KNOWLEDGE ECOLOGY INTERNATIONAL

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Via email: david.lambertson@nih.gov

Re: Prospective Grant of an Exclusive Patent License: The Development of an Anti-GPC3 Radionuclide Immunoconjugate for the Treatment of GPC3-Expressing Cancers (84 FR 57743).

Dear Dr. Lambertson:

Knowledge Ecology International (KEI), the Union for Affordable Cancer Treatment (UACT) and Social Security Works (SSW) are writing to comment on the prospective grant of an exclusive patent license for the development of an anti-GPC3 radionuclide immunoconjugate for the treatment of GPC3-expressing cancers to Xsto BioSciences, Inc. (Xsto), as described at 84 FR 57743.

Xsto BioSciences

According to the Federal Register notice, the National Institutes of Health (NIH) intends to grant an exclusive license to "Xsto BioSciences, Inc. (Xsto)." The only information about this company that the NIH provided in the Federal Register notice, besides its name, is that it is located in San Carlos, California. Xsto appears to be a little known company that seems to lack a website, has not filed forms with the Securities Exchange Commission (SEC), and lacks other sources of information that the public can use to understand whether it would be an appropriate licensee.

The only relevant source of publicly available information we found for this company were documents filed with the California Secretary of State business registry. Xsto was registered in California on January 5, 2018 and then dissolved on November 26, 2018. At the time of registration Xsto BioSciences listed Shawn Melley as its Chief Executive Officer and Mufaddal

Bootwala as its Chief Financial Officer. According to his LinkedIn profile, Shawn Melley currently works as Project Team Lead for the ADU-S100 project at Aduro Biotech.[1] This project is being conducted in collaboration with Novartis, according to Aduro Biotech's website[2] and 10-K forms filed with the Securities Exchange Commission (SEC).[3] Prior to Aduro Biotech Shawn Melley also worked for Onyx Pharmaceuticals, Eisai, Amgen, and AstraZeneca.[4]

According the forms filed with the California Secretary of State, Xsto BioSciences was located at 1532 Greenwood Ave San Carlos, CA 94070, a residential area south of San Francisco.

GPC3-expressing cancers

The proposed exclusive license would cover "monoclonal antibodies that are specific for the cell surface domain of GPC3."[5] According to the Federal Register notice, "[t]hese antibodies can potentially be used for the treatment of GPC3-expressing cancers such as HCC."[6]

According to the NIH's Genetics Home Reference, the GPC3 gene provides instructions for making a protein called glypican 3.[7] Although glypican 3 is known primarily as an inhibitor of cell growth and cell division, in some tissues it appears to have the opposite effect. The Genetics Home Reference cites research suggesting that "in certain types of cells, such as cells in the liver, glypican 3 may interact with proteins called growth factors to promote cell growth and cell division."[8] In particular, GPC3 has been observed to be elevated in hepatocellular carcinomas (HCCs).[9] Capurro et al. revealed that 72% of HCCs were GPC3-positive.[10] Based on the HCC-specific expression of GPC3 in liver, it is an emerging target for liver cancer therapy.[11]

HCC is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide.[12] In the United States, HCC is the ninth leading cause of cancer deaths.[13] Although there are multiple treatment approaches, only orthotopic liver transplantation (OLT) or surgical resection is curative.[14] In recent years the oral multitargeted tyrosine kinase inhibitor

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[1] https://www.linkedin.com/in/melleys
[2] https://www.aduro.com/pipeline/clinical-trials/
[3] See, for example:
https://www.sec.gov/Archives/edgar/data/1435049/000156459019004942/adro-10k_20181231.htm
[4] https://www.linkedin.com/in/melleys
[5] https://www.federalregister.gov/d/2019-23481
[6] https://www.federalregister.gov/d/2019-23481
[7] https://ghr.nlm.nih.gov/gene/GPC3#
[8] https://ghr.nlm.nih.gov/gene/GPC3#
[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5108608/#b8-jhc-3-063
[10] https://doi.org/10.1016/S0016-5085(03)00689-9
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5108608/
[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063561/
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063561/
[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063561/

sorafenib has become the standard of treatment for advanced HCC with a reported increased median survival from 7.9 months in the placebo group to 10.7 months in the treatment group.[15]

We note, however, that although the Federal Register notice cites HCC as an example of GPC3-expressing cancers, the proposed field of use is not limited to HCC. There are other types of GPC3-expressing cancers in addition to the HCC. For example, the expression of the GPC3 gene has also been observed to be increased in lung cancer tissues,[16] malignant salivary gland tumors,[17] melanoma,[18] and others.[19] According to our analysis, several of the claims for the patents included in the Federal Register notice are directed to methods for using the disclosed anti-GPC3 antibody in the treatment of melanoma, lung cancer and ovarian cancer. Therefore, we will assume that the license will also cover all other types of GPC3-expressing cancers.

Studies related to the HN3 antibody

The Federal Register notice states that the field of use of the proposed license may be limited to:

> (I) The development and commercialization of glypican-3 (GPC3) antibody-based radionuclide conjugates comprising of at least:
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> a. The complementary determining region (CDR) sequences of the anti-GPC3 antibody known as HN3, and
>
> b. A radionuclide, including but not limited to an alpha, beta, positron, gamma or auger emitting radionuclide, for the treatment of GPC3-expressing cancers.
>
> (II) The development of an FDA-approved *in vivo* radiopharmaceutical, using a binder having the CDR sequences of the anti-GPC3 antibody known as HN3, for the diagnosis and monitoring of GPC3-expressing cancers.

The HN3 antibody was described in a 2013 paper co-authored by several of the inventors named in the patents included in the proposed license.[20] This paper reported that "HN3 shows unprecedented and direct inhibition of GPC3-positive cell proliferation."[21] Based on studies conducted in mice, the paper also suggested that "HN3 inhibits liver tumor growth in mice and

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[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063561/
[16] https://www.geneticsmr.com/sites/default/files/articles/year2015/vol14-3/pdf/gmr4731.pdf
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6170252/
[18] https://clincancerres.aacrjournals.org/content/10/19/6612.long
[19] https://ajp.amjpathol.org/article/S0002-9440(18)30129-9/pdf
[20] 10.1073/pnas.1217868110
[21] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3607002/

should be evaluated further as a therapeutic candidate for the treatment of liver cancer."[22] A 2017 study also co-authored by several inventors named in the covered patents reported that "significant tumor regression and increased survival was observed in mice with HCC tumors treated with HN3-mPE24."[23] Based on this observation, this study suggested that "HN3-mPE24 deserves further clinical development for the treatment of HCC."[24]

On November 12, 2019, we asked Dr. Lambertson the stage of development of the inventions that would be covered in the proposed license, and whether these inventions are being investigated in clinical trials. We have not heard back yet.

The inventions appear to be related to the development of a biologic drug, in which case it will benefit from 12 years of test data protection, and will possibly qualify as an orphan product, benefiting from a 25 percent tax credit on qualifying trials and orphan drug exclusivity in the United States (7 years), European Union (10 years), and in several other high income countries.

In the event that the NIH decides to grant an exclusive license, 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-owned 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 Xsto BioSciences to disclose the steps it will take to enable the timely registration and availability of the

[22] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3607002/
[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5464801/
[24] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5464801/

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 do not object to the use of an exclusive license in this case. However, If the NIH proceeds with the license, we ask that the license incorporates the provisions listed herein that are designed to protect the public's investment in the subject technologies.

Sincerely,

Knowledge Ecology International
Union for Affordable Cancer Treatment
Social Security Works