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Re: Prospective Grant of Exclusive License: AAV-Mediated Aquaporin Gene Transfer To Treat Sjögren's Syndrome

Dear Dr. Hu,

Knowledge Ecology International (KEI) is responding to the Notice published in the Federal Register on April 29, 2016, entitled "Prospective Grant of Exclusive License: AAV-Mediated Aquaporin Gene Transfer To Treat Sjögren's Syndrome" (81 FR 25683), available at: <https://federalregister.gov/a/2016-09978>.

The National Institutes of Health is considering the grant of a worldwide exclusive license for United States government-owned patents relating to "AAV-mediated aquaporin gene transfer to treat Sjögren's syndrome" to MeiraGTx, comprising the following intellectual property:

- U.S. Provisional Patent Application No. 61/695,753;
- PCT Application No. PCT/US2013/057632;
- Australia Patent Application No. 2013308470;
- Canada Patent Application No. 2882763;
- European Patent Application No. 13773443.0; and
- U.S. Patent Application No. 14/423,774.

According to the Federal Register notice, the field of use may include "adeno-associated virus (AAV) vector mediated gene delivery of human aquaporin-1 (hAQP1) in Sjögren's syndrome patients with associated xerostomia and/or xerophthalmia."

KEI opposes the grant of exclusive license in this case unless:

1. The NIH conducts sufficient analysis and limits the terms and scope of the license as required under 37 CFR 404.7 (a)(1)(iiii);
2. The license contains sufficient safeguards regarding affordability and reasonable pricing of the products developed under the patent licenses;
3. The license places restrictions on charging US residents higher prices than the median prices charged in countries with the seven largest GDP and per capita incomes of 50 percent or more than the United States per capita income;
4. The license requires products are affordable in developing countries, and explicitly allows the NIH to grant licenses to the patents to the Medicines Patent Pool (MPP) for use in developing countries; and
5. The license requires transparent reporting on drug development costs, royalties and revenues.

About the commenters

Knowledge Ecology International (KEI) is a nongovernmental organization based in Washington, DC, with an office in Geneva, Switzerland, that advocates for access to affordable medicines, with a focus on human rights and social justice. For more information, see: <http://keionline.org>.

Why the may AAV mediated gene transfer of aquaporin-1 be important

Sjögren's syndrome is a chronic autoimmune disease where endocrine glands, such as those secreting tears or saliva, are destroyed primarily by the individual's T lymphocytes. This disease affects one to four million Americans and 35 million people worldwide.^{1,2} Salivary gland damage can also affect those undergoing radiation therapy — such as cancer patients — and those individuals can benefit from treatments developed for Sjögren's syndrome.

People living with Sjögren's syndrome typically present with dry eyes and mouth, but the syndrome can also affect other mucous membranes. Unfortunately, as there is no treatment for this syndrome, the current standard therapy is restricted to symptom management.

In 1997, the NIH found that gene transfer of Aquaporin-1 increased salivary secretion in mice with irradiated damaged glands.³ Aquaporin-1 gene therapy was first used in patients who suffered from salivary hypofunction caused by radiation therapy.⁴

¹ <http://www.ninds.nih.gov/disorders/sjogrens/sjogrens.htm>

² Z. Lai *et al.* Aquaporin gene therapy corrects Sjögren's syndrome phenotype in mice. *Proc Natl Acad Sci U S A.* 2016 May 2.

³ C. Delporte *et al.* Increased fluid secretion after adenoviral-mediated transfer of the aquaporin-1 cDNA to irradiated rat salivary glands. *Proc Natl Acad Sci U S A.* 1997 Apr 1;94(7):3268-73.

⁴ B. Baum. Development of a gene transfer-based treatment for radiation-induced salivary hypofunction. *Oral Oncol.* 2010 Jan;46(1):4-8

Most methods of gene delivery to salivary glands, including liposomal transfection and other viral transduction methods, are highly inefficient and can induce local inflammation.⁵ In contrast, AAV transduction have been found to be superior to other methods and sustain gene expression while avoiding an inflammatory response.

Success of an AAV based gene therapy would mean treatment for a condition that is currently incurable.

The role of the NIH in the development of the AAV mediated gene transfer of aquaporin-1

Dr. John Chiorini, a senior investigator at the National Institute of Dental and Craniofacial Research (NIDCR) and inventor of the technology for the license currently under consideration, has worked on Adeno-Associated Virus vectors since 1994. Since 2007 his lab has received NIH funding totaling \$17,686,279 for a research project entitled “Adeno-Associated Virus and utilization for Gene Transfer” (NIH Project # 1ZIADE000695, 8-16). This project produced approximately 92 peer reviewed publications, and 5 patents (see table below).

Patent Number	Patent Title
8927269	Avian adeno associated virus and uses thereof
8137960	Bovine adeno-associated viral (BAAV) vector and uses thereof
8685722	Bovine adeno-associated viral (BAAV) vector and uses thereof
8808684	Epidermal growth factor receptor (EGFR) and methods of use in adenoviral-associated virus type 6 (AAV6) transduction
8283151	Isolation, cloning and characterization of new adeno-associated virus (AAV) serotypes

Currently, Dr. Chiorini is the senior investigator in an upcoming phase 1/2 clinical trial entitled “Safety of a Single Administration of AAV2hAQP1, an Adeno-Associated Viral Vector Encoding Human Aquaporin-1 to One Parotid Salivary Gland in People With Irradiation-Induced Parotid Salivary Hypofunction” (NCT02446249), sponsored by the NIDCR. A primary objective is to assess the safety of AAV2hAQP1 gene therapy in humans.

Dr. Ilias G Alevizos, also an NIDCR investigator, conducted an earlier phase 1/2 clinical trial to study the “Effect of AdhAQP1 on Salivary Flow in Patients Treated With Radiation for

⁵ R. Zufferey, P. Aebischer. Salivary glands and gene therapy: the mouth waters. Gene Ther. 2004 Oct;11(19):1425-6.

Head and Neck Cancer” (NCT00372320). This was the first time the aquaporin-1 gene was delivered to humans using adenoviral vectors.

Both clinical trials investigate the use of AAV vectors to deliver the hAQP1 gene in Humans.

Gene therapy is still highly experimental, so determining the right delivery mechanisms is key in moving this technology forward. Of the many gene therapy strategies funded by the NIH, it has brought the application of AAV in salivary gland dysfunction to Phase 1 clinical trials. Considering the investment and the risk taken on by the NIH to develop this technology, it is important to include reasonable pricing assurances in any licenses that may be granted on this technology.

Why patent license terms are important

We are concerned that the NIH exclusive licensing of patent rights of AAV mediated gene transfer of aquaporin-1 to MeiraGTx will result in:

1. MeiraGTx would require U.S. residents to pay more than other countries for a AAV mediated gene transfer of aquaporin-1 developed at public expense (see <http://keionline.org/xtandi> for a petition to the NIH relating to a prostate cancer drug invented at UCLA on federal grants and priced far higher in the United States than in any other country);
2. Delays in the entry of competitive suppliers for the manufacturing and distribution of the MeiraGTx that will increase affordability and reduce supply shortages; and
3. Barriers to innovation, including enhancements that make the therapy more effective in low resource settings.

Federal regulations on the use of exclusive licenses

As noted in the Federal Register notice, the licenses are expected to comply with the public safeguards found in 35 U.S.C. § 209 and 37 CFR part 404.

Specifically, we are concerned about the obligations in 35 U.S.C. § 209(a)

§209. Licensing federally owned inventions

(a) Authority.—A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if—

(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;

(2) the Federal agency finds that the public will be served by the granting of the license, as indicated by the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public;

(3) the applicant makes a commitment to achieve practical application of the invention within a reasonable time, which time may be extended by the agency upon the applicant's request and the applicant's demonstration that the refusal of such extension would be unreasonable;

(4) granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws; and

(5) in the case of an invention covered by a foreign patent application or patent, the interests of the Federal Government or United States industry in foreign commerce will be enhanced.

We also note that the term "practical application" is defined by 35 U.S.C. 201(f) as follows:

(f) The term "practical application" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms. [emphasis added]

Under 37 CFR 404.7(a), the NIH is required to make determinations regarding the necessity of the grant of an exclusive license:

(1) Exclusive, co-exclusive or partially exclusive domestic licenses may be granted on Government owned inventions, only if

...

(ii) After expiration of the period in § 404.7(a)(1)(i) and consideration of any written objections received during the period, the Federal agency has determined that;

(A) The public will be served by the granting of the license, in view of the applicant's intentions, plans and ability to

bring the invention to the point of practical application or otherwise promote the invention's utilization by the public.

(B) Exclusive, co-exclusive or partially exclusive licensing is 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; and

(C) The proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public[.]

We ask the NIH to provide additional assurances that the products developed under this license be made available to the public at prices that are reasonable and affordable. Among other things, this can include a provision in the license that states:

The NIH will normally expect the licensee to make products available to the public in the United States at prices no higher than the median price charged in the seven countries with the largest GDP, that have per capita incomes of at least half that of the United States.

If the geographic area includes worldwide rights, the products should be made available at affordable prices in developing countries.

However, as far as we know, the NIH has not demonstrated why granting an exclusive license to the company is necessary. We request that the NIH or NIDCR provide public evidence that the NIH has determined an an exclusive license is necessary for the development of the patented inventions, and there exists a written analysis which establishes that this evaluation has been done. Calling for public comment on the license, and then providing almost none of the relevant information, makes the public comment process ineffective, as regards the public's role in objecting to licenses that undermine their rights to obtain access to the benefits of the inventions on favorable terms, or in addressing other public interest issues.

The NIH should also have the option of providing a non-exclusive license to the Medicines Patent Pool (MPP) to permit competitive supply by generic drug manufacturers, for use in developing countries. Here we note that GSK has recently announced it has begun negotiations with the MPP to license the patents for its oncology products. Certainly the NIH can be at least as sensitive to the health needs of patients living in developing countries as is the big pharma company GSK.

Since the statute requires that the "scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application" we

request a copy of any analysis, if any, that was done to consider how many years of exclusive rights were necessary to bring the invention to practical application. We also propose the following terms for the contract:

The exclusive rights will extend to five years from the first sale of a product receiving approval by the U.S. FDA, or until the license holder recovers at least \$1 billion in global sales from the product, whichever is shorter, and thereafter, the license will become non-exclusive. After the first five years of exclusivity, the NIH can extend the exclusivity by another 3 years, upon a showing that such extension is reasonable in light on the risk adjusted R&D costs to bring the product market, and the net revenues from sales.

KEI notes that the 5 year period, with possible extensions, follows NIH practice, prior to 1984, and other NIH licenses have had terms shorter than the life of patent. For example, in October 2001, the NIH exercised an option to make the licenses for the AIDS drug DDI non-exclusive, ten years after the initial FDA registration (see: Videx® Expanding Possibilities: A Case Study, NIH, National Institutes of Health Office of Technology Transfer, September 2003) in order to expand access to the drug, and to obtain lower cost supplies for federal programs.

The NIH could consider different time periods for exclusivity, but if the answer is always life of patent, no matter what the facts are, then the NIH is no longer meeting the requirements of 35 U.S.C. § 209 to ensure that the “scope of exclusivity is not greater than reasonably necessary.”

Transparency

KEI is also asking for more transparency regarding the costs of developing new products, and the pricing, sales and royalty payments on products.

We object to any license that is not made public. Moreover, all reports specified in the license, including those described in the license appendices, should be public. If the NIH insists on transparency (as was common practice and acceptable in earlier years), [Company] would agree. The company is getting the license before making any significant investments, and the NIH's invention may be worth several billion dollars.

We ask the NIH to create a requirement for annual reports on R&D outlays, including an obligation that the company reports the following for each clinical trial that tests products covered by the patents:

1. ClinicalTrials.Gov identifier
2. Phase
3. Conditions
4. Interventions
5. Title Acronym/Titles

6. Outcome Measures
7. Sponsor/Collaborators
8. Other Study IDs
9. Expenditure (for that year)

With regard to sales prices, we request an annual report that provide data on the following variables:

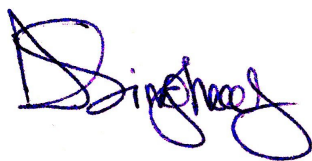
1. Units of sales, by country
2. Revenue for sales, by country

With regard to government subsidies for research, we request a report that provides data for the following, by year:

1. Grants and research contracts from government agencies, with data on the funding agency, the identifier of the grant or contract, and the amount of the grant or contract;
2. Tax credits associated with R&D for the product, including the U.S. orphan drug tax credit, broken out by the type of credit and the expenditure the credit was associated with (such as a specific trial); and
3. Other government R&D subsidies.

We hope the NIH will seriously consider these comments, and use its authority to advance affordable access to medical technologies that will benefit the overall health of the American public and society at large.

Respectfully submitted,



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