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Re: Prospective Grant of Exclusive License: The Development of Anti-CD70 Chimeric Antigen Receptors (CARs) for the Treatment of Chronic Myelogenous Leukemia

Dear Dr. Burke,

Knowledge Ecology International (KEI) is responding to the notice published in the Federal Register on April 22nd, 2016 entitled "Prospective Grant of Exclusive License: The Development of Anti-CD70 Chimeric Antigen Receptors (CARs) for the Treatment of Chronic Myelogenous Leukemia" [81 FR 23737], available at: https://federalregister.gov/a/2016-09324

The National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (HHS), is considering the grant of a worldwide exclusive license for United States owned patents for "Anti-CD70 Chimeric Antigen Receptors" (Patent Application No. 62/088,882,) and "Anti-CD70 Chimeric Antigen Receptors" (PCT Application No. PCT/US2015/025047) to a Maryland-based company, Dedalus Pharma, LLC ("Dedalus")

According to the Federal Register notice, the field of use may include the use of anti- CD70 chimeric antigen receptor (CAR) in autologous adoptive T-cell transfer therapy for the treatment of chronic myelogenous leukemia.

KEI opposes the grant of exclusive license in this case unless:

1. The NIH conducts sufficient analysis and limits the terms and scope of the license as required under 37 CFR part 404.7(a)(1)(iiii),

2. The license contains sufficient safeguards regarding affordability and reasonable pricing of the products developed under the patent licenses,
3. The license places restrictions on charging US residents higher prices than the median prices charged in countries with the seven largest GDP and per capita incomes of 50 percent or more than the United States per capita income,
4. The license requires products be affordable in developing countries, and explicitly allows the NIH to grant licenses for the patents to the Medicines Patent Pool (MPP) for use in developing countries;
5. The license requires transparent reporting on drug development costs, royalties and revenues.

About the KEI

Knowledge Ecology International (KEI) is a nongovernmental organization based in Washington, DC, with an office in Geneva, Switzerland, that advocates for access to affordable medicines, with a focus on human rights and social justice. For more information, see: http://keionline.org.

Why the anti-CD70 CAR may be important

Chronic myeloid leukemia (CML) is a cancer where bone marrow produces too many myeloid white blood cells. According to the American Cancer society, there will be an estimated 8,220 new cases and 1,070 death from CML in 2016.[1] By 2020 the prevalence of CML is expected to reach 112,000 in the US.[2] On average someone with CML can expect to live until the age of 78 years, but they must remain on treatment for the rest of their lives. Current treatments range from tyrosine kinases, such as Imatinib, to stem cell transplants.

Inducing cytotoxic t-cells to kill a patient's own malignant cells was first proven effective by maturing and activating dendritic cells to present the proper cancer targeting antigens to one's t-cells. A new wave of autologous cellular immunotherapy therapy takes this concept a step further and directly equips t-cells with the ability to seek out tumors. Promising results from anti-CD19 CAR used to treat B-cell acute lymphoblastic leukaemia have reinvigorated this field.[3] Ultimately, the best outcome would be for the patient to develop lifelong immunological memory and therefore the ability to mount a persistent antitumor response. This is especially relevant for chronic neoplasms. However, scientists must determine the proper ligands or receptors to target that would minimise adverse reactions such as severe cytokine release syndrome. A potential candidate is the CD27 ligand, CD70. CARs directed

[1] American Cancer Society: Cancer Facts and Figures 2016. Atlanta, Ga: American Cancer Society, 2016.Available online.Exit Disclaimer Last accessed January 14, 2016.

[2] Huang X et al. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer.2012 Jun 15;118(12):3123-7.

[3] Khalil DN et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol. 2016 May;13(5):273-90.

against CD70 have shown promising results in murine animal studies.[4] The added advantage of using CD70 is that it is over expressed on a variety of different cancer cells including myeloid leukemia cells.

The NIH role in the development of the CD70 CARs

The NIH and specifically the NCI has a long history with CML research and treatment dating back to the 1960s. The NCI takes pride in the fact that its funding was instrumental in discovery of a breakthrough drug, imatinib, that changed CML from a death sentence to a chronic illness.[5]

Currently, clinicaltrials.gov lists 17 active or open clinical trials sponsored and/or funded by the NIH that include CAR based therapies. According to the NIH- RePort, the NIH has spent $140,634,329 in grants relating to CAR research.[6] NCI senior investigator Dr. Steven Rosenberg has over a thousand co-authored publications, and is a pioneer in both basic and clinical research in cell based immunotherapies. Dr. James C. Yang, also a senior investigator, is the lead inventor behind the anti-CD70 CARs designed at the NCI.

A reasonable search has uncovered no public records available on Dedalus Pharma, LLC. It is alarming that the NIH is considering licensing a medical technology developed entirely by public funds to a company where it's impossible to determine their capacity or capability in further developing adoptive cell transfer therapy. This puts into question the credibility of this company.

The NIH has invested considerable public resources into CAR research and has at the very least the infrastructure to conduct phase 1 clinical trials. It is therefore unsettling how untransparent the licensing process is.

Federal regulations on the use of exclusive licenses

As noted in the Federal Register notice, the licenses are expected to comply with the public safeguards found in 35 U.S.C. 209 and 37 CFR part 404.

Specifically, we are concerned about the obligations in 35 U.S.C. 209 (a):

> ***§209. Licensing federally owned inventions***
>
> (a) Authority.—A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if—
>
> (1) granting the license is a reasonable and necessary incentive to—

[4] Shaffer DR., T cells redirected against CD70 for the immunotherapy of CD70-positive malignancies. Blood. 2011 Apr 21;117(16):4304-14.
[5] http://www.cancer.gov/research/progress/discovery/gleevec
[6] https://projectreporter.nih.gov (search term "chimeric antigent receptor")

(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;

(2) the Federal agency finds that the public will be served by the granting of the license, as indicated by the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public, and 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;

(3) the applicant makes a commitment to achieve practical application of the invention within a reasonable time, which time may be extended by the agency upon the applicant's request and the applicant's demonstration that the refusal of such extension would be unreasonable;

(4) granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws; and

(5) in the case of an invention covered by a foreign patent application or patent, the interests of the Federal Government or United States industry in foreign commerce will be enhanced.

We also note that the term “practical application” is defined by 35 U.S.C. 201(f) as follows:

(f) The term "practical application" means to manufacture in the case of a composition or product, to practice in the case of a process or method, or to operate in the case of a machine or system; and, in each case, under such conditions as to establish that the invention is being utilized and that its benefits are to the extent permitted by law or Government regulations available to the public on reasonable terms. [emphasis added]

Under 37 CFR 404.7(a), the NIH is required to make determinations regarding the necessity of the grant of an exclusive license:

“(1) Exclusive, co-exclusive or partially exclusive domestic licenses may be granted on Government owned inventions, only if
…
(ii) After expiration of the period in § 404.7(a)(1)(i) and consideration of any written objections received during the period, the Federal agency has determined that;

(A) The public will be served by the granting of the license, in view of the applicant's intentions, plans and ability to bring the invention to the point of practical application or otherwise promote the invention's utilization by the public.

(B) Exclusive, co-exclusive or partially exclusive licensing 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; and

(C) 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 ask the NIH to provide additional assurances that the products developed under this license be made available to the public at prices that are reasonable and affordable. Among other things, this can include a provision in the license that states:

> The NIH will normally expect the licensee to make products available to the public in the United States at prices no higher than the median price charged in the seven countries with the largest GDP that have per capita incomes of at least half that of the United States.

If the geographic area includes worldwide rights, the products should be made available at affordable prices in developing countries.

To the best of our knowledge, the NIH has not demonstrated why granting an exclusive license to the company is necessary. We request the NIH or NCI provide the public with evidence that they have determined an exclusive license is necessary for the development of the patented inventions, and there exists a written analysis which establishes that this evaluation has been done. Calling for public comment on the license, and then providing almost none of the relevant information, renders the public comment process ineffective, with regards to the public's role in objecting to licenses that undermine their rights to obtain access to the benefits of the inventions on favorable terms, or address other public interest issues.

The NIH should also have the option of providing a non-exclusive license to the Medicines Patent Pool (MPP) to permit competitive supply by generic drug manufacturers, for use in developing countries. Here we note that GlaxoSmithKline (GSK) has recently announced it has begun negotiations with the MPP to license the patents for its oncology products. Certainly the NIH can be at least as sensitive to the health needs of patients living in developing countries as is the big pharma company GSK.

Since the statute requires that the "scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application" we request a copy of any analysis, if any, that was done to consider how many years of

exclusive rights were necessary to bring the invention to practical application. We also propose the following terms for the contract:

> The exclusive rights will extend to five years from the first sale of a product receiving approval by the U.S. FDA, or until the license holder recovers at least $1 billion in global sales from the product, whichever is shorter, and thereafter, the license will become non-exclusive. After the first five years of exclusivity, the NIH can extend the exclusivity by another 3 years, upon a showing that such extension is reasonable in light on the risk adjusted R&D costs to bring the product to market, and the net revenues from sales.

KEI notes that the 5 year period, with possible extensions, follows NIH practice, prior to 1984, and other NIH licenses have had terms shorter than the life of patent. For example, in October 2001, the NIH exercised an option to make the licenses for the AIDS drug DDI non-exclusive, ten years after the initial FDA registration (see: Videx® Expanding Possibilities: A Case Study, NIH, National Institutes of Health Office of Technology Transfer, September 2003) in order to expand access to the drug and to obtain lower cost supplies for federal programs.

The NIH could consider different time periods for exclusivity, but if the answer is always life of patent, no matter what the facts are, then the NIH is no longer meeting the requirements of 35 U.S.C. 209 to ensure that the "scope of exclusivity is not greater than reasonably necessary."

Transparency

KEI is also asking for more transparency regarding the costs of developing new products, the pricing, sales and royalty payments on products.

We object to any license that is not made public. Moreover, all reports specified in the license, including those described in the license appendices, should be public. If the NIH insists on transparency (as was common practice and acceptable in earlier years), the prospective license applicants would agree. The company is getting the license before making any significant investments, and the NIH's invention may be worth several billion dollars.

We ask the NIH to create a requirement for annual reports on R&D outlays, including an obligation that the company reports the following for each clinical trial that tests products covered by the patents:

1. ClinicalTrials.Gov identifier
2. Phase
3. Conditions
4. Interventions:
5. Title Acronym/Titles

6. Outcome Measures
7. Sponsor/Collaborators
8. Other Study IDs
9. Expenditure (for that year)

With regards to sales prices, we request an annual report that provides data on the following variables:

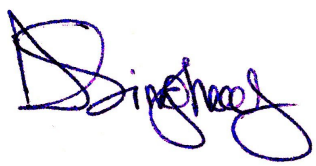
1. Units of sales, by country
2. Revenue for sales, by country

With regards to government subsidies for research, we request a report that provides data for the following, by year:

1. Grants and research contracts from government agencies, with data on the funding agency, the identifier of the grant or contract, and the amount of the grant or contact.
2. Tax credits associated with R&D for the product, including the U.S. orphan drug tax credit, broken down by the type of credit and the expenditure the credit was associated with (such as a specific trial).
3. Other government R&D subsidies.

We hope the NIH will seriously consider these comments, and use its authority to advance affordable access to medical technologies that will benefit the overall health of the American public and society at large.

Respectfully submitted,



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