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June 15, 2020

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Via Email: jim.knabb@nih.gov

Re: Prospective Grant of Two Exclusive Patent Licenses to Anti-CD33 Chimeric Antigen Receptor (CAR) Therapies

Dear Dr. Knabb:

Knowledge Ecology International (KEI) and the Union for Affordable Cancer Treatment (UACT) are writing to comment on two prospective exclusive patent licenses: the "Prospective Grant of an Exclusive Patent License: Development and Commercialization of Mono-Specific Chimeric Antigen Receptor (CAR) Therapies for the Treatment of Cluster of Differentiation 33 (CD33) Expressing Malignancies" to "Vor Biopharma Inc." (the "Vor Biopharma License"), and the "Prospective Grant of an Exclusive Patent License: Development and Commercialization of Logic-Gated Chimeric Antigen Receptor (CAR) Therapies for the Treatment of Cluster of Differentiation 33 (CD33) Expressing Cancers" to Senti Bio, (the "Senti Bio License"). Both licenses are described at 85 FR 28966.

The proposed licenses involve a chimeric antigen receptor (CAR) therapy that targets the CD33 surface antigen, which is expressed in acute myelogenous leukemia (AML) and a form of chronic myeloid leukemia (CML). The invention is being investigated in Clinical Trial No. NCT03971799, which is taking place at the National Institutes of Health (NIH) campus in Bethesda and at Children's Hospital of Philadelphia.

The NIH may not grant the licenses unless it first determines that exclusivity is necessary to incentivize a company to commercialize the invention, and that the scope of exclusivity is not broader than the necessary incentive, for each license. The NIH must also seek the antitrust advice of the U.S. Attorney General before executing the licenses.

The NIH has not responded to the majority of the questions that KEI asked about the licenses, stating that the questions had been answered with respect to past licenses or were dependent on the outcome of the notice and comment period, and negotiations.

Based upon the NIH's overall approach toward its technology transfer responsibilities under the Bayh-Dole Act and its other legal duties, we are concerned that the NIH has not engaged in the type of analysis required by 35 U.S.C. § 209(a)(1)-(2), and it is our assumption that the NIH has failed to seek the advice of the U.S. Attorney General, as is required by 40 U.S.C. § 559.

Background

The Invention

The prospective licenses cover NIH Invention No. E-097-2018-0: "Anti-CD33 Chimeric Antigen Receptors for Treatment of Human Acute Myeloid Leukemia", and two patent documents related to that invention: U.S. Provisional Patent Application 62/643,015, filed March 14, 2018; and International Patent Application PCT/US2019/022,309, filed March 14, 2019.[1]

The inventors listed for PCT/US2019/022,309 are Terry Fry and Haiying Qin.[2] PCT/US2019/022,309 contains the following statement of government interest:

> This invention was made with Government support under project number ZIA BC 01 1565 by the National Institutes of Health, National Cancer Institute. The Government has certain rights in the invention.[3]

The U.S. Provisional Patent Application is not available for inspection at the U.S.P.T.O. online database Public Patent Application Information Retrieval (Public PAIR), as of the date of these comments.

[1] 85 Fed. Reg. 28966 (May 14, 2020), https://www.federalregister.gov/documents/2020/05/14/2020-10303/prospective-grant-of-an-exclusive-patent-license-development-and-commercialization-of-logic-gated (for the Vor Biopharma License); 85 Fed. Reg. 28966-67, (May 14, 2020), https://www.federalregister.gov/documents/2020/05/14/2020-10303/prospective-grant-of-an-exclusive-patent-license-development-and-commercialization-of-logic-gated (for the Senti Bio License).
[2] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019178382.
[3] *Id.*

ZIA BC 011565 is an NIH intramural grant awarded to Terry Fry titled, “Adoptive T Cell Therapy for Pediatric Leukemia.” The grant funded Dr. Fry’s research from Fiscal Years 2014 to 2018, for a total of $5,228,123.

Dr. Jim Knabb, the point of contact for the licenses, confirmed that the invention is being investigated in Clinical Trial No. NCT03971799, “Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults With Relapsed/Refractory Acute Myeloid Leukemia.” NCT03971799 is a Phase 1/2 trial with 34 children and young adults enrolled.[4] It is sponsored by the Center for International Blood and Marrow Transplant Research, with the National Marrow Donor Program and the St. Baldrick’s Foundation listed as “Collaborators”.[5] The trial began on January 8, 2020 and its anticipated “Primary Completion Date” is December 2024.[6] It is taking place at the National Cancer Institute in Bethesda, Maryland and the Children’s Hospital of Philadelphia.[7]

Scope of the Licenses

The Vor Biopharma License

The territorial reach of exclusivity for the Vor Biopharma License “may be worldwide[.]”[8] The proposed fields of use are:

> The development of a chimeric antigen receptor (CAR) therapy mono-specific for CD33 for the prophylaxis or treatment of CD33-expressing hematological malignancies wherein the CAR is comprised of the CD33-binding domain referenced as Hu195 or hP67.6, is delivered via lentiviral transduction, and the T cells are:
>
> 1. Derived autologously (meaning cells derived from one individual who is both the donor and the recipient) in the first-line or relapsed/refractory setting, or
>
> 2. derived allogeneically (meaning cells derived from a matched healthy donor), in the post-transplant setting.[9]

[4] https://clinicaltrials.gov/ct2/show/NCT03971799
[5] *Id.*
[6] *Id.*
[7] *Id.*
[8] 85 Fed. Reg. 28966.
[9] *Id.*

The Senti Bio License

The territorial reach of exclusivity for the Senti Bio License "may be worldwide[.]" [10] The proposed fields of use are:

> "1. The development of a CD33-specific logic-gated CAR-based immunotherapy using autologous human T cells transduced with lentiviral vectors, wherein the viral transduction leads to the expression of a CAR that targets CD33 (comprised of the CD33-binding domain referenced as Hu195 or hP67.6 in the invention as well as an intracellular signaling domain), for the prophylaxis or treatment of CD33-expressing cancers; and
> "2. The development of a CD33-specific logic-gated CAR-based immunotherapy using allogeneic human NK cells transduced with lentiviral vectors, wherein the viral transduction leads to the expression of a CAR that targets CD33 (comprised of the CD33-binding domain referenced as Hu195 or hP67.6 in the invention as well as an intracellular signaling domain), for the prophylaxis or treatment of CD33-expressing cancers."[11]

Neither of the Federal Register notices for the licenses state the proposed term of exclusivity for the license.

The Prospective Licensees

Vor Biopharma

Vor Biopharma is based in Massachusetts and registered to conduct business in the state in February of 2016, according to Massachusetts' online business records.

Vor's "lead product candidate" is VOR33, which "consists of engineered hematopoietic stem cells (eHSCs) that lack the protein CD33."[12] Vor believes that VOR33 may be able to "improve the therapeutic window and effectiveness of CD33-targeted therapies, thereby potentially broadening the clinical benefits to patients suffering from AML."[13]

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[10] 85 Fed. Reg. 28966-67.
[11] *Id.*
[12] https://www.vorbiopharma.com/therapeutic-focus/.
[13] *Id.*

Senti Bio

Senti Bio is headquartered in South San Francisco, California.[14] It is incorporated in Delaware. Senti Bio describes itself as "a technology-driven therapeutics company here to lead the next generation of medicine—where cells are the hardware and gene circuits are the software."[15]

Discussion

1. It appears that the NIH has not meaningfully evaluated whether exclusivity is a necessary incentive and the scope of exclusivity is not broader than necessary for the licenses.

The NIH may not grant an exclusive license to a federally-owned invention unless "granting the license is a reasonable and necessary incentive to—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).

If the NIH determines that exclusivity is a necessary incentive, it must also ensure that the scope of the license is not broader than necessary. *See* 35 U.S.C. § 209(a)(2) conditioning a federal agency's grant of an exclusive license on, among other things, the agency finding 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[.]"

We are concerned that the NIH has not properly analyzed the criteria at 35 U.S.C. § 209(a)(1)-(2) for both of the proposed licenses.

KEI emailed Dr. Knabb a list of questions about the licenses. Among other inquiries, KEI asked how the NIH determined that exclusivity is a necessary incentive and that the scope of the license does not exceed the necessary incentive. He responded follows:

> This invention is being evaluated in the clinical trial that you reference. Aside from that question, the other questions have either: been addressed for previous licenses, are pending the public

[14] https://www.sentibio.com/about.
[15] *Id.*

> comment/objection period to the grant of the license, or will be negotiated in the agreements (should we proceed to the agreement negotiation).

Based on the NIH's previous statements regarding exclusive patent licenses, we can assume that it did not perform the analysis required by 35 U.S.C. § 209(a)(1)-(2).

In the past, KEI has raised two main questions with respect to exclusivity and the scope of proposed licenses: whether the NIH performed any economic analysis of the necessity of exclusivity and whether it considered limiting the term of exclusivity to shorter than life of patent. The NIH has answered both those questions in the negative, stating that for early stage therapeutics there is no demand for non-exclusive licenses, and, more controversially, that companies will not commit to commercializing an invention unless they are granted exclusivity for life of patent.[16]

We have also asked whether the NIH has considered limiting exclusivity to high-income countries, or to non-U.S. markets, but have not received a response to either question. The majority, if not all, of the Federal Register notices regarding NIH exclusive patent licenses state that the territorial reach of exclusivity "may be worldwide[,]" however. And the NIH Office of Technology Transfer website states:

> Most biomedical companies, whether large or small, **require worldwide patent protection** to secure foreign markets or to use their assets in establishing strategic alliances with foreign companies who provide important foreign marketing expertise.[17]

As a whole, the statements of Dr. Rohrbaugh and NIH technology transfer officers, and the proposed license terms disclosed in Federal Register notices strongly indicate that the NIH routinely grants exclusive licenses with terms most favorable to licensees and least favorable to U.S. taxpayers who funded the invention. The NIH appears to assume that no company will invest in developing a technology unless granted the maximum level of incentives on every possible front.

A policy of making such broad assumptions instead of applying the statutory criteria for each proposed patent license would violate the Bayh-Dole Act. As the NIH has recognized, every invention is different and has unique commercial value. The Bayh-Dole Act thus requires a case-specific analysis for each license.

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[16] Letter from Mark Rohrbaugh, Ph.D., J.D., NIH Special Advisor for Technology Transfer, to KEI (Nov. 26, 2019)(on file with KEI).

[17] https://www.ott.nih.gov/faqs/licensing-faqs#11 (emphasis added).

Specifically, in order to conclude that exclusivity is necessary and that the scope of the license is not broader than the necessary incentive, 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. As Dr. Maria Friere, former head of Technology Transfer at NIH, testified to Congress:

> NIH strategy is to negotiate non-exclusive licenses for its intramural technologies whenever possible . . . . We recognize that companies need an exclusive market to offset the risk, time, and expense of developing biomedical diagnostic or therapeutic products. However, companies do not necessarily need to achieve that position **solely by exclusively licensing** a government technology used to develop the product. Instead, companies are frequently able to add their own proprietary technologies to the invention licensed from the government to ultimately achieve some level of uniqueness and exclusivity for the final product.[18]

In addition to considering other methods of obtaining exclusivity, the NIH must consider the investment value of the invention and remaining costs to bring it to market, which are influenced by the development stage of the technology, among other things. Dr. Mark Rohrbaugh, a senior technology transfer advisor for the NIH, has acknowledged that the value of an invention from a commercial standpoint is dependent on its stage of development, testifying to Congress that "[t]he closer a technology is to the marketplace, the lower the risk and cost to the licensee, and the more valuable the technology[.]"[19]

Finally, the NIH must consider the possibility that a license for shorter than life of patent will be adequate to incentivize a company to commercialize a federally-owned invention, as it has done with numerous products for the treatment of cancer, including cases where products were only protected by five years of exclusive rights in regulatory test data, with no patents.

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[18]Maria Freire, Director, Office of Technology Transfer, NIH, Statement of the National Institutes of Health Before Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies, Maria Freire, Director, Office of Technology Transfer (August 1, 2001) https://stemcells.nih.gov/policy/statements/080101freire.htm (emphasis added).

[19] Mark L. Rohrbaugh, *NIH: Moving Research from the Bench to the Bedside, Testimony before the House Committee on Energy and Commerce, Subcommittee on Health*, 108th Cong. (July 10, 2003), https://www.govinfo.gov/content/pkg/CHRG-108hhrg88429/html/CHRG-108hhrg88429.htm.

Regarding exclusivity, both Vor Biopharma and Senti Bio appear to have patented inventions that they can use in combination with the licensed invention to create exclusivity over any final product embodying the invention. The companies will also gain a level of exclusivity by obtaining FDA approval of the invention. CAR therapies are biological products, and biologics are granted marketing exclusivity for 12 years.[20] Moreover, one of the indications for the licenses, AML, has a patient size of 64,512 people in the United States, making it a "rare disease" under the Orphan Drug Designation Program.[21] This designation gives the sponsor of a drug or biologic to treat a rare disease a seven-year period of market exclusivity.[22]

The NIH must have considered whether these other methods of establishing exclusivity would have sufficed.

Regarding the value of the invention and the appropriate scope of the license, we note the following factors:

- The development stage of the invention is advanced compared to technologies in the discovery or preclinical phases. As noted above, the invention is being investigated in a Phase 1/2 trial that is being sponsored by third parties—an expense that the licensees and/or investors will not have to bear. The preclinical research was funded by a $5 million project of the NIH.
- Because there are limited treatment options for relapsed AML[23]—one of the disease indications for the license—the invention will likely qualify for incentives that speed up approval by the FDA, such as fast track designation, breakthrough therapy designation, and priority review designation.[24]
- One or both the licensees may be eligible for orphan drug designation for the invention, which, in addition to granting seven years of market exclusivity, confers a 25 percent tax credit on eligible clinical trial expenses[25] and authorizes the Secretary of Health and Human Services to provide grants and execute contracts "to assist in defraying the costs of developing drugs for rare diseases or conditions, including qualified testing expenses."[26]

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[20] 42 U.S.C. § 262(k)(7)(A)..
[21] 21 U.S.C. § 360ee(b)(2).
[22] 21 U.S.C. § 360cc.
[23] https://www.ott.nih.gov/technology/e-097-2018.
[24] The programs are described by the FDA at https://www.fda.gov/drugs/development-approval-process-drugs.
[25] 26 U.S.C. § 45C.
[26] 21 U.S.C. § 360ee.

- Because a potential commercial application for the invention is to treat acute lymphoblastic leukemia,[27] a rare disease primarily affecting children,[28] the invention may qualify for a rare pediatric disease priority review voucher,[29] a freely-transferable incentive recently traded for approximately $100 million.[30]

All of the factors described above make the invention valuable from an investment perspective.

If the NIH did not investigate the possibility of granting a non exclusive or co-exclusive license, limiting the term of the proposed license, or otherwise limiting the terms, such as limiting exclusivity only to non-U.S. high income countries or shortening the term of exclusivity, it has not satisfied its obligations under 35 U.S.C. § 209(a)(1)-(2).

2. The NIH has not been fully transparent about the licenses, limiting the public's right to comment, as guaranteed by 35 U.S.C. § 209(e).

The NIH may not grant an exclusive patent license until it "has considered all comments received before the end of the comment period in response to [] public notice" of the intent to grant the license.[31] In order to comment meaningfully on a proposed exclusive license, the public must have basic information about it.

As noted above, KEI emailed Dr. Knabb a list of questions about the invention and the proposed licenses. While Dr. Knabb acknowledged that Clinical Trial No. NCT03971799 is associated with the invention, he declined to answer the remainder of the questions, stating that the questions had been previously answered, were pending the notice and comment period, or pertained to terms that had not yet been negotiated.

That answer was inaccurate. The questions KEI asked were specific to these licenses and were straightforward inquiries such as how much the NIH has spent to develop the invention, what grant numbers are associated with the invention, how the NIH determined that exclusivity is a necessary incentive, and how the NIH determined that the scope of the licenses were not broader than necessary. These issues are independent of the notice and comment period, and should be answerable before the NIH proposes granting the license. For example, the NIH

[27] https://www.ott.nih.gov/technology/e-097-2018.
[28] https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/key-statistics.html.
[29] 21 U.S.C. § 360ff.
[30] http://drugdatabase.info/priority-review-vouchers/.
[31] 35 U.S.C. § 209(e).

does not publish notice of a prospective license before it has determined that exclusivity is proper. Rather, it determines that exclusivity is warranted and then publishes the Federal Register notice, stating that it will proceed with the license unless it receives evidence or argument stating that the license is inconsistent with 35 U.S.C. § 209. In order for the notice and comment period to have any meaning, the NIH cannot refuse to share basic information about the license, nor can it decline to disclose material terms of the license, such as the period of exclusivity, on the basis that those terms are "yet to be negotiated."

This lack of transparency has improperly limited the public's ability to comment on the licenses, in conflict with 35 U.S.C. § 209(e).

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.

We object to the license because the NIH has not first obtained the antitrust advice of the United States Attorney General before disposing of government-owned property.

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."[32]

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." The statute exempts personal property if the fair market value is less than $3,000,000, but specifically excludes "a patent, process, technique, or invention" from that exception.

The regulation 41 C.F.R. § 102-75.270 also makes clear the inclusion of patents "irrespective of cost."

KEI asked Dr. Knabb whether the NIH requested the advice of the U.S. Attorney General concerning the licenses. Dr. Knabb 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

[32] 40 U.S.C. § 559(b)(1).

activities, which are principally governed by the Bayh-Dole Act and its regulations.

We disagree.

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.

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 an exclusive license in a federally-owned invention, it is disposing of a government property interest so as to trigger 40 U.S.C. § 559.

4. We recommend that the NIH includes a series of provisions designed to safeguard the public interest in the licenses and ensure that the licenses implement the governing principles listed in the Public Health Service (PHS) technology transfer manual.

In the event that the NIH proceeds with the licenses, KEI requests that the NIH includes the following provisions to protect the public's interest in NIH-funded technology:

1. **Geographic scope of exclusivity.** If the NIH decides to grant exclusive rights to the subject invention, it should limit exclusivity to the European Union, Japan and other high-income countries, but not the United States, so that countries that did not fund the R&D underlying the inventions would bear the costs of the exclusivity, while the U.S. residents would not. The NIH should also limit exclusivity in moderate and lower income countries, where the monopoly is likely to have an adverse impact on access with almost no benefit in terms of the incentives for the company.

2. **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.

3. **Low and middle income countries.** The exclusive licenses 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."

4. **Global registration and affordability.** The licenses should require Vor Biopharma and Senti Bio to disclose the steps that each 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.

5. **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.

6. **Years of exclusivity.** We propose the licenses 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 licenses 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 licenses 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[.]”

7. **Transparency of R&D outlays.** The licensees 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 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 licenses for the reasons stated herein. In the event that the NIH grants the licenses, we ask that they incorporate the provisions listed above, which are designed to protect the public interest in the licensed technologies and to accomplish the policies outlined in the PHS Technology Transfer Manual and Section 200 of the Bayh-Dole Act.

Sincerely,

Knowledge Ecology International
Union for Affordable Cancer Treatment