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Via email: changke@mail.nih.gov

Re: 84 FR 2555. Prospective Grant of an Exclusive Patent License: Virus-Like Particles Vaccines Against Human Polyomaviruses, BK Virus (BKV) and JC Virus (JCV) to BioE Holdings Inc. (parent company, Biological E Ltd.) located in Los Altos, California.

Dear Kevin W. Chang,

We are writing to express our opposition to an exclusive license on the patent portfolio described in 84 FR 2555, related to Particles Vaccines Against Human Polyomaviruses, BK Virus (BKV) and JC Virus (JCV) to BioE Holdings Inc. (parent company, Biological E Ltd.) located in Los Altos, California.

With regards to the prospective licensee, the Federal Register notice merely describes it as “BioE Holdings Inc. (parent company, Biological E Ltd.) located in Los Altos, California.” We searched the California Secretary of State business database and found no records of a company named “BioE Holdings” or “Biological E”. Several pharmaceutical companies use terms like “bio” or “biological” in their names, which makes it hard to find further information on the prospective licensee described in the 84 FR 2555 notice. The NIH could have provided more information about this company beyond its name and location, such as current CEO or members of its Board of Directors, but failed to do so. Without detailed information about the prospective licensee company, such as its ownership or whether it has business relations with other pharmaceutical companies, it is difficult for the public to determine if an exclusive license would be a reasonable and necessary incentive as provided under 35 U.S. Code § 209.

The Federal Register notice 84 FR 2555 lists 11 issued patents or pending applications filed in Australia, Canada, the European Patent Office, Japan, the United States, and via the Patent Cooperation Treaty (PCT). However, the notice also states that the territory of the license may be “worldwide” and that it may include “foreign patent applications claiming priority to the aforementioned applications.” Therefore, it is not clear whether the prospective license will include patents or pending applications filed in other countries beyond Australia, Canada, the European Union, Japan and the United States, nor whether it will include developing countries.

The field of use of the prospective exclusive license described in the notice is as follows:

> "Virus-Like Particle (VLP) BKV and JCV polyomavirus vaccine(s) for the prevention and/or treatment of BKV and/or JCV associated diseases in organ/kidney transplantation, bone marrow transplantation, and progressive multifocal leukoencephalopathy (PML)."

The Federal Register notice 84 FR 2555 provides the following description of the technology:

> This technology discloses vaccine compositions and methods for eliciting immune responses to prevent or treat infections by two human polyomaviruses, BK virus (BKV) and JC virus (JCV), and their associated diseases using the vaccine compositions, which employ the capsid protein of certain serotypes of BKV and JCV as the immunogen. In particular, the vaccine is composed of virus-like particles that are formed from the capsid proteins of the viruses.

According to Mengxi Jiang et al. (2008):[1]

> Seroconversion for both viruses is widespread and occurs in childhood, with BKV seropositivity reaching 90% in children aged 5 to 9 and JCV seropositivity reaching 50 to 60% after the age of 10 (Knowles, 2006).
> [...]
> Adult seroprevalence for BKV and JCV is very high: more than 90% of the adult population is seropositive for BKV (Knowles et al., 2003), while 50 to 80% of adults have antibodies to JCV (Khalili et al., 2007; Knowles, 2006).
> [...]
> For BKV, reactivation is most common in bone marrow transplant (BMT) and renal transplant patients, where BKV lytic infection results in hemorrhagic cystitis (HC) and polyomavirus nephropathy (PVN), respectively. In addition, reactivation has been observed in individuals with altered immune conditions including other solid organ transplantations, autoimmune diseases such as systemic lupus erythematosus (SLE), and patients with acquired immunodeficiency syndrome (AIDS) (Chang et al., 1996a; Munoz et al., 2005; Sundsfjord et al., 1999).
> [...]
> The most common underlying cause of immunosuppression leading to JCV reactivation is AIDS. Reactivation results in the lytic infection of oligodendrocytes in the brain and the development of PML. Other immune-altering conditions in which cases of PML have been reported include lymphoproliferative diseases such as lymphomas and leukemias, myeloproliferative diseases, transplantation, chemotherapy, multiple sclerosis (MS), and

[1] Mengxi Jiang, Johanna R.Abend, Silas F.Johnson, Michael J.Imperiale. The role of polyomaviruses in human disease. Virology. Volume 384, Issue 2, 20 February 2009, Pages 266-273. Available here: https://doi.org/10.1016/j.virol.2008.09.027

inherited immunodeficiences (Berger, 2003; Berger and Concha, 1995; Brooks and Walker, 1984).

On February 20, 2019, we asked the NIH the following questions about this proposed license: a) How much money has the NIH spent on research directly related to the technology to be licensed? and b) What is the status of the development of this technology? Specifically, what trials if any has the NIH funded or undertaken relating to this technology/treatment? As of today, the NIH has not provided answers to these questions.

Before the NIH grants a new or expanded license to BioE Holdings Inc., 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.

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 has addressed 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 vaccine 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.”

3. **Global registration and affordability.** The license should require BioE Holdings Inc. to disclose the steps it will take to enable the timely registration and availability of the vaccines 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 vaccines 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 vaccines.

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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