June 3rd, 2016

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Re: Prospective Grant of Exclusive Start-up Option License: Anti-TNF Induced Apoptosis (ATIA) Diagnostic Markers and Therapies

Dear Mr.Greene,

Knowledge Ecology International (KEI) is responding to the Notice published in the Federal Register on May 19th, 2016 entitled *"Prospective Grant of Exclusive Start-up Option License: Anti-TNF Induced Apoptosis (ATIA) Diagnostic Markers and Therap*ies," (81 FR 31652), available at: https://federalregister.gov/a/2016-11769

The National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services is considering the grant of a worldwide exclusive license for United States owned patents for "Anti-TNF Induced Apoptosis (ATIA) Diagnostic Markers and Therapies"(Patent Application No. 13/322863, PCT/US2010/36394 and 61/182072) to IntelliPanel Medical, LLC based in Philadelphia.

According to the Federal Register notice, the field of use may include "Anti-TNF Induced Apoptosis (ATIA) for the diagnosis, monitoring, and treatment of Glioblastoma Multiforme (GBM)."

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)(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 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 may ATIA be important

Glioblastoma is a rare and aggressive form of brain cancer. It is the most fatal type of brain cancer and even under treatment the median overall survival is about 15 months. Currently, treatment consists of surgical resection followed by chemotherapy and radiation therapy. Several forms of immunotherapy against glioblastoma are under investigation in clinical trials and show promising results. An important component in immunotherapy is identifying markers that are specific to the cancer being treated.

Diagnosing and monitoring glioblastoma include MRI and CT scans but there are important limitations to consider. The first hurdle lies in identifying the type of neoplasm at the time of diagnosis. Secondly, monitoring cancer progression using brain imaging techniques following tumor resections can be challenging due to post-surgical inflammation. Therefore, a qualitative serum based diagnostic test would be very beneficial.

Dr. Zhenggang Liu, the listed inventor, discovered that Anti-TNF Induced Apoptosis (ATIA) is highly expressed in glioblastoma. This would make it an attractive marker for use in immunotherapy. Moreover, ATIA appears to confer a protective phenotype against apoptosis, consequently, an inhibitor against ATIA could make tumors cells susceptible to cells death.

In vitro results indicate that ATIA also exists in soluble form in the presence of cells overexpressing ATIA, suggesting that a serum based diagnostic assay can also be developed to detect glioblastoma specifically.

Altogether the properties of ATIA would make it a versatile target for both drug and diagnostic development for cancer patients, whose prognosis are grim.

The NIH's role in Glioblastoma research

The NCI is currently running 139 active clinical trial for treatments against Glioblastoma.[1] In 2013 it spent around $171,170,883 on brain cancer research.[2] Dr. Zheng-Gang Liu is a senior investigator at the NCI's Laboratory of Genitourinary Cancer Pathogenesis and studies TNF signaling in macrophage differentiation. Since 2007 his lab has received $7,137,095 in NIH funding to to study cell signaling and apoptosis.

Glioblastoma multiforme is an orphan diseases and the company that will sponsor an ATIA based treatments to combat this form of brain cancer will surely benefit from the Orphan Drug Tax Credit.

Treatment for orphan and rare diseases are often priced extraordinarily high. The average cost per patient per year of an orphan drug is $137,782.[3] Lenalidomide, for example, indicated for multiple myeloma, cost $164,859 per patient in 2014.[3]

These prices are detrimental to treatment accessibility for patients in the Unites States and even more so for patients living in developing countries. A company that benefits from publicly funded and owned research and, tax rebates should be required to make their treatments available at a reasonable price that will not put an undue burden on patients. Any license awarded by the NIH should include terms that guarantees the affordability of the end products. This is discussed further below.

Why patent license terms are important

We are concerned that the NCI exclusive licensing of patent rights to IntelliPanel Medical will result in:

1. IntelliPanel Medical requiring U.S. residents to pay more than other countries for a [med tech] 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 IntelliPanel Medical that will increase affordability and reduce supply shortages,
3. Barriers to innovation, including enhancements that make the vaccines more effective in low resource settings.

Federal regulations on the use of exclusive licenses

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[1] http://www.cancer.gov/about-cancer/treatment/clinical-trials/search/results?protocolsearchid=15058674

[2] http://fundedresearch.cancer.gov/nciportfolio/search/ResultManager (search: Brain cancer)

[3] ORPHAN DRUG REPORT 2014. Evaluate Pharma, from: http://info.evaluategroup.com/rs/evaluatepharmaltd/images/2014OD.pdf

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—
>
> (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 or NCI provide public evidence that they have 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."

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), [Company] 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:

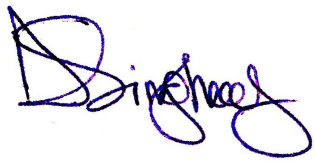
1. Units of sales, by country
2. Revenue for sales, by country

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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