From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 7 Apr 2016 18:57:58 +0000
To: Dugan, Vivien (NIH/NIAID) [E]
Cc: Yao, Alison (NIH/NIAID) [E]
Subject: RE: Baric Gof
Attachments: Whitley Draft_Response _April_2016.docx

Attached was Maureen's first review of the request. I'd suggested that she send his original request to the committee (Teresa attached it to the agenda) and then use this document as the basis for her discussion.

From: Dugan, Vivien (NIH/NIAID) [E]
Sent: Thursday, April 07, 2016 2:56 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6)
Subject: RE: Baric Gof

Thanks, Erik!

Vivien G. Dugan, Ph.D.
Program Officer in Systems Biology
Office of Genomics and Advanced Technologies (OGAT)
Division of Microbiology and Infectious Diseases/NIAID/NIH/DHHS
5601 Fishers Lane Room 7A29 MSC 9826
North Bethesda, MD 20892-9826
(b)(6) (phone)
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, April 07, 2016 2:45 PM
To: Dugan, Vivien (NIH/NIAID) [E] (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6)
Subject: Baric Gof

Hi Vivien and Alison,
Maureen will be presenting this at the Gof meeting tomorrow. Teresa just included it on the agenda she sent today.

Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.

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Dear Dr. Whitley, Dr. Baric, and Dr. Denison:

Thank you for your email of March 29, 2016, describing your proposed plans to generate novel viruses that may be considered as a gain of function experiments as outlined in the October 17, 2014 White House announcement of a U.S. Government-wide pause on certain gain-of-function experiments (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). The generation and use of the proposed viruses was not included in the original award. The pause pertains to gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, SARS, or MERS viruses such that the resulting virus has enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID reviewed the information provided in your email as it relates to the U19AI109680 award, PI: Richard Whitley, Antiviral Drug Discovery and Development Center, and has made the following assessments regarding the proposed addition of new research components to Project 2 - Inhibitors of Coronavirus Fidelity and Cap Methylation as Broadly Applicable Therapeutics (PIs:Dr. Mark Denison and Dr. Ralph Baric).

A. Two proposed Recombinant Strains: MERS-like CoV HKU5 Mav-nsp-12 and MERS-CoV MA-S (MERS-15S)

The U19AI109680 cooperative agreement supports the Antiviral Drug Discovery and Development Center. Project 2 is focused on the identification and development of inhibitors of coronavirus high fidelity replication. A candidate therapeutic has been identified – GS-5734 - which has been shown to have activity against SARS-CoV and MERS-CoV *in vitro* and was identified as a good candidate for *in vivo* testing. Initial experiments revealed that the GS-5734 compound (and related nucleoside analogs) are very sensitive to esterase 1 activity and require testing in esterase 1 -/- deficient mice.

GS-5734 has been shown to inhibit the SARS-CoV nsp12 gene product, RNA dependent RNA polymerase (RdRp), and protect mice, when using a mouse-adapted SARS-CoV virus (SARS-CoV MA15) to infect esterase 1 -/- mice. The investigators would like to assess *in vivo* activity of GS-5734 against the MERS-CoV nsp-12 gene RdRp, however the esterase 1 -/- mouse strain does not express a permissive dipeptidyl peptidase receptor for MERS-CoV docking entry, thus they are not able to infect esterase 1 -/- mice with the existing mouse adapted MERS-CoV strain. The investigators have the option to generate a genetically appropriate mouse strain by backcrossing the esterase 1 -/- genotype into the existing 288/330 DPP4 mouse strain, which is susceptible to the existing mouse adapted MERS-CoV virus. The investigators note that this approach is estimated to take one year to obtain sufficient mice for testing. To address the possible lengthy delay, the investigators are proposing to generate two possible recombinant strains that could allow them to test the *in vivo* activity of GS-5734 against the MERS-CoV virus in a mouse model within a month or so if these experiments are not subject to the pause on gain-of-function research.

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1. New recombinant MERS-like CoV HKU5 Mav-nsp-12 strain

The investigators are proposing to include new research to modify the existing recombinant MERS-like KHU5-S MAv strain, which is a mouse-adapted MERS-like virus that has the capability to infect mouse cells. They are proposing to replace the nsp12 RdRp gene in MERS-like KHU5-S MAv strain with the MERS-CoV nsp 12 RdRp gene. A challenge to this approach is the prospect of non-viable viruses for two reasons:

1) Substitution of nsp12 involves swapping of a ribosomal frameshift RNA pseudoknot structure in the 5'end of the region encoding nsp12in increases the likelihood of generating detrimental or lethal alterations in RNA structure and an effect of the translation of ORF 1a/b
2) Other studies with coronavirus replicase proteins have demonstrated that substitution of outside a closely related genogroup has not been possible.

NIAID assessment: Given that other studies have demonstrated that this genetic modification has failed to generate viable viruses, this research is not reasonably anticipated to confer attributes to the SARS-CoV virus such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. Therefore, the experiments are not subject to the pause on gain-of-function research

Commented [BM1]: Not sure about this

However, given the potential major scientific weaknesses and likelihood of failure, NIAID does not support the performance of this proposed new research under the cooperative agreement research program.

Commented [BM2]: Just my thoughts at this point. I will have to get my section's input on this

2. New recombinant MERS-CoV MA-S (MERS-15S) strain

The investigators are proposing to include new research to modify the existing mouse-adapted strain of MERS-CoV (MERS-15). They are proposing to replace the MERS-CoV S (spike) gene with the SARS-CoV S glycoprotein to generate a new MERS-15S strain that will be capable of infecting esterase 1 -/- mice.

NIAID assessment: This research is reasonably anticipated to confer attributes to the MERS-15 virus such that the resulting virus has enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. At a minimum, it will enable the MERS-15 virus to infect a new genetic background in mice and therefore, the experiments are subject to the pause on gain-of-function research.

Commented [BM([3]: Need to get Erik's thoughts

While it will involve a longer period of time, it is fortunate that an alternative approach is available to enable the investigators to test the *in vivo* activity of GS-5734 against the MERS-CoV virus in a mouse model via generation of a 288/330 DPP4 esterase 1 -/- mouse strain.

B. Proposed Development of two Mouse Adapted SARS-like Prepandemic Viruses

The U19AI109680 cooperative agreement supports the Antiviral Drug Discovery and Development Center. Project 2 is focused on the identification and development of inhibitors of coronavirus high fidelity replication. The investigators are focusing on two SARS-like strains which circulate in bats (WIV1 and SHC014) and are capable of efficient replication in human airway epithelial cells. Because these strains replicate poorly in mice, the investigators are proposing to include new research to generate mouse-adapted WIV1 and SHC014 stains that are more pathogenic. While these specific strains are not included in the U.S. government-wide pause on gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, SARS, or MERS viruses, the resulting SARS-like viruses will have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID assessment: WIV1 and SHC014 are not currently human pathogens. Project 2 is focused on the on the identification and development of inhibitors of coronavirus high fidelity replication to be used as treatments for human diseases. While it may have implications for future outbreaks, the proposed new research does not sufficiently align with the translational goals of therapeutics development for the Antiviral Drug Discovery and Development Center and NIAID does not support the performance of this proposed new research under the cooperative agreement award.

Commented [BM4]: Just my thoughts at this point. I will have to get my section's input on this

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 SARS-CoV virus in mammals via the respiratory route at any time during the course of conducting these experiments, you are encouraged to voluntarily pause these research activities and provide the NIAID Program Officer and Grants Management Specialist with the relevant data and information related to this change in anticipated outcomes.

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

Sincerely yours,

Maureen Beanan, NIAID Program Officer

Jorge Machuca, NIAID Grants Management Specialist

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Fri, 15 Apr 2016 14:53:54 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: FW: Re: Grant Number: 2 R01 AI 089728 - 06, Li (PI)
Attachments: Li 2R01AI 089728-06 GOF Response 2016-v3-1.pdf, sars improve binding mouse ace2 schedule g-1.pdf, schedule g sars improve ace2 binding-1.pdf

Yes they just submitted a response. I forgot I sent it to the wrong person why you didn't receive it.

From: Kevin McKoskey (b)(6)
Sent: Friday, April 15, 2016 2:25 PM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6) Stempinski, Erin (NIH/NHLBI) [C] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6)
Cc: Fang Li (b)(6) Lynn F Weber-1 (b)(6) Carrie L DeJarlais-1 (b)(6) Erin Jondahl (b)(6)
Subject: Fwd: Re: Grant Number: 2 R01 AI 089728 - 06, Li (PI)

Dear Devon Bumbray-Quarles,

Institutional endorsement on behalf of the Regents of the University of Minnesota is provided for Fang Li's attached response to your request for additional information on the above referenced grant.

Please contact Fang Li with programmatic matters and Erin Knudsen, of my staff, at (b)(6) (b)(6) or (b)(6) if you have administrative questions.

Thank you for your support of the University of Minnesota.

Regards,

Kevin McKoskey
Director

-

Subject: Grant Number: 2 R01 AI 089728 - 06, Li (PI)
Date: Thu, 31 Mar 2016 15:41:37 +0000
From: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
To: 'Kevin McKoskey' (b)(6)

CC: (b)(6) awards@umn.edu <awards@umn.edu>, Kirker, Mary (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E]
(b)(6) Stempinski, Erin (NIH/NHLBI) [C]
(b)(6) Bumbray-Quarles, Devon (NIH/NIAID) [E]
(b)(6)

Dear Mr. McKoskey,

NIAID has determined that the above subject grant may include Gain of Function (GoF) research that is subject to the recently announced U.S. Government (USG) funding pause (http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf), issued on October 17, 2014.

Please see the attached letter for more detailed information.

If you have any questions or concerns, please do not hesitate to ask.

Thank you.

Sincerely,
Ms. Devon Bumbray-Quarles
Grants Management Specialist
Grants Management Program
DHHS, NIH, NIAID, GMP
5601 Fishers Lane, Room 4E28, MSC 9824
Bethesda, MD 20892-9824
Overnight Mail Only: Use Zip Code 20852
P: (b)(6)
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(b)(6)

National Institute of Allergy and Infectious Diseases

"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."

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Response to GOF Pause Letter – 2R01AI 089728–06, Li (PI)/Baric (co-I)

On March 31, 2016, NIAID informed us that our grant application 2R01AI089728–06 may include GOF research that is subject to the recently-announced U.S. Government funding pause issued on October 17, 2014. Program has identified subaim 2.1 that may involve research covered under the pause. Therefore, we have been requested to address: (1) whether the mutations introduced to bat SLCoVs as well as passaging of bat SLCoVs in cell culture may result in SLCoVs that have enhanced pathogenicity and/or transmissibility in mammals; (2) information on the strains of SARS-CoV that we have engineered with "super binding affinity" for human and civet ACE2 receptors; (3) if subaim 2.1 does include GOF work, what changes (either in research design or in budget) can be made to maintain subaim 2.1.

Summary of subaim 2.1:

Rationale for subaim 2.1: Recently three bat SLCoVs have been identified that can infect human cells and use human ACE2 as their receptor (PMID: 24172901). The overall goal of this subaim is to identify the receptor and viral determinants of the cross-species transmission of these three bat SLCoVs.

Experiment #1: We will construct, express, and purify the RBDs from these three bat SLCoVs and ACE2 from different species (including human and bat). We will then measure the binding affinity between each of the RBDs and each of the ACE2 molecules. The research tools we will use include ELISA, surface plasmon resonance, AlphaScreen, and pseudovirus entry.

Experiment #2: Based on the sequence comparisons of ACE2 from different species (Fig.10A), we can identify a number of residue differences among them that potentially regulate cross-species determinants for bat SLCoVs. We will introduce mutations into bat ACE2 corresponding to the residue differences between bat ACE2 and ACE2 from other species, and measure the binding between the mutant bat ACE2 and bat SLCoV RBDs. In addition, we will introduce the reverse mutations into ACE2 from non-bat species, and measure the binding between bat SLCoV RBDs and mutant ACE2 from other species.

A

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ACE2    21          31          41
Human   IEEQAKTFLD  KFNHEAEDLF  YQSSLASWNY
Civet   TEELAKTFLE  TFNYEAQELS  YQSSVASWNY
Bat     TEDEAKMFLD  KFNTKAEDLS  HQSSLASWDY
Mouse   TEENAKTFLN  NFNQEAEDLS  YQSSLASWNY
          *: ** **: .** :*::*  :***:***:*

ACE2    71          81          321         351
Human   AFLKEQSTLA  QMYPLQEIQN  PNMTQGFWEN  LGKGDFRILM
Civet   AYYEEQSKLA  QTYPLAEIQD  PNMTQGFWEN  LGKGDFRIKM
Bat     AFYEEQSKLA  KNYSLEQIQN  PNMTEGFWNN  LGKGDFRIKM
Mouse   AFYEEQSKTA  QSFSLQEIQT  PHMTQGFWAN  LGHGDFRIKM
          *: :***. * : : * :**  *.**:*** * **:***** *
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B

SARS-CoV	436	442	472	479	480	487
Human (Tor02)	Y	Y	L	N	D	T
Civet (Sz02)	Y	Y	L	K	D	S
Human/Civet (Gd03)	Y	Y	P	N	G	S
Mouse (PMID: 22072787)	H	Y	L	N	D	T
Bat (rs3366)	Y	S	F	N	D	N
Bat (shc014)	Y	W	P	R	P	A
Bat (wiv1)	Y	S	F	N	D	N

Figure 10. Receptor and viral determinants of SLCoV/ACE2 interactions. (A) Sequence comparisons of ACE2 from different animal species. In red are residues that are critical to the major species barriers between hosts for SARS-CoV infections. In blue are residues that directly contact SARS-CoV. Asterisks indicate positions which have a single, fully conserved residue. Colons indicate positions which have strongly conserved residues. Periods indicate positions which have weakly conserved residues. (B) Sequence comparisons of S1-CTDs from different SARS-CoV strains and bat SLCoVs. The strain names are in parenthesis. Shown are six residue positions that are critical for ACE2 binding and are also prone to evolution.

Experiment #3: Based on our knowledge about the RBD residues that play key roles in receptor binding (Fig.10B), we will introduce mutations into bat SLCoV RBDs corresponding to the residue differences between bat SLCoV RBDs and human, civet or mouse SARS-CoV RBDs. We will then measure the binding between mutant bat SLCoV RBDs and ACE2 from different species.

Experiment #4: Based on results from Experiments #1-3, we will introduce mutations into recombinant bat

SLCoVs using reverse genetics, and evaluate virus usage of ACE2 from different species in cell culture. In parallel, we will passage bat SLCoVs in cell culture, using experimental evolution to select for novel receptor enhancing mutations in the bat SLCoVs.

Response:

Experiments #1, #2, and #3: These experiments will all be carried out using either recombinant proteins or pseudoviruses. The pseudoviruses consist of replication-deficient retroviruses that are pseudotyped with SLCoV spike proteins, and hence can only enter cells without replicating themselves. No infectious SARS-CoV or SLCoV will be involved, and thus these experiments are not subject to the GOF pause.

Experiment #4: This is the only experiment in the entire proposal that involves infectious SLCoVs.

Rationale for Experiment #4: A growing body of evidence supports the hypothesis that a potentially large population of SARS-like bat coronaviruses (SLCoV) exist in nature that efficiently use the human, bat and civet ACE2 receptor, can cross the species barrier and replicate efficiently in human cells (PMC4801244, PMC4797993, PMC4810638, PMID 24172901). However, it remains uncertain whether these SLCoV will require additional adaptive mutations to efficiently utilize the human ACE2 receptor, especially in the context of primary airway epithelial cells. Mutations which alter ACE2 interactions across species will likely forecast the potential for more serious human disease patterns, as seen during the SARS-CoV epidemic. Therefore, identifying key mutations and mutation patterns that might forecast SLCoV emergence would: i) assist policy makers in resource allocation decisions, ii) forecast disease patterns in human populations, and iii) inform human monoclonal antibody therapeutic efficacy. While several groups have used phylogenetic approaches and some biochemistry to predict emerging coronavirus epidemic and disease severity patterns in human populations (PMC4810480, PMC4702133), these studies are highly speculative because they lack robust empirical support, potentially misinforming epidemic risk potential and outbreak management prioritizations. We hypothesize that detailed studies on RBD mutation and evolution may provide critical information for informing the greater public health risk potential during an expanded outbreak. Consequently, the experiments in this section are therefore of very high impact. These experiments are designed to reveal fundamental mechanisms and patterns of SLCoV RBD mutation that regulate emergence (e.g., civet, mouse, human), identify new strains with high epidemic risk potential in humans and animals based on sequence patterns, and inform early choice selection for immunotherapeutic control in an outbreak setting. This information will potentially mitigate disease spread to health care workers, predict and reduce the severity of the expanded epidemic in human populations.

List of mutations that will be introduced to bat SLCoVs using reverse genetics:

(i) For bat SLCoV rs3366 and bat SLCoV wiv1: Y442S, L472F, T487N (from strain Tor02); Y442S, L472F, K479N, S487N (from strain Sz02); Y442S, P472F, G480D, S487N (from strain Gd03); H436Y, Y442S, L472F, T487N (from mouse-adapted SARS-CoV).

(ii) For bat SLCoV shc014: Y442W, L472P, N479R, D480P, T487A (from strain Tor02); Y442W, L472P, K479R, D480P, S487A (from strain Sz02); Y442W, N479R, G480P, S487A (from strain Gd03); H436Y, Y442W, L472P, N479R, D480P, T487A (from mouse-adapted SARS-CoV).

Expected results from Experiment #4: When the residues from human SARS-CoV strain Tor02 are introduced to bat SLCoVs, the mutant bat SLCoVs may have enhanced binding affinity for human ACE2 because human SARS-CoV strain likely has been adapted to use human ACE2 more efficiently than bat

SLCoVs do. Similarly, when the residues from civet or mouse SARS-CoV strains are introduced to bat SLCoVs, the mutant bat SLCoVs may have enhanced binding affinity for civet ACE2 or mouse ACE2, respectively. In addition, passage of bat SLCoVs in human cell culture may lead to mutant bat SLCoVs with enhanced affinity for human ACE2. However, the enhanced affinity of SLCoVs for ACE2 doesn't necessarily lead to enhanced viral infectivity or transmissibility (see below).

GOF concerns over introducing mutations into SLCoVs using reverse genetics: The current paradigm argues that increased virus-receptor interactions correlate directly with increased virus growth and pathogenesis. However, this has never been empirically tested. It is possible that increased virus-receptor interactions attenuate viral infectivity by hindering viral release from infected cells. It is also possible that RBD-receptor interactions are highly tuned to regulate associations and dissociations during entry, and as such, both lower and higher affinity RBD-ACE2 interactions may actually ablate receptor biding or downstream S protein conformational reprogramming events that are critical for activation of the fusion domain and entry. Moreover, higher affinity interactions can also result in dominant negative effects on virus replication, e.g., the production of defective "spike less" progeny virion because high affinity S glycoprotein-ACE2 complexes become tethered on membranes and S cannot participate in virion maturation and release. A similar phenomena on virus maturation and release occurs when the receptor is over-expressed in cells (PMID 9123839). Finally, it is also important to consider that RBD interactions are dependent on backbone sequence context, which varies in rs3366, WIV1, SHC014 and SARS-MA; thus, mutations that enhance SARS-MA interaction with a particular ACE2 receptor may subtly enhance, attenuate or ablate interactions across different RBD sequence backbones. Because WIV1, SHC014 and SARS-MA can already use the human, civet, mouse and bat ACE2, it is anticipated that most cross mammal responses will be subtle and less than 10 fold over the parental backbone, in either direction. Thus, it cannot be reasonably expected that these mutations will result in increased pathogenesis or transmission in any mammalian host.

Should any of these recombinants show evidence of enhanced virus growth >1 log in cells expressing the human, bat, mouse or civet ACE2 receptor over wildtype parental backbone SARS-CoV strain or grow more efficiently in primary human airway epithelial cells (HAE), we will immediately: i) stop all experiments with the mutant, ii) inform program and the UNC IBC of these results and iii) participate in decision making trees to decide appropriate paths forward.

GOF concerns over in vitro passage experiments: The gain of function documents are very clear and focus on experiments that are reasonably anticipated to increase transmissibility or pathogenesis in any mammal. Cells in culture are not mammals and in fact in vitro passage has long been used as a strategy to attenuate virus pathogenesis, as viruses adapt to the in vitro environment, losing the capacity to replicate efficiently and produce disease in vivo. We had proposed to passage viruses in primary human airway epithelial cell cultures (HAE) or in DBT cells expressing ACE2 receptors from different mammals (human, civet, mouse, bat). Recognizing that primary human cells may be pushing the envelope and the intent of the original GOF document, we will only passage recombinant viruses in mouse astraglial cells (DBT) expressing different ACE2 receptors. We believe these experiments are safe as entry is governed by programmed interactions with receptors, entry proteases and other cellular components, which clearly will be different in mouse DBT cells and primary HAE cells, the latter being the normal target for virus infection. Thus, entry protease and innate immune program differences in continuous astraglial cell types (as compared to HAE) would likely select for different adaptive mutations resulting in less fit experimentally evolved virus phenotypes when measured in primary HAE and in vivo . After in vitro passage, we can evaluate the replication efficiently and perform fitness competition assays of wildtype and experimentally evolved viruses in HAE and DBT cells expressing various receptors, providing definitive information on the replication kinetics and fitness in vitro.

Should any of these recombinants show evidence of enhanced virus growth >1 log in cells expressing the human, bat, mouse or civet ACE2 receptor over wildtype parental backbone SARS-CoV strain or grow more

efficiently in primary human airway epithelial cells (HAE), we will immediately: i) stop all experiments with the mutant, ii) inform program and the UNC IBC of these results and iii) participate in decision making trees to decide appropriate paths forward.

GOF concerns over the engineered SARS-CoV RBDs with "super binding affinity" for human or civet ACE2 receptor: Previously we have engineered SARS-CoV RBDs with "super binding affinity" for human. mouse or civet ACE2 receptor, respectively (PMID: 22291007/ PMC3308800). The study was carried out in 2012. The initial study only involved recombinant proteins and pseudoviruses. No infectious SARS-CoV was involved. The study was mentioned as background information for subaim 2.1. Independently, the Baric laboratory obtained IBC approval for engineering the hPREDICT and mPREDICT recombinant viruses (see appended recombinant DNA documents) in 2012-2013. Shortly thereafter, the Baric group isolated recombinant hPREDICT and mPREDICT recombinant viruses, however these viruses have not demonstrated any substantial change in disease phenotype in mice or expanded growth phenotypes in Vero cells, as compared to the parental controls. Recombinant virus growth kinetics have not been evaluated in primary human airway epithelial cells nor in DBT cells, expressing the civet, human or bat ACE2 receptor. For safety considerations, the Baric laboratory is willing to evaluate the growth of these recombinants in HAE cultures and inform program of the results. In relationship to this grant application, these experiments are not part of the proposal, and we have no plan to revisit these recombinant viruses encoding these mutant RBDs. Thus there are no GOF concerns over these mutant RBDs with respect to this proposal.

Alternative plans if NIAID still has concerns over these potential gain-of-function mutations that may enhance the binding affinity of SLCoVs for host ACE2, but may not enhance viral infectivity or transmissibility (we note that loss of function is not anywhere near as powerful a determination of causality as gain of function experiments, which provide more certain determinations of sequence and structure guided function).

(i) We could replace the potential gain-of-function mutations with loss-of-function mutations. Specifically, because human SARS-CoV strain likely has been adapted to use human ACE2 more efficiently than bat SLCoVs, instead of introducing residues from human SARS-CoV strains into bat SLCoVs, we will introduce residues from bat SLCoVs into human SARS-CoV strains. Correspondingly, instead of generating mutant bat SLCoV strains with enhanced affinity for human ACE2, we will generate mutant human SARS-CoV strains with reduced affinity for human ACE2. The new set of mutations are the reverse of the mutations listed previously in this response. We will characterize the receptor-binding affinity of mutant viruses using biochemical assays before we introduce these mutations into infectious viruses.

A

```
ACE2   21          31          41
Human  IEEQAKTFLD  KFNHEAEDLF  YQSSLASWNY
Civet  TEELAKTFLE  TFNYEAQELS  YQSSVASWNY
Bat    TEDEAKMFLD  KFNTKAEDLS  HQSSLASWDY
Mouse  TEENAKTFLN  NFNQEAEDLS  YQSSLASWNY
        *: ** **: .** :*::*  :***:***:*

ACE2   71          81          321         351
Human  AFLKEQSTLA  QMYPLQEIQN  PNMTQGFWEN  LGKGDFRILM
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Bat    AFYEEQSKLA  KNYSLEQIQN  PNMTEGFWNN  LGKGDFRIKM
Mouse  AFYEEQSKTA  QSFSLQEIQT  PHMTQGFWAN  LGHGDFRIKM
        *: :***. * : : * :**  *.**:*** * **:***** *
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B

SARS-CoV	436	442	472	479	480	487
Human (Tor02)	Y	Y	L	N	D	T
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Human/Civet (Gd03)	Y	Y	P	N	G	S
Mouse (PMID: 22072787)	H	Y	L	N	D	T
Bat (rs3366)	Y	S	F	N	D	N
Bat (shc014)	Y	W	P	R	P	A
Bat (wiv1)	Y	S	F	N	D	N
Bat (LYRall) (PMID: 26719272)	F	S	E	S	T	V

Modified Figure 10. Receptor and viral determinants of SLCoV/ACE2 interactions. (A) Sequence comparisons of ACE2 from different animal species. In red are residues that are critical to the major species barriers between hosts for SARS-CoV infections. In blue are residues that directly contact SARS-CoV. Asterisks indicate positions which have a single, fully conserved residue. Colons indicate positions which have strongly conserved residues. Periods indicate positions which have weakly conserved residues. (B) Sequence comparisons of S1-CTDs from different SARS-CoV strains and bat SLCoVs. The strain names are in parenthesis. Shown are six residue positions that are critical for ACE2 binding

(ii) Similarly, loss-of-function mutations will also be introduced into civet SARS-CoV strains and mouse-adapted SARS-CoV strains, respectively, to generate mutant civet SARS-CoV strains and mutant mouse-adapted SARS-CoV strains with reduced affinity for civet ACE2 and mouse ACE2, respectively. The new sets of mutations are the reverse of the mutations listed previously in this response. We will characterize the receptor-binding affinity of mutant viruses using biochemical assays before we introduce these mutations into infectious viruses.

Although we expect these new sets of mutations to cause loss-of-function of human, civet, and mouse-adapted SARS-CoV strains, we will carefully monitor the receptor usage and cell infectivity of these mutant SARS-CoV strains on cell lines constitutively expressing the civet, human, bat and mouse ACE2 receptor. Should any of these recombinants show evidence of enhanced virus growth >1 log in cells expressing the human, bat, mouse or civet ACE2 receptor over wildtype parental backbone strain or grow more efficiently in primary human airway epithelial cells (HAE), we will immediately: i) stop all experiments with the mutant, ii) inform program and the UNC IBC of these results and iii) participate in decision making trees to decide appropriate paths forward.

(iii) We could remove the experiment involving the passage of bat SLCoVs in cell culture. However, we caution against this decision as virus passage very likely reveal novel and unanticipated mutational pathways to improved receptor usage, critical information for public health planning, epidemic monitoring and human antibody immunotherapeutic treatment regimen selection.

(iv) We will expand Experiment #4 by incorporating a newly published bat SLCoV strain (LYRall) (PMID: 26719272 / PMC4810638), which is listed in the modified Figure 10b. Again, we will only study potentially loss-of-function mutations, and carefully monitor the changes of receptor usage and cell infectivity of any mutant SARS-CoV strains. The potential loss-of-function mutations that will be introduced from bat SLCoV strain LYRall to other SARS-CoV strains include: F436Y, S442Y, E472L, S479N, T480D, V487T (to strain Tor02); F436Y, S442Y, E472L, S479K, T480D, V487S (to strain Sz02); F436Y, S442Y, E472P, S479N, T480G, V487S (to strain Gd03); F436H, S442Y, E472L, S479N, T480D, V487T (to mouse-adapted SARS-CoV strain).

(v) We will also expand Experiment #4 by examining the interactions between wild-type bat SLCoVs and mutant ACE2 from human, civet, mouse, and bat (similar experiments will be done in Experiment #2 using recombinant proteins and pseudoviruses). The goal is to identify receptor determinants of the cross-species transmission of bat SLCoVs using wild-type infectious viruses. To this end, mutations will be introduced to ACE2 molecules from non-bat species, the mutant ACE2 molecules will be expressed in cultured cells, and then the infectivity of bat SLCoVs in these cells will be measured. *Because all of the mutations will be introduced to host ACE2, not viruses, these experiments are not subject to GOF pause.*

In the event that the committee decides that our GOF determinations prove unexceptablethen in the modified Experiment #4 involving infectious viruses, we will focus on loss-of-function mutations in different SARS-CoV strains, expand the scope of the experiment to incorporate a newly published bat SLCoV strain, and also introduce mutations to host ACE2 receptors.

Conclusion: We can either (1) maintain the originally proposed Experiment #4 through carefully monitoring any changes in viral infectivity or (2) modify Experiment #4 to remove all potential gain-of-function mutations in infectious viruses. We prefer the former. In either case, the budget for Experiment 4 in subaim 2.1 can be maintained.

LSP ID: 20157190
Sched G ID: 11374

UNIVERSITY OF NORTH CAROLINA
LABORATORY SAFETY PLAN

Principal Investigator: (b)(6) **Building:** (b)(6)

SCHEDULE G RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES

CLASSIFICATION OF EXPERIMENTS ACCORDING TO NIH GUIDELINES:
You must provide this information to obtain IBC approval. Please consult the Classification Summary Page for NIH Guidelines to determine which section defines your experiments. Choose one category: III-D

DESCRIPTION OF RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES RESEARCH (Section II)

1. Project Title: Generating a SARS-CoV (b)(4)

2. If experiment involve a deliberate attempt to obtain an expression of foreign gene, identify what proteins will be produced:
No foreign genes will be expressed

To (b)(4)
(b)(4)
SARS-CoV was intranasally inoculated into mice, allowed to replicate, the nares and lungs harvested and used to inoculate subsequent sets of mice. (b)(4)
(b)(4)

3. Will recombinant or synthetic nucleic acid molecules, recombinant RNA, virus particles or other micro-organisms containing recombinant or synthetic nucleic acid molecules or RNA, or cells containing recombinant or synthetic nucleic acid molecules or RNA be introduced into whole plants or animals (including insects)? YES

4. Will recombinant or synthetic nucleic acid molecules, recombinant RNA, virus particles or other micro-organisms containing recombinant or synthetic nucleic acid molecules or RNA, or cells containing recombinant or synthetic nucleic acid molecules or RNA be introduced into humans for clinical trial(s)? NO

5. What is the source/how was the DNA obtained? (Is it synthetic-for example synthesized de novo from sequence information by a core facility or company OR was it derived/amplified from a biological source?):

6. Containment conditions specified in the NIH Guidelines:

☐ **BSL 1** ☐ **BSL 2** ☑ **BSL 3**

7. IACUC # (or web ID):

8. Recipient organisms or cells to be used (e.g. E.coli, mouse, Arabidopsis, mouse primary liver cells, strain type of animal.):
E. coli to propagate the pieces of the infectious clone, VeroE6 or murine delayed brain tumor cells (b)(4) (b)(4) cells to propagate the virus, and mice

9. Vectors to be used and source (e.g. pCMV plasmids, E1A deleted adenovirus): all of the fragments in our infectious clone are in pSMART, the SARS-CoV infectious clone backbone will be used (b)(4) fragments ordered from BioBasics will be shipped in pUC57

10. Nature of the inserted sequences (payload) and original source of the DNA (e.g. E.coli galactosidase driven by CMV-IE promoter, mus creating kinase promotor driving duck myosin gene, synthetic, hormone-responsive promotor drivingrat TGFa): we will purchase a DNA fragment from BioBasics containing (b)(4) which will then be ligated in place of the wild type (b)(4)

11. Description of the Experiments: The (b)(4) is a SARS-CoV variant (b)(4)
(b)(4)

Of the three independently derived mouse-adapted SARS-CoVs, each contain substitutions in the (b)(4) the spike glycoprotein. (b)(4)
(b)(4)

(b)(4) will be generated by synthesis of a 1200bp cassette by Biobasic and then incorporated into the standard reverse genetics clone of the Urbani strain of SARS-CoV. (b)(4)
(b)(4)

Assessment of the (b)(4) and pathogenesis studies in mice. Initial characterization will compare the (b)(4) virus to the MA15 and Urbani strains, including measures of mortality, weight loss, lung titer, and histology. Future studies may assess the effectiveness of neutralizing antibodies against (b)(4) both in vivo and in vitro, (b)(4)
(b)(4)

12. Do these experiments use recombinant or synthetic nucleic acid molecules or RNA that encode microbial toxins? NO

13. Do these experiments involve more than 10 liters of culture at one time? NO

14. Do these experiments involve release of genetically modified organisms to the environment? NO

Life sciences research is essential to scientific advances that underpin improvements in public health and safety, agricultural crops and other plants, animals, the environment, materiel, and national security. Despite its value and benefits, some research may provide knowledge, information, products, or technologies that could be misused for harmful purposes.The updated Dual Use Policy, including the list of regulated agents and toxins can be found at:
http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf

Research is not necessarily prohibited, however a risk analysis must be made to determine its Dual Use potential

15. Is the material a select agent/toxin or is it derived from a select agent or toxin? NO

16. Could the experiments proposed in this Schedule G change the select agent/toxin status of the material? NO

17. Do these experiments raise dual concern? NO

Categories of experiments that are regulated are those that:
a) Enhance the harmful consequences of the agent or toxin;
b) Disrupt immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification;
c) Confer to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies;
d) Increase the stability, transmissibility, or the ability to disseminate the agent or toxin;
e) Alter the host range or tropism of the agent or toxin;
f) Enhance the susceptibility of a host population to the agent or toxin; or
g) Generate or reconstitute an eradicated or extinct agent or toxin listed in the link above.

18. Do these experiments meet the definition of a Major Action?
"The deliberate transfer of a drug resistance trait to a microorganism, when such a transfer could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, is a Major Action (see Section III-A-1-a of the NIH Guidelines). Because of the potential implications for public health, animals or agriculture such experiments warrant special review."NO

GENE TRANSFER EXPERIMENTS INVOLVING WHOLE ANIMALS OR PLANTS (Section III)

1. Provide a description of the vector. (Provide relevant literature citations, if available, or a preprint.): the SARS-CoV molecular clone published in 2003 Yount et al PNAS 100(22):12995-13000

2. Provide a physical map of the vector: (b)(4)

3. Who constructed this vector? (Name, institution): (b)(6) at the University of North Carolina at Chapel Hill

4. List specific DNA or RNA segments from any human, veterinary, or plant pathogen included in the recombinant or synthetic nucleic acid molecules (include regulatory elements): SARS-CoV

5. How was the vector produced or packaged: Individual clones will be manipulated at BL2 but full length assembly and in vitro transcription will be performed in the BL3 facility. In vitro transcripts will be electroporated in Vero cells and viruses isolated by plaque purification or blind serial passage.

6. If a viral packaging or expression system is used, have experiments been done to show that replication competent viruses are excluded?: No

7. Which lab (Principal Investigator, Institution, Company, etc.) produced the DNA to be used in these experiments: (b)(6) (b)(6) University of North Carolina at Chapel Hill

8. Will attempts be made to insert recombinant or synthetic nucleic acid molecules into germ lines in order to establish a trangenic animal or plant line: No

On behalf of the institution, the Principal Investigator is responsible for complying fully with UNC policies and NIH Guidelines in conducting any recombinant or synthetic nucleic acid molecules research.
Agreed and **Signed By:** (b)(6)

This registration was approved by IBC Chair, _____ on 12/06/2011

LSP ID: 20157190
Sched G ID: 11361

UNIVERSITY OF NORTH CAROLINA
LABORATORY SAFETY PLAN

Principal Investigator: (b)(6) **Building:** (b)(6)

SCHEDULE G RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES

CLASSIFICATION OF EXPERIMENTS ACCORDING TO NIH GUIDELINES:
You must provide this information to obtain IBC approval. Please consult the Classification Summary Page for NIH Guidelines to determine which section defines your experiments. Choose one category: III-D

DESCRIPTION OF RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES RESEARCH (Section II)

1. Project Title: Generating a SARS-CoV Mutant (b)(4)

2. If experiment involve a deliberate attempt to obtain an expression of foreign gene, identify what proteins will be produced:
No foreign genes will be expressed

(b)(4)

3. Will recombinant or synthetic nucleic acid molecules, recombinant RNA, virus particles or other micro-organisms containing recombinant or synthetic nucleic acid molecules or RNA, or cells containing recombinant or synthetic nucleic acid molecules or RNA be introduced into whole plants or animals (including insects)? NO

4. Will recombinant or synthetic nucleic acid molecules, recombinant RNA, virus particles or other micro-organisms containing recombinant or synthetic nucleic acid molecules or RNA, or cells containing recombinant or synthetic nucleic acid molecules or RNA be introduced into humans for clinical trial(s)? NO

5. What is the source/how was the DNA obtained? (Is it synthetic-for example synthesized de novo from sequence information by a core facility or company OR was it derived/amplified from a biological source?):

6. Containment conditions specified in the NIH Guidelines:

☐ **BSL 1** ☐ **BSL 2** ☑ **BSL 3**

7. IACUC # (or web ID):

8. Recipient organisms or cells to be used (e.g. E.coli, mouse, Arabidopsis, mouse primary liver cells, strain type of animal.): E. coli to propagate fragments of the infectious clone, VeroE6 cells or murine delayed brain tumor cells (b)(4) (b)(4) in addition, we will infect primary airway epithelial cell cultures

9. Vectors to be used and source (e.g. pCMV plasmids, E1A deleted adenovirus): all of the infectious clone fragments are cloned into the E. coli vector pSMART, the SARS-CoV infectious clone backbone will be used to introduce the changes (b)(4) (b)(4) fragments ordered from BioBasics will be shipped in pUC57

10. Nature of the inserted sequences (payload) and original source of the DNA (e.g. E.coli galactosidase driven by CMV-IE promoter, mus creating kinase promotor driving duck myosin gene, synthetic, hormone-responsive promotor drivingrat TGFa): we will purchase the DNA insert containing the desired mutations from BioBasics, which will then be ligated in place of the wild type (b)(4)

11. Description of the Experiments: The (b)(4)
(b)(4)

(b)(4)

12. Do these experiments use recombinant or synthetic nucleic acid molecules or RNA that encode microbial toxins? NO

13. Do these experiments involve more than 10 liters of culture at one time? NO

14. Do these experiments involve release of genetically modified organisms to the environment? NO

Life sciences research is essential to scientific advances that underpin improvements in public health and safety, agricultural crops and other plants, animals, the environment, materiel, and national security. Despite its value and benefits, some research may provide knowledge, information, products, or technologies that could be misused for harmful purposes.The updated Dual Use Policy, including the list of regulated agents and toxins can be found at: http://oba.od.nih.gov/oba/biosecurity/pdf/united_states_government_policy_for_oversight_of_durc_final_version_032812.pdf

Research is not necessarily prohibited, however a risk analysis must be made to determine its Dual Use potential

15. Is the material a select agent/toxin or is it derived from a select agent or toxin? NO

16. Could the experiments proposed in this Schedule G change the select agent/toxin status of the material? NO

17. Do these experiments raise dual concern? NO

Categories of experiments that are regulated are those that:
a) Enhance the harmful consequences of the agent or toxin;
b) Disrupt immunity or the effectiveness of an immunization against the agent or toxin without clinical or agricultural justification;
c) Confer to the agent or toxin resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies;
d) Increase the stability, transmissibility, or the ability to disseminate the agent or toxin;
e) Alter the host range or tropism of the agent or toxin;
f) Enhance the susceptibility of a host population to the agent or toxin; or
g) Generate or reconstitute an eradicated or extinct agent or toxin listed in the link above.

18. Do these experiments meet the definition of a Major Action?
"The deliberate transfer of a drug resistance trait to a microorganism, when such a transfer could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, is a Major Action (see Section III-A-1-a of the NIH Guidelines). Because of the potential implications for public health, animals or agriculture such experiments warrant special review."NO

On behalf of the institution, the Principal Investigator is responsible for complying fully with UNC policies and NIH Guidelines in conducting any recombinant or synthetic nucleic acid molecules research.
Agreed and **Signed By:** (b)(6)

This registration was approved by IBC Chair, _____ on 12/06/2011

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thu, 21 Apr 2016 11:37:04 -0400
To: Beanan, Maureen (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Denison-Baric gofroc draft response
Attachments: Whitley response AQF 4-20-16.docx, GoF PAUSE letter UNC 5U19AI107810-02 05152015.pdf, GoF Letter_FINAL version (2).pdf, AI 123359-01 Manicassamy GoF final letter.pdf

Hey Maureen,

Thanks for following-up. Per our brief discussion, attached is the draft letter in which the language you provided was reformatted in accordance with past letters regarding GoF topics. There are several comment boxes, some containing questions and others clarifying why I did something. Also, attached are a couple of examples of past letters that you may wish to view as you review this latest draft.

Eric – considering your extensive interaction with Dr. Baric and review of these complex letters, could you please review and provide comments/edits on the draft letter as well. Feel free to send your edits/comments to the two of us.

Lastly, before sending to GMS for signature and sending to UAB, I would like to review the letter after the additional edits/comments are incorporated.

Should you have any questions please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 10:00 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Andrew,
Sorry to pester you - I'm just checking in to see if you have an estimate of when you'll have a chance to look at the Denison-Baric draft response.
Thanks,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:51 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

I will take a look and get back to you.

Thanks,
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:40 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Denison-Baric gofroc draft response

Hello Andrew,
I've summarized the committee's recommendations in this draft response letter. Please review and revise. I'm happy to discuss if that would be easier.
Thanks very much for your assistance,
Maureen

Maureen J. Beanan, Ph.D.
Program Officer

Translational Centers of Excellence and Research Coordination Section
DMID/NIAID/NIH
5601 Fishers Lane, Rm, 8G28 MSC 9825
Rockville, MD 20852-9825
Phone: (b)(6)

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
The University of Chicago
6030 South Ellis Avenue
Chicago, IL 60637

RE: 5 U19 AI109680 03

Dear XXXX:

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 North Carolina and Drs. Whitley, Denison, and Baric, and made the following assessments:

- NIAID is in agreement that the experiment proposed in _____ 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 of the results.
- 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

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?

Commented [FA([4]: 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 ____".

Commented [FA([5]: This is what Baric uses in the letter to Whitley.

Commented [FA([6]: I added to clarify that the growth pertains to any mammalian cells and not only human cells.

Commented [FA([7]: 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?

Commented [FA([8]: Placeholder as Maureen checks Denison's affiliation.

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 this new research area NIAID requests that the Scientific Advisory Committee for this Center, including internal and external members, review the proposed research, 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 the recommendation and a detailed explanation for the recommendation within 15 days of the date of this letter.

Commented [FA([9]: Is this the correct comparator?

Commented [FA([10]: In the Baric/Denison correspondence to Whitley, they do not specifically call out a strain of mouse, can this be written clearer?

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,

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

May 15, 2015

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

Digitally signed by Chernay Mason
DN: cn=Chernay Mason, o=NIAID, ou=NIH, (b)(6) c=US
Date: 2015.05.15 13:54:57 -04'00'

Chernay Mason
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

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,

(b)(6)

Laura Eisenman
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

March 29, 2016

Ms. Lara Poeppelmeier
The University of Chicago
6030 South Ellis Avenue
Chicago, IL 60637

RE: 1 R01 AI123359-01

Dear Ms. Poeppelmeier:

Thank you for your correspondence of February 19, 2016, 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 grant application and additional information provided by the University of Chicago and Dr. Manicassamy, and made the following assessments:

- NIAID is in agreement that the experiments proposed in Aim 1 to investigate the role of ADAR1 in acquisition of resistance mutations and influenza natural evolution are not subject to the GoF research funding pause. This determination is based on the following: (1) the proposed experiments utilize an A/Vietnam/1203/2004 H5N1 influenza virus lacking the HA polybasic cleavage site ($VN04^{Low}$) that is attenuated compared to the wild-type HPAI H5N1 parental virus ($VN04^{Hi}$); (2) the preliminary data provided by Dr. Manicassamy indicates that serial passage of $VN04^{Low}$ in cell culture results in decreased virulence in mice compared to the non-passaged virus; and (3) Dr. Manicassamy anticipates that passage of $VN04^{Low}$ or $VN04^{Low}$ carrying a mutation in the PB1 polymerase subunit (V43I) that increases the fidelity of the viral polymerase ($VN04^{Low\ V43I}$) in cells in the presence of oseltamivir and/or viral mutagens (i.e., 5-fluorouracil or ribavirin) will not result in the generation of viruses with enhanced replication or virulence in mammals.
- NIAID is in agreement that the experiments proposed in Sub-Aims 2a and 2c to evaluate the contribution of ADAR1-NS1 interactions to species tropism and viral adaptation are not subject to the GoF research funding pause. This determination is based on the following: (1) the proposed experiments utilize wild-type viruses, attenuated viruses

(i.e., VN04^{Low}), or loss-of-function mutant viruses (i.e., VN04^{Low} defective in NS1-ADAR1 interactions); and (2) the experimental conditions are not reasonably anticipated to result in the generation of viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

- NIAID's determination is that the experiments proposed in Sub-Aim 2b which involve the generation of a 6:2 avian-human reassortant influenza virus containing the HA and NA from a seasonal human influenza virus (A/Netherlands/602/2009 H1N1) and the internal genes from a low pathogenic avian influenza virus (A/Duck Alberta/35/1976 (DK76) H1N1) containing mutations in the avian NS1 that allow for interactions with and enhancement of human ADAR1 are subject to the GoF research funding pause and cannot be funded. This determination is based on the following: the introduction of internal genes from an avian influenza virus to which the population lacks widespread immunity, which have been modified to enhance ADAR1 editing, is reasonably anticipated to result in a reassortant virus with enhanced pathogenicity in mammals when compared to the wild-type H1N1 virus. As suggested by the University of Chicago DURC Task Force, you may instead use the HA and NA from the mouse-adapted A/Puerto Rico/8/1934 (PR8) H1N1 influenza virus for generation of this reassortant virus; the PR8:DK76 reassortant virus is not reasonably anticipated to exhibit enhanced pathogenicity and/or transmissibility in mammals via the respiratory route compared to either parental strain.
- NIAID is in agreement that the experiments proposed in Aim 3 to investigate the role of ADAR1 in influenza viral fitness and tissue tropism are not subject to the GoF research funding pause. This determination is based on the following: (1) the proposed experiments utilize wild-type viruses, loss-of-function mutant viruses (i.e., VN04^{Hi} defective in NS1-ADAR1 interactions), or viruses modified in a manner that is not reasonably anticipated to enhance pathogenicity and/or transmissibility in mammals via the respiratory route (i.e., VN04^{Hi} that is fluorescently tagged or expressing miRNAs targeting host genes); and (2) the experimental conditions are not reasonably anticipated to result in the generation of viruses with enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

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 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,

(b)(6)

Roberta Wolcott
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

Teresa M. Hauguel
Program Officer
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

CC: Dr. Balaji Manicassamy
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Fri, 22 Apr 2016 09:27:41 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Denison-Baric gofroc draft response
Attachments: Whitley response AQF 4-20-16_MJB_4-21-16.docx

Hi Erik,
This request is, as they say, the gift that keeps on giving…I've entered my initial edits and would appreciate any thoughts you may have on the comments highlighted in green. Please let me know if it would be easier to meet and discuss.
Thanks very much,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 11:37 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

Thanks for following-up. Per our brief discussion, attached is the draft letter in which the language you provided was reformatted in accordance with past letters regarding GoF topics. There are several comment boxes, some containing questions and others clarifying why I did something. Also, attached are a couple of examples of past letters that you may wish to view as you review this latest draft.

Eric – considering your extensive interaction with Dr. Baric and review of these complex letters, could you please review and provide comments/edits on the draft letter as well. Feel free to send your edits/comments to the two of us.

Lastly, before sending to GMS for signature and sending to UAB, I would like to review the letter after the additional edits/comments are incorporated.

Should you have any questions please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892

(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 10:00 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Andrew,
Sorry to pester you - I'm just checking in to see if you have an estimate of when you'll have a chance to look at the Denison-Baric draft response.
Thanks,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:51 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

I will take a look and get back to you.

Thanks,
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:40 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Denison-Baric gofroc draft response

Hello Andrew,
I've summarized the committee's recommendations in this draft response letter. Please review and revise. I'm happy to discuss if that would be easier.
Thanks very much for your assistance,
Maureen

Maureen J. Beanan, Ph.D.
Program Officer
Translational Centers of Excellence and Research Coordination Section
DMID/NIAID/NIH
5601 Fishers Lane, Rm, 8G28 MSC 9825
Rockville, MD 20852-9825
Phone: (b)(6)

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 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.
- 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

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]: 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([5]: This is what Baric uses in the letter to Whitley.

Maureen: ok

Commented [FA([6]: I added to clarify that the growth pertains to any mammalian cells and not only human cells.
Maureen: thanks

Commented [FA([7]: 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?

Commented [FA([8]: Placeholder as Maureen checks Denison's affiliation.

Maureen: He's at Vanderbilt University Medical Center

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 receptor?

- 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,

Jorge Machuca

Commented [FA([9]: Is this the correct comparator?

Commented [FA([10]: 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

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([11]: 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.

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Tue, 26 Apr 2016 11:41:19 -0400
To: Ford, Andrew (NIH/NIAID) [E]
Cc: Stemmy, Erik (NIH/NIAID) [E]; Schaefer, Michael (NIH/NIAID) [E]
Subject: FW: Denison-Baric gofroc draft response
Attachments: Whitley response_draft_final_4-26.docx

Hello Andrew,
I edited the letter in response to Erik's and your comments. Please review my edits/comments and let me know if you'd like to discuss.
Thanks,
Maureen

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, April 26, 2016 9:27 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Maureen,
I've read through the letter and really only have one comment, about the bullet where you ask them to test GS-5734 with an esterase inhibitor. The rest of that bulleted section are NIAID's determinations. It seems out of place to ask a question there. My suggestion would be to maybe move that to the end of the first bullet (where we tell them they can make the variant), and to modify it so that it's a statement rather than a question. Something like: "If the MERS-like CoV HKU5 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." Could also fit at the end of the second bullet, since it would be an alternative approach to that work which we determined to be GoF.

Just my thoughts. Feel free to keep or toss.

Thanks!
Erik

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Friday, April 22, 2016 9:28 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Denison-Baric gofroc draft response

Hi Erik,
This request is, as they say, the gift that keeps on giving…I've entered my initial edits and would appreciate any thoughts you may have on the comments highlighted in green. Please let me know if it would be easier to meet and discuss.
Thanks very much,

Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 11:37 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

Thanks for following-up. Per our brief discussion, attached is the draft letter in which the language you provided was reformatted in accordance with past letters regarding GoF topics. There are several comment boxes, some containing questions and others clarifying why I did something. Also, attached are a couple of examples of past letters that you may wish to view as you review this latest draft.

Eric – considering your extensive interaction with Dr. Baric and review of these complex letters, could you please review and provide comments/edits on the draft letter as well. Feel free to send your edits/comments to the two of us.

Lastly, before sending to GMS for signature and sending to UAB, I would like to review the letter after the additional edits/comments are incorporated.

Should you have any questions please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 10:00 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Andrew,
Sorry to pester you - I'm just checking in to see if you have an estimate of when you'll have a chance to look at the Denison-Baric draft response.
Thanks,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:51 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

I will take a look and get back to you.

Thanks,
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:40 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Denison-Baric gofroc draft response

Hello Andrew,
I've summarized the committee's recommendations in this draft response letter. Please review and revise. I'm happy to discuss if that would be easier.
Thanks very much for your assistance,
Maureen

Maureen J. Beanan, Ph.D.
Program Officer

Translational Centers of Excellence and Research Coordination Section
DMID/NIAID/NIH
5601 Fishers Lane, Rm, 8G28 MSC 9825
Rockville, MD 20852-9825
Phone: (b)(6)

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.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tue, 26 Apr 2016 11:45:27 -0400
To: Beanan, Maureen (NIH/NIAID) [E]
Cc: Schaefer, Michael (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

You beat me to it again. I will look at your draft and incorporate any comments edits. Thanks Erik for taking a look at the letter and getting back to us.

Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Tuesday, April 26, 2016 11:41 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] Schaefer, Michael (NIH/NIAID) [E]
(b)(6)
Subject: FW: Denison-Baric gofroc draft response

Hello Andrew,
I edited the letter in response to Erik's and your comments. Please review my edits/comments and let me know if you'd like to discuss.
Thanks,
Maureen

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, April 26, 2016 9:27 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Maureen,
I've read through the letter and really only have one comment, about the bullet where you ask them to test GS-5734 with an esterase inhibitor. The rest of that bulleted section are NIAID's determinations. It seems out of place to ask a question there. My suggestion would be to maybe move that to the end of the first bullet (where we tell them they can make the variant), and to modify it so that it's a statement rather than a question. Something like: "If the MERS-like CoV HKU5 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." Could also fit at the end of the second bullet, since it would be an alternative approach to that work which we determined to be GoF.

Just my thoughts. Feel free to keep or toss.

Thanks!
Erik

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Friday, April 22, 2016 9:28 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Denison-Baric gofroc draft response

Hi Erik,
This request is, as they say, the gift that keeps on giving…I've entered my initial edits and would appreciate any thoughts you may have on the comments highlighted in green. Please let me know if it would be easier to meet and discuss.
Thanks very much,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 11:37 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

Thanks for following-up. Per our brief discussion, attached is the draft letter in which the language you provided was reformatted in accordance with past letters regarding GoF topics. There are several comment boxes, some containing questions and others clarifying why I did something. Also, attached are a couple of examples of past letters that you may wish to view as you review this latest draft.

Eric – considering your extensive interaction with Dr. Baric and review of these complex letters, could you please review and provide comments/edits on the draft letter as well. Feel free to send your edits/comments to the two of us.

Lastly, before sending to GMS for signature and sending to UAB, I would like to review the letter after the additional edits/comments are incorporated.

Should you have any questions please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Thursday, April 21, 2016 10:00 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hi Andrew,
Sorry to pester you - I'm just checking in to see if you have an estimate of when you'll have a chance to look at the Denison-Baric draft response.
Thanks,
Maureen

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:51 AM
To: Beanan, Maureen (NIH/NIAID) [E] (b)(6)
Subject: RE: Denison-Baric gofroc draft response

Hey Maureen,

I will take a look and get back to you.

Thanks,
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Beanan, Maureen (NIH/NIAID) [E]
Sent: Monday, April 18, 2016 8:40 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Denison-Baric gofroc draft response

Hello Andrew,
I've summarized the committee's recommendations in this draft response letter. Please review and revise. I'm happy to discuss if that would be easier.
Thanks very much for your assistance,
Maureen

Maureen J. Beanan, Ph.D.
Program Officer
Translational Centers of Excellence and Research Coordination Section
DMID/NIAID/NIH
5601 Fishers Lane, Rm, 8G28 MSC 9825
Rockville, MD 20852-9825
Phone: (b)(6)

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Mon, 9 May 2016 09:58:41 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Great. Thank you

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Monday, May 09, 2016 9:57 AM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
Yes. There is one part of a subaim that we deemed to be GoF. I've drafted a response letter and it is being reviewed by our GoF group. We should be able to get it to you by the end of the week.

Erik

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Monday, May 9, 2016 9:56 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Good Morning Erik,

Has there been a decision made on this grant? It's ready to go pending the PO checklist and GoF approval.

Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, April 20, 2016 12:07 PM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
No, I haven't reached out to the PI about the concerns. We have been reviewing the Gain-of-Function response, and will discuss in the GoF committee meeting next Friday (4/29). We'll make our final GoF determination then.

Thanks!
Erik

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Wednesday, April 20, 2016 12:05 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Erik,

Have you reached out to the Grantee to receive a response for the following Summary Statement concerns? I didn't want to send a duplicate request and there wasn't anything submitted in the JIT.

BIOHAZARD COMMENT: There are concerns that recombinant coronaviruses altered to enhance proteolytic cleavage or binding of the human angiotensin converting enzyme 2 (ACE 2) receptor may have novel and unexpected virulence phenotypes. Therefore, biosafety level-3 (BSL-3) protections, training, and monitoring procedures should be considered unless otherwise indicated.

BUDGETARY OVERLAP: There is potential for budgetary overlap with the project R01AI110700 titled, "Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis" awarded to PI Ralph Baric (co-investigator on this proposal).

Thanks.

Sincerely,
Ms. Devon Bumbray-Quarles
Grants Management Specialist
Grants Management Program
DHHS, NIH, NIAID, GMP
5601 Fishers Lane, Room 4E28, MSC 9824
Bethesda, MD 20892-9824
Overnight Mail Only: Use Zip Code 20852
P: (b)(6)
F: 301.493.0597
(b)(6)

NIH National Institute of Allergy and Infectious Diseases

"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 10 May 2016 12:50:55 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]
Subject: FW: For Review - GoF Determination Latter, PI: Fang Li
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-6-2016.docx, Li 2R01AI 089728-06 GOF Response 2016-v3-1.pdf

Hi Teresa,
So sorry, I just realized that I somehow missed adding you to the email below when I sent it out last week. If you have a chance would you mind having a look at the draft? No need to rush for tomorrow… I'm just hoping to get the draft to Andrew this week sometime.

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 10, 2016 8:48 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Dugan, Vivien (NIH/NIAID) [E] (b)(6)
Subject: RE: For Review - GoF Determination Latter, PI: Fang Li

Hi Everyone,
Friendly reminder to let me know if you have any comments on the attached GoF response letter by tomorrow. Thanks!

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, May 06, 2016 9:38 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6); Dugan, Vivien (NIH/NIAID) [E] (b)(6)
Subject: For Review - GoF Determination Latter, PI: Fang Li

Hi Everyone,
Attached is a draft response letter to Fang Li regarding our GoF assessment of his renewal application that we discussed last week. Can you please review and let me know if you have any comments? If possible I would like to send the draft on to Andrew/Irene by Wednesday next week (5/11). I've also attached the PI's original response letter for your reference.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch

Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email (b)(6)

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.

****

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

May XX, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

RE: 2 R01AI089728-06

Dear Mr. McKoskey:

Thank you for your correspondence of April 15th, 2016, 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 regarding Subaim 2.1 of the above-reference grant:

- NIAID is in agreement that the work you proposed under Experiments 1, 2, and 3 are not subject to the GoF research funding pause. This determination is based on the fact that the work will be carried out using either recombinant proteins or replication-deficient pseudoviruses, and will therefore not generate a replicating SARS-CoV variant with enhanced pathogenicity and/or transmissibility via the respiratory route.
- NIAID's determination is that the work proposed under Experiment 4 to generate SARS-Like viruses with enhanced affinity for human receptors (via both reverse genetics and serial passaging) are subject to the GoF research funding pause, and therefore may not be conducted under this grant. Given the lack of empiric evidence that increased receptor binding alone is insufficient to increase pathogenicity, NIAID has determined that it may be reasonably anticipated this work may create a SARS-Like virus with enhanced pathogenicity. As suggested in your response letter, you may instead pursue the alternative strategies you proposed using loss-of-function mutations, or mutations targeting the ACE2 receptor. NIAID acknowledges your

statement that if any mutant viruses you generate demonstrate either enhanced virus growth >1 log compared to the wildtype parental backbone strain or more efficient growth in primary human airway epithelial cells, you will immediately stop all experiments with the mutant and inform UNC's IBC and NIAID.

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,

Devon Bumbray-Quarles
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

CC: Dr. Fang Li
Ms. Erin Knudsen
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Dugan, Vivien (NIH/NIAID) [E]
Sent: Tue, 10 May 2016 14:53:30 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: For Review - GoF Determination Latter, PI: Fang Li
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-6-2016.vgd.docx

Hi Erik,
My .02 attached, very minor – thanks!
Vivien

Vivien G. Dugan, Ph.D.
Program Officer in Systems Biology
Office of Genomics and Advanced Technologies (OGAT)
Division of Microbiology and Infectious Diseases/NIAID/NIH/DHHS
5601 Fishers Lane Room 7A29 MSC 9826
North Bethesda, MD 20892-9826
(b)(6) (phone)
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 10, 2016 8:48 AM
To: Lambert, Linda (NIH/NIAID) [E] <(b)(6); Spiro, David (NIH/NIAID) [E] (b)(6); Post, Diane (NIH/NIAID) [E] (b)(6); Dugan, Vivien (NIH/NIAID) [E] (b)(6)
Subject: RE: For Review - GoF Determination Latter, PI: Fang Li

Hi Everyone,
Friendly reminder to let me know if you have any comments on the attached GoF response letter by tomorrow. Thanks!

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Sent: Friday, May 06, 2016 9:38 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6); Spiro, David (NIH/NIAID) [E] (b)(6); Post, Diane (NIH/NIAID) [E] (b)(6); Dugan, Vivien (NIH/NIAID) [E] (b)(6)
Subject: For Review - GoF Determination Latter, PI: Fang Li

Hi Everyone,

Attached is a draft response letter to Fang Li regarding our GoF assessment of his renewal application that we discussed last week. Can you please review and let me know if you have any comments? If possible I would like to send the draft on to Andrew/Irene by Wednesday next week (5/11). I've also attached the PI's original response letter for your reference.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

May XX, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

RE: 2 R01AI089728-06

Dear Mr. McKoskey:

Thank you for your correspondence of April 15th, 2016, 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 regarding Subaim 2.1 of the above-reference grant:

- NIAID is in agreement that the work you proposed under Experiments 1, 2, and 3 are not subject to the GoF research funding pause. This determination is based on the fact that the work will be carried out using either recombinant proteins or replication-deficient pseudoviruses, and will therefore not generate a replicating SARS-CoV variant with enhanced pathogenicity and/or transmissibility via the respiratory route.
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Commented [VGD1]: I remember someone suggesting to be very specific about which alternative strategies are deemed viable. Li lists 5 alternatives and #4 and #5 expand on experiment 4. Perhaps be more specific that alternative strategies i and ii may be pursued? Just a suggestion.

acknowledges your statement that if any mutant viruses you generate demonstrate either enhanced virus growth >1 log compared to the wildtype parental backbone strain or more efficient growth in primary human airway epithelial cells, you will immediately stop all experiments with the mutant and inform UNC's IBC and NIAID.

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.

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

Sincerely,

Devon Bumbray-Quarles
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

CC: Dr. Fang Li
Ms. Erin Knudsen
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 12 May 2016 15:28:05 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016.docx, Li 2R01AI 089728-06 GOF Response 2016-v3-1.pdf

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Erik

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

May XX, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

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CC: Dr. Fang Li
Ms. Erin Knudsen
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Fri, 13 May 2016 10:28:36 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016 (002) AQF.docx

Hey Erik,

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Thanks
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Andrew Q. Ford, Ph.D.
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NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

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Sent: Thursday, May 12, 2016 11:28 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

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NIAID/NIH/DHHS

(b)(6)

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Division of Microbiology and Infectious Diseases
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CC: Dr. Fang Li
Ms. Erin Knudsen
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Dr. Andrew Ford
Dr. Ralph Baric

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Sent: Tue, 17 May 2016 15:59:13 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-17-2016.docx

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Erik

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Sent: Friday, May 13, 2016 10:29 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

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Should you have any questions, or would like to meet to discuss, please let me know.

Thanks
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Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
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Sincerely,

Devon Bumbray-Quarles
Grants Management Specialist
NIAID/NIH/DHHS
(b)(6)

Program Officer
Division of Microbiology and Infectious Diseases
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Sent: Tue, 17 May 2016 14:45:01 -0400
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Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-17-2016 AQF.docx

Hey Erik,

Apologies for the delay. I made the changes we discussed and added the following sentence regarding the alternative strategies. Let me know if you have any questions. Thanks – Andrew

- NIAID acknowledges that in lieu of generating SARS-Like viruses with enhanced affinity for human receptors you will pursue alternative strategies using *loss-of-function* mutations, or mutations targeting the ACE2 receptor.

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:00 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yep, I'm around. Come up whenever.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 1:58 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Do you have a couple of minutes? I can come up.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
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5601 Fishers Lane Room 7G64
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(b)(6)

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Ms. Erin Knudsen
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Dr. Irene Glowinski
Dr. Andrew Ford
Dr. Ralph Baric

Commented [FA([9]: Considering the UNC IBC is being referenced, it seemed as though Dr. Baric should be included.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 17 May 2016 18:53:17 +0000
To: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-17-2016.docx

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Thanks.

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P: (b)(6)
F: 301.493.0597
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

May XX, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

RE: 2 R01AI089728-06

Dear Mr. McKoskey:

Thank you for your correspondence of April 15, 2016, 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 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 original grant application, and the additional information provided by you, and made the following assessments regarding Subaim 2.1 of the above-referenced grant:

- NIAID is in agreement that the work you proposed under Experiments 1, 2, and 3 is not subject to the GoF research funding pause. This determination is based on the fact that the work will be carried out using either recombinant proteins or replication-deficient pseudoviruses, and will not involve the generation of a replicating SARS-CoV variant with enhanced pathogenicity and/or transmissibility via the respiratory route.
- NIAID's determination is that the work proposed under Experiment 4 to generate SARS-Like viruses with enhanced affinity for human receptors (via both reverse genetics and serial passaging) is subject to the GoF research funding pause, and therefore may not be conducted under this grant. Given the lack of empiric evidence that increased receptor binding alone is insufficient to increase pathogenicity, NIAID has determined that the proposed work is reasonably anticipated to result in a SARS-Like virus with enhanced pathogenicity. NIAID acknowledges that in lieu of generating SARS-Like viruses with enhanced affinity for human receptors you will pursue alternative strategies using *loss-of-function* mutations, or mutations targeting the ACE2 receptor. NIAID also acknowledges your statement that if any mutant viruses you generate demonstrate either enhanced virus growth >1 log compared to the

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

Sincerely,

Devon Bumbray-Quarles
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

Program Officer
Division of Microbiology and Infectious Diseases
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CC: Dr. Fang Li
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Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Will do. I'll do first thing in the morning, so the document can be scanned in, teleworking today.

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 13 May 2016 13:35:28 +0000
To: Spiro, David (NIH/NIAID) [E]
Subject: Frieman Regeneron Bullets
Attachments: Frieman Regeneron Bullets.docx

Hi,
Attached are the bullets you asked for. Let me know if you need more info on anything.

Erik

Frieman/Regeneron Bullets

MERS Mouse Model Development

- Matt Frieman at UMD, has R01 on SARS
- We supplemented him in 2013 for MERS animal model development
- Through his collaboration with Regeneron he developed a transgenic mouse model where the mDPP4 gene was replaced with the hDPP4 gene, and expression is governed by the native mouse promoter.
- This model may be the most physiologically relevant mouse model, and can also use wild type MERS as a challenge strain
- When published Regeneron did not allow citation of NIAID support for model development
- In general Regeneron discourages the model being used for development of competitor therapeutics (have heard unofficially that they charge high licensing fees), but they have allowed pathogenesis work

GoF

- Mouse model development was paused due to GoF
- NIAID obtained an exception for the work to continue
- Information relating to the exception was part of a GoF FOIA request in January 2015
- Regeneron was uncomfortable with any GoF work being associated with the company so they halted any passaging work associated with the project

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Wed, 18 May 2016 06:51:49 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: FW: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-17-2016.docx

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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May 18, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

RE: 2 R01AI089728-06

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CC: Dr. Fang Li
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Sent: Wed, 18 May 2016 07:08:19 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

I found them, disregard.

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
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To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Erik,

Have you reached out to the Grantee to receive a response for the following Summary Statement concerns? I didn't want to send a duplicate request and there wasn't anything submitted in the JIT.

BIOHAZARD COMMENT: There are concerns that recombinant coronaviruses altered to enhance proteolytic cleavage or binding of the human angiotensin converting enzyme 2 (ACE 2) receptor may have novel and unexpected virulence phenotypes. Therefore, biosafety level-3 (BSL-3) protections, training, and monitoring procedures should be considered unless otherwise indicated.

BUDGETARY OVERLAP: There is potential for budgetary overlap with the project R01AI110700 titled, "Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis" awarded to PI Ralph Baric (co-investigator on this proposal).

Thanks.

Sincerely,
Ms. Devon Bumbray-Quarles
Grants Management Specialist
Grants Management Program
DHHS, NIH, NIAID, GMP
5601 Fishers Lane, Room 4E28, MSC 9824
Bethesda, MD 20892-9824
Overnight Mail Only: Use Zip Code 20852
P: (b)(6)
F: 301.493.0597
(b)(6)

NIH National Institute of Allergy and Infectious Diseases

"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Wed, 18 May 2016 07:10:10 -0400
To: 'Kevin McKoskey'
Cc: (b)(6) awards@umn.edu; Kirker, Mary (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; (b)(6) Baric, Ralph; Bumbray-Quarles, Devon (NIH/NIAID) [E]
Subject: Grant Number: 2 R01 AI 089728 - 06, Li (PI)
Attachments: NIAID Response to GoF- 2R01AI089728-06.pdf

Dear Mr. McKoskey,

Please find attached NIAID's response for Gain of Function (GoF) on the above subject grant.

If you have any questions or concerns, please do not hesitate to ask.

Thank you.

Sincerely,
Ms. Devon Bumbray-Quarles
Grants Management Specialist
Grants Management Program
DHHS, NIH, NIAID, GMP
5601 Fishers Lane, Room 4E28, MSC 9824
Bethesda, MD 20892-9824
Overnight Mail Only: Use Zip Code 20852
P: (b)(6)
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(b)(6)

National Institute of Allergy and Infectious Diseases

"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."

any statement made that are the sender's own and not expressly made on behalf of the NIAID by one of its representatives.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

May 18, 2016

Mr. Kevin McKoskey
Director, Sponsored Projects
University of Minnesota
450 McNamara Alumni Center
200 Oak Street SE
Minneapolis, MN 55455-2070

RE: 2 R01AI089728-06

Dear Mr. McKoskey:

Thank you for your correspondence of April 15, 2016, 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 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 original grant application, and the additional information provided by you, and made the following assessments regarding Subaim 2.1 of the above-referenced grant:

- NIAID is in agreement that the work you proposed under Experiments 1, 2, and 3 is not subject to the GoF research funding pause. This determination is based on the fact that the work will be carried out using either recombinant proteins or replication-deficient pseudoviruses, and will not involve the generation of a replicating SARS-CoV variant with enhanced pathogenicity and/or transmissibility via the respiratory route.
- NIAID's determination is that the work proposed under Experiment 4 to generate SARS-Like viruses with enhanced affinity for human receptors (via both reverse genetics and serial passaging) is subject to the GoF research funding pause, and therefore may not be conducted under this grant. Given the lack of empiric evidence that increased receptor binding alone is insufficient to increase pathogenicity, NIAID has determined that the proposed work is reasonably anticipated to result in a SARS-Like virus with enhanced pathogenicity. NIAID acknowledges that in lieu of generating SARS-Like viruses with enhanced affinity for human receptors you will pursue alternative strategies using *loss-of-function* mutations, or mutations targeting the ACE2 receptor. NIAID acknowledges your statement that if any mutant

viruses you generate demonstrate either enhanced virus growth >1 log compared to the wildtype parental backbone strain or more efficient growth in primary human airway epithelial cells, you will immediately stop all experiments with the mutant and notify NIAID and the IBCs at the University of Minnesota and the University of North Carolina at Chapel Hill of these results.

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 SARS or SARS-Like 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 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 GoF research funding 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,

(b)(6)

Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

CC: Dr. Fang Li
Ms. Erin Knudsen
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford
Dr. Ralph Baric

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Mon, 23 May 2016 11:34:12 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Subject: FW: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang
Attachments: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-17-2016.docx

Hi Erik,

Are we waiting on a response back from the Grantee or was this just for information purposes only? If not, I would really like to get this one released.

Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:53 PM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
Attached please find our response letter for the GoF assessment. Can you please review, and if you have no comments or edits date the letter and send it to the institution (copying the folks on the CC line?). Let me know if you have any questions.

Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 11:59 AM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
We're just finalizing the letter now. Should have the draft to you for review/signature by later today or tomorrow morning.

Thanks!
Erik

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
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Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Good Morning Erik,

Any updates? I have a management meeting this Thursday and this is one of the grants they will ask about.

Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Monday, May 09, 2016 9:57 AM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
Yes. There is one part of a subaim that we deemed to be GoF. I've drafted a response letter and it is being reviewed by our GoF group. We should be able to get it to you by the end of the week.

Erik

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Monday, May 9, 2016 9:56 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Good Morning Erik,

Has there been a decision made on this grant? It's ready to pending the PO checklist and GoF approval.

Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, April 20, 2016 12:07 PM
To: Bumbray-Quarles, Devon (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Hi Devon,
No, I haven't reached out to the PI about the concerns. We have been reviewing the Gain-of-Function response, and will discuss in the GoF committee meeting next Friday (4/29). We'll make our final GoF determination then.

Thanks!
Erik

From: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Sent: Wednesday, April 20, 2016 12:05 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)

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Subject: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 23 May 2016 15:37:22 +0000
To: Bumbray-Quarles, Devon (NIH/NIAID) [E]
Subject: RE: Grant Number: 2R01AI089728 - 06 PI Name: Li, Fang

Most other institutions have acknowledged the letter, but I don't think we need an official response from them. I'm working with our GrantOps to finalize the GoF terms of award for this one, and will complete the checklist once that's finished.

Erik

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BUDGETARY OVERLAP: There is potential for budgetary overlap with the project R01AI110700 titled, "Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis" awarded to PI Ralph Baric (co-investigator on this proposal).

Thanks.

Sincerely,
Ms. Devon Bumbray-Quarles
Grants Management Specialist
Grants Management Program
DHHS, NIH, NIAID, GMP
5601 Fishers Lane, Room 4E28, MSC 9824
Bethesda, MD 20892-9824
Overnight Mail Only: Use Zip Code 20852
P: (b)(6)
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NIH National Institute of Allergy and Infectious Diseases

"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final

reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 25 May 2016 17:06:24 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016
Attachments: NIAID Response to GoF- 2R01AI089728-06.pdf

Hi Andrew,
Pasted below are my draft terms for the Li award. Actual terms have quotation marks around them; the other text is what I plan to include in the checklist. Can you please review? I've also attached the final version of the determination letter in case you want to refer back to it.

You'd mentioned sending them to Victoria Connors as well. Will she need to OK them before I complete the checklist?

Erik

The grant proposal contains experiments determined to be subject to the USG Gain-of-Function (GoF) Research Funding Pause. See correspondence with PI/Institution in the official grant file.

The following GOF T1&T2 term of award and specific language regarding which experiments are not permitted to be done with NIAID funds should be included in the NoA:

"No funds are provided and no funds can be used to support gain-of-function research covered under the October 17, 2014 White House Announcement (NIH Guide Notice NOT-OD-15-011)."

"Per the letter dated May 18th, 2016 to Mr McKoskey and Dr Li, NIAID funding may not be used to generate SARS-like viruses with enhanced affinity for human receptors (via either reverse genetics or serial passaging). NIAID funding may be used for the alternative loss-of-function approaches described in your letter dated April 15th, 2016. If any of the alternative experiments proposed, or any experiments proposed under the other Aims, result in a virus with a phenotype of enhanced pathogenicity and/or transmissibility via the respiratory route, or enhanced growth by more than 1 log compared to wild type strains, you must immediately stop the work and notify the NIAID Program Officer and Grants Management Specialist."

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:51 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yes. Sounds good with respect to the other items.

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:48 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Sounds good to me, thanks! Ok for me to send it to the GMS? I'll move on to working on the terms of award and will send those to you before the end of the week. Along with the other letter I'm working on for Daszak that we discussed last Friday…

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:45 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Apologies for the delay. I made the changes we discussed and added the following sentence regarding the alternative strategies. Let me know if you have any questions. Thanks – Andrew

- NIAID acknowledges that in lieu of generating SARS-Like viruses with enhanced affinity for human receptors you will pursue alternative strategies using *loss-of-function* mutations, or mutations targeting the ACE2 receptor.

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

received this e-mail in error please inform the sender and delete it from your mailbox or any other storage devices. National Institute of Allergy and Infectious Diseases shall not accept liability for any statements made that are sender's own and not expressly made on behalf of the NIAID by one of its representatives.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:00 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yep, I'm around. Come up whenever.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 1:58 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Do you have a couple of minutes? I can come up.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 11:59 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hi Andrew,
Edited version attached. Can you please take a quick look? Mainly just the last paragraph where the IBCs are referenced… Let me know if you agree and if I should send it to the GMS. Thanks!

Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Friday, May 13, 2016 10:29 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Incorporated into the attached version are a few comments, edits, and questions for your consideration.

Should you have any questions, or would like to meet to discuss, please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, May 12, 2016 11:28 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hi Andrew,
Attached is the draft response letter for the Fang Li renewal. Can you please review and let me know if you have any comments? I've also attached his original response as well for your reference. It's been a while since I've had one of these… do you forward them on to GMS after reviewing or should I? The grant is on the release list and I think the GMS is eager to get it awarded. Do you also usually review the terms of award that are placed in the NoAs?

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 25 May 2016 18:22:22 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yep, one of the questions asks if there are any special terms to be added. Thanks!

Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Wednesday, May 25, 2016 2:22 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

I will take a look and send them to Victoria and the GMS. Yes, Victoria will need to Ok them before completing the checklist. I assume the terms are part of the checklist.

Thanks
andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
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5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:48 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Sounds good to me, thanks! Ok for me to send it to the GMS? I'll move on to working on the terms of award and will send those to you before the end of the week. Along with the other letter I'm working on for Daszak that we discussed last Friday…

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:45 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Apologies for the delay. I made the changes we discussed and added the following sentence regarding the alternative strategies. Let me know if you have any questions. Thanks – Andrew

- NIAID acknowledges that in lieu of generating SARS-Like viruses with enhanced affinity for human receptors you will pursue alternative strategies using *loss-of-function* mutations, or mutations targeting the ACE2 receptor.

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:00 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yep, I'm around. Come up whenever.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 1:58 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Do you have a couple of minutes? I can come up.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 11:59 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hi Andrew,
Edited version attached. Can you please take a quick look? Mainly just the last paragraph where the IBCs are referenced… Let me know if you agree and if I should send it to the GMS. Thanks!

Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Friday, May 13, 2016 10:29 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Incorporated into the attached version are a few comments, edits, and questions for your consideration.

Should you have any questions, or would like to meet to discuss, please let me know.

Thanks
Andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
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NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, May 12, 2016 11:28 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hi Andrew,
Attached is the draft response letter for the Fang Li renewal. Can you please review and let me know if you have any comments? I've also attached his original response as well for your reference. It's been a while since I've had one of these… do you forward them on to GMS after reviewing or should I? The grant is on the release list and I think the GMS is eager to get it awarded. Do you also usually review the terms of award that are placed in the NoAs?

Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thu, 26 May 2016 08:42:18 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Thanks. I will be in touch.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, May 26, 2016 8:39 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Looks great. Please go ahead and send to Victoria and Devon.

Thanks!

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, May 26, 2016 8:35 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hey Erik,

Apologies for not getting back to you yesterday. I made a few edits to the draft term below; see red font. Some of the edits were to bring it more in line with the letter (e.g. I added in language about the ACE2 receptor). If you are ok with the changes, and do not have any additional ones, I can go ahead and send it to Victoria and Devon for review and approval.

Thanks
andrew

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, May 25, 2016 1:06 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Hi Andrew,
Pasted below are my draft terms for the Li award. Actual terms have quotation marks around them; the other text is what I plan to include in the checklist. Can you please review? I've also attached the final version of the determination letter in case you want to refer back to it.

You'd mentioned sending them to Victoria Connors as well. Will she need to OK them before I complete the checklist?

Erik

The grant proposal contains experiments determined to be subject to the USG Gain-of-Function (GoF) Research Funding Pause. See correspondence with PI/Institution in the official grant file.

The following GOF T1&T2 term of award and specific language regarding which experiments are not permitted to be done with NIAID funds should be included in the NoA:

"No funds are provided and no funds can be used to support gain-of-function research covered under the October 17, 2014 White House Announcement (NIH Guide Notice NOT-OD-15-011)."

"Per the letter dated May 18th, 2016 to Mr McKoskey at the University of Minnesota, ~~nd Dr Li,~~ NIAID funding ~~may~~ cannot be used to generate SARS-like viruses with enhanced affinity for human receptors (via either reverse genetics or serial passaging). NIAID funding ~~may~~ will instead be used to pursue ~~for the~~ alternative loss-of-function strategies or mutation of the ACE2 receptor as ~~approaches~~ described in the ~~your~~ letter from the University of Minnesota dated April 15th, 2016. If any of the alternative experiments proposed, or any experiments proposed under the other Aims, result in a virus with a phenotype of enhanced pathogenicity and/or transmissibility via the respiratory route, or enhanced growth by more than 1 log compared to wild type strains, you must immediately stop the work and notify the NIAID Program Officer and Grants Management Specialist."

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, May 17, 2016 2:51 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: GoF PAUSE letter - R01AI089728 - NIAID Response - 5-12-2016

Yes. Sounds good with respect to the other items.

Andrew Q. Ford, Ph.D.
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

5601 Fishers Lane Room 7G64
Rockville, MD 20892
(b)(6)

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Sent: Tuesday, May 17, 2016 2:48 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
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received this e-mail in error please inform the sender and delete it from your mailbox or any other storage devices. National Institute of Allergy and Infectious Diseases shall not accept liability for any statements made that are sender's own and not expressly made on behalf of the NIAID by one of its representatives.

From: Stemmy, Erik (NIH/NIAID) [E]
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Should you have any questions, or would like to meet to discuss, please let me know.

Thanks
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To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
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Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 1 Jun 2016 15:39:54 +0000
To: Spiro, David (NIH/NIAID) [E]
Subject: RE: Question on MERS CoV

Some additional background, if (b)(6) is talking about the NIH MAb (as opposed to the VRC Vx). The MAb was developed by Dimiter Dimitrov at NCI. As far as I know no NIAID support for the development. He has collaborated with some NIAID investigators for testing, though: Kanta most recently, as well as Shibo Jiang and Kent Tseng.

If (b)(6) question is about licensing the NIH antibody for KSA use, I'm not sure we will be able to assist in that since the IP is likely with NCI. Unless IP is central for NIH? Might be useful to consult TTIPO before the call?

Prophylaxis With a Middle East **Respiratory Syndrome** Coronavirus (**MERS**-CoV)-Specific Human Monoclonal Antibody Protects Rabbits From **MERS**-CoV Infection.
Houser KV, Gretebeck L, Ying T, Wang Y, Vogel L, Lamirande EW, Bock KW, Moore IN, **Dimitrov** DS, Subbarao K.
J Infect Dis. 2016 May 15;213(10):1557-61. doi: 10.1093/infdis/jiw080. Epub 2016 Mar 3.
PMID: 26941283

Junctional and allele-specific residues are critical for **MERS**-CoV neutralization by an exceptionally potent germline-like antibody.
Ying T, Prabakaran P, Du L, Shi W, Feng Y, Wang Y, Wang L, Li W, Jiang S, **Dimitrov** DS, Zhou T.
Nat Commun. 2015 Sep 15;6:8223. doi: 10.1038/ncomms9223.
PMID:26370782

From: Spiro, David (NIH/NIAID) [E]
Sent: Wednesday, June 1, 2016 11:17 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Question on MERS CoV

Thanks

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, June 01, 2016 11:10 AM
To: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: Question on MERS CoV

Yep I'm all up to date. Unless the GoF meeting hasn't been deleted yet.

Sent with Good (www.good.com)

-----Original Message-----
From: Spiro, David (NIH/NIAID) [E]
Sent: Wednesday, June 01, 2016 11:00 AM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: FW: Question on MERS CoV

Is your calendar up to date?
I would like to set a time up with (b)(6) for tomorrow or Friday.

From: (b)(6) [mailto: (b)(6) @state.gov]
Sent: Wednesday, June 01, 2016 10:45 AM
To: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: Question on MERS CoV

Hi David,
Free now? What is a good number?

(b)(6)

SBU
This email is UNCLASSIFIED.

From: Spiro, David (NIH/NIAID) [E] [mailto: (b)(6)
Sent: Wednesday, June 01, 2016 10:41 AM
To: Ruscio, Bruce A
Cc: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Question on MERS CoV

Hi (b)(6)

We are supporting a number of therapeutics for MERS-CoV and have had a quite a bit of contact with KSA.
Glad to have a call in the near future to discuss.
Let me know when you are free.

Best,

David

From: (b)(6) [http://redirect.state.sbu/?url=mailto:(b)(6)@state.gov]
Sent: Tuesday, May 31, 2016 12:00 PM
To: Heilman, Carole (NIH/NIAID) [C] (b)(6)
Cc: Handley, Gray (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E]
(b)(6)
Subject: RE: Question on MERS CoV

Dear Carole,
Thanks you very much and (b)(6) I hope all the best to you.

Hello David,
I did not know MERS was also in your portfolio. If you would like to know more, I would be happy to chat at your convenience.

Best
(b)(6)

SBU
This email is UNCLASSIFIED.

From: Heilman, Carole (NIH/NIAID) [C] [http://redirect.state.sbu/?url=mailto (b)(6)
Sent: Tuesday, May 31, 2016 10:38 AM
To: (b)(6)
Cc: Handley, Gray (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: Re: Question on MERS CoV

Dear (b)(6)

I have copied David Spiro whose group has responsibility for MERS. They should be able to help you. As an aside, I have (b)(6)

Best

Carole

On May 31, 2016, at 10:27 AM, (b)(6) (b)(6)@state.gov> wrote:

Dear Carole,
I hope all is well and you had very nice holiday weekend. I had a new issue pop up today and was hoping you may be able to help, or point me in the right direction.

The State Department has an ongoing Science Envoy program focused specifically on Vaccine diplomacy in the MENA region. I have been the State contact person on this program and have been working with the King Saud University (KSU) over the past 2 years. Today I received question that KSU wants to proceeding with research on a monoclonal antibody to MERS coronavirus developed at NIH. Apparently NIH licensed this technology to a French company which is not doing much with it in terms of development. KSU has access to the sequence but would like a non-exclusive license to develop it for internal purposes (within the Kingdom of Saudi Arabia). Do you have thoughts on how they should proceed?

Kindest Regards,
(b)(6)

-----Original Message-----
From: Heilman, Carole (NIH/NIAID) [E] [http://redirect.state.sbu/?url=mailto:(b)(6)
Sent: Wednesday, February 03, 2016 10:56 AM
To: (b)(6)
Cc: Handley, Gray (NIH/NIAID) [E]
Subject: Re: The International Vaccine Institute invitation to US to Join.

Thx (b)(6)

Carole

> On Feb 3, 2016, at 7:39 AM, (b)(6) <(b)(6)@state.gov> wrote:
>
> HI Carol,
> Thanks for taking the time to discuss. I am pretty sure we have all we need. We will have a State meeting next week to close the loop on this. I will follow up with everyone after we meet. Like a lot of folks Zika is consuming our time right now.
>
> Best
> (b)(6)
>
> Sent from my BlackBerry 10 smartphone.
> From: Heilman, Carole (NIH/NIAID) [E]
> Sent: Tuesday, February 2, 2016 4:00 PM
> To: (b)(6)
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
>
> (b)(6)
>
> I never circled back to you --- did you get what you needed?
>
> From: (b)(6)
[http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto(b)(6)@state.gov]
> Sent: Thursday, January 21, 2016 9:50 AM
> To: Heilman, Carole (NIH/NIAID) [E] <(b)(6)>
> Subject: RE: The International Vaccine Institute invitation to US to Join.

>
> retry
>
>
>
> This email is UNCLASSIFIED.
>
>
> From: (b)(6)
> Sent: Thursday, January 21, 2016 9:47 AM
> To: 'Heilman, Carole (NIH/NIAID) [E]'
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> Hi Carol the line is open and we are on it now.
>
> Conference Line: (b)(7)(E) Code: (b)(7)(E)
>
>
>
> This email is UNCLASSIFIED.
>
>
> From: Heilman, Carole (NIH/NIAID) [E]
[http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto:(b)(6) (b)(6)
> Sent: Thursday, January 21, 2016 9:44 AM
> To: (b)(6)
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> (b)(6)
>
> Just wanted to let you know that I was a bit late to the call in --- but haven't been able to connect. If there is any chance that we could have a short conversation between now and 10:30 --- it would be great
>
> From: (b)(6)
[http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto(b)(6)@state.gov]
> Sent: Friday, January 15, 2016 9:15 AM
> To: Heilman, Carole (NIH/NIAID) [E]
(b)(6)<http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto(b)(6)>
> Cc: Handley, Gray (NIH/NIAID) [E]
(b)(6)<http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto(b)(6)>
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> HI Carole,
> Done.
>
> Best
> (b)(6)

>
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> From: Heilman, Carole (NIH/NIAID) [E]
[http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto[redacted]
> Sent: Friday, January 15, 2016 8:49 AM
> To: [redacted]
> Cc: Handley, Gray (NIH/NIAID) [E]
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> [redacted]
>
> Would you please add Gray to this call. Many thanks
>
> Carole
>
> From: [redacted]
[http://redirect.state.sbu/?url=mailto[redacted]@state.gov]
> Sent: Thursday, January 14, 2016 10:45 AM
> To: Glass, Roger (NIH/FIC) [E]
<[redacted]<http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto[redacted]>>; Gellin, Bruce (HHS/OASH)
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<[redacted]@state.gov<http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto[redacted]@state.gov>>; [redacted]
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(b)(6)@state.gov>>; Stern, Amy M
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(b)(6)@state.gov>>
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> Good Morning Roger,
> Absolutely. Expect another invite for next week. It is just an issue of coordinating a call that fits schedules.
>
>
> Best
> (b)(6)
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>
> This email is UNCLASSIFIED.
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>
> From: Glass, Roger (NIH/FIC) [E]
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edirect.state.sbu/?url=http://redirect.state.sbu/?url=http://redirect.state.sbu/?url=mailto (b)(6)
> Sent: Thursday, January 14, 2016 10:41 AM
> To: (b)(6) Gellin, Bruce (HHS/OASH); Heilman, Carole (NIH/NIAID) [E]; (b)(6)
(b)(6) (b)(6)
> Cc: Glass, Roger (NIH/FIC) [E]
> Subject: RE: The International Vaccine Institute invitation to US to Join.
>
> (b)(6)
>
> I see our discussion concerning IVI has been cancelled. I do hope that we have another chance to speak about this issue of real scientific relevance.
>
> Roger
>
>
> -----Original Appointment-----
> From: (b)(6)
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> Sent: Thursday, January 14, 2016 8:29 AM
> To: Gellin, Bruce (HHS/OASH); Glass, Roger (NIH/FIC) [E]; Heilman, Carole (NIH/NIAID) [E]; (b)(6)
(b)(6)
> Subject: Canceled: The International Vaccine Institute invitation to US to Join.
> When: Friday, January 15, 2016 1:00 PM-2:00 PM (UTC-05:00) Eastern Time (US & Canada).
> Where: (b)(5); Deliberative / Inter-Agency and/or Intra-Agency
> Importance: High
>
>
> The International Vaccine Institute in Seoul has again invited the United States to join, as it has done before. In the past there were some legal impediments to the United States joining IVI based on the nature of its governing structure. We would like to have a discussion on the level of interest in joining IVI and considerations of associated issues with potential membership.
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>
> Please let me know if you have any questions.
>

> Best
> (b)(6)
>
>

SBU
This email is UNCLASSIFIED.

Selection of Influenza Viruses with Increased Fidelity

We propose to select influenza A viruses with increased fidelity (i.e., lower error rates of the viral replication complex). In the presence of sub-lethal concentrations of so-called 'mutagens' such as ribavirin or 5-fluorouracil (5-FU), we may select (polymerase) mutants with a decreased error rate (higher fidelity). Viruses with increased fidelity are typically attenuated because of their reduced ability to adjust to environmental changes. On the other hand, such variants are attractive vaccine candidates because of their genomic stability and attenuated phenotype.

Briefly, we plan sequential passages of a lab-adapted influenza virus (such as A/WSN/33 or A/PR/8/34) or of a seasonal human H3N2 or H1N1 virus in cultured cells in the presence of sub-lethal doses of ribavirin and/or 5-FU. Experiments will be carried out with wild-type virus and with virus libraries possessing random mutations in one or several viral genes.

- In one approach, virus (libraries) will be passaged at a predetermined concentration of the mutagen until virus titers increase.
- In another approach, virus (libraries) will be passaged at increasing concentration of the mutagen.
- Both approaches may be combined.

Viruses with increased resistance to mutagens will then be sequenced and further tested for their fidelity (by performing deep-sequencing analyses of viral genomes after replication in cultured in the absence or presence of mutagens), fitness (by performing competition studies between wild-type and mutant viruses), replicative ability in cultured cells, and virulence in mice and ferrets.

Note that Section III-A-1 (Major Actions under the NIH Guidelines) does not apply: Section III-A-1-a defines a Major Action as "The deliberate transfer of a drug resistance trait to microorganism that are not known to acquire the trait naturally (…), if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture …". Ribavirin and 5-FU are not licensed in the US for treatment of influenza virus infections; hence, Section III-A-1-a does not apply.

GoF Assessment

Increases in fidelity (i.e., reduced error rates) typically lead to virus attenuation (reviewed in *Smith EC, Sexton NR, Denison MR. Thinking Outside the Triangle: Replication Fidelity of the Largest RNA Viruses.* Annu Rev Virol 1:111-132, 2014). Therefore, the proposed experiments are not reasonably anticipated to create viruses that are more virulent or transmissible than the parental virus.