DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of Allergy
and Infectious Diseases
Bethesda, Maryland 20892

April XX, 2016

~~Ms. Lara Poeppelmeier~~Dr. Richard Whitley
~~The~~ University of ~~Chicago~~Alabama at Birmingham
~~6030 South Ellis Avenue~~1600 7th Avenue South
~~Chicago, IL~~Birmingham, AL 35233 ~~60637~~

RE: 5 U19 AI109680 03

Dear Dr. Whitley:

Thank you for your email of March 29, 2016, describing your proposed request to generate and use novel viruses that were not included in the original research proposal. The proposed research was evaluated to determine if it is subject to the U.S. Government-wide research funding pause on certain gain-of-function (GoF) experiments announced by the White House on October 17, 2014 (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). The research funding pause pertains to GoF research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the resulting virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID reviewed the grant application and additional information provided by the University of Alabama at Birmingham ~~North Carolina~~ and Drs. ~~Whitley,~~ Denison~~,~~ and Baric, and made the following assessments:

- NIAID is in agreement that the experiment proposed to replace the nsp12 RdRp gene in MERS-like HKU5-S MAv strain with the MERS-CoV nsp 12 RdRp gene is not subject to the GoF research funding pause. This determination is based on the following: (1) Drs. Baric and Denison anticipate the resulting virus to be severely attenuated; (2) the experimental conditions are not reasonably anticipated to result in the generation of a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. NIAID acknowledges the statement that if any unanticipated outcomes are observed including enhanced virus growth >1 log in any mammalian cells or enhanced death in mice, 10 fold or greater reduced LD50, when compared to the MERS like HKU5-S MAv strain, you will immediately stop these research activities and notify NIAID and the IBCs at the University of Alabama-Birmingham, UNC-Chapel Hill, and Vanderbilt University Medical Center of the results. If the MERS-like HKU5-S Mav-nsp-12 strain is neither viable, nor sufficient, NIAID recommends you pursue alternative approaches such as evaluating the activity of GS-5734 against MERS-CoV when administered in the presence of an esterase inhibitor in mice expressing the human DPP4 receptor.

Commented [FA([1]: Needs completed before sending to GMS for signature and sending.

Commented [FA([2]: Will need changed based on UAB address.

Commented [FA([3]: Who sent the incoming correspondence? Do we know the business official at UAB?

The PI sent the email

Commented [BM4]: The information was sent by Rich Whitley at UAB

Commented [BM5]: Andrew: Are these specific projects (e.g. project 1: swapping nsp 12 RdRp) or aims? In other letters we were able to say "NIAID is in…proposed in Aim 2 to…". If not, we can simply delete "in ____".

Maureen: It could be confusing to include a specific aim identifier, so I deleted in

Commented [FA([6]: This is what Baric uses in the letter to Whitley.

Maureen: ok

Commented [FA([7]: I added to clarify that the growth pertains to any mammalian cells and not only human cells.
Maureen: thanks

Commented [FA([8]: This is what Baric uses in the letter to whitley. While we have seen the growth parameters from Baric before, he has not sent similar parameters for death. Are these acceptable?

Maureen: Discussed with Erik. The previous work was all in vitro, so death parameters wouldn't apply. This will involve in vivo research and these death parameters seem appropriate.

Commented [FA([9]: Placeholder as Maureen checks Denison's affiliation.

Maureen: He's at Vanderbilt University Medical Center

Commented [BM10]: Moved this information in response to Erik's suggestion.

- NIAID's determination is that the experiment proposed ~~in~~ ~~_____~~ to replace the MERS-CoV S (spike) gene with the SARS-CoV S glycoprotein to generate a new MERS-15S strain capable of infecting esterase 1 -/- mice is subject to the GoF research funding pause and cannot be funded. This determination is based on the following: the resulting MERS-15S strain containing the SARS-CoV S glycoprotein is reasonably anticipated to have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route when compared to MERS-CoV.

~~- If the MERS-like CoV HKU5 MAv-nsp-12 strain is neither viable nor sufficient, is it possible to evaluate the activity of GS-5734 against MERS-CoV, when administered in the presence of an esterase-inhibitor, in mice expressing the human DPP4?~~

- NIAID is in agreement that the experiments proposed ~~in~~ ~~_____~~ to generate mouse-adapted WIV1 and SHC014 CoV strains with enhanced pathogenicity and/or transmissibility in mice are not subject to the GoF research funding pause. This determination is based on the following: neither WIV1, SHC014 CoVs, nor the mouse-adapted WIV1 and SHC014 strains are subject to the GoF research funding pause. However, with the focus of this Center on the identification and development of inhibitors of coronavirus high fidelity replication for treatment of human diseases, before ~~considering~~ approving the ~~is~~ new research ~~area~~ to generate two mouse-adapted SARS-like pre-pandemic viruses, NIAID requests that the Scientific Advisory Committee for this Center~~, including internal and external members,~~ review the proposed research~~.~~ The committee should comment on ~~including~~ its impact on the resources available to advance the development of therapeutics for SARS and MERS, and provide a recommendation regarding the research's importance for advancing the development of candidate human antiviral therapeutics. Please provide their assessment, including comments, ~~recommendation and a detailed explanation for the recommendation~~ within 15 business days of the date of this letter.

Please remember that the institution must comply in full with all terms and conditions placed on this grant. If your research evolves to include experiments that may be subject to the GoF research funding pause or you observe enhanced pathogenicity and/or transmissibility of influenza viruses in mammals via the respiratory route at any time during the course of conducting these experiments, you must immediately stop these research activities and provide the NIAID Program Officer and Grants Management Specialist with the relevant data and information related to these unanticipated outcomes.

As indicated above, NIAID determinations are based on information from multiple sources, but primarily on our communication with you about the details of your proposed experiments and your research results. Should NIAID's determinations change based on information obtained through the U.S. Government GoF deliberative process, described here http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf, you will be notified; however, until such time, or until the pause is lifted, NIAID's determinations, indicated above, are final.

Please let us know if you have any questions, or if you require additional information.

Sincerely,

Commented [FA([11]: Is this the correct comparator? Maureen: Discussed with Eirk - this is the correct comparator.

Commented [FA([12]: In the Baric/Denison correspondence to Whitley, they do not specifically call out a strain of mouse, can this be written clearer?

Maureen: seems ok as is. They may need to test several mice strains.

Jorge Machuca
Grants Management Specialist
NIAID/NIH/DHHS

Maureen Beanan
Program Officer
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

CC: Dr. Ralph Baric
Dr. Mark Denison
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

Commented [FA([13]: Depending on to whom the letter is addressed, Dr. Whitley may need to be added to this list.

Maureen: the letter will be addressed to Dr. Whitley.