DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

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Ms. Barbara Entwisle
Vice Chancellor for Research
University of North Carolina at Chapel Hill
CB 4000
312 South Building
Chapel Hill, NC 27599-4000

Ralph Baric, PhD
Professor, Department of Epidemiology
School of Public Health
University of North Carolina at Chapel Hill
3304 Michael Hooker Research Building, CB #77435
Chapel Hill, NC 27599-7435

RE: 5U19 AI107810-02

Dear Ms. Entwisle and Dr. Baric:

Thank you for your correspondence of January 20, 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, progress report, and additional information provided by you on March 3, 2015 and March 25, 2015 and made the following assessments.

Project 1: Role of Uncharacterized Genes in High Pathogenic Human Coronavirus Infection-Ralph S. Baric, PhD-Project Leader.

- **Specific Aims 2 and 3. Novel Functions in Virus Replication *in vitro* and *in vivo***

NIAID is in agreement that the proposed research in Aims 2 and 3 to generate SARS and MERS coronaviruses (CoV) lacking specific open reading frames, hypothetical genes, or noncoding RNAs to characterize unknown genes regulating virus replication efficiency and host responses *in vitro* and *in vivo* is not subject to the GoF research funding pause. This determination is based on the additional data you provided indicating that these viruses are either: 1) wild-type viruses; 2) mutant viruses lacking genes that are attenuated when compared to wild-type viruses; or 3) mutant viruses lacking genes that are anticipated to be attenuated when compared to wild-type viruses and therefore are not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID is in agreement that the completed research involving recombinant SARS-MA15 coronavirus (CoV) containing either SCH014 or WIV1 bat CoV spike glycoproteins is not subject to the GoF research funding pause. This determination is based on the additional data you provided indicating that these recombinant viruses were generated prior to the GoF research funding pause. Your work regarding the characterization of these viruses may proceed as these viruses are attenuated *in vivo* when compared to the parental SARS-CoV MA15 strain and therefore are not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Please note that further studies beyond characterization or additional work that would alter the existing recombinant viruses may be subject to the GoF research funding pause and need to be approved by NIAID. Thus, prior to further altering the mutant viruses for these studies you must provide NIAID with a detailed description of the proposed alterations and supporting evidence for the anticipated phenotypic characteristics of each virus. Additionally, NIAID requests that any publications involving experiments with these recombinant viruses indicate that they were generated prior to the GoF research funding pause. Please acknowledge compliance with this request.

NIAID is in agreement that future experiments to generate recombinant SARS-CoV containing other group 2b bat coronavirus S genes, and other SARS, MERS and bat CoVs lacking specific open reading frames, hypothetical genes, or noncoding RNAs are not subject to the GoF research funding pause. This determination is based on the additional data you provided indicating that these viruses are anticipated to be attenuated when compared to wild-type parental viruses and therefore are not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID acknowledges that if any unanticipated outcomes are observed including enhanced virus growth >1 log in any mammalian cells, enhanced virus titers by > 1 log in any mammalian cells, or enhanced clinical disease or death in mice as defined by significantly increased weight loss, percent mortality, or decreased mean day to death, you will immediately stop all experiments and notify NIAID and the UNC-Chapel Hill IBC of the results. NIAID requests that these actions be taken for any mutant MERS or SARS virus generated under this grant. Please note that the GoF research funding pause applies to enhanced pathogenicity and/or transmissibility in any mammalian species and is not limited to effects in humans.

Project 2: Determining the functions of novel genes for influenza A and Ebola viruses (EBOV) - Yoshihiro Kawaoka, PhD- Project Leader

- **Specific Aim 2. To determine the significance of uncharacterized IAV and EBOV genes in viral replication.**

  NIAID is in agreement that the proposed research in Aim 2, to generate mutant influenza viruses lacking specific open reading frames, incompletely characterized genes, hypothetical genes, or noncoding RNAs to determine their effect on viral replication and host responses *in vitro* is not subject to the GoF research funding pause. This determination is based on the additional data you provided indicating that that these influenza viruses are either: 1) wild-type viruses; 2) mutant viruses lacking hypothetical genes including lab-adapted influenza viruses, human H1N1 and H3N2 influenza viruses, low pathogenic avian influenza viruses including H7N9, highly pathogenic H5N1 influenza viruses, and pandemic 1918 influenza viruses that are anticipated to be attenuated *in vitro* when compared to their respective parental wild-type viruses; or 3) mutant A/Puerto Rico/8/1934 (PR8) H1N1 influenza viruses lacking incompletely characterized genes or unknown open reading frames that are anticipated to be attenuated *in vitro* when compared to the parental wild-type PR8 H1N1 strain and therefore are not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Please note that further studies altering these mutant influenza viruses (e.g. disabling more than one gene target, introducing mutations or other genetic alterations) may be subject to the GoF research funding pause and need to be approved by NIAID. Thus, prior to generating mutant influenza viruses for these studies you must provide NIAID with a detailed description of the proposed alterations and supporting evidence for the anticipated phenotypic characteristics of each virus.

  NIAID acknowledges that for any unanticipated outcomes, including enhanced virus growth or enhanced viral titers when compared to the parental wild-type virus in any mammalian cell, you will stop all experiments and immediately notify NIAID and IBCs at the University of Wisconsin-Madison and UNC-Chapel Hill of the results. NIAID requests that these actions be taken for any influenza virus generated under this grant. Please note that the GoF research funding pause applies to enhanced pathogenicity and/or transmissibility in any mammalian species and is not limited to effects in humans.

- **Specific Aim 3. To determine the significance of uncharacterized IAV and EBOV genes in virus pathogenicity.**

  NIAID is in agreement that the proposed research in Aim 3, to generate mutant influenza viruses lacking specific open reading frames, incompletely characterized genes, hypothetical genes, or noncoding RNAs to determine their effect on viral replication and host responses *in vivo* is not subject to the GoF research funding pause. This determination is based on the additional data

you provided indicating that that these viruses are either: 1) mutant lab-adapted influenza viruses lacking hypothetical genes that are anticipated to be attenuated *in vivo* when compared to currently circulating seasonal human wild-type viruses; 2) mutant viruses lacking hypothetical genes including human H1N1 and H3N2 influenza viruses, low pathogenic avian influenza viruses including H7N9, highly pathogenic H5N1 influenza viruses, and pandemic 1918 influenza viruses that are anticipated to be attenuated *in vivo* when compared to their respective parental wild-type viruses; or 3) mutant A/Puerto Rico/8/1934 (PR8) H1N1 influenza viruses lacking incompletely characterized genes that are anticipated to be attenuated *in vivo* when compared to currently circulating seasonal human influenza H1N1 viruses and therefore are not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID acknowledges that for any unanticipated outcomes including increased virulence you will immediately stop all experiments and notify NIAID and IBCs at the University of Wisconsin-Madison and UNC-Chapel Hill of the results. NIAID requests that these actions be taken for any influenza virus generated under this grant.

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 any influenza, MERS, or SARS virus worked with under this grant 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 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,

Chernay Mason

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Chernay Mason
Grants Management Specialist
NIAID/NIH/DHHS

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Vivien G. Dugan, Ph.D.
Program Officer
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

CC:

Ms. Robin Cyr
Ms. Sherrie Settle
Ms. Mary Kirker
Dr. Irene Glowinski