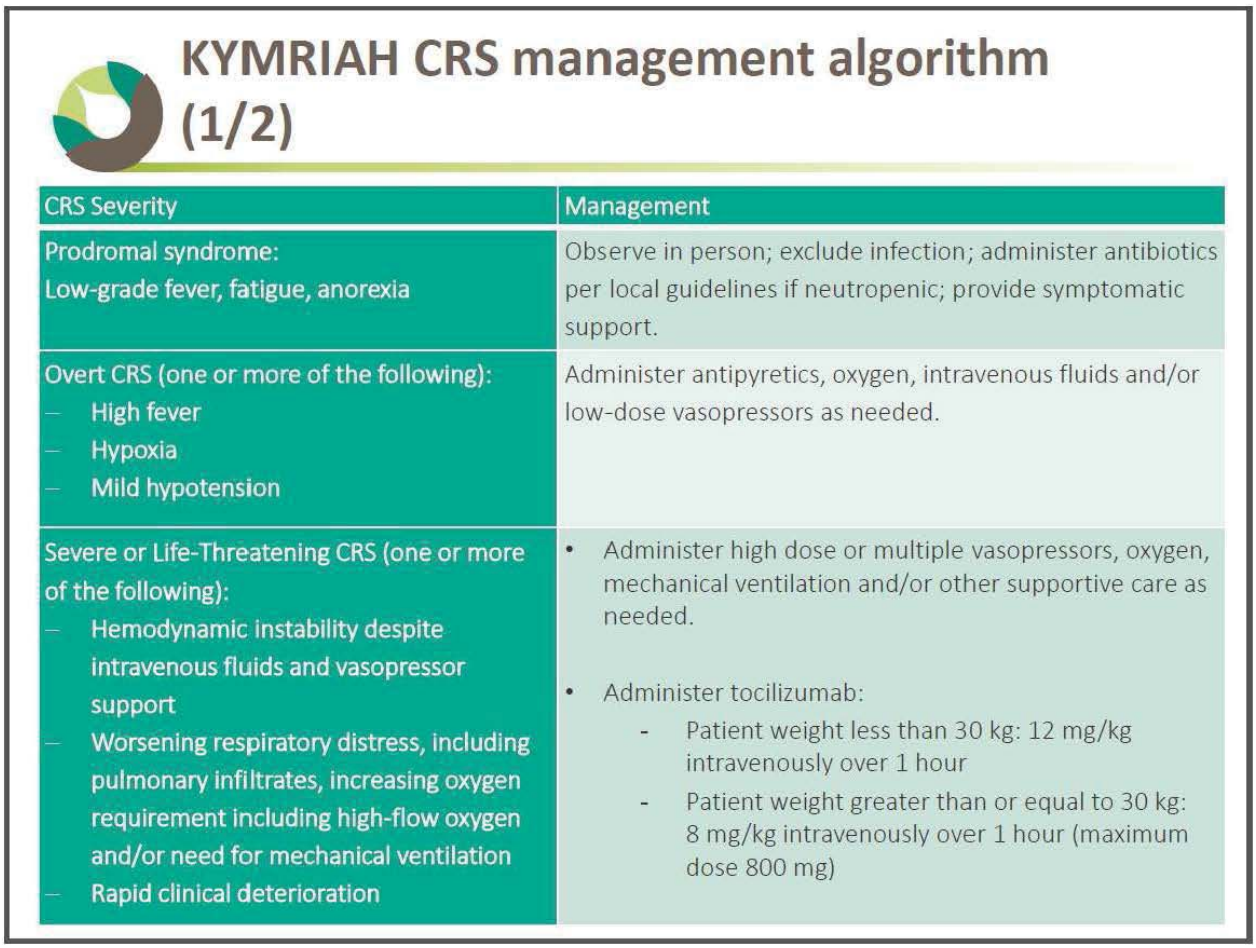
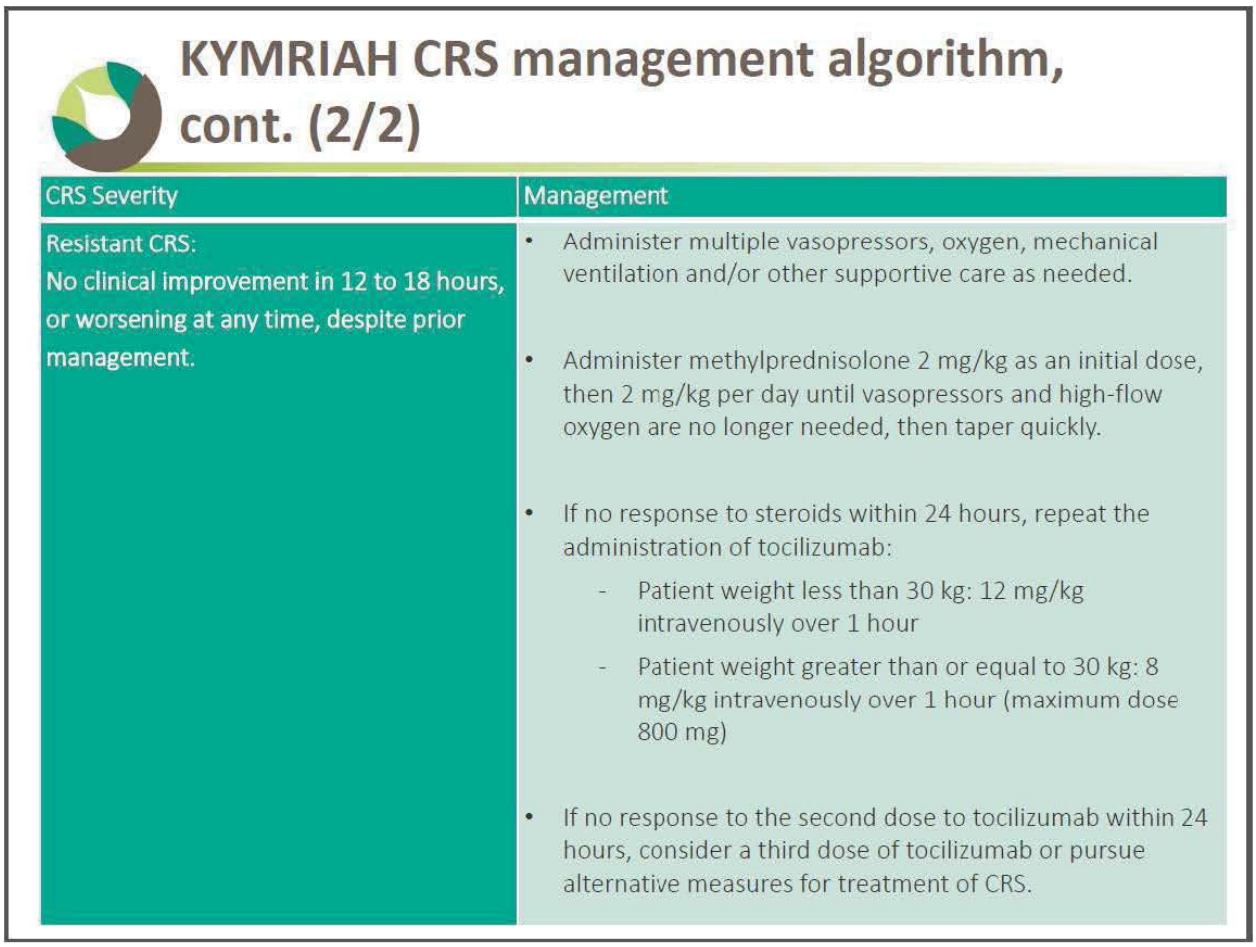
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion



KYMRIAH CRS management algorithm (1/2)

CRS Severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
Overt CRS (one or more of the following): – High fever – Hypoxia – Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
Severe or Life-Threatening CRS (one or more of the following): – Hemodynamic instability despite intravenous fluids and vasopressor support – Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation – Rapid clinical deterioration	• Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer tocilizumab: - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)



KYMRIAH CRS management algorithm, cont. (2/2)

CRS Severity	Management
Resistant CRS: No clinical improvement in 12 to 18 hours, or worsening at any time, despite prior management.	• Administer multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. • Administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper quickly. • If no response to steroids within 24 hours, repeat the administration of tocilizumab: - Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) • If no response to the second dose to tocilizumab within 24 hours, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS.

Vasopressor use with KYMRIAH

Definition of high-dose vasopressors

Vasopressor	Dose for ≥ 3 Hours
Norepinephrine monotherapy	≥ 0.2 µg/kg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 0.1 µg/kg/min
If on vasopressin	High dose if vasopressin + norepinephrine equivalent of ≥ 0.1 µg/kg/min (using VASST formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min (using VASST formula)

VASST[1] Vasopressor Equivalent Equation

Norepinephrine-equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) ÷ 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) ÷ 10]

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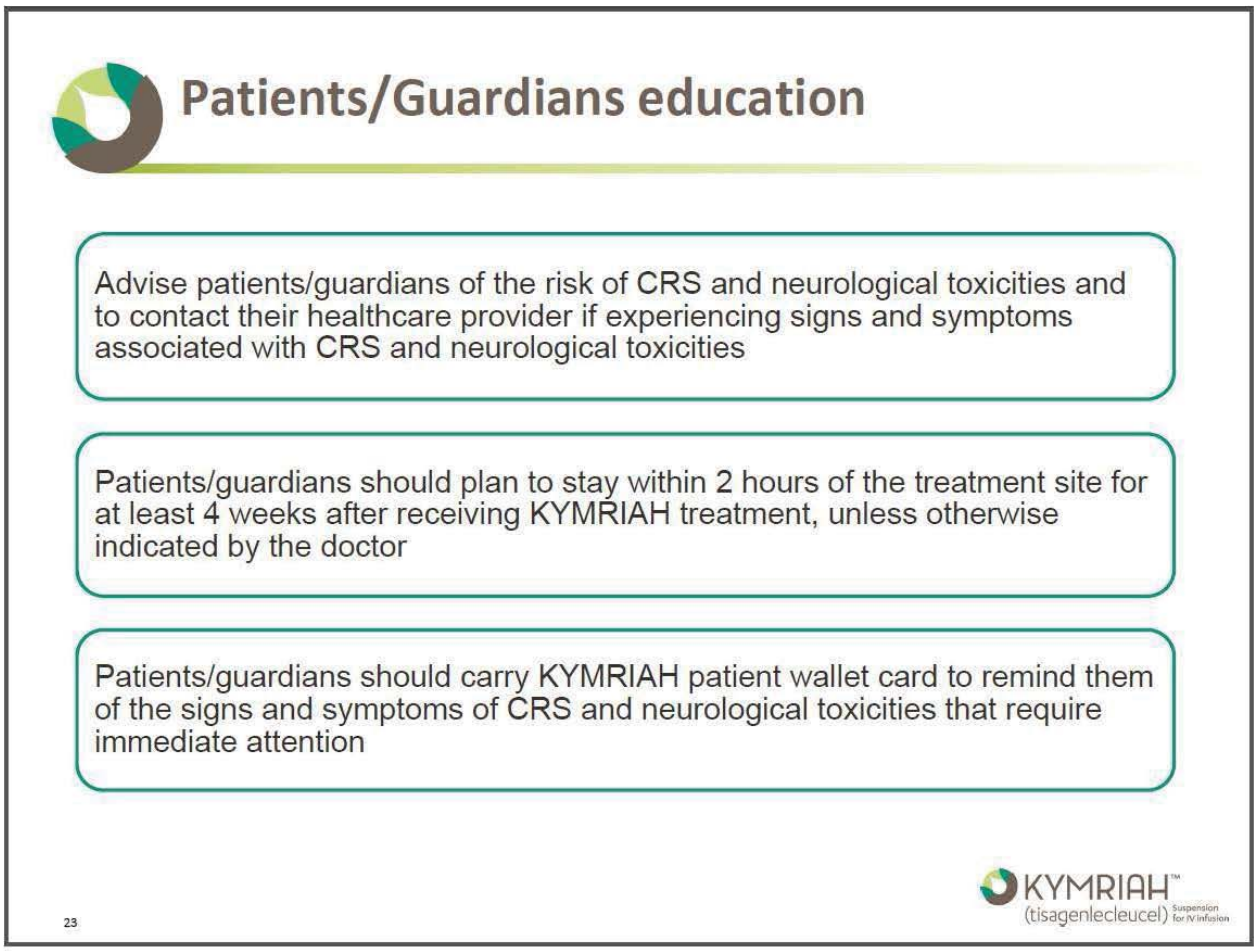
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


Patients/Guardians education
Advise patients/guardians of the risk of CRS and neurological toxicities and to contact their healthcare provider if experiencing signs and symptoms associated with CRS and neurological toxicities
Patients/guardians should plan to stay within 2 hours of the treatment site for at least 4 weeks after receiving KYMRIAH treatment, unless otherwise indicated by the doctor
Patients/guardians should carry KYMRIAH patient wallet card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate attention
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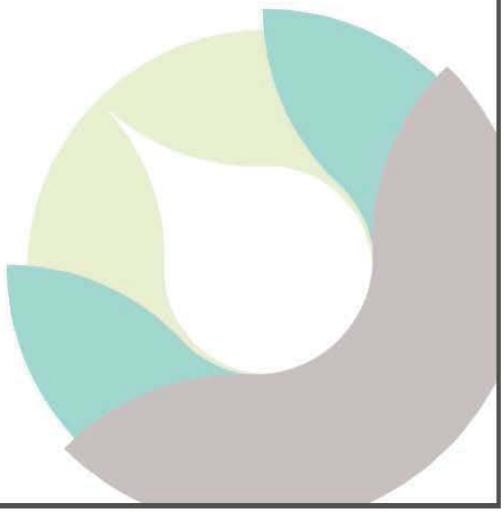
KYMRIAH™
(tisagenlecleucel) Suspension for IV Infusion

KYMRIAH-associated neurological toxicities



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Neurological toxicities

- Neurological toxicities, which may be severe or life-threatening can occur following treatment with KYMRIAH
- In KYMRIAH pivotal clinical trial in pediatric and young adult patients with r/r ALL, neurological toxicities were seen in:
  - 44% of patients if headache is excluded
  - 65% of patients if headache is included
  - Grade 3 or 4 neurological toxicities were seen in 18% of patients
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer KYMRIAH are trained about the management of neurological toxicities

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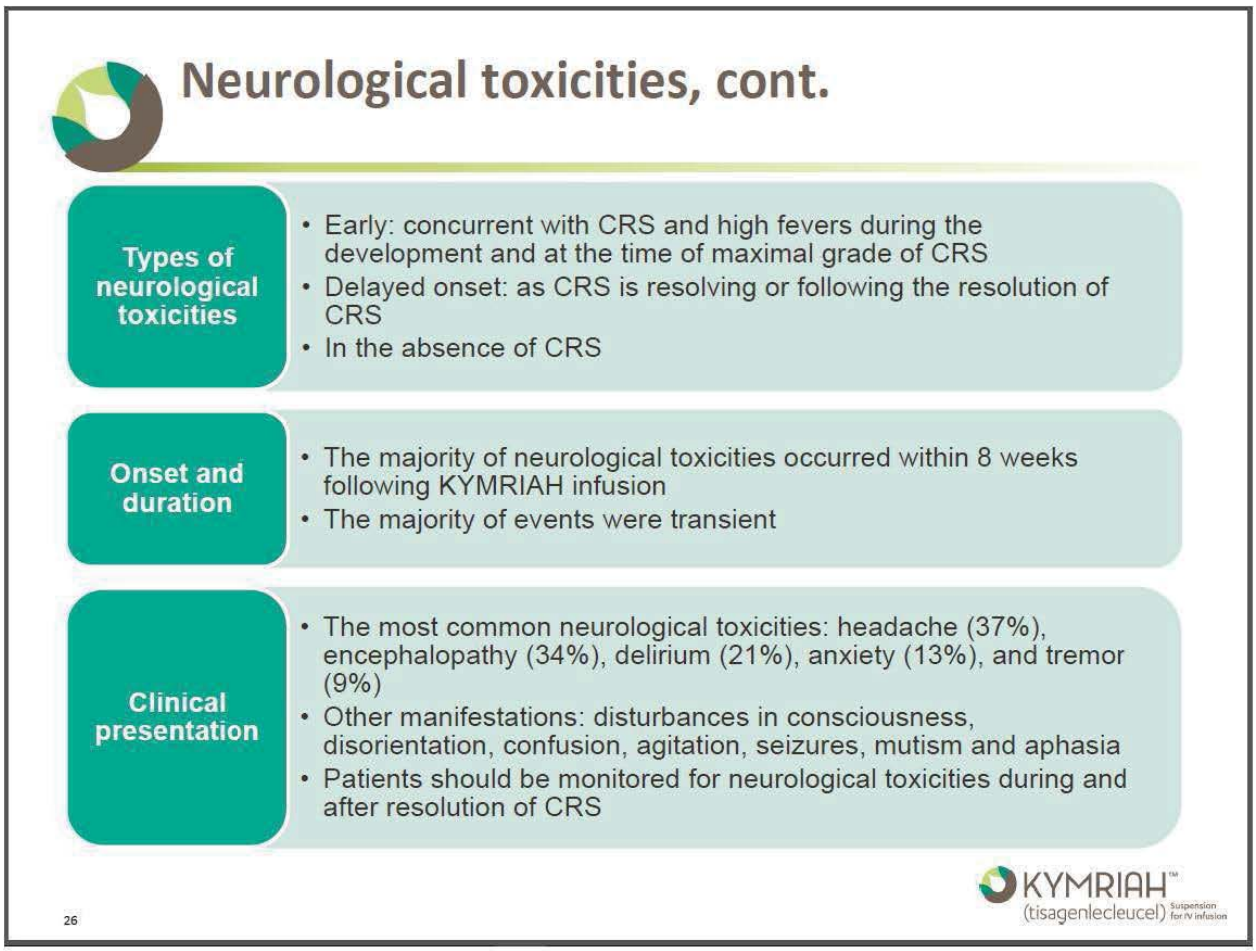
KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion


Neurological toxicities, cont.
Types of neurological toxicities
• Early: concurrent with CRS and high fevers during the development and at the time of maximal grade of CRS
• Delayed onset: as CRS is resolving or following the resolution of CRS
• In the absence of CRS
Onset and duration
• The majority of neurological toxicities occurred within 8 weeks following KYMRIAH infusion
• The majority of events were transient
Clinical presentation
• The most common neurological toxicities: headache (37%), encephalopathy (34%), delirium (21%), anxiety (13%), and tremor (9%)
• Other manifestations: disturbances in consciousness, disorientation, confusion, agitation, seizures, mutism and aphasia
• Patients should be monitored for neurological toxicities during and after resolution of CRS
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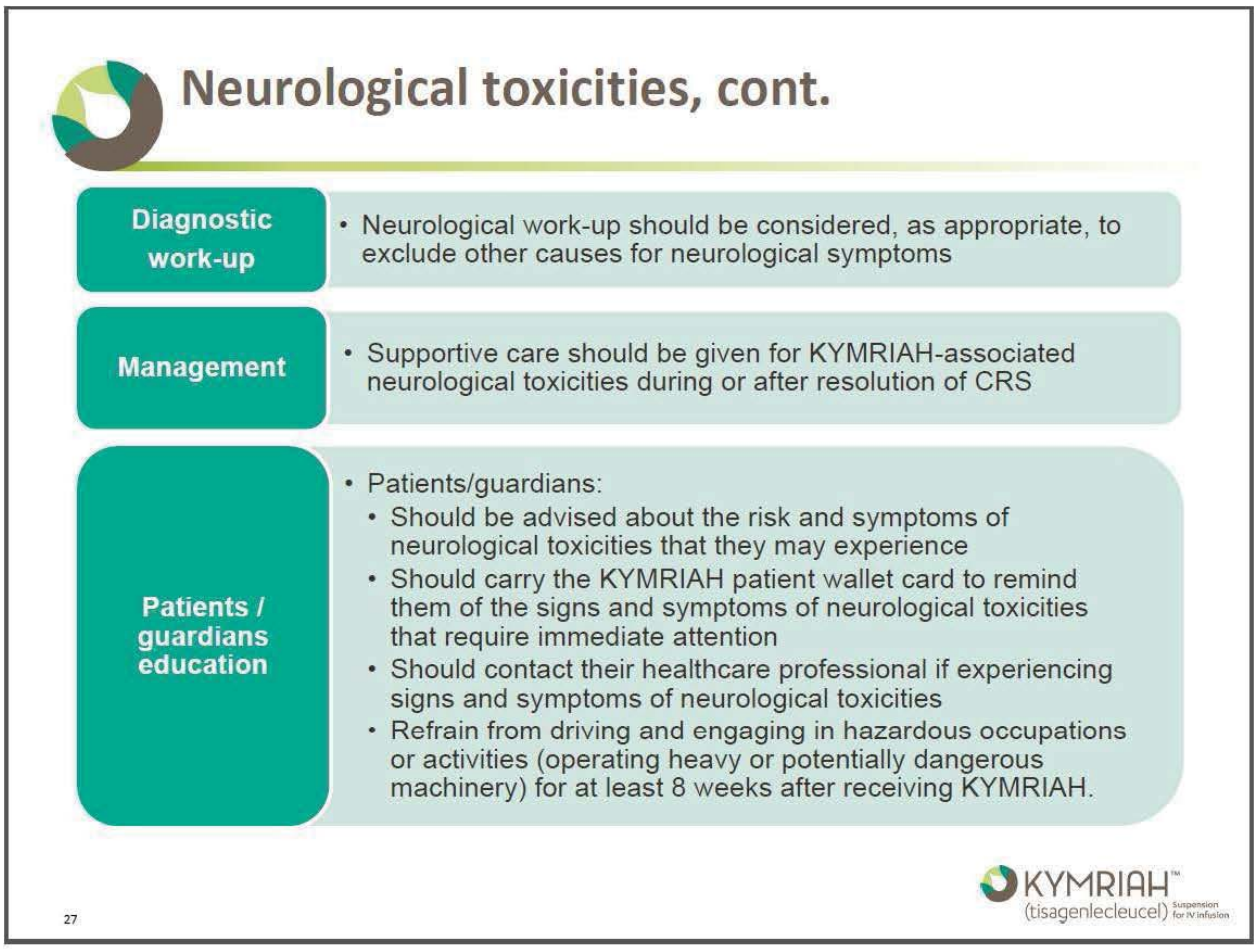
KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion


Neurological toxicities, cont.
Diagnostic work-up
• Neurological work-up should be considered, as appropriate, to exclude other causes for neurological symptoms
Management
• Supportive care should be given for KYMRIAH-associated neurological toxicities during or after resolution of CRS
Patients / guardians education
• Patients/guardians:
• Should be advised about the risk and symptoms of neurological toxicities that they may experience
• Should carry the KYMRIAH patient wallet card to remind them of the signs and symptoms of neurological toxicities that require immediate attention
• Should contact their healthcare professional if experiencing signs and symptoms of neurological toxicities
• Refrain from driving and engaging in hazardous occupations or activities (operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving KYMRIAH.
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For further information, please visit
www.KYMRIAH-REMS.com or call
1-844-4KYMRIAH(1-844-459-6742)
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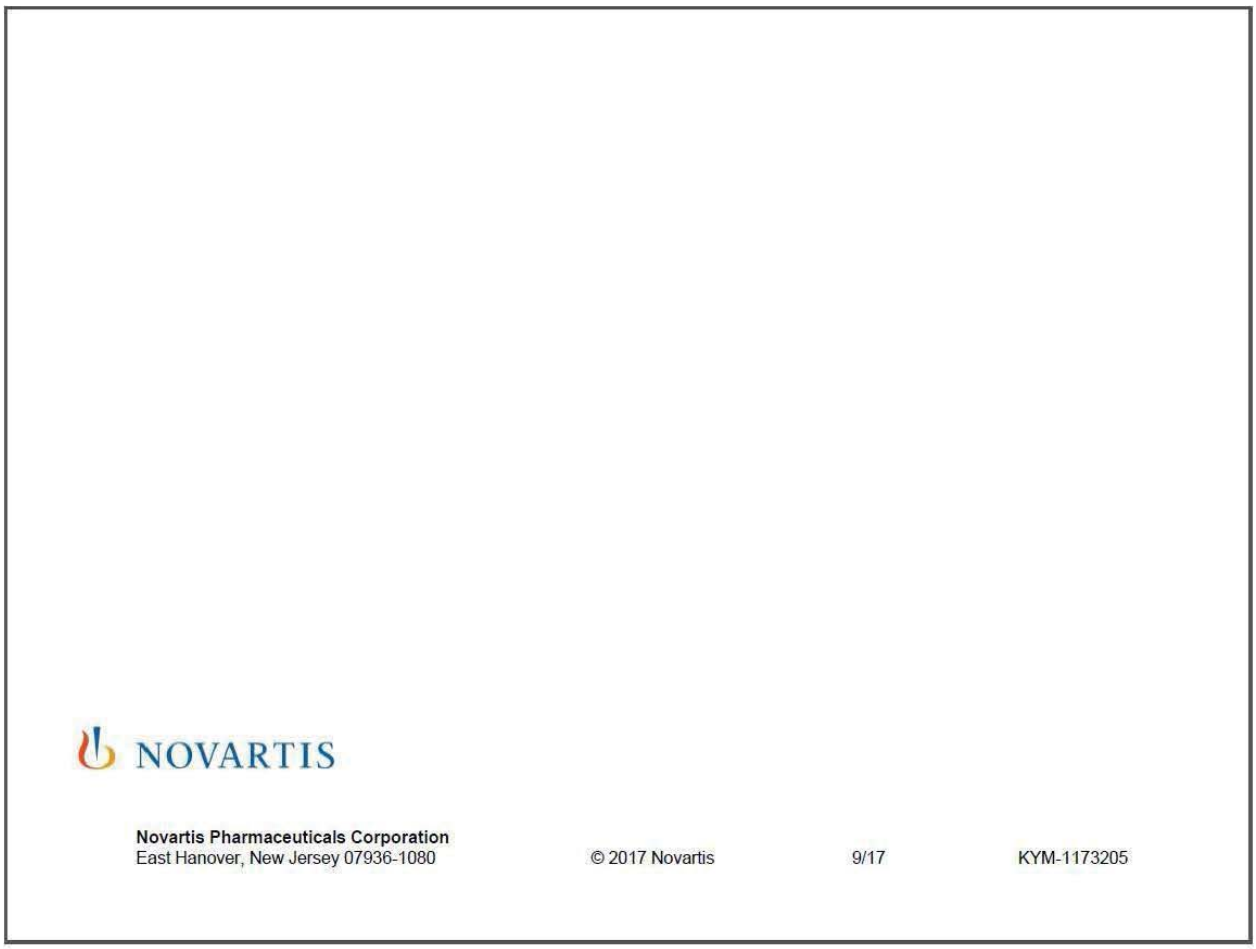
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KYM-1173205

Appendix 2

Kymriah REMS Program Knowledge Assessment

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion

REMS PROGRAM KNOWLEDGE ASSESSMENT

Hospital Information (All Fields Required)

Hospital Name:		
Hospital National Provider Information (NPI)#:		
Address:		
City:	State:	Zip Code:
Phone:	Fax:	
First Name:	Last Name:	
Credentials: ☐ DO ☐ MD ☐ R.Ph ☐ NP/PA ☐ Other (please specify)		
Phone:	Fax:	E-mail:
Authorized Representative: ☐ Yes ☐ No		
Signature:		**Date (MM/DD/YYYY):**

If you are the Authorized Representative for your hospital, please complete and submit the knowledge assessment to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com. All others please complete and send the form to your hospital's Authorized Representative. Completion of this knowledge assessment does not guarantee your hospital will be certified to administer Kymriah™.

1- Kymriah™ (tisagenlecleucel) is indicated for the treatment of:
- ❍ a. Pediatric and young adult patients up to 25 years of age newly diagnosed B-cell acute lymphoblastic leukemia (ALL)
- ❍ b. Pediatric and young adult patients up to 25 years of age with refractory or in 2nd or later relapse B-cell ALL
- ❍ c. Pediatric and young adult patients newly diagnosed non-Hodgkin lymphoma (NHL)
- ❍ d. Pediatric and young adult patients up to 25 years of age with relapsed refractory NHL

2- Cytokine release syndrome (CRS) is the most common adverse event observed with Kymriah. The severity of CRS was correlated with the following, **except**:
- ❍ a. Infused Kymriah dose
- ❍ b. Leukemia burden
- ❍ c. Concurrent infection
- ❍ d. Early onset of fever

3- Clinically, patients with CRS can manifest with the following signs and symptoms, **except**:
- ❍ a. High grade fever
- ❍ b. Hypotension
- ❍ c. Skin ulcers
- ❍ d. Respiratory distress
- ❍ e. Encephalopathy

4- Which one of the following is true regarding the time to onset of CRS? It typically occurs:
- ❍ a. 7-14 days following Kymriah infusion, with a median time to onset of 10 days
- ❍ b. 7-21 days following Kymriah infusion, with a median time to onset of 10 days
- ❍ c. 1-22 days following Kymriah infusion, with a median time to onset of 3 days
- ❍ d. Rarely starts during the first week following Kymriah infusion

Page 1 of 2

5- As a part of planning for infusion, it is required to have two doses of tocilizumab on site prior to dispensing and administering Kymriah to patients:
- ❍ a. True
- ❍ b. False

6- A 5-year-old male with refractory ALL was treated with Kymriah. One day following infusion, he developed high grade fever (40-41°C) and was hospitalized. On day 2, he developed hypotension, which improved with fluid resuscitation. He was transferred to the PICU for close observation, and later developed recurrent hypotension, mild tachypnea and hypoxia (O_2 saturation 91%). He was startec on norepinephrine at a low dose and O_2 supplement via nasal cannula. The patient is now stable with normalization of blood pressure and O_2 saturation. What is the next step in management:
- ❍ a. Administer one dose of tocilizumab (IL-6 receptor antibody)
- ❍ b. Start IV methylprednisolone at 2 mg/kg/day
- ❍ c. Start myeloid growth factor to expedite neutrophil recovery
- ❍ d. Continue supportive care and close monitoring of hemodynamic, respiratory and neurological status

7- Neurological toxicities were observed with Kymriah, and the patient and the caregiver should be informed about this risk. All of the following are correct **except**:
- ❍ a. May occur in the context of CRS, following the resolution of CRS or without CRS
- ❍ b. Symptoms range from headache and confusion to encephalopathy and seizures
- ❍ c. The majority of events were transient and self-limiting
- ❍ d. Can be prevented with the administration of tocilizumab

8- All of the following about neurological toxicities as a result of Kymriah are correct, **except**:
- ❍ a. Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
- ❍ b. Management includes supportive care
- ❍ c. Routine management includes high dose systemic corticosteroids
- ❍ d. Majority occurred within 30 days following Kymriah infusion

9- A 12-year-old female with relapsed ALL following an allogeneic transplantation was treated with Kymriah. One day post-infusion, she developed high grade fever (40°C) and myalgia, and started on broad spectrum antibiotics. Subsequently, she developed hypotension requiring multiple fluid boluses and high dose vasopressors (norepinephrine and epinephrine); hypoxia at 90% O_2 saturation requiring high flow O_2 supplement; elevated liver enzymes, serum creatinine and ferritin; and mild confusion. She was treated with one dose of tocilizumab, which resulted in transient improvement. 12 hours following tocilizumab administration, the patient's clinical status started deteriorating with worsening hypotension requiring increase in vasopressor doses, worsening respiratory distress and altered mental status. What is/are the appropriate next step/s in management:
- ❍ a. Cortisol level for the evaluation of adrenal insufficiency
- ❍ b. Start IV methylprednisolone at 2 mg/kg/day
- ❍ c. Second dose of tocilizumab if no improvement with steroids within 24 hours (inability to wean vasopressors and persistent fever)
- ❍ d. All of the above

10-A 10-year-old female with multiply relapsed ALL treated with Kymriah. On day 3 following infusion, the patient developed symptoms consistent with severe CRS including persistent high grade fevers, hypotension requiring high dose vasopressors, progressive respiratory distress requiring intubation and mechanical ventilation, liver and renal function abnormalities. She was treated with 2 doses of tocilizumab, IV methylprednisolone at 2 mg/kg/day, and broad spectrum antibiotics. The patient had transient short-lived improvement in hemodynamic status, with inability to wean vasopressors or ventilator settings. What is/are the appropriate next step/s in management:
- ❍ a. Evaluate the patient for sepsis
- ❍ b. Consider a third dose oftocilizumab
- ❍ c. Check platelet count, PT/INR/PTT and fibrinogen and replace with platelets, fresh frozen plasma and/or cryoprecipitate as needed
- ❍ d. All of the above

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Appendix 3

Kymriah REMS Program Hospital Enrollment Form

KYMRIAH™
(tisagenlecleucel) Suspension for IV Infusion

Phone: 1-844-4KYMRIAH
Fax: 1-844-590-0840
E-mail: KymriahREMS@ubc.com
www.Kymriah-REMS.com

KYMRIAH™ REMS PROGRAM HOSPITAL ENROLLMENT FORM

Instructions

Kymriah is only available through the Kymriah Risk Evaluation and Mitigation Strategy (REMS) Program. Hospitals and their associated clinics that dispense Kymriah must be certified in the Kymriah REMS Program. In order to become specially certified to dispense Kymriah, hospitals and associated clinics must designate an Authorized Representative to:

- **Complete the certification process by completing the *Kymriah REMS Program Hospital Enrollment Form* on behalf of the hospital and their associated clinics.**
- **Oversee implementation and compliance with the Kymriah REMS Program requirements as outlined below.**

Please complete all required fields below and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com. You will receive a confirmation via E-mail.

If you have any questions, require additional information, or need further copies of any of the Kymriah REMS Program documents, please visit the REMS program website at www.Kymriah-REMS.com, or call the Kymriah REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

Authorized Representative Responsibilities

On behalf of my hospital/associated clinics, I understand and agree to comply with the following Kymriah REMS Program requirements:

- I must complete the *Kymriah REMS Live Training Program* and successfully complete the *Kymriah REMS Program Knowledge Assessment*.
  - Those participating in Kymriah clinical trials and/or the pre-approval safety training will be exempt from the live training but will be required to review the REMS materials on the REMS website.
- I must submit this completed *Kymriah REMS Program Hospital Enrollment Form* to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.
- I must submit the completed *Kymriah REMS Program Knowledge Assessment* form to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.
- I will oversee implementation and compliance with the Kymriah REMS Program.
- I will ensure that my hospital and associated clinics will establish processes and procedures that are subject to monitoring by Novartis Pharmaceuticals Corporation (NPC), FDA, or a third party acting on behalf of NPC or FDA to help ensure compliance with the requirements of the Kymriah REMS Program, including the following, before administering Kymriah:
  a. Ensuring all relevant staff involved in the prescribing, dispensing or administering of Kymriah are trained on the REMS Program requirements and successfully complete the *Kymriah REMS Program Knowledge Assessment*, and maintain records of staff training.
  b. Performing routine re-education of all staff involved in the prescribing, dispensing or administering of Kymriah and maintaining records of training if Kymriah has not been dispensed at least once annually from the date of certification in the Kymriah REMS Program.
  c. Prior to dispensing Kymriah, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on site for each patient and are ready for immediate administration (within 2 hours).
  d. Prior to dispensing Kymriah, provide patients/caregivers the *Patient/Caregiver Wallet Card*.

As a condition of certification, the certified hospital must:

- Ensure that if the hospital designates a new authorized representative, the new authorized representative must review the *Kymriah REMS Live Training Program*, complete the *Kymriah REMS Program Knowledge Assessment*, complete a new *Kymriah REMS Program Hospital Enrollment Form* and submit the forms via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com.
- Report any adverse events suggestive of CRS, neurological toxicities, or suspected, unexpected serious adverse reactions to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088 or Novartis at 1-888-669-6682.
- Dispense Kymriah to patients only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
- Maintain documentation of all processes and procedures for the Kymriah REMS Program and provide documentation upon request to Novartis, FDA, or a third party acting on behalf of Novartis or FDA.
- Comply with audits by Novartis, FDA, or a third party acting on behalf of Novartis or FDA.

Hospital Information (All Fields Required)

Hospital Name:		
Hospital National Provider Information (NPI)#		
Address:		
City:	State:	Zip Code:
Phone:	Fax:	

Authorized Representative Information (All Fields Required)

First Name:	Last Name:	
Credentials: ☐ DO ☐ MD ☐ RPh ☐ NP/PA ☐ Other (please specify)		
Phone:	Fax:	E-mail:
Authorized Representative Signature:		**Date (MM/DD/YYYY):**

Next Steps

1. Please complete all required fields above and submit this enrollment form to the REMS Call Center via fax to 1-844-590-0840 or E-mail at KymriahREMS@ubc.com. You will receive a confirmation via E-mail.
2. Completion of this form does not guarantee your hospital will be certified to administer Kymriah.
3. NPC will assess and provide confirmation of certification via E-mail after processing this enrollment form and a successfully completed Kymriah REMS Program Knowledge Assessment form.
4. Product orders cannot be placed until hospital certification is complete.

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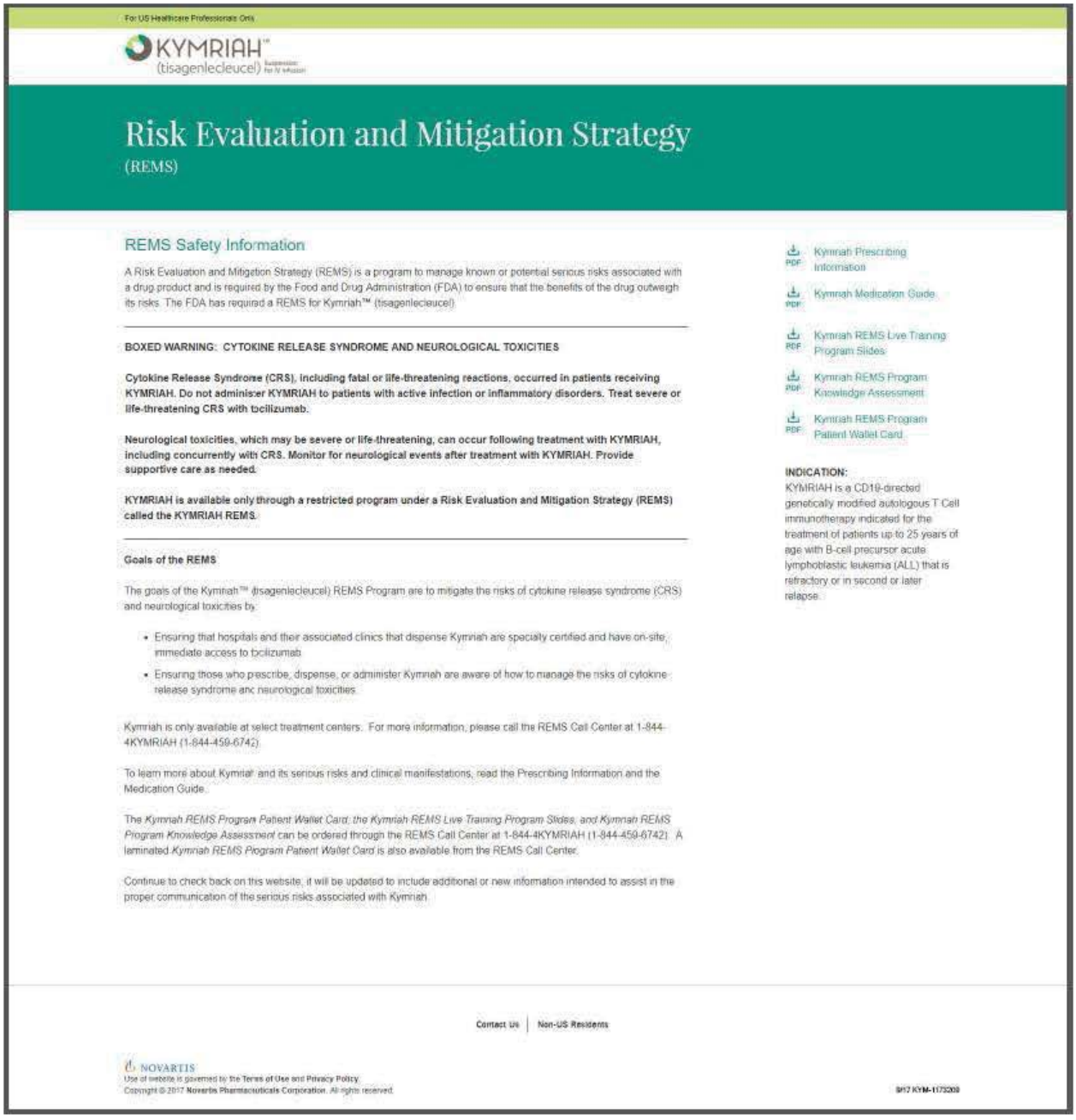
Appendix 4

Kymriah REMS Program website



For US Healthcare Professionals Only

KYMRIAH™ (tisagenlecleucel)

Risk Evaluation and Mitigation Strategy

(REMS)

REMS Safety Information

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has required a REMS for Kymriah™ (tisagenlecleucel).

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving KYMRIAH. Do not administer KYMRIAH to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.

Neurological toxicities, which may be severe or life-threatening, can occur following treatment with KYMRIAH, including concurrently with CRS. Monitor for neurological events after treatment with KYMRIAH. Provide supportive care as needed.

KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS.

Goals of the REMS

The goals of the Kymriah™ (tisagenlecleucel) REMS Program are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their associated clinics that dispense Kymriah are specially certified and have on-site, immediate access to tocilizumab
- Ensuring those who prescribe, dispense, or administer Kymriah are aware of how to manage the risks of cytokine release syndrome and neurological toxicities

Kymriah is only available at select treatment centers. For more information, please call the REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742).

To learn more about Kymriah and its serious risks and clinical manifestations, read the Prescribing Information and the Medication Guide.

The *Kymriah REMS Program Patient Wallet Card*, *the Kymriah REMS Live Training Program Slides*, and *Kymriah REMS Program Knowledge Assessment* can be ordered through the REMS Call Center at 1-844-4KYMRIAH (1-844-459-6742). A laminated *Kymriah REMS Program Patient Wallet Card* is also available from the REMS Call Center.

Continue to check back on this website, it will be updated to include additional or new information intended to assist in the proper communication of the serious risks associated with Kymriah.

PDF Kymriah Prescribing Information

PDF Kymriah Medication Guide

PDF Kymriah REMS Live Training Program Slides

PDF Kymriah REMS Program Knowledge Assessment

PDF Kymriah REMS Program Patient Wallet Card

INDICATION:
KYMRIAH is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Contact Us | Non-US Residents

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9/17 KYM-1173200

Appendix 5

Kymriah REMS Patient Wallet Card

PATIENT WALLET CARD

Have This Card With You At All Times

Show It To Any Doctor That Sees You And When You Go To The Hospital

You should plan to stay within 2 hours of the location where you received your treatment for at least 4 weeks after getting Kymriah. Your healthcare provider will check to see if your treatment is working and help you with any side effects that occur.

Patient Information

Kymriah may cause side effects that are severe or life-threatening.

Call your oncologist or go to the emergency room if these signs appear.

SIGNS AND SYMPTOMS MAY INCLUDE:

- Difficulty breathing
- Fever (100.4°F/38°C or higher)
- Chills/shaking chills
- Confusion
- Severe nausea, vomiting, diarrhea
- Severe muscle or joint pain
- Very low blood pressure
- Dizziness/lightheadedness

NOVARTIS

Novartis Pharmaceuticals Corporation

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INFORMATION FOR THE HEALTHCARE PROVIDER

This patient has received Kymriah (CAR-T cell) therapy

Following Kymriah treatment, Cytokine Release Syndrome (CRS) can happen. It may include neurological toxicities. It typically occurs 1-22 days after the infusion.

Please contact his/her treating oncologist in the following situations:

- before giving steroids or cytotoxic medications
- if the patient has a serious infection
- before the patient undergoes an invasive procedure

fold *fold*

Date received Kymriah:_____

Oncologist Name (for Kymriah therapy): _____

Phone Number:_____

Kymriah is a CD19-directed genetically modified autologous T Cell immunotherapy indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

KYMRIAH™
(tisagenlecleucel) Suspension for IV infusion