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Via email: prabhuyo@niaid.nih.gov

Re: "Prospective Grant of Exclusive Patent License: Development of Regulatory T-Cell Therapies for the Treatment of Hemophilia A (HA)"

Dear Dr. Prabhu:

Knowledge Ecology International (KEI) is writing to comment on "Prospective Grant of Exclusive Patent License: Development of Regulatory T-Cell Therapies for the Treatment of Hemophilia A (HA)"[1] to TeraImmune, Inc. ("TeraImmune"), a start-up located in Maryland.

The federal government has conducted the basic and preclinical research for the invention and has granted TeraImmune over $3 million to support its commercial development.

Yong Chan Kim, one of the co-inventors of the technology while employed with the National Institutes of Health (NIH), is TeraImmune's Chief Scientific Officer.

Due to the invention's indication in acquired Hemophilia A, a rare disorder and unmet health need,[2] it is likely to qualify for valuable regulatory incentives such as orphan drug market exclusivity and expedited FDA review.

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[1] 85 FR 3062, available at https://www.federalregister.gov/documents/2020/01/17/2020-00721/prospective-grant-of-exclusive-patent-license-development-of-regulatoryt-cell-therapies-for-the.

[2] https://rarediseases.org/rare-diseases/hemophilia-a/; https://rarediseases.org/rare-diseases/acquired-hemophilia/.

The NIH must account for the value of the invention when negotiating this prospective license, and it must seek the advice of the United States Attorney General concerning antitrust law before executing it.

If the NIH proceeds with the license after conducting the necessary analysis and determining that it satisfies Section 209 of the Bayh-Dole Act, KEI requests that the license incorporates provisions designed to safeguard the public's investment and interest in the technology, as well as the stated policy objectives of the Public Health Service (PHS) Technology Transfer Manual.

Background

The Invention

The proposed license involves an invention titled "Methods of Producing T Cell Populations Enriched for Stable Regulatory T-Cells," U.S. Patent No. 9,481,866;[3] and U.S. Divisional Application No.15/284,840.[4]

The inventors listed in the patent are Yong Chan Kim and Ethan Shevach. Kim, who is the Chief Scientific Officer of TeraImmune, was employed with National Institute of Allergy and Infectious Diseases (NIAID) until December of 2011 - the month U.S. Provisional Patent Application 61/576,837, priority to U.S. patent 9,481,866, was filed. Co-inventor Ethan Shevach is an immunologist with NIAID.

The 9,481,866 patent is directed to "methods for producing cell populations enriched for stable, regulatory T cells (Tregs)." The 15/284,840 patent application is directed to "methods for producing cell populations enriched for stable, regulatory T cells (Tregs)" and compositions "enriched for stable, regulatory T cells." The "Potential Commercial Applications" for the invention are "autoimmune diseases, such as Graft vs. Host Disease, Organ Graft Rejection Type 1 Diabetes, Multiple Sclerosis."[5]

Terms of the License

The license territory will be the United States and the field of use "will be limited to

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[3] http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PTXT&s1=9,481,866&OS=9,481,866&RS=9,481,866.

[4] http://appft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.html&r=1&f=G&l=50&s1=%2220170022478%22.PGNR.&OS=DN/20170022478&RS=DN/20170022478

[5] https://www.ott.nih.gov/technology/e-279-2011.

'Human cell-based therapeutics for the treatment of Hemophilia A in patients that have inhibitory Factor VIII antibodies.'"[6]

The Federal Register notice does not state the proposed duration of the license, and the NIH did not respond to our question about the license term.

Prospective Licensee

TeraImmune is a limited liability company located in Maryland and incorporated in Delaware.

From what we can tell, TeraImmune was formed in order to develop regulatory T-cells as a platform technology with indications in various autoimmune disorders for a worldwide market.

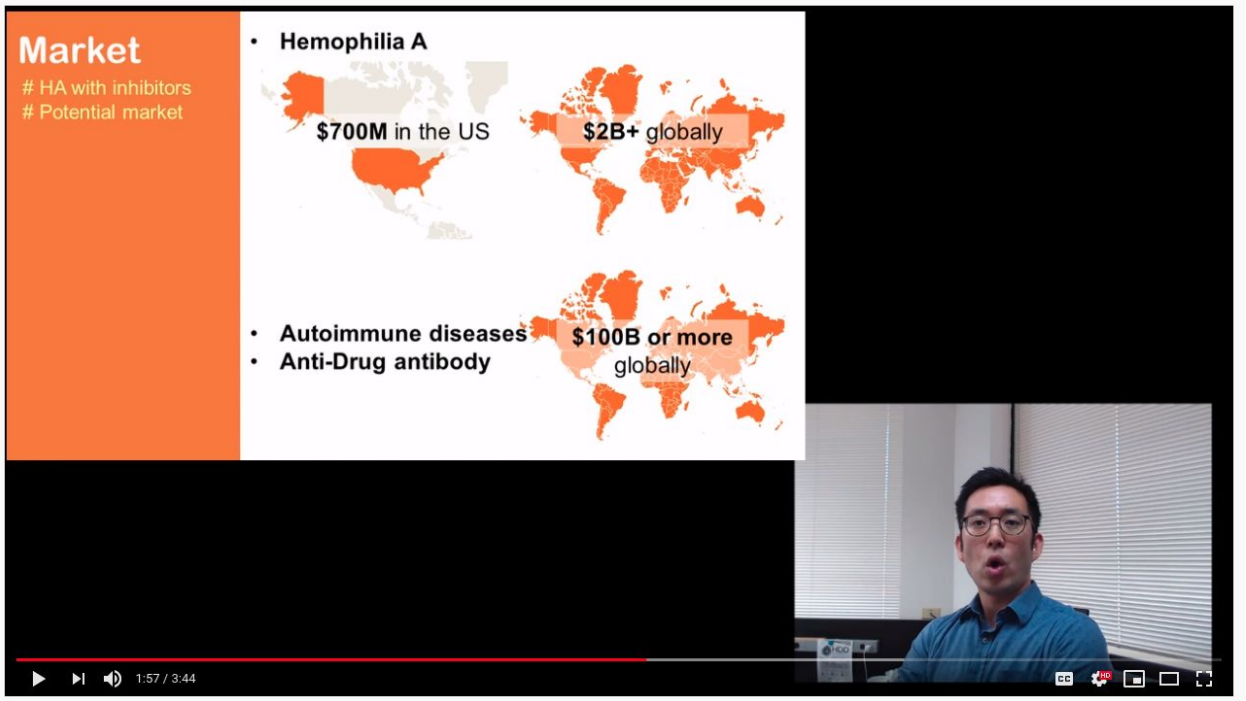
In a pitch to investors accessible at YouTube.com, Kim and TeraImmune CEO Jay Park, Ph.D., discuss the company's plans for developing the invention, which they call "T-regs" or "T-reg therapy."[7]

Kim states that the invention will treat Hemophilia A in patients that have developed inhibitory Factor VIII antibodies, and in doing so, will fulfill an unmet health need.

Park says that the potential market for the invention is $700 million in the U.S. and $2 billion worldwide in five years. He states that TeraImmune "will further explore autoimmune diseases with its platform technology. The next one will be multiple sclerosis." The video states that the global market size is $2 billion annually for Hemophilia A and $100 billion for autoimmune disorders.

6 https://www.federalregister.gov/documents/2020/01/17/2020-00721/prospective-grant-of-exclusive-patent-license-development-of-regulatoryt-cell-therapies-for-the.

7 https://www.youtube.com/watch?v=5CFK7wHRdyU.



Treg therapy (Teraimmune, Inc.), UKC 2019 Startup Pitch in English

128 views • Jun 25, 2019 2 0 SHARE SAVE

The video includes a side-by-side comparison of TeraImmune, Kite Pharma, Juno Therapeutics, and Cabaletta Bio. It notes that Kite and Juno were acquired for $11.9 billion and $9 billion (respectively) and projects that TeraImmune will be acquired for more than $5 billion.

According to the video, TeraImmune received $3,225,000 in public funding from the NIH to develop its Treg therapy ($225,000 from an SBIR grant, and $3 million from a PACT grant).

The company is seeking $8 million from investors to conduct a Phase I clinical trial to test the invention in patients with Hemophilia A.

Discussion

1. The NIH has not demonstrated that it properly evaluated the necessity of granting an exclusive license or that it has ensured that the scope of rights will not be broader than reasonably necessary to induce the investment needed to commercialize the subject technology.

The NIH may not license an invention on an exclusive basis unless, among other criteria, it finds that:

(1) "granting the license is a reasonable and necessary incentive to -- (A) call forth the investment capital and expenditures needed to bring the invention to practical application; or (B) otherwise promote the invention's utilization by the public;" and

(2) "the public will be served by the granting of the license … and [] the proposed scope of exclusivity is not greater than reasonably necessary[.]"

35 U.S.C. § 209(a)(1)-(2).

Determining the incentive necessary for bringing an invention to practical application is a fact-specific inquiry: As the NIH has acknowledged, "[t]he value of patent commercialization licenses are not uniform and depend on many factors[.]" These factors include:

- The potential market size of the drug or biologic;
- "Existing incentives, such as the Orphan Drug Act, and fast track FDA review that affect how quickly the drug can be brought to market and offer financial incentives";
- Clinical trial costs; and
- "Projected manufacturing costs upon FDA approval[.]"[8]

Another important factor influencing the value of a biomedical invention is its stage of research and development. As Dr. Mark Rohrbaugh[9] testified to Congress, "[t]he closer a technology is to the marketplace, the lower the risk and cost to the licensee, and the more valuable the technology[.]"[10]

Below is a discussion of how the relevant factors bear on the invention's commercial value.

[8] Aylin Sertkaya et al., U.S. Dept. of Health & Hum. Serv., *Examination of Clinical Trial Costs and Carriers for Drug Development* (2014), https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development.
[9] Special Advisor for Technology Transfer to the NIH Deputy Director for Intramural Research.
[10] Mark L. Rohrbaugh, *NIH: Moving Research from the Bench to the Bedside, Testimony before the House Committee on Energy and Commerce, Subcommittee on Health*, July 10, 2003, available at https://www.govinfo.gov/content/pkg/CHRG-108hhrg88429/html/CHRG-108hhrg88429.htm.

Research and Development Stage & Cost of Additional R&D Required to Bring Invention to Market

The development stage of the technology is "preclinical." In the investment pitch video, Park states that TeraImmune hopes to raise $8 million for a Phase I clinical trial to investigate T-regs in Hemophilia A patients. Eight million dollars is a notable contrast from the "hundreds of millions of dollars" Dr. Rohrbaugh has claimed it costs to conduct clinical trials in cell and gene therapies, as a justification for granting expansive license terms in NIH-owned inventions. It is consistent with KEI's research of the cost of clinical trials in cell and gene therapies.

Government Investment in the Technology

In addition to the intramural support for the invention's basic and preclinical research, TeraImmune is benefitting from at least two federal grants totalling nearly $3.25 million to support the commercial development of the technology.

The first, 1R43HL140748-01A1, is a Small Business Innovation Research (SBIR) Grant for $224,941 awarded by the National Heart, Lung, and Blood Institute (NHLBI) to Teraimmune in 2018. The title of the grant is "Factor VIII (FVIII)-Specific Therapeutic Tregs and Related CGMP Manufacturing Process for Hemophilia A Patients with Inhibitors."

NHLBI also awarded TeraImmune a "Production Assistance for Cellular Therapies" (PACT) grant worth $3 million. According to the NHLBI, "Production Assistance for Cellular Therapies (PACT) is a National Heart, Lung, and Blood Institute (NHLBI) funded resource initiative, comprised of five Cell Processing Facilities and a Coordinating Center, created to provide regulatory services, assistance with cellular therapy translational research and the manufacture of cellular therapy products."[11]

According to the "Results" tab for the SBIR Grant at projectreporter.nih.gov, the PACT grant is covering all of TeraImmune's costs in developing "Standard Operating Procedures (SOPs) for the manufacture and supply of Tregs to the clinical site for the initial clinical trial" as well as all cell production costs. The Results webpage states further that TeraImmune has participated in a "pre-pre-IND" (Initial Targeted Engagement for Regulatory Advice) meeting with the FDA's Center for Biologics Evaluation and Research regarding the invention, "with supports from the PACT program and Emmes Corporation, a Clinical Research Organization."

[11] https://www.pactgroup.net/.

Regulatory Incentives

Another factor relevant to an invention's commercial value is the availability of regulatory incentives, such as orphan drug status, that provide additional market exclusivities and expedited FDA review.[12]

Hemophilia A is a rare disorder,[13] and, according to Kim, Hemophilia A with inhibitory Factor VIII antibodies is an unmet health need. The invention is thus likely to qualify for these incentives, which include a 25 percent tax credit and seven years of Orphan Drug regulatory exclusivity.

Potential Revenues

The TeraImmune investor pitch states that Hemophilia A has a market size of $700 million in the United States.

TeraImmune considers the invention to be a profitable investment. The company expects to be worth $200 million at the time of an IPO and more than $5 billion when it is acquired.

The NIH's Analysis of the License

KEI asked Dr. Yogikala Prabhu, the point of contact for the license, whether the NIH had conducted an economic analysis of what would be required to bring the invention to practical application. We also asked about the terms of the license and how the NIH will ensure that they satisfy the Bayh Dole Act. As of the date of these comments, he has not responded.

KEI's past correspondence with the NIH about its licensing practice indicates that the agency routinely grants exclusive, life-of-patent licenses in cell and gene therapies.

For example, a letter to KEI from Dr. Rohrbaugh dated November 26, 2019 states as follows:

- "[NIH] works in a market for these early-stage therapeutic technologies in which there is *essentially no demand for nonexclusive licenses.*"

- "[C]ompanies and investors have choices as to which early stage technologies to develop and, in taking on this risk and committing to commercialization, *require an exclusive license for the full patent term.*"[14]

[12] https://www.priorityreviewvoucher.org/.
[13] https://rarediseases.org/rare-diseases/hemophilia-a/.
[14] *Id.*

If, in fact, the NIH has not assessed the commercial potential of the covered invention on an individualized basis, it has not satisfied Section 209(a)(1)-(2) of the Bayh-Dole Act for the instant license.

2. Under 40 U.S.C. § 559, the NIH is required to obtain the antitrust advice of the United States Attorney General before executing the license.

We object to the license unless the NIH first obtains the antitrust advice of the United States Attorney General, who confirms that the license would not be anticompetitive.

Under the Federal Property and Administrative Services Act, 40 U.S.C. §§ 101 *et seq.*, "[a]n executive agency shall not dispose of property to a private interest until the agency has received the advice of the Attorney General on whether the disposal to a private interest would tend to create or maintain a situation inconsistent with antitrust law." 40 U.S.C. § 559(b)(1).

This includes when the NIH proposes to grant an exclusive license in federally-owned technology. "Property" is defined at 40 U.S.C. § 102 to mean "any interest in property," with certain exceptions that do not include patents. Similarly, Section 559 creates certain exceptions that do not include patents.

41 C.F.R. § 102-75.270 supports the notion that the term "property" in Section 559 includes intellectual property rights such as patents.

41 C.F.R. § 102-75.270 - Must antitrust laws be considered when disposing of property?

Yes, antitrust laws must be considered in any case in which there is contemplated a disposal to any private interest of -

(a) Real and related personal property that has an estimated fair market value of $3 million or more; or

(b) Patents, processes, techniques, or inventions, irrespective of cost.

In the past, the NIH has asserted its position with respect to 40 U.S.C. § 559 as follows:

> "The statute you reference is directed to the disposal (assignment) of government property. It has little relevance to our patent licensing activities, which are principally government by the Bayh-Dole Act and its regulations."

The NIH's interpretation of 40 U.S.C. § 559 is incorrect.

The Bayh-Dole Act expressly incorporates federal antitrust laws. 35 U.S.C. § 209(a)(4) allows a federal agency to grant an exclusive license only if the license "will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws." 35 U.S.C. § 211 provides that "[n]othing in this chapter shall be deemed to convey to any person immunity from civil or criminal liability, or to create any defenses to actions, under any antitrust law[.]" The Bayh-Dole Act sets out the areas in which the statute "shall take precedence over any other Act which would require a disposition of rights in subject inventions[,]" 35 U.S.C. § 210, and mentions 21 separate statutes, but not the FPASA.

Second, the term "disposal" is not a defined term under 40 U.S.C. § 102 of the FPASA, and is not limited to "assignment" or "sale." In fact, there are many examples of regulations and laws that include licensing amongst dispositions, either explicitly or by implication.

If the NIH has not consulted with the Attorney General regarding the license, it has not complied with 40 U.S.C. § 559.

3. In the event that the NIH decides to grant the license, we recommend that the NIH includes a series of provisions designed to safeguard the public interest and ensure that the license implements the governing principles in the PHS Technology Transfer Manual.

In the event that the NIH proceeds with the license, KEI requests that it includes the following provisions to protect the public's interest in the technology:

1. **Price discrimination.** Any medical technology using the patented invention should be available in the United States at a price that does not exceed the median price in the seven largest economies by GDP that have at least 50 percent of the GNI per capita as the United States, using the World Bank Atlas method. This is a modest safeguard.

2. **Years of exclusivity.** We propose the license reduce the years of exclusivity when revenues are large. The NIH has many options, including by providing an option for non-exclusive licensing, such as was done in the ddI case. We propose that the exclusivity of the license be reduced when the global cumulative sales from products or services using the inventions exceed certain benchmarks. For example, the period of exclusivity in the license could be reduced by one year for every $500 million in global cumulative revenue after the first one billion in global sales. This request is consistent with the statutory requirements of 35 U.S.C. § 209, which requires that "the proposed scope of exclusivity is not greater than

reasonably necessary to provide the incentive for bringing the invention to practical application."

3. **Transparency of R&D outlays.** The licensee should be required to file an annual report to the NIH, available to the public, on the research and development (R&D) costs associated with the development of any product or service that uses the inventions, including reporting separately and individually the outlays on each clinical trial. We will note that this is not a request to see a company business plan or license application. We are asking that going forward the company be required to report on actual R&D outlays to develop the subject inventions. Reporting on actual R&D outlays is important for determining if the NIH is meeting the requirements of 35 U.S.C. § 209, that "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application." Specifically, having data on actual R&D outlays on each clinical trial used to obtain FDA approval provides evidence that is highly relevant to estimating the risk adjusted costs of bringing NIH licensed inventions to practical application.

Concluding comments

We support the NIH's efforts to license the subject invention to a commercial partner who appears to be qualified to bring it to practical application.

It is our understanding that licensing a patent to a company employing the inventor does have the advantage that the inventor may bring unique insights into the technology, and a passion to see the technology reach the market. That said, it does raise some issues regarding the self dealing at the NIH, with government funded inventions being licensed to former employees. This is particularly relevant given the general lack of interest by the NIH in negotiating licensing terms that protect the public from excessive monopoly power over this taxpayer funded invention. In this regard, KEI notes that the company claims that it requires just $8 million for the proposed clinical trial, and that the company sees the market for the licensed technology to reach $2 billion per year, for the Hemophilia A indication (of which 35 percent will come from U.S. patients). Further, the company business plan is to sell out to another company for more than $5 billion. This suggests that the proposed license is a better deal for Teralmmune than it is for the public that has financed the R&D so far. Also, Teralmmune is likely to charge extremely high prices if the license is granted and the technology reaches the U.S. market.

The terms of the license must satisfy the Bayh-Dole Act and federal regulations, and before the NIH executes the license, it must consult the United States Attorney General. Finally, KEI requests that the license incorporates the provisions listed above, which are designed to promote the public interest in the invention and implement the policy objectives of the PHS Technology Transfer manual.

Sincerely,

Knowledge Ecology International