DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

March 19, 2015

Robin Cyr
Associate Vice Chancellor for Research
Director, Office of Sponsored Research
University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-7435

RE: R01AI110700-01A1 PI: Baric

Dear Ms. Cyr:

Thank you for your correspondence of January 21, 2015, regarding the October 17, 2014 White House announcement of a U.S. Government-wide pause on certain gain-of-function (GoF) experiments and its potential impact on your research (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). The 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 original grant application, and the additional information provided by you, and made the following assessments:

- Aims 1.1, 1.2, and 1.3: NIAID is in agreement that the experiments proposed in these aims that utilize biochemical assays and replication-deficient pseudotyped viruses are not reasonably anticipated to create a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Therefore, these experiments are not subject to the GoF research funding pause.
- Aim 1.4: Recombinant Virus Design and Experiment Evolution *in vitro*:
    - NIAID agrees that the experiments proposed to create recombinant MERS-CoV viruses with receptor binding domains (RBDs) from other CoVs are unlikely to expand the host range and are not reasonably anticipated to create a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Therefore, these alternative experiments are not subject to the GoF research funding pause. NIAID acknowledges your statement that if you unexpectedly observe any mutations that

enhance recombinant MERS-CoV growth by more than 1 log in any cell line you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.

- NIAID agrees that given the number of genetic bottlenecks present in CoV genomes altering the RBD residues in isolation to create recombinant HKU4 variants containing MERS-CoV residues is not reasonably anticipated to result in viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. NIAID also acknowledges your statement that if you unexpectedly observe enhanced growth of any of the HKU4 variants in excess of 1 log above wild type virus strains you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.
- NIAID acknowledges your statement that you will not perform the blind serial passaging of wild-type MERS-CoV proposed, and that in lieu of those studies you will expand your research strategy to include other group 2c CoVs using pseudotype virus systems to evaluate DPP4 receptor usage, and then to create recombinant viruses based on the other 2c CoV variants. NIAID also acknowledges your statement that if you observe a phenotype of enhanced growth in excess of 1 log above wild type virus strains you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.

- Aim 2.3: NIAID acknowledges that the work proposed will involve only CoV-spike-packaged pseudoviruses and recombinant CoV spike proteins and that no replication efficient viruses will be used. Therefore, it is not reasonably anticipated that a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route will be created. These experiments are <u>not</u> subject to the GoF research funding pause.
- Aim 2.4: Recombinant Virus Interactions with Entry Proteases:
  - Since MERS-CoV already uses bat proteases efficiently, NIAID agrees that the experiments proposed to remove/alter the human protease cleavage site from MERS-CoV, are not reasonably anticipated to result in a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Therefore, these experiments are <u>not</u> subject to the GoF research funding pause. However, NIAID acknowledges your statement that if you unexpectedly observe any mutations that result in enhanced recombinant MERS-CoV growth by more than 1 log in any cell line you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.
  - NIAID agrees that given the number of genetic bottlenecks present in CoV genomes altering the proteolytic cleavage sites in isolation to create recombinant HKU4 variants containing proteolytic site(s) from MERS-CoV is not reasonably anticipated to result in viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. NIAID also acknowledges your statement that if you unexpectedly observe enhanced growth of any of the HKU4 variants in excess of 1 log above wild type virus strains you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.

- Aim 3: Pathogenesis of MERS-CoV and MLCoV. You proposed to "passage MERS-CoV, HKU4, and select derivative viruses in the CRISPR/Cas mice, selecting for more pathogenic variants." NIAID has determined that this passaging work is reasonably anticipated to create a virus with enhanced pathogenicity in mammals via the respiratory route. Therefore these experiments are subject to the GoF research funding pause and cannot be funded.
    - Aim 3.1: NIAID agrees with your assessment that altering the MERS-CoV RBD to contain residues from HKU4, or to mutate the MERS-CoV RBD to more efficiently bind to camel and bat DPP4, are likely to result in attenuated viruses compared to wild-type MERS-CoV. Therefore, these experiments are not reasonably anticipated to result in a virus with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. These experiments are not subject to the GoF research funding pause. However, if you unexpectedly observe a phenotype of increased pathogenicity and/or transmissibility you should immediately stop the work and notify the NIAID Program Officer and Grants Management Specialist.
    - Aims 3.1 and 3.2: NIAID agrees that given the number of genetic bottlenecks present in CoV genomes altering either the RBD residues and/or proteolytic sites in isolation to create recombinant HKU4 variants containing these characteristics derived from MERS-CoV is not reasonably anticipated to result in viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. NIAID also acknowledges your statement that if you unexpectedly observe enhanced growth of any of the HKU4 variants in excess of 1 log above wild type virus strains you will immediately stop these research activities and notify the NIAID Program Officer and Grants Management Specialist.
    - Aim 3.3: NIAID also considered your request for an Exception from the GoF research funding pause for the additional *in vivo* viral passaging work proposed in this aim. Based on the policy referenced above, the basis of an Exception request is that the work is "urgently necessary to protect public health or national security." NIAID has considered the proposed work in this context and determined that at this time, it does not meet this criteria. As such, this work will not be recommended to the NIH Director for an Exception from the research pause.

For the work that NIAID determined to be subject to the GoF research funding pause you may propose alternative experiments that would not be subject to the GoF research funding pause or you may remove the experiments from the research plan and request to have your award budget renegotiated.

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 pause or you observe enhanced pathogenicity and/or transmissibility of MERS-CoV 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 determination change based on information obtained through the U.S. Government gain-of-function 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 determination, indicated above, is final.

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

Sincerely,

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Laura Eisenman
Grants Management Specialist
NIAID/NIH/DHHS

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Erik J. Stemmy, Ph.D.
Program Officer
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

CC: Dr. Ralph Baric
Dr. Irene Glowinski
Ms. Mary Kirker