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Via Email: andy.burke@nih.gov

Re: Prospective Grant of an Exclusive Patent License: Development and Commercialization of Cell Therapies for Cancer, 84 FR 52890

Dear Dr. Burke:

Knowledge Ecology International (KEI) and the Union for Affordable Cancer Treatment (UACT) are writing to object to the "Prospective Grant of an Exclusive Patent License: Development and Commercialization of Cell Therapies for Cancer," to Ziopharm Oncology, Inc. ("Ziopharm"), as described in the Federal Register notice located at 84 FR 52890.

The license would grant Ziopharm exclusive, worldwide rights in two T-cell therapies that target common cancer mutations, adding to a platform technology that Ziopharm is developing. The first cell therapy is primarily directed at mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene, while the second targets mutations in the p53 tumor protein. KRAS is expressed in a variety of cancers, including pancreatic, lung, endometrial, and ovarian cancer. Mutations in p53 are expressed in cancers such as cholangiocarcinoma, melanoma, colon cancer, rectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer, glioblastoma, uterine cervical cancer, head and neck cancer, breast cancer, pancreatic cancer, and bladder cancer. Considering the broad range of potential applications and indications, the NIH's decision about this license carries great weight for cancer patients.

We have the following objections to the proposed exclusive license to Ziopharm:

1. Our correspondence with the National Institutes of Health (NIH) concerning the prospective license indicates that the NIH has not faithfully applied the criteria in 35 U.S.C. § 209 and 37 C.F.R. § 404.7;

2. The NIH has not been completely transparent about the license, impeding the public's right to comment under 35 U.S.C. § 209(e); and
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 note that Drew Deniger, a former NIH scientist who discovered at least one of the subject inventions, joined Ziopharm in July 2019.[1] We appreciate the fact that an inventor can play an important role in bringing an invention to practical application, by bringing passion, vision and expertise to the endeavor. That said, when an NIH employee who discovers an invention in his or her capacity as an NIH researcher is soon after employed by the company to which the NIH licenses the invention, it is particularly important for the NIH to demonstrate that it properly evaluated the criteria for granting exclusive patent licenses, located at 35 U.S.C. § 209, which includes a responsibility to protect the public's interests in the inventions it financed.

In the event that the NIH grants the license over our objections, we request that the license agreement incorporates provisions designed to safeguard the public interest and effectuate the policy objectives of the Bayh-Dole Act, as well as the governing principles of the Public Health Service (PHS) Technology Transfer Policy Manual.

Background

The prospective license concerns T-cell therapies developed by the NCI:

- E-029-2019, "HLA Class-II Restricted T Cell Receptors Against RAS with G12R Mutation" ("Invention A"); and
- E-135-2019, "T Cell Receptors Recognizing R175H or Y220 C Mutation in P53" ("Invention B").

The license would add to Ziopharm's "Sleeping Beauty platform," a suite of intellectual property rights in T-cell receptors targeting certain KRAS and p53 mutations that Ziopharm acquired from NIH pursuant to an exclusive license agreement executed on May 28, 2019.[2] Ziopharm believes

[1] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-names-ncis-dr-drew-deniger-direct-tcr-t-cell

[2] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-announces-exclusive-license-national-cancer. Dr. Andrew Burke, the point of contact for the license, confirmed in an email to KEI dated October 17, 2019, that the prospective exclusive patent license referenced in the Federal Register at 84 FR 2537 was executed on May 28, 2019.

that the Sleeping Beauty platform "will be foundational technology to successfully targeting and treating metastatic solid tumors."[3]

The table below, constructed by the NCI's Office of Technology Transfer, demonstrates how the prospective license would complete the transfer of rights in NCI's "Collection of mutated KRAS TCRs" to Ziopharm.

Table 1: Collection of mutated KRAS TCRs.

No.	TCR (ID in Reference)	KRAS Variant	HLA Restriction	Epitope (variant underlined)	TCR Origin	Reference
1	TCR (TRAV12N-3*01/TRBV4*01)	G12D	A*11:01	VVVGADGVGK, 10-mer	Murine	E-028-2015
2	TCR (TRAV19*01/TRBV13-1*02)	G12V	A*11:01	VVVGAVGVGK, 10-mer	Murine	E-180-2015
3	TCR (TRAV3-3*01/TRBV4*01)	G12V	A*11:01	VVGAVGVGK, 9-mer	Murine	E-180-2015
4	TCR (TRAV4*01/TRBV5-6*01)	G12D	C*08:02	GADGVGKSA, 9-mer	Human	E-265-2015
5	TCR-1 (TRAV4*01/TRBV5-6*01)	G12D	C*08:02	GADGVGKSA, 9-mer	Human	E-175-2016
6	TCR-2 (TRAV4*01/TRBV5-6*01)	G12D	C*08:02	GADGVGKSA, 9-mer	Human	E-175-2016
7	TCR-3 (TRAV4*01/TRBV5-6*01)	G12D	C*08:02	GADGVGKSA, 9-mer	Human	E-175-2016
8	TCR-4 (TRAV12-2*01/TRBV10-2*01)	G12D	C*08:02	GADGVGKSAL, 10-mer	Human	E-175-2016
9	TCR (TRAV13-1/TRBV20-1)	G12V	DRB1*07:01	EYKLVVVGAVGVGKS, 15-mer	Human	E-181-2017
10	TCR (TRAV24/TRBV12-4)	G12C	DRB1*11:01		Human	E-181-2017
11	TRC (TRAV14/DV4*02/TRBV5-1*01)	G12V	A11:01	VVGAVGVGK	Human	E-239-2017
12	TCR (TRAV12-3*03/TRBV1*01)	G12V	HLA-A3	VVVGAVGVGK, 10-mer	Human	E-166-2018
13	TCR (TRAV29/TRBV19*02)	G12R	DRB5*01		Human	E-029-2019
14	TCR (TRAV12*-2*01/TRBV20-1*01)	G12R	HLA-DQA1*05:05:HLA-DQB1*03:01		Human	E-029-2019

Source: https://techtransfer.cancer.gov/availabletechnologies/e-175-2016.

The first 12 KRAS TCRs listed in Table 1 were licensed to Ziopharm as part of the May 28, 2019 Exclusive Licensing Agreement.[4] The last two are assigned the NIH Reference No. E-029-2019, which is covered by the instant license.

Neither of the patent applications concerning Inventions A and B has been published, limiting our ability to evaluate the technology.

We note, however, that NCI scientist Drew Deniger, who joined Ziopharm in July 2019,[5] is one of the inventors of Invention B.[6] He is also one of the inventors of several of the technologies

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[3] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-names-ncis-dr-drew-deniger-direct-tcr-t-cell

[4] In February 2019, the NIH announced that it was proposing licensing Inventions No. E-028-2015, E-265-2015, E-175-2016, E-181-2017, E-239-2017, and E-166-2018. *See* 84 Fed. Reg. 2537, https://www.federalregister.gov/documents/2019/02/07/2019-01431/prospective-grant-of-an-exclusive-patent-license-development-and-commercialization-of-cell-therapies. In email correspondence with KEI, Dr. Burke confirmed that the license referenced at 84 Fed. Reg. 2537 was executed on May 28, 2019.

[5] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-names-ncis-dr-drew-deniger-direct-tcr-t-cell

[6] https://www.ott.nih.gov/technology/e-135-2019

covered by the May 28, 2019 Exclusive License Agreement, which was executed fewer than two months before Dr. Deniger joined Ziopharm.

A Ziopharm press release describes Dr. Deninger's role in developing the company's Sleeping Beauty platform as follows:

> Since 2013, Dr. Deniger has worked at the NCI under Dr. Steven Rosenberg where he has served as Lead Investigator for the group's efforts in three initiatives: Identifying "hotspot" neoantigens for T-cell therapy; targeting neoantigens in metastatic endometrial and ovarian cancers; and non-viral gene therapy using the Sleeping Beauty platform to generate TCR-modified T cells targeting neoantigens.
>
> "At the foundation of our TCR-T program is the partnership we have developed with Dr. Rosenberg and his team at the NCI. As an integral part of that group, Dr. Deniger has helped harness our Sleeping Beauty technology to express neoantigen-specific T-cell receptors and prepare for the start of the upcoming clinical trial in patients with solid tumors," said Laurence Cooper, M.D., Ph.D., Chief Executive Officer of Ziopharm. "As a recognized leader in the identification of neoantigens in hotspots, advancing innovative immunotherapy approaches into the clinic, and with years of expertise with the Sleeping Beauty system, we're delighted to welcome Drew to Ziopharm."
>
> Author of multiple peer-reviewed manuscripts describing detection of neoantigen-reactive T cells for personalized cancer immunotherapy and T-cell responses to hotspot mutations, Dr. Deniger has also written validating publications related to the non-viral Sleeping Beauty transposon-transposase system. Dr. Deniger is the named inventor on patents related to TCRs recognizing mutated p53 and methods of isolating T cells having antigenic specificity for a p53 cancer specific-mutation, and has been the recipient of numerous awards in cancer immunotherapy.[7]

Ziopharm Oncology, Inc., the Prospective Licensee

Ziopharm was registered in Delaware on May 16, 2005 and in Massachusetts on December 19, 2006.

According to its most recent SEC 10-K form, Ziopharm is "a biopharmaceutical company focused on discovering, acquiring, developing and commercializing next generation immunotherapy platforms that leverage cell- and gene-based therapies to treat patients with cancer."[8] Ziopharm states in its 10-K that the company is developing "two immuno-oncology platform technologies that utilize the patient's immune system by employing novel, controlled gene expression and innovative cell engineering technologies to designed deliver safe,

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[7] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-names-ncis-dr-drew-deniger-direct-tcr-t-cell

[8] https://www.sec.gov/Archives/edgar/data/1107421/000119312519063978/d678734d10k.htm

effective, and scalable cell- and viral-based therapies for the treatment of multiple cancer types."[9]

According to its March 5, 2019 SEC 10-K form, Ziopharm "ha[d] not demonstrated an ability to perform the functions necessary for the successful commercialization of any product candidates."[10] The company's operations "have been limited to organizing and staffing [the] company, acquiring, developing and securing [their] proprietary product candidates, and undertaking preclinical and clinical trials of [their] product candidates."[11] The report states further that Ziopharm "do[es] not have internal research capabilities," and that the company is "dependent upon pharmaceutical and biotechnology companies and academic and other researchers to sell or license [to them] their product candidates and technology."[12]

In 2017, Ziopharm announced that it signed a Cooperative Research and Development Agreement (CRADA) with NCI to develop adoptive cell transfer, or ACT-based immunotherapies genetically modified using the Sleeping Beauty transposon/transposase system to express TCRs for the treatment of solid tumors.[13]

Ziopharm has executed several exclusive licenses over related inventions, including with the University of Texas MD Anderson Cancer Center over patents directed to certain non-viral Sleeping Beauty system and CAR+ T cell and bioprocessing technology; as well as the May 28, 2019 license with the NIH referenced above, over patents directed to T-cell receptors targeting certain KRAS and p53 mutations.[14]

Argument

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.

Before it may execute the proposed license, NIH must find both that granting the license is a reasonable and necessary incentive to induce a company to commercialize the technology, and

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[9] https://www.sec.gov/Archives/edgar/data/1107421/000119312519063978/d678734d10k.htm
[10] https://www.sec.gov/Archives/edgar/data/1107421/000119312519063978/d678734d10k.htm
[11] https://www.sec.gov/Archives/edgar/data/1107421/000119312519063978/d678734d10k.htm
[12] https://www.sec.gov/Archives/edgar/data/1107421/000119312519063978/d678734d10k.htm
[13] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-and-intrexon-announce-cooperative-research-and
[14] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-oncology-announces-exclusive-license-national-cancer

"that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]" 35 U.S.C. § 209(a)(1)-(2).

We are concerned that the NIH has not conducted the analysis required by 35 U.S.C. § 209 to evaluate the necessity of granting exclusivity and determine the proper scope of the license. We address the NIH's analysis of the necessity of exclusivity and the scope of the license below.

Necessity of Exclusivity

We are concerned that NIH has not given any meaningful consideration to the first criteria for granting an exclusive license under Section 209: that "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[.]" 35 U.S.C. § 209(a)(1).

It is our understanding that the NIH has not undertaken a serious evaluation of the adequacy of existing incentives and subsidies, relating to practical application of the inventions, in order to evaluate whether or not exclusivity is a "reasonable and necessary incentive."

KEI asked Dr. Andrew Burke, the point of contact for the license, how the NIH determined that exclusivity is a reasonable and necessary incentive, including what analysis, if any, the NIH has undertaken in reaching that conclusion. Dr. Burke responded as follows: "An identified public health need, license applicant's commercial development ability at the time of application, 35 U.S.C. 209 and 37 CFR part 404." He did not answer KEI's questions about an economic analysis and consideration of other incentives.

The exchange is copied and pasted below.

KEI's Correspondence with Dr. Burke's Response regarding Exclusivity

3. On what basis did the NIH conclude that an exclusive license to Ziopharm was a necessary incentive under 35 U.S.C. § 209(a)(1)? **Answer: An identified public health need, license applicant's commercial development ability at the time of application, 35 U.S.C. 209 and 37 CFR part 404.**
a. Did you perform any analysis of other incentives such as Orphan Drug exclusivity, pediatric rare disease priority review vouchers, test data exclusivity, etc? **[No Answer]**
b. Did you estimate the cost of bringing the technologies to market? **[No Answer]**

Dr. Burke's response does not follow federal law and regulations governing exclusive licenses in federally-owned inventions. Neither 35 U.S.C. § 209 nor 37 C.F.R. § 404.7 refers to "[a]n identified public health need" or a "license applicant's commercial development ability at the time of application." Rather, they call upon the relevant agency to determine whether exclusivity 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[.]"

We interpret the word "necessary" in accordance with its plain meaning. Merriam-Webster defines "necessary" as "absolutely needed" or "required[,]" which is a different analysis from whether there is a public health need and the prospective licensee has the capacity to fulfill that need. A prospective licensee's capacity to commercialize a federally-owned invention certainly is relevant to whether it should be awarded a license. But Section 209 requires consideration of more than the licensee's capacity: it goes to whether there would be a willingness to undertake the investment in bringing a federally-owned invention to market, absent an exclusive license.

In order to conclude that an exclusive license is a 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. Dr. Burke's statements to KEI indicate that the NIH has not undertaken such an analysis.

Even if NIH's construction of Section 209(a)(1) were correct, we question how NIH concluded that Ziopharm is financially qualified to commercialize the subject technology. Ziopharm's own statements call into question its capacity to bring the licensed inventions to market.

In its most recent SEC 10-Q filing, Ziopharm states as follows:

> We have not generated significant revenue and have incurred significant net losses in each year since our inception. For the six months ended June 30, 2019, we had a net loss of $28.1 million, and, as of June 30, 2019, we have incurred approximately $594.4 million of accumulated deficit since our inception in 2003. We expect to continue to incur significant operating expenditures and net losses.[15]

The PHS Technology Transfer Policy Manual states that "no license applicant shall be awarded a license if that applicant [] has a current PHS license for use of a PHS invention and is delinquent in the payment of any royalties or fees due the PHS or is not meeting any commercial development milestone under the license agreement[.]"[16]

KEI asked Dr. Burke whether Ziopharm is "delinquent in the payment of any royalties or fees due on any patent license with NCI" and whether it "[h]as failed to meet any commercial development milestones[.]" Dr. Burke declined to answer, stating that "[t]his information is confidential."

[15] https://ir.ziopharm.com/sec-filings/sec-filing/10-q/0001193125-19-216056
[16] https://www.ott.nih.gov/sites/default/files/documents/policy/pdfs/300-policy.pdf

Scope of the License

Even if NIH properly evaluated the necessity of exclusivity, before it may grant the proposed license to Ziopharm, the NIH must engage in an additional analysis: It must establish "that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]" 35 U.S.C. § 209(a)(2).

The NIH may adjust the scope of an exclusive patent license along the following parameters:

- Term of exclusivity - how long the licensee may claim a monopoly on the right to market and sell the invention (i.e., five years, ten years, life of patent, etc.);
- Territorial reach (worldwide or limited to the U.S. or a particular geographic region); and
- Field of use (i.e., targeted diseases).

Under Section 209, the scope of the license must be balanced against the incentive necessary to induce a company to commercialize a federally-owned invention. There are at least six factors that should be considered when evaluating the necessary incentive:

1. The costs of financing research and development and bringing the invention to market, including obtaining FDA approval;
2. The government's investment in R&D and the development stage of the technology;
3. Any expected additional subsidies from governments or charities, including, for example, the Orphan Drug Tax Credit or additional grants or continued or new collaborations with the NIH or other government agencies;
4. The existence of other incentives, including, for example, test data protection, Orphan Drug exclusivity and awards of priority review vouchers;
5. The anticipated cost to manufacture the resultant invention; and
6. The expected post-market entry profitability of the invention, by year.

KEI asked Dr. Burke "[h]ow has/will NIH ensured that the licensing terms satisfy 35 U.S.C § 209(a)(2); namely, that the scope of the license is no broader than necessary." He responded that the determination can only be made after the public comment period has closed.

With respect to the duration of the license specifically, KEI asked:

> Is the period of exclusivity for the license to be life of patent or less than life of patent? If your answer is that the period of exclusivity is yet to be negotiated, have you ever considered a shorter period of exclusivity than life of patent? Will you consider one with respect to this license?

Dr. Burke responded: "The term of the license has not yet been established." He did not answer whether NIH has ever considered a shorter period of exclusivity than life of patent, or whether he would consider a shorter term than life of patent for the instant license.

Based on previous correspondence between KEI and Dr. Burke, as well as with other NIH technology transfer officers, it appears that the NIH's policy, when determining the scope of an exclusive patent license, is to consider only whether to limit the field of use, and to routinely grant the broadest possible rights in terms of duration of the license and territorial reach.

The terms of the May 28, 2019 Exclusive License Agreement, disclosed in Ziopharm's most recent SEC 10-q report, appear to confirm this. The duration of the May 28, 2019 license agreement is life of patent and the territorial reach is worldwide.[17] Other NIH technology transfer officers have told KEI that NIH typically grants exclusive licenses for "life of patent."

Section 209(a)(2) requires that the analysis regarding the scope of an exclusive license is a fact-specific, case-by-case determination. If, in every instance, the NIH negotiates a license for "life-of patent" when a shorter time period would suffice, it is not complying with Section 209.

3. The NIH has not been fully transparent about the license, impeding the public's right to comment under 35 U.S.C. § 209(e).

A federal agency may not grant an exclusive license in government-owned technology without first notifying the public of the prospective license, allowing a minimum 15-day period for the public to comment, and considering all timely submitted comments. 35 U.S.C. § 209(e).

In order for the public to meaningfully participate in the notice-and-comment process, it must have basic information about the licenses.

We appreciate the fact that Dr. Burke answered some of KEI's questions. He failed, however, to answer several questions that were directed at information germane to the analysis required under Section 209. The questions Dr. Burke declined to answer were as follows:

- "Did you perform any analysis of other incentives such as Orphan Drug exclusivity, pediatric rare disease priority review vouchers, test data exclusivity, etc?"
- "Did you estimate the cost of bringing the technologies to market?"
- "If . . . the period of exclusivity is yet to be negotiated, have you ever considered a shorter period of exclusivity than life of patent? Will you consider one with respect to this license?"
- "Did you seek the antitrust advice of the U.S. Attorney General regarding the license?"
- "What are royalty rates/payments will the NCI receive for the license?" and

[17] https://www.sec.gov/Archives/edgar/data/1107421/000119312519216056/d777738d10q.htm

- "Is Ziopharm delinquent in the payment of any royalties or fees due on any patent license with NCI? Has it failed to meet any commercial development milestones under any exclusive patent license agreement with NCI?"

With respect to all but the last two questions listed above, Dr. Burke declined to provide any answer whatsoever. With respect to the questions regarding royalty payments, Dr. Burke declined to answer on the basis that the requested information is confidential. We note that in Ziopharm's most recent SEC 10-q filing, the company disclosed in detail the terms of its May 28, 2019 Exclusive License Agreement with NCI, including the terms of its royalty payments.

We thus object to the license on the grounds that the NIH has withheld relevant information without a valid basis for doing so, impeding the public's right of comment under Section 209(e).

4. The NIH apparently 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.

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 Dr. Burke whether the NIH requested the advice of the U.S. Attorney General concerning the license. He 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 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.

This is a particularly important issue in this license, where a non-exclusive license to the subject T-cell therapies can and should be available to any firm developing these inventions. The NIH is creating a monopoly where a monopoly should not exist.

5. 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 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 Ziopharm 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 object to the proposed license for the reasons stated herein. If the NIH proceeds with the license over our objections, we urge that it 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