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Via Email: Tedd.Fenn@nih.gov

Re: "Prospective Grant of an Exclusive Patent License: Compositions, Devices and Processes for Production and Delivery of Cell Grafts of Manufactured Retinal Pigment Epithelium Cell(s) Alone, or in Combination With Photoreceptor Cells, and on a Biodegradable Support Scaffold Transplanted Subretinally for Intra-Ocular Ophthalmic Treatment of Conditions of Degeneration, Dysfunction or Terminal Injury of Retinal Pigment Epithelium and/or Photoreceptors in Humans," 84 FR 52889

Dear Mr. Fenn:

Knowledge Ecology International (KEI) is writing to object to the "Prospective Grant of an Exclusive Patent License: Compositions, Devices and Processes for Production and Delivery of Cell Grafts of Manufactured Retinal Pigment Epithelium Cell(s) Alone, or in Combination With Photoreceptor Cells, and on a Biodegradable Support Scaffold Transplanted Subretinally for Intra-Ocular Ophthalmic Treatment of Conditions of Degeneration, Dysfunction or Terminal Injury of Retinal Pigment Epithelium and/or Photoreceptors in Humans" to Opsis Therapeutics, LLC, ("Opsis") located in Madison Wisconsin and its affiliate, FUJIFILM Cellular Dynamics, Inc., as described in the Federal Register notice located at 84 FR 52889.

The license would grant Opsis exclusive, worldwide rights in at least six separate inventions developed by the National Eye Institute (NEI). According to the Federal Register notice, "[t]he technologies relate to the development of compositions, devices and processes for production and delivery of RPE-containing tissue graft therapies for treating a range of retinal function disorders, including retinal degenerative conditions in humans."[1]

[1] https://www.govinfo.gov/content/pkg/FR-2019-10-03/pdf/2019-21520.pdf

We object to the proposed license to Opsis for the following reasons:

1. Our correspondence with the National Institutes of Health (NIH) concerning the prospective license indicates that the NIH has not faithfully applied the criteria in 35 U.S.C. § 209 and 37 C.F.R. § 404.7;
2. The NIH has not been completely transparent about the license, impeding the public's right to comment under 35 U.S.C. § 209(e); and
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.

For a license as expansive as this one, covering six separate NIH-owned methods and devices that can be used to develop cures for blindness, it is important for the NIH to demonstrate that it properly evaluated the criteria for granting exclusive patent licenses, located at 35 U.S.C. § 209.

In the event that the NIH grants the license over our objections, we request that the license agreement incorporates provisions designed to safeguard the public interest and effectuate the policy objectives of the Bayh-Dole Act, as well as the governing principles of the Public Health Service (PHS) Technology Transfer Policy Manual.

Background

The prospective license concerns the following methods and devices for developing retinal cell graft therapies that were invented by the NEI:

- E-192-2014, Surgical Tool for Sub-retinal Tissue Implantation;
- E-212-2015, Method for Reproducible Differentiation of Clinical Grade Retinal Pigment Epithelium Cells;
- E-293-2016, Tissue Clamp for Repeated Opening and Closure of Incisions/Wounds;
- E-094-2016, Devices for Improved Tissue Cryopreservation and Recovery;
- E-058-2018, Machine Learning and/or Neural Networks to Validate Stem Cells and Their Derivatives for Use in Cell Therapy, Drug Delivery, and Diagnostics; and
- E-015-2019, Biodegradable Tissue Implantation and its Use.

The fields of use for the license is listed as follows:

> The development, production and commercialization of allogeneic cell grafts of manufactured Retinal Pigment Epithelium cell(s) alone, or in combination with photoreceptor cells, and on a biodegradable support scaffold transplanted subretinally for intra- ocular ophthalmic treatment of conditions of degeneration, dysfunction or terminal injury of retinal pigment epithelium and/or photoreceptors in humans.

Opsis Therapeutics is a biotech company whose mission is "to advance a pipeline of first-in-class cell replacement therapies targeting Age Related Macular Degeneration ('AMD') and inherited retinal diseases including Retinitis Pigmentosa ('RP')."[2] To that end, Opsis is developing a "technology platform" which builds upon recent advances that enable scalable manufacture of authentic human retinal cells from induced-pluripotent stem cells ('iPSCs')."[3]

Argument

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.

Before it may proceed with the proposed exclusive license, NIH must find both that granting the license is a reasonable and necessary incentive to induce a company to commercialize the technology and "that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]" 35 U.S.C. § 209(a)(1)-(2).

We are concerned that the NIH has not conducted the required analysis with respect to the proposed exclusive license to Opsis.

Necessity of Exclusivity

NIH may not grant the proposed license to Opsis unless and until it determines that "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[.]" 35 U.S.C. § 209(a)(1).

It is our understanding that the NIH has not undertaken a serious evaluation of the adequacy of existing incentives and subsidies, relating to practical application of the inventions, in order to evaluate whether or not exclusivity is a "reasonable and necessary incentive."

KEI asked Edward Fenn, the point of contact for the license, how the NIH determined that an exclusive license is a necessary incentive under 35 U.S.C. § 209(a)(1). Mr. Fenn responded as follows: "An identified public health need, license applicant's commercial ability at the time of application, 35 U.S.C. 209 and 37 CFR part 404[.]"

[2] https://opsistx.com/
[3] https://opsistx.com/

Mr. Fenn's answer did not track federal law and regulations governing exclusive licenses of federally-owned inventions. Neither 35 U.S.C. § 209 nor 37 C.F.R. § 404.7 refers to "[a]n identified public health need" or a "license applicant's commercial development ability at the time of application." Rather, they refer to "a reasonable and necessary incentive to call forth the investment capital and expenditures needed to bring the invention to practical application or otherwise promote the invention's utilization by the public[.]"

We interpret the word "necessary" in accordance with its plain meaning. Merriam-Webster defines "necessary" as "absolutely needed" or "required[,]" which is a different analysis from whether there is a public health need and the prospective licensee has the capacity to fulfill that need. A prospective licensee's capacity to commercialize a federally-owned invention certainly is relevant to whether it should be awarded a license. But Section 209 requires consideration of more than the licensee's capacity: it goes to whether there would be a willingness to undertake the investment in bringing a federally-owned invention to market, absent an exclusive license.

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. Mr. Fenn's statements to KEI indicate that the NIH has not undertaken such an analysis.

Scope of the License

In addition to determining whether an exclusive license is necessary, before it may grant the proposed license to Opsis, the NIH must establish "that the proposed scope of exclusivity is not 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 a license may vary along the following parameters:

- Term of exclusivity - how long the licensee may claim a monopoly on the right to market and sell the invention (i.e., five years, ten years, life of patent, etc.);
- Territorial reach (worldwide or limited to the U.S. or a particular geographic region); and
- Field of use (i.e., targeted diseases).

Under Section 209, the scope of the license must be balanced against the incentive necessary to induce a company to commercialize a federally-owned invention. There are at least six factors that should be considered when evaluating the necessary incentive:

1. The costs of financing research and development and bringing the invention to market, including obtaining FDA approval;
2. The government's investment in R&D and the development stage of the technology;

3. Any expected additional subsidies from governments or charities, including, for example, the Orphan Drug Tax Credit or additional grants or continued or new collaborations with the NIH or other government agencies;
4. The existence of other incentives, including, for example, test data protection, Orphan Drug exclusivity and awards of priority review vouchers;
5. The anticipated cost to manufacture the resultant invention; and
6. The expected post-market entry profitability of the invention, by year.

KEI asked Mr. Fenn how NIH determined that the scope of the license was appropriate. He responded: "The scope of exclusive rights is limited and reasonably necessary to bring the invention(s) to practical application or otherwise promote its utilization by the public." Also with regard to scope, KEI asked Mr. Fenn "[w]hat is the duration of the license" and he responded: "not yet determined at this time."

Mr. Fenn's answer was not helpful to KEI in its efforts to comment meaningfully on the proposed license. KEI asked about the scope of rights precisely because we are aware of the relevant legal standard and were interested in learning how NIH applied that standard. Reciting that standard back to KEI did nothing to shed light on whether and how the NIH conducted the required analysis.

Based on previous correspondence between KEI and NIH technology transfer officers, it appears that the NIH's policy, when determining the scope of a proposed license, is to consider only the field of use, and to routinely grant the broadest possible rights in terms of duration of the license and territorial reach.

This would be an erroneous construction of the relevant legal standard. Section 209(a)(2) requires that the analysis regarding the scope of the license is a fact-specific, case-by-case determination. If, in every instance, the NIH negotiates a license for "life-of patent" when a shorter time period would suffice, it is not conducting the analysis required by law.

3. The NIH has not been fully transparent about the license, impeding 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).

In order for the public to meaningfully participate in the notice-and-comment process, it must have basic information about proposed exclusive patent licenses in federally-owned inventions.

We appreciate the fact that Mr. Fenn answered some of our questions regarding the proposed

license to Opsis. We note, however, that he failed to answer the following questions, which were germane to the analysis mandated by Section 209:

- "Please provide a list of other companies that applied to license any of the above-listed inventions"; and
- "Has the NIH sought the antitrust advice of the U.S. Attorney General in relation to the license(s)?"

In addition, Mr. Fenn provided a "non-answer" in response to KEI's question, "[h]ow has the NIH ensured that the license(s) will not tend to substantially lessen competition?" Mr. Fenn responded: "The prospective license application is made in accordance with 35 U.S.C. 209 and 37 CFR part 404." Similarly, Mr. Fenn's answers regarding how NIH analyzed the necessity of exclusivity and the scope of the license, discussed above, were stated in conclusory terms and did not shed light on the NIH's analysis. It is inconceivable why the NIH refuses to explain how it applies the criteria limiting its authority to license a publicly-owned invention, which is a matter of great import to public health outcomes and the nation's fiscal health, especially when the governing statute guarantees the public the right to comment on the license.

By providing conclusory "non answers" and straight out refusing to answer some of KEI's questions regarding the license, the NIH has limited our ability to participate in the notice-and-comment process in a meaningful way, in conflict with 35 U.S.C. 209(e).

4. The NIH apparently has not sought the antitrust advice of the U.S. Attorney General regarding the license, as it is required to do under 40 U.S.C. § 559.

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.

KEI asked Mr. Fenn whether the NIH requested the advice of the U.S. Attorney General concerning the license. He 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."

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 NIH grants a fully-exclusive license to a federally-owned invention for life of patent, and allows termination of the license only in narrow, vaguely-defined circumstances, then it is effectively disposing of a government property interest so as to trigger 40 U.S.C. § 559.

This is a particularly important issue in this instance, where non-exclusive licenses to the patented inventions can and should be available to any firm who wishes to utilize these tools.

5. 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 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 NIH-funded 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. **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."

3. **Global registration and affordability.** The license should require Opsis 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.

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 developing countries, upon a finding by 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 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.”

6. **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 for the reasons stated herein. If the NIH proceeds with the license over our objections, we urge that it incorporate the provisions listed herein that are designed to protect the public’s investment in the subject technologies.

Sincerely,

Knowledge Ecology International