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Via Email: Shmilovm@mail.nih.gov

Re: "Prospective Grant of an Exclusive Patent License: Gene Therapy for Ocular Disease"

Dear Mr. Shmilovich:

Knowledge Ecology International (KEI) is writing to comment on the "Prospective Grant of an Exclusive Patent License: Gene Therapy for Ocular Disease" to OcQuila Therapeutics, Ltd., as described in the Federal Register (FR) notice 84 FR 65169.[1] The license involves an adeno-associated virus (AAV) gene therapy that was tested in nine subjects in a single-site, Phase I/II, NIH-sponsored clinical trial that began in early 2015.

KEI supports the NIH's efforts to secure a commercial partner to develop the technology, which targets a disorder for which no FDA-approved treatment exists.[2] However, the terms of the license must reflect the value of the invention. Given its relatively advanced research and development stage, the regulatory incentives the licensee is likely to receive, the government's investment in the technology, and the price that OcQuila likely will be able to charge for the treatment, the NIH should negotiate a license with terms that are favorable to the public.

Unfortunately, the NIH's statements about the license indicate that it plans to grant exclusive, life-of-patent rights to the invention without accounting for its unique investment value.

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[1] https://www.federalregister.gov/documents/2019/11/26/2019-25685/prospective-grant-of-an-exclusive-patent-license-gene-therapy-for-ocular-disease.
[2] https://www.ott.nih.gov/technology/e-284-2012.

Background

The proposed license covers an NIH invention described in two abstracts: E-284-2012, "Methods And Compositions For Treating Genetically Linked Diseases Of The Eye"[3] and E-164-2018, "Newly Improved Method and Composition for Treating Genetically Linked Diseases of the Eye."[4]

The invention is an AAV gene therapy, AAV8-scRS/IRBPhRS (hereinafter, "AAV-RS1"), which may offer a cure for x-linked juvenile retinoschisis (XLRS), a genetic disease that leads to juvenile macular degeneration and affects 1:15,000 males in the United States.[5]

The second abstract, E-164-2018, describes the use of an electric current to improve the efficacy of AAV-RS1. It characterizes the invention as a "[p]otentially curative therapy for XLRS, retinoschisis, age-related macular degeneration, diabetic retinopathy, Leber congenital amaurosis, retinal detachment, cysts, cystoid, macular edema, retinitis pigmentosa, and senile schisis."[6]

According to the Notice, the prospective licensee, OcQuila Therapeutics, is incorporated in Delaware and the UK.

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 conditions:

> (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[.]"

[3] https://www.ott.nih.gov/technology/e-284-2012.
[4] https://www.ott.nih.gov/technology/e-164-2018.
[5] https://www.ott.nih.gov/technology/e-284-2012.
[6] https://www.ott.nih.gov/technology/e-164-2018.

35 U.S.C. § 209(a)(1)-(2).

As explained below, KEI is concerned that the license does not satisfy these criteria. Rather than engaging in a fact-specific inquiry to determine the necessary incentive, the NIH appears to have assumed that an exclusive license for life of patent is appropriate because the subject invention is an "early-stage" gene therapy.

(a) Determining the necessary incentive requires a fact-specific analysis of the factors that influence a biomedical invention's commercial potential.

Determining the incentive necessary for bringing a federally-owned 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**[.]"[7]

The factors that influence pharmaceutical investment decisions 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 detailed discussion of how some of the relevant factors bear on the subject invention's commercial value.

Research and Development Stage

As the NIH concedes, to determine the value of a patent license, the NIH must consider "the state of development" of the subject invention.[11]

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[7] Attachment A (emphasis added).
[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.
[11] Attachment A.

Development of new drugs and cell or gene therapies consist of four main stages -- discovery, preclinical testing, clinical trials involving human subjects, and the regulatory review by the FDA and other government regulators.[12] An invention's risk of failure varies widely based on its development stage.

AAV-RS1 has advanced to the third of the four development stages - clinical testing involving human subjects. It is being investigated in a single-site, Phase I/IIa clinical trial (NCT02317887) that started in February of 2015, after the NIH submitted, and the FDA approved, an IND application showing positive results from preclinical studies in rabbits[13] and mice.[14] Preliminary results from the human subject clinical trial indicate that the therapy is generally well tolerated.[15]

In assessing the terms and need for exclusivity in this license, the NIH has not accurately accounted for the invention's development stage.

KEI asked Mr. Shmilovich, the point of contact for the license, how the NIH is "negotiating this license in a way that reflects th[e] commercial potential of [AAV-RS1]."[16]

He responded:

> The present invention is early stage . . . . The question has also been previously answered in Dr. Rohrbaugh's November 26, 2019 letter (enclosed), and the answer in that letter applies to the current case as well.[17]

There are two problems with this answer.

First, it mischaracterizes the invention's development stage. According to some widely quoted estimates, drug development takes, on average, fifteen years from start to finish,

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[12] U.S. Gov't Accountability Office, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts* (2006), https://www.gao.gov/assets/260/253726.pdf.
[13] Marangoni, Dario et al., *Preclinical safety evaluation of a recombinant AAV8 vector for X-linked retinoschisis after intravitreal administration in rabbits*, Human gene therapy. Clinical development vol. 25,4 (2014): 202-11. doi:10.1089/humc.2014.067.
[14] Bush, Ronald A et al., *Preclinical Dose-Escalation Study of Intravitreal AAV-RS1 Gene Therapy in a Mouse Model of X-linked Retinoschisis: Dose-Dependent Expression and Improved Retinal Structure and Function,* Human gene therapy vol. 27,5 (2016): 376-89. doi:10.1089/hum.2015.142.
[15] Catherine Cukra et al., *Retinal AAV8-RS1 Gene Therapy for X-Linked Retinoschisis: Initial Findings from a Phase I/IIa Trial by Intravitreal Delivery*, https://doi.org/10.1016/j.ymthe.2018.05.025.
[16] Attachment A.
[17] *Id*.

with basic discovery and preclinical testing lasting six and one half years, clinical trials taking seven years, and FDA approval lasting one and a half years.[18]

While there are fewer estimates of the time periods associated with the development of gene therapies, the estimates for drug development are at least a useful proxy for evaluating the assertion that a technology is at an "early stage."

AAV-RS1 began clinical research involving human subjects -- the third of the four development stages -- five years ago.

There is evidence that FDA approval periods for a gene therapy may be shorter than approval periods for drugs.

The BLA for Luxturna, a gene therapy for blindness, was filed on May 16, 2017, and the FDA approval was given on December 19, 2017, just seven months later. The BLA for Zolgensma, a gene therapy for spinal muscular atrophy, was filed October 1, 2018, and FDA approval was granted on May 24, 2019, less than eight months later.

It is also useful to note that Novartis spend $8.7 billion to acquire AveXis, which was the owner of Zolgensma, on April 9, 2018, nearly six months before the Zolgensma BLA was even filed.

We do not consider it reasonable to describe a gene therapy in clinical trials as "early stage," although that may describe other indications including "schisis cavity associated ocular disease or injury" which is among the fields of use in the license.

The November 26 letter pertains to two other licenses/inventions, which were in the discovery and preclinical stages of development at the time of notice and comment, and thus, were not comparable to a technology in clinical testing involving human subjects.

The November 26 letter is the NIH's response to two appeals to exclusive patent licenses. The first license pertained to a CAR T-cell therapy whose development stage was described as "**Discovery (Lead Identification)**" by the NIH in the relevant abstract.[19] The second involved a gene therapy that was described as "preclinical" by the NIH Office of Technology Transfer (OTT) officer designated to answer questions about the license.

It is inconsistent with the Bayh-Dole Act requirement "that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing

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[18] U.S. Gov't Accountability Office, *New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts* (2006), https://www.gao.gov/assets/260/253726.pdf.

[19] https://www.ott.nih.gov/technology/e-205-2018 (emphasis added).

the invention to practical application" for the NIH to lump an invention that has performed successfully in a clinical trial into the same category as technologies that are still in the discovery or preclinical stages of development, and to treat those inventions the same when determining the necessary incentive and negotiating license terms.

The table below demonstrates how the NIH negotiates the same patent terms for inventions that vary in terms of development phase.

Table 1 - Cell or Gene Therapy NIH Patent License Comparison

Proposed License(s)	Allogeneic Therapy Using Bicistronic Chimeric Antigen Receptors Targeting CD19 and CD20 (84 FR 33270) and Autologus Therapy Using Bicistronic Chimeric Antigen Receptors Targeting CD19 and CD20 (84 FR 33272).	Genetically-Modified Lymphocytes for Cancer Therapy (84 FR 45503)	Gene Therapy for Ocular Disease (84 FR 65169)
Licensee	Kite Pharma	Intima Bioscience	OcQuila Therapeutics
Development stage, at time of notice and comment	**Discovery (lead identification)**	**Preclinical**	**Phase I/II clinical trial started in February of 2015.**
License terms	Exclusive, life of patent, worldwide[20]	Exclusive, life of patent, worldwide	Exclusive, life of patent, worldwide

Regulatory Incentives

Another factor relevant to an invention's commercial value is the availability of regulatory incentives that provide additional market exclusivities, expedited FDA review, and valuable financial benefits.

As the NIH has noted, XLRS is an orphan disease and thus will receive Orphan Drug designation, a regulatory incentive that confers seven years' Orphan Drug market exclusivity and a twenty-five percent credit toward R&D costs,[21] as well as other benefits such as 12 years of exclusive rights in regulatory test data.

[20] Although the NIH would not confirm the terms of these patent licenses, based on Dr. Rohrbaugh's statements that the NIH typically negotiates licenses for life of patent, and that no pharmaceutical company would invest in developing a gene therapy without full exclusivity for life of patent, it can safely be inferred that these licenses in cell and gene therapies were exclusive, with worldwide rights, for life of patent.

[21] 26 U.S.C. § 45C.

In addition, therapeutics such as AAV-RS1 that treat rare diseases or satisfy an unmet medical need qualify for expedited review programs such the FDA's fast-track,[22] breakthrough therapy,[23] accelerated approval,[24] and priority review designation,[25] reducing the time and thus expense of further drug development and increasing the time that the sponsor may claim exclusive marketing rights in the invention.[26] Finally, because XLRS is a serious,[27] rare disorder that occurs in children, the invention's sponsor likely will receive a priority review voucher, a financial incentive likely worth roughly $100 million, based upon recent sales of PRVs.[28]

Depending on the costs of any necessary further drug development, these incentives may enable the NIH to secure a qualified commercial partner without granting exclusive, worldwide rights for life of patent in the invention.

Government Investment in the Technology

Dr. Rohrbaugh has characterized the NIH as being "like any other licensor of technology,"[29] when it grants exclusive patent licenses but that is not an accurate statement.

Unlike private-sector licensors, the NIH allocates millions of taxpayers' dollars toward the research and development costs of the inventions it seeks to license. The NIH does not appear to maximize its income from the licensing of NIH or NIH funded technologies. Indeed, according to the NIH technology transfer office, the total annual revenues from patent licenses in fiscal year 2018[30] were less than $111 million. This can be compared to the $176 million AveXis paid in 2018 for use of the patents on Zolgensma, a single gene therapy, before Zogensma was approved by the FDA.

The government's investment in a technology is a key factor that bears on the appropriate terms of its patent licenses, as recognized by 35 U.S.C. § 209(a).

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[22] 21 U.S.C. § 356(b).
[23] 21 U.S.C. § 356(a).
[24] 21 U.S.C. § 356(c).
[25] 21 U.S.C. § 360ff.
[26] Food & Drug Admin., *For Industry, Developing Products for Rare Diseases & Conditions*, https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditi/default.htm [https://perma.cc/NX5L-CJQW].
[27] According to the OTT, "XLRS causes progressive vision loss, and affected individuals are unable to perform simple daily activities such as reading, writing and driving. This condition can lead to vitreous hemorrhage and retinal detachment in up to 40% of patients – resulting in total blindness." https://www.ott.nih.gov/technology/e-164-2018.
[28] The average sale price for priority review vouchers approved thus far (for which information is publicly available) is *at least* $144 million. Table 2, Oulu Wang, *Buying and Selling Prioritized Regulatory Review: The Market for Priority Review Vouchers As Quasi-Intellectual Property*, 73 Food & Drug L.J. 383 (2018); Selina McKee, *GW Sells Priority Review Voucher for $105m*, Pharma Times, March 18, 2019. http://www.pharmatimes.com/news/gw_sells_priority_review_voucher_for_$105m_1281953
[29] Attachment B.
[30] https://www.ott.nih.gov/reportsstats/ott-statistics

The NIH has directed millions of dollars toward developing AAV-RS1.

At least two intramural research grants supported the invention. An article describing NCT02317887, titled "Retinal AAV8-RS1 Gene Therapy for X-Linked Retinoschisis: Initial Findings from a Phase I/IIa Trial by Intravitreal Delivery," states that "[t]he Phase I/IIa trial and clinical assays" were supported by Project No. 1ZIADC000065,[31] an NIH grant titled "Preclinical and Clinical Development of Treatment for X-Linked Retinoschisis." According to RePORTER, 1ZIADC000065 has cost nearly $7 million to date.

The second intramural research grant associated with the invention, Project No. 1ZIADC000077, is titled "Pathophysiology and Treatment of Retinal Degenerations in Animal Models." The Principal Investigator for the project is Paul Sieving, former director of the NEI and one of the inventors of AAV-RS1.[32] The abstract for the project describes preclinical testing of various methods of delivery of an AAV gene therapy to treat XLRS. The "Results" tab for the project lists some of the same scientific articles that the NIH has attributed to the licensed inventions. Funding to date has totalled over $3.2 million.

Additional R&D Required to Bring Invention to Market

The next factor relevant to the "necessary incentive" is the likely cost of any additional research and development required to bring a technology to practical application. This, too, varies from invention to invention.

Dr. Rohrbaugh's November 26, 2019 letter states that full exclusivity is justified for "early-stage therapeutics" because their clinical trials cost hundreds of millions of dollars. KEI disputes this estimate, especially when it comes to cell and gene therapies, but even if it were correct, NIH patent licenses required individualized consideration. Clinical trial costs vary by size of the patient population, number of sites, disease indication, investigational product, and a variety of other factors.[33] The small patient enrollment of NCT02317887 -- a single-site trial consisting of 9 enrolled subjects -- indicates that additional clinical research costs for AAV-RS1 could be relatively low. By way of contrast, PhRMA, in describing the costs of research and development needed to bring a new drug to market, claimed that Phase I trials may involve up to 100 patients, Phase II

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[31] Catherine Cukra et al., *Retinal AAV8-RS1 Gene Therapy for X-Linked Retinoschisis: Initial Findings from a Phase I/IIa Trial by Intravitreal Delivery*, https://doi.org/10.1016/j.ymthe.2018.05.025.

[32] 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=sieving.INNM.&OS=IN/sieving&RS=IN/sieving.

[33] 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.

trials average 100 to 500 patients, and Phase III trials "may enroll 1,000 to 5,000 patients or more across numerous clinical trial sites around the world."[34]

Luxturna (voretigene neparvovec-rzyl), another vector-based gene therapy to treat an inherited eye disorder, provides a helpful reference point for estimating the enrollment size of any further clinical studies necessary to gain FDA approval of AAV-RS1. Luxturna was approved on the basis of a Phase I trial and Phase III trial, consisting of 12 and 31 subjects, respectively.[35]

Any trials needed to secure regulatory approval of AAV-RS1 are highly unlikely to require enrolling hundreds or thousands of patients to obtain FDA approval, and such trials are also highly unlikely to cost "hundreds of millions of dollars" - an assumption upon which Dr. Rohrbaugh bases his licensing decisions for gene therapies such as the instant invention.

Potential Revenues

The license is an attractive investment because of the high prices that the licensee likely will be able to charge for the resultant product. AAV-RS1, if successful, will be the first therapy to treat XLRS, meaning that it will face no competition in that disease indication. Further, because AAV-RS1 treats a potentially debilitating condition, patients will tolerate higher prices. Finally, Luxturna's price of $425,000 per eye sets the stage for how similar gene therapies will be priced. AAV-RS1 may have an advantage over Luxturna in arguing for high reimbursements because it is administered intravitreally - a much less invasive method of administration to that of Luxturna, which is delivered subretinally.[36] It is safe to say that if it makes it to market (particularly under the current expected exclusive licensing terms), and if the NIH refuses to curb excessive prices, AAV-RS1 likely will command very high prices.

Other Factors

In addition to the factors discussed above, the License Opportunity notices for the invention list the following advantages:

- The use of a low-seroprevalence, non-pathogenic AAV8 vector favors efficacy in a high percentage of the patient population;
- The use of a tissue specific promoter limits non-specific gene expression;

[34] http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.
[35] https://www.fda.gov/media/110141/download.
[36] Joan W. Miller et al., *Breaking and Sealing Barriers in Retinal Gene Therapy*, Molecular Therapy Vol. 26 No 9, https://doi.org/10.1016/j.ymthe.2018.08.003.

- Demonstrated GMP manufacturing process;[37] and
- Elicits a minimal immune response since humans have a high preexisting immunity to AAV2.

(b) The NIH's analysis of the proposed license does not satisfy 35 U.S.C. § 209(a)(1)-(2) because the NIH has not engaged in a fact-specific consideration of the factors relevant to the invention's investment value.

The NIH's statements about this license indicate that it has not performed the analysis mandated by Section 209 because it has not accounted for the factors that bear on the invention's commercial value.

KEI asked Mr. Shmilovich, the point of contact for the license, whether the NIH had conducted an economic analysis of what would be required to bring AAV-RS1 to practical application. He responded: "This is not required for a grant of an exclusive license."[38]

Mr. Shmilovich's answer begged the question: If an economic analysis is not required for a grant of an exclusive license, then what analysis does 35 U.S.C. § 209(a)(1) require?

In a follow-up email, KEI asked what analysis, if any, the NIH had undertaken before deciding to license the invention on an exclusive basis. Mr. Shmilovich answered: "XLRS is a rare disease and information about its incidence is readily available."[39] By citing the disease's prevalence, Mr. Shmilovich implied that an exclusive license is necessary in this instance because the invention's small patient population makes it a less desirable investment.

As KEI has explained, however, the invention's indication in a rare pediatric disease also makes it eligible for valuable regulatory incentives, and there is plenty of readily available evidence that treatments for rare diseases also charge extraordinarily high prices, and can generate significant revenues. For example, consider this report on the $3.4 billion in 2018 sales for Soliris:

> Alexion Pharmaceuticals ($ALXN) may not have a huge market for Soliris, but it does have a recipe for success: an essential treatment for a frightening rare disease and a very, very hefty price tag.
>
> Soliris was originally developed as a treatment for the life-threatening blood disorder paroxysmal nocturnal hemoglobinuria, a disease that only affects about 8,000 Americans. But at up to $400,000 per year, Soliris--recognized as the world's most expensive drug--doesn't have to reach many patients to hit the blockbuster threshold.[40]

[37] Companies must adhere to the FDA's good manufacturing practices (GMP) regulations. http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.
[38] Attachment A.
[39] *Id.*
[40] https://www.fiercepharma.com/special-report/soliris.

Mr. Shmilovich's statement also ignores the fact that the license has commercial applications in other disorders, some with much larger patient populations, such as age-related macular degeneration (affecting 30 million people worldwide), diabetic retinopathy (more than three million cases per year in the United States), Leber congenital amaurosis, retinal detachment, cysts, cystoid, macular edema, retinitis pigmentosa, and senile schisis,[41] making the potential market size much larger.

In a follow-up email, KEI asked Mr. Shmilovich if the NIH had considered any factors other than the prevalence of XLRS when concluding that an exclusive license was justified, and why he had not acknowledged the invention's other potential commercial applications. In an email apparently not intended for KEI, Dr. Rohrbaugh advised Mr. Shmilovich not to respond, and he never did.[42]

If the NIH's analysis started and ended with the fact that the invention treats an orphan disease, it does not satisfy Section 209.

Based on past statements of Dr. Rohrbaugh, the only other fact the NIH appears to have considered with respect to the prospective license is that it involves a gene therapy. This, too, would be insufficient to satisfy the Bayh-Dole Act.

The following statements from Dr. Rohrbaugh's November, 26, 2019 letter indicate that, as a general matter, the NIH automatically assumes that exclusive, life of patent licenses are always required for gene therapies:

- "[NIH] works in a market for these early-stage therapeutic technologies in which there is essentially no demand for nonexclusive licenses."[43]
- "[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."[44]

In failing to assess the commercial potential of the covered inventions on an individualized basis, the NIH has not satisfied Section 209(a)(1)-(2) of the Bayh-Dole Act for the instant license.

2. The NIH 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.

[41] https://www.ott.nih.gov/technology/e-164-2018.
[42] Attachment C.
[43] Attachment B (emphasis added).
[44] *Id.*

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. Shmilovich whether the NIH requested the advice of the U.S. Attorney General concerning the license. He responded "not required." 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.

3. 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 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. **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 OcQuila 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 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 support the NIH's efforts to license AAV-RS1 to a commercial partner who appears to be qualified to bring it to practical application.

Commercializing a truly innovative therapy that satisfies an unmet medical need is certainly a positive. It is far less positive if all U.S. taxpayers funded a substantial portion of the expense of developing the invention, and only a narrow segment of society likely will be able to afford it without facing financial hardship.

This outcome may be avoidable if the NIH does its job, and exercises the significant leverage it has to at least make reasonable efforts to negotiate favorable licensing terms, such as a co-exclusive license or shorter period of exclusivity. Such a course of action is not merely desirable, it is required.

Federal law dictates that before granting this license on an exclusive basis, the NIH must conduct the analysis required by 35 U.S.C. § 209(a)(1)-(2) and conclude that no qualified firm would develop the inventions without a fully-exclusive license for life of patent.

We believe this is unlikely. Far from being a gleam in the eye of an NIH scientist, AAV-RS1 has successfully completed the riskiest phases of drug development and part of a Phase I/II clinical trial, and that legwork was funded by the public. The license that the NIH negotiates must reflect the inventions' commercial value.

Sincerely,

Knowledge Ecology International