July 2, 2019

Michael Shmilovich, Esq.
Senior Licensing and Patent Manager
31 Center Drive, Room 4A29, MSC2479
Bethesda, MD 20892-2479

Via email: shmilovm@mail.nih.gov

Re: 84 FR 28063, Prospective Grant of Exclusive Patent License: Lutetium-177 Radiotherapeutics Against Somatostatin-Receptor Expressing Neuroendocrine Tumors, to Molecular Targeting Technologies, Inc. (MTTI), a Delaware corporation, with its principal place of business in West Chester, Pennsylvania.

Dear Michael Shmilovich:

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 a Lutetium-177 radiotherapeutics against somatostatin-receptor expressing neuroendocrine tumors, to Molecular Targeting Technologies, Inc. (MTTI), a Delaware corporation.

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 25, 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 26, 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."

The Bayh-Dole Act 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

With regards to the intellectual property to be licensed under the proposed agreement, the Federal Register notice 84 FR 28063 provides a list with one Patent Cooperation Treaty (PCT) international application and five additional patent documents.

The NIH Federal Register notice failed to explain whether the five patent documents (not including the PCT application) are issued patents or pending applications. The NIH notice also failed to explain where these five patent applications were filed, but we infer, based on their NIH reference number, that these applications were filed in the United States (2), China (1), the European Patent Office (1), and Japan (1). However, as we explain in more detail below and as you have confirmed to us in your email dated June 27, 2019, the proposed license also includes a national patent application filed in Singapore via the PCT procedure.

NIH reference number	Patent document	Filing date	Title
E-150-2016-0-US-01	62/333,427	5/9/2019	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.
E-150-2016-0-PCT-02	PCT/US2017/031696	5/9/2017	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.
E-150-2016-0-CN-03	201780029003X	11/9/2018	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.
E-150-2016-0-EP-04	17796666	11/12/2018	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.
E-150-2016-0-JP-05	2018-558662	11/8/2018	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.
E-150-2016-0-US-06	16/099,488	11/7/2018	Chemical Conjugates of Evans Blue Derivatives and Their Use as Radiotherapy and Imaging Agents.

The field of use and geographical scope is described as follows in the Federal Register notice:

> "The prospective patent license will be granted worldwide and limited to the extent that the above referenced patents or patent applications cover lutetium-177 radiotherapeutics for somatostatin-receptor expressing neuroendocrine tumors."

In addition to the six patent documents listed above, the Federal Register notice has a catchall phrase stating that the intellectual property of the proposed exclusive license also includes "[...] all continuing U.S. and foreign patents/patent applications thereof [...]" As we interpret it, this phrase implies that all additional applications that entered their national phase via the PCT procedure PCT/US2017/031696 will be covered in the intellectual property scope of this license.

A search for the PCT application PCT/US2017/031696 using the WIPO database PatentScope returns one document, which has the publication number WO2017196806.[1] According to PatentScope, the PCT application PCT/US2017/031696 entered the national phase in the European Patent Office, Japan, the United States, but also in Singapore. The national number in Singapore according to PatentScope is 11201809982R. A search for the patent application number 11201809982R using the Intellectual Property Office of Singapore online search[2] returns one document, which has the United States of America as applicant and is titled *Chemical conjugates of evans blue derivatives and their use as radiotherapy and imaging agents*. This is the exact same title of the patent documents listed in the Federal Register notice.

In your June 27, 2019 email response to our questions you confirmed that the Singapore application 11201809982R will be covered in the proposed license and that it was not listed in the Federal Register notice because the filing number had not been reported to you on time. We thank you for confirming that this application will be covered in the license.

We also note that the NIH has the obligation to provide, when available, complete and accurate information about the intellectual property that it intends to license exclusively, including the national patent offices where relevant applications have been filed, in order to allow the public to fully evaluate and comment on whether the geographical scope of a proposed exclusive license complies with 35 U.S.C. § 209, or if the license will be consistent with the policies set out in the "United States Public Health Service Technology Transfer Policy Manual, Chapter No. 300, PHS Licensing Policy," which states that "PHS seeks to promote commercial development of inventions in a way that provides broad accessibility for developing countries."

Molecular Targeting Technologies, Inc.

According to the Delaware Department of State Division of Corporations, MTTI was incorporated on December 20, 2001.[3] MTTI's website is http://www.mtarget.com/SFNT.html, which you confirmed to us in your June 27, 2019 email. According to its website, the mission of

[1] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2017196806
[2] https://www.ip2.sg/RPS/WP/CM/SearchSimpleP.aspx?SearchCategory=PT
[3] https://icis.corp.delaware.gov/Ecorp/EntitySearch/NameSearch.aspx

MTTI is to "translate novel radiopharmaceuticals for treatment and diagnosis of rare diseases."[4] The website describes four targets for therapeutics and diagnostics, which are "supported by published data and ongoing Phase I clinical trials."[5]

One of the targets for therapeutics that Molecular Targeting Technologies lists on its website is "EBTATE (Lu-177-EB-DOTA-TATE)", which is described as follows:

> "EBTATE (Lu-177-EB-DOTA-TATE), a neuroendocrine tumor therapy (NET). EBTATE shows several-fold increase of blood half-life and enhanced tumor uptake over existing peptide receptor radionuclide therapy (PRRT)."[6]

MTTI also notes the following about its EBTATE target:

> "First-in-human studies demonstrated a single low-dose EBTATE treatment appears to be safe and effective in the treatment of NEN. Demonstrated remarkably higher uptake and retention in neuroendocrine neoplasms. EBTATE could be effective with fewer, significantly lower doses than Lutathera®. An EBTATE suitable patient population includes metastatic, SSRTpositive NET patients.
>
> "EBTATE is a peptide receptor radionuclide therapy (PRRT) for the treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors. The drug binds to the somatostatin receptor expressing NET cells and destroys them. 80% NETs overexpress somatostatin receptors (particularly SSTR2).
>
> "EBTATE was designed to overcome rapid clearing of Lutathera® by chemically incorporating an Evans Blue moiety in that framework. By increasing residence in albumin, EBTATE substantially lengthens the in vivo half-life increasing the probability of binding between drug and target. That enables fewer, lower doses of the radiotherapeutic."[7]

MTTI also states on its website that the intellectual property related to MTTI's EBTATE target is the PCT patent application PCT/US2017/054863, and that it holds a worldwide exclusive license over this patent application granted by the NIH.[8]

Previous NIH license to MTTI

On July 27, 2018, the NIH published the Federal Register notice 83 FR 35663, which also described a prospective exclusive license to Molecular Targeting Technologies (hereinafter "the

[4] http://www.mtarget.com/SFNT.html
[5] http://www.mtarget.com/SFNT.html
[6] http://www.mtarget.com/SFNT.html
[7] http://www.mtarget.com/mm5/pdfs/pipeline/MTTI%20Asset%20EBTATE.pdf
[8] http://www.mtarget.com/mm5/pdfs/pipeline/MTTI%20Asset%20EBTATE.pdf

2018 exclusive license").[9] On August 27, 2018, KEI and UACT filed comments regarding the 2018 exclusive license, which are available here: https://www.keionline.org/28697.

The Federal Register notice for the 2018 exclusive license described one patent document:

> "HHS Ref. E-150-2016-1-PCT-01, International Patent Application PCT/US2017/054863 filed October 3, 2017, entitled "Chemical Conjugates of Evans Blue Derivatives and Their Use As Radiotherapy And Imaging Agents."

The PCT patent application listed in the Federal Register notice of the 2018 exclusive license[10] has the same title as the applications listed in the Federal Register notice for the 2019 proposed license. The PCT application listed in the Federal Register notice of the 2018 exclusive license has two inventors, Xiaoyuan Chen and Orit Jacobson Weiss, who are the same two inventors listed in the PCT application described in the 2019 Federal Register notice. The geographical scope and the field of use of the 2018 exclusive license were described as follows:

> "The prospective patent license will be granted worldwide and in a field of use not broader than radiotherapeutics for somatostatin-receptor expressing neuroendocrine tumors."

A press release from Molecular Targeting Technologies dated October 8, 2018 and excerpted below suggests that the 2018 proposed license was indeed executed with this company:

> "Molecular Targeting Technologies, Inc. (MTTI) announced today that the National Institute of Biomedical Imaging and Bioengineering (an Institute within the National Institutes of Health) granted MTTI an exclusive worldwide patent commercialization license. This patent estate invented by Drs. Xiaoyuan Chen and Orit Jacobson covers a radiotherapeutic (177Lu-DOTA-EB-TATE (EBTATE)) with potential uses for treating Neuroendocrine Neoplasms (NENs)."[11]

The 2019 Federal Register notice says that the proposed license would amend "an existing license."[12] In your June 27, 2019 email you confirmed that the license in the Federal Register notice 83 FR 35663 has been executed and that this was the license that would be amended by the current Federal Register notice. You also confirmed in the same email that the 2018 exclusive license was executed. We thank you for clarifying that the license that would be amended is the 2018 exclusive license. We also note that the Federal Register notice could have been more specific and, for instance, cite the Federal Register notice of the license that would be amended.

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[9] https://www.federalregister.gov/d/2018-16065
[10] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2019070236
[11] http://www.mtarget.com/mm5/pdfs/2018Oct8NETNIH.pdf
[12] https://www.federalregister.gov/d/2019-12708

We asked you how the proposed license would amend the 2018 exclusive license. Our question on this issue and your answer in your June 27, 2019 email are copied below.

> "How 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 35663?"
>
> "The amendment adds the IP rights listed in this FR notice but narrows the field of use of the license to 177Lu radiotherapeutics. If you look through the claims of the published PCT there is a list of other potential radionuclides that can be used therapeutically."

We asked you what is the rationale for granting additional exclusive rights to a company that presumably has outstanding obligations under a previous license. Our question and your June 27, 2019 response are copied below.

> "What is the rationale for granting additional exclusive rights to a company that presumably has outstanding obligations under a previous license?"
>
> "The company has no outstanding obligations. The company and NIH discussed that the instant patent rights should be included to complete the patent portfolio licensed by the company so long as it is constrained by field of use."

177 Lu-DOTA-EB-TATE therapeutics

The Federal Register notice provides the following description of the invention:

> "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. 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 “DOTA-EB-TATE” returns two phase I clinical trials, NCT03308682[13] and NCT03478358,[14] both related to neuroendocrine tumors. These trials were co-sponsored by the Peking Union Medical College Hospital and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), according to clinicaltrials.gov.

We asked you whether these trials were related to the proposed license, and you replied that they were not. Our exchange on this question, including your answer, is copied below.

> “A clinicaltrials.gov search for the term “DOTA-EB-TATE” returns two phase I clinical trials, NCT03308682 and NCT03478358, both related to neuroendocrine tumors. These trials were co-sponsored by the Peking Union Medical College Hospital and the National Institute of Biomedical Imaging and Bioengineering (NIBIB), according to clinicaltrials.gov. Are these trials related to the proposed exclusive license?”
>
> “Not related.”

However, a paper published November 2018 in the Journal of Nuclear Medicine by Xiaoyuan Chen, one of the inventors in the PCT application covered in the proposed license, and eight other co-authors reported the results of the clinical trial NCT03308682.[15] That paper describes the clinical trial NCT03308682 as a “noncontrolled, nonrandomized, nonblinded first-in-humans study” that explored “the safety and dosimetry of a long-acting radiolabeled somatostatin analog, 177Lu-1, 4, 7, 10-tetra-azacyclododecane-1, 4, 7, 10-tetraacetic acid-Evans blue-octreotate (177LuDOTA-EB-TATE).”[16]

The paper co-authored by Xiaoyuan Chen suggests that in “a recently finished phase III clinical trial, a treatment with 177Lu-DOTATATE resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide long-acting repeatable (LAR) among patients with advanced midgut NET.”[17] The paper further explains that “the promising results from this trial” led to the approval of Lutathera by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[18] According to the FDA approval letter dated January 26, 2018, Lutathera is indicated “for the treatment of somatostatin receptor positive GEP-NETs including foregut, midgut, and hindgut neuroendocrine tumors in adults.”[19] The original FDA NDA applicant was Advanced Accelerator Applications USA, Inc.[20]

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[13] https://clinicaltrials.gov/ct2/show/NCT03308682
[14] https://clinicaltrials.gov/ct2/show/NCT03478358
[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[19] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208700Orig1s000ltr.pdf
[20] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208700Orig1s000ltr.pdf

The NCT03308682 trial exposed five patients to 177Lu-DOTA-EB-TATE and compared them with three patients that received Lutathera (177Lu-DOTATATE).[21] The conclusion of this clinical trial, as reported by Xiaoyuan Chen et al. in the Journal of Nuclear Medicine, was the following:

> "By introducing an albumin-binding moiety, 177Lu-DOTA-EBTATE showed significantly higher NET uptake and retention over 177Lu-DOTATATE. This first-in-humans study demonstrates that 177Lu-DOTA-EB-TATE is safe and well tolerated in NET patients.[22]

We recall that Molecular Targeting Technologies, the prospective licensee in this case, states on their website that: "EBTATE was designed to overcome rapid clearing of Lutathera® by chemically incorporating an Evans Blue moiety in that framework. By increasing residence in albumin, EBTATE substantially lengthens the in vivo half-life increasing the probability of binding between drug and target. That enables fewer, lower doses of the radiotherapeutic."[23]

We also recall that the Federal Register notice 84 FR 28063 states the following: "EB-TATE displayed significantly more favorable pharmacokinetics than TATE alone by achieving higher tumor to non-tumor penetration as evidenced by positron emission tomography."

In summary, based on our own research and information available in the Federal Register notice, 177Lu-DOTA-EBTATE potentially has more favorable pharmacokinetics compared to 177Lu-DOTATATE, a therapy for neuroendocrine tumors recently approved by the FDA. We asked you whether this was correct. Our exchange on this question is copied below.

> KEI: "Based on our own research, our understanding is that the invention covered in the proposed license, 177Lu-DOTA-EBTATE, has more favorable pharmacokinetics compared to 177Lu-DOTATATE, a therapy for neuroendocrine tumors recently approved by the FDA and marketed under the brand name Lutathera. Is this correct?"
>
> NIH: "We hope so as does the company; however, this remains to be determined through controlled clinical trials."

NIH RePORTER project number EB000073

A NIH RePORTER search for "NCT03308682" in the "ClinicalTrials.gov ID" field returns one project identified with the number EB000073and titled *Laboratory of molecular imaging and nanomedicine*. This project received $27,897,781 in funding over the course of 9 years. The principal investigator in this project was Xiaoyuan Chen, who is also one of the inventors in the PCT application PCT/US2017/031696. The table below provides information on the total cost by year of the project number EB000073, based on data retrieved from the NIH RePORTER.

[21] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[22] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6225536/pdf/1699.pdf
[23] http://www.mtarget.com/mm5/pdfs/pipeline/MTTI%20Asset%20EBTATE.pdf

Project	Project Title	Contact PI/ Project Leader	FY	Admin IC	Total Cost
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2018	NIBIB	$3,716,858
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2017	NIBIB	$2,628,647
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2016	NIBIB	$4,443,729
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2015	NIBIB	$3,090,898
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2014	NIBIB	$3,046,083
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2013	NIBIB	$2,833,485
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2012	NIBIB	$2,930,853
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2011	NIBIB	$3,139,811
EB000073	LABORATORY OF MOLECULAR IMAGING AND NANOMEDICINE	CHEN, XIAOYUAN	2010	NIBIB	$2,067,417

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 drug 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 Molecular Targeting Technologies, Inc, to disclose the steps it will take to enable the timely registration and availability of the drug 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 drug 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 drug 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 one 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 Ardizzone 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