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Re: Prospective Grant of an Exclusive License: The Development of an Anti-GPC3 Chimeric Antigen Receptor (CAR) Based on HN3 and YP7 for the Treatment of Human Cancers

Dear Dr. Lambertson,

Knowledge Ecology International (KEI) is responding to the Notice published in the Federal Register on May 18th, 2016 entitled "*Prospective Grant of an Exclusive License: The Development of an Anti-GPC3 Chimeric Antigen Receptor (CAR) Based on HN3 for the Treatment of Human Cancers*" (81 FR 31246) and *"Prospective Grant of an Exclusive License: The Development of an Anti-GPC3 Chimeric Antigen Receptor (CAR) Based on YP7 for the Treatment of Human Cancers"* (81 FR 31251), available at: https://federalregister.gov/a/2016-11659 and https://federalregister.gov/a/2016-11660

The National Institutes of Health (NIH), Department of Health and Human Services (HHS), is considering the grant of an exclusive license for United States owned patents for "High-affinity Monoclonal Antibodies To Glypican-3 And Use Thereof"(Patent Applications 61/654232, PCT/US2013/043633 and 14/403896) to Lentigen Technology, Inc. in the United States, Australia, Canada, the European Union, Russia, China, Hong Kong, Japan, Taiwan, South Korea and Singapore.

According to the Federal Register notice, the field of use may include the development of a chimeric antibody receptor (CAR) based autologous transplant using lymphocytes transduced with anti-Glypican-3 (GPC3) expressing constructs for antibody's HN3 or YP7 to treat cancers expressing GPC3.

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 404.7 (a)(1)(iiiii);

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 that products are affordable in developing countries, and explicitly allows the NIH to grant licenses to the patents to the Medicines Patent Pool (MPP) for use in developing countries; and
5. The license requires transparent reporting on drug development costs, royalties and revenues.

About the commenters

Knowledge Ecology International (KEI) is a non-profit, non-governmental 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 anti-GPC3 antibodies may be important

Liver cancer is the sixth most common cancer globally and the 3rd most deadly cancer.[1] Up to 90% of all liver cancers develop from chronic liver disease, most often due to viral infection or chronic alcohol use. While incidence rates of liver cancer in Japan and Europe have either stabilized or declined, they are still increasing in the US.[2] American prospective cohort studies have established that obesity also plays an important role in the development of hepatocarcinoma, especially in men.[3] Hepatocellular carcinoma (HCC) is the most common form of liver cancer. Early detection is crucial for curative treatment of HCC since once symptoms set in, the cancer can not be treated with currently available therapies.[3] Standard therapy for earlier stages of HCC include surgery, radiation, sorafenib or transplantation.[4] With such limited treatment options for both later stage cancer and non-invasive treatment options for early phase HCC, better therapeutics are greatly needed.

In recent years, the use of antibodies in cancer treatment has been a game changer. Antibody based therapies are often better tolerated by patients and more efficacious than conventional cytotoxic agents. Furthermore, antibodies can also be directed against soluble cancer markers making them practical tools for non-invasive diagnostics. It is therefore crucial to identify markers that are specific to tumors.

Glypican-3 (GPC3) is overexpressed in HCC cells even when the tumors are small and make a good biomarker candidate for early stage HCC. Furthermore, GPC3 is also found in

[1] http://globocan.iarc.fr/Pages/fact_sheets_population.aspx
[2] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma.Lancet. 2012 Mar 31;379(9822):1245-55.
[3] de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol. 2012;56
[4] http://www.cancer.gov/types/liver/hp/adult-liver-treatment-pdq#section/_64

blood serum and can be used both for histological and serum diagnosis of HCC. It would therefore be very valuable to develop antibodies with high specificity and avidity against GPC3.[5]

Accordingly, Chugai Pharmaceuticals with Roche and, Bristol- Myers Squibb are developing anti-GPC3 for HCC treatment. Roche's GC33 (RO5137382) antibody has completed phase 2 clinical trials (NCT01507168). BMS has MDX-1414 in preclinical development.

Dr. Mitchell Ho's lab at the NCI has developed two antibodies against GPC3, identified as HN3 and YP7 and are the subject of the licences discussed in these comments. The Human antibody HN3, has the added advantage of being able to inhibit HCC growth and makes it an especially a good candidate for treatment.[6] Ho *et al.,* tested both HN3 and YP7 conjugated to the immunotoxin PE33 and found both to have anti-tumor activity in mice, HN3-PE33 being particularly effective. This study indicates that HN3 would be an attractive candidate to develop an antibody drug/ immunotoxin conjugate against HCC.

The field of use for the prospective exclusive license of HN3 and YP7 is for Chimeric antibody receptors (CAR) for immunotherapy against cancer.

The NIH role in the development of the anti-GPC3 antibodies and CARs

The NIH has considerable interest in both liver cancer and CARs.

In 2013 alone, the National Cancer Institute has invested over $63,977,360 into research relating to liver cancer and, of that funding, approximately 35% went into the research and development of treatments.[7] Since 2008, Dr. Ho, the listed inventor of the HN3 and YP7 antibodies, received a total of $5,746,146 in grant funding from the NIH for antibody based cancer therapies.[8]

The NIH is considering an exclusive license to Lentigen Technologies Inc. for the use of it's anti- GPC3 for CAR based immunotherapy. However, the NCI houses CAR development platforms and is already conducting research in CAR based therapies and other similar immunotherapies at its NCI cancer research center and NIH clinical center.[9] Infact, the researcher who pioneered CAR t-cell therapy is a senior investigator and chief of surgery at the NIH clinical center. Why has the NIH chosen to exclusively license out its technology to a private company if it has the infrastructure and expertise to conduct the research and development in-house?

[5] Glypican-3 antibodies: a new therapeutic target for liver cancer

[6] Gao W, Tang Z, Zhang YF, Feng M, Qian M, Dimitrov DS, Ho M. Immunotoxin targeting glypican-3 regresses liver cancer via dual inhibition of Wnt signalling and protein synthesis. Nat Commun.2015 Mar 11

[7] http://fundedresearch.cancer.gov/nciportfolio/search/SearchForm (search term: cancer type liver)

[8] https://projectreporter.nih.gov/reporter.cfm

[9] http://www.cancer.gov/about-cancer/treatment/research/car-t-cells

Currently the NIH Clinical center is conducting (active or recruiting) at least 8 clinical trials using CARs (table 1).

Table 1: Active Clinical trials sponsored by the NCI at the NIH clinical center [10]

Clinical trial identifier	Title	Target	disease	Phase (Status)
NCT02659943	T Cells Expressing a Fully-Human Anti-CD19 Chimeric Antigen Receptor for Treating B-cell Malignancies	CD19	advanced B-cell cancer	Phase 1 (recruiting)
NCT02658929	A Phase 1 Study of bb2121 in BCMA-Expressing Multiple Myeloma	BCMA	Multiple Myeloma	Phase 1 (recruiting)
NCT02315612	Phase I Dose Escalation Study of Anti-CD22 Chimeric Receptor T Cells in Pediatric and Young Adults with Recurrent or Refractory CD22-expressing B Cell Malignancies	CD22	B-cell malignancies	Phase 1 (recruiting)
NCT02107963	A Phase I Trial of T Cells Expressing an Anti-GD2 Chimeric Antigen Receptor in Children and Young Adults with GD2+ Solid Tumors	GD2	GD2+ solid tumors	Phase 1 (recruiting)
NCT01593696	Anti-CD19 White Blood Cells for Children and Young Adults With B Cell Leukemia or Lymphoma	CD19	B Cell Leukemia or Lymphoma	Phase 1 (ongoing)
NCT01454596	A Phase I/II Study of the Safety and Feasibility of Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Malignant Gliomas Expressing EGFRvIII	EGFRvIII	Malignant Gliomas	Phase 1/ 2 (ongoing)
NCT01087294	Administration of Anti-CD19-Chimeric-Antigen-Receptor-Transduced T-cells from the Original Transplant Donor to Patients with Recurrent or Persistent B-Cell Malignancies After Allogeneic Stem Cell Transplantation	CD19	B-cell Malignancies	Phase 1 (ongoing)
NCT00924326	Assessment of the Safety and Feasibility of Administering T cells Expressing an anti-CD19 Chimeric Antigen Receptor to Patients with B-cell Lymphoma	CD19	B-cell Lymphoma	Phase 1 (ongoing)

[10] http://clinicalstudies.info.nih.gov/index.html (search term: chimeric antigen receptor)

With the NIH being critical in the development of CAR based therapies, it reasonable to expect the public to not pay high prices for this form of therapy. Without having access to the licenses, there is no way for the public to ensure that these therapies be made affordable as this would be important for the medical technology to have practical application to the public.

Transparency is also lacking in how the NIH prioritizes the granting of its licenses. For example, has the NIH considered developing HN3 as an ADC since proof-of-concept experiments have been conducted in Dr. Ho's lab?[11] It would seem that a HN3 based ADC would reach the market before an HN3 based CAR immunotherapy. The answers to these questions are difficult to ascertain from publicly available resources. Furthermore, we tried to contact Dr. Ho regarding these questions and have yet to hear back from him.

Further concerns regarding transparency are raised in the related section below.

Why patent license terms are important

We are concerned that the NIH's exclusive licensing of patent rights of HN3 and YP7 to Lentigen Technology will result in:

1. Lentigen requiring U.S. residents to pay more than other countries for a anti-GPC3 bassed therapeutics developed at public expense (see http://keionline.org/xtandi for a petition to the NIH relating to a prostate cancer drug invented at UCLA on federal grants and priced far higher in the United States than in any other country);
2. Delays in the entry of competitive suppliers for the manufacturing and distribution of the Lentigen that will increase affordability and reduce supply shortages,
3. Barriers to innovation, including enhancements that would make CARs more effective in low resource settings.

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—

[11] Gao W, Tang Z, Zhang YF, Feng M, Qian M, Dimitrov DS, Ho M. Immunotoxin targeting glypican-3 regresses liver cancer via dual inhibition of Wnt signalling and protein synthesis. Nat Commun.2015 Mar 11

(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 changed 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.

However, as far as we know, the NIH has not demonstrated why granting an exclusive license to the company is necessary. We request that the NIH provide public evidence that the NIH has determined an 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, makes the public comment process ineffective, as regards 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 in addressing 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 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 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."

NIH Start-Up Exclusive License Agreements

According to the notice, Lentigen Technology Inc. is seeking to obtain the exclusive licences as a Start-Up company. This program is meant to assist start-up companies and provide financial incentives to "minimize the barriers to entry". The NIH Office of Technology Transfer defines start up companies as "less than 50 employees, in operation less than 5 years, less than $5M in funding since incorporation, and majority owned by individuals, hedge funds, or venture funds or by a company that is majority owned by individuals, hedge funds or venture funds".[12] Furthermore, under 37 CFR 404.7(a)(1)(iv) "The Federal agency has given first preference to any small business firms submitting plans that are determined by the agency to be within the capability of the firms and as having equal or greater likelihood as those from other applicants to bring the invention to practical application within a reasonable time."

We object to the grant of Start-Up Exclusive License because Lentigen Technology Inc. is a "**wholly owned subsidiary** of Miltenyi Biotec".[13] Miltenyi Biotec is a 25 year old company known for their high quality antibodies and instruments used in cell separation, flow cytometry and other characterization assays important in biomedical research. Additionally,

[12] https://www.ott.nih.gov/nih-start-exclusive-license-agreements
[13] http://lentigen.com/about-us/

they conduct clinical trials and provide analytical and manufacturing support for medical research. They are headquartered in Germany, have centers and subsidiaries all over the world and employ over 1200 scientist, physicians and engineers. Miltiny is not a Start-up company and it would be unfair to other start-up companies if Lentigen Technology Inc. were to benefit from an NIH Start-Up Exclusive License Agreement.

Transparency

KEI is also asking for more transparency regarding the costs of developing new products, and 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), Lentigen 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 regard to sales prices, we request an annual report that provide data on the following variables:

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

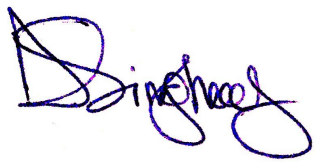
With regard to government subsidies for research, we request a report that provides data for the following, by year:

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 out by the type of credit and the expenditure the credit was associated with (such as a specific trial); and

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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