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April 28, 2020

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Via Email: vlado.knezevic@nih.gov

Re: Prospective Grant of an Exclusive Patent License: AAV Mediated Exendin-4 Gene Transfer to Salivary Glands To Protect Subjects From Diabetes or Obesity

Dear Dr. Knezevic:

Knowledge Ecology International (KEI) and James Love are writing to comment on the "Prospective Grant of an Exclusive Patent License: AAV Mediated Exendin-4 Gene Transfer to Salivary Glands To Protect Subjects From Diabetes or Obesity" to Kriya Therapeutics, Inc.[1]

The invention covered by the license, which was successful in preclinical studies, could help regulate blood sugar in patients with diabetes and promote weight loss in individuals suffering from obesity—conditions affecting large numbers of Americans and hundreds of millions of people worldwide.

The National Institutes of Health (NIH) may not execute the license unless it considers all timely-submitted public comments and concludes that the criteria listed at 35 U.S.C. § 209(a) are satisfied. The NIH did not answer the majority of the questions KEI asked about the license, limiting our ability to comment on it.

From what KEI can tell, the license does not satisfy the criteria located at 35 U.S.C. § 209(a), because the NIH apparently has not engaged in an individualized assessment to determine whether exclusivity is a reasonable and necessary incentive, nor has it limited the proposed scope of exclusivity to not broader than the necessary incentive.

[1] 85 Fed. Reg. 20508, available at https://www.federalregister.gov/documents/2020/04/13/2020-07706/prospective-grant-of-an-exclusive-patent-license-aav-mediated-exendin-4-gene-transfer-to-salivary.

Because the license disposes of government-owned property, the NIH may not grant it unless the NIH first requests the antitrust advice of the U.S. Attorney General, which it apparently has not done.

If the NIH grants the license, we request that it incorporates a series of provisions designed to safeguard the public interest in the invention, promote the policy objectives of the Bayh-Dole Act, and implement the policies outlined in the Public Health Service (PHS) Technology Transfer Manual.

Background

The proposed license covers an invention involving the use of an adeno-associated viral vector to deliver exendin-4 to the salivary gland as a treatment for diabetes and obesity.

The abstract for the invention at the NIH Office of Technology Transfer website states that the invention "resulted in improved glucose homeostasis and weight profile in two rat models of obesity and type 2 diabetes."[2]

The prospective licensee, Kriya Therapeutics, Inc., is incorporated in Delaware and registered to conduct business in California. Kriya Therapeutics' website contains little information apart from a two-paragraph description of the company and short biographies of its executive officers. The website does not list which, if any, products are in Kriya Therapeutics' pipeline, but states that the company's mission is "to expand the reach of gene therapy to address highly prevalent diseases affecting millions of patients."[3] This is consistent with a company that applied for a license to a potential treatment for diabetes and obesity.

Discussion

As explained in greater detail below, KEI notes the following points about the proposed license:

1. The NIH was not transparent about the license, limiting our ability to comment on it, a right provided to the public by 35 U.S.C. § 209(e);
2. The license does not satisfy the criteria located at 35 U.S.C. § 209(a), because the NIH apparently has not engaged in an individualized assessment to determine whether exclusivity is a reasonable and necessary incentive, nor has it limited the proposed scope of exclusivity to not broader than the necessary incentive;
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; and

[2] https://www.ott.nih.gov/technology/e-142-2011.
[3] https://web.archive.org/save/https://kriyatherapeutics.com/.

4. If the NIH proceeds with the license, we recommend that it includes a series of provisions designed to safeguard the public interest and ensure that the license implements the governing principles listed in the PHS Technology Transfer Manual.

1. The NIH was not transparent about the license, limiting our ability to comment on it, a right provided to the public by 35 U.S.C. § 209(e).

A federal agency may not grant an exclusive license to 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).

For the public to meaningfully comment on a proposed license, it must have basic information relevant to the license, and in particular, to the controlling issue—whether the license is authorized because it satisfies all of the criteria listed at 35 U.S.C. § 209(a).

On April 24, 2020, KEI emailed Dr. Vladimir Knezevic, the point of contact for the license, a list of eight questions. He answered only the first two questions, both of which concerned the development stage of the invention. In declining to answer the remaining questions, he stated that those questions either were irrelevant or had already been answered. Both assertions are incorrect.

Among the questions that Dr. Knezevic refused to answer were (1) how the NIH concluded that exclusivity is a necessary incentive and (2) how it concluded that the scope of exclusivity is not broader than necessary. These are two of the requirements that the NIH must satisfy before it may grant an exclusive license. By failing to answer questions that relate to whether the proposed license satisfies 35 U.S.C. § 209, the NIH withheld information that is directly relevant to the issue at hand.

Nor had the NIH ever answered the questions that Dr. Knezevic refused to answer. The questions that KEI emailed Dr. Knezevic were unique to the instant patent license, and April 24, 2020 was the first and only time KEI asked about this license.

The Bayh-Dole Act gives the public a role in licensing decisions concerning inventions that are owned by the public. Because the questions KEI asked and Dr. Knezevic failed to answer were relevant and had not previously been answered, Dr. Knezevic had no basis for not answering them. The NIH's lack of transparency undermined KEI's ability to comment on the license.

2. The NIH apparently has not meaningfully applied the criteria for granting an exclusive license.

The NIH may not license a federally-owned invention on an exclusive or partially-exclusive basis unless, among other criteria:

> (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 [NIH] finds that the public will be served by the granting of the license . . . and that the proposed scope of exclusivity is not greater than reasonably necessary[.]"

35 U.S.C. § 209(a)(1)-(2).

As noted previously, KEI asked Dr. Knezevic how he evaluated the above-listed criteria to determine that an exclusive license is a reasonable and necessary incentive, and that "the proposed scope of exclusivity is not greater than reasonably necessary," tracking the language of 35 U.S.C. § 209(a)(1)-(2).

In declining to answer those questions, Dr. Knezevic stated that they had already been answered. While that statement is inaccurate, his response is consistent with past statements by NIH technology transfer officials, who employ across-the-board assumptions for exclusive patent licenses. For example, Dr. Mark Rohrbaugh, Special Advisor for Technology Transfer to the NIH Deputy Director for Intramural Research, stated in a letter to KEI that the NIH "works in a market for these early-stage therapeutic technologies in which there is essentially no demand for nonexclusive licenses" and that "companies and investors . . . require an exclusive license for the full patent term." In relation to a previous proposed exclusive patent license, an NIH technology transfer officer stated: "I do not personally have any licenses on my docket granted for a term shorter than the full patent term and am unaware of any that may have been granted by my colleagues at other Institutes."

(For clarity, KEI notes that the NIH has been requested to limit the term of exclusivity of the license, not the term of the license.)

Dr. Knezevic's reference to past NIH statements about unrelated licensing decisions indicates that the answers to KEI's unanswered questions are as follows:

- The NIH is proposing an exclusive license because it assumes that no company will commit to licensing the technology without full exclusivity; and
- The NIH is proposing to grant the broadest possible rights to the technology because it assumes that no company will commit to licensing the technology without the broadest scope of exclusivity.

Because each license presents unique technologies and circumstances, such a one-size-fits-all approach is not consistent with the Bayh-Dole Act. Where it is possible to limit rights to an invention, the agency proposing to grant an exclusive or partially exclusive license must do so.

The subject technology has performed well in preclinical studies—the riskiest stage of development—and the preclinical research was funded by the public sector.[4] If successful, the technology will have a huge market size, considering the prevalence of diabetes and obesity. In 2018, 34.2 million Americans, or 10.5 percent of the population, had diabetes.[5] According to the Centers for Disease Control and Prevention, in the United States, "[t]he prevalence of obesity was 42.4 percent in 2017~2018."[6] In addition, this is a worldwide license. According to the World Health Organization (WHO), in 2014, the global prevalence of diabetes among adults over 18 years of age was estimated at 8.5 percent or the world population.[7] The WHO also estimated there were more than 300 obsese adults in 2000.[8]

Given the potential value of the technology and the requirement to limit the scope of the license, it is concerning that the proposed scope of the license has not been limited in any discernible way.

Considering the NIH's previous gene therapy licensing practices, we can safely assume that the period of exclusivity for this license is life-of-patent—the broadest possible duration.

The proposed territorial reach for the license is also as broad as possible—worldwide.

Likewise, the proposed field of use is as wide as possible. While the NIH will not concede that it is required to limit the duration of an exclusive patent license, it does acknowledge that it is required to limit the field of use for such licenses. Here, however, the field of use apparently embraces all potential commercial applications for the subject invention: "prevention and treatment of type-2 diabetes and obesity."[9]

If, in fact, the NIH has not considered whether a non-exclusive or partially-exclusive license is possible, and it has not explored whether it could narrow the duration of the license, territorial reach, or field of use—perhaps to either diabetes or obesity, but not both indications—it has not satisfied 35 U.S.C. § 209(a)(1)-(2).

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[4] Di Pasquale, Giovanni et al. "Sustained exendin-4 secretion through gene therapy targeting salivary glands in two different rodent models of obesity/type 2 diabetes." PloS one vol. 7,7 (2012): e40074. doi:10.1371/journal.pone.0040074.

[5] https://www.diabetes.org/resources/statistics/statistics-about-diabetes.

[6] https://www.cdc.gov/obesity/data/adult.html.

[7] https://www.who.int/news-room/fact-sheets/detail/diabetes.

[8] https://www.who.int/nutrition/topics/obesity/en/.

[9] https://www.federalregister.gov/documents/2020/04/13/2020-07706/prospective-grant-of-an-exclusive-patent-license-aav-mediated-exendin-4-gene-transfer-to-salivary. According to the invention abstract, the potential commercial application for the invention is "[t]herapy for diabetes or obesity." https://www.ott.nih.gov/technology/e-142-2011.

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 statute 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. Knezevic whether the NIH requested the advice of the U.S. Attorney General concerning the licenses. Dr. Knezevic 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 governed 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 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. **Geographic Scope of Exclusivity.** If the NIH decides to grant exclusive rights to the subject invention, it should limit exclusivity to any country with at least 35 percent of the per capita income of the United states, but not the United States, so that high income countries that did not fund the R&D underlying the invention would bear the costs of the exclusivity, while U.S. residents would not. The NIH should license the invention on a non-exclusive basis in countries with per capita incomes less than 35 percent of the United States. For countries of moderate or low income, the monopoly is likely to have an adverse impact on access with fewer benefits in terms of the incentives for investors.

1. **Price discrimination.** In the event that exclusivity is extended to the United States, 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. **Low and middle income countries.** As noted, the exclusive license should not extend to countries with a per capita income less than 35 percent of that of the United States, in order to ensure that the patents do not lead to restricted and unequal access. 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."

3. **Global registration and affordability.** The license should require Kriya Therapeutics 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 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.

4. **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 any country where there is a finding by the Department of Health and Human Services (HHS) or the WHO that people in these markets do not have sufficient access to the medical technology.

5. **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 invention 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."

6. **Transparency of R&D outlays.** Kriya Therapeutics should be required to file an annual report to the NIH, available to the public, on the R&D costs associated with the development of any product or service that uses the invention, 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 invention. Reporting on actual R&D outlays is important for determining if the NIH is meeting the requirements of 35 U.S.C. § 209, including 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

The NIH's failure to answer KEI's questions about this license has undermined our ability to comment on it, a right that is protected by 35 U.S.C. § 209(e). The NIH may not execute the license unless it fulfills all criteria listed at 35 U.S.C. § 209(a), and blanket assumptions may not replace the necessary individualized assessment. Because the license disposes of government-owned property, the NIH may not grant the license unless it first requests the antitrust advice of the U.S. Attorney General. 40 U.S.C. § 559. 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,

1. Knowledge Ecology International

2. James Love (in his individual capacity)