

August 27, 2018

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RE: Prospective Grant of Exclusive Patent License: Radiotherapeutics Against Somatostatin-Receptor Expressing Neuroendocrine Tumors, 83 FR 35663 (<https://www.federalregister.gov/d/2018-16065>)

Dear Michael Shmilovich:

Knowledge Ecology International and the Union for Affordable Cancer Treatment (UACT) are writing to provide comments on the prospective grant of an exclusive patent license for a radiotherapeutic against neuroendocrine tumors that express somatostatin receptors to Molecular Targeting Technologies, Inc. (MTTI), a Delaware corporation.

According to the Federal Register notice, the prospective patent license will be granted “worldwide” and for a field of use “not broader than radiotherapeutics for somatostatin-receptor expressing neuroendocrine tumors.”

According to the Delaware Department of State Division of Corporations, MTTI was incorporated on December 20, 2001. As described on their website, “MTTI is a privately held biotechnology company translating novel radiopharmaceuticals for disease treatment and diagnosis.”¹ The co-founder and CEO of MTTI is Koon Yan “Chris” Pak, Ph.D.

Dr. Pak has previously worked with Centocor and has served as the President of the Chinese American Society of Nuclear Medicine, the Vice Chair of the Global Monte Jade Science and Technology Association, and the Chairman of the Chinese Entrepreneur Association which he co-founded.²

MTTI currently has several therapeutics and diagnostics indications in their pipeline.³

The Federal Register notice 83 FR 35663 describes the invention as follows:

¹ <https://web.archive.org/web/20180808003041/http://www.mtarget.com/>

² <https://web.archive.org/web/20180826003534/http://www.mtarget.com/ABUS.html>

³ <https://web.archive.org/web/20180826034052/http://www.mtarget.com/PIPE.html>

The invention pertains to a radiotherapeutic against neuroendocrine tumors that express somatostatin receptor. Radionuclide therapies directed against tumors that express somatostatin receptors (SSTRs) have proven effective for the treatment of advanced, low- to intermediate-grade neuroendocrine tumors. The subject radiotherapeutic covered by the subject patent estate includes a somatostatin (SST) peptide derivative like octreotate (TATE), conjugated to an Evans Blue (EB) analog, and further chelated via DOTA to therapeutic radionuclide ¹⁷⁷Lu, a beta emitter. The EB analog reversibly binds to circulating serum albumin and improves the pharmacokinetics of SST peptide derivatives and reduce peptide-receptor radionuclide therapy toxicity. EB analog conjugated to octreotate (EB-DOTATATE) has been shown by the inventors to provide reversible albumin binding in vivo and extended half-life in circulation. When EB-TATE is slowly released into the tumor microenvironment, tumor uptake and internalization into SSTR positive tumors resulted in delivery of radioactive particles and tumor cell killing. EB-TATE displayed significantly more favorable pharmacokinetics than TATE alone by achieving higher tumor to non-tumor penetration as evidenced by positron emission tomography.

A Clinicaltrials.gov search for the term “EB-TATE” reflects that there are at least 2 clinical trial studies recruiting that relate to EB-TATE for the treatment of neuroendocrine tumors⁴. These two clinical studies are identified as NCT03308682 and NCT03478358. These two studies received funding from the NIH and are co-sponsored by the Peking Union Medical College Hospital and the NIH’s National Institute for Biomedical Imaging and Bioengineering (NIBIB), according to Clinicaltrials.gov. Both are Phase 1 studies, started in April 30, 2017 and their estimated completion date is May 1, 2018 (NCT03308682) and August 1, 2018 (NCT03478358). Their estimated enrollment is 30 participants (NCT03308682), and 20 participants (NCT03478358), respectively.

https://docs.google.com/spreadsheets/d/1zfprL_CelaGQ8BExHPUzslnahVQdXNk40nQfA5Wi33U/edit?usp=sharing

The Federal Register notice 83 FR 35663 only describes one patent document, the International Patent Application PCT/US2017/054863 filed October 3, 2017. This is a very recent application and, at the time this comment is being filed, this patent document does not appear published in the WIPO PatentScope database nor other patent databases. A patent search based on the phrase “Evans Blue Derivatives and Their Use As Radiotherapy” returns one PCT document filed by the NIH with Xiaoyuan Chen and Orit Jacobson Weiss as inventors, but identified with the International Patent Application No. PCT/US2017/031696, which is different from the patent document described in the Federal Register notice 83 FR 35663. The lack of clear and publicly available information regarding the actual scope of the invention claimed in the application that the NIH plans to license to MTTI undermines the general public’s ability to comment on this prospective exclusive license.

⁴ <https://clinicaltrials.gov/ct2/results?cond=EB-TATE&term=&cntry=&state=&city=&dist=&Search=Search>

Moreover, according to the Federal Register notice 83 FR 35663 in addition to the International Patent Application PCT/US2017/054863, the prospective exclusive license will include “all continuing U.S. and foreign patents/patent applications thereof.” The Federal Register notice does not explain how many additional “continuing U.S. and foreign” applications the NIH has filed or plans to file based on the same priority number, nor whether the NIH plans to start the national PCT phase for this invention in developing countries. In order to analyze whether in this case an exclusive license is a reasonable and adequate incentive consistent with the statutory requirements of 35 USC § 209, and to properly respond to the Federal Register notice, it is necessary to have complete information on the actual geographical scope of the prospective exclusive license, and to have a discussion of the role of government agencies in funding research related to the invention, and the expected costs of bringing a new treatment to market. The notice 83 FR 35667 does not contain such information.

At this point, KEI opposes the granting of an exclusive license, on the grounds that the NIH have not provided sufficient information to evaluate a request for an exclusive license.

However, in the event that the NIH does issue an exclusive license, we propose several conditions on the exclusive license to ensure that the benefits of the invention are available to the public on reasonable terms,⁵ and that the scope of the exclusive rights are limited to that which are reasonably necessary to induce the investment necessary to achieve practical application of the invention.⁶

1. No discrimination against US residents in pricing

We ask that the NIH include language in the proposed exclusive license to ensure that the prices in the U.S. for any drug, vaccine, medical device or other health technology using the inventions are not higher than the median price charged in the seven countries with the largest gross domestic product (GDP), that also have a per capita income of at least 50 percent of the United States, as measured by the World Bank Atlas Method.

We consider this a modest request to protect U.S. residents, who paid for the R&D that created the licensed inventions.

2. Reduce term of exclusivity when revenues are large

In addition to an external reference pricing test, we propose that the exclusivity of the license in the U.S. should be reduced when the global cumulative sales from products or services using the inventions exceed certain benchmarks.

⁵ Required by 35 USC § 201(f).

⁶ 35 USC § 209.

Given the modest cost of acquiring an NIH patented invention, the amount of money the developer needs in sales to justify additional investments in R&D is reduced, as compared to cases where a company develops or acquires the technology from non government sources.

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.”

One possible implementation of revenue benchmarks is as follows: exclusivity will be reduced by one year for every \$500 million in revenue equivalents, earned after the first \$1 billion, where revenue equivalent is defined as global cumulative sales plus market entry rewards as well as government grants or tax credits, for the product or products using the invention. However, the NIH could choose different benchmarks, so long as the limits on exclusivity address the requirements of 35 USC 209, that the incentive is “not greater than reasonably necessary.”

3. Developing countries

We are concerned that several NIH-funded inventions are not accessible in developing countries, due to prices that are high and not affordable in markets where per capita incomes are significantly lower than the United States. For this reason, we ask the NIH to limit the exclusivity in the license to countries that have per capita incomes that are at least 30 percent of the United States.

We also ask the NIH to reach out to the Medicines Patent Pool (MPP), in order to enter into an agreement that gives the MPP an option to negotiate non-exclusive open licenses for the inventions in developing countries.

4. Transparency

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 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 USC § 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 market.

Sincerely,

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