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Via Email: andy.burke@nih.gov

RE: 84 FR 2537. Prospective Grant of an Exclusive Patent License: Development and Commercialization of Cell Therapies for Cancer to Ziopharm Oncology, Inc.

Dear Dr. Burke,

We are writing to express our opposition to an exclusive license on the patent portfolio described in 84 FR 2537, related to Development and Commercialization of Cell Therapies for Cancer to Ziopharm Oncology, Inc. ("Ziopharm"), headquartered in Boston, MA.

Ziopharm Oncology, Inc, was registered in Delaware on May 16, 2005. According to their most recent 10-K filed with the Securities and Exchange Commission (SEC), for the fiscal year ending December 31, 2017, Ziopharm "is a biopharmaceutical company focused on discovering, acquiring, developing and commercializing next generation immunotherapy platforms that leverage gene- and cell-based therapies to treat patients with cancer on its own and with partners."[1] Ziopharm states that they are developing "two immuno-oncology platform technologies designed to utilize the patient's immune system by employing novel, controlled gene expression and innovative cell engineering technologies to deliver safe, effective, and scalable cell- and viral-based therapies for the treatment of multiple cancer types."[2]

Ziopharm Oncology, Inc, has several licensing and collaboration agreements with other entities[3], including a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) and Intrexon for the development of adoptive cell transfer (ACT)-based

[1] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 4
[2] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 4
[3] https://ziopharm.com/about/partnerships/

immunotherapies genetically modified using the Sleeping Beauty transposon/transposase system to express T-cell receptors (TCRs) for the treatment of solid tumors.[4]

As of December 31, 2017, Ziopharm Oncology, Inc, had incurred approximately $712.4 million of accumulated deficit and had approximately $70.9 million of cash and cash equivalents.[5]

According to their March 2018 SEC 10-K, Ziopharm Oncology, Inc, "have not demonstrated an ability to perform the functions necessary for the successful commercialization of any product candidates."[6] Their operations "have been limited to organizing and staffing our company, acquiring, developing and securing our proprietary product candidates, and undertaking preclinical and clinical trials of our product candidates."[7] Ziopharm Oncology, Inc, stated in their March 2018 SEC 10-K that they "neither have nor intend to establish internal research capabilities"[8] and they are "dependent upon pharmaceutical and biotechnology companies and academic and other researchers to sell or license us their product candidates and technology."[9]

The Federal Register notice 84 FR 2537 lists 47 patent documents filed in Argentina, Australia, Canada, China, the European Patent Office (EPO), Hong Kong, Israel, Japan, Korea, Mexico, New Zealand, Saudi Arabia, Singapore, Taiwan, the United States, and via the Patent Cooperation Treaty (PCT). According to the notice, all of the documents covered in the license are applications, as opposed to issued patents, including 11 provisional patent applications filed in the United States. Most of the 47 applications were filed less than 2 years ago, and many have not been published by their respective patent offices, which makes it impossible to examine the actual scope of the intellectual property assets that the NIH plans to license.

We note that, as described in the Federal Register notice 84 FR 2537, the proposed exclusive license currently covers patent documents filed in several developing countries. However, 8 of the patent documents listed in the Federal Register notice are PCT procedures. 5 of these applications were filed on September 2018, or afterwards, which means that they are well within the deadline to enter the national phase as provided under article 22 of the PCT. The notice states that the territory of the license "may be worldwide", but does not explains where the NIH plans to enter the PCT national phase. Therefore, the notice does not fully explains whether the proposed license will include patent documents filed in additional countries beyond the ones currently listed, or the totality of developing countries that will be covered by the license.

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[4] https://ir.ziopharm.com/news-releases/news-release-details/ziopharm-and-intrexon-announce-cooperative-research-and

[5] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 40

[6] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 47

[7] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 47

[8] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 47

[9] https://www.sec.gov/Archives/edgar/data/1107421/000119312518067077/d531986d10k.htm Page 47

The Federal Register notice divides the patents applications into 5 groups: A, B, C, D, and E. According to the notice, the field of use of the exclusive license will be specific to each of these 5 groups. The field of use for each group is described in the Federal Register notice as follows:

> Intellectual Property Group A is primarily directed to isolated T cell receptors (TCRs) reactive to mutated Kirsten rat sarcoma viral oncogene homolog (KRAS), within the context of several human leukocyte antigens (HLAs). Mutated KRAS, which plays a well-defined driver role in oncogenesis, is expressed by a variety of human cancers, including: pancreatic, lung, endometrial, ovarian and prostate. Due to its restricted expression in precancerous and cancerous cells, this antigen may be targeted on mutant KRAS-expressing tumors with minimal normal tissue toxicity.
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> Intellectual Property Group B is primarily directed to isolated TCRs reactive to mutated tumor protein 53 (TP53 or P53), within the context of several HLAs. P53 is the archetypal tumor suppressor gene and the most frequently mutated gene in cancer. Contemporary estimates suggest that >50% of all tumors carry mutations in P53. Because of its prevalence in cancer and its restricted expression to precancerous and cancerous cells, this antigen may be targeted on mutant P53-expressing tumors with minimal normal tissue toxicity.
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> Intellectual Property Group C is primarily directed to isolated TCRs reactive to mutated epidermal growth factor receptor (EGFR), within the context of HLA DPA1*02:01 and HLA DPB1*01:01. EGFR is a transmembrane protein involved in cell growth and proliferation signaling. Mutations in the gene encoding EGFR can lead to its overexpression, causing several types of cancer (e.g., non-small cell lung cancer (NSCLC)). Because of its prevalence in certain cancers and its restricted expression to precancerous and cancerous tissues, this antigen may be targeted on mutant EGFR-expressing tumors with minimal normal tissue toxicity.
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> Intellectual Property Group D is primarily directed to methods of isolating T cells which are reactive to mutated P53 antigens. Briefly, pools of 25-mer peptides covering known P53 “hotspot” mutations have been generated. These peptides may be pulsed into autologous antigen presenting cells which are subsequently co-cultured with the patient's isolated T cells. Reactive T cells are then purified and may be used as source material for the further isolation of mutant P53-targeting TCRs.
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> Intellectual Property Group E is primarily directed to a method of selectively sorting and expanding T cells which have been engineered to stably express a murine-human hybrid TCR; a TCR wherein the human constant region has been replaced with the corresponding murine constant region sequences. Unlike

typical OKT3 antibody-mediated cell expansion protocols, which operate in a non-specific manner to stimulate all T cells via the CD3 complex, the H57 antibody utilized in the claimed method(s) binds specifically to the mouse constant region domain of the hybrid TCR, leading to selective expansion of T cells expressing the desired exogenous receptor.

Based on size of the patent portfolio and the intent to include 5 different field of uses, this appears to be a fairly broad exclusive license. The NIH has not provided meaningful information to explain how they determined that the proposed license covering 47 patent documents and 5 different field of use, to be granted exclusively one company, meets the "reasonable and necessary" requirement as provided under 35 U.S. Code § 209.

From our reading of the license, IP groups A, B, and C relate to specific oncology targets (KRAS, p53, EGFR) of modified T cell receptors (including, we believe, CAR-T receptors). Since they are limited to specific targets and generation of the modified T cell by transposons, they may be reasonable, although we have not had the time to review the patent applications, much less predict what claim scope may issue.

IP groups D and E are broader, in that they relate to general methods that are not limited to the KRAS, p53, and EGFR targets. Insofar as the license is purported to be exclusive, it would be appropriate to limit the field to KRAS, p53, and EGFR and to use of transposon cell modification. Indeed, some of the IP groups specifically exclude retroviral and CRISPR modification techniques, and the more narrow limitation of the field would be appropriate an exclusive license.

On February 20, 2019, we asked the NIH the following questions about this proposed license: a) How much money has the NIH spent on research directly related to the technology to be licensed? and b) What is the status of the development of this technology? Specifically, what trials if any has the NIH funded or undertaken relating to this technology/treatment? As of today, the NIH has not provided answers to these questions.

Before the NIH grants a new or expanded license to Ziopharm Oncology, Inc., we expect the NIH to seek the advice of the Department of Justice antitrust authorities, as is required by

40 U.S. Code § 559 - Advice of Attorney General with respect to antitrust law.

The NIH should also make it clear that it has the responsibility under 35 USC § 209(a) to limit the scope of rights to that which are reasonably necessary to induce investment, and that among the options the NIH as are to limit the field of use or the years of exclusivity, and demonstrate to DOJ that the NIH has addressed this restriction in good faith.

In the event that the NIH decides to grant this exclusive license, we ask that the following safeguards be placed on the license.

1. **Price discrimination.** Any drug or other 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 does 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." There is ample evidence that federally funded inventions for the treatment of cancer are not widely available in developing countries. Examples of the access problems include Xtandi and the two new CAR T treatments, to mention a few.

3. **Global registration and affordability.** The license should require Ziopharm Oncology, Inc. to disclose the steps it will take to enable the timely registration and availability of the drug 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)/ 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 drug 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 drug.

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 USC § 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.

Sincerely,

James Love
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On behalf of the following organization and individuals:

Organizations:

- Knowledge Ecology International (KEI)
- Public Citizen
- Social Security Works (SSW)
- Union for Affordable Cancer Treatment (UACT)

Individuals

- James Love
- Manon Ress