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Re: Prospective Grant of an Exclusive Patent License: Methods and Compositions for Adoptive Cell Therapy

Dear Dr. Burke:

Knowledge Ecology International (KEI) and Union for Affordable Cancer Treatment (UACT) are writing to comment on the "Prospective Grant of an Exclusive Patent License: Methods and Compositions for Adoptive Cell Therapy" to Lyell Immunopharma, Inc. ("Lyell").[1] The proposed license encompasses six inventions related to adoptive cell therapy for indications "in cancer in humans." A former National Institutes of Health (NIH) scientist who co-invented all six inventions in his capacity as an NIH employee is an executive officer with Lyell who joined in July 2019.

With the NIH proposing to grant Lyell a monopoly over six taxpayer-funded inventions that may improve adoptive cell therapies for terminal cancer, in all forms of cancer in humans, the terms of the license regarding pricing and affordability and years of exclusivity are of great importance to cancer patients and to anyone who is responsible for paying the costs of the treatments.

The NIH may not grant the license unless all the criteria listed at 35 U.S.C. § 209(a) have been satisfied.

We object to the license for the following reasons:

[1] 85 Fed. Reg. 18577, available at https://www.federalregister.gov/documents/2020/04/02/2020-06922/prospective-grant-of-an-exclusive-patent-license-methods-and-compositions-for-adoptive-cell-therapy.

1. The NIH apparently has not analyzed whether exclusivity is a reasonable and necessary incentive or limited the scope of the license to not broader than necessary, as required by 35 U.S.C. § 209(a)(1)-(2);
2. The NIH has not been transparent about the license, refusing to answer six out of nine questions submitted by KEI, and limiting our ability to comment on the license, which is guaranteed by 35 U.S.C. § 209(e); and
3. The NIH has not sought the antitrust advice of the U.S. Attorney General with respect to the license, as required by 40 U.S.C. § 559.

If the NIH grants the license over our objections, we request that the license incorporates a series of provisions designed to safeguard the public interest in the technologies and promote the policies outlined in the Public Health Service (PHS) Technology Transfer Manual.

Background

The Inventions

The proposed license covers six publicly-owned inventions grouped into three categories: Group A, Group B, and Group C. Group A contains a method of identifying the cancer patients who are likely to respond to adoptive cell therapy. Groups B and C contain methods of generating T-cells that may be able to overcome some of the limitations in current cell therapies.

According to articles reporting the inventions, the following NIH grants funded the research underlying the subject technology:

- ZIA BC010763, FYs 2009 to 2019, for a total of $54,856,083;
- K08 CA197966, FYs 2015 to 2019, for a total of $874,800; and
- ZIA BC011480, FYs 2013 to 2019, for a total of $7,351,653.

Because we do not know when each invention was finalized, it is possible that not all of the funded years of the grants listed above supported the research behind the subject inventions. We asked Dr. Andrew Burke, the point of contact for the license, how much federal funding contributed to the inventions, and he did not answer. We would be able to report more specific information regarding funding of inventions if the NIH improved its reporting mechanisms and were more transparent about the role of public funding in federally-funded inventions.

The Prospective Licensee

The prospective licensee, Lyell, is a biotech company founded by Rick Klausner, the former head of the National Cancer Institute (NCI), a former executive director for global health at the Bill and Melinda Gates Foundation, and a co-founder of Juno Therapeutics.[2]

Nicholas Restifo, one of the inventors of all six inventions covered by the license, is Executive Vice President, Research for Lyell. Restifo helped conceptualize the inventions while funded by an NIH grant, ZIA BC010763, which awarded a total of $54,856,083 to fund his research from 2009 to 2019. Restifo joined Lyell in July of 2019.

Lyell's website contains little information other than a short description of the company and biographies of its executive officers. The webpages for "Press Releases," "Publications," and "News," direct viewers to check back later for updates.

Lyell's business model appears to be focused on developing technologies to make adoptive T-cell therapies more effective and licensing them to biotech companies with immunotherapies in their pipeline.

In October of 2019, Lyell entered into a five-year collaboration with GlaxoSmithKline (GSK) in which Lyell will contribute its technologies to improve the T-cell performance of GSK's cell therapy products.[3]

On March 17, 2020, Eureka Therapeutics, Inc., "a clinical stage biotechnology company developing novel T cell therapies for solid tumors," announced that the company had entered into a "strategic collaboration" with Lyell "to develop therapies against several undisclosed solid tumor targets expressed across multiple cancer types."[4] Lyell's role in the partnership is "to improve the efficacy of engineered T cells in solid tumors."[5]

Discussion

1. The NIH apparently has not meaningfully applied the statutory criteria governing exclusive licenses.

The NIH's technology transfer policy favors nonexclusive licenses, and exclusive licenses may not be granted unless all of the criteria listed at 35 U.S.C. § 209 are satisfied.[6] These criteria

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[2] https://endpts.com/exclusive-gsks-hal-barron-allies-with-rick-klausners-600m-cell-therapy-startup-looking-to-break-new-ground-blitzing-solid-tumors/.

[3]

[4] https://www.eurekatherapeutics.com/media/press-releases/031720/.

[5] *Id.*

[6] PHS Technology Transfer Policy Manual Chapter No. 305, "PHS Policy for Making Determinations Regarding the Grant of Exclusive or Partially Exclusive Commercialization Licenses." https://www.ott.nih.gov/sites/default/files/documents/policy/pdfs/305-policy.pdf.

include that exclusivity is a reasonable and necessary incentive to enable the commercialization of the subject technology, and that the scope of the license is not broader than necessary.[7]

The NIH's correspondence with KEI regarding this license appears to indicate that the NIH has failed to give meaningful consideration to the statutory criteria.

KEI asked Dr. Burke how the NIH determined that an exclusive license to the subject inventions is a reasonable and necessary incentive, and that the scope of the license is not broader than necessary. He declined to answer, stating that the question had already been answered, and referring KEI to NIH's past answers to unrelated licensing decisions.

The NIH's past statements regarding how it applies 35 U.S.C. § 209(a)(1) to exclusive patent licenses indicate that the NIH grants an exclusive license whenever doing so will promote commercial development. As KEI has explained in previous comments, that policy violates the statutory standard, which allows exclusivity only when it is necessary and not when it is merely helpful.

In order to conclude that an exclusive license is necessary, some analysis must be undertaken, including, for example, consideration of the other types of incentives provided by law, such as test data protection, Orphan Drug exclusivity, etc., and the likely case that the developer can bring other patented inventions into the project, for which exclusivity exists. The NIH's statements indicate that no such analysis has been performed. As Dr. Mark Rohrbaugh, Senior Advisor for Technology Transfer, has stated to KEI, the NIH assumes that exclusivity is necessary, because it "works in a market for these early-stage therapeutic technologies in which there is essentially no demand for nonexclusive licenses."

Similarly, the NIH's past statements regarding the scope of a license indicate that it does not properly apply the statutory criteria.

The scope of an exclusive license must "not [be] greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]" 35 U.S.C. § 209(a)(2).

The scope of an exclusive patent license may vary in terms of the period of exclusivity, territorial reach, and field of use, among other parameters. Each license requires individualized consideration to determine the appropriate scope.

The fields of use for the license and its territorial scope are extremely broad. According to the Federal Register Notice, the fields of use "may be limited to":

- "Manufacture and commercialization of companion diagnostics approved or cleared by the FDA . . . for Licensee-proprietary T cell therapy products" (Group A);

[7] 35 U.S.C. § 209(a)(1)-(2).

- "Manufacture and commercialization of adoptive T cell therapy products generated from autologously-derived, induced pluripotent stem cells for the treatment of cancer in humans" (Group B); and
- "Manufacture and commercialization of adoptive T cell therapy products isolated from peripheral blood for the treatment of cancer in humans" (Group C).

The proposed territorial reach of the license is "worldwide."[8]

In testimony explaining NIH licensing practices to Congress, Dr. Rohrbaugh described how the field of use for a license can be narrowed as follows:

> [M]ultiple aspects of a single technology may be exclusively licensed to multiple parties. For example, a technology for treating a variety of cancers might be licensed to one company for lung cancer therapeutics and to another for liver and pancreatic cancer therapeutics.[9]

The field of use should be narrowed further so that it would not embrace all cancer in humans, which is overbroad.

The NIH surely must know that companies that develop such technologies routinely enter into contracts that limit exclusivity in other ways as well, for example, granting exclusivity in some markets, but not others. The United States could grant exclusivity to the European Union, Japan and other high income countries, but not to the United States, for example, so that countries that did not fund the R&D would bear the costs of the exclusivity, while U.S. residents would not. And the U.S. could limit exclusivity in moderate and lower income countries, where the monopoly is likely to have an adverse impact on access with almost no benefit in terms of the incentives for the company.

The NIH could also grant exclusivity for a period less than the term of the patent, or only until a company achieved a certain level of global revenue from sales.

The NIH has stated, however, that it generally does not limit the duration of its exclusive patent licenses, because "companies and investors . . . require an exclusive license for the full patent term."

If the NIH did not investigate the possibility of limiting the term of the proposed license, or using non-US high income countries only for the exclusivity, it has not satisfied its obligations under 35 U.S.C. § 209(a)(1)-(2).

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[8] *Id.*

[9] 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.

2. The NIH was not transparent about the license, limiting the public's right to comment under 35 U.S.C. § 209(e).

A federal agency may not grant an exclusive license in government-owned technology without first notifying the public of the prospective license, allowing a minimum 15-day period for the public to comment, and considering all timely-submitted comments. 35 U.S.C. § 209(e).

The NIH has not been transparent about the license, impeding our ability to exercise the right to comment guaranteed by 35 U.S.C. § 209(e).

For the public to meaningfully comment on a proposed license, it must have basic information about it. Our ability to comment on the license has been limited by the NIH's refusal to answer six of the nine questions that KEI submitted to Dr. Burke. Rather than answering the questions, Dr. Burke stated that the questions have already been answered, and referred KEI to those supposed past answers. Of course, Dr. Burke's statement was not and could not be true. KEI's list of questions was specific to the instant license, about which KEI had never previously inquired. KEI pointed that out to Dr. Burke, in a follow-up email, but he never responded.

In the past, the NIH has asserted two main reasons for refusing to answer KEI's questions: 1) that the information sought was irrelevant and 2) that the information was confidential. Neither assertion is true.

The questions Dr. Burke refused to answer related to how the NIH had applied the criteria at 35 U.S.C. § 209 governing a federal agency's authority to grant an exclusive license. There can be no issue more directly relevant to a licensing decision than how the NCI determined that an exclusive license was a reasonable and necessary incentive (35 U.S.C. § 209(a)(1)) and how it concluded that the scope of the license is not broader than necessary (35 U.S.C. § 209(a)(2)). Yet these are two of the questions Dr. Burke failed to answer.

Nor was the information that Dr. Burke refused to answer confidential business information.

The NIH has stated that it cannot answer many of KEI's questions about its licensing practices because NIH "has a duty to safeguard" confidential information contained in license applications, such as "proposed commercial plans, including earnings, proposed expenditures, and trade secret information."

KEI did not request any sensitive information contained in a license application. For example, one question KEI asked, and Dr. Burke refused to answer, was which, if any, other companies have submitted an application for the license.

Federal law and regulations regarding government patent licenses do not make all aspects of license applications confidential. Rather, they establish the confidentiality only of a license applicant's commercialization plans and periodic utilization reports. The identity of an applicant for a license is not a commercialization plan or periodic utilization report.

The Bayh-Dole Act appropriately gives the public a role in licensing decisions concerning inventions that are funded and owned by the public. Because the questions KEI asked and Dr. Burke refused to answer were relevant and non-confidential, Dr. Burke had no basis for refusing to answer them and undermined our ability to comment on the license.

3. The NIH apparently has not sought the antitrust advice of the U.S. Attorney General regarding the license, as required by 40 U.S.C. § 559.

We object to the license because the NIH has not first obtained the antitrust advice of the United States Attorney General.

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." The statue exempts personal property if the fair market value is less than $3,000,000, but specifically excludes "a patent, process, technique, or invention" from that exception.

The regulation 41 C.F.R. § 102-75.270 also makes clear the inclusion of patents "irrespective of cost."

KEI asked Dr. Burke whether the NIH requested the advice of the U.S. Attorney General concerning the licenses. Dr. Burke did not answer. 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.

We disagree.

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.

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 NIH grants an exclusive license in a federally-owned invention, it is disposing of a government property interest so as to trigger 40 U.S.C. § 559.

4. In the event that the NIH decides to grant the license over our objections, 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 listed in the Public Health Service (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 NIH-funded technology:

1. **Exclusivity.** If the NIH decides to grant exclusive rights to the subject inventions, it should limit exclusivity to the European Union, Japan and other high-income countries, but not the United States, so that countries that did not fund the R&D underlying the inventions would bear the costs of the exclusivity, while the U.S. residents would not. The NIH should also limit exclusivity in moderate and lower income countries, where the monopoly is likely to have an adverse impact on access with almost no benefit in terms of the incentives for the company.

2. **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.

3. **Low and middle income countries.** The exclusive license should not extend to countries with a per capita income less than 30 percent of the United States, in order to ensure that the patents do not lead to restricted and unequal access in developing countries. If the NIH rejects this suggestion, it needs to provide something that will give effect to the policy objective in the "United States Public Health Service Technology Transfer Policy Manual, Chapter No. 300, PHS Licensing Policy," which states the following: "PHS seeks to promote commercial development of inventions in a way that provides broad accessibility for developing countries."

4. **Global registration and affordability.** The license should require Lyell Immunopharma to disclose the steps it will take to enable the timely registration and availability of the medical technology at an affordable price in the United States and in every country with a demonstrated need, according to the Centers for Disease Control and Prevention (CDC) and/or the World Health Organization (WHO), either by supplying a country directly at an affordable, publicly disclosed price and with sufficient quantities, or by providing technology transfer and rights to all intellectual property necessary for third parties to do so.

5. **Medicines Patent Pool.** The NIH should retain a right to grant the WHO, the Medicines Patent Pool or other governments the rights to use the patent rights to procure the medical technology from competitive suppliers, including technology transfer, in developing countries, upon a finding by HHS or the WHO that people in these markets do not have sufficient access to the medical technology.

6. **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."

7. **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.

Conclusion

We object to the proposed license to Lyell for the reasons stated herein. In the event that the NIH grants the license, we ask that it incorporates the provisions listed above, which are designed to protect the public interest in the licensed technologies and to accomplish the policies outlined in the PHS Technology Transfer Manual.

Sincerely,

Knowledge Ecology International
Union for Affordable Cancer Treatment