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Michael Shmilovich, Esq.
Senior Licensing and Patent Manager
31 Center Drive, Room 4A29, MSC2479
Bethesda, MD 20892-2479
phone number 301-435-5019
Via: shmilovm@mail.nih.gov

Re: Comments by KEI on Prospective Grant of Exclusive Patent License: MicroRNA Therapeutics for Treating Squamous Cell Carcinomas to miRecule, Inc.

Dear Mr. Shmilovich,

Knowledge Ecology International (KEI) is writing to comment on the Prospective Grant of Exclusive Patent License: MicroRNA Therapeutics for Treating Squamous Cell Carcinomas to miRecule, Inc., noticed in the Federal Register on August 7, 2017 (82 FR 36809). In this letter, we ask several questions about the prospective license, and propose license terms to address four areas, pricing, transparency, access to know-how and materials, and working of the patent.

1. Context

We were unable to find much information about miRecule from a search of Internet linked pages. On August 8, 2017, the company web page, http://mirecule.com, was a WordPress Blog

with just three public pages. The page on technology says “Our lead candidate is MIR101, a miR mimic designed to treat head and neck squamous cell cancer (HNSCC).”

We were able to identify Anthony Saleh, PhD, as a contact for the company, and Dr. Saleh provided KEI with information about himself and the company.

This is a case in which the NIH is proposing to give an exclusive license to a company created by a former NIH employee, whose work on the same technology was financially and logistically supported by the NIH for several years, as a government employee, with access to various NIH resources and facilities.

As publicly disclosed on his LinkedIn profile, Dr. Anthony Saleh was employed by the NIH from 2008 to May 2016.

From May 2011 to August 2014, according to Dr. Saleh’s LinkedIn profile, his employment at the NIH included the following:

1. Awarded a competitive RNAi screening Grant ($100,000)
2. Published six peer-reviewed papers and two employee invention reports
3. Developed cell-based assays that screen siRNAs and miRNA mimics targeting oncogenic signaling and survival in head and neck squamous cell cancer (HNSCC)
4. Integrated genomic and functional screening data to identify superior drug targets with clear patient subpopulations in HNSCC
5. Designed and synthesized a microRNA mimicking therapeutic agent that displays strong anti-tumor activity in xenograft HNSCC models
6. During Dr. Saleh’s last two years with the NIH he also claims to have been employed by a private company, BioHealth Innovation, Inc. as an Associate Entrepreneur in Residence.

From August 2014 to May 2016, according to the same LinkedIn profile, Dr. Saleh:

1. Directed analyses as part of 100-member TCGA Head and Neck, Cervical, Pan-Cancer Immunity, and Pan-Squamous Cell Cancer working groups
2. Designed and executed orthotopic and xenograft mouse models of breast and head and neck cancers, testing single agent and radiation and chemotherapy combinations including PD-L1

During his employment at the NIH, Dr. Saleh published 3 articles on head/neck cancers.

1. Conditional deletion of nonmuscle myosin II-A in mouse tongue epithelium results in squamous cell carcinoma.
2. Tapping microRNA regulation networks through integrated analysis of microRNA-mRNA high-throughput profiles.

3. Signaling Networks of Activated Oncogenic and Altered Tumor Suppressor Genes in Head and Neck Cancer.

It is our opinion that Dr. Saleh has done impressive research at the NIH on the inventions to be licensed, and he seems to be both a talented researcher and a good salesperson for the technology.

At present, miRecule has no salaried employees, and is seeking funding and/or partnerships from third parties to advance the development of the drug.

The Federal Register notice mentions that "the inventors . . . currently have a CRADA with NIDCD exploring . . . in treating head and neck squamous cell carcinoma (HNSSC)." Dr. Saleh confirmed in a phone call that miRecule recently signed CRADA with the NIH relating to the licensed technology, but declined to give KEI a copy.

For KEI to constructively comment on the prospective license, we should be able to see what the Cooperative Research and Development Agreement (CRADA) says.

2. Questions about the prospective license

Q1. Can you tell us the names of the inventors of the licensed technology?

Q2. When was the CRADA signed?

Q3. Please provide a copy of the CRADA mentioned in the federal register notice.

Q4. Can you tell us if MIR101 is a compound that originated at the NIH or from a non-federal source?

Q5. Can you provide any information about federal government funding of the technology that the NIH is proposing to license? Or, does the NIH even keep track or summarize its role in these projects?

Q6. Is the NIH proposing or considering providing Dr. Saleh and/or miRecule with any funding to develop this technology into a treatment for cancer?

Q7. Did the NIH undertake any economic analysis to see if the terms of the license for the patented inventions are limited as to the years of exclusivity or other conditions, so that, as required by 35 USC 209, "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application"?

Q8. Has the NIH proposed any terms that ensure that a product developed from the invention would be “available to the public on reasonable terms,” as is required by the Bayh-Dole Act?

Q9. Has the NIH proposed that the product be no more expensive in the United States than in other high income countries?

Q10. What efforts did the NIH undertake to market the licenses to these patents to others, including, for example, firms or other organizations with more financial capacity to develop a product?

Q11. Did any other persons or firms express interest in licensing these patents?

Q12. Does the NIH have a conflict of interest policy as regards licensing inventions to former employees who worked on the same technology? If so, what do those policies say?

Q13. How many years will miRecule have exclusive rights over the technology which is the subject of the prospective license?

Q14. What is the royalty on the license?

Q15. What are the obligations of the miRecule to invest in clinical testing of the invention? For example, if there is no clinical testing initiated with 3 years, does miRecule retain the exclusive rights?

3. Suggestions regarding the license terms

We have four areas of concern with this license. These include pricing, transparency, access to know-how and materials, and working of the patent. Our proposals for terms in the license to protect the public interest are as follows:

Available to the public on reasonable terms

Pursuant to 35 USC 209(a)(3), patents that are licensed from a federal agency require the applicant make a commitment to achieve “practical application” of the invention within a reasonable time. The term “practical application” is defined in 35 USC 201(f) to include an obligation to ensure that the invention benefits are “available to the public on reasonable terms.” This often does not happen. In order to make the obligation more actionable, we propose the following terms:

(1) [The party obtaining the license] agrees to disclose the steps it will take to enable the registration and availability of the product at an affordable price in every country with a

demonstrated need, 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; and

(2) [The party obtaining the license] agrees to make the product available to the public in the U.S. at publicly disclosed prices no higher than the median price charged in Canada plus the seven countries with the largest GDP, which have per capita incomes of at least half that of the U.S.

Transparency

The public has profound interest in knowing how federally funded inventions are developed, to understand how best to manage the intellectual property from billions of dollars of taxpayer investments, and to gain deeper insights into the economics of drug development in order to fashion policies on intellectual property, and reimbursement and pricing policies. For any patent license, we propose the following terms on access to transparency.

[The party obtaining the license] agrees to provide a report every year that will be made available to the public, waiving all claims of confidentiality, that provides the following information:

(a) Outlays on R&D spending on products that use the licensed invention, including spending on each clinical trial separately,
(b) The average and marginal costs of manufacturing products based upon the licensed invention,
(c) The total number of units and revenue of sales in every country where the product is registered and sold,
(d) The royalties paid to the NIH for use of the invention,
(e) Subsidies for R&D received from any government or charity, or any tax credits relating to the development and distribution of the products,
(f) Outlays relating to marketing the product, and
(g) Outlays relating to legal issues or governmental affairs, including lobbying activities.

Access to manufacturing know-how and materials

The public has an interest in obtaining low cost versions of products as soon as the time limited monopoly expires, and for as long as the drug is on the market. Lack of access to manufacturing know-how and materials can delay entry of generic versions of a drug, and reduce the number of competitors. Open access to know-how and materials is an important benefit for U.S. residents and taxpayers. For any patent license, we propose the following terms on access to manufacturing know-how and materials.

(1) [The party obtaining the license] agrees to make available the following to any manufacturer seeking marketing approval for any generic or biosimilar product in any OECD country or for WHO prequalification for any small molecule or biologic drug or vaccine:
    a. Materials:,
        i. Cellular clones and hybridoma stocks
        ii. Plasmids, plasmid maps, and sequences of antibody complementarity determining regions (CDR)
        iii. Physicochemical/ biophysical characterization
        iv. sufficient quantities of the approved medication for a generic developer's testing
    ii. Methods:
        i. Growth conditions and protocols
        ii. Attenuation or inactivation protocols
        iii. Extraction and purification protocols
        iv. Synthetic work-up and schemes

(2) [The party obtaining the license] agrees to allow the developer to join, a single, shared system of Elements To Assure Safe Use (ETASU) of the medication.

Working the Patent

The entity seeking the license currently has no salaried employees, and may fail to obtain financing to advance development of the technology. The NIH should include terms that ensure that other firms have an opportunity to work the invention if miRecule, Inc. is unable to perform within a reasonable period of time.

35 USC 209(a)(3) requires licence holders to achieve practical application of the invention "within a reasonable time." miRecule is a firm with no salaried employees and no track record of drug development. It is possible that the leaders of miRecule will be successful in obtaining the partners and/or financing that is needed to achieve practical application of the inventions, but if the company cannot advance to clinical testing within at least three years, another firm should have the opportunity to do so. The following is suggested to address the working requirement:

> [The party obtaining the license] will agrees to initiate at least Phase 2 clinical testing of a drug based upon the invention within three years of signing the license, and Phase 2 clinical testing with five years of signing the license.

4. Concluding Comments

KEI recognizes that in cases where a technology requires significant investments to achieve practical application of the invention, the use on an exclusive license may be justified. KEI is asking the NIH to include in the license provisions protecting the public from abuses of those exclusive rights. The NIH is also asked to recognize and address the public's interest in limiting the scope and the length of the monopoly to that which is reasonably necessary.

When the NIH licenses patents to a firm with limited resources, such as miRecule, and indeed to any firm, the license should contain sufficient obligations to work the patent, and specifically to ensure that the exclusive rights granted in a license do not impede the timely development of a promising technology by others when the license holder fails to achieve timely practical application of the technology.

KEI also notes that the license is being offered to a former NIH employee. In cases where the NIH is offering a license to a former employee, it has a responsibility to ensure (1) the licensing negotiations are as transparent as possible, and (2) that the terms include sufficient public interest safeguards.

Sincerely,

James Love

Knowledge Ecology International
1621 Connecticut Avenue, Suite 500
Washington, DC 20009
http://keionline.org
james.love@keionline.org
Tel. 202.332.2670