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September 9, 2019

Michelle Bulls
Director
Office of Policy for Extramural
Research Administration (OPERA)
National Institutes of Health
Via Email: michelle.bulls@nih.gov

Re: Apparent Failure to Disclose Government Funding Associated with Two Patents in "Enhanced AAV-Mediated Gene Transfer for Retinal Therapies," Invented by Jean Bennett and Others and Assigned to the University of Pennsylvania

Dear Ms. Bulls:

Knowledge Ecology International (KEI) requests that the National Institutes of Health (NIH) investigate the apparent failure to disclose federal support of two patents in adeno-associated viral (AAV) gene therapies, in violation of the Bayh-Dole Act, 35 U.S.C. §§ 200 *et seq.*

The patents, both titled "Enhanced AAV-mediated gene transfer for retinal therapies," are U.S. Patent Nos. 9,567,376 (the "'376 patent") and 10,266,845 (the "'845 patent"). The inventors listed on the patents are Jean Bennett, Therese Cronin, and Luk Vandenberghe. Both patents were assigned to the Trustees of the University of Pennsylvania.

Evidence suggests that the inventions benefited from grants from the NIH. Specifically, in the paper "Efficient transduction and optogenetic stimulation of retinal bipolar cells by a synthetic adeno-associated virus capsid and promoter,"[1] there is strong evidence that NIH funding is related to both the '367 and the '845 patents.

Among other similarities to the patents, the paper:

- was authored by Bennett, Cronin and Vandenberghe (the inventors on the patents);

[1] EMBO Mol Med. 2014 Sep; 6(9): 1175–1190, Published online 2014 Aug 4, Bennett, Cronin, Vandenberghe and nine co-authors, doi: 10.15252/emmm.201404077.

- describes an AAV vector to treat blindness involving the same amino acid sequence as the inventions described in the patents; and
- lists, as a conflict of interest, that Bennett, Cronin and Vandenberghe "are co-authors on a U.S. patent application for 'Enhanced AAV mediated gene transfer for retinal therapies,'" the exact same title as the '376 and '845 patents.

The paper discloses two NIH grants, "NEI/NIH 8DP1 EY023177," and "1R24EY019861-01A1," including one grant, EY023177, for which Jean Bennett was the principal investigator, at or around the time that the subject inventions were likely discovered.

While the paper discloses two NIH grants, the patents contain no statement of government support, which is required for any invention developed pursuant to a federal funding agreement.

When federal grants support a new technology, the grant recipient must make certain disclosures to the funding agency. These disclosures alert the government to the rights that it retains in federally-sponsored inventions, including a "nonexclusive, nontransferrable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any subject invention throughout the world," 35 U.S.C. § 202(c)(4), and the right to "march-in" and compel additional licensing of an invention when, among other reasons, the contractor, assignee or licensee has not taken steps to achieve practical application, 35 U.S.C. § 203(a).

Failure to comply with the Bayh-Dole Act's reporting requirements undermines one of the stated policy objectives of the legislation: "to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions." 35 U.S.C. § 200. If an agency is not aware of inventions it has supported, it cannot ensure that the objectives of the Act is being met.[2]

We respectfully urge the NIH to investigate the apparent non-disclosures and take appropriate remedial action, including asserting the government's rights in the patented inventions.

The Law

The Bayh-Dole Act and federal regulations and guidelines make clear several obligations for contractors in the disclosure of government rights in subject inventions, including: (1) a requirement to disclose that federal funding contributed to an invention; (2) NIH contractual requirements for disclosure; and (3) required language to be inserted in patent applications and patents, stating the role of federal funding and the government's rights.

[2] Department of Health and Human Services Office of Inspector General, *Underreporting Federal Involvement in New Technologies Developed at the Scripps Research Institute* (June 15, 1994).

Under 35 U.S.C. § 202(c)(1), any contractor that receives funding from the federal government is required to "disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters."

Under 37 C.F.R. § 401.3(a), each federal funding agreement shall contain the "standard patent rights clause" found at 37 C.F.R. § 401.14, barring specific circumstances and exceptions. Subsection (c)(1) of the patent rights clause outlines the disclosure requirements.

37 C.F.R. § 401.14(c)(1)

(c) Invention Disclosure, Election of Title and Filing of Patent Application by Contractor

(1) The contractor will disclose each subject invention to the Federal Agency within two months after the inventor discloses it in writing to contractor personnel responsible for patent matters. The disclosure to the agency shall be in the form of a written report and shall identify the contract under which the invention was made and the inventor(s). It shall be sufficiently complete in technical detail to convey a clear understanding to the extent known at the time of the disclosure, of the nature, purpose, operation, and the physical, chemical, biological or electrical characteristics of the invention. The disclosure shall also identify any publication, on sale or public use of the invention and whether a manuscript describing the invention has been submitted for publication and, if so, whether it has been accepted for publication at the time of disclosure. In addition, after disclosure to the agency, the Contractor will promptly notify the agency of the acceptance of any manuscript describing the invention for publication or of any on sale or public use planned by the contractor.

According to 37 C.F.R. § 401.14(f)(4) and NIH Guidelines for Grants and Contracts, grant recipients must include the following language in their patent applications and patents:

> "This invention was made with Government support under (grant/contract number) awarded by the (Federal agency). The Government has certain rights in the invention."

Finally, under 35 U.S.C. § 202(c)(6) and 37 C.F.R. § 1.77(b)(3), contractors are required to state within the patent application or patent that the federal government contributed funding to support the discovery of the invention and that the government retains certain rights.

35 U.S.C. § 202(c)(6)

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.

The Patents

The inventions described in the patents are "capsid proteins and adeno-associated viruses capable of targeting various types of ocular cells including bipolar and horizontal cells[,]" as well as their methods of administration to treat ocular disorders. The patents claim "[a] method of preventing, arresting progression of, or ameliorating vision loss associated with an ocular disorder in a subject, [with] . . . a composition comprising a recombinant adeno-associated virus (AAV) having a recombinant AAV capsid comprising a mutation in aa 587-595 of the AAV8 capsid protein sequence[.]"

Both patents list an earliest priority date of February 8, 2013. Accordingly, KEI assumes that the inventions described in the February 8, 2013 application occurred in 2011 or 2012.

Bennett is listed as an inventor on nine patents featuring AAV vectors assigned to Penn, with earliest priority dates ranging from 2001 to 2014, including the '376 and '845 patents. Of the nine patents, five disclose support from NIH grants. Bennett was listed as the Principal Investigator for two of those grants: EY-010820 (1995 to 2007), and EY-023177 (2011 to 2015).

It thus appears that when the subject invention was "conceived or first actually reduced to practice in the performance of work under a funding agreement," Bennett was receiving funding from the NIH to research gene therapies to treat ocular disorders.

The Article

As noted previously, KEI discovered strong links between the '376 and '845 patents and a PubMed article that discloses two NIH grants.

The article titled "Efficient transduction and optogenetic stimulation of retinal bipolar cells by a synthetic adeno-associated virus capsid and promoter," first published in August of 2014, lists Therese Cronin, Luk Vanderberghe, and Jean Bennett as three of nine authors. As previously noted, Cronin, Vanderberghe, and Bennett are the co-inventors on the patents.

The technology described in the article is almost identical to that of the patents. The article describes how the researchers "adapted the capsid library approach to enhance AAV-mediated retinal bipolar cell expression" and how "[a] favorable variant, derived through . . . AAV8 capsid mutants, was identified." It lists almost the exact same gene location (between amino acids 585

and 593/594) as do the patents (585 to 595). Likewise, the two patents both claim "[a]n adeno-associated virus (AAV) having a recombinant AAV capsid comprising a mutation, in aa 587-595 of the AAV8 capsid protein sequence[.]"

Most compellingly, the article's "conflict of interest statement" discloses that Therese Cronin, Luk Vanderberghe, and Jean Bennett "are co-authors on a US patent application for 'Enhanced AAV-mediated gene transfer for retinal therapies[,]'" which is the exact title of the two patents.

PubMed's conflict-of-interest policy requires authors to disclose any financial relationship with "any for-profit product discussed or implied in the text of the article[.]"[3] The conflict-of-interest statement in the PubMed article, disclosing Cronin, Vanderberghe, and Bennett's rights in a patent application having the same title as the patents, is compelling evidence that the technology discussed in the article and the patented inventions are one in the same, especially considering the overlap in the timing, substance, and authorship of the patents and article.

Other Evidence Linking the Inventions

The article discloses the support of NIH Grant Nos. EY-023177 and EY-019861. Jean Bennett is the principal investigator listed on EY-023177, which funded her research from 2011 to 2015. KEI also notes that Therese Cronin worked in Bennett's lab, and Luk Vandenberghe also worked at the University of Pennsylvania and was also funded by several Penn grants.

"Subject Inventions"

As noted previously, the Bayh-Dole Act and implementing federal regulations impose a series of disclosure requirements on recipients of federal grants, with respect to any "subject invention."

The Bayh-Dole Act defines a "subject invention" as "any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement," and defines a contractor as "any person, small business firm, or nonprofit organization that is party to a funding agreement." 35 U.S.C. § 201(e),(c).

The technology described in the PubMed Article was developed with the support of NIH Grant Nos. EY-023177 and EY-019861. If, as KEI suspects, the inventions covered by the '376 and '845 patents are the same as the technology described in the article, then the inventions are "subject inventions" under the Bayh-Dole Act, and disclosure was required.

Neither the '376 nor the '845 patent discloses any federal funding or includes a government interest statement, in apparent violation of the Bayh-Dole Act and associated federal regulations.

[3] https://www.nlm.nih.gov/bsd/policy/conflict_of_interest.html.

Patent 9,567,376
Title: “Enhanced AAV-mediated gene transfer for retinal therapies”
Inventors: Therese Cronin, Jean Bennett, and Luk Vandenberghe
Filing Date: August 14, 2014
Earliest Priority: U.S. Provisional Patent Application No. 61/762,775, filed Feb. 8, 2013

Patent 10,266,845
Title: “Enhanced AAV-mediated gene transfer for retinal therapies”
Inventors: Therese Cronin, Jean Bennett, and Luk Vandenberghe
Filing Date: August 24, 2016
Earliest Priority: U.S. Provisional Patent Application No. 61/762,775, filed Feb. 8, 2013

Grant EY-023177
Title: “Broad Spectrum Molecular Therapy for Blinding Retina Disorders”
PI/Project Leader: Jean Bennett
Organization: University of Pennsylvania
Grants in RePORTER from 2012 to 2015
Project Start: September 30, 2011
Project End: July 31, 2017

Grant: 1R24EY019861-01A1
Title: “Therapeutic Approaches for ABCA4-Associated Disorders”
PI/Project Leader: Rando L. Allikmets
Organization: Columbia University Health Sciences
Year of Award: 2011
Budget Start: August 1, 2011
Budget End: July 31, 2012

Remedies

KEI respectfully urges the NIH to promptly investigate the apparent non-disclosure and take all appropriate remedial action, including taking title to the patents. Failure to disclose subject inventions pursuant to 35 U.S.C. § 202(c)(1) permits the federal government to “receive title to any subject invention not disclosed to it within such time[.]”

If the NIH never revokes a patent or imposes any meaningful sanctions, universities and other contractors will continue to underreport federal funding. A certificate of correction on the patent, as Penn and other institutions have issued in the past, does not send a strong enough signal regarding the public’s right to know its rights in patented inventions.

Here, the failure to disclose concerns a gene therapy that may promise a great benefit to patients, but could come at a steep cost to patients, third-party payors, and the U.S. healthcare

system. The inventions expand upon the technology behind voretigene neparvovec-rzyl (Luxturna™), an AAV vector gene therapy that treats an inherited form of blindness. Luxturna was discovered by Jean Bennett and others and is sold by Spark Therapeutics for $850,000 ($425,000 per eye).[4]

The disclosure requirements were designed to protect the government's rights in federally-sponsored technology such as biomedical inventions. We are asking the NIH to ensure that when taxpayer investments are relevant to an invention, the government is diligent in ensuring that the public's rights are acknowledged and secured. In order to protect the public's rights, we ask that the government take possession of patents when grant recipients do not make timely disclosures, as is required by law, and as appears to be the case here.

Sincerely,

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[4] Bill Berkrot, *Spark's price for Luxturna blindness gene therapy too high: ICER*, Reuters (Jan. 12, 2018), https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298.