July 2, 2019

Andrew Burke, Ph.D.
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Via email: andy.burke@nih.gov

Re: 84 FR 28063, Prospective Grant of an Exclusive Patent License: Development and Commercialization of Cell Therapies for Cancer, to Tailored Therapeutics, LLC ("Tailored"), located in Potomac, MD.

Dear Dr. Burke:

Knowledge Ecology International (KEI) and the Union for Affordable Cancer Treatment (UACT) are writing to provide comments on the prospective grant of an exclusive patent license for the development and commercialization of cell therapies for cancer, to Tailored Therapeutics, LLC. ("Tailored"), located in Potomac, MD.

On June 24, 2019, Claire Cassedy from KEI emailed you five questions about the proposed license. You replied with answers to her questions on June 24, 2019. On June 26, 2019, Luis Gil Abinader from KEI emailed you eight additional questions about the proposed license. You replied with answers to his questions on June 27, 2019. Thank you again for your replies. Claire Cassedy also emailed you on June 24, 2019 regarding whether the NIH has sought advice from the Attorney General as is required under 40 U.S.C. § 559, we have yet to receive a reply to that inquiry. We are providing a copy of these emails, including your replies, attached with our comments.

The NIH should comply with 40 U.S.C. § 559, which is not preempted by the Bayh-Dole Act.

At the appropriate time in the licensing process, we expect the NIH to obtain advice from the Attorney General (as is required under 40 U.S.C. § 559) to determine if the "disposal to a private interest would tend to create or maintain a situation inconsistent with antitrust law."

40 U.S.C. § 559 is not preempted by the Bayh-Dole Act, which 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[.]" 35 U.S.C. § 211.

The Bayh-Dole Act sets out the areas where 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 does not include 40 U.S.C. § 559.

Intellectual property

The Federal Register notice divides the intellectual property covered in the proposed license into two groups: Group A and Group B. Group A includes two U.S. provisional patent applications. Group B includes one U.S. provisional patent application and a PCT procedure.

	NIH Reference Number	**Type**	**Number**	**Filing Date**	**Title**
Group A	E-166-2018-0-US-01	Provisional	62/749,750	October 24, 2018	HLA-A3-RESTRICTED T CELL RECEPTORS AGAINST MUTATED RAS
	E-029-2019-0-US-01	Provisional	62/795,203	January 22, 2019	HLA CLASS II-RESTRICTED T CELL RECEPTORS AGAINST RAS WITH G12R MUTATION
Group B	E-094-2018-0-US-01	Provisional	62/661,941	April 24, 2018	METHODS OF PRODUCING T CELL POPULATIONS USING HYDROXYCITRIC ACID AND/OR A SALT THEREOF
	E-094-2018-0-PCT-02	PCT	PCT/US2019/028513	April 22, 2019	METHODS OF PRODUCING T CELL POPULATIONS USING HYDROXYCITRIC ACID AND/OR A SALT THEREOF

We searched the three U.S. provisional patent applications using the USPTO Public Patent Application Information Retrieval (PAIR) system and the Patent Application Full Text and Image Database (AppFT). This search returned zero results. We note that these provisional applications were filed in April 2018, October 2018, and January 2019, and the USPTO normally does not publish these types of applications for 18 months, pursuant to 35 U.S.C. § 122.

We also searched the PCT application PCT/US2019/028513 using the WIPO PatentScope database, and obtained zero results. We infer from the Federal Register notice that the earliest priority of the PCT procedure was the U.S. provisional application 62/661,941, filed April 2018. Article 21 of the Patent Cooperation Treaty provides that, subject to exceptions, "the international publication of the international application shall be effected promptly after the expiration of 18 months from the priority date of that application."[1] If the priority was indeed filed on April 2018, the application PCT/US2019/028513 may not be published for several more months.

Our search suggests that none of the patent documents listed in the Federal Register notice have been published. In your June 27, 2019 email you confirmed that none of these applications have been published. In order to have a clear understanding of the intellectual property that will be covered in the license we have to be able to read the patent claims. Patent documents often contain additional useful information, such as the name of the inventors involved. Not being able to scrutinize those documents prior to the deadline established in the Federal Register notice undermines our ability to understand and comment on whether the proposed license is "a reasonable and necessary incentive" as provided under 35 U.S.C. § 209.

According to the Federal Register notice the territory of the proposed license "may be worldwide." The PCT application was filed in April 2019, which means that it is still well within the deadline to start the national phase in PCT member countries, including several developing countries. The Federal Register notice failed to explain in which countries the NIH intends to start the national phase, despite the fact that this is information necessary to understand and comment on whether the proposed license is "a reasonable and necessary incentive" as provided under 35 U.S.C. § 209. Nevertheless, we will assume that the geographical scope of the license could include several developing countries via the PCT procedure.

Field of use

The proposed license divides the field of use in two: one that applies to Groups A and B, and one that applies to Group B. The field of use that applies to Groups A and B is the following:

> "Development, manufacture and commercialization of autologous, peripheral blood T cell therapy products engineered by CRISPR to express T cell receptors reactive to mutated KRAS, as claimed in the Licensed Patent Rights, for the treatment of human cancers. Specifically excluded from this field of use are retrovirally-engineered peripheral blood T cell therapy products for the treatment of human cancers.
>
> Development, manufacture and commercialization of companion diagnostics approved or cleared by the FDA or equivalent foreign regulatory agency for Licensee-proprietary T cell therapy products."

[1] https://www.wipo.int/pct/en/texts/articles/a21.html#_21

The field of use that applies to Group B is the following:

> "Development, manufacture and commercialization of autologous, peripheral blood T cell therapy products engineered by CRISPR to express T cell receptors reactive to mutated p53, as claimed in the Licensed Patent Rights, for the treatment of cancer in humans.
>
> "Development, manufacture and commercialization of autologous, tumor infiltrating lymphocyte (TIL)-based adoptive T cell therapy products reactive to mutated p53, isolated as claimed in the Licensed Patent Rights, for the treatment of human cancers. Specifically excluded from this field of use are genetically engineered TIL cell therapy products for the treatment of human cancers.
>
> Development, manufacture and commercialization of companion diagnostics approved or cleared by the FDA or equivalent foreign regulatory agency for Licensee-proprietary T cell therapy products."

The Federal Register notice further explains the following about Group A:

> "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."

The Federal Register notice provides the following information about Group B:

> "Intellectual Property Group B is primarily directed to methods of preparing isolated populations of T cells by culturing them in the presence of hydroxycitric acid and/or a salt thereof, and methods of treating cancer using populations of T cells cultured in such a manner."

KEI sought the advice of a scientist and attorney with extensive expertise in intellectual property in the field of life sciences, who provided us with the following comment:

> "The Field is fairly limited to CRISPR-facilitated T cell modification; it excludes the kind of technology found in CART therapies (good and bad; limited license that encourages a competitive alternative to CART, but not competition within CART). It's also limited to specific T cell receptor sequences to KRAS oncoprotein targets, and to targeting p53 oncoproteins by chemically modifying T cells. Without looking at the patent claims it's hard to guess what they are hoping for; what they will get is likely to be narrower. So it

could be an important license but from this first pass not an unduly broad or anti-competitive one."

On June 24, 2019, Claire Cassedy from KEI asked you the following questions via email:

1. At what stage of development are the inventions listed?

2. Has the government funded any clinical trials relevant to these technologies?

3. If the government has provided funding, how much has been spent by the government on these trials? Can you provide NCT numbers?

4. How many years of exclusivity have been offered in this agreement, and what will the royalty rate be?

5. Regarding the company to receive the licenses, Tailored Therapeutics, LLC are any former NIH employees associated with the company?

On June 24, 2019, you emailed a reply with answers to each question. An excerpt of your email is reproduced below and a full copy is attached to these comments.

1. At what stage of development are the inventions listed?
Answer: With respect to the advertised fields of use, the technologies are at a "pre-clinical" stage of development.

2. Has the government funded any clinical trials relevant to these technologies?
Answer: I am not aware of any US government-funded clinical trials utilizing the referenced technologies within the advertised fields of use.

3. If the government has provided funding, how much has been spent by the government on these trials? Can you provide NCT numbers?
Answer: NA

4. How many years of exclusivity have been offered in this agreement, and what will the royalty rate be?
Answer: These terms will be the subject of negotiation and are not known at this time.

5. Regarding the company to receive the licenses, Tailored Therapeutics, LLC are any former NIH employees associated with the company?
Answer: Questions regarding employees or associates of the company should be directed to the company.

Tailored Therapeutics, LLC

According to the Maryland Business Entity Search website, Tailored Therapeutics was registered on June 5, 2018.[2] Tailored Therapeutics describes itself as "a development stage biotechnology company working on a new way of treating cancer – cell therapy – that uses the patient's own immune cells to attack the tumor."[3] According to its website, Tailored Therapeutics has four product candidates, all of which are in preclinical stage: TCEL-100, TCEL-200, and TT-400 for solid tumors; and TT-300 for pancreatic, colorectal, and lung.

The previous license to Tailored Therapeutics, LLC

On September 28, 2018, the NIH published the Federal Register notice 83 FR 49109, which also described a prospective exclusive license to Tailored Therapeutics (hereinafter the "2018 exclusive license").[4] We asked you whether the 2018 exclusive license and the current license concerned the same company, and you replied in the affirmative in your June 27, 2019 email. We also asked you whether the 2018 exclusive license had been executed, and you replied in the affirmative in your June 27, 2019 email. Although we note that the NIH could have mentioned in the Federal Register notice that the proposed license intended to amend an existing license, describe the existing license, and explain the extent of the proposed amendment, we appreciate your June 27, 2019 email in response to our questions.

Our questions on the 2018 exclusive license and your June 27, 2019 reply are copied below.

> "Is the prospective licensee mentioned in the Federal Register notice 84 FR 28063, Tailored Therapeutics, the same company that appeared as prospective licensee in the Federal Register notice 83 FR 49109, published on September 28, 2018?"
>
> "Answer: Yes, both FR notices concern the same company."
>
> "Was the license proposed in the Federal Register notice 83 FR 49109 executed?"
>
> "Answer: Yes, the license was executed."
>
> "Will the exclusive license proposed in the Federal Register notice 84 FR 28063 amend the previous license described in the Federal Register notice 83 FR 49109? In which ways and to what extent?"
>
> "Answer: If the proposed license described in 84 FR 28063 is executed, it will be as an amendment to the company's existing license. Should this occur, the existing license would be amended to include the patent rights listed in 84 FR 28063 in the fields of use described in the same."

[2] https://egov.maryland.gov/BusinessExpress/EntitySearch/BusinessInformation/W18873646
[3] https://tailored-therapeutics.com/
[4] https://www.federalregister.gov/d/2018-21096

> “If this is the case, what is the rationale for granting additional exclusive rights to a company that presumably has outstanding obligations under a previous license?”
>
> “Answer: The company requested a broader scope to their existing license and provided an adequate commercial development plan describing how it will bring the referenced patent rights to practical application within the fields of use described.”

The 2018 exclusive license included 36 patent documents divided into three groups: Groups A, B, and C. The 36 applications were filed in Australia, Canada, China, the European Patent Office, Hong Kong, Israel, Japan, Korea, Mexico, New Zealand, Saudi Arabia, Singapore, the United States, and included three international PCT applications.

The 2018 exclusive license described its intellectual property groups A, B, and C 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.”
>
> “Intellectual Property Group C 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 may be purified and expanded in vitro to generate an autologous cell therapy product. The expanded cells may be administered to the patient and mediate tumor regression.”

With regards to the field of use there appear to be some coincidences in both Federal Register notices. For example, both notices have the following paragraph in their field of use sections:

"Development, manufacture and commercialization of autologous, peripheral blood T cell therapy products engineered by CRISPR to express T cell receptors reactive to mutated KRAS, as claimed in the Licensed Patent Rights, for the treatment of human cancers. Specifically excluded from this field of use are retrovirally-engineered peripheral blood T cell therapy products for the treatment of human cancers."

The Ziopharm Oncology exclusive license

On February 7, 2019, the NIH published the Federal Register notice 84 FR 2537, describing a prospective exclusive license to Ziopharm Oncology, Inc. KEI, Public Citizen, Social Security Works, and UACT filed comments to the NIH on this license, which are available here: https://www.keionline.org/29777

Although the prospective licensee in that case is a different company, there is a least one patent document, 62/749,750, that is listed in the Federal Register notice 84 FR 2537 as well as the current Federal Register notice, 84 FR 28063. In your June 27, 2019 reply to our email you explained that you were not aware of a relationship between Tailored Therapeutics and Ziopharm Oncology. It is unclear whether Ziopharm Oncology and Tailored Therapeutics have any business relationship, or share any of their stockholders, nor whether these proposed licenses include safeguards against potential anti-competitive behaviors that these two companies may engage in during the exploitation of the underlying exclusive rights.

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 cell therapy 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 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 Tailored Therapeutics to disclose the steps it will take to enable the timely registration and availability of the cell

therapy or other 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 cell therapy or other 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 cell therapy or other 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 $1 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.

Sincerely,

Kathryn Ardizzsone and Luis Gil Abinader, on behalf of:

Knowledge Ecology International (KEI)
Union for Affordable Cancer Treatment (UACT)

And in their personal capacity,

James Love
Manon Ress
Luis Gil Abinader