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November 26, 2019

Knowledge Ecology International
1621 Connecticut Avenue NW
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Via email: kathryn.ardizzone@keionline.org

Re: (1) Exclusive license in bicistronic chimeric antigen receptor (CAR) constructs targeting CD19 and CD20 to Kite Pharma, Inc., described in Federal Register Notices 84 FR 33270 and 33272.
(2) Exclusive license in genetically-modified lymphocytes for cancer therapy to Intima Bioscience, Inc., described in Federal Register Notice 84 FR 45503

Dear Knowledge Ecology International:

Thank you for your letters of September 13 and October 26, 2019 regarding the proposed licenses referenced above. Several of the issues you raised in your letters are shared by the two matters, and I will attempt to address each of them below

(1) License in bicistronic chimeric antigen receptor (CAR) constructs to Kite Pharma, Inc.

In your letter of September 13, 2019, you raised six issues with respect to this proposed exclusive license.

1. Did the NIH properly evaluate the necessity of granting an exclusive license in the subject inventions as required by statute.

You suggest that the NIH did not properly evaluate the necessity of granting an exclusive license to Kite Pharma, Inc. ("Kite") for the bicistronic CAR constructs ("the constructs"). This is because you believe that NIH did not consider FDA regulatory protection of test data and orphan drug exclusivity of two other products, Yescarta and Kymriah, marketed by Kite and Novartis, respectively.

NIH is aware of the role of regulatory protection in preserving market space for its licensees, but these are only part of the exclusivity necessary for a company like Kite to risk technology failure and the enormous investment necessary to bring therapies to market. As you know, these cutting-edge therapies have the potential to extend the lives of patients significantly and, in some cases, even offer a complete cure. However, they are still largely experimental and hundreds of millions of dollars are typically necessary to conduct the clinical trials required to obtain regulatory approval and bring them to market. The likelihood that any one therapy will reach the market is small. The costs and risks are even higher for these trials and therapies because of the complex methods required to process the therapeutic cells and introduce them back into the patient concurrent with hospitalization and treatment of ill effects of the therapy.

Missing in your analysis is that the National Institutes of Health ("NIH"), like any other licensor of technology, works in a market for these early-stage therapeutic technologies in which there is essentially no demand for nonexclusive licenses. This is unlike other markets, for example diagnostics, in which nonexclusive licensing may be the norm. NIH has no authority to commercialize the technologies itself, and so it partners with companies assessed to be most capable of bringing therapies to patients as quickly as possible. NIH exclusive license agreements include benchmarks and milestones that preserve NIH's right to pull back the license if the licensee fails to make adequate progress in bringing the therapy to patients. NIH determined that granting an exclusive license to this technology was necessary to "promote the commercialization and public availability"[1] of the technology as called for by the Bayh-Dole Act, while including terms in the license agreement to assure that no part of the invention remains untried or under developed.

2. Did NIH meet its statutory responsibility to limit the scope of rights to that which is reasonably necessary to induce investment to bring the invention to practical application?

You argue further in your letter that NIH did not meet its statutory responsibility to limit the scope of rights to that which is reasonably necessary to induce the investment required to bring the invention to practical application. That statement is not supported by the facts. The Federal Register Notice ("FRN") in which the proposed license is noticed recites that the license will be limited to:

> The development, production and commercialization of an anti-CD19 anti-CD20 dual targeting chimeric antigen receptor (CAR)-based immunotherapy using autologous (meaning one individual is both the donor and the recipient) immune cells transfected with either a viral or non-viral vector, wherein the vector expresses a CAR having at least: (1) A dual antigen specificity; (2) the complementary determining region (CDR) sequences of the anti-CD19 antibody known as Hu19; (3) the complementary determining region (CDR) sequences of the anti-CD20 antibody known as 2.1.2; and (4) a T cell signaling domain; for the treatment of B-cell derived human cancers.

[1] 35 U.S.C. § 200.

The FRN further recites that Non-Hodgkin Lymphoma (NHL), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) might be treated using this technology. The fields of use granted in NIH license agreements must be supported by the licensee's detailed commercialization plan for each disease indication. A pull-back clause permits NIH to withdraw any field of use not being developed by the licensee and provide those rights to another company. Consequently, no field of use will lie fallow. Each indication to which the licensee can commit its resources improves the chances of success for the other indications it has licensed, since the licensee's motivation is driven by its overall chance of success.

The scope of treatment approaches using this technology is effectively limited by the scope of the patent claims involving the CDR sequence limitations. Changing one amino acid in any of 12 different sequences could move such an approach outside the patent claims. NIH is thus aware of its responsibility to tailor the scope of rights as reasonably necessary to induce investment and make the technology available to the public, and it has done so in the case of these CAR constructs.

You also note that the term of the exclusive license should be shorter. NIH and recipients of NIH funding normally grant exclusive commercial licenses for the life of the patents. Prior to June 1995, several decades could pass before all the patents in a family expired 17 years from each of the succeeding issue dates, initially an unknown time period. The term of patents in a given family could have run for several decades following the initial application filing.

Patent families now have clearly defined, limited terms of 20 years from the initial filing date, regardless of the time needed to bring the related patent applications to issuance. After many years of development to reach FDA approval, the remaining patent term for a marketed product is a fraction of the entire patent term. Depending on the product, the regulatory exclusivity granted at the time of FDA marketing approval may run for a longer period than the remaining patent term. Given these risks, companies are not willing to develop products from very early stage technologies without a license for the term of the patent. It is quite rare in the drug and therapeutic field that NIH would not have licensed a patent covering a product already on the market, in which case a company would have no choice but to take a license. By contrast, companies and investors have choices as to which early stage technologies to develop and, in taking on this risk and committing to commercialization, require an exclusive license for the full patent term.

3. Did the NIH request the advice of the Attorney General, pursuant to 40 U.S.C. § 559?

As you noted in your letter, NIH has previously explained[2] that the assertion that 40 U.S.C. § 559 requires NIH to obtain the advice of the Attorney General "regarding whether a patent license would tend to create or maintain a situation inconsistent with antitrust law" is not the long-standing NIH interpretation of the statute.

[2] Attachment J of your September 13, 2019 letter.

4. Will the licenses tend to substantially lessen competition by creating undue market concentration, in violation of 35 U.S.C. § 209(a)(4)?

You assert in your letter that the proposed license would violate 35 U.S.C. § 209(a)(4)[3] because it will tend to substantially lessen competition. This is also not supported by the facts.

CAR technologies are specific for certain surface molecules in a similar manner as antibodies. There are thus multiple types of CAR T-cells that could be developed against a given surface marker. In this case, many CD19 and CD20 antibodies have been produced and have the potential to build competing therapeutics to the ones in this patent family. Scientists are also developing different ways of growing up large numbers of altered T cells in cell cultures and different ways of delivering them back into patients. Changes to the CDR sequences covered by these patents would place an alternative approach outside the scope of the patent. As a result, many different therapeutic permutations can be devised, with the patents subject to this proposed license covering only a limited number.

There are dozens of CAR T-cell companies. NIH itself has granted exclusive and nonexclusive licenses to at least four of them, including Celgene, Cartesian Therapeutics and Novartis. All these companies compete in this field and contribute to the body of scientific knowledge. NIH licenses have encouraged this competition, providing the intellectual property and know-how to make the therapies work and permitting on-going research to develop improved technologies. The companies' success encourages others into the marketplace, with or without technology developed by the NIH.

As you noted in your letter, some of these therapies have been granted orphan drug status by the FDA. That status is reserved by the FDA for therapies or diagnostics with patient populations of 200,000 or less. Because these populations have been historically underserved, Congress created the designation and the exclusivity that goes with it. NIH's grant of exclusive rights for technologies that have the potential to benefit populations with rare diseases is consistent with Congress' intent in this regard, and consistent with the requirements of the Bayh-Dole Act, to provide incentives for companies to develop new therapeutics.

You noted the prices charged by Novartis and Gilead for Yescarta and Kymriah and expressed your concern about prices that may ultimately be charged for therapies resulting from this license. NIH is also concerned about the high prices of drugs and therapies. But NIH has made it clear throughout the years in its public statements[4] that this problem is one that Congress is in the best position to address. I emphasize that in NIH's judgment for this technology and market,

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[3] A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if... granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws...

[4] https://www.ott.nih.gov/sites/default/files/documents/policy/March-In-Norvir2013.pdf

refusing to grant exclusive rights to these inventions would risk severely limiting the chance that new therapies would be developed for the patients who need them.

5. Was the public's right to evaluate a proposed license undermined by NIH's alleged lack of transparency?

Your assertion that NIH has been less than transparent in its correspondence with KEI regarding exclusive licenses is inaccurate and misleading. From 2016 to 2018, KEI lodged 34 objections to the grant of exclusive licenses out of a total of 51 Federal Register notices of proposed licenses from NIH. In 2019, KEI has lodged objections to nearly all proposed exclusive licenses. NIH has been committed to providing as much information as possible to KEI without breaching its duty to protect confidential information received from its license applicants. NIH cannot, however, provide information that is not available to us, use government resources to create data and reports, or engage in research for KEI.

NIH also declines to address inquiries that have no relevance to the question of whether an exclusive license should be granted. Your letter references communications with NIH's Dr. Lambertson, who you complain did not address several of your questions. These included questions like "in working towards executing this license, has the NIH sought advice from the Attorney General (as is required under 40 USC § 559) to determine if the disposal to a private interest would tend to create or maintain a situation inconsistent with antitrust law." This of course had been answered previously and has nothing to do with whether NIH should grant an exclusive license. Accordingly, this, and others like it, were properly left unaddressed.

6. Has NIH implemented the objective in the Public Health Service (PHS) Technology Transfer Policy Manual regarding promoting access in developing countries?

That objective, one of at least ten aspirational goals set forth in NIH's policy manual, reads as follows: "PHS seeks to promote commercial development of inventions in a way that provides broad accessibility for developing countries." Another goal in the policy document recites that "PHS seeks to ensure that commercial partners expeditiously develop the licensed invention." There is, of course, no way to make an invention available in a developing country if there is no commercial partner in the first place who is willing to commit its resources to develop the invention. Achievement of such a goal is even more unlikely if the licensee is hamstrung by restrictions built into its license that limit its marketing activities a dozen years hence. That is the case here, even as NIH continues efforts in appropriate circumstances and to the extent possible to obtain assurances of broad accessibility for developing countries. More generally, NIH leaves doors open for others to commercialize NIH technologies in low income countries by rarely obtaining patents in these jurisdictions.

(2) <u>License in genetically-modified lymphocytes</u> <u>to Intima Biosciences, Inc.</u>

You raised five issues with respect to this proposed license.

1. Did the NIH properly evaluate the necessity of granting an exclusive license in the subject inventions as required by statute.

In your letter regarding the proposed license to Intima Biosciences, Inc. ("Intima") you suggest that, because KEI has been unable to obtain information on the internet regarding the company, the proposed grant is improper.

All patent applications under this proposed license were filed by Intima during a multi-year CRADA with NIH that, unfortunately, failed for scientific reasons to reach its desired endpoints. NIH is aware of the capabilities of the company by virtue of its extensive working relationship in a way that KEI could not be. The patent applications were jointly-invented by Intima, NIH and the University of Minnesota, and their subject matter falls outside of the CRADA research plan. NIH has little scientific interest in developing these inventions further because it believes its resources can be best spent on other candidates.

In your letter you request NIH to reverse it decision to proceed with the license and reopen the license to "competitive bidding."[5] But NIH did open the license to comments and provided the interested public an opportunity to "bid" on the license when NIH advertised the proposed license grant. That proposed grant is an exclusive license in the government's partial interest in the co-owned patent rights to Intima. NIH received no objections from any potential licensees. Note that, for anyone to bring these inventions to market by obtaining support from investors, they would have to consolidate the rights of all three parties. An exclusive license to NIH's rights in the invention would be *de facto* non-exclusive rights without a consolidation of the other two parties' rights. The best chance that these inventions have for someday reaching the bedside is for the company most interested and invested in them to take them to market. In NIH's considered judgement that company is Intima because it co-owns the patent portfolio and has already invested heavily in its success.

2. Did NIH meet its statutory responsibility to limit the scope of rights to that which is reasonably necessary to induce investment to bring the invention to practical application?

As discussed above, the necessity of granting an exclusive license in this case is indisputable. The scope of the license must also be as broad as needed to attract the necessary investment to get a candidate into a clinical trial. This invention will compete with candidates for the same indication that already appear to be promising.

3. Has the NIH withheld relevant, nonconfidential information about the license from the public, impeding its right to comment on the proposed licenses?

NIH has in fact gone out of its way to respond to each inquiry from KEI, who has objected to virtually every exclusive license proposed by NIH during a several-year campaign. Each of these inquiries comprise approximately twenty pages of questions, many of which have been asked by KEI (and answered by NIH) countless times before or are not relevant to the decision to grant a particular license. Applications that NIH receives from potential licensees typically comprise significant amounts of business confidential information related to their proposed

[5] Note that NIH does not engage in bidding of license applications based on proposed royalties. Royalties and other terms of a license are not negotiated until the FN period ends and a decision has been made to move forward with a particular license.

commercial plans, including earnings, proposed expenditures and trade secret information. NIH has a duty to safeguard that confidential information. Nevertheless, NIH understands its duty to satisfy the statutory requirements and has made significant efforts to provide non-confidential information available to KEI that is relevant to the license grant.

4. Did the NIH request the antitrust advice of the Attorney General, pursuant to 40 U.S.C. § 559?

As noted above, your conclusion that 40 U.S.C. § 559 is relevant to the grant of exclusive licenses to government-owned inventions is incorrect.

5. Has NIH implemented the objective in the Public Health Service (PHS) Technology Transfer Policy Manual regarding promoting access in developing countries?

That objective, one of at least ten aspirational goals set forth in NIH's policy manual, reads as follows: "PHS seeks to promote commercial development of inventions in a way that provides broad accessibility for developing countries." Another goal in the policy document recites that "PHS seeks to ensure that commercial partners expeditiously develop the licensed invention." It is, of course, not possible to make an invention available in a developing country if there is no commercial partner willing to commit its resources to develop the invention initially and if there is no patent protection in those countries. Your letter hyperbolically concludes, without evidence or foundation, that "not even making this part of the negotiation is *appalling* and inconsistent with PHS's own stated licensing policies." (Emphasis added) Moreover, KEI can have no way of knowing what has taken place or will take place in NIH negotiations with a potential license because those conversations are strictly confidential. NIH strives to reflect the goals set forth in its licensing policy in the license agreement to the extent possible and appropriate.

Standing

Citing 37 C.F.R. 404.11(a), you assert in your letter that you are entitled to file an appeal of NIH's decision to grant an exclusive license in these cases because KEI employee Clare Love is a lymphoma patient "who could be damaged by the licenses."

37 C.F.R. 404.11states the following:

> In accordance with procedures prescribed by the Federal agency, the following parties may appeal to the agency head or designee any decision or determination concerning the grant, denial, interpretation, modification, or termination of a license: (a) A person whose application for a license has been denied, (b) A licensee whose license has been modified or terminated, in whole or in part; or (c) A person who timely filed a written objection in response to the notice required by § 404.7(a)(1)(i) or § 404.7(b)(1)(i) and who can demonstrate to the satisfaction of the Federal agency that such person may be damaged by the agency action.

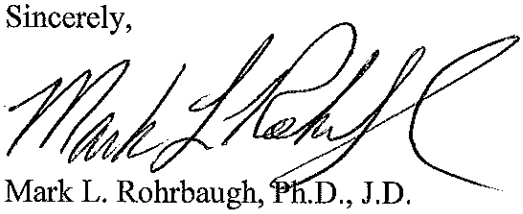
While KEI and associates did apparently file a timely objection to the grant of the exclusive licenses, NIH has determined that neither Ms. Love nor KEI and associates could have, or will be, damaged by the grant of this exclusive license. On the contrary, patients suffering from

cancers presenting these molecular targets might one day be completely cured by the therapies resulting from this early research. As discussed above, NIH determined that, without the grant of an exclusive license in these cases, the likelihood of the development of therapies utilizing these inventions would be significantly diminished. Consequently, if there is any effect at all, it most likely will be that Ms. Love, KEI and its associate will benefit from the grant of the licenses. This is precisely the goal of the NIH patenting and licensing program.

Furthermore, Ms. Love and KEI and associates are too remotely situated to be damaged by this agency action in the sense intended by paragraph (c) of the regulation cited above. That paragraph is generally directed to persons and companies in competition with the intended licensee or participating in the same marketplace. Finally, paragraph (c) clearly leaves the decision as to whether a party has been damaged to the reasonable discretion of the agency, and NIH has determined that you could not be damaged by the grant of this exclusive license.

On behalf of NIH, I thank you again for your comments and your interest in NIH's licensing program.

Sincerely,



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