June 7, 2019

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Via email: ahsans@mail.nih.gov

Re: 84 FR 23798, Prospective Grant of an Exclusive Patent License: The Development and Use of a Therapeutic STAT3 Inhibitor, GLG-302, in All Proliferative Diseases, Where STAT3 Is Present, to GLG Pharma LLC located in Jupiter, Florida, USA.

With regards to the intellectual property that will be contained in the proposed license, the Federal Register notice (84 FR 23798) list two patent documents and a catchall phrase:

- United States Provisional Patent Application No. 62/481,960, filed April 5, 2017 and entitled “Improved STAT3 Inhibitor Formulation” [HHS Reference No. E-035-2017/0-US-01];

- PCT Patent Application No. PCT/US2018/026228, filed April 5, 2018 and entitled “STAT3 Inhibitor Formulation” [HHS Reference No. E-035-2017/0-PCT-02];

- and U.S. and foreign patent applications claiming priority to the aforementioned applications.

The NIH should comply with 40 USC § 599

At the appropriate time in the licensing process, we expect the NIH to obtain advice from the Attorney General (as is required under 40 USC § 599) 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 “Nothing 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 USC § 211 – Relationship to antitrust laws].

The Bayh-Dole Act sets out the areas where the Bayh-Dole Act “shall take precedence over any other Act which would require a disposition of rights in subject inventions” [35 USC § 210 – Precedence of chapter], and mentions 21 separate statutes, but does not include 40 USC § 599.

The overly broad scope of the license

The territory of the proposed license "may be worldwide" according to the Federal Register notice, and the field of use "may be limited to: 'The development and commercialization of a therapeutic STAT3 inhibitor, GLG-302, in all proliferative diseases, where STAT3 is present.'"

The Merriam-Webster Dictionary of Medical Terms defines the term "proliferative" as 1) "capable of or engaged in proliferation" and 2) "of, marked by, or tending to proliferation."[1] There are no entries in the Merriam-Webster Dictionary of Medical Terms for the phrase "proliferative diseases." There are no entries for this phrase in the NCI Dictionary of Cancer Terms either.[2] Some academic papers have used this phrase apparently to refer to several diseases linked to the excessive proliferation of cells, including cancers. For example, Sporn and Harris (1981) used it as an "unifying concept that excessive proliferation of cells and turnover of cellular matrix contribute significantly to the pathogenesis of several diseases, including cancer, atherosclerosis, rheumatoid arthritis, psoriasis, idiopathic pulmonary fibrosis, scleroderma and cirrhosis of the liver."[3] But the phrase "proliferative diseases", or similar phrases, have also been used in other contexts. For instance, "proliferative bone diseases" has been used to define "a variety of conditions characterized by exuberant bone and entheseal ossifications and calcifications."[4]

We will assume that the field of use of the proposed license may include all forms of cancers and all other diseases linked to the excessive proliferation of cells. However, we also note that the use of the phrase "all proliferative diseases" in the field of use of a proposed license, without providing any definition, may create confusion as to the actual scope of the field of use, may create legal uncertainty, and, as will be explained in more detail below, is overly broad.

The Federal Register notice (84 FR 23798) described the technology as follows:

> "This technology discloses the use of the STAT3 inhibitor GLG-302 with Trizma salts for preclinical anti-cancer and cancer preventive activity. GLG-302 is a proprietary compound developed by GLG Pharma LLC. Trizma salts allow GLG-302 to remain in solution for oral administration. This formulation has been demonstrated to be effective in the modulation of STAT3 signaling and proliferation in normal mammary ductal epithelium, and this formulation has demonstrated mammary cancer preventive efficacy in rat (ER+) and mouse (ER−) models. The technology provides improved sample handing and oral bioavailability suggesting that a therapeutic product derived from this technology would be applicable for the treatment of cancer where STAT3 is present."

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[1] https://www.merriam-webster.com/medical/proliferative

[2] https://www.cancer.gov/publications/dictionaries/cancer-terms/search?contains=true&q=proliferative+diseases

[3] https://www.sciencedirect.com/science/article/pii/0002934381908329

[4] https://www.sciencedirect.com/sdfe/pdf/download/eid/3-s2.0-B9780323316965001029/first-page-pdf

The Genetics Home Reference website provides the following description for the STAT3 gene[5]:

> "The STAT3 gene is part of a family known as the STAT genes. These genes provide instructions for making proteins that are part of essential chemical signaling pathways within cells. When STAT proteins are activated by certain chemical signals, they move into the nucleus and attach (bind) to specific areas of DNA. By binding to regulatory regions near genes, STAT proteins can regulate whether these genes are turned on or off. STAT proteins are called transcription factors on the basis of this action.
>
> "The STAT3 protein is involved in many cellular functions. It regulates genes that are involved in cell growth and division, cell movement, and the self-destruction of cells (apoptosis). The STAT3 protein is active in tissues throughout the body. It plays an important role in the development and function of several body systems and is essential for life. In the immune system, the STAT3 protein transmits signals for the maturation of immune system cells, especially T cells and B cells. These cells help control the body's response to foreign invaders such as bacteria and fungi. In addition, the protein is involved in the regulation of inflammation, which is one way the immune system responds to infection or injury. In the skeletal system, the STAT3 protein is involved in the formation of specialized cells that build and break down bone tissue. These cells are necessary for the normal development and maintenance of bones."

The Genetics Home Reference website lists several health conditions that have been identified as related to mutations of STAT3 gene.[6] They are: "autosomal dominant hyper-IgE syndrome", "autoimmune lymphoproliferative syndrome", "Crohn disease", "prostate cancer", "Shingles autoimmune disorders", "cancers." According to the Genetics Home Reference website:

> "STAT3 gene mutations are found in approximately one-third of cases of a blood cancer called large granular lymphocytic leukemia (LGL), which is characterized by the accumulation of white blood cells (lymphocytes) that are abnormally large and contain structures called granules. Affected individuals may also have an autoimmune disorder, primarily rheumatoid arthritis or autoimmune hemolytic anemia, and other blood cell abnormalities, such as pure red cell aplasia. There are two forms of the condition, based on the type of white blood cell involved: T-cell large granular lymphocytic leukemia (T-LGL) and chronic lymphoproliferative disorders of NK cells (CLPD-NKs). Both forms have the same signs and symptoms."[7]

Siveen, Sikka, Surana, Dai, Zhang, Kumar, Tan, Sethi, Bishayee (2014) provide an overview of some diseases that have been linked to the STAT3 gene, which is as follows:

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[5] https://ghr.nlm.nih.gov/gene/STAT3
[6] https://ghr.nlm.nih.gov/gene/STAT3
[7] https://ghr.nlm.nih.gov/gene/STAT3

> "Numerous studies have demonstrated constitutive activation of STAT3 in a wide variety of human tumors, including hematological malignancies (leukemias, lymphomas, and multiple myeloma) as well as diverse solid tumors (such as head and neck, breast, lung, gastric, hepatocellular, colorectal and prostate cancers). There is strong evidence to suggest that aberrant STAT3 signaling promotes initiation and progression of human cancers by either inhibiting apoptosis or inducing cell proliferation, angiogenesis, invasion, and metastasis. Suppression of STAT3 activation results in the induction of apoptosis in tumor cells, and accordingly its pharmacological modulation by tyrosine kinase inhibitors, antisense oligonucleotides, decoy nucleotides, dominant negative proteins, RNA interference and chemopreventive agents have been employed to suppress the proliferation of various human cancer cells in culture and tumorigenicity in vivo. However, the identification and development of novel drugs that can target deregulated STAT3 activation effectively remains an important scientific and clinical challenge."[8]

GLG-302 was identified by structure-based virtual screening of the National Cancer Institute's chemical libraries.[9] A paper by Robert H. Shoemaker, who appears as one of the inventors listed in the PCT patent document WO/2018/187551, included in the Federal Register notice, and other co-authors, states that "strong evidence suggests that aberrant constitutive activation of STAT3 promotes the initiation and progression of human breast and other cancers."[10] This paper also suggests that "in preliminary work, GLG-302 was shown to block STAT3 signaling and inhibit growth of ER-negative MDA-MB-231 breast tumors."[11]

The same paper describes a project from the NIH's PREVENT Cancer Preclinical Drug Development Program program evaluating the potential of GLG-302. According to that paper, the goal of this project is "to determine whether long-term oral exposure to GLG-302 can prevent malignant transformation of breast epithelium and formation of ER-positive mammary tumors in methylnitrosourea (MNU)-treated female rats and ER-negative mammary tumors in MMTV-Neu mice. Initial safety studies indicate GLG-302 is well tolerated in mice, rats, and dogs."[12]

There are two projects listed in the NIH PREVENT program website[13] that cite GLG-302: 261201200021I-0-26100004-1 and 261201500036I-0-26100003-1. Both are described as breast cancer projects. The NIH RePORTER entries for these projects describe a total funding of $395,906 (for project number 261201200021I-0-26100004-1, in 2013)[14] and $577,292 (for project number 9261201500036I-0-26100003-1, in 2015).[15]

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[8] https://www.ncbi.nlm.nih.gov/pubmed/24388873
[9] https://europepmc.org/articles/pmc4789768
[10] https://europepmc.org/articles/pmc4789768
[11] https://europepmc.org/articles/pmc4789768
[12] https://europepmc.org/articles/pmc4789768
[13] https://prevention.cancer.gov/major-programs/prevent-cancer-preclinical/supported-projects
[14] https://projectreporter.nih.gov/project_info_details.cfm?aid=8760588&icde=0
[15] https://projectreporter.nih.gov/project_info_details.cfm?aid=9163077

A paper written by two of the inventors listed in the PCT document WO/2018/187551, and three other co-authors states the following about the STAT3 inhibitor GLG-302:

> "GLG-302 (S3I-201, NSC 74859) from the National Cancer Institute chemical libraries was identified as a STAT3 antagonist using structure-based virtual screening with a computer model of the Stat3 SH2 domain bound to its Stat3 phosphotyrosine peptide derived from the x-ray crystal structure of the Stat3 homodimer. In addition to preclinical therapeutic efficacy in breast, glioma, and pancreatic cancer, it ameliorated the resistance to cetuximab and doxorubicin in models of liver cancer."[16]

According to the same paper, GLG-302 "was well tolerated in mice, rats and dogs in pilot safety studies. Since our laboratories have shown that activated STAT3 is present in normal mammary tissue of young mice and mammary cancers, we evaluated the efficacy of GLG-302, given orally, for its preventive activity in female MMTV-Neu mice that develop spontaneous estrogen receptor negative (ER−) mammary cancers. Previous studies had shown that acute dosing with GLG-302 would suppress the growth of established mammary cancers in mouse models at tolerable doses. We conducted a dose selection study lasting 3 months indicating that doses of GLG-302 as high as 500 mg/kg BW/day (administered by gavage 5X/week) would not alter body weights or induce other signs of toxicity."[17]

In summary, based on our own research, GLG-302 was identified by structure-based virtual screening of the National Cancer Institute's chemical libraries; and has the potential to inhibit a gene, STAT3, that has been linked to several diseases including breast cancer, large granular lymphocytic leukemia, glioma, and pancreatic cancer, liver cancer, and prostate cancer, and breast cancers.

Considering the above, a license that would cover development and commercialization of the STAT3 inhibitor GLG-302 "in all proliferative diseases" is overly broad.

Developing country access

A search for the PCT Patent Application No. PCT/US2018/026228 using the WIPO database PatentScope returns one document, published under the number WO/2018/187551.[18] As described in the Federal Register notice and also in the WIPO database, this application was filed on April 5, 2018, which means that it is still well within the deadline to start the national phase in countries that are members of the Patent Cooperation Treaty (PCT), including several developing countries. As of today, the WIPO database does not contain information about the national phase procedures for this application. The NIH failed to provide specific information

[16] http://cancerres.aacrjournals.org/content/75/15_Supplement/4657
[17] http://cancerres.aacrjournals.org/content/75/15_Supplement/4657
[18] https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2018187551

about the countries where it intends to start PCT national phase procedures, and instead the NIH merely included a catchall phrase staying that the proposed exclusive license may include "[...] foreign patent applications claiming priority to the aforementioned applications." The secrecy around the geographical scope of this proposed license makes it impossible to evaluate whether this scope complies with the requirements provided under 35 U.S. Code § 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."

GLG Pharma LLC

GLG Pharma LLC was registered with the Florida Division of Corporations on May 2009.[19] According to their website, GLG Pharma LLC "is a private, clinical-stage biotechnology company delivering next-generation therapies for hyper-proliferative diseases."[20] This company is "developing novel STAT3 pathway targeted therapies and an innovative platform we believe will laser focus these therapies to help forge a new generation of Precision Oncology."[21]

The company lists three compounds in clinical development programs, including GLG-302 for triple negative breast cancer which, according to their website, is in preclinical stage.[22]

In 2013, GLG Pharma LLC announced that it had been selected to receive funding from the NIH's PREVENT Cancer program "to study the effects of its STAT3 signaling inhibitor, GLG-302 as a breast cancer chemopreventive."[23]

We assume that GLG Pharma LLC is related to GLG Pharma, which has a separate web page. Several company documents available from http://glgpharma.biz/ are only available in Polish.

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

[19] http://search.sunbiz.org/Inquiry/CorporationSearch/ByName
[20] http://www.glgpharma.com/
[21] http://www.glgpharma.com/
[22] http://www.glgpharma.com/clinical-programs
[23] http://www.glgpharma.com/glg-pharma-STAT-blog/bid/99370/GLG-302-Selected-by-NCI-for-Funding-in-Cancer-Prevent-Program

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 GLG Pharma LLC 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 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,

Knowledge Ecology International
Union for Affordable Cancer Treatment (UACT)

And in their personal capacity,

James Love
Manon Ress
Luis Abinader