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Via email: greenejaime@mail.nih.gov

Re: 84 FR 1764. Prospective Grant of an Exclusive Patent License: Use of the CD47 Phosphorodiamidate Morpholino Oligomers for the Treatment, Prevention, and Diagnosis of Solid Tumors to Morphiex Biotherapeutics ("Morphiex") located in Boston, MA.

Dear Jaime Greene,

We are writing to express our opposition to an exclusive license on the patent portfolio described in 84 FR 1764, regarding the "Use of the CD47 Phosphorodiamidate Morpholino Oligomers for the Treatment, Prevention, and Diagnosis of Solid Tumors" to Morphiex Biotherapeutics.

Morphiex Biotherapeutics, Inc, was registered in Delaware on February 27, 2018, and is located in Boston, Massachusetts. According to its website, this company "is developing phosphorodiamidate morpholino oligomers (PMOs) for the treatment of cancer."[1] Morphiex further notes in their website that their lead candidate, MBT-001, "was developed at the National Cancer Institute (NCI) at the National Institutes of Health (NIH)."[2]

The CEO of Morphiex is Anthony Schwartz, PhD. According to his bio in the Morphiex website, Dr. Schwartz worked at the National Institutes of Health (NIH) National Cancer Institute (NCI) "to advance Morphiex's lead CD47 asset, MBT-001, into the clinic."[3] Dr. Schwartz worked four years at the NIH/NCI and left on December 2017[4], shortly before Morphiex was registered.

A Federal Register notice published on May 15, 2018, 83 FR 22501, noticed the prospective grant of another exclusive license to Morphiex. That notice covered a portfolio comprised of 17 patent documents, a territory that "may be worldwide" and a field of use that may be limited to the use of CD47 "for the treatment, prevention, and diagnosis of hematological cancers (e.g. lymphoma, leukemia, multiple myeloma), excluding uses in combination with radiotherapy."

[1] http://morphiex.com/site/?page_id=6
[2] http://morphiex.com/site/?page_id=6
[3] http://morphiex.com/site/team/
[4] https://www.linkedin.com/in/anthonyschwartzphd/

The current Federal Register notice (84 FR 1764) published on February 5, 2019, covers the same 17 patent documents as well as a territory that “may be worldwide”, but a different field of use that may be limited to the use of CD47 “for the treatment, prevention, and diagnosis of solid tumors, excluding uses in combination with radiotherapy.”

Therefore, what the prospective exclusive license noticed in 84 FR 1764 will do is expand a previous exclusive license that covered the use of CD47 on hematological cancers to now include the use of these inventions in the treatment, prevention and diagnosis of solid tumors.

The Federal Register notice 84 FR 1764 merely cites the previous prospective exclusive license to Morphiex, suggesting that the current notice “is in reference to a previous notice 83 FR 22501 [...]” and describing the field of use of that previous license. Despite that general mention, the NIH has not provided an explanation of how the NIH has determined that expanding the exclusive license granted to this company is a reasonable and adequate incentive to induce development, given that Morphiex already has existing obligations to bring the inventions to practical application for for the treatment, prevention, and diagnosis of hematological cancers.

The Federal Register notice 84 FR 1764 describes the CD47 technology as follows:

> This technology concerns CD47, originally named integrin-associated protein, which is a receptor for thrombospondin-1 (TSP1), a major component of platelet α-granules from which it is secreted on platelet activation. A number of important roles for CD47 have been defined in regulating the migration, proliferation, and survival of vascular cells, and in regulation of innate and adaptive immunity. Nitric Oxide (NO) plays an important role as a major intrinsic vasodilator, and it increases blood flow to tissues and organs. Disruption of this process leads to peripheral vascular disease, ischemic heart disease, stroke, diabetes and many more significant diseases. The inventors have discovered that TSP1 blocks the beneficial effects of NO and prevents it from dilating blood vessels and increasing blood flow to organs and tissues. Additionally, they discovered that this regulation requires TSP1 interaction with its cell receptor, CD47. These inventors have also found that blocking TSP1-CD47 interaction through the use of antisense morpholino oligonucleotides, peptides or antibodies have several therapeutic benefits including the treatment of cancer.

Before the NIH grants a new or expanded license to Morphiex, we expect the NIH to seek the advice of the Department of Justice antitrust authorities, as is required by

> 40 U.S. Code § 559 - Advice of Attorney General with respect to antitrust law.

In such a review, the NIH should note that the expanded field of use will create a legal monopoly on the use of the inventions for the treatment, prevention, and diagnosis of solid tumors, and foreclose non-exclusive licenses for these uses. The NIH should also make it clear

that it has the responsibility under 35 USC § 209(a) to limit the scope of rights to that which are reasonably necessary to induce investment, and that among the options the NIH as are to limit the field of use or the years of exclusivity, and demonstrate to DOJ that the NIH as address this restriction in good faith.

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 does 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." There is ample evidence that federally funded inventions for the treatment of cancer are not widely available in developing countries. Examples of the access problems include Xtandi and the two new CAR T treatments, to mention a few.

3. **Global registration and affordability.** The license should require Morphiex to disclose the steps it will take to enable the timely registration and availability of the drug 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)/ 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 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.

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 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."

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,

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