From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 08:38:29 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

Looking now….

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 7:18 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

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Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, June 30, 2016 10:49 AM
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Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: Cancelled: 7/1 DURC/GoF Meeting

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Have a nice holiday!

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Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS

5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
Phone: (b)(6)
Email: (b)(6)

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From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 08:53:15 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

Well that explains why no draft!
Thanks. Let me finish reading their response!!!

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 8:47 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Hi Linda,
I didn't have a draft final determination letter yet. This was just clarifying which IBC was responsible to oversee the work since the PI referenced UNC. Since we didn't meet in person last week I wanted to be sure the group was OK with the Chinese collaborator's IBC, and that there weren't any other concerns. If that all sounds good I'll finish the checklist and draft the response saying we agree with their determination.

Sorry for the confusion!
Erik

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Sent: Tuesday, July 05, 2016 8:40 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Can you resend your draft response?

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To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
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From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 09:41:01 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

Thank you Erik for the recap.
Read Daszak's response. Good to see the correction that it will be the Wuhan IBC where the work will be done/IBC oversight.
No further comments from me – apart from saying how much I appreciate those of you who keep track of all of the technical details for the back and forth with our investigators/their institutions – that support the decisions that our group makes.
L

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Sent: Tue, 5 Jul 2016 13:43:25 +0000
To: Lambert, Linda (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

They are proposing both MERS and WIV, but both are likely to be less pathogenic than WT because the spikes are not closely related.

Thanks!

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:38 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Thank you Erik. Had it in my brain from reading his response that the WIV1 was the clone he was making changes to and therefore technically not covered by the pause.
While true, the chimerics in the MERS CoV is where the potential for GoF lies. He's got all the right stoppage in place if he sees increased path/tm.
Will respond to the group.
L

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:33 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Hi Linda,
The MERS infectious clone will be the starting point for the MERS/Bat CoV chimeras. That will be their wild type strain, and the chimeras will only have the spike gene changed. These will then go into the in vitro/vivo work.

Does that make sense?
Erik

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:28 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

HI Erik
Read it. Understand nearly all except the below. Can respond to all if you can clarify the below.
Questions
I understand he's inserting various bat spikes into WIV1 – and that WIV1 isn't captured under the funding pause.

He does say that he is making a MERS infectious clone from sequence data. So he's also making MERS/bat spike chimeras – for comparison purposes? Or is the generation of the MERS infectious clone only serving as a positive control for the cell/animal work?

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Sent: Tue, 5 Jul 2016 13:56:11 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: Daszak GoF Term

Hi Andrew,
I hadn't thought about adding GoF terms to the Daszak award since we determined it wasn't GoF. But in talking with Teresa this morning she put the general term on a recent award of hers. If I use the same language does this still need to be cleared by Mary Kirker? Here's what I'd put in the checklist:

- 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 June 8, 2016 from Dr Peter Daszak, EcoHealth Alliance, if any of the MERS-CoV or WIV1 chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must cease work with these viruses and provide the NIAID Program Officer, Grants Management Specialist, and Institutional Biosafety Committee at the Wuhan Institute of Virology with the relevant data and information related to these unanticipated outcomes.

Let me know if it's ok to complete the checklist.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 15:25:08 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Daszak GoF Term

Yes. Plan to finish it shortly. Should be fairly simple since we agreed with their determination.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 11:23 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

That could work. Do you think you will have a draft of the letter today?

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 11:08 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

I needed to be sure that the group didn't have any issues with the IBC oversight before drafting the letter, so I'm working on that now. The only other award I had that we determined not to have GoF was from way back in 2014 and we didn't put any terms on it so I didn't think about terms for this one until this morning. Maybe we can just send everything to the GMS and have her date the term to match the response letter?

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 11:00 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Do you not plan to send the letter before the funds are released?

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 10:42 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Only comment is that the final determination letter hasn't gone back yet so that's why I referenced the June 8th letter from the PI. Does that make a difference?

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 10:37 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Hey Erik,

I will send the draft terms to Mary/Victoria/Jenny. However, to keep them in line with the others we had them review, I would make the proposed changes (see red font); most of the edits simply reinforces language EcoAlliance used in their response. Do you have any problems with these edits?

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:56 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Daszak GoF Term

Hi Andrew,
I hadn't thought about adding GoF terms to the Daszak award since we determined it wasn't GoF. But in talking with Teresa this morning she put the general term on a recent award of hers. If I use the same language does this still need to be cleared by Mary Kirker? Here's what I'd put in the checklist:

- 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 Julyne 8XX, 2016 to Mr. Aleksei Chmura at ~~from Dr Peter Daszak,~~ EcoHealth Alliance, ~~if~~ should any of the MERS-CoV or WIV1 chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must ~~cease~~ stop all experiments ~~work~~ with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee ~~at the~~ with the relevant data and information related to these unanticipated outcomes.

Let me know if it's ok to complete the checklist.

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.

****

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 12:23:02 -0400
To: Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Subject: Call for agenda items - 7/8 DURC/GoF meeting

Hi All,

Please let me know if you have any agenda items for this Friday's DURC/GoF meeting by **COB tomorrow (7/6)**.

Thanks,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
Phone: (b)(6)
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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.

Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 16:48:48 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: For Review - Daszak GoF Response Letter
Attachments: GoF PAUSE letter - R01AI110964 NIAID Response.docx, Response to GoF letter, 5R01AI110964 - 03 DASZAK, PETER.pdf

Hi Everyone,
Thanks for your feedback on Daszak's IBC oversight. I've drafted the attached response letter indicating we agree with the institutional assessment that the work isn't subject to the pause. Can you please review and let me know if you have any comments?

Thank you!
Erik

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

July XX, 2016

Mr. Aleksei Chmura
Senior Coordinator of Operations
EcoHealth Alliance
460 W. 34th Street – 17th Floor
New York, NY 10001

RE: 5 R01AI110964-03

Dear Mr. Chmura:

Thank you for your correspondence of June 28th, 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 Aim 3 of the above-referenced grant:

- NIAID is in agreement that the work proposed under Aim 3 to generate MERS-like or SARS-like chimeric coronaviruses (CoVs) is not subject to the GoF research funding pause. This determination is based on the following: (1) the chimeras will contain only S glycoprotein genes from phylogenetically distant bat CoVs; and (2) recently published work demonstrating that similar chimeric viruses exhibit reduced pathogenicity. Therefore it is not reasonably anticipated that these chimeric viruses will have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.
- NIAID acknowledges that if any of the chimeric viruses created under this grant unexpectedly exhibit a phenotype of enhanced growth greater than 1 log compared to the parental strain Dr Daszak will immediately stop all experiments with these viruses and provide the NIAID Program Officer, Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

Please remember that the institution must comply in full with all terms and conditions placed on this grant. 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,

Jenny Greer
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. Peter Daszak
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 12:52:20 -0400
To: Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Dixon, Dennis M. (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

Concur.

From: Spiro, David (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 10:12 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

I do not have any concerns either.

David

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:42 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

I don't have any concerns.

Teresa M. Hauguel, Ph.D.

Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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Please consider the environment before printing this e-mail 

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, June 30, 2016 10:49 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: Response Requested: Daszak Project GoF Update
Importance: High

Hi Everyone,
I finally received a response from Dr Daszak on our questions about his IBC oversight. As a quick refresher, this award is an active R01 that proposed making MERS mutants in their year 2 progress report. They plan to create MERS chimeras containing bat CoV spike genes to understand the origin and emergence of MERS. These bat CoVs are not very closely related to MERS (63-66% homology to MERS S protein), and the anticipation is that the chimeras will all be attenuated compared to MERS and unable to use the human receptor. We agreed with this rationale, but the question arose about IBC oversight since in his letter the PI said that the UNC IBC would be notified if they did observe enhanced growth in any mutant. Baric/UNC had provided a letter of support, but is not a performance site on the award. All BSL3 work with live viruses was supposed to take place at their foreign site in China. Dr Daszak confirmed in his updated response (attached) that UNC was a typo. All work will be performed at their China site at the Wuhan Institute of Virology, and that Wuhan's IBC will oversee the work.

Please let me know if you have any concerns, or if it's ok to proceed with the T5 award. Since this T5 was supposed to be awarded on July 1 I would appreciate if you could send me any comments by noon

Tuesday July 5th. That way I can complete the checklist and the GMS can make the award quickly. Let me know if you have any questions.

Thanks!
Erik

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, June 29, 2016 1:40 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: Cancelled: 7/1 DURC/GoF Meeting

Hi Everyone,

There are no pressing agenda items so this Friday's DURC/GoF meeting is cancelled.

Erik does have one item to share with the group regarding additional information on the Daszak R01 we discussed at the 6/15 meeting. He will be circulating that via email for your input.

Have a nice holiday!

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 09:41:17 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: FW: GOF Response Concerning K22 AI116588-01A1
Attachments: FW: New GoF Term-of-Award

Example of terms of award for a recent K22.

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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Bethesda, MD 20892
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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.

Please consider the environment before printing this e-mail

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Friday, June 24, 2016 4:45 PM
To: Kindbom, Jordan (NIH/NIAID) [E] (b)(6)
Subject: RE: GOF Response Concerning K22 AI116588-01A1

Jordan,

Below are the terms of award to add to the NoA for Dr. Brooke's K22, as approved by Victoria (see attached email).

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 June 24, 2016 to Dr. Novakofski at the University of Illinois at Urbana-Champaign, should any of the recombinant influenza viruses generated under this grant exhibit a statistically significant 10-fold or more increase in plaque-forming unit (PFU) or TCID50 titers compared to parental viruses, you must immediately cease work with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and the University of Illinois at Urbana-Champaign Institutional Biosafety

Committee and Office of the Vice Chancellor for Research, with the relevant data and information related to these unanticipated outcomes.

I have included them in the Type 1 program checklist as well, which is now completed and signed. Please let me know if you need anything else from me to complete the award.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
Phone: (b)(6)
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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.

Please consider the environment before printing this e-mail 

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Friday, June 24, 2016 12:58 PM
To: Kindbom, Jordan (NIH/NIAID) [E] (b)(6)
Subject: RE: GOF Response Concerning K22 AI116588-01A1

Jordan,

Attached is NIAID's response to the institutional assessment for Dr. Brooke's pending K22 grant, 1K22AI116588-01A1, for you to sign and send to the institution. Please cc the PI, Mary Kirker, Irene Glowinski, Andrew Ford, and myself.

We will need to add a specific term of award to the grant as well. The language for that term is currently under review. Once it is finalized, I will let you know and also note it on the Type 1 checklist.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases

NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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From: Arseneau, Linda Marie [mailto (b)(6)]
Sent: Friday, June 03, 2016 5:54 PM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Kindbom, Jordan (NIH/NIAID) [E] (b)(6)
Cc: Brooke, Christopher Byron (b)(6) Shisler, Joanna L (b)(6) Maddox, Carol W (b)(6) Miller, Monica A (b)(6) Novakofski, Jan E (b)(6)
Subject: RE: GOF Response Concerning K22 AI116588-01A1

Dear Drs. Kindbom and Hauquel,
On May 19, 2016, the Office for the Vice Chancellor for Research received a request from you regarding a grant application (K22 AI116588-01A1) submitted by Dr. Chris Brooke, an Assistant Professor in the Department of Microbiology, for clarification on whether or not this proposed research is subject to the Gain of Function (GOF) funding pause. Please find the University's response and supplemental statement regarding GOF.
Please let us know if you need any other information.
Best regards,
Linda

Linda Arseneau
Assistant Director, Biosafety Officer
Division of Research Safety
University of Illinois Urbana-Champaign
Phone: (b)(6)
Fax: (b)(6)
www.drs.illinois.edu

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Fri, 24 Jun 2016 15:52:55 -0400
To: Hauguel, Teresa (NIH/NIAID) [E]
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E]
Subject: FW: New GoF Term-of-Award

Hey Teresa,

Per Victoria's email below, the terms-of-award have been okayed. In the version below, I inserted the date the letter was sent and made the change to the last line pertaining to the Vice Chancellor's office.

Should you have any questions or need anything 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: Connors, Victoria (NIH/NIAID) [E]
Sent: Friday, June 24, 2016 3:08 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E]
(b)(6) Kindbom, Jordan (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term-of-Award

Thanks Andrew. We don't have any problem with this language but we do need to issue this award by Tuesday. Will the date for the letter below be ready?

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, June 23, 2016 11:11 AM
To: Kirker, Mary (NIH/NIAID) [E] (b)(6) Connors, Victoria (NIH/NIAID) [E]
(b)(6) Kindbom, Jordan (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew

(NIH/NIAID) [E] (b)(6)
Subject: New GoF Term-of-Award

Dear Jordan, Mary, and Victoria,

In accordance with past practices, DMID is considering a term-of-award for a grant (1 K22 AI116588-01A1) that was the subject of GoF discussions and involved correspondence with the investigator/institution regarding the specifics of the proposed experiments. The research was determined **not** to be subject to the GoF research funding pause; however, the letter to the institution will acknowledge actions the institution and investigator will take should any unanticipated outcomes be observed. Considering the specifics, and in keeping with past practices, program drafted additional text to be included along with the standard GoF term-of-award. The language below mirrors the language that appears in the attached letter. Do you have any issues/concerns with the proposed term-of-award below? The letter to the institution is not attached because Teresa is considering edits/comments on other sections. Happy to discuss if you like. Thanks – Andrew

- 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 June 24, 2016 to Dr. Novakofski at the University of Illinois at Urbana-Champaign, should any of the recombinant influenza viruses generated under this grant exhibit a statistically significant 10-fold or more increase in plaque-forming unit (PFU) or $TCID_{50}$ titers compared to parental viruses, you must immediately cease work with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and the University of Illinois at Urbana-Champaign Institutional Biosafety Committee and Office of the Vice Chancellor for Research, with the relevant data and information related to these unanticipated outcomes.

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
Rockville, MD 20892
(b)(6)
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 5 Jul 2016 18:45:41 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]
Subject: RE: For Review - Daszak GoF Response Letter

Thanks!

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 2:44 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: For Review - Daszak GoF Response Letter

Looks good to me. I don't have any edits.

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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Email: (b)(6)

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Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 12:49 PM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: For Review - Daszak GoF Response Letter

Hi Everyone,
Thanks for your feedback on Daszak's IBC oversight. I've drafted the attached response letter indicating we agree with the institutional assessment that the work isn't subject to the pause. Can you please review and let me know if you have any comments?

Thank you!

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 6 Jul 2016 15:29:24 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Daszak GoF Term
Attachments: GoF PAUSE letter - R01AI110964 NIAID Response.docx

Hi Andrew,
Attached is the draft response letter. Can you please review and let me know if you have any comments? If it looks good I can get it to the GMS to send out.

Thanks!
Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 5, 2016 1:00 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Thanks

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 12:51 PM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

I've just finished the draft and sent it to the RDB folks for comments. I'll send that to you as soon as I hear back.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 11:23 AM

To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

That could work. Do you think you will have a draft of the letter today?

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)
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 11:08 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

I needed to be sure that the group didn't have any issues with the IBC oversight before drafting the letter, so I'm working on that now. The only other award I had that we determined not to have GoF was from way back in 2014 and we didn't put any terms on it so I didn't think about terms for this one until this morning. Maybe we can just send everything to the GMS and have her date the term to match the response letter?

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Sent: Tuesday, July 05, 2016 11:00 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Do you not plan to send the letter before the funds are released?

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 10:42 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Only comment is that the final determination letter hasn't gone back yet so that's why I referenced the June 8th letter from the PI. Does that make a difference?

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 10:37 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Hey Erik,

I will send the draft terms to Mary/Victoria/Jenny. However, to keep them in line with the others we had them review, I would make the proposed changes (see red font); most of the edits simply reinforces language EcoAlliance used in their response. Do you have any problems with these edits?

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 9:56 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Daszak GoF Term

Hi Andrew,
I hadn't thought about adding GoF terms to the Daszak award since we determined it wasn't GoF. But in talking with Teresa this morning she put the general term on a recent award of hers. If I use the same language does this still need to be cleared by Mary Kirker? Here's what I'd put in the checklist:

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Let me know if it's ok to complete the checklist.

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)

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Wed, 6 Jul 2016 16:00:11 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Daszak GoF Term
Attachments: GoF PAUSE letter - R01AI110964 NIAID Response AQF.docx

Hey Erik,

Incorporated into the attached version are a few edits and comments; most of the edits were to bring the language in line with that which appears in the letter from EcoHealth Alliance and the draft term-of-award. Please note the question in the second paragraph regarding nomenclature. Essentially, should the viruses be referred to as MERS- and SARS-like chimeras or MERS-CoV and WIV1 chimeras? Different nomenclature appears in different places and it needs to be consistent. Let me know what you would like to do and if any changes are needed to the term-of-award I can make those and resend it to the group.

Let me know if you have any questions.

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, July 06, 2016 11:29 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Hi Andrew,
Attached is the draft response letter. Can you please review and let me know if you have any comments? If it looks good I can get it to the GMS to send out.

Thanks!
Erik

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 5, 2016 1:00 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Daszak GoF Term

Thanks

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
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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
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(b)(6)
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Office of Scientific Coordination and Program Operations
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5601 Fishers Lane Room 7G64
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Let me know if it's ok to complete the checklist.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
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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

July XX, 2016

Mr. Aleksei Chmura
Senior Coordinator of Operations
EcoHealth Alliance
460 W. 34th Street – 17th Floor
New York, NY 10001

RE: 5 R01AI110964-03

Dear Mr. Chmura:

Thank you for your correspondence of June ~~2~~8th, 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 Aim 3 of the above-referenced grant:

- NIAID is in agreement that the work proposed under Aim 3 to generate MERS-like or SARS-like chimeric coronaviruses (CoVs) is not subject to the GoF research funding pause. This determination is based on the following: (1) the chimeras will contain only S glycoprotein genes from phylogenetically distant bat CoVs; and (2) recently published work demonstrating that similar chimeric viruses exhibited reduced pathogenicity. Therefore it is not reasonably anticipated that these chimeric viruses will have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.
- NIAID acknowledges that if any of the ~~chimeric~~ MERS-CoV or WIV-1 chimeras ~~viruses created~~ generated under this grant ~~unexpectedly exhibit a phenotype of~~show evidence of enhanced virus growth greater than 1 log over ~~compared to~~ the parental backbone strain, Dr. Daszak will immediately stop all experiments with these viruses and provide the NIAID Program Officer and, Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

Commented [FA([1]: Naïve question. Is it correct to assume that this is the same as the spike envelope gene?

Commented [FA([2]: This is the language that is used in the draft term-of-award. Should this be referenced here?

Also, I notice that in the first bullet the letter references MERS- and SARS-like chimeric viruses; should that nomenclature be used here and in the term-of-award?

Please remember that the institution must comply in full with all terms and conditions placed on this grant. 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,

Jenny Greer
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. Peter Daszak
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 7 Jul 2016 12:58:18 +0000
To: Greer, Jenny (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER
Attachments: GoF PAUSE letter - R01AI110964 NIAID Response 7-7-2016.docx

Hi Jenny,
Attached is the draft response letter. Can you please review? If you don't have any comments can you then send it to the PI, copying the folks on the CC line? Also, we wanted to make one minor edit to the term of award to be consistent with this response letter. Andrew will be circulating that to the group again shortly. He did note that Victoria usually gives us the ok for the terms, and that she's out until the 18th. Do you know if anyone else can review and approve them for us while she's out?

Thanks again so much for your help and patience! Let me know if you have any questions.
Erik

From: Greer, Jenny (NIH/NIAID) [E]
Sent: Wednesday, July 06, 2016 11:14 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

It looks like there's been some movement on this grant based on the attached email from Andrew Ford. From my side, it is worked up and ready to go, pending the finalization of the term and the completion of the PO checklist. Please let me know when you've completed (or expect to complete) the PO checklist.

Thanks!

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
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

July XX, 2016

Mr. Aleksei Chmura
Senior Coordinator of Operations
EcoHealth Alliance
460 W. 34th Street – 17th Floor
New York, NY 10001

RE: 5 R01AI110964-03

Dear Mr. Chmura:

Thank you for your correspondence of June 28th, 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.

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

Sincerely,

Jenny Greer
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. Peter Daszak
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Greer, Jenny (NIH/NIAID) [E]
Sent: Thu, 7 Jul 2016 10:00:16 -0400
To: (b)(6) (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]
Subject: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER
Attachments: 110964 Daszak GoF Determination Letter 7-7-2016.pdf

Aleksei and Peter,

Please find attached a determination regarding your grant.

As always, don't hesitate to contact us with any questions.

All the best,

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
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

July 7, 2016

Mr. Aleksei Chmura
Senior Coordinator of Operations
EcoHealth Alliance
460 W. 34th Street – 17th Floor
New York, NY 10001

RE: 5 R01AI110964-03

Dear Mr. Chmura:

Thank you for your correspondence of June 28th, 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.

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

Sincerely,

(b)(6)

Jenny Greer
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. Peter Daszak
Ms. Mary Kirker
Dr. Irene Glowinski
Dr. Andrew Ford

From: Aleksei Chmura
Sent: Fri, 8 Jul 2016 01:28:21 +0800
To: Greer, Jenny (NIH/NIAID) [E]
Cc: Stemmy, Erik (NIH/NIAID) [E]; Dr. Peter Daszak
Subject: Re: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Fantastic to hear!

Many thanks,

-Aleksei

On Jul 7, 2016, at 20:36, Greer, Jenny (NIH/NIAID) [E] (b)(6) wrote:

Dear Aleksei,

Thanks for checking in. We did receive your updated letter and are working through our internal review processes. We'll let you know as soon as we have an update.

All the best,

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Aleksei Chmura [mailto (b)(6)
Sent: Thursday, July 07, 2016 12:37 AM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: Re: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Dear Jenny,

We received an out-of-office message from Eric last month and I just wanted to make sure that you both received my email with the updated letter from Dr. Daszak.

If you have any questions or require additional documents, please call me (b)(6) or email anytime.

Many thanks!

Aleksei Chmura
Senior Coordinator of Operations

EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(b)(6) (direct)
(b)(6) (mobile)
(b)(6) Skype)

www.ecohealthalliance.org

Visit our blog: www.ecohealthalliance.org/blog

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that promote conservation and prevent pandemics.

On Jun 29, 2016, at 11:58, Aleksei Chmura (b)(6) wrote:

Dear Erik,

Prof. Zhengli Shi has confirmed that the Wuhan Institute of Virology Institutional Biosafety Committee would be immediately notified as per Peter's comments below. Please find the updated letter attached.

If you require further details, let us know anytime.

Sincerely,

-Aleksei

Aleksei Chmura
Authorized Organizational Representative &
Senior Coordinator of Operations

EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(b)(6) (direct)
(b)(6) (mobile)
(b)(6) (Skype)

www.ecohealthalliance.org

Visit our blog: www.ecohealthalliance.org/blog

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that promote conservation and prevent pandemics.

On Jun 28, 2016, at 11:22, Stemmy, Erik (NIH/NIAID) [E] <(b)(6)> wrote:

Thanks Peter! Please have Aleksei send us an updated letter once you have one.

Erik

Sent with Good (www.good.com)

-----Original Message-----
From: Peter Daszak (b)(6)
Sent: Tuesday, June 28, 2016 08:02 AM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Greer, Jenny (NIH/NIAID) [E]; Aleksei Chmura
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Sorry for not responding more quickly Erik – I've been at meetings for the last couple of weeks. You are correct to identify a mistake in our letter. UNC has no oversight of the chimera work, all of which will be conducted at the Wuhan Institute of Virology. This was a clerical error because we used some language that I asked Ralph Baric to give me because I wanted to make sure we followed an approach that has some precedence.

We will clarify tonight with Prof. Zhengli Shi exactly who will be notified if we see enhanced replication, and then amend and re-send the letter to you so it is clear. I will also confirm with Zhengli the make-up of the Wuhan Institute of Virology's Institutional Biosafety Committee. However, my understanding is that I will be notified straight away, as PI, and that I can then notify you at NIAID.

Apologies for the error!

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance

460 West 34th Street – 17th Floor
New York, NY 10001

(b)(6) (direct)
(b)(6) (fax)
www.ecohealthalliance.org

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that promote conservation and prevent pandemics.

From: Stemmy, Erik (NIH/NIAID) [E] [mailto (b)(6)
Sent: Monday, June 27, 2016 3:49 PM
To: Peter Daszak
Cc: Greer, Jenny (NIH/NIAID) [E]; Aleksei Chmura
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Hi Peter,
Just wanted to follow up with you to see if you had a chance to look in to the IBC question I sent earlier this month. Please let us know.

Thanks,
Erik

Sent with Good (www.good.com)

-----Original Message-----
From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, June 17, 2016 03:38 PM Eastern Standard Time
To: Dr. Peter Daszak
Cc: Greer, Jenny (NIH/NIAID) [E]; Aleksei Chmura
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Hi Peter,
Thanks very much for providing the additional information. I did have a couple of follow up questions for you. Can you clarify where the work with the chimeric viruses will actually be performed? Your original application described the BSL3 facilities at the Wuhan Institute of Virology, but your response letter indicated that you would notify the UNC IBC if you observed enhanced replication with any of the proposed chimeras. Therefore it's not clear where the studies are being performed. Please also clarify whether EcoHealth Alliance has its own IBC, and how the UNC IBC would be involved in the oversight of this work.

Many 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
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Email: (b)(6)

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From: Greer, Jenny (NIH/NIAID) [E]
Sent: Thursday, June 09, 2016 5:56 PM
To: Aleksei Chmura (b)(6)
Cc: Dr. Peter Daszak (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6)
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Thank you for your quick response!

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

Infectious Diseases shall not accept liability for any statements made that are the sender's own and not expressly made on behalf of NIAID by one of its representatives.

From: Aleksei Chmura [mailto (b)(6)
Sent: Thursday, June 09, 2016 5:43 PM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Dr. Peter Daszak (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: Re: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Dear Jenny,

I concur with the detailed response that Dr. Daszak just sent to you in response to the Gain of Function questions in your email from 28th May. Please let me know anytime, if you require any further information.

Many thanks!

Aleksei Chmura
Authorized Organizational Representative &

Senior Coordinator of Operations

EcoHealth Alliance
460 West 34th Street – 17th floor
New York, NY 10001

(b)(6) (direct)
(b)(6) (mobile)
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On Jun 9, 2016, at 17:37, Greer, Jenny (NIH/NIAID) [E] (b)(6) wrote:

Peter,

Thank you for providing this response. We will review it shortly. In the meantime, I look forward to receiving concurrence from your authorized business official.

Thanks again!

Jenny

Jenny Greer

Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Peter Daszak [mailto: (b)(6)
Sent: Thursday, June 09, 2016 5:23 PM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6) Aleksei Chmura (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER
Importance: High

Dear Jenny and Erik,

Please find our response letter to your email below, attached. I really appreciate you giving us the chance to clarify these details and look forward to your decision on our proposed work. As stated clearly in the letter, we will not (of course) move forward with any of the proposed work in Specific Aim #3 until we hear back from you with directions.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

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+1.212.380.4465 (fax)
www.ecohealthalliance.org

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that promote conservation and prevent pandemics.

From: Greer, Jenny (NIH/NIAID) [E] [mailto (b)(6)
Sent: Saturday, May 28, 2016 5:15 PM
To: Aleksei Chmura
Cc: Stemmy, Erik (NIH/NIAID) [E]; Peter Daszak; Kirker, Mary (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]
Subject: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Dear Mr. Chmura,

Please find attached an important message about this grant. Your immediate response will be much appreciated.

All the best,

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
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"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: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Thu, 7 Jul 2016 13:52:23 -0400
To: Glowinski, Irene (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]
Cc: Powell, Shunetta (NIH/NIAID) [E]
Subject: Cancelled: 7/8 DURC/GoF Meeting

Hi Everyone,

There are no pressing agenda items so tomorrow's DURC/GoF meeting is cancelled.

Our next meeting is scheduled for Friday, July 15th from 2-3:30pm.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
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Division of Microbiology and Infectious Diseases
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Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 8 Jul 2016 13:18:28 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

Thanks! They'd included a select agent section in the original application because they are collecting samples from wild/market animals and said there may be a risk of finding and/or exposure to SARS or other CoVs, but they stated no planned Select Agent work. The progress reports haven't changed the select agent status, and only report the MERS work and chimeric WIV-1 with SARS S protein.

I'll check with Diane too.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 9:10 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Erik,

If it's not select agent work I don't believe so. You may want to clarify that point – that there is no select agent work being done. I would also check with Diane as she has a lot more experience with BSL3 work at foreign sites through CEIRS.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 8:20 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Hey Teresa,
Are there other approvals that we need to do for BSL3 work? I thought if there were no biohazard or select agent bars to award the PI had done all the necessary steps. I don't remember ever sending anything to DEA for review, other than checking the select agent checklist question.

The Wuhan Institute is one of the biggest virology centers in China and they have the country's first BSL4 and are a WHO collaborating center.

Erik

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Thursday, July 7, 2016 5:35 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

If we are sending money to China, wouldn't their BSL-3 facility have to be "approved" through with our process for international research via DEA? Has that already happened?

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, July 06, 2016 7:31 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Yes, most of the budget for this award goes to China. The FACTS clearance reports about $160,000 to the Wuhan Institute for Virology for years 3-5. Slightly less for the first two years. There is a second site in China that will receive around $40-50,000 for years 3-5. This mainly supports the surveillance and sample collection from the live markets. Let me know if you need the exact amounts or need more info.

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Wednesday, July 6, 2016 4:43 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Is any of our money going to China?

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, June 30, 2016 10:49 AM

To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: Response Requested: Daszak Project GoF Update
Importance: High

Hi Everyone,
I finally received a response from Dr Daszak on our questions about his IBC oversight. As a quick refresher, this award is an active R01 that proposed making MERS mutants in their year 2 progress report. They plan to create MERS chimeras containing bat CoV spike genes to understand the origin and emergence of MERS. These bat CoVs are not very closely related to MERS (63-66% homology to MERS S protein), and the anticipation is that the chimeras will all be attenuated compared to MERS and unable to use the human receptor. We agreed with this rationale, but the question arose about IBC oversight since in his letter the PI said that the UNC IBC would be notified if they did observe enhanced growth in any mutant. Baric/UNC had provided a letter of support, but is not a performance site on the award. All BSL3 work with live viruses was supposed to take place at their foreign site in China. Dr Daszak confirmed in his updated response (attached) that UNC was a typo. All work will be performed at their China site at the Wuhan Institute of Virology, and that Wuhan's IBC will oversee the work.

Please let me know if you have any concerns, or if it's ok to proceed with the T5 award. Since this T5 was supposed to be awarded on July 1 I would appreciate if you could send me any comments by noon Tuesday July 5th. That way I can complete the checklist and the GMS can make the award quickly. Let me know if you have any questions.

Thanks!
Erik

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, June 29, 2016 1:40 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: Cancelled: 7/1 DURC/GoF Meeting

Hi Everyone,

There are no pressing agenda items so this Friday's DURC/GoF meeting is cancelled.

Erik does have one item to share with the group regarding additional information on the Daszak R01 we discussed at the 6/15 meeting. He will be circulating that via email for your input.

Have a nice holiday!

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 8 Jul 2016 14:58:12 +0000
To: Post, Diane (NIH/NIAID) [E]
Subject: RE: Foreign BSL3 Question

Thanks!

From: Post, Diane (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 10:52 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Re: Foreign BSL3 Question

Hi Erik

It's just for select agent work. I've had to do it for HPAI studies. I don't think there is anything to do with BSL3 work that isn't a select agent.

Diane

On Jul 8, 2016, at 9:26 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Diane,
Quick question for you about foreign BSL3 work. For that Daszak GoF project Irene asked me if DEA has approved the BSL facility since we're sending money there. I haven't ever sent anything to DEA to review for other awards, though I don't really have many foreign sites doing BSL3 work. If there were no biohazard or select agent bars to award I just complete the PO checklist and do the FACTS clearance. Is there something else that usually needs to be done for BSL3 work at foreign sites? There's no select agent work with this award, just the MERS and chimeric WIV-1 with SARS S protein.

Teresa said she didn't think there was anything else but suggested I check with you since you have more experience with foreign sites with BSL3 facilities.

Erik
<mime-attachment>

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Fri, 8 Jul 2016 11:15:24 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: back-up (b)(6)?

That would be great if you could run the meeting on the (b)(6). I will take care of the agenda so no need to worry about that part. Just an FYI – (b)(6). I'd rather not be (haha) but we may have to postpone leaving until the (b)(6) depending on (b)(6) work schedule. I will know for by Wednesday of next week.

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 11:13 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: back-up (b)(6)?

Great! Let me know if you'll need me to run the GoF meeting while you're out, too.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 11:12 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: back-up (b)(6)?

Yes, can't wait ☺ Thanks so much! I will let you know if there are any outstanding items around mid-week next week. I am not anticipating any as of now.

Teresa M. Hauguel, Ph.D.

Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 11:07 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: back-up (b)(6) ?

Sure. I'm around and happy to be your backup. (b)(6)

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 11:05 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: back-up (b)(6) ?

Hi Erik,

I will be on AL(b)(6) If you will be in the office are you willing to be my back-up?

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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From: Dixon, Dennis M. (NIH/NIAID) [E]
Sent: Fri, 8 Jul 2016 11:47:16 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: Response Requested: Daszak Project GoF Update

I will return to the office (b)(6) following (b)(6) If you need to reach me immediately, please call (b)(6)

From: Dixon, Dennis M. (NIH/NIAID) [E]
Sent: Fri, 8 Jul 2016 11:54:42 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]
Cc: Dixon, Dennis M. (NIH/NIAID) [E]
Subject: RE: Response Requested: Daszak Project GoF Update

For some of the toxin based genes yes, generally not for the microbes. If this is just one gene, and it is not the sole basis for the pathology, then should be OK.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 11:47 AM
To: Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

It's not a MERS-SARS chimera. The chimeras are MERS with various bat-CoV Spike genes and WIV-1 (a bat CoV) with the SARS S gene. Would the SA rules apply for a single gene from the select agent?

From: Dixon, Dennis M. (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 11:39 AM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Dixon, Dennis M. (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Is this technically a MERS-SARS chimera? If so, I might need to check with CDC SAP to see if they would hold the work to SARS standards. Any Select Agent-Non Select Agent chimera could be viewed that way. If so, they could need SA approval. Not simple. If not, then I think anyone receiving our funds needs to adhere to our guidance for working with BSL3 agents.

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 11:05 AM
To: Dixon, Dennis M. (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: FW: Response Requested: Daszak Project GoF Update

Dennis – can you respond please?

Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 11:04 AM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Hi Irene,
This award doesn't have select agent work involved, just MERS and now chimeric WIV-1 with SARS S gene. The original application didn't have any biohazard concerns noted so I just did the usual checklist and FACTS clearance. Is there additional review needed for non-select agent BSL3 work? The Wuhan Institute is a major virology research center and in addition to the BSL3 facilities has China's first BSL4. They're also a WHO collaborating center.

Erik

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Thursday, July 7, 2016 5:35 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

If we are sending money to China, wouldn't their BSL-3 facility have to be "approved" through with our process for international research via DEA? Has that already happened?

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, July 06, 2016 7:31 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Yes, most of the budget for this award goes to China. The FACTS clearance reports about $160,000 to the Wuhan Institute for Virology for years 3-5. Slightly less for the first two years. There is a second site in China that will receive around $40-50,000 for years 3-5. This mainly supports the surveillance and sample collection from the live markets. Let me know if you need the exact amounts or need more info.

From: Glowinski, Irene (NIH/NIAID) [E]
Sent: Wednesday, July 6, 2016 4:43 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: Response Requested: Daszak Project GoF Update

Is any of our money going to China?

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, June 30, 2016 10:49 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E]

(b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6)
Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E]
(b)(6)
Subject: Response Requested: Daszak Project GoF Update
Importance: High

Hi Everyone,
I finally received a response from Dr Daszak on our questions about his IBC oversight. As a quick refresher, this award is an active R01 that proposed making MERS mutants in their year 2 progress report. They plan to create MERS chimeras containing bat CoV spike genes to understand the origin and emergence of MERS. These bat CoVs are not very closely related to MERS (63-66% homology to MERS S protein), and the anticipation is that the chimeras will all be attenuated compared to MERS and unable to use the human receptor. We agreed with this rationale, but the question arose about IBC oversight since in his letter the PI said that the UNC IBC would be notified if they did observe enhanced growth in any mutant. Baric/UNC had provided a letter of support, but is not a performance site on the award. All BSL3 work with live viruses was supposed to take place at their foreign site in China. Dr Daszak confirmed in his updated response (attached) that UNC was a typo. All work will be performed at their China site at the Wuhan Institute of Virology, and that Wuhan's IBC will oversee the work.

Please let me know if you have any concerns, or if it's ok to proceed with the T5 award. Since this T5 was supposed to be awarded on July 1 I would appreciate if you could send me any comments by noon Tuesday July 5th. That way I can complete the checklist and the GMS can make the award quickly. Let me know if you have any questions.

Thanks!
Erik

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, June 29, 2016 1:40 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E]
(b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David
(NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara
(NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher
(NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E]
(b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: Cancelled: 7/1 DURC/GoF Meeting

Hi Everyone,

There are no pressing agenda items so this Friday's DURC/GoF meeting is cancelled.

Erik does have one item to share with the group regarding additional information on the Daszak R01 we discussed at the 6/15 meeting. He will be circulating that via email for your input.

Have a nice holiday!

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

Please consider the environment before printing this e-mail 

From: Peter Daszak
Sent: Mon, 11 Jul 2016 14:28:11 +0000
To: Greer, Jenny (NIH/NIAID) [E]; Aleksei Chmura
Cc: Stemmy, Erik (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Joseph Riccardi
Subject: Re: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Dear Jenny,

This is terrific! We are very happy to hear that our Gain of Function research funding pause has been lifted.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

(b)(6) (direct)
+1.212.380.4465 (fax)
www.ecohealthalliance.org

EcoHealth Alliance leads cutting-edge research into the critical connections between human and wildlife health and delicate ecosystems. With this science we develop solutions that promote conservation and prevent pandemics.

From: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Sent: Thursday, July 7, 2016 10:00 AM
To: Aleksei Chmura; Peter Daszak
Cc: Stemmy, Erik (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]
Subject: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Aleksei and Peter,

Please find attached a determination regarding your grant.

As always, don't hesitate to contact us with any questions.

All the best,

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tue, 12 Jul 2016 13:56:37 -0400
To: Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Subject: Call for agenda items - 7/15 DURC/GoF meeting

Hi All,

Below is the agenda for this Friday's DURC/GoF meeting. Please let me know if you have any additional agenda items by **COB tomorrow**.

Thanks,
Teresa

Weekly DURC/GoF Meeting Agenda
Friday, July 15, 2016
2:00-3:30pm
5601/7G31
Call in number: (b)(6)
Passcode: (b)(6)

1. Projects for GoF Review
    a. Yen (CEIRS) – Eurasian swine flu viruses – Diane
    b. Kawaoka (CEIRS) – (b)(4) flu viruses – Diane
2. Overview of NAS DURC Communication Meeting – Teresa
3. Updates
    a. NSABB WG – Dennis, Diane, Teresa
    b. DURC/BSAT Sub-IPC – Dennis
    c. ISARG – Dennis/Ken/Tricia
    d. Erasmus RMP – Diane/Ken/Tricia
4. Round Robin/Other Items

Teresa M. Hauguel, Ph.D.
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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.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wed, 13 Jul 2016 09:51:04 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]
Subject: RE: Friday's DURC/GoF meeting

Ok thanks Erik.

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
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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.

Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 9:50 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E]
(b)(6)
Subject: RE: Friday's DURC/GoF meeting

If we need to meet I'm happy to help run the meeting. Just let me know.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 9:44 AM
To: Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6)
Subject: Friday's DURC/GoF meeting

Hi Diane & Erik,

Based on Outlook calendars, it looked like most of the committee members would be in this office this Friday. However, after some email exchanges it now appears as though all of leadership (b)(6) that day. So I will be cancelling this Friday's meeting.

Our next meeting is not scheduled until August 5th. Diane, I know you have some agenda items you have wanted to discuss for a few weeks now. Would you like me to try and schedule a meeting before August 5th? It looks like next Friday, July 22nd is free (except for Irene, she has a tentative meeting on her calendar). If so, I can schedule with Shunetta but would need you or Erik to organize the agenda and run the meeting because I will be on (b)(6)

Best,
Teresa

Teresa M. Hauguel, Ph.D.
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Please consider the environment before printing this e-mail

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wed, 13 Jul 2016 10:26:51 -0400
To: Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Friday's DURC/GoF meeting

Sounds good. I will ask Shunetta to reschedule this Friday's meeting to the 22nd. Keep an eye out for an invite. Once the invite goes out I will email the group to let them know of the scheduling change.

Erik – Thanks for offering to the run the meeting. I will send you the draft agenda that I have later today but you may want to take a poll of program staff early next week to see if anything else comes up.

Teresa M. Hauguel, Ph.D.
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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.

Please consider the environment before printing this e-mail

From: Post, Diane (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 10:03 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E]
(b)(6)
Subject: RE: Friday's DURC/GoF meeting

Hi Teresa,

There a few things that would of been sitting for quite some time if we wait until August 5th. If possible I would like to try to have a meeting on the 22nd.

Thanks Teresa!
Diane

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 9:50 AM

To: Hauguel, Teresa (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]
Subject: RE: Friday's DURC/GoF meeting

If we need to meet I'm happy to help run the meeting. Just let me know.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 9:44 AM
To: Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6)
Subject: Friday's DURC/GoF meeting

Hi Diane & Erik,

Based on Outlook calendars, it looked like most of the committee members would be in this office this Friday. However, after some email exchanges it now appears as though all of leadership (b)(6) (b)(6) So I will be cancelling this Friday's meeting.

Our next meeting is not scheduled until August 5th. Diane, I know you have some agenda items you have wanted to discuss for a few weeks now. Would you like me to try and schedule a meeting before August 5th? It looks like next Friday, July 22nd is free (except for Irene, she has a tentative meeting on her calendar). If so, I can schedule with Shunetta but would need you or Erik to organize the agenda and run the meeting because I will be on (b)(6)

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
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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.

Please consider the environment before printing this e-mail

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Thu, 14 Jul 2016 11:07:27 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: back-up (b)(6)

Thanks!

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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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.

Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, July 14, 2016 11:03 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: RE: back-up (b)(6)

Sounds good. Hope you have a (b)(6) ☺

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Thursday, July 14, 2016 10:54 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: back-up (b)(6)

Hi Erik,

Thanks for agreeing to be my back-up. Hopefully it's a quiet week.

I have one application scheduled for review next week with the ZRG1 IDM-W(50)R study section. The SRO, Marci Scidmore, should be sending you call-in information and any relevant status emails.

SCIDMORE, MARCI	2016/10 ZRG1 IDM-W(50)R Mtg Roster	07/20/2016	Bethesda Marriott Suites	Agenda Report	• Antibody responses in humans after infection with avian influenza viruses • 1R01AI128821-01	ESI	M51B B	KRAMMER, FLORIAN	AI16-006	201610

And of course there is the DURC/GoF meeting that we rescheduled for next Friday. Attached is the draft agenda email I started. The areas in yellow will need to be updated if you receive additional agenda items and if the dial-in information changes. I asked Shunetta to verify that the dial-in was correct but have not heard back yet.

The only other thing that may come up are Type 7 checklists for PI institution changes. I have two that have been pending for a few months and if they move forward while I am away they can likely wait until I get back. But I wanted to put them on your radar anyway in case you are contacted by the GMS and there is a very short turnaround time.

1. Jie Sun – Mayo Clinic – 5R01AI112844-02 & 5R21AI119612-02 – I already completed the Type 7 checklist for the R21 but the R01 is still pending
2. Scott Hensley – Univ. Pennsylvania – 5R01AI108686-02 & 5R01AI113047-03

If anything urgent comes up you can reach me at (b)(6)

Thanks again!

Best,
Teresa

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

Please consider the environment before printing this e-mail

From: Powell, Shunetta (NIH/NIAID) [E] on behalf of Glowinski, Irene (NIH/NIAID) [E]
Sent: Fri, 15 Jul 2016 10:46:54 -0400
To: Post, Diane (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Cc: Powell, Shunetta (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]
Subject: DURC/GoF Committee Meeting
Attachments: FW: Conference Details (JUL 22, 2016--03:00 PM ET--Conf# 9348806)

Call-in number: (b)(6)
Passcode: (b)(6)

From: NIH Teleconferencing (b)(6)
Sent: Fri, 15 Jul 2016 10:46:00 -0400
To: Powell, Shunetta (NIH/NIAID) [E]
Cc: Teleconferencing
Subject: FW: Conference Details (JUL 22, 2016--03:00 PM ET--Conf# 9348806)

-----Original Message-----
From: norepliesplease@mymeetings.com [mailto:norepliesplease@mymeetings.com]
Sent: Friday, July 15, 2016 10:41 AM
To: NIH Teleconferencing (b)(6) <nihteleconf@mail.nih.gov>
Subject: Conference Details (JUL 22, 2016--03:00 PM ET--Conf# 9348806)

Your conference details are enclosed.
Meeting Information:
Leader: DR TERESA HAUGUEL
Phone number: (b)(6)
Contact: TESSA MELBOURN
Phone number: (b)(6)
Service level: Unattended
Number of lines: Total=10 Dialout=0 Meet Me=10 Meet Me Toll=0
Call date: JUL-22-2016 (Friday)
Call time: 03:00 PM EASTERN TIME
Duration: 1 hr 30 min
Confirmation number: 9348806
Company: NWX-NIAID-DMID-1
CRC:

Passcodes/Pin codes:
Participant passcode: (b)(6)
For security reasons, the passcode will be required to join the conference.

Dial in numbers:

Country	Toll Numbers	Freephone/Toll Free Number
USA		(b)(6)

Restrictions may exist when accessing freephone/toll free numbers using a mobile telephone.

In-Conference Features:
All participants must use a touch-tone phone to participate in an Audio Conference. The following features are available for you to use on your phone during an active conference:

1) Press *0 operator assistance (small fee may apply).
2) Press *6 mute/unmute individual line.

Selected Conference Features:

Audio

Tones

A cancellation fee will be assessed per reserved line, in the event that the conference is not cancelled within 30 minutes prior to the scheduled start time.

An overbooking fee will be assessed for each unused, reserved line after the first 50 unused lines, per completed conference. There will be no fee assessed for the first 50 unused, reserved lines.

Leaders can schedule, modify or cancel a reservation by using the Conference Scheduling Assistant, an online scheduling tool. To reschedule or cancel this reservation, go to https://www.mymeetings.com/confassist/calist?customHeader=mymeetings .

For additional assistance, contact customer service at 866-900-1011

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If you would prefer not to receive these messages, you may unsubscribe now at https://www.mymeetings.com/emeet/remove.jsp. Thank you.

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Fri, 15 Jul 2016 18:49:54 +0000
To: Ford, Andrew (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Conversation with Ford, Andrew (NIH/NIAID) [E]

Ford, Andrew (NIH/NIAID) [E] 2:38 PM:
Hey Erik. Did you hear anything from GMS regarding the GoF TOA?

Stemmy, Erik (NIH/NIAID) [E] 2:38 PM:
No. I'd been meaning to check in with the GMS this week, but didn't have a chance to. Looks like both folks that approve the terms were (b)(6) so Jenny did say we may need to wait until then

Ford, Andrew (NIH/NIAID) [E] 2:45 PM:
Yes, I was meaning to check with them as well. Perhaps a mid-morning/afternoon email on Monday will flag it for them. Of at least Jenny could approach them in person to ensure it is at the top of their to-do list.

Stemmy, Erik (NIH/NIAID) [E] 2:46 PM:
Good idea. I'll put it on my calendar to check in with Jenny monday morning. Thanks!

Ford, Andrew (NIH/NIAID) [E] 2:47 PM:
Actually. I meant that as an action item for me. But thanks, I will hold off if you reach out.

Stemmy, Erik (NIH/NIAID) [E] 2:47 PM:
No worries. I'll copy you as well.

Ford, Andrew (NIH/NIAID) [E] 2:47 PM:
thanks

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 18 Jul 2016 14:18:29 +0000
To: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: New GoF Term - 5 R01 AI110964-03

Thanks! My surface has decided today is a good day to break so I may not be able to finish the checklist until tomorrow morning. Waiting on IT now.

Sent with Good (www.good.com)

-----Original Message-----
From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 09:56 AM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: FW: New GoF Term - 5 R01 AI110964-03

Hey Erik,

I added the date and removed the WIV-1 language from the term below. I think this is ready to go now.

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: Connors, Victoria (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 9:53 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E]

(b)(6)

Subject: RE: New GoF Term - 5 R01 AI110964-03

Hi Andrew –

I discussed this with Mary and the draft term below is fine. Thanks!

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, July 07, 2016 9:03 AM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term

Dear Jenny, Victoria, and Mary,

I am following up with respect to the email below. Upon speaking with Erik, one change was made to the draft term-of-award to bring it in line with the response letter to the institution; please see the red font. Do you have any issues/concerns with the proposed term-of-award? Thanks – Andrew

- 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 July 7, 2016 to Mr. Aleksei Chmura at EcoHealth Alliance, should any of the MERS-like or SARS-like chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

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

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 1:39 PM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: New GoF Term

Dear Jenny, Mary, and Victoria,

In accordance with past practices, DMID is considering a term-of-award for a grant (5 R01 AI110964-03) that was the subject of GoF discussions and involved correspondence with the investigator/institution regarding the specifics of the proposed experiments. The research was determined **not** to be subject to the GoF research funding pause; however, the letter to the institution will acknowledge actions the institution and investigator will take should any unanticipated outcomes be observed. Considering the specifics, and in keeping with past practices, program drafted additional text to be included along with the standard GoF term-of-award. The language below mirrors the language that will appear in the letter to the institution; the letter is currently being reviewed in the division. Do you have any issues/concerns with the proposed term-of-award below? Thanks – Andrew

- 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 July XX, 2016 to Mr. Aleksei Chmura at EcoHealth Alliance, should any of the MERS-CoV or WIV1 chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 18 Jul 2016 14:19:25 +0000
To: Greer, Jenny (NIH/NIAID) [E]
Subject: RE: New GoF Term - 5 R01 AI110964-03

Will do. My computer has crashed so I'll do it as soon as IT has me up and running again.

Thanks!

Sent with Good (www.good.com)

-----Original Message-----
From: Greer, Jenny (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 10:06 AM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: FW: New GoF Term - 5 R01 AI110964-03

Finally….

Let me know when you have completed the PO checklist so I can make this award.

Thanks!

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 9:54 AM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E]

(b)(6)
Subject: RE: New GoF Term - 5 R01 AI110964-03

Thanks Victoria.

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: Connors, Victoria (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 9:53 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E]
(b)(6)
Subject: RE: New GoF Term - 5 R01 AI110964-03

Hi Andrew –

I discussed this with Mary and the draft term below is fine. Thanks!

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, July 07, 2016 9:03 AM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E]
(b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew
(NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term

Dear Jenny, Victoria, and Mary,

I am following up with respect to the email below. Upon speaking with Erik, one change was made to the draft term-of-award to bring it in line with the response letter to the institution; please see the red font. Do you have any issues/concerns with the proposed term-of-award? Thanks – Andrew

- 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 July XX, 2016 to Mr. Aleksei Chmura at EcoHealth Alliance, should any of the MERS-like or SARS-like ~~WIV1~~ chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

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

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 1:39 PM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: New GoF Term

Dear Jenny, Mary, and Victoria,

In accordance with past practices, DMID is considering a term-of-award for a grant (5 R01 AI110964-03) that was the subject of GoF discussions and involved correspondence with the investigator/institution regarding the specifics of the proposed experiments. The research was determined **not** to be subject to the GoF research funding pause; however, the letter to the institution will acknowledge actions the institution and investigator will take should any unanticipated outcomes be observed. Considering the specifics, and in keeping with past practices, program drafted additional text to be included along with the standard GoF term-of-award. The language below mirrors the language that will appear in the letter to the institution; the letter is currently being reviewed in the division. Do you have any issues/concerns with the proposed term-of-award below? Thanks – Andrew

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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: Ford, Andrew (NIH/NIAID) [E]
Sent: Mon, 18 Jul 2016 08:11:11 -0400
To: Connors, Victoria (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: New GoF Term
Attachments: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Hey Victoria,

(b)(6) This has **not** been taken care of. Per the attached email, Jenny did loop in others (Donna and Ann) within grants management.

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: Connors, Victoria (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 8:08 AM
To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term

Just (b)(6) so checking to make sure this was taken care of already?

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thursday, July 07, 2016 9:03 AM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term

Dear Jenny, Victoria, and Mary,

I am following up with respect to the email below. Upon speaking with Erik, one change was made to the draft term-of-award to bring it in line with the response letter to the institution; please see the red font. Do you have any issues/concerns with the proposed term-of-award? Thanks – Andrew

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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: Ford, Andrew (NIH/NIAID) [E]
Sent: Tuesday, July 05, 2016 1:39 PM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: New GoF Term

Dear Jenny, Mary, and Victoria,

In accordance with past practices, DMID is considering a term-of-award for a grant (5 R01 AI110964-03) that was the subject of GoF discussions and involved correspondence with the investigator/institution regarding the specifics of the proposed experiments. The research was determined **not** to be subject to the GoF research funding pause; however, the letter to the institution will acknowledge actions the institution and investigator will take should any unanticipated outcomes be observed. Considering the specifics, and in keeping with past practices, program drafted additional text to be included along with

the standard GoF term-of-award. The language below mirrors the language that will appear in the letter to the institution; the letter is currently being reviewed in the division. Do you have any issues/concerns with the proposed term-of-award below? Thanks – Andrew

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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: Greer, Jenny (NIH/NIAID) [E]
Sent: Thu, 7 Jul 2016 10:04:25 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Ford, Andrew (NIH/NIAID) [E]
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

I've forwarded the term to Donna and Ann in Victoria's absence, (b)(6) But I'll check in with Donna later today if I haven't heard anything from her.

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, July 07, 2016 8:58 AM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

Hi Jenny,
Attached is the draft response letter. Can you please review? If you don't have any comments can you then send it to the PI, copying the folks on the CC line? Also, we wanted to make one minor edit to the term of award to be consistent with this response letter. Andrew will be circulating that to the group again shortly. He did note that Victoria usually gives us the ok for the terms, and that she's (b)(6) (b)(6) Do you know if anyone else can review and approve them for us while she's out?

Thanks again so much for your help and patience! Let me know if you have any questions.
Erik

From: Greer, Jenny (NIH/NIAID) [E]
Sent: Wednesday, July 06, 2016 11:14 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 5R01AI110964 - 03 PI Name: DASZAK, PETER

It looks like there's been some movement on this grant based on the attached email from Andrew Ford. From my side, it is worked up and ready to go, pending the finalization of the term and the completion

of the PO checklist. Please let me know when you've completed (or expect to complete) the PO checklist.

Thanks!

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 11:33:37 +0000
To: Greer, Jenny (NIH/NIAID) [E]
Subject: RE: New GoF Term - 5 R01 AI110964-03

Done! IT wasn't able to get me up and running yesterday, (b)(6). Let me know if you need anything else from me to make the award.

Thanks so much for your help and patience!
Erik

From: Greer, Jenny (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 10:07 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: FW: New GoF Term - 5 R01 AI110964-03

Finally….

Let me know when you have completed the PO checklist so I can make this award.

Thanks!

Jenny

Jenny Greer
Grants Management Specialist
DHHS/NIH/NIAID/DEA/GMP
5601 Fishers Lane, Room 4E49, MSC 9833
Bethesda, MD 20892-9824
Phone: (b)(6)
Email: (b)(6)

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Sent: Monday, July 18, 2016 9:54 AM
To: Connors, Victoria (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term - 5 R01 AI110964-03

Thanks Victoria.

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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To: Ford, Andrew (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term - 5 R01 AI110964-03

Hi Andrew –

I discussed this with Mary and the draft term below is fine. Thanks!

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Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: RE: New GoF Term

Dear Jenny, Victoria, and Mary,

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Office of Scientific Coordination and Program Operations
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NIAID/NIH/DHHS
5601 Fishers Lane Room 7G64
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(b)(6)
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From: Ford, Andrew (NIH/NIAID) [E]
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To: Connors, Victoria (NIH/NIAID) [E] (b)(6) Kirker, Mary (NIH/NIAID) [E] (b)(6) Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6)
Subject: New GoF Term

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Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

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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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 11:36:05 +0000
To: Hanson, Christopher (NIH/NIAID) [E]
Subject: RE: Rescheduled: 7/15 DURC/GoF meeting - new date: 7/22

Thanks Chris!

From: Hanson, Christopher (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 12:46 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: FW: Rescheduled: 7/15 DURC/GoF meeting - new date: 7/22

Erik,

FYI. Nothing from DIR to report this week.

I've actually got another time request for Friday at 3pm. Do you have an idea of the agenda to discuss for this cmte?

Thanks.

-Chris

From: Teresa Hauguel (b)(6)
Date: Wednesday, July 13, 2016 at 4:47 PM
To: Irene Glowinski (b)(6) Dennis Dixon (b)(6) Linda Lambert (b)(6) "Spiro, David (NIH/NIAID) [E]" (b)(6) Teresa Hauguel (b)(6) "Post, Diane (NIH/NIAID) [E]" (b)(6) "Stemmy, Erik (NIH/NIAID) [E]" (b)(6) "Brown, Liliana (NIH/NIAID) [E]" (b)(6) "Mulach, Barbara (NIH/NIAID) [E]" (b)(6) Andrew Ford (b)(6) "Strickler-Dinglasan, Patricia (NIH/NIAID) [E]" (b)(6) Chris Hanson (b)(6) "Delarosa, Patricia (NIH/NIAID) [E]" (b)(6) "Santora, Kenneth (NIH/NIAID) [E]" (b)(6)
Cc: "Powell, Shunetta (NIH/NIAID) [E]" (b)(6)
Subject: Rescheduled: 7/15 DURC/GoF meeting - new date: 7/22

Hi Everyone,

There are a number of people out of the office this Friday, 7/15, so we will not be holding our weekly DURC/GoF meeting.

This meeting has been **rescheduled for Friday, July 22nd from 3-4:30pm** because we have a few agenda items to discuss. You should have received an Outlook invite with the new meeting time. (b)(6) but Erik has kindly agreed to run the meeting and will send out the agenda next week.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

Please consider the environment before printing this e-mail 

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 11:38:07 +0000
To: DMID GrantOps
Subject: RE: PO checklists still needed

Hi GrantOps,
Grants Management finally approved the GoF term of award that I've been waiting on so I completed the checklist for the Daszak award listed below.

Erik

From: DMID GrantOps
Sent: Monday, July 18, 2016 5:45 PM
To: Challberg, Mark (NIH/NIAID) [E] (b)(6) Eichelberg, Katrin (NIH/NIAID) [E] (b)(6) Sizemore, Christine (NIH/NIAID) [E] (b)(6) Wali, Tonu (NIH/NIAID) [E] (b)(6) Hiltke, Thomas (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Degrace, Marciela (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Gezmu, Misrak (NIH/NIAID) [E] (b)(6) Kraigsley, Alison (NIH/NIAID) [E] (b)(6)
Cc: DMID GrantOps (b)(6)
Subject: FW: PO checklists still needed

Dear all:

As of this morning, the GMO reported as incomplete the following Type 5 checklists which were due on 7/10. If you have not already, would you please complete your checklist(s) by tomorrow and reply to GrantOps and the assigned GMS with a status update?

Note: The report below is supplied by the GMO and we recognize that it may not take into account your most recent actions or correspondence with the GMS regarding these grants.

If one of your Type 5s is not yet received, please assist by contacting your PI. Future funding may be impacted by their delayed PR submission.

Thank you for your assistance!
Karen
DMID GrantOps

From: Connors, Victoria (NIH/NIAID) [E]
Sent: Monday, July 18, 2016 9:54 AM
To: DMID GrantOps (b)(6)
Subject: PO checklists still needed

Please see the list below

Thanks!

DMID Start Date	PO Signature	T5 Received	T	Grant Number	PCC	STATUS	PI	GMS	PO
8/1/16		6/22/16	5	R01AI106307-04	M32A	35	LUO	Vily,Aytaj	Challberg
8/1/16		6/3/16	5	U19AI111211-03	M33A B	35	BLUMBERG	Machuca,Jorge	Eichelberg
7/1/16		7/6/16	5	R01AI099603-05	M33BBR	35	Stoltz	Cooper,Kim	Sizemore
8/1/16		6/15/16	5	R01AI107588-04	M44B	35	Gause	Halary,Azita	Wali
8/1/16		7/15/16	5	R01AI044033-15	M48	35	Maurelli	Normil,Carine	Hiltke
6/1/16		5/13/16	5	R01AI110964-03	M51C	35	DASZAK	Greer,Jenny	Stemmy
8/1/16		6/14/16	5	R01AI108993-03	M51JB	35	Gray	Hartman,Jeffrey	DeGrace
8/1/16		6/14/16	5	R01AI108888-03	M63E	35	Ye	Saletta,Jill	Brown
8/1/16		6/20/16	5	R01AI107721-03	M71	35	Kulldorff	Rodriguez,Cynthia	Gezmu

From: Dixon, Dennis M. (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 08:13:46 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: 7/22 DURC/GoF meeting -Agenda Items?

I will be out of the office Monday - Wednesday for a series of local meetings. I will be reading email intermittently. If you need to reach me immediately, please call (b)(6)

From: Strickler-Dinglasan, Patricia (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 08:13:46 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: 7/22 DURC/GoF meeting -Agenda Items?

Thank you for your email. I will be offline (b)(6) with only intermittent access to email. Please contact Karen Bateman (DMID GrantOps) for any grant-related questions or Barbara Mulach for any other questions.

If you need to reach me directly, please contact me at (b)(6) and I will return your call as soon as possible.

Thank you,
Trish Strickler-Dinglasan

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 08:13:46 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: 7/22 DURC/GoF meeting -Agenda Items?

Thank you for your email. I will be out of the office (b)(6) with limited access to email. For urgent grant-related matters please contact Dr. Erik Stemmy (b)(6)

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Tue, 19 Jul 2016 18:58:18 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Mulach, Barbara (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]
Subject: RE: 7/22 DURC/GoF meeting -Agenda Items?

Hey Erik,

BUGS does not have anything to add.

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, July 19, 2016 8:14 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: 7/22 DURC/GoF meeting -Agenda Items?

Hi Everyone,
Below is the agenda for Friday's DURC/GoF meeting.

Please let me know if there are any additions by COB Wednesday July 20th.

Thanks!
Erik

Weekly DURC/GoF Meeting Agenda
Friday, July 22, 2016
3:00-4:30pm
5601/7G31
Call in number: (b)(6)
Passcode: (b)(6)

1. Projects for GoF Review
    a. Yen (CEIRS) – Eurasian swine flu viruses – Diane
    b. Kawaoka (CEIRS) – (b)(4) flu viruses – Diane
2. Overview of CEIRS Meeting – Diane
3. Updates
    a. NSABB WG – Dennis, Diane, Teresa
    b. DURC/BSAT Sub-IPC – Dennis
    c. ISARG – Dennis/Ken/Tricia
    d. Erasmus RMP – Diane/Ken/Tricia
4. Round Robin/Other Items

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wednesday, July 13, 2016 4:47 PM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] (b)(6)
Subject: Rescheduled: 7/15 DURC/GoF meeting - new date: 7/22

Hi Everyone,

There are a (b)(6) this Friday, 7/15, so we will not be holding our weekly DURC/GoF meeting.

This meeting has been **rescheduled for Friday, July 22nd from 3-4:30pm** because we have a few agenda items to discuss. You should have received an Outlook invite with the new meeting time. (b)(6) but Erik has kindly agreed to run the meeting and will send out the agenda next week.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

Please consider the environment before printing this e-mail 

From: Perlman, Stanley
Sent: Wed, 20 Jul 2016 22:20:20 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Re: Pre-application submission
Attachments: PPG letter-2016.pdf, P01 Preapproval Worksheet 2016.pdf, 2P01AI060699-11.pdf, detailed budget-0716.xlsx, Other support-PPG 2016-composite.pdf, composite-response to review.pdf, proj 1-4SPECIFIC AIMS.pdf

Erik,

Please find attached 7 files for our pre-application submission:

1. Cover letter.
2. Pre approval worksheet
3. Previous review.
4. Our response to previous reviews.
5. New specific aims.
6. Other support.
7. Detailed budget.

This may be more information than you actually want, but I decided to send everything.

Take care.

Stanley

Stanley Perlman, MD, Ph.D.
Professor
Depts of Microbiology and Pediatrics
BSB 3-712
University of Iowa
Iowa City, IA 52242
(b)(6)

THE UNIVERSITY OF IOWA

Department of Microbiology
Iowa City, Iowa 52242
(b)(6)

20 June 2016

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 20892-7630

Re: PO1 060699

Dear Erik,

Please find attached a presubmission application for the above-referenced PO1 grant including:

1. Pre approval worksheet.
2. Previous reviewer comments.
3. Response to reviewer comments.
4. Detailed budget. This is included because the budget increased substantially. We had mistakenly not taken F & A costs into consideration when calculating budgets for Projects 2 and 4, which are both subcontracts.
5. New Specific Aims.
6. Other support.

Please let me know if you need additional information.

Take care.

Sincerely yours,

(b)(6)

Stanley Perlman, M.D., Ph.D.
Professor, Departments of Microbiology and Pediatrics

Stanley Perlman 3-712 Bowen Science Building College of Medicine phone (b)(6) fax (319) 335-9006

BIG GRANT NOMINATION FOR PRE-APPROVAL

DATE:	20 July 2016
DMID BRANCH:	RDB
PROGRAM OFFICER:	Erik Stemmy
MISSION (IID or BIOD):	BIOD
ACTIVITY (P01 or Large R01):	P01

PART A: INVESTIGATOR INFORMATION

APPLICATION NUMBER (if re-submission):	PO1 AI060699
INVESTIGATOR(S):	**Stanley Perlman, Thomas Gallagher, Paul McCray, Luis Enjuanes**
Multi-PI Appl: (Y / N)	Yes, PO1 grant
INSTITUTION:	University of Iowa
PROJECT TITLE:	MERS-CoV/SARS-CoV-Host Cell Interactions and Vaccine Development.
PROPOSED RECEIPT DATE:	25 September 2016

ESTIMATED BUDGET:

Year	Direct Cost	Total Cost
07/01/2016	1,457,000	1,896,425
07/01/2017	1,500,710	1,939,799
07/01/2018	1,545,731	1,997,993
07/01/2019	1,592,103	2,057,933
07/01/2020	1,639,866	2,119,671

Please note that this budget is increased from the first application because we neglected to include subcontract F & A costs in our calculation of Direct Costs.

PART B: SCIENTIFIC INFORMATION (2 pages or less)

SUMMARY JUSTIFICATION FOR ACCEPTANCE: (no more than 2-3 sentences)

This proposal addresses key outstanding issues in understanding the pathogenesis of, and developing anti-viral therapies and vaccines for MERS and SARS. From MERS model development to engineering of recombinant virus clones to understanding pathogenesis and developing anti-CoV vaccines and antiviral therapies, our progress has been substantial and is a direct consequence of the PPG funding mechanism, which facilitates and encourages interactions among the groups.

SUMMARY OF PROPOSED RESEARCH: (Address the following, at a minimum.)

- Describe the significance of the work and how it will move the field forward.

- How is (are) the proposed investigator(s) qualified to perform the proposed research?
- Demonstrate the track record of collaboration between project leads (e.g., top shared publications).
- For a renewal (**Type 2**), describe the accomplishments from the prior segment. Cite top publications.
- For a resubmission (**A1**), how has the applicant sufficiently addressed reviewer concerns? (attach previous summary statement and applicant response separately) (**ATTACHED).**
- For P01s only
    - Why is a multi-project coordinated approach required or uniquely advantageous?
    - Describe the central focus and coherent direction, outlining the synergy and integration among components.
    - Demonstrate the track record of collaboration between project leads (e.g., top shared publications)
- Other Support (Attach separately.)

Describe the significance of the work and how it will move the field forward: (please see attachment for details of specific projects). MERS continues to be an ongoing threat to human health and for cultural/religious reasons, little is known about pathogenesis. Vaccine development has concentrated on the anti-coronavirus antibody response, with focus on methods designed to produce neutralizing antibodies for passive immunization or immunogens that induced anti-CoV antibody responses. These approaches are important, but too little is known about pathogenesis and protective immune responses to conclude that these anti-CoV antibodies will provide long term protection. Therefore, the approach taken in this proposal, which involves development and analysis of novel animal models for MERS and entails contributions from experts in coronavirus biology (Perlman, Gallagher, Enjuanes), pathogenesis (Perlman, McCray, Enjuanes), anti-viral therapy development (Gallagher, Enjuanes) and vaccine development (Perlman, Enjuanes) will provide insight into largely unknown areas of coronavirus disease and therapy and thereby move the field forward.

How is (are) the proposed investigator(s) qualified to perform the proposed research? Each of the Project Leaders is independent and internationally recognized for contributions to coronavirology as well as other relevant fields such as airway epithelia biology. Dr. Perlman is expert in coronavirus pathogenesis, in viral evasion of the T cell response, in the role of eicosanoids in immune responses in CoV-infected mice and in the anti-virus T and B cell responses. Dr. Gallagher is well recognized for his work in coronavirus entry and assembly. Dr. McCray has expertise in airway biology, in gene therapy and in the innate immune response in the respiratory tract. Dr. Enjuanes is well known for his work in coronavirus reverse genetics, coronavirus pathogenesis, virus transcription mechanisms and vaccine development. As described below, our accomplishments are far greater than any of us could have accomplished alone.

Demonstrate the track record of collaboration between project leads (e.g., top shared publications). For a renewal (Type 2), describe the accomplishments from the prior segment. Cite top publications.

1. Development of mouse models for MERS. (publications 7, 8, 20 below). We described the development of the first mouse model for MERS, which used prior treatment with an attenuated human adenovirus (Ad) to sensitize mice for infection with MERS-CoV. This was a collaborative effort between all four projects (Perlman, Gallagher, McCray, Enjuanes) and this model continues to be the most widely used one in the field. We have also developed mice that are transgenic and others that are "knocked-in" for the expression of the human receptor for MERS (hDPP4). We have isolated, plaque purified and sequenced mouse adapted MERS-CoV causing lethal disease in knock-in mice. We are characterizing the mouse-adapted MERS-CoVs that cause lethal disease. All projects are actively engaged in these studies.

2. Development of reverse genetics systems for SARS-CoV and MERS-CoV. (publications 5, 13).

We described a reverse genetics system for MERS-CoV, based on the same principles that we used to develop a SARS-CoV recombination system. This reverse genetics system was developed by Project 4 (Enjuanes) and modified by Project 1 (Perlman).

3. Development of live attenuated and VRP-based vaccines for SARS/MERS. (publications 4, 11, 18, 22) We described the development and characterization of live attenuated vaccines for SARS. We are using the same approaches to develop live attenuated vaccines for MERS. These vaccines differ from most other proposed vaccines by their ability to induce both antibody and T cell responses. These studies are a collaborative effort between Projects 1 (Perlman), 3 (McCray) and 4 (Enjuanes). Project 4 developed live attenuated vaccines and Project 1 demonstrated their efficacy in mice and determined the T cell response after vaccination and challenge. Projects 1 and 3 developed and used VRP-based vaccines.

4. Identification of E protein as an important virulence factor for SARS-CoV and, most likely, MERS-CoV. (publications 1, 6, 10, 12). Project 4 (Enjuanes) showed that the E protein was critical for virulence, so that in its absence, pro-inflammatory cytokines and chemokines were induced to lower levels and edema in the lungs was reduced. Exogenous E protein expression in the context of other infections showed similar effects, demonstrating that these manifestations were E protein-intrinsic.

5. Dysregulated dendritic cell migration and T cell function in SARS-CoV-infected mice. (publications 2, 9). Project 1 (Perlman) showed that in all instances, poor outcomes in SARS-CoV infected mice were characterized by poor T cell responses to the virus. Poor T cell responses reflected decreased migration of dendritic cells to the draining lymph nodes. In aged mice, these defects resulted from age-dependent increases in expression of a single prostaglandin (PG), PGD_2, and blockade of PGD_2 signaling greatly improved survival.

6. Detailed localization of the MERS-CoV receptor DPP4 in healthy and diseased human lung tissue. (publication 24). Project 3 performed detailed analysis of the spatial and cellular localization of hDPP4 in the human lung to evaluate for a relationship with MERS clinical disease. DPP4 was rarely detected in the surface epithelium from nasal cavity to conducting airways with a slightly increased incidence in distal airways. DPP4 was also found in a subset of mononuclear leukocytes and in serous cells of submucosal glands. In the parenchyma, DPP4 was found principally in type I and II cells and alveolar macrophages, and was also detected in vascular endothelium (e.g. lymphatics) and in pleural mesothelia. Subjects with chronic lung disease such as chronic obstructive pulmonary disease and cystic fibrosis exhibited increased DPP4 immunostaining in alveolar epithelia (type I and II cells) and alveolar macrophages with similar trends in reactive mesothelia. This suggests that pre-existing pulmonary disease could increase MERS-CoV receptor abundance and predispose individuals to MERS morbidity and mortality, consistent with current clinical observations. We speculate that the preferential spatial localization of DPP4 in alveolar regions may explain why MERS is characterized primarily by lower respiratory tract disease.

Top and top/shared publications:

1. DeDiego, M.L., Nieto-Torres, J.L., Jimenez-Guardieno, J.M., Regla-Nava, J.A., Alvarez, E., Oliveros, J.C., Zhao, J., Fett, C., Perlman, S., Enjuanes,L. 2011. Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis. PLoS Pathogens 7: e1002315. PMCID: PMC3197621

2. Zhao, J., Zhao, J., Legge., K., Perlman, S., 2011. Impaired respiratory DC migration diminishes T cell responses in respiratory virus-infected aged mice and is reversed with PGD_2 antagonists. J. Clin. Invest. 121(12):4921-30. Epub 2011 Nov 21. PMCID: PMC3226008.

3. Zhao, J., Wohlford-Lenane, C., Zhao, J. Fleming, E., Lane, T.E., McCray, P.B., Jr., Perlman, S., 2012 Intranasal treatment with poly I:C protects aged mice from lethal respiratory viral infections, J. Virol., 86:11416-24. PMCID: PMC3486278

4. Fett, C., DeDiego, M., Regla-Nava, J., Enjuanes, L., Perlman, S. (2013). Complete protection against SARS-CoV Complete protection against SARS-CoV-mediated lethal respiratory disease in aged mice

by immunization with a mouse adapted virus deleted in E protein. J. Virol. 87:6551-6559. PMCID-PMC3676143.
5. Almazan, F., DeDiego, ML, Sola, I., Zuniga, S., Nieto-Torres, JL, Marquez-Jurado, S. Andres, G, Enjuanes, L. (2013) Engineering a replication-competent, propagation-deficient Middle East Respiratory syndrome cornaivrus as a vaccine candidate. MBio 4:e00650-13.
6. DeDiego, M., Nieto-Torres, J., Regla-Nava, J., Jimenez-Guardeño, J., Fernandez-Delgado, R., Fett, C., Castaño-Rodriguez, C., Perlman, S., Enjuanes, L., 2014. Inhibition of NF-κB mediated inflammation in Severe Acute Respiratory Syndrome coronavirus-infected mice increases survival. J.Virol. 88:913-924. PMCID: PMC3911641.
7. Barlan, A., Zhao, J., Sarkar, M., Li, K., McCray, PB Jr., P., Perlman, S., Gallagher, T., 2014, Receptor variation and susceptibility to MERS coronavirus infection. J. Virol. 88:4953-61. PMCID: PMC3993797.
8. Zhao J, Li K, Wohlford-Lenane C, Agnihothram SS, Fett C, Zhao J, Gale MJ Jr, Baric RS, Enjuanes L, Gallagher T, McCray PB Jr, Perlman S. 2014. Rapid generation of a mouse model for Middle East respiratory syndrome. Proc Natl Acad Sci. 111:4970-5. PMCID: PMC3977243
9. Channappanavar, R, Fett, C, Zhao, J, Meyerholz, D, Perlman, S (2014) Virus-specific memory CD8 T cells provide substantial protection from lethal SARS-CoV infection. J. Virol. 88:11034-44. PMCID: PMC4178831
10. Nieto-Torres, JL, DeDiego, ML, Verda-Baguena, C., Jiminez-Guardeno, JM, Regla-Nava, JA, JM, Fernandez-Delgado, Castaño-Rodriguez C, Alcaraz A, Torres J, Aguilella VM, Enjuanes L (2014) Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. PLoS Patho 10:e1004077.
11. Regla-Nava, J., Nieto-Torres, J., Jimenez-Guardeño, J., Fernandez-Delgado, R., Fett, C. Castaño-Rodriguez, C., Perlman, S., Enjuanes, L., DeDiego, M. (2015) SARS coronaviruses with mutations in E protein are attenuated and promising vaccine candidates. J. Virol. 89:3870-87. PMCID: PMC4403406.
12. Jimenez-Guardeño JM, Nieto-Torres JL, DeDiego ML, Regla-Nava JA, Fernandez-Delgado R, Castaño-Rodriguez C, Enjuanes L. (2014). The PDZ-binding motif of severe acute respiratory syndrome envelope protein is a determinant of viral pathogenesis. PLoS Pathog.10:e1004320.
13. Fehr, A.R., Athmer, J., Channappanavar, R., Phillips, J.M., Meyerholz, D.K., Perlman, S. (2015). The NSP3 macrodomain promotes virulence in mice with coronavirus-induced encephalitis. J. Virol. 89:1523-1536. PMCID: PMC4300739.
14. Zhao, J., Perara, R., Kayali, G.,Meyerholz, D., Perlman, S., Peiris, M.,(2015) Passive immunotherapy with dromedary camel immune serum in an experimental animal model for MERS coronavirus infection. J.Virol. 89:6117-6120. PMCID: PMC4442417.
15. Earnest JT, Hantak MP, Park JE, Gallagher T. (2015) Coronavirus and influenza virus proteolytic priming takes place in tetraspanin-enriched membrane microdomains. J.Virol. 89:6093-6104.
16. Zumla, A., Hui, D., Perlman, S. (2015). The Middle East Respiratory Syndrome. Lancet Jun 3. pii: S0140-6736(15)60454-8. doi: 10.1016/S0140-6736(15)60454-8. [Epub ahead of print].
17. Corti, D., Zhao, J., Pedotti, M., Simonelli. L., Sudhakar, A., Fernando-Rodriguez, B., Foglierini, M., Agatic, G., Vanzetta, F., Gopal, R., Langrish, C.J., Barrett, N., Sallusto, F., Baric, R., Varani, L., Zambon, M., Perlman, S. Lanzavecchia, A. (2015), Prophylactic and therapeutic efficacy of a potent human monoclonal antibody against MERS-coronavirus. Proc. Natl, Acad, Sci (in press)
18. Jimenez-Guardeño, J., Regla-Nava, J.,Nieto-Torres, J.L., DeDiego, M., Castaño-Rodriguez, C., Fernandez-Delgado, R., Perlman, S. and Enjuanes, L., Identification of the mechanisms causing reversion to virulence in an attenuated SARS-CoV for the design of a genetically stable vaccine. PLoS Pathogens, 11(10):e1005215. PMCID: PMC4626112.
19. Vijay, R., Hua, X., Meyerholz, D., Miki, Y., Yamamoto, K., Gelb, M., Murakami, M., Perlman, S. (2015) Critical role of Phospholipase A2 group IID in age-related susceptibility to Severe Acute Respiratory Syndrome-CoV infection. J. Exp Med. 212:1851-1868. PMCID: PMC4612096
20. Li., K., Wohlford-Lenane, C., Perlman, S., Zhao, HJ., Jewell, A., Reznikov, L., Gibson-Corley, K., Meyerholz, D.K., McCray, Jr., P., (2015) Middle East Respiratory Syndrome Coronavirus causes

multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. J. Infect. Dis 213(5):712-22. PMCID: PMC4747621.
21. Channappanavar, R., Fehr, A., Vijay, R., Mack, M., Zhao, J., Meyerholz, D., Perlman, S. (2016). Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 19:181-193. PMCID: PMC4752723
22. Zhao, J., Zhao, J., Mangalam, A., Channappanavar, R., Fett, C., Meyerholz, D., Agnihothram, S., Baric, R.S., David, C., Perlman, S. (2016) Airway memory CD4 T cells orchestrate protective immunity against emerging human respiratory coronaviruses. Immunity, 44:1379-1391, PMCID: PMC4917442.
23. Alshukairi, A., Khalid, I., Ahmed, W., Dada, A., Bayumi, D., Malic, L., Althawadi, S., Ignacio, K., Alsalmi, H., Al-Abdely, H., Wali, G., Qushmaq, I., Alraddadi, B., Perlman, S. (2016) Longevity of antibody responses in health care worker Middle East Respiratory Syndrome survivors and relation to disease severity, Emerg. Inf. Dis., 2016 Jun;22(6). doi: 10.3201/eid2206.160010.
24. Meyerholz DK, Lambertz AM, McCray PB Jr. (2016) Dipeptidyl peptidase-4 distribution in the human respiratory tract: Implications for the Middle East Respiratory Syndrome. Am J Path, 186:78-86. PMCID: PMC4715219

For P01s only

- Why is a multi-project coordinated approach required or uniquely advantageous?
- Describe the central focus and coherent direction, outlining the synergy and integration among components.
- Demonstrate the track record of collaboration between project leads (e.g., top shared publications) **(see above)**.

The PO1 format has been critical for the success of this project and will continue to be so. Certainly the importance of our project, focused on pathogenesis, vaccines and antiviral therapies in the context of pathogenic coronaviruses, has been accentuated by the ongoing outbreak of MERS in Saudi Arabia and other countries on the Arabian peninsula. The outbreak in South Korea demonstrated how destructive an outbreak can be on a population.

The focus of the PPG is tight and we have complementary expertise**.** The projects all pose questions probing how SARS-CoV and MERS-CoV cause disease and about how anti-virus vaccines and therapies should be developed and evaluated. Each of the Project Leaders is independent and internationally recognized for contributions to coronavirology as well as other relevant fields such as airway epithelia biology. Our complementary expertise is described above. Combining these research groups in a shared research program has and will yield the greatest creativity and innovation and enhance the chance for success. Two of the Leaders are not located at the University of Iowa but our productive interactions over the past funding cycle show that we communicate frequently and co-authored many manuscripts.

Development and analysis of recombinant SARS-CoV and MERS-CoV is a shared enterprise. Project 4 developed reverse genetics systems for SARS-CoV and MERS-CoV, and shared this with Project 1 and the Animal/Virology Core so that both of these components now have the ability to develop recombinant viruses. Project 1 modified the reverse genetics system and shared these changes with Project 4. Projects 1 and 4 and the Animal/Virology Core work together to construct new viruses, both for these projects and for Projects 2 and 3, which do not routinely develop recombinant viruses. Project 2 does not have access to a BSL3 laboratory, so while Project 2 will develop Bac clones encoding recombinant viruses of interest, the PO1 format is essential for providing information about the effects of these changes in the context of infectious viruses. Project 3 has occasional need for recombinant CoV for tracing virus spread in infected mice and for analyzing the effects of new therapies. Rather than

establish the reverse genetics system separately, which would be an unnecessary duplication of effort, the Animal/Virology Core has and will construct all recombinant CoV for this project.

Development of Animal Models for MERS is an ongoing process that is enhanced by the PO1 format. All four projects contributed to the development of the first mouse model for MERS, in which mice were sensitized to infection by expression of the human receptor. We have now developed transgenic mice expressing hDPP4 and humanized (hDPP4 knock in) mice. The transgenic mice develop lethal encephalitis while the humanized mice remain asymptomatic even though virus replicates to high levels. However, mouse adaptation by serial passage resulted in a set of MERS-CoV that are more virulent in mice. This mouse-adapted virus will be heavily used by all of the projects. The PO1 format was essential for developing this improved model for MERS; the humanized hDPP4 knock-in mice are now available at both the Iowa City and [redacted] sites so that experiments can be performed most efficiently. The projects are working together to characterize the mouse adapted virus (Projects 1-4 and Animal/Virology Core), to use it to understand virus entry (Projects 2 and 3) and to use it in studies of pathogenesis (Projects 1, 3, 4). Projects 1 and 3 and the Animal/Virology Core will analyze antibody and T cell responses in hDPP4-KI mice. Project 4 will continue to develop anti-MERS-CoV vaccines, which will be evaluated by the Animal/Virology Core and Project 1.

Analysis of vaccines and anti-MERS-CoV and anti-SARS-CoV therapies requires expertise of all four projects. Projects 1 and 4 will identify, develop and evaluate vaccines and therapies that will be useful in MERS (and SARS, if it recurs) patients. In the case of live attenuated virus vaccines, Project 4 will develop and evaluate vaccine candidates in tissue culture cells in [redacted] and ship promising candidates to Iowa for further analysis. Project 1 will evaluate the effects of these interventions on the immune response and Project 3 will evaluate the changes in lung pathology and gene expression. The Animal/Virology Core will continue to prepare samples and perform the basic analyses of these interventions (clinical, virological, histological, immunological).

Common animal models, reagents and assays will be used by PPG members, standardizing data comparison. Since nonrecombinant and recombinant viruses will be prepared and propagated by the Core and used by all members of the PPG, and many of the animal studies will be performed by the Animal/Virology Core, results will be directly comparable.

Additional new areas of collaborative investigation.

A. Development of dual expressing adenoviruses. Transduction of mice with Ad5-hDPP4 sensitizes mice for MERS-CoV infection. We now have developed dual expressing Ad5, which express hDPP4 and a second gene. This approach, which we have validated for factors involved in cell entry, will be used by Projects 1, 2 and 3 to probe the role of specific proteins in MERS-CoV pathogenesis.

B. Development of anti-MERS-CoV therapies. The teams will take several approaches to antiviral discovery. Project 1 will focus on approaches to inhibit eicosanoids that inhibit the development of a potent immune response to CoV. Project 2 will assess factors important in cell entry. Project 3 will evaluate drugs that inhibit DPP4 enzymatic function. Projects 2 and 4 will focus on interventions that inhibit edema formation. In all cases, all of the projects will collaborate in evaluating useful targets and drugs that are developed. Project 3 will evaluate lung pathological changes while project 1 will screen for effects on pathogenesis and antibody and T cell responses. Identification and development of these antiviral drugs will be much faster and successful if performed in the context of our PPG.

C. Aged populations and co-morbidities: CoV pathogenesis and vaccine development. MERS and SARS disproportionately kill the elderly. Further, severe MERS occurs primarily in patients with co-morbidities. Studies of aged animals have been a focus of Projects 1, 3 and 4 as this group is much

more susceptible to MERS-CoV and SARS-CoV than younger animals. Projects 1 and 4 have collaborated on vaccine development, studies of the host immune response and pathogenesis studies using aged mice and these studies will continue as we devote more of our efforts to MERS. Projects 1 and 3 will collaborate on studies of the effects of diabetes and other co-morbidities on outcomes in MERS-CoV-infected mice. The anti-MERS-CoV therapies described above will be assessed in aged animals, as a collaborative effort between all of the Projects. These analyses in aged populations will be greatly enhanced under a PPG structure.

D. Development of robust models for MERS pathogenesis and vaccine and antiviral therapies.

Second generation adenovirus vectors expressing hDPP4. As mentioned above, development of adenovirus (Ad) vectors expressing hDPP4 was a major accomplishment of the PPG and involved all four projects. These Ad5-hDPP4 vectors have been provided to laboratories worldwide. We are now developing Ad5 vectors that express hDPP4 and a second gene as described above. Much of the Ad vector development will be performed under the auspices of the Animal/Virology Core in collaboration with the University of Iowa Viral Vector Core Facility. Development and analysis of this set of constructs is labor-intensive and requires input from all of the projects. It is an excellent example of how the PPG is more powerful than the four individual projects.

Development of mouse-adapted MERS-CoV. A major problem in advancing studies of MERS pathogenesis and vaccine and antiviral drug development is the lack of a robust animal model. Now that we have developed hDPP4-KI mice and a mouse-adapted MERS-CoV, all of the projects will collaborate together to determine the factors important for developing a lethal virus. An advantage of the PPG format is that we will be able to use the reverse genetics system developed by Project 4 and modified by Project 1 to manipulate the virus if appropriate. The expertise in pathogenesis of Projects 1 and 3 will be useful for actually identifying and characterizing mouse-adapted MERS-CoV. Project 2's expertise has and will be invaluable in understanding changes in virus entry that result in adaptation.

E. Development of live attenuated vaccines. Projects 1 and 4 and the Animal/Virology Core collaborated on the development and analysis of novel SARS-CoV vaccines based on deletion of the E protein. Projects 1 and 4 along with the Core will continue to work on development of SARS-CoV and MERS-CoV vaccines, recognizing that different strategies are necessary. Unlike SARS-CoV, infectious virus is not produced in MERS-CoV infected cells if E protein is deleted.

Summary.

We want to emphasize again that leaders of the PPG have interacted closely over the past several years, have published manuscripts together and have collaborated multiple times in the past. We share excitement in each other's findings, and we are each other's toughest critics. All of the investigators realize that they achieve more working together programmatically than they ever could working alone. The initial development and continuing evolution of this Program followed directly from scientific interactions between the investigators. Drs. Perlman and Gallagher have collaborated on experiments involving the role of the S protein in pathogenesis for over 24 years. Drs. McCray, Gallagher and Perlman, with their common interests in virus entry and pathogenesis, have extensively discussed mechanisms of coronavirus entry into cells, with special emphasis on entry into airway cells and on the development of new animal models and therapeutic interventions for MERS. Drs. Perlman and Enjuanes have worked on SARS-CoV and MERS-CoV vaccine development. Drs. Enjuanes and Gallagher share interests in virus assembly and egress, with special reference to the E protein. Drs. McCray, Gallagher, Enjuanes and Perlman share interests in the host innate immune response to SARS-CoV and MERS-CoV. All of us have frequent interactions by phone or Skype and in the case of Drs. McCray and Perlman, at conferences and in the hallway. We think that the best predictor that the Program will have be a collaborative, integrated and synergistic approach is our track record over the past 5 years of the current PPG. This history of collaboration and discovery predicts continued highly productive interactions.

SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **07/05/2016**
Erik Stemmy ***Revised Date:***
(b)(6)
(b)(6)

Application Number: **2 P01 AI060699-11**

Principal Investigator

PERLMAN, STANLEY

Applicant Organization: UNIVERSITY OF IOWA

Review Group: **ZAI1 AMC-M (S1)**
National Institute of Allergy and Infectious Diseases Special Emphasis Panel
NIAID Investigator Initiated Program Project Applications (P01)

Meeting Date: **06/16/2016** ***RFA/PA:*** **PAR13-254**
Council: **OCT 2016** ***PCC:*** **M51C B**
Requested Start: **12/01/2016**

Project Title: **PPG: SARS-CoV-host cell interactions and vaccine development**

SRG Action: **Impact Score** (b)(6)
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **44-Human subjects involved - SRG concerns**
Animal Subjects: **44-Vertebrate animals involved - SRG concerns**
Gender: **4A-Gender representation unknown, scientifically acceptable**
Minority: **4A-Minority representation unknown, scientifically acceptable**
Children: **3A-No children included, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
11	1,227,104	1,869,791
12	1,227,104	1,869,791
13	1,227,104	1,869,791
14	1,227,104	1,869,791
15	1,227,104	1,869,791
TOTAL	6,135,520	9,348,955

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

2P01AI060699-11 Perlman, S.

FOREIGN INSTITUTION (Project 4)
SELECT AGENTS (Project 1, 4, and Animal/Virology Core)
VERTEBRATE ANIMALS UNACCEPTABLE (Project 4)
PROTECTION OF HUMAN SUBJECTS UNACCEPTABLE (Project 1, 3, and 4)

RESUME AND SUMMARY OF DISCUSSION: This excellent renewal application entitled "SARS-CoV-Host Cell Interactions and Vaccine Development" is submitted in response to PAR-13-254: NIAID Investigator Initiated Program Project Applications by the University of Iowa, with Dr. Stanley Perlman as Program Director (PD). The Project Leaders are Dr. Thomas Gallagher of Loyola University, Dr. Paul McCray of the University of Iowa, and Dr. Luis Enjuanes of the Centro Nacional de Biotecnologia in Madrid, Spain. The overall goal of the proposed Program Project is to better understand the contributing factors in MERS and SARS disease, including viral factors, immune responses, age, and co-morbidities. The application includes four projects and two cores. Project 1 focuses on the impact of small lipid mediators on the inflammatory milieu in the lung following MERS-CoV or SARS-CoV infection. Project 2 aims to better understand coronavirus pathogenesis through the study of spike protein mutations identified in a mouse-adapted strain of MERS-CoV, $MERS_{MA}$. Project 3 examines additional factors which may contribute to pathogenesis, including co-morbidities, receptor function, and non-spike protein $MERS_{MA}$ mutations. Project 4 investigates ion channel activity in SARS-CoV induced lung injury, regulation of non-coding RNA, and development of live attenuated coronavirus vaccines. Coordination of the four projects is managed by the Administrative Core, including program budget, personnel, and interactions between program investigators and advisory committees. The Animal/Virology Core supports the program through standardized assessment of virus infected mice and production of recombinant coronaviruses.

Project 1, Project 2, and Project 3 scored in the (b)(6) range and Project 4 scored in the (b)(6) range. The Administrative Core and Animal/Virology Core were rated (b)(6) respectively.

The proposed Program Project is a continuation of the investigators' established, highly productive collaboration, and focuses upon the study of SARS and MERS coronavirus host-viral interactions, mechanisms of pathogenesis, and implications for targeted vaccines and therapeutic interventions. The PPG team is highly qualified and uniquely poised to exert a sustained, powerful influence on the coronavirus pathogenesis field, based on combined expertise in coronavirus biology, immunology and respiratory virus disease. The questions addressed in each of the four projects are distinct and highly relevant in SARS- and MERS-CoV disease, including age, co-morbidities, receptor distribution and viral adaptation. The Program Director, Dr. Stanley Perlman, has demonstrated outstanding leadership over the course of the collaboration, working in close coordination with the Project Leaders and adapting quickly to new urgencies in the field, as evidenced by the shift in focus of this renewal application to MERS-CoV.

The recent emergence of MERS-CoV severe respiratory disease in humans lends great significance to this program, particularly given the probability for continued human infections and the lack of available preventative and therapeutic interventions, development of which has been hindered by limited understanding of the mechanisms of MERS-CoV pathogenesis. The investigators propose to leverage valuable tools developed in the previous grant period. These include transgenic mice expressing the human MERS-CoV receptor DPP4 as well as a virulent MERS-CoV strain developed through long term passage in the mice. These tools focus the efforts of all four projects on a common experimental model, facilitating direct comparison of results and greatly enhancing the potential for significant scientific advances beyond what could be accomplished by each project independently.

- It is unclear whether the mechanisms of host-pathogen interaction and adaptive changes in MERS-CoV that are observed in the hDPP4-knock in mice can be directly applied to human disease. This issue is mitigated to some extent by the inclusion of confirmatory studies in human leukocytes and airway epithelial cells. The application would be greatly strengthened by additional studies designed to directly implicate human immune and host cell targets for therapeutic intervention.

Should the experimental models prove to be accurate surrogates for human coronavirus infection, concerns remain regarding the ambitious scope of the application. Proposed studies often include multiple approaches and a large number of exploratory parameters. While study execution may be fairly straightforward for the experienced scientific team, the potential complexity of data interpretation is not fully recognized. Discussion of supportive preliminary data, technical limitations, data analysis strategies and alternative hypotheses is limited. There is a significant possibility that the body of work proposed will require a much greater amount of time and effort than anticipated, particularly should additional studies be required in order to de-convolute unexpected results. The full program may not be achievable within the funding period, given the level of personnel commitment described. The investigators may wish to consider diverting one or more aims into independent research projects, in order to ensure successful completion of the extensive studies required to fully address the questions proposed.

This limitation is most pronounced in Project 4. Novel hypotheses are proposed to explain aspects of SARS- and MERS-CoV induced disease, including a role for the viral E protein in resolution of pulmonary edema and for non-coding RNAs in inflammation. The experiments outlined to address these questions do not reflect a thorough understanding of the complex biological systems to be studied. In the case of E protein, the mechanism proposed for involvement in edema does not appear to consider alternative roles for E protein in initial fluid transport, or the potential involvement of CFTR or CaCl ion channels. The discussion of non-coding RNAs is over-simplified as well. Should coronaviruses express miRNA, changes in expression in highly pathogenic respiratory infections are very likely due to pathology and inflammation, rather than a direct consequence of viral infection. Unique molecular characteristics of miRNAs are not discussed. Preliminary deep sequencing data, presented as a premise for further studies, is dominated by miRNA species which are unlikely to have significant functional impact, due to low copy number and/or relatively small changes in expression level.

Despite some limitations, enthusiasm is high for this PPG. The overall body of work proposed represents a synergistic collaboration amongst four highly qualified investigators. The PPG has the potential to reveal fundamental insights into SARS- and MERS-CoV disease processes, with implications for development of vaccines and anti-viral compounds against MERS-CoV and other respiratory viruses.

Based upon the evaluation of scientific and technical merits of the projects and cores and the interactions among them in the overall Program, this Program Project received an Overall Impact score of (b)(6)

Project 1:
Title: Project 1
Project Leader: Perlman, S.

Project 1 investigates the role of small lipid mediators in MERS-CoV immunobiology, particularly in the context of aging. The specific aims are to determine: (1) the mechanism of PLA_2G2D upregulation and the role of PLA_2G2D in vaccine responses in 12 month old mice, (2) the role of PGD_2-DP1 signaling in

the immune response to SARS-CoV in 12 month old mice, and (3) whether infection with MERS-CoV is also age-dependent and whether PGD_2 and PLA_2G2D contribute to poorer outcomes. Project 1 will interact with all other PPG components.

Project 1 proposes to examine the role of small lipid mediators in the age-dependent severity of MERS and SARS. This project builds effectively on demonstrated age-dependent disease susceptibility to SARS-CoV and has the potential to inform vaccine development for CoVs, and likely other pathogens as well. The investigators showed outstanding productivity in the previous funding period, including generation of valuable mouse models and many high impact publications, which strengthens this application.

The PL, Dr. Perlman, is a leader in the field, contributing numerous groundbreaking findings in pathogenesis and immunity of both mouse and human coronaviruses. His outstanding leadership of the PPG is evidenced by numerous co-authored papers and swift adaptability to a rapidly evolving field in emerging coronavirus infections. Studying both SARS-CoV and MERS-CoV has the potential to dilute efforts and reduce the chance for success with either pathogen, but this potential weakness is mitigated by similarities between SARS-CoV and MERS-CoV, the PL's expertise and record, and synergy with Projects 2-4. The environment at the University of Iowa is excellent, and includes appropriate BSL-3 laboratory and animal facilities. There is some concern that the efforts of senior staff on this project may be diluted by responsibilities in the Animal/Virology Core.

The nature of age-dependent susceptibility to MERS in humans is a significant unanswered question, supported in this project by innovative combination of animal models. These models may provide valuable information about pathogenesis and disease in humans. The project effectively combines outstanding tools to assess vaccine strategies. Relevance to human disease is strengthened by use of mice with knocked in human receptor (hDD4-KI), as well as human leukocytes.

The research is based on novel and highly relevant published findings regarding age-dependent increases of the phospholipase A2 (PLA2) group IID (PLA_2G2D) following SARS-CoV infection of aged mice, and their contribution to increased disease severity. Using middle-aged mice instead of older mice will likely miss more extensive effects of age on multiple aspects of immune function. However, this may help to more specifically focus on effects of PLA_2G2D and PGD_2 increases, which are present in middle-aged mice.

The three specific aims are logical extensions of previous work. Experiments designed to test specific hypotheses are balanced with experiments yielding broader results that will likely guide future work. Pharmacologic blockade of DP and EP receptors, for example, has the potential to provide results with translational implications. The redundancy of receptor signaling mechanisms may complicate interpretation of any results, but this could be alleviated by simultaneous blockade of multiple receptors.

Demonstrating a link between oxidative damage and stress, increased PLA_2G2D, and thus increased coronavirus susceptibility is crucial to unravel the mechanism of PLA_2G2D upregulation. However, given that approaches using low dose LPS are likely to induce both pro- and anti-inflammatory components in addition to eliciting oxidative stress, the results may be difficult to interpret, especially if pro-inflammatory lipid mediators are induced.

Overall, many approaches proposed in this application include a large number of distinct, exploratory parameters. The application would benefit from a more extensive discussion of preliminary data, technical limitations, data analysis strategies and alternative hypotheses, particularly for approaches new to this group. Despite these potential limitations, enthusiasm is very high for this project, which has

the potential to reveal fundamental new insights relevant to human coronavirus pathogenesis and disease in humans.

Based upon the evaluation of scientific and technical merit, Project 1 received an Overall Impact score of (b)(6)

Project 2:
Title: Adaptive MERS Coronavirus-cell Entry Pathways and Their Relevance to Virulence
Project Leader: Gallagher, T.

Project 2 proposes to better understand MERS-CoV entry via mouse-adaptive spike protein mutations, protease inhibitors and small molecule inhibitors. The specific aims are to: (1) identify adaptive mutations responsible for MERS-CoV pathogenesis in mice, (2) determine how MA mutations affect spike structure and function, (3) determine whether viruses with MA spike mutations exhibit “early” cell entry, (4) identify the proteases activating MERS-CoV *in vivo*, and (5) identify and characterize coronavirus cell entry inhibitors. Project 2 will interact with all other PPG components.

The proposed research may provide significant insight into how MERS-CoV interacts with host cell proteases during the entry process, and how it adapts to new host species. This may have implications for development of vaccines and anti-viral compounds against MERS-CoV and other respiratory viruses. Relevance to human disease is uncertain, however, as specific proteases critical for infection in mice may not be conserved in human disease, and MERS-CoV is able to cross over from camel to human hosts and induce disease without further adaptation.

Dr. Gallagher has a sustained record of accomplishment, and his collaboration with pioneering lipid conjugation scientist Dr. Matteo Porotto is a strength of the project. The intellectual environment at Loyola University is outstanding, providing opportunities for multiple collaborations. Concerns regarding distance from University of Iowa are minimized given demonstrated productive interaction during the previous grant period. Progress from the previous funding period appears acceptable, with consideration given to the transition of focus to MERS-CoV.

The proposed approach takes full advantage of available resources within the PPG team to better understand MERS-CoV host cell entry, and is likely to provide important additional information on MERS-CoV entry and pathogenesis. The investigators leverage the $MERS_{MA}$ mutant developed during the previous grant period, introducing individual S protein mutations to MERS-CoV in order to examine their impact on structure and function. The reverse genetics required appears to be fairly straightforward, and the investigators are highly qualified to complete this work. The plan to integrate the results of the subsequent functional analysis into pathogenesis studies via Project 3 is a strength of this project.

However, the functional analysis proposed represents a substantial amount of work and data interpretation may be significantly more complex than anticipated. Based upon previous work with MHV and the fact that the mouse adaptive viruses on average carry 30 mutations in multiple genes, it seems likely that many of the recombinant S protein mutant viruses generated for this project will present partial phenotypes, necessitating careful assessment of LD_{50} values. Given this possibility, the use of multiple approaches including pseudotyped and VLP constructs is well justified and may simplify the analysis.

Functional analysis in this project is significantly strengthened by the proposed use of a split GFP protein assay to characterize hDPP4 mediated vesicle fusion with S mutant MERS-CoVs. This

innovative approach should facilitate study of the impact of S protein mutations on membrane fusion, and allow unambiguous identification of proteases involved in the fusion process, which is a critical step in development of antiviral pharmacologic targets for future drug discovery. The application would benefit from additional information regarding the lipids to be used, however, given the important effects of lipid composition on membrane fusion. Consideration of lipid composition could provide an opportunity to gain additional insight into the intracellular location for membrane fusion and virus entry.

Aim 5 further examines membrane fusion based upon previous work to direct known fusion inhibitory HR2 peptides towards therapeutic application. This approach has a high potential for success, given established validation of the peptides in MERS-CoV and the availability of expertise needed to examine and understand any unexpected results. However, given the highly ambitious nature of the project as a whole and the extensive series of studies required to fully appreciate the therapeutic potential of these peptides, it is recommended that the PL consider dropping this aim and seeking additional funding opportunities to complete the work, as mentioned in the application.

Overall, the stated aims have the potential to offer significant insights into MERS-CoV host cell entry and pathogenesis, with direct implications for development of therapeutic anti-viral compounds. However, the proposed scope of work is extremely ambitious and the outcomes speculative. Completion of the full set of objectives may not be feasible based upon the progress in the previous funding period and with the personnel described.

Based upon the evaluation of scientific and technical merit, Project 2 received an Overall Impact score of (b)(6)

Project 3:
Title: Project 3
Project Leader: MCCRAY, P.

Project 3 proposes to examine the impact of viral receptor distribution and adaptive mutations in MERS-CoV on pathogenesis in mice. The specific aims are to: (1) understand how an *in vivo* evolved MERS-CoV causes lethal lung disease, (2) investigate how adaptive mutations in MERS-CoV contribute to enhanced virulence, and (3) investigate how hDPP4 abundance and function influence MERS disease pathogenesis. Project 3 will interact with all other PPG components.

This highly significant project has great potential to address critical knowledge gaps in MERS-CoV pathogenesis. Dr. Paul McCray, the PL on this project, is a well-regarded expert in airway epithelial cell biology and host defense mechanisms, and has extensive experience studying the interaction of SARS-CoV and MERS-CoV with the lung. His laboratory played a central, productive role in previous iterations of the PPG, including in publication of multiple relevant, high quality publications in prominent journals. The scientific environment at the University of Iowa is well suited for the proposed research, and Dr. McCray has enlisted the assistance of several highly qualified collaborators, all of whom enhance the likelihood of success for the project.

The hDPP4 knock-in mouse represents a significant advance in small animal models of MERS. In combination with $MERS_{MA}$, these tools position Project 3 to yield important insight into ways in which distribution and function of hDPP4 and specific adaptive mutations in viral nucleocapsid and accessory proteins (orf4b and nsp9) contribute to MERS-CoV virulence. Preliminary data provide solid support for the proposed experiments, particularly for Aims 1 and 2. Experiments designed to test specific hypotheses are balanced nicely by work that is likely to generate data to guide future efforts (e.g., RNA-seq).

The proposed project is further strengthened by expansion of scope from the lung to include cardiac function. Even if virus is not detected in cardiac tissue, evaluation of cardiac inflammation and function may prove relevant if increased circulating hDPP4 in infected mice adversely affects cardiac outcomes. These measurements may be useful to include in the hDPP4 inhibition experiments outlined in Aim 3.

It is noted that reliance on a mouse model, particularly a single mouse strain, may make it difficult to generalize results to understand human disease. This relatively minor weakness is mitigated, however, by the inclusion of two co-morbidity models in Aim 1, as well as the use of relevant human cell types *in vitro* to confirm results of work in the mouse experiments.

The co-morbidity models proposed may represent the first application to investigate pre-disposing factors for severe coronavirus disease apart from aging. Investigations into the interaction between diabetes and MERS-CoV infection have the potential to provide some insight into the mechanism by which diabetes is a co-morbidity factor for MERS in humans. However, a strong rationale is not provided for use of the chronic LPS administration model of metabolic syndrome with chronic inflammation as a co-morbidity factor. The effect of LPS in activating macrophage pro-coagulants could complicate the interpretation of the results obtained from experiments with this model. Developing both models seems very ambitious, and it is not entirely clear how complex phenotypes will be examined.

The results obtained from generation of recombinant MERS-CoV constructs in Aim 2 may also be more difficult to interpret than envisioned. As discussed in the critique for Project 2, it is likely that many of the viruses to be generated for this project will have partial phenotypes, necessitating a careful assessment of LD_{50} which is not currently proposed.

Overall, the inclusion of multiple approaches to each aim is to be commended. The project takes a more expanded view of the role of other cell types in coronavirus disease, supported by a strong, unique set of models, investigators, and environment. These studies should be straightforward to perform, although interpretation of results may be less so.

Based upon the evaluation of scientific and technical merit, Project 3 received an Overall Impact score of (b)(6)

Project 4:
Title: Project 4
Project Leader: Perlman, S.

Project 4 proposes to study the molecular basis of coronavirus induced lung edema through investigation of signaling pathways and de-convolution of natural virulence gene mutations. The specific aims are to: (1) determine factors involved in edema induction and resolution during human CoV infection, (2) investigate the role of non-coding RNAs in SARS- and MERS-CoV induced inflammation, and (3) develop safe live attenuated vaccines for MERS-CoV. Project 4 will interact with all other PPG components.

SARS-CoV and MERS-CoV, as well as other potential coronavirus zoonoses, represent an important threat to human health, and novel strategies for treatment and vaccination are clearly called for. This project may provide recombinant viruses and other reagents that could benefit the coronavirus field, informing development of new vaccine candidates and anti-coronaviral therapies. The Project Leader, Dr. Enjuanes, has an outstanding record in the study of coronaviruses. The (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism Preparedness and is well equipped to support the proposed studies, although there is some concern as to whether the bioinformatics support required will be available on site.

The successful collaboration of Drs. Enjuanes and Perlman is documented by ten joint publications relevant to the application, and the interaction with the PPG investigators based in the United States is well defined. The recombinant MERS-CoVs engineered as part of this project will be critical for examining the mutations important in the enhanced pathogenesis of MERS-CoV in mouse adapted models.

Identification of new peptide candidates to block potentially pathogenic interactions between PDZ-binding motifs of viral proteins and host PDZ-containing cellular proteins is an innovative approach to treat SARS-CoV and MERS-CoV infections. These studies may provide novel information about key cell processes hijacked by the virus. These processes may be required for virus replication, immune evasion, or other pathological changes. However, it is unclear why the proposed approaches are favored over others that could be used for identification of PDZ domain proteins relevant to coronavirus pathogenesis. It may be prudent to first down-select PDZ-containing proteins expressed in the lung, and consider full length protein expression of priority candidates. The short protein motifs as proposed may not express efficiently or mimic the entire protein.

The examination of the role of coronavirus protein E ion channel activity in resolution of pulmonary edema has the potential to elucidate a fundamental mechanism of MERS-CoV pathogenesis. This group is well-positioned for this investigation, but the mechanism proposed is greatly over-simplified. Discussion of alternative possibilities such as defects in initial fluid transport is omitted. In addition, validation of inhibitory peptide candidates is proposed to be performed in animal models to test effects on resolution of MERS and other coronavirus diseases. This approach, as described, is unrealistic and misses intermediate HTS or MTS steps in cell based models.

Identification of miRNA and svRNA involved in host-pathogen interactions may be a druggable target. However, Aim 2 seems to be somewhat exploratory overall, and the proposed studies do not reflect expert knowledge of the subject area. Evidence of miRNAs encoded by any RNA virus other than retroviruses is lacking, and coronaviruses are unlikely to be an exception. In the context of a mouse undergoing a highly pathogenic respiratory infection, changes in miRNA or lncRNA expression are very likely due to pathology and inflammation rather than a direct effect of the virus.

If coronaviruses encode miRNAs, these would be 22±2 nt in size, would have a very discrete 5’ end to maintain seed function, would be loaded into RISC and would derive from the upper ~22 bp of an ~33 bp stem. These issues are not fully considered or discussed. In addition, miRNAs expressed at <100 copies per cell are unlikely to have a significant functional impact. This appears to include the majority of miRNA that change expression significantly (Figure 6).

The recombinant reverse genetics approaches proposed in Aim 3 to generate MERS-CoV with various mutations are highly innovative, and E-deficient, replication competent viruses may have utility for immunized protection or even therapeutic vaccines. The idea of introducing sites for lung miRNAs into CoV to reduce replication and pathogenicity has merit as well. Introducing artificial miRNAs that target host genes, however, is unlikely to be effective given the short time frame between infection and host cell death, and could have unexpected consequences which are not discussed.

Overall, each of the aims are too broad in scope and are not well integrated. Each aim in itself could be an entire grant. Methodologies are largely molecular or systems biological in nature and testing in infection models is not proposed beyond very cursory studies. Overall, Project 4 proposes an ambitious body of work, and there is significant concern as to the feasibility of completing the project successfully within the time period proposed.

Based upon the evaluation of scientific and technical merit, Project 4 received an Overall Impact score of (b)(6)

Admin Core-001: Administrative Core
Core Leader: Perlman, S.

The Administrative Core proposes to serve as the logistical center of the Program Project, managing the day to day and strategic interactions between the projects, allocating funds, and ensuring reporting requirements are met. The specific aims are to: (1) provide overall guidance to the scientific directions of the projects, (2) manage financial aspects of the grant, (3) prepare scientific progress reports and renewal applications, and (4) arrange monthly scientific meetings of the PPG and organize meetings of the PPG members with the internal and external advisory committees. The Administrative Core will interact with all other PPG components.

The Administrative Core is critical for coordination of the overall program, and is led by Dr. Perlman. Dr. Perlman has demonstrated outstanding leadership of the PPG during the previous grant period, adapting to new urgencies in the field, establishing new collaborations and maintaining close contact with Project Leaders. His (b)(4); (b)(6) level of effort is justified.

The personnel roles and responsibilities are well described, and the support of a financial administrator at (b)(4); (b)(6) effort and an administrative assistant at (b)(4); (b)(6) effort is consistent with the support required. The core will fill the important role of arranging meetings between the investigators as well as with advisory committees. The chain of responsibility and conflict resolution are clear. The application does not address potential complexities in managing select agent research, including monitoring of updated guidelines and international transport of recombinant MERS-CoVs, but this is a minor weakness.

The Administrative Core received an Overall Impact score of (b)(6)

Core-001: Animal/Virology Core
Core-001 Leader: Perlman, S.

The Animal/Virology core serves as a central service laboratory, ensuring standardization of animal studies and propagation of recombinant SARS and MERS-CoV. The specific aims are to: (1) function as a service laboratory for monitoring and analysis of mice infected with SARS-CoV or MERS-CoV, (2) propagate and titer MA15, recombinant SARS-CoV, non-recombinant and mouse-adapted MERS-CoV and recombinant MERS-CoV, and (3) engineer MERS-CoV recombinants. The Animal/Virology Core will interact with all other PPG components.

The Animal/Virology Core is an essential component of several of the projects and critical to the success of the PPG. The use of a single core to perform all the various assays in mice is efficient, enhances reproducibility, lowers overall cost, and facilitates collaborative efforts.

The scientific leadership and experience of the personnel is a major strength of the core. Dr. Perlman is a leading coronavirologist and viral immunologist, and Dr. Channappanavar has worked in the BSL-3 core for 3.5 years under the previous iteration of this Program Project. His involvement, along with that of (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism Preparedness and Response Act) will ensure that there is consistency in the design and execution of mouse-based experiments for all projects.

However, it is not clear that the personnel resources devoted to the Animal/Virology Core are adequate to support the level of activity described. It is stated that Dr. Channappanavar will spend (b)(6) effort on the core, but even with the full support of the research assistant, this is unlikely to be sufficient to

manage studies utilizing 1000 mice per year. In addition, as in the previous submission, the issue of how many cages are available for mice is not clearly addressed. The application states that there are (b)(4) while the budget calls for 100 cages at any time. It is not clear if this includes the uninfected hDPP4 knock-in mice mentioned on page 174. Therefore, the current size of this core is clearly not adequate as described.

These concerns are mitigated by the knowledge that although the same issues were raised by the panel reviewing the previous iteration of this program, the core clearly served the PPG well. In addition, the statement in the application that Dr. Channappanavar will spend as much time as needed on the Core, along with the assurance that the (b)(4) suggests that Dr. Perlman is well aware of these issues. A more precise estimate of time and effort should be provided and a plan to do this without detracting from Project 1 should be developed.

Core-001 received an Overall Impact score of (b)(6)

DESCRIPTION (provided by applicant): The emergence of the Severe Acute Respiratory Syndrome (SARS) in 2002-2003 and the Middle East Respiratory Syndrome (MERS) in 2012 demonstrates that zoonotic coronaviruses (CoV) have and will likely continue to spread from zoonotic sources to infect human populations. MERS-CoV continues to circulate in camels and to spread to susceptible humans, highlighting the need to better understand the pathogenesis of diseases mediated by pathogenic human respiratory CoV. In this PPG, investigators with experience in coronavirus pathogenesis, molecular biology, immunology and vaccinology will work together to understand how virus factors and dysregulated innate and adaptive immune responses contribute to MERS and SARS disease in young and aged animals and in animals with co-morbidities. All of the projects will utilize newly developed mice expressing human MERS receptor (hDPP4) in lieu of the mouse receptor (hDPP4-KI) and a mouse-virulent MERS-CoV, selected in these mice ($MERS_{MA}$). Project 1 will use $MERS_{MA}$ to investigate the role of aging in infected mice. Project 1 is also based on published data showing that specific eicosanoids with anti-inflammatory properties and their upstream phospholipases increase during aging, contributing to a delayed immune response after SARS-CoV (and by extension, perhaps $MERS_{MA}$) infection. Project 2 is based on preliminary data showing that MERS-CoV has a greater dependence on host cell proteases for virus entry than does SARS-CoV. This project will investigate unique mutations found in the surface (S) glycoprotein of $MERS_{MA}$ that appear to affect protease function. Project 3 will investigate how $MERS_{MA}$ causes more severe disease than the initial human EMC/2012 strain, with focus on the ORF4b accessory protein. This project will also investigate how hDPP4 contributes to disease severity. Project 4 is based on published data showing that the CoV E protein has ion channel activity, is a virulence factor and contains a PDZ binding domain (PBM), which is critical for virus viability. This project will focus on how the E protein causes edema in lungs and on the role of the PBM in pathogenesis. A novel PBM in the C terminal domain of E arose in $MERS_{MA}$ during mouse passage and its role will be studied. This project will also continue to develop safe, live attenuated MERS and SARS vaccines. All of the projects will use the Animal/Virology Core, which will provide non-recombinant and recombinant MERS-CoVs and SARS-CoVs and will monitor and analyze infected mice. Using the Core for these purposes will maximize experimental quality control and effective use of our resources. These projects are all interrelated and collaborative, will take advantage of the unique skills and expertise of the project leaders and provide new information about MERS and SARS pathogenesis that is essential to vaccine development.

PUBLIC HEALTH RELEVANCE: The overarching goal of this Program Project Grant is to increase understanding of severe pulmonary infections caused by MERS-CoV, SARS-CoV, and by extension, other respiratory viral pathogens in young and aged animals. Results will facilitate the development of novel vaccines and anti-viral therapies, which is critical since MERS-CoV continues to infect camels and other zoonotic CoV circulate in the wild.

Project-001: Project 1
Project Leader (PL): Perlman, S.

DESCRIPTION (provided by applicant): Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) are coronavirus-induced human respiratory diseases with high case-fatality rates. Disease is especially severe in aged populations. In the previous funding period, we showed that age-dependent increases in prostaglandin D2 (PGD_2) and an upstream phospholipase A2, PLA_2G2D, contributed to poor immune responses and decreased survival. The lung is in a state of chronic inflammation, resulting from continued exposure to environmental antigens. We postulated that PLA_2G2D, which has anti-inflammatory properties, is upregulated to counter this low grade inflammation, resulting in delayed responses to innocuous antigens but also to rapidly replicating viruses like MERS-CoV and SARS- CoV. In contrast, genetic absence of DP1, the PGD_2 receptor on myeloid cells, appears to result in poor respiratory dendritic cell activation suggesting that PGD_2-DP1 signaling may have pro-inflammatory properties at early times after infection. Our central hypothesis is that small lipid mediators are major factors in the inflammatory milieu in the lung, affecting many aspects of the immune response to MERS-CoV, SARS-CoV and other respiratory pathogens. This hypothesis will be approached in the following specific aims: 1. To determine the mechanism of PLA_2G2D upregulation and the role of PLA_2G2D in vaccine responses in 12m old mice. CoV replication includes extensive cellular membrane rearrangements. The role between these rearrangements, the induction of oxidative stress and the upregulation of PLA_2G2D will be investigated. 2. To determine the role of PGD_2-DP1 signaling in the immune response to SARS-CoV in 12 m mice. The absence of PGD_2-DP1 signaling results in diminished rDC activation and type I IFN (IFN-I) expression and increased inflammasome activation. Our goal is to determine whether changes in inflammasome activation are the major pathogenic effect of absent PGD_2-DP1 signaling or if other factors are also involved. 3. To determine whether disease severity in murine MERS is age-dependent and whether PGD_2 and PLA_2G2D contribute to poorer outcomes. Using our newly developed hDPP4-KI mice and mouse-adapted MERS-CoV, we will determine whether MERS-CoV in mice also causes an age-dependent disease. We will also assess whether changes in eicosanoid expression contribute to more severe disease. MERS-CoV, unlike SARS-CoV, productively infects macrophages. In this aim we will determine whether productive infection of human and murine macrophages modulates PLA_2G2D expression.

CRITIQUE 1

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: The project will provide a new knowledge about the role of PLA_2G2D and DP1 signaling in the age-dependent severity of MERS and SARS. Overall impact is enhanced by a combination of animal models of MERS and PLA_2G2D and DP1 knockouts. Several weaknesses were identified. They include somewhat diffuse and not well integrated description of studies in Aim 1, need for more rigorous analysis of signaling downstream of PLA_2G2D which defines severity of SARS outcome, under-developed studies addressing potential impact of oxidized phospholipids, inconsistent utilization of young and middle-aged groups in different sub-Aims, and descriptive (although valuable) agenda of Aim 3 which recapitulates studies in previous Aims, but performed in the new mouse model of mouse-adapted MERS. Middle-aged PLA_2G2D-KO mice are protected from MA15; but DP1-/- mice die. This question to the main hypothesis of this study also was not well explained. Overall, this is a

good proposal which will benefit from more careful consideration of mechanistic aspects but still provides valuable new information.

1. Significance:
Strengths

- Human studies of MERS are not feasible, and development of animal models recapitulating main MERS/SARS features including increased severity dictated by age and other co-morbidities is a significant breakthrough.
- The application addresses an issue of high significance for human health, due to the lethality of SARS and the lack of approved vaccines or treatments. The results of this study may provide important insights for developing vaccines and treatments for SARS.
- The central hypothesis that age-dependent susceptibility to SARS may depend on elevated oxidant stress and production of oxidized phospholipids is novel.

Weaknesses

- Most studies are confirmatory in nature; they recapitulate preliminary studies and previous publications by the PL.
- It is not clear how these studies will delineate the major mechanisms of MERS pathogenesis.

2. Investigators:
Strengths

- Dr. Perlman is a well-known and respected expert in the field of coronavirus infection and immunity.
- The Investigator has significant experience in managing team research by PPG investigators.
- The strong group of collaborators with expertise in different aspects of this proposed project is a strength.
- The record of prior publications indicates high productivity and active collaborations between PPG investigators.

Weaknesses

- The investigators have limited expertise in analytical methods and approaches of phospholipid quantification, characterization, data analysis and interpretation..

3. Innovation:
Strengths

- The nature of age-dependent susceptibility to MERS remains unknown, and this study attempts to address this question.
- New models, including knock-outs, knock-ins and transgenic mice provide additional mechanistic strength to the proposed studies.

Weaknesses

- Conceptual innovation is limited to testing MERS severity in new genetic models recently developed by this group and a DP1 knockout model provided by Dr. Narumiya.
- Advancement of studies performed in the previous funding cycle of this project is somewhat incremental.
- The investigators propose minimal technical innovations.

4. Approach:
Strengths:

- The selection of a pathogenic, mouse-adapted SARS-CoV isolate (MA15) for these studies is very appropriate.
- Proposed studies are generally supported by previous publications by this group.
- Highly relevant SARS-CoV pathogenesis studies in middle-aged mice will be extended to MERS-CoV.
- Use of genetic models to study the impact of PLA_2G2D and PGD_2-DP1 signaling on severity of SARS/MERS in mouse models is unique and may provide valuable information about pathogenesis of disease.

Weaknesses:

- Overall, the studies in Aim 1 are unlikely to delineate the precise mechanism of age-dependent PLA_2G2D induction in MERS model. The research plan suffers from superficial description of proposed studies and their interpretation, including approaches new to this group. "Membrane rearrangements" are not defined; unclear how they will be monitored.
- The rationale for the role of OxPLs in PLA_2G2D induction in the context of MERS severity and TLR4 signaling as the main mechanism would be better justified by presenting supportive preliminary data. Also, other DAMPs and PAMPs besides oxidized phospholipids may contribute to TLR4 activation in MERS settings or in the LPS model proposed by the PL.
- Oxidant stress hypothesis of LPS-induced OxPL generation as a mechanism dictating increased susceptibility to MERS should consider other effects of LPS.
- Technical limitations of using EO6 for OxPLs detection are not discussed.
- A plan for identification of specific OxPLs potentially contributing to PLA_2G2D induction and MERS severity is not included in the application.
- Systematic comparison of young and aged mice in different settings is inconsistent between experiments in this project.
- What new information will be gained from studies using attenuated vaccine virus in comparison to MA15 infection used in other sub-aims is unclear.
- No alternative hypotheses and approaches were proposed. Justification of expected outcomes is limited.
- Focus on PLA_2G2D-induced PGD_2 as the main lipid mediator and DP1 as the main receptor is a liability. PLA2-induced release of arachidonic acid is an initial step in synthesis of many prostaglandins, thromboxanes and leukotrienes with pro- and anti-inflammatory potential. Role of these products was not discussed.

- Preliminary results in Aim 2 showing increased mortality in MA15-infected DP1-/- mice contradict to the proposed role of DP1 activation in increased severity of SARS and MERS infection in middle-aged mice. Observed results in rDC and myeloid cells do not support a view of DP1 as one-directed signaling mechanism defining susceptibility to MERS/SARS infection.
- Testing functional relevance of PGD_2-DP1 signaling by "knockout mice" and blocking antibodies to Tiam1/Rac1, ERK1/2 and Akt is of limited feasibility and unlikely to provide meaningful information. No discussion of anticipated results and data interpretation has been provided.
- Genome-wide gene expression differences in DP1-/- and control mice do not include age as a variable and are unlikely to provide specific information in regards to investigated mechanism. Many other unrelated genes may be affected but gene validation to confirm hits is not described.

5. Environment:
Strengths

- Environment is excellent for this type of research.
- Appropriate laboratory and animal facilities are available, including BSL-3 facilities.

Weaknesses

- Unclear if expertise and equipment for functional analysis of pulmonary edema and lung injury parameters is fully available in the PL institution.

Renewal Acceptable Comments: Progress report is abbreviated; mentioning specific publications pertinent to three aims of previous funding cycle would be helpful.

CRITIQUE 2

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: This project studies how PLA_2G2D together with other members of the small lipid mediator pathways modulate the inflammatory state of the lung during SARS- and MERS-CoV infection and vaccination. The (b)(6) impact score is based on novel high impact publications supporting both the influence of the phospholipase PLA_2G2D to SARS-CoV disease as well as the protective role of airway T cells. The PL has an outstanding record in converting innovative findings to high impact projects and rapidly assimilating research to a vast evolving field. He has played a leading role in developing mouse models for huCoV and characterizing innate as well as adaptive immune responses. The environment, co-investigators and collaborators are excellent. The research plan, while expansive and including limited detail and alternatives, will reveal fundamental new insights into the interplay of eicosanoids with dendritic cell migration/function, memory T cell generation, and inflammasome activation. While the research plan comprises some moderate weaknesses with respect to LPS mediated stimulation and strain specific effects of anti-inflammatory eicosanoids, overall enthusiasm is high.

1. Significance:
Strengths

- Human CoV causing severe respiratory illness is likely to re-emerge due to persistence in animal hosts. Development of animal models for SARS- and MERS-CoV as well as the study of protection correlates are crucial for therapeutic and vaccine approaches.
- Unraveling the mechanisms underlying increased susceptibility to severe and lethal infection in the elderly using murine models is directly relevant to devise strategies to overcome such deficiencies.

Weaknesses

- Inclusion of studies using monocytes from young versus older adults would enhance translatability of the findings.

2. Investigators:
Strengths

- The PL has been a leader in contributing numerous groundbreaking findings in pathogenesis and immunity of both neurotropic and respiratory mouse and human CoV. He published many seminal papers on innate and adaptive immune control, T cell regulation and APC function in vivo and in vitro.
- The overall research record of the previous funding period shows outstanding productivity, including generation of valuable mouse models of SARS and MERS-CoV. The record of publications on human respiratory CoV is excellent, many are cutting edge and in high impact journals, e.g. Immunity, J Exp Med, Plos Path, PNAS, Am J Pathol, J Clin Invest, J Immunol and J Virol. Many are co-authored between the PPG investigators.
- Outstanding leadership of the PPG is evidenced by numerous co-authored papers and swift adaptability to a rapidly evolving field in emerging CoV infections.

Weaknesses

- None noted

3. Innovation:
Strengths

- Characterizing the link between age dependent eicosanoid levels and poor immune responses in the context of distinct viral respiratory infections has the potential to new treatment and vaccination strategies.
- Development of the mouse adapted MERS CoV model will reveal commonalities and differences to SARS-CoV and may provide useful concepts in combating human infections, especially in the elderly.
- Establishing a link between PGD_2–DP1 signaling, innate responses and inflammasome regulation is novel.

Weaknesses

- Technologies and approaches are state of the art, but do not comprise novel innovative strategies.

4. Approach:
Strengths

- The research is based on novel and highly relevant published findings that the age-dependent increases of the phospholipase A2 (PLA2) group IID (PLA_2G2D) contribute to worse disease in aging B6 mice infected with mouse adapted SARS-CoV (MA15).
- Three aims logically build on the central hypothesis that PLA_2G2D together with other members of the small lipid mediator pathways modulate the inflammatory state of the lung.
- The murine SARS-CoV model is well established with respect to age dependent disease and immune responses in both B6 and BALB/c mice. The investigators have also taken the lead to establish the MERS-CoV model using mice with knocked in human receptor (hDPP4-KI. These are outstanding tools to assess vaccine strategies.
- Studies comparing generation and recall of adaptive immune responses in wt and Pla2g2d−/− mice (Aim 1C) are critical to assess whether T cells are intrinsically impaired due to increased PLA_2G2D. Adoptive transfer approaches, measurement of T cell functionality, and challenge studies are well within the expertise of the PI. A recent publication on the protective role of airway CD4 T cells supports relevance.
- Approaches using PGE_2 antagonists (Aim 1E) to supplement only partial protection mediated by PGD_2 receptor antagonist (compared to PLA_2G2D deficiency) are necessary.
- Aim 2 adds a new perspective of dual roles of PGD_2-DPI signaling based on preliminary findings that DP1 KO mice succumb to MA15 infection and show defects in IFNa/b induction following infection with neurotropic CoV. These studies reveal a novel link between DP1 signaling and IFNa/b induced PYDC3, a suppressor of casp-1 inflammasome activation in myeloid cells. Many of the approaches are exploratory, e.g. characterization of pathogenesis in DP1 KO similar to PLA_2G2D KO mice, gene profiling of CD11c+ cells, etc. Yet these are necessary first steps.
- Aim 3 largely follows approaches similar to MA15 infected mice and will reveal whether rDC migration and T cell responses are similarly impaired in aging mice, and whether immune responses are regulated by PLA_2G2D.

Weaknesses

- Moderate: The vast differences in pathogenesis of SARS-CoV in young B6 (mild) versus BALB/c mice (severe) indicate either very distinct strain dependent PLA_2G2D mechanisms or additional critical factors in determining disease. Similar concerns reside in studies using MERS-CoV. This issue is not discussed throughout, but is of critical significance to the overall hypothesis.
- Moderate: Aim 1: Demonstrating a link between oxidative damage/stress, increased PLA_2G2D, and thus increased M15 susceptibility is crucial to unravel the mechanism of PLA_2G2D upregulation. However, approaches using low dose LPS are likely to induce both pro- and anti-inflammatory components in addition to eliciting oxidative stress. The results may be difficult to interpret, especially if pro-inflammatory lipid mediators are induced. Pitfalls are not discussed.
- Overall, an almost overwhelming number of distinct parameters are analyzed with very little consideration of how they all tie together, e.g. combined effects of pro- vs anti-inflammatory lipid mediators, opposing results of PD1 KO mice with antagonists.

- Some approaches are described too cursorily to evaluate. For example in Aim 1C, why is the delta E virus mutant chosen? Is it immunogenic in 'more resistant' B6 mice? In Aim 1Dd, what is the relevance of membrane rearrangements of cells transduced with nsp3/4/6?
- In Aim 2a, inhibition of IL1b is likely to affect DC activation thereby mediating impaired T cell responses, which is not discussed.
- Interactions with other projects are only eluded to in a cursory manner.

5. Environment:
Strengths

- The scientific environment is outstanding with respect to expertise in immunology, virology, pathogenesis and respiratory infections.
- Core facilities outside the two PPG cores are on site to support all approaches.
- Lab and animal facilities, including BSL-3 animal space is on site.

Weaknesses

- None noted

Renewal Comments: Progress in the previous funding period was excellent resulting in many high impact publications, most coauthored with other members of the PPG. The PL/PD showed strong leadership in rapidly adapting to program to develop a mouse model of MERS-CoV. Project 1 builds largely on age dependent disease susceptibility to SARS-CoV and continues to reveal underlying mechanisms of inadequate immune control.

CRITIQUE 3

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

Overall Impact: This project is led by an established and experienced investigator in the field of coronavirus pathogenesis. Work outlined in the application addresses an issue that is very significant to human health – the potential lethality of SARS-CoV and MERS-CoV – given the probability for continued human infections with those pathogens and the lack of preventative and therapeutic measures. Mouse models are essential tools for studying viral pathogenesis, and the mouse models used in the proposed work are likely to provide important insight into the pathogenesis of both SARS-CoV and MERS-CoV. The project builds nicely on results with studies of SARS-CoV pathogenesis from the previous funding period. In a reasonably coordinated manner, it addresses the central hypothesis that lipid mediators such as PGD_2 modulate host immune responses to CoV infection. Emphasis is placed on changes in modulatory effects that may occur with age, linking the work with mouse models to increased susceptibility to severe disease that has been observed in older humans infected with SARS-CoV and MERS-CoV. In general, the aims are comprehensive and detailed. Preliminary data are provided to support some of the key hypotheses that will be tested, although preliminary data are lacking for work with MERS in Aim 3. If successful, the proposed work is likely to provide important insight into CoV pathogenesis that may help to guide vaccine development.

1. Significance:
Strengths

- There are many gaps in knowledge regarding innate and adaptive immune responses to SARS-CoV and MERS-CoV infection. Animal models, such as the mouse model used by the investigator to study SARS-CoV and the new mouse model that will be used to study MERS-CoV, are valuable tools to address those gaps. In particular, the opportunity to characterize MERS-CoV pathogenesis in the hDPP4-KI mouse model will be a significant advance.
- Epidemiological data indicate that disease caused by SARS-CoV and MERS-CoV infection is worse in older patients. This proposal is based on the premise that chronic inflammation that develops with aging upregulates anti-inflammatory factors, which may then increase susceptibility to infection. Previous work led by the investigator has identified one potential mechanism (increased PLA_2G2D/PGD_2) for this age-based effect during SARS-CoV infection. The proposed studies will develop those findings further to address this important aspect of pathogenesis.
- By providing increased characterization of T cell and rDC responses to CoV infection, the project has the potential to inform vaccine development.
- Although the project is focused on CoV pathogenesis, findings that stem from the proposed work will likely be relevant for other pathogens.

Weaknesses

- Studying both SARS-CoV and MERS-CoV has the potential to dilute efforts and reduce the chance for success with either pathogen, particularly with limited specific data to guide studies of MERS-CoV. This potential weakness is mitigated by potential similarities between SARS-CoV and MERS-CoV, the PL's expertise and record, and synergy with Projects 2-4.

2. Investigators:
Strengths

- The Project Leader is an established investigator in the field of CoV pathogenesis. His expertise is well-suited to the proposed work.
- He has been productive during the project's previous funding period, with a substantial number of publications that are relevant to the proposed work.

Weaknesses

- Dr. Channappanvar, a postdoctoral fellow, will devote (b)(4); (b)(6) calendar months to this project. Dr. Channappanvar will also serve as the Core Director for the Animal/Virology Core ((b)(4); calendar months). There is some concern that Dr. Channappanvar's efforts on this project may be diluted by responsibilities in the Animal/Virology Core, which will evidently be used extensively by all four PPG projects.

3. Innovation:
Strengths

- Use of hDPP4-KI mice is an innovative approach to study MERS-CoV pathogenesis.
- The hypothesis that PLA_2G2D and PGD_2 are increased in the lungs of older mice due to ongoing pulmonary inflammation, and that these changes influence viral pathogenesis, is innovative.

Weaknesses

- The techniques that will be used to study SARS-CoV and MERS-CoV are not particularly novel, but they do seem appropriate for the proposed work.

4. Approach:
Strengths

- The three specific aims are logical extensions of previous work. They relate to each other well without being totally dependent on each other.
- Experiments designed to test specific hypotheses are balanced with experiments yielding broader results (e.g., microarray data from Pla2g2d$^{-/-}$ and DP1$^{-/-}$ CD11c^{+} cells in Aims 1 and 2) that will likely guide future work.
- The approach to studying age-based effects seems valid. Using middle-aged mice instead of older mice will likely miss more extensive effects of age on multiple aspects of immune function. However, this may help to more specifically focus on effects of PLA_2G2D and PGD_2 increases, which are present in middle-aged mice.
- Pharmacologic blockade of DP and EP receptors has the potential to provide results with translational implications. The redundancy of receptor signaling mechanisms (e.g., increased cAMP with DP1, EP2, and EP4) may complicate interpretation of any results, but this could be alleviated by simultaneous blockade of multiple receptors. The use of PGE_2-deficient mice (such as mPGES-1 knockout mice) could be considered as an alternative.
- Experiments with human cells in Aims 1 and 2 (SARS-CoV) and Aim 3 (MERS-CoV) are useful additions that strengthen relevance to human disease.
- Both male and female mice will be used in this project. In Aim 1, all studies will be performed in female mice, and key results will be verified in male mice. Presumably this will be done in Aims 2 and 3 as well, although no details are provided in those aims.

Weaknesses

- Although no formal power analysis is provided to justify numbers, plans for numbers of mice and repetition of experiments seem appropriate. However, there is a somewhat cursory description of methods in some instances. Controls are sometimes implied without being fully described.
- Alternatives to the proposed experiments are not always developed well, raising some questions about what will happen in response to negative or unexpected results.
- *In vitro* and *in vivo* studies are proposed to evaluate the potential for oxidative stress to mediate age-associated differences in pathogenesis. Consideration could be given to including antioxidant treatment in the proposed experiments in order to further support links between LPS-induced oxidative stress, PLA_2G2D/PGD_2, and susceptibility to infection.

5. Environment:
Strengths

- The environment at the University of Iowa is excellent. All necessary resources are available.

Weaknesses

- No weaknesses were noted.

Renewal Comments: The investigators have made very good progress during the previous funding period. Multiple publications focused on both SARS-CoV and MERS-CoV solidify the basis for this application. The development of the hDPP4-KI mouse model for studies of MERS-CoV pathogenesis is a significant strength.

CRITIQUE 4

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: This project aims to understand SARS-CoV and MERS-CoV infections in aged mice, with a focus on PGD_2 and its signaling through DP1. The work is interesting and important in the context of vaccination schemes for coronaviruses. This forms the basis of Aims 1 and 2 of the application. Aim 3 explores whether equivalent age-dependent mechanisms also exist for MERs-CoV in the context of the new mouse model of MERS-CoV derived by the PPG team. The outcome of these studies is uncertain. The team of investigators is strong.

1. Significance:
Strengths

- Information on MERS-CoV in the context of co-morbidities in a mouse model could be of high significance.

Weaknesses

- No comments were provided.

2. Investigators:
Strengths

- The PL and team are outstanding.

Weaknesses

- No comments were provided.

3. Innovation:
Strengths

- The development and use of the new mouse model is highly innovative.

Weaknesses

- No comments were provided.

4. Approach:
Strengths

- The use of aging models and co-morbidities is considered a strength of this project

Weaknesses

- While important to test, much of Aim 3 may not be possible if there is no age-dependent to MERS-CoV infection.

5. Environment:
Strengths

- The environment is excellent.

Weaknesses

- No comments were provided.

Project-002: Adaptive MERS coronavirus-cell entry pathways and their relevance to virulence and antiviral strategies
Project Leader (PL): Gallagher T.

DESCRIPTION (provided by applicant): The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a zoonotic virus that can cause fatal disease in patients with underlying co-morbidities. Further recognition of this respiratory syndrome and prevention strategies will require a small animal infection model as well as an additional understanding of the virus. This PPG describes a mouse model of MERS-CoV disease. In this model, the viruses causing disease are adapted variants, specialized for mouse lung infection. By contrast, non-adapted MERS-CoVs cause infection in the mouse but do not cause disease. The central hypothesis of this project is that mouse-adapted variants can efficiently enter host cells through pathways that are not available to the non-adapted viruses. To address this hypothesis, recombinant MERS-CoVs will be constructed and evaluated to determine whether mouse-adaptive mutations in the cell entry-mediating viral spike proteins correlate with efficient mouse lung infection. Surrogate MERS-CoV pseudo-viruses will be constructed and evaluated to address the focused hypothesis that mouse adapted variants mediate an “early” plasma-membrane cell entry that is unavailable to non-adapted viruses. The project will dissect mechanisms by which spike proteins mediate early cell entry through plasma membranes versus late cell entry through endosomes. The basis for selection of early versus late cell entry will be determined by identifying host cell factors promoting or restricting either pathway. This project will also identify appropriate antiviral strategies that operate by preventing early and late virus-cell entry. The rationale for all of these aims is that additional understanding of MERS-CoV cell entry pathways will identify correlates of robust infection and disease, and will also provide insights on the best ways to prevent infection and disease with innovative virus entry inhibitors.

CRITIQUE 1

Significance:	(b)(6)
Investigator(s):	
Innovation:	
Approach:	
Environment:	

Overall Impact: Project 2 is focused toward elucidating mechanisms of MERS-CoV specific cell entry using information from the recently mouse adapted MERS-CoV studies in which several mutations were identified in the S protein following adaptation. This area of investigation is important in light of the plausible emergence of MERS-CoV as a global public health concern. The proposed work here is a continuation of Project 4 from the previous funding period. Overall the conceptual framework is excellent, and identifies a number of areas that may clarify the mechanisms by which MERS-CoV enters cells and leads to zoonotic transmission. The integration of reverse genetics approaches, the scientific cores and Projects 1, 3 and 4 are outstanding and deemed a strength. The focus toward shRNA and peptide inhibitors is also considered an outstanding strength. The weaknesses include a very ambitious set of aims, and a lack of preliminary data given the previous funding period, since much of the approach is based on anticipation of findings from mutational analysis in Aim 1. Overall, the anticipation of findings is speculative, as the approach seeks to implicate mouse adaptive S protein mutations leading to enhanced fusion, protease cleavage mechanisms, and endosomal restriction factors as reasons for the enhanced mouse adaptation. It is not clear that adaptation to mouse cells is informative to human pathogenesis, although the identification of inhibitors could be informative. Preliminary data identifying a specific mechanism of viral entry by mouse adapted MERS-CoV and protease/S protein targets for drug targeting, and investigation of human airway epithelium throughout the application would increase enthusiasm. At times, the primary endpoints supporting the aims are not described, nor is the interpretation of expected results as they pertain to the aims.

1. Significance:
Strengths

- The study of emerging pathogens that have now become global is highly significant.
- Elucidation of possible pharmacologic targets is extremely important and may have implications across CoV phylogeny and even respiratory viruses.

Weaknesses

- The episodic nature of the outbreaks and the lack of further SARS-CoV outbreaks suggest that zoonotic transmission of CoVs may have severe limitations in sustainability in the human population. This is a minor concern though.

2. Investigators:
Strengths

- The PL has a sustained, productive record of publication and accomplishment.
- The lab and collaborative personnel are appropriate.

Weaknesses

- Progress in the previous funding period in the area of MERS-CoV viral entry and protease dependent specificity is rather modest.
- The request for a FTE postdoctoral fellow and technician for the breadth of studies proposed here appears too modest.

3. Innovation:
Strengths

- The use of reverse genetics for assessment of MERS-CoV adaptation is highly innovative.
- A number of biological assays are proposed that are innovative to the CoV field.

Weaknesses

- It is unclear what concepts of human adaptation will be elucidated.

4. Approach:
Strengths

- The approach focuses on a strength of the group, that being requirement for proteolytic cleavage for CoV entry and endosomal escape.
- Aim 1 will utilize the expertise in Project 4 and the Animal/Virology Core for assessment of MERS-CoV mutations that enhance virulence/pathogenicity. This will identify the mutations that confer mouse adaptation. The investigation of mutations in a relevant model is deemed a strength.
- Aim 2 will examine structure and function of various S protein mutations on cleavage site and fusion domains arising from previous mouse adaptation. This aim exemplifies the most involved and daunting of the aims described. The use of PPs and VLPs may simplify the analysis.
- Aim 3 will examine viral entry mechanisms in mutant, adapted MERS-CoV in various cell lines. The extension of the studies from Aim 2 to Aim 3 is received enthusiastically despite some technical challenges.
- Aim 4 will implicate various proteases in MERS-CoV entry using Ad-mediated delivery of shRNA against candidate proteases. The elucidation of distinct protease targets will be critical for identifying antiviral pharmacologic targets for future drug discovery.
- Aim 5 will examine fusion inhibitors of the HR2 domain using lipid-conjugated HR2 peptides provided by a collaborator (Porotto). The inhibitors have already been validated for MERS-CoV, and have a high potential for being successful.

Weaknesses

- Overall, one distinct weakness is that the investigators are primarily studying mouse adaption of a human MERS-CoV, with the notion that this will inform about how zoonotic transmission occurs in adaptation to humans. It is plausible the camelid-to-human zoonosis may involve other mechanisms not identified here.
- Overall, the stated aims are exhaustive, and do not appear feasible in light of the progress in the previous funding period and with the personnel described.
- Aims 2-5 rely on information gathered from Aim 1, and the outcomes expected are speculative. It is plausible that mutations outside of the S protein are critical for mouse adaptation, and if so, the extent of information required from these subsequent aims would be greatly minimized.
- Aim 2 seeks to examine both the fusion and cleavage site domains. The functional analysis is exhaustive, and appears to be a substantial amount of work. There is no time line to indicate how long this analysis will take. There is no structural analysis described, although the functional characterization may be enough.
- Aim 3, and to some extent the rest of the application, would benefit from more standardized cell studies, in particular, primary human airway epithelial cells. The aims described and the preliminary data presented use a variety of cell lines, although no explanation of which ones are appropriate is given. While this expertise (i.e. primary cultures) is clearly in hand with Dr.

McCray's group, the feasibility of the studies proposed here, especially with Ad transduction, etc., are questionable.

- Aim 4 represents the studies likely proposed in the previous funding period. It is unclear what new information can be gleaned from these studies.
- Aim 5 will test HR2 domain peptides conjugated to various lipids for antiviral properties. It appears from the preliminary data that these inhibitors are highly functional for antiviral activity. In light of the previous critique that the aims are too ambitious, this aim should be dropped. If the utility of these inhibitors were to be tested, then a series of studies from in vitro dose range finding evaluations, to delivery, to rodent efficacy studies should be proposed. The PL indicates that they intend to seek additional funding opportunities for this approach, and that seems more appropriate.

5. Environment:
Strengths

- The Loyola University environment appears outstanding.

Weaknesses

- The distance to U. Iowa is considered a minor concern. The previous interaction with the PD and the U. Iowa investigators minimizes this concern, although some of the studies proposed would be facilitated by being in the same location.

Renewal Comments: Progress from the previous funding period appears acceptable, with consideration given to the transition of focus to the MERS-CoV.

CRITIQUE 2

Significance:	(b)(6)
Investigator(s):	
Innovation:	
Approach:	
Environment:	

Overall Impact: This is an excellent application from Dr. Tom Gallagher, a senior experienced coronavirologist. The PI proposes to study MERS-CoV entry using the mouse adapted MERS-CoVs developed during the previous grant period. Strengths of the application are the experience of the PL and his collaborators, an experimental plan that utilizes multiple approaches to identify proteases important in MERS-CoV entry, the cellular site(s) of entry in different cell types, the effect of mutations arising during mouse adaptation on entry, a novel split GFP assay that will permit in vitro examination of proteases need to activate membrane fusion, and the incorporation of two aims with some translational potential in the future. Successful completion of the proposed aims will advance our understanding of MERS-CoV entry. Weaknesses detracting from enthusiasm for the application are the focus on understanding adaptation of MERS-CoV to the huDPP4 knock-in mouse without some attempt to translate this information to infection of human cells, the absence of a plan for how partial phenotypes, likely to be obtained when looking at recombinant viruses containing subsets of the approximately 30 mutations found in the mouse adapted virus, will be interpreted, and a similar limited discussion of how potential complications in interpretation of in vivo shRNA experiments targeting proteases will be dealt with.

1. Significance:
Strengths

- MERS is a severe respiratory illness with high mortality. Due to zoonotic transmission, likely from camels, and its ability to transmit from human to human, this disease will remain a threat to public health for some time. The proposed studies will increase our understanding of MERS-CoV, and potentially other coronaviruses, entry into cells, a key step in pathogenesis. Thus, the proposed research is highly significant.
- The proposed research will shed light on how MERS-CoV adapts to a new host and the interactions of the MERS-CoV with host cell proteases and their effect on MERS-CoV entry.
- Aims 4 and 5 investigate the possibility of blocking viral entry with specific protease inhibitors or by enhancing fusion inhibitors with lipid adducts, respectively. Aim 5 will also explore the possibility of developing relatively broad-spectrum fusion inhibitors for CoVs. This would be a significant step in future development of antivirals for CoVs.

Weaknesses

- The proposed studies of adaptation to mice may be of limited relevance to human disease since MERS-CoV from camels is able to infect humans and induce disease without further adaptation.

2. Investigators:
Strengths

- Dr. Tom Gallagher, the PL on this project, is a well-regarded senior coronavirologist with over twenty years of experience studying coronavirus entry into cells. He is well qualified to lead this project.
- Dr. Gallagher was an investigator on the previous iterations of this PPG and thus has had a long-standing productive collaboration with the other investigators on this PPG. This is a strength of the project.
- Enlisting Dr. Matteo Porotto, a pioneer in the use of lipid conjugates to peptide viral entry inhibitors, as a collaborator strengthens Aim 5.

Weaknesses

- None

3. Innovation:
Strengths

- The application of split GFP protein to study viral fusion is a technical innovation applicable to other fields where vesicle fusion is studied.
- The hypothesis that mutations in MERS-CoV S protein effecting susceptibility to proteolytic processing can confer specific cell tropisms is important in the pathogenesis of MERS and has not been explored previously.
- The studies of specific protease inhibitors as antivirals for MERS-CoV and the potential of lipid conjugates to peptide fusion inhibitors has not been previously explored for coronaviruses.

Weaknesses

- Studies with lipid conjugates to peptide fusion inhibitors have been performed with other viruses and changes in the cleavage sequence affecting cell tropism have previously been demonstrated for other respiratory viruses.

4. Approach:
Strengths

- Aim 1, to determine the mutations in the S gene that are responsible for the ability of the mouse-adapted MERS-CoVs to produce lethal disease is straightforward, although interpretation of the results may be less so.
- The experimental plan for Aims 2 and 3 is extensive with multiple approaches to identify proteases important in MERS-CoV entry, the cellular site(s) of entry in different cell types, and the effect of mutations arising during mouse adaptation on entry. This is likely to provide important additional information on MERS-CoV entry and pathogenesis. The use of primary cells will ensure that observations made in cultured cells carry over to primary cells of interest.
- The use of both pseudotyped, VLP, and rMERS-CoV constructs to determine effects of mutations on viral entry is prudent in light of discordant results obtained for SARS-like CoVs.
- The use of a split GFP protein assay to study S-DPP4 mediated vesicle fusion in vitro where conditions can be precisely controlled is an advance on cell-based assays and should allow unambiguous identification of proteases that cleave various S protein constructs and their effect on membrane fusion.
- Aims 4 and 5 have some potential to identify targets for future development of antivirals.

Weaknesses

- In light of previous work with MHV and the fact that the mouse adapted viruses on average carry 30 mutations in multiple genes, it seems likely that many of the recombinant viruses generated for this project will have partial phenotypes. Careful assessment of LD_{50} values for these viruses will be needed, but these assays are not proposed.
- The split GFP vesicle fusion assay is inadequately described. Lipid composition has important effects on membrane fusion, yet there is no description of the lipid(s) to be used. Although the PL proposes to take advantage of differences in lipid composition of different membrane compartments to target HR2 peptide-lipid conjugates in Aim 5, experiments to investigate the effect of lipid composition on fusion are not proposed in Aim 2, although the PL has an ideal system for doing so in the split GFP vesicle fusion assay and these might provide additional insight into the intracellular location for membrane fusion and virus entry.
- No attempt will be made to determine if observations on viral entry in primary mouse cells carry over to human cells. This could be done in collaboration with Project 3.
- The use of Ad5-shRNA-DPP4 transducing vectors in mice to interrogate proteases mediating S cleavage in cleavage is fraught with potential complications. Although expression of DPP4 and the shRNA will provide cell specific protease inhibition, it will not inhibit any proteases present in the pulmonary extracellular environment, complicating the interpretation of results. Multiple proteases may play a role in S cleavage, yet this will further complicate interpretation of results. There is no plan described to deal with these complications.

5. Environment:

Strengths

- The intellectual environment provided by the PPG and the Loyola University is excellent and provides opportunities for multiple collaborations with other investigators within the PPG.
- The PL's laboratory and core facilities at Loyola are sufficient for the proposed studies.

Weaknesses

- The lack of a BSL-3 facility at Loyola requires all work with live MERS-CoV to be carried out at the University of Iowa in the Animal/Virology Core.

Renewal: Acceptable

ADDITIONAL COMMENTS TO APPLICANT: More care in proof reading the application could have been taken. There are at least two instances where notations about citations remain in the text and there are PDF conversion errors in Figure 2 and Table 1 which made these somewhat difficult to read.

CRITIQUE 3

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: The impact of this work will be quite high. MERS-CoV (as with all coronaviruses) exhibits a complicated entry pathway, with change in the entry pathway potentially driving pathogenesis in a major way

1. Significance:

Strengths

- Knowledge of MERS-CoV entry is still quite limited, the work proposed will add substantially to our understanding of this virus.
- The study of the fusion-inhibitory peptides may lead to new therapeutic possibilities.

Weaknesses

- It is unclear how much useful information will be gained by the proposed experiments that aim to identify *in vivo* proteases.

2. Investigators:

Strengths

- The PL is an expert in the area of study, and the work is well integrated with that of the other PLs in the PPG.

Weaknesses

- No comments were provided.

Innovation:

Strengths

- The study of MERS-CoV$_{MA}$ is a unique and therefore innovative study.
- The application of lipid-conjugated HR2 peptides, while founded with paramyxoviruses, is innovative in the context of coronavirus infections, and has the potential for impact on all coronavirus diseases.
- The exploration of the connection between the virus entry pathway and interferon signaling (Aim 3) is innovative

Weaknesses

- While having a solid experimental basis, the approaches used are for the most part not highly innovative.

3. Approach:

Strengths

- The approach outlined in Aim 1 to construct four recombinant viruses to examine whether the spike mutations are a primary driver in pathogenesis, and to test these in the mouse model, is a realistic one.
- The approach in Aim 2, to map the mutations in spike in PP and VLP systems is a very solid one. The approach to examine the FD mutation is well thought out and justified.
- The plan to integrate information from Aim 2 on the effect of specific mutations into pathogenesis studies with recombinant viruses, either in cell culture or in mice, via Project 3 is a good one.
- The approach to determine whether MA viruses have a different route of entry and shift to an early pathway is well described.
- Aim 5 is a good extension of previous work to direct the known (and highly-active) fusion-inhibitory function HR2 peptides towards therapeutic application. The collaboration with Dr. Porotto is very beneficial in this regard. The applicant acknowledges that the inhibitor may shift the entry pathway with unexpected results, but is well positioned to examine and understand this.

Weaknesses

- The experimental plan for Aim 1, while necessary to map the genes driving pathogenesis, may ultimately only give limited information.
- The use of protease inhibitors in Aim 2 is described with insufficient detail. There is only limited attention given to proportion convertases (PCs) as activating proteases. The addition of basic residues in the cleavage site creates novel dibasic sequences that may be recognized by PC family members.
- The focus on cathepsin K in Aim 2 is not well justified, and the generation of the un-cleaved mutants is not well described.
- The basis of Aim 4, to identify *in vivo* proteases by selected knock down of four proteases in mice, does not adequately cover the possible redundancy and lack of information about the spectrum of possible proteases acting on MERS-CoV.

4. Environment:

Strengths

- The environment is excellent.

Weaknesses

- No comments were provided.

Renewal Comments: Progress during the previous project period was good and the PL successfully transitioned the project to MERS-CoV.

ADDITIONAL COMMENTS TO APPLICANT: Most of the figures contain strange characters which sometimes make the figures hard to understand, this may be a PDF conversion issue. Some of the referencing is incomplete or in draft form.

Project-003: Project 3
Project Leader (PL): McCray, P.

DESCRIPTION (provided by applicant): Middle East Respiratory Syndrome (MERS) was recognized as a significant illness on the Saudi Arabian peninsula in mid-2012, and the causative agent was rapidly identified as a novel coronavirus (CoV), termed MERS-CoV. MERS has a high mortality (~35%), associated with severe lung disease. Similar to the SARS virus that caused an epidemic in 2003-4, there is ongoing global concern due to MERS high fatality rate. To date, cases of MERS have been reported in 26 countries. Dipeptidyl peptidase 4 (DPP4, CD26) is the receptor for MERS-CoV. Epidemiologic studies have established that MERS is zoonotic in origin, with evidence for a closely related virus in dromedary camels on the Arabian Peninsula and throughout Africa. Spread from camels to people is documented, as well as person-to-person spread among health care workers in hospital settings. A lack of autopsy studies from MERS fatalities has hindered understanding of MERS-CoV pathogenesis. Thus, MERS is the most recent confirmation that coronaviruses can jump from their animal hosts, infect humans, and cause severe disease of global significance. There is a pressing need to better understand MERS disease pathogenesis and to develop vaccines and therapies. There are 3 specific aims. Aim 1. To understand how an *in vivo* evolved MERS-CoV causes lethal lung disease. We developed mice that have the human receptor for MERS-CoV. Using these animals we developed a mouse-adapted virus that causes significant lung disease. These studies will advance our knowledge of the causes of MERS-related lung disease. Aim 2. To investigate how adaptive mutations in MERS-CoV contribute to increased virulence. We sequenced the mouse-adapted virus strains and assembled their genomes. We will use this genetic information to investigate relationships between the virus gene products and the host responses that lead to severe lung disease. Aim 3. To investigate how DPP4 abundance and function influence MERS disease pathogenesis. DPP4 has enzymatic activity that cleaves two amino acids off of target protein substrates, thereby changing protein functions. DPP4 abundance and enzymatic activity may contribute to disease. These experiments will advance our knowledge of how DPP4 activities may underlie to disease outcomes.

CRITIQUE 1

Significance:
Investigator(s):
Innovation:
Approach:

Environment: (b)(6)

Overall Impact: This is an excellent application from a senior experienced investigator. Dr. McCray will utilize infection of a newly developed huDPP4 knock-in mouse with mouse adapted-isolates of MERS-CoV as a model of MERS. Strengths of the application include the experience of the PL and the strength of his collaborators, the use of this novel mouse model, examination of cellular, virologic, and immunologic aspects of mouse adapted MERS-CoV infection in these mice, investigation of infection in obese knock-in diabetic mice to investigate this disease as a co-morbidity factor for MERS in humans, and studies of the role of shed DDP4 during infection by MERS-CoV and its role in pathogenesis with a focus on the role of shed DDP4's enzymatic activity. Successful completion of the proposed experiments should advance our understanding of MERS pathogenesis. Weaknesses detracting from enthusiasm for the application mostly revolve around Aim 2. The focus of Aim 2 is on identifying mutations responsible for adaptation to mice. These are interesting experiments but they may be difficult to interpret due to partial phenotypes and may not provide much information relevant to human disease since MERS-CoV isolates from camels do not seem to require significant adaption to cause disease in humans. There are relatively minor technical weaknesses with this aim as well.

1. Significance:
Strengths

- MERS is a severe respiratory illness with high mortality. Due to zoonotic transmission, likely from camels, and its ability to transmit from human to human, this disease will remain a threat to public health for some time. The proposed studies will increase our understanding of MERS pathogenesis and how MERS-CoV, and potentially other coronaviruses, adapts to a new host. Thus the proposed research is highly significant.
- The DPP4 knock-in mouse combined with mouse adapted MERS CoV provides a small animal model of MERS suitable for pathogenesis, vaccine and antiviral studies. This is a significant advance over current small animal models.

Weaknesses

- Current knowledge suggests that MERS-CoV circulating in camels is able to transmit to humans and cause severe disease with minimal if any further adaptation. The proposed studies of adaptation to mice may be of limited relevance to human disease although they are likely to be informative for coronavirus biology.

2. Investigators:
Strengths

- Dr. Paul McCray, the PL on this project, is a well-regarded expert in airway epithelial cell biology and host defense mechanisms and a pediatric pulmonologist. He has extensive experience studying the interaction of SARS-CoV and MERS-CoV with the lung. His laboratory played a central role in creating various mouse models of MERS-CoV infection. He is well-qualified to lead this project. Dr. Kun Li is a postdoctoral research associate and will work full time on this project. He has three publications with Dr. McCray on MERS.
- Dr. McCray was an investigator on the previous iterations of this PPG and thus has had a long-standing productive collaboration with the other investigators on this PPG. This is a strength of the project.
- Dr. Meyerholz of the Animal/Virology Core of the PPG is listed as a collaborator/consultant and will provide pathology consultation and evaluation for this project. Additional collaborators that Dr. McCray has enlisted for this project include Dr. E. Dale Abel, Chair of

Medicine and Director of the Diabetes Research Center, Dr. Tom Bair, Director of Bioinformatics for the Iowa Institute of Genetics, and Dr. Joseph Zabner, Director of the Cell and Tissue Core of the U of Iowa CF Center. Dr. Abel and the Diabetes Center will provide a valuable collaboration on investigations of MERS infection of diabetic obese huDPP4 knock-in mice which are proposed in Aim 1. Dr. Bair will provide bioinformatics support on gene expression studies, and Dr. Zabner will provide human airway epithelial cell cultures. These collaborators all enhance likelihood of success.

Weaknesses

- None

3. Innovation:
Strengths

- The huDPP4 knock-in mouse and mouse adapted strains of MERS-CoV that cause significant pulmonary disease in mice developed by Dr. McCray with other PPG members provide an innovative model for studying MERS pathogenesis.
- This may be the first application to investigate predisposing factors to severe coronavirus disease other than aging.
- The application contains several novel hypotheses. The first is that expression of huDPP4 on the surface of immune effector cells and endothelial cells makes a major contribution to the pathogenesis of MERS. The second is that the enzymatic activity of soluble DPP4 (sDPP4) released during infection contributes to pathogenesis of MERS.

Weaknesses

- None

4. Approach:
Strengths

- The majority of the studies proposed in Aim 1 investigate the hypothesis that differences in outcome during mouse adapted MERS-CoV infection of mice transduced by rAd5-huDPP4 and the huDPP4 knock-in mice are due to the expression of DPP4 on cells of the immune system, endothelial cells, in addition to pulmonary epithelial cells, and are well supported by preliminary data. The proposed assays are well within the expertise of the McCray lab and his collaborators in the Animal/Virology Core and Project 1 and should produce important, although largely descriptive, data on this model. These experiments may also produce results which suggest additional collaborative efforts with Project 2. Investigations into the role of infection of endothelial cells in pulmonary vascular injury in their mouse model are particularly intriguing. Investigations into the interaction between diabetes and MERS-CoV infection have the potential to provide some insight into the mechanism by which diabetes is a co-morbidity factor for MERS in humans.
- The studies proposed in Aim 2 will use a reverse genetic approach to attempt to determine the role of mutations in the ORF4B and nsp9 proteins during adaptation to mice. These studies should be straightforward to perform, although interpretation of results may not be quite so straightforward.
- The use of both pharmacologic and genetic approaches in Aim 3 to investigate the role of sDPP4 in the pathogenesis of MERS is to be commended. The use of bone marrow

chimeric mice to investigate the role of DPP4 expression on these cells is also a strength of the application.

- The PL has done a nice job in highlighting where findings in his project may inform other projects leading to new experiments.
- The use of human airway epithelial cell cultures in several experiments strengthens the project by ensuring that findings are not specific to their mouse model.

Weaknesses

- A rationale for use of the chronic LPS administration model of metabolic syndrome with chronic inflammation as a co-morbidity factor for MERS is not provided. The effect of LPS in activating macrophage pro-coagulants will complicate the interpretation of the results obtained from experiments with this model.
- The results obtained in Aim 2 may be more difficult to interpret than envisioned by the PL particularly since the mouse adapted MERS viruses carry an average of about 30 mutations. Based on prior work in the MHV system it is likely that mutations in the S gene will have the greatest effect on pathogenesis, thus many of the viruses to be regenerated for this project are likely to have partial phenotypes. Careful assessment of LD_{50} for these viruses will be needed but these assays are not proposed.
- One of the mutations to be studied in the context of adaptation to mice results in a 190 amino acid in frame deletion in ORF4B. This deletion will ablate the cyclophosphodiesterase activity of this protein that interferes with the OAS-RNase L pathway while leaving the NLS intact. Given that ORF4B has been shown to bind to KPNA4, TBK1, IKKε, and the RUVBL1 transcription factor, biochemical studies to determine the effect of this deletion on stability of the 4B protein, and these binding activities should be done to provide a more detailed mechanistic insight into how this truncation contributes to any observed phenotype.
- The experiments to characterize the M39L mutation are underdeveloped.

5. Environment:
Strengths

- The core facilities at the University of Iowa are excellent and will make important contributions to this project. Excellent consultants and collaborators have been enlisted.
- The intellectual environment provided by the PPG and the University of Iowa is excellent and provide opportunities for multiple collaborations.

Weaknesses

- None

Renewal: Acceptable

CRITIQUE 2

Significance:
Investigator(s):
Innovation:

(b)(6)

Approach:
Environment: (b)(6)

Overall Impact: This is a very well written application with clear aims that are supported by strong published and additional preliminary data. The project leader is an established investigator with extensive experience in the study of host-pathogen interactions in the lung. The project addresses an important area of human health, disease caused by MERS-CoV infection. The proposed research will characterize MERS-CoV pathogenesis using a mouse-adapted virus that causes disease in hDPP4-KI mice that resembles disease observed in humans. Results from the work are likely to make a lasting impact on the field of CoV research by defining ways in which host (DPP4) and pathogen (MERS-CoV orf4b and nsp9) factors contribute to pathogenesis. Although largely based on work in a mouse model, the project's relevance to human health is enhanced by incorporating into mouse infection experiments co-morbidities such as obesity and chronic inflammation, and by the use of relevant human cells in complementary *in vitro* experiments. If successful, the proposed work may identify DPP4 inhibitors as useful therapeutic candidates. This project stands alone nicely, but it is clear how the PPG's other projects will contribute to this work and how results from this work will enhance the other projects.

1. Significance:
Strengths

- There are many gaps in knowledge regarding host and pathogen factors that contribute to MERS-CoV pathogenesis. The mouse model of MERS-CoV infection that will be characterized in this project has great potential to address those gaps. The underlying premise that both virus (adaptive mutations in orf4b and nsp9) and host (DPP4) factors make significant contributions to MERS-CoV pathogenesis is justified by existing published and preliminary data from studies of MERS-CoV, SARS-CoV, and other models.
- Results from the proposed studies will likely provide important insight into ways in which specific adaptive mutations contribute to MERS-CoV virulence.
- The work may identify a host protein (DPP4) that could be targeted to in order to reduce manifestations of disease caused by MERS-CoV.

Weaknesses

- Reliance on a mouse model, particularly a single mouse strain, may make it difficult to generalize results to understand human disease. This relatively minor weakness is mitigated by the use of relevant human cell types *in vitro* to confirm results of work in the mouse experiments.

2. Investigators:
Strengths

- The project leader, Dr. McCray, is an established investigator with expertise in the study of respiratory epithelial biology, innate immunity, and host-pathogen interactions. He is well qualified to lead this project.
- Established and productive collaborations with investigators from Projects 1, 3, and 4 are an important strength.

Weaknesses

- No weaknesses were noted.

3. Innovation:
Strengths

- The hDPP4-KO mouse and the mouse-adapted MERS-CoV are innovative tools to study MERS-CoV
- Studying DPP4 function with regards to potential immunomodulatory effects during infection is an innovative approach to defining mechanisms of MERS-CoV disease.

Weaknesses

- The techniques that will be used in the project are not particularly novel. However, they are appropriate for the proposed work, and this is not a major weakness.

4. Approach:
Strengths

- There are well defined aims that will determine the effects of receptor distribution and type of cell infected on overall phenotype (Aim 1), define contributions of specific mutations in the viral genome to disease (Aim 2), and characterize effects of DPP4 on pathogenesis (Aim 3). Possible outcomes and alternative approaches are addressed in sufficient detail.
- Preliminary data provide solid support for the proposed experiments, particularly for Aims 1 and 2.
- Experiments designed to test specific hypotheses are balanced nicely in some cases by work that is likely to generate data to guide future efforts (e.g., RNA-seq).
- Work in Aim 2 involves a comprehensive approach to study effects of adaptive mutations that were identified in mouse-adapted MERS-CoV, pairing KI mouse infection experiments with complementary *in vitro* work exploring potential mechanisms involving NF-kB and IFNs.
- Aim 3 is based on the interesting hypothesis that the enzymatic activity of DPP4, the receptor for MERS-CoV, modulates host inflammatory responses during infection. Demonstrating that that DPP4 inhibition inhibits viral replication and/or improves manifestations of disease would be a significant advance.
- Investigation of MERS-CoV pathogenesis will not be limited to the lung. This strengthens the proposed work, since effects on cardiac function are likely to be relevant to human disease. The application would be further strengthened by a more detailed description of how cardiac tissues will be evaluated in 3.1.b.i. Even if virus is not detected in cardiac tissue, evaluation of cardiac inflammation (cytokines, inflammatory cells) and function (serum cardiac troponin I, heart size, echocardiography measurements of function) may prove relevant if increased circulating DPP4 in infected mice adversely affects cardiac outcomes. These measurements may be useful to include in the DPP4 inhibition experiments outlined in Aim 3.

Weaknesses

- In Aim 1 (3.1.b.iv), two different models will be used to study potential effects of co-morbidities on MERS-CoV pathogenesis (obesity and insulin resistance using mice fed a high-fat diet; systemic inflammation/metabolic syndrome using mice exposed to endotoxin). This is a relevant line of investigation that may ultimately yield promising results. However, both co-morbidities are very likely to affect pathogenesis in many ways. Developing both models seems very ambitious, and it is not entirely clear how various possibilities (for example, effects on DPP4 abundance and distribution, effects on host immune function) will be sorted out.

- Sitagliptin will be used in Aim 3 to inhibit DPP4 enzymatic activity *in vitro* and *in vivo*. As the investigator discusses, sitagliptin has been noted to have anti-inflammatory effects in other models. A genetic approach is offered as an alternative should results with sitagliptin prove inconclusive. However, it may also be useful to consider the use of other DPP4 inhibitors, which may have differential activity *in vivo* (for instance, see Steven et al. Basic Res Cardiol 2015, 110(2):6).
- Reciprocal BMT experiments described in 3.3.b.ii will investigate the possibility that infection of hematopoietic cells expressing DPP4 contributes to pathogenesis. This work depends to some extent on the ability of $MERS_{MA}$ to infect hematopoietic cells, a possibility that is suggested by preliminary data showing viral antigen in alveolar macrophages and that will be further assessed in 3.1.b.ii. BMT itself has pronounced suppressive effects on many aspects of immune function that are independent of effects mediated by pharmacologic immunosuppression and that persist when marrow is fully reconstituted. Although these effects will be controlled for to some extent, since all mice will undergo BMT, they may complicate the interpretation of the results of these experiments.

5. Environment:
Strengths

- The environment at the University of Iowa is excellent. All necessary resources are available.

Weaknesses

- No weaknesses were noted.

Renewal Comments: There has been fairly good productivity during the last funding period. Three publications from Dr. McCray's laboratory are mentioned in the progress report, along with unpublished work on ACE2 in SARS-CoV and influenza infection that is unpublished. The published work is of high quality, is in prominent journals, and is directly relevant to this renewal. Dr. McCray is a co-author on three other publications listed in the application's Progress Report Summary List, one of which is a commentary on person-to-person spread of MERS-CoV.

CRITIQUE 3

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

Overall Impact: This is well designed project implicating innovative models of mouse-adapted MERS which were generated in preliminary studies. The project will yield important information about the role of DPP4 expression and activity in host cells. Several points were raised regarding unclear separation of specific proposed studies and alternative experiments.

1. Significance:
Strengths

- The project addresses important aspects of lung inflammation during SARS-CoV and MERS-CoV infection that has high significance.
- The significance for human health is further emphasized by high lethality of SARS and MERS, unclear factors contributing to severity of disease and the lack of approved vaccines or treatments.
- There are significant gaps in our understanding of response to MERS-CoV by different lung cell types which will be addressed in this study.

Weaknesses

- None noted

2. Investigators:
Strengths

- The Project Leader, Dr. McCray, is an established clinical research scientist with a strong background in pulmonology and a long-standing interest in host-pathogen interactions.
- He has an excellent record of publication and extramural support.
- In this Project he will expand a repertoire of lung cell types to characterize cell-specific expression of coronavirus receptor (DPP1) and its potential role in severity of MERS. The PL is well qualified for the proposed studies.
- Dr. McCray has established excellent collaborations with the PD and other project leaders in the PPG.

Weaknesses

- None noted

3. Innovation:
Strengths

- Generation of animal models recapitulating human MERS/SARS by the PL is highly innovative.
- First to obtain and genetically characterize P30 generation of MERS-MA coronavirus
- The central hypothesis that adaptive mutations in MERS-CoV contribute to increased virulence is novel.
- Approaches for $MERS_{MA}$ functional effects are standard, but will provide essential information.

Weaknesses

- Aim-1 will further characterize already developed KI mice.

4. Approach:
Strengths:

- Well-written application with critical evaluation of existing literature and new preliminary data

- Obtained multiple virus generations from KI and Tg mice with distinct mutations for the further analysis
- Thoughtful discussion of anticipated results and alternative strategies
- Bone marrow transfer is an elegant approach to evaluate the role of immune effector and non-hematopoietic cell types in the $MERS_{MA}$ lethal phenotype.

Weaknesses:

- DPP4 receptor will be characterized in several cell types. How do different cell types with different DPP4 expression levels contribute to disease outcome?
- Unclear description of pharmacological strategies using acetylsalicylic acid, PAF receptor antagonists and ticlopidine: will they be used in this study? If so, for what reason?
- If DPP4 is important for MERS severity, it is unclear why it was not compared between young and middle-aged lungs, the model used in Project 1.
- Limited number of experiments to characterize $MERS_{MA}$-specific effects on lung vasculature and EC cultures
- No functional tests were proposed to evaluate parameters of lung injury and edema in infected mice.
- From description of research plans it is sometimes unclear which experiments will be done and which experiments are planned as a potential alternative.
- Use of a single DPP4 inhibitor is a minor weakness.
- Studies using models of co-morbidities are under-developed. Plans for analysis of potential mechanisms contributing to MERS infection morbidity and mortality in the models of obesity/diabetes and chronic inflammation were not disclosed.

5. Environment:
Strengths

- Environment at University of Iowa is excellent for this type of research

Weaknesses

- None noted

Renewal: Acceptable

Project-004: Project 4
Project Leader (PL): Perlman, S.

DESCRIPTION (provided by applicant): To prevent deadly CoV infections we propose to study the molecular basis of coronavirus-induced lung edema and its resolution, through the identification of (i) signaling pathways resulting in severe lung disease to inform inhibitors as antiviral candidates; and (ii) virus virulence genes. Deletion of these genes will lead to attenuated vaccine candidates. Three aims are proposed: Aim 1. To determine the factors involved in edema induction and resolution during CoV infection. We have shown that both E and 3a proteins of SARS-CoV, and proteins E and 5 of MERS-

CoV include two sequence domains involved in virulence, one containing a PDZ binding motif (PBM), and another one encoding ion channel (IC) activity. The binding of the SARS-CoV E protein PBM to proteins containing the PDZ motif causes Acute Respiratory Disease Syndrome in infected animals. The importance of the PBM is likely associated with its ability to bind to more than 400 cellular proteins and, therefore, to regulate many cell signaling pathways. We will study the whole-proteome interactions between PBMs in MERS-CoV, and cellular PDZs. This interactome will be the basis for the identification of peptides interfering with PBM-PDZ binding, using peptide libraries. The mechanism of inflammasome activation by MERS-CoV proteins with IC activity will be studied. Edema resolution is possible by two enzymatic activities: epithelial sodium channel activity (ENa+C) and Na+/K+ ATPase that move Na+ ions from the alveolar fluid into the interstitium promoting water elimination. We showed that SARS-CoV E protein binds Na+/K+ ATPase and have postulated that this binding reduces Na+/K+ ATPase activity, leading to lung edema; this will be investigated in this project. Aim 2. We propose to identify viral and host non-coding RNAs involved in MERS-CoV pathogenesis and lung inflammation, as potential targets in antiviral and anti-edema strategies. Aim 3. To develop safe live-attenuated vaccines for MERS-CoV. The construction of MERS-CoVs defective in propagation, and the generation of attenuated, dissemination competent rMERS- CoVs are proposed. Maximizing biosafety and genetic stability of the vaccine candidates are main goals of the project.

CRITIQUE 1

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: While Project 4 seeks to address key aspects in the development of vaccines or antivirals relevant to SARS-CoV or MERS-CoV, this project was not described effectively, as noted below. All three aims have significant concerns and Aim 2 is quite weak. Nevertheless, based on progress over the last funding period, this research could yield important insights into CoV Biology.

1. Significance:
Strengths

- SARS-CoV and MERS-CoV, as well as other potential CoV zoonoses, represent an important threat to human health, and novel strategies for treatment and vaccination are clearly called for.
- The generation of a MERS-CoV able to produce pathology in mice would potentially be very useful to the field.

Weaknesses

- In Aim 1, it is unclear why the proposed approaches are favored over other potential approaches that could be used for identification of PDZ domain proteins relevant to CoV pathogenesis.
- Aim 2 does not demonstrate expert knowledge of the subject area. For example, there are no known miRNAs encoded by any RNA virus, other than retroviruses that go through a DNA intermediate, and CoV is unlikely to be an exception. Requirements for miRNA validation are clear but are not correctly discussed here. Certainly, long ncRNAs might be

important but figuring out their function is very difficult and this problem is not addressed. This aim seems overall somewhat phenomenological.

- Aim 3 seems quite similar to what was proposed for Project 4 in 2010, yet little progress seems to have been made.

2. Investigators:
Strengths

- Dr. Enjuanes has a good record in the study of CoVs. He is productive at the level of specialist journals and well qualified to perform this work.

Weaknesses

- None

3. Innovation:
Strengths

- The availability of animal models for MERS-CoV and SARS-CoV is important and distinguishes this application.

Weaknesses

- The proposed approaches in Project 4 are not especially innovative and, in some cases, seem to be suboptimal.

4. Approach:
Strengths

- The use of novel mouse models for SARS-CoV and MERS-CoV is novel and appropriate.
- The proposed goals, especially in Aims 1 and 3, are important and potentially achievable.

Weaknesses

- Aim 1: The proposed strategy to identify PDZ motifs that bind the viral PDMs seems odd. Short protein motifs encompassing the PDZs may not express efficiently, or mimic the entire protein; expression of the entire protein should be considered. Why not first determine which PDZ-containing proteins are expressed in the lung? Why not use a tandem affinity tag approach instead? The logic of this goal was not entirely clear.
- Inhibitory peptides identified by phage display may not be able to enter the cytoplasm of cells to inhibit PBM:PDZ interactions, as is proposed in the first aim.
- In Aim 1, it may not be wise to propose infecting the lung of an animal suffering from CoV-induced edema and inflammation with an adenovirus vector, as this could potentially exacerbate lung pathology.
- Aim 1: The selection of a MERS-CoV able to cause more pathology in the mouse represents a concern as this could also increase pathogenicity in humans. Gain-of-function mutants in viruses need to be carefully monitored.
- Aim 2: No doubt, miRNAs can affect CoV replication, but this aim is not well considered. If CoV encodes miRNAs, these would be 22±2 nt in size, would have a very discrete 5' end to

maintain seed function, would be loaded into RISC and would derive from the upper ~22 bp of an ~33 bp stem. These issues are not fully considered or discussed.

- Aim 2: Yes, long ncRNAs might also affect CoV replication but simply cataloguing those that go up or down >2-fold is not that useful. How will the function of these lncRNAs be elucidated?
- Aim 2: Yes, it is important to be in a physiological setting but in the context of a mouse undergoing a highly pathogenic respiratory infection, changes in miRNA or lncRNA expression are very likely due to pathology and inflammation, not a direct effect of the virus.
- Aim 2: Antagomirs, generally locked nucleic acid (LNA) based, would bind not just any CoV small RNA but the CoV genome itself with high affinity. As such any inhibitory effect (Fig. 7) is difficult to interpret.
- Aim 2: In terms of miRNAs, those expressed at <100 copies per cell are functionally irrelevant. As cells express a total of ~50,000 miRNAs, this means that miRNAs expressed at less than ~2,000 counts per million are unimportant. So, in Fig. 6, those miRNAs below ~2^{10} can be ignored. This appears to include the majority of miRNA that change expression significantly.
- Aim 3: While the idea of introducing sites for lung miRNAs into CoV to reduce replication and pathogenicity is a good one, the idea of introducing artificial miRNAs that target host genes is not. This could have unexpected consequences and is, in any event, likely to be ineffective. CoV infected cells likely die fairly rapidly after infection and the time available to express an encoded miRNA is therefore quite short. Once made, processed and loaded into RISC, the miRNA can inhibit a target mRNA, but pre-existing levels of the encoded protein are not directly affected. Unless the protein is fairly unstable, you therefore would see only a moderate decline in protein level by the time the infected cell dies.

5. Environment:
Strengths

- The (b)(6); (b)(3):42 U.S.C. 262a(b)(1) (Public Health is well equipped to support the proposed studies.
- The interaction with the groups in the USA is well defined.

Weaknesses

- None

Renewal Comments: The grant overall has made good progress, especially in the development of mouse models for SARS-CoV, and the definition of PBMs in CoV proteins by Project 4 is an important step in defining how CoV causes pathogenesis. On the other hand, efforts in CoV vaccine development over the last project period are somewhat disappointing, with no candidate vaccine yet at hand.

CRITIQUE 2

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: Project 4 seeks to utilize emerging molecular, systems, and cellular biology techniques to elucidate mechanisms of MERS-CoV pathogenesis and develop effective vaccines. The PL is an outstanding molecular and cellular CoV virologist with a productive record of accomplishment in the previous funding period. Three specific aims are proposed. First, a proteomics/systems approach will be used to identify targets for viral-host protein through PDZ domains that have been identified by this group, with the focus toward inflammasome induction by CoV-encoded ion channel activity. In addition, recombinant MERS-CoVs will be generated to support studies of Projects 1-3. Secondly, the role of host- and viral-encoded miRNAs and svRNAs will be examined for interactions conferring MERS-CoV pathogenesis. Lastly, live-attenuated vaccines will be developed and characterized for interactions with various immune cell populations. Overall, the aims proposed are very broad in scope, lack depth of study to support interpretation and are not well integrated. Few details are provided in terms of expected results or, in the case of systems-wide approaches, how various candidate proteins or networks will be parsed and selected for further investigations. The vaccine studies of Aim 3 do not include challenge studies to assess efficacy. Many of the studies proposed appear to be surveys or cataloguing of interactions but do not lead to fundamental new understandings of MERS-CoV pathogenesis.

1. Significance:
Strengths

- MERS-CoV is an emerging global pathogen with little understanding of pathogenesis, and no vaccines or antivirals are available.
- This project may provide recombinant viruses and reagents that could benefit the CoV field.

Weaknesses

- The studies proposed are largely molecular or systems biological in nature and do not propose testing ideas in infection models beyond very cursory studies.

2. Investigators:
Strengths

- The PL is an accomplished CoV virologist, well suited for these studies.
- The scientific team appears outstanding.

Weaknesses

- No comments were provided.

3. Innovation:
Strengths

- The recombinant reverse genetics approaches to generate MERS-CoV with various mutations are highly innovative.
- The proteomics studies of PDZ binding of host proteins could be hypothesis generating.
- The development of E-deficient, replication competent MERS-CoVs as potential vaccines could yield new information for vaccines.

Weaknesses

- Despite the innovative technologies used, it is not clear that new information is forthcoming.

- It is not clear that bioinformatics and biostatistician capabilities that will be required are on hand.

4. Approach:
Strengths

- Aim 1 will provide important recombinant viruses that will be utilized by each of the other projects. The reverse genetics approach will be critical for examining the mutations important in the enhanced pathogenesis of MERS-CoV in mouse adapted models.
- The examination of the role of ion channel activity of protein E has the potential to elucidate a fundamental mechanism of MERS-CoV pathogenesis. This group is well-positioned for this investigation.
- Aim 3 intends to develop vaccines of E-deficient, replication competent viruses which may have utility for immunized protection or even therapeutic vaccines.

Weaknesses

- Overall, each of the aims are too broad in scope and are not well integrated. Each aim in itself could be an entire grant.
- Aim 1 seeks to identify the E protein as important in the resolution of pulmonary edema. It is more likely a cause of the initial fluid transport defect, and not resolution. Regardless, there are no studies proposed to ascertain either scenario. Furthermore, it is known that lung inflammation can lead to pneumonia, and the impact of this in conjunction with the virus-mediated ion transport is not proposed. Other channels such as CFTR and CaCl may be involved as well. There are no studies proposed to actually address ion transport, just Na/K ATPase activity. The role a paracellular fluid regulation is not addressed.
- The peptide screening library studies will almost certainly target many aspects of cell homeostasis, including ion transport, and it is unclear how the investigators will discern mechanisms specific to Na/K ATPase inhibitors. The number of false positives is likely to be very high.
- Aim 2 is largely exploratory, and the mechanisms of small RNA-mediated biological effects are not well explained. The promiscuity of small RNA binding is well recognized, and many miRNAs have large numbers of putative targets. In light of the large numbers of small RNAs that will certainly be identified, and the even larger number of possible targets, it is hard to imagine how the scientific team will be able to focus on targets central to MERS-CoV biology. This aim is the most peripheral to the overall application, and the other studies proposed in Project 4.
- Aim 3 seeks to develop MERS-CoV vaccines from E-deficient, replication competent viruses. The approach does not indicate any studies to examine efficacy in vivo. There is no indication that the molecular approaches for vaccine virus propagation are consistent with regulatory concerns and that the approach could be scaled to large quantities. There are no studies to examine the nature, magnitude and duration of protective immune responses, including neutralizing antibodies critical to protection, and no indication that the scientific team can develop correlates of vaccine-mediated protection *in vivo*.

5. Environment:
Strengths

- The [redacted] appears excellent.

Weaknesses

- It is unclear what international transportation issues will arise with the shipment of recombinant MERS-CoV candidates.

Renewal Comments: The progress from the previous funding period is modest, and the breadth of studies proposed here are received with some skepticism given the progress from the previous period.

CRITIQUE 3

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: This project will use state-of-the-art approaches including bacterial peptide library screening, systems biology, reverse genetics, viral mutagenesis, whole genome proteomics, non-coding and viral RNA screening to identify novel pathologic signaling mechanisms and generate new mechanism-based therapeutics for future MERS-CoV and SARS-CoV. The Project Leader's qualifications are outstanding, and the high capabilities of this group are reflected by stellar publications. The research environment is optimal for this type of research. The significance of the project is high. Some concerns relate to the overly ambitious research agenda and underdeveloped plan for *in vivo* validation of inhibitory peptides and miRNAs in mice infected with MERS-CoV, SARS-CoV and other coronaviruses. Overall, enthusiasm is high for this exciting application.

1. Significance:
Strengths

- Using a systems biology approach for analysis of a whole-proteome interactome with hundreds of interactions that could contribute to virus pathogenesis may lead to identification of previously unknown signaling pathways activated or inhibited during SARS-CoV and MERS-CoV infection.
- Identification of inhibitors affecting essential signaling pathways may lead to development of new anti-coronaviral therapies.

Weaknesses

- Overly ambitious agenda of the project raises some question about successful completion of the whole volume of proposed studies.
- Over-simplified mechanism of CoV-induced pulmonary edema through inhibition of ENaC activity by viral protein E

2. Investigators:
Strengths

- Dr. Enjuanes has an outstanding record in the study of coronaviruses for over 30 years, with almost 200 peer-reviewed publications on this topic.

- He was the first to carry out full-length reverse genetics for a coronavirus, which was subsequently extended to SARS-CoV. In the previous funding cycle he generated a prototype SARS-CoV vaccine.
- The investigator has made significant contributions to our understanding of E protein function.
- Successful collaboration of Drs. Enjuanes and Perlman is documented by 10 joint publications relevant to the application.

Weaknesses

- None noted

3. Innovation:
Strengths

- Identification of new peptide candidates to block potentially pathogenic interactions between PDZ-binding motifs of viral proteins (E, 3a, 5) and host PDZ-containing cellular proteins is an innovative approach to treat SARS-CoV and MERS-CoV infections. These studies may provide novel information about key cell processes hijacked by virus and required for virus replication immune evasion or other pathological changes.
- Identification of miRNA and svRNA involved in host-pathogen interactions may be a druggable target.

Weaknesses

- Viral vaccine development was proposed in the previous funding cycle. How new viral vaccines are expected to match with the efficacy of previously generated vaccines was not discussed.

4. Approach:
Strengths:

- Systems biology approach to characterize host proteins interacting with viral PBMs and predict their functional significance
- Innovative strategies to identify new peptide inhibitors
- Engineering of new MERS-CoV live attenuated vaccines is state-of-the-art.

Weaknesses:

- Over-ambitious agenda. The study proposes analysis of whole-proteome interactions between PBMs in MERS-CoV and 400 cellular PDZ containing candidates, and to identify peptides interfering with PBM-PDZ binding, using peptide libraries.
- Overexpression of ENaC in lung is proposed as a rescue alternative to peptide inhibition of E-protein binding to ENaC. This approach is not feasible as a therapeutic strategy.
- No functional assays were proposed to evaluate edema formation and effects of blocking peptides.
- Validation of inhibitory peptide candidates during screening of 10^6 peptides in peptide library is proposed to be performed in animal models to test effects on resolution of MERS and

other coronavirus diseases. This approach, as described, is unrealistic and misses intermediate HTS or MTS steps in cell based models.

- Similarly, validation of ARDS-related miRNAs differentially expressed in MERS-infected lungs from 31 annotated and 386 non-annotated small RNAs detected in preliminary studies will be performed in SARS-CoV-infected mice. The outcome of such screening is not clear.
- Over-simplified view of ARDS resolution in MERS-CoV-infected lungs via activation of ENaC activity

5. Environment:
Strengths

- The scientific environment and (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism Preparedness and is exceptional to perform the proposed experiments. This is documented by a number of publications over the past years.

Weaknesses

- Programmatic links between research agenda of this project with other projects are not obvious.

Renewal: Acceptable

CRITIQUE 4

Significance:
Investigator(s):
Innovation:
Approach:
Environment:

(b)(6)

Overall Impact: This application is from a highly experienced investigator. The project follows on from previous work on SARS-CoV to study the effects of the E and accessory genes of MERS-CoV. The investigators have identified both PDZ-binding and ion channel activity, which act as virulence factors in the context of infection. This will be explored in Aim 1 using the new mouse model of MERS. Aim 3 details the creation of safe live-attenuated vaccines for MERS-CoV. While this is an important area of study some of the approaches are unclear and do not seem to represent much of an advance from the previous PPG. Aim 2 is relatively speculative, but is potentially of high impact.

1. Significance:
Strengths

- The creation of safe live-attenuated vaccines for MERS-CoV is a very important goal.

Weaknesses

- No comments were provided.

2. Investigators:
Strengths

- Dr. Enjuanes is a very accomplished virologist with much expertise with coronaviruses.

Weaknesses

- No comments were provided.

3. Innovation:
Strengths

- The approaches used are innovative, but there are concerns with practicality.

Weaknesses

- No comments were provided.

4. Approach:
Strengths

- Approaches to generate novel live attenuated vaccines are a strength of this application.

Weaknesses

- Many of the approaches used for Aim 2 appear not to be well-conceived.

5. Environment:
Strengths

- The environment is excellent.

Weaknesses

- No comments were provided.

Admin-Core-001: Administrative Core
Core Leader (CL): Perlman, S.

DESCRIPTION (provided by applicant): The Administrative Core will coordinate the activities of the projects and the Animal/Virology Core. It will be responsible for encouraging the exploration of new research directions and for arranging consultations with the Internal and External Advisory Committees. It will be responsible for preparing scientific progress reports and renewal applications. It will organize the monthly meetings of the projects at which research progress is presented. It will be responsible for budget allocation and for monitoring expenses. It will allocate travel funds. Two of the projects of the PPG are located offsite, in (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Thus, important functions of the Administrative Core will be to facilitate discussions between the projects by arranging videoconferences between the Iowa, Loyola and projects and to coordinate two meetings per year at the University of Iowa of all of the Project Directors. In summary, the Administrative Core will have a critical role in making sure that the PPG is efficiently organized and is productive as possible.

(b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism Preparedness and Response Act)

CRITIQUE 1

Strengths

- Dr. Perlman has demonstrated outstanding leadership of the PPG as evidenced by explorations into new research directions, adapting to new urgencies in the field, establishing new collaborations and keeping the project directors engaged. He will continue to devote (b)(4); (b)(6) effort, which is justified.
- The core supports a PPG administrator at (b)(4); (b)(6) effort as a liaison to the University business office in charge of finances, and an administrative assistant at (b)(4); (b)(6) effort, responsible for coordinating meetings and other non-financial aspects. The core is physically located in the vicinity of the PLs, allowing frequent contact. Scientific and administrative responsibilities, including financial accounting and allocation are concisely laid out.
- Chain of responsibility and conflict resolution are clear.
- The core fulfills the important role of arranging monthly scientific meetings between the project directors forming the executive committee, an annual meeting with an internal advisory committee as well as external advisory committee. The monthly meeting is via Skype and Dr. Enjuanes is expected to visit twice a year.
- Budgetary items such as travel expenses, publication costs, communication, and office supplies are centralized in this core.

Weaknesses

- The Administrative Core should also be responsible for monitoring updated guidelines and compliance of select agent research.

CRITIQUE 2

Strengths

- This core is critical for coordination of the overall program.
- Dr. Perlman has substantial experience in managing large collaborative projects.
- The financial oversight is important for determining whether other projects may be impacted by budgetary issues with other projects.
- Coordination is key to make sure the projects are moving forward in an integrated manner.

Weaknesses

- The Administrative Core does not appear to consider some of the complexity involved in the movement of recombinant MERS-CoVs. Assurances of safety during transport are not acknowledged. It is unclear if couriers are in place to handle such shipment.

Renewal Comments: This application represents a renewal to a third cycle of PPG originally submitted to study SARS-CoV. The group appropriately has transitioned the focus to the emerging MERS-CoV, and some of the effort in the previous grant has been used to create mice with the human DPP4 protein receptor for the MERS-CoV. The progress in the previous period is good to excellent, but not outstanding, but transition to MERS-CoV and the effort in this transition is appreciated. Together with adaptation of the MERS-CoV in mouse models, this group has generated reagents critical for advancing our knowledge of this emerging pathogen. Beyond the generation of more pathogenic mouse models, it is unclear from the previous funding period what was learned from the study of SARS-CoV in mouse models that can be applied to the study of MERS-CoV. In some ways, this application is reiterative in regards to its approach to previous awards. It is plausible that nothing can

be gleaned from SARS-CoV, but if so, then this grant application should focus on identifying what is similar about these two CoVs. There is concern that the MERS-CoV epidemic will slip into oblivion just as SARS-CoV has done, and by the time this grant cycle is complete, we will know much about a virus that may never return. Thus, it is critical for this group to take a leadership role in understanding overarching concepts on CoV biology and pathogenesis, and not focus on specific mutations used in mouse adaptation.

Core-001: Animal/Virology Core
Core Leader (CL): Perlman, S.

DESCRIPTION (provided by applicant): Animal/Virology Core Laboratory is directed by a senior, experienced postdoctoral fellow, Dr. Rudragouda Channappanavar, under the guidance of the Core Director, Dr. Perlman. The Core will be primarily based in a University of Iowa BSL-3 laboratory that is equipped for tissue culture and animal work. Personnel working in the Core are experienced in virological and cell culture techniques and in handling, infecting and analyzing mice. The Animal/Virology Core has several functions that are critical for success of this P01 grant. 1. It will maintain colonies of hDPP4-knock-in mice. 2. It will propagate and titer non-recombinant and recombinant mouse- adapted and human strains of MERS-CoV and SARS-CoV and will infect mice with these viruses. 3. It will monitor mice for clinical disease and weight loss and will harvest tissue. 4. The Core will prepare samples for histological and immunohistochemical analysis and will prepare RNA and protein from infected tissue. 5. The Core will analyze mice for virus-specific antibody and T cell responses. 6. The Core will develop recombinant MERS-CoV and SARS-CoV using BAC DNA clones prepared by the individual projects. The Core will also be responsible for ensuring that protocols for working with animals and for working under BSL-3 laboratory conditions are up-to-date. While the Core will teach members of the PPG methods important for analysis of mice under BSL-3 conditions, it will primarily be responsible for performing most of these analyses. The Core will provide reagents and perform common assays efficiently, thereby standardizing results and enhancing synergistic interactions. Additionally, all projects will interact with the Core, thereby facilitating interactions between members of the PPG. By providing these services, the Core will allow Program investigators to focus on issues related to MERS and SARS pathogenesis and to the development of anti-viral therapies and vaccines.

CRITIQUE 1

OVERALL IMPACT : The Animal/Virology Core will provide essential services to all 4 projects, growing and regenerating MERS-CoV and stocks, titering these stocks, infecting mice with these viruses, and providing monitoring after infection, including preparation and analysis of samples. This arrangement is well-justified and should make results from the various projects easier to compare, increase reproducibility, and lower overall costs. The scientific leadership and experience of the personnel is a major strength of the Core. There is some concern that the Core is under-resourced in personnel considering the number of mice needed for the experiments proposed by various projects.

Strengths

- The core makes major contributions to Projects 2-4. The core will be involved in the design and performance of the mouse-based experiments for these projects. The core will make a more limited contribution to Project 1, as Project 1 personnel will be performing the bulk of the work on their mouse-based experiments. The core's involvement in all 4 projects will facilitate collaborative efforts.

- The scientific leadership and experience of the personnel is a major strength of the Animal/Virology Core. Dr. Perlman is a leading coronavirologist and viral immunologist. Dr. Channappanavar has worked in the BSL-3 core for 3.5 years under the previous iteration of this Program Project. His involvement in the BSL-3 experiments in Project 1 will ensure that there is consistency in the design and execution of mouse-based experiments for all projects. A research assistant, [redacted] has 6 years of experience in BSL-3 and with coronaviruses. [redacted] a board certified veterinary pathologist, has been involved for the past several years in examining, interpreting and scoring slides of MERS-CoV and SARS-CoV-infected lungs and will provide pathology services related to the core.
- Standardization of experimental design, biologic reagents, and assays employed for mouse experiments will make results from the various projects easier to compare, increase reproducibility, and should lower overall costs.

Weaknesses

- Studies utilizing 1000 mice per year are proposed. In addition, Project 1 will use another [redacted] It is not clear that the personnel resources devoted to the Animal/Virology Core are adequate to support this level of activity, particularly since Dr. Channappanavar will devote [redacted] calendar months to the core lab, with the remainder of his effort devoted to Project 1, leaving the Research Assistant 2, [redacted] to do the vast majority of the work.
- Related to the previous concern, it is stated that Dr. Channappanavar will spend [redacted] effort on the project, but in actuality, he will spend as much time as needed on the Core since his project, funded primarily in the context of Project 1, involves extensive use of the BSL-3 laboratory. This statement suggests that Dr. Perlman is aware that additional time devoted to the core is likely to be required. A more precise estimate of time and effort should be provided and a plan to do this without detracting from Project 1 should be developed.
- Additional assays, such as pulse oximetry, and equipment to directly measure pulmonary function would enhance the core.

Renewal: Acceptable.

Comments: For the prior submission the focus of the core was on analyses of SARS-CoV infected mice. With the outbreak of MERS in 2012 the core refocused on generating mouse models for MERS and on generating a mouse adapted strain of MERS-CoV. These two goals have been achieved and are largely the basis for the current submission.

CRITIQUE 2

Strengths

- The Animal/Virology core is clearly an essential component of several of the projects and, as such, is certainly needed if this project is to succeed.
- The use of a single core to perform all the various assays in mice is efficient and enhances reproducibility.

Weaknesses

- As in the previous submission, the issue of how many cages there are for mice is not clearly addressed. The application states that there are [redacted] at present but that

(b)(4) while the budget calls for 100 cages at any time and it is not clear if this includes the uninfected hDPP4 knock-in mice mentioned on page 174. Therefore, the current size of this core is clearly not adequate as described.

(b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heat Security and Bioterroris Preparedness and Response Act

- As previously, the personnel assigned to this core are Dr. Perlman as overall supervisor with (b)(4); (b)(6) effort and the Core laboratory director is Dr. Channappanavar, also with (b)(4); effort. Finally, is assigned to work (b)(4); of the time. Although it is stated that Dr. Channappanavar can increase his effort as required, this still seems like a lot of work for one person and one back-up, if they are going to infect mice, monitor 100 cages, generate viral stocks, etc.

Renewal Comments: The core was a key contributor to the progress made during the last budget period.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: UNACCEPTABLE (CODE 44)

Project 1: UNACCEPTABLE. HS EXEMPTION 4 is claimed, but is found to be inappropriate. Exemption 4 applies only to existing data/specimens which are publicly available and un-linkable to individuals. Leukocytes/LRS cones are not considered existing specimens, as is stated in the Protection of Human Subjects section of this application (page 224): “We submit a request for an LRS cone to the Blood Bank. Personnel in the Blood Bank call the laboratory when the cone is available.”

In addition, although leukocytes/LRS cones are provided by the University of Iowa Blood Bank to PPG investigators “anonymous to our laboratory personnel,” verification that identifying information cannot be derived from the “anonymous numbers of subjects” and/or will not be provided to PPG investigators under any circumstances is required. If such documentation is provided, Protection of Human Subjects will be Not Applicable (CODE 10) based upon current NIH Guidelines.

Project 2: NOT APPLICABLE

Project 3: UNACCEPTABLE. HS EXEMPTION 4 is claimed, but is found to be inappropriate. Exemption 4 applies only to existing data/specimens which are publicly available and un-linkable to individuals. Leukocytes/LRS cones are not considered existing specimens, as is stated in the Protection of Human Subjects section of this application (page 224): “We submit a request for an LRS cone to the Blood Bank. Personnel in the Blood Bank call the laboratory when the cone is available.”

In addition, although leukocytes/LRS cones are provided by the University of Iowa Blood Bank to PPG investigators “anonymous to our laboratory personnel,” verification that identifying information cannot be derived from the “anonymous numbers of subjects” and/or will not be provided to PPG investigators under any circumstances is required. If such documentation is provided, Protection of Human Subjects will be Not Applicable (CODE 10) based upon current NIH Guidelines.

Primary airway cells will be obtained from the University of Iowa Cell Culture Core Repository from anonymized donors and a Usage Agreement is provided. This Usage Agreement includes conditions stipulated by the University of Iowa IRB stating clearly that subjects' identifying information will not be provided under any circumstances (page 331). Protection of Human Subjects is Not Applicable to these samples (CODE 10) based upon current NIH Guidelines.

Project 4: UNACCEPTABLE. HS EXEMPTION 4 is claimed, but is found to be inappropriate. Exemption 4 applies only to existing data/specimens which are publicly available and un-linkable to individuals. Leukocytes/LRS cones are not considered existing specimens, as is stated in the Protection of Human Subjects section of this application (page 224): "We submit a request for an LRS cone to the Blood Bank. Personnel in the Blood Bank call the laboratory when the cone is available."

In addition, although leukocytes/LRS cones are provided by the (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Preparedness and to PPG investigators "anonymous to our laboratory personnel," verification that identifying information cannot be derived from the "anonymous numbers of subjects" and/or will not be provided to PPG investigators under any circumstances is required. If such documentation is provided, Protection of Human Subjects will be Not Applicable (CODE 10) based upon current NIH Guidelines.

Admin Core-001/Administrative Core: NOT APPLICABLE

Core-001 / Animal/Virology Core: NOT APPLICABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE (CODE 4A)

Project 1: ACCEPTABLE. Donors are anonymous, so inclusion of women is not known.

Project 2: NOT APPLICABLE

Project 3: ACCEPTABLE. Donors are anonymous, so inclusion of women is not known.

Project 4: ACCEPTABLE. Donors are anonymous, so inclusion of women is not known.

Admin Core-001/Administrative Core: NOT APPLICABLE

Core-001 / Animal/Virology Core: NOT APPLICABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE (CODE 4A)

Project 1: ACCEPTABLE. Donors are anonymous, so inclusion of minorities is not known.

Project 2: NOT APPLICABLE

Project 3: ACCEPTABLE. Donors are anonymous, so inclusion of minorities is not known.

Project 4: ACCEPTABLE. Donors are anonymous, so inclusion of minorities is not known.

Admin Core-001/Administrative Core: NOT APPLICABLE

Core-001 / Animal/Virology Core: NOT APPLICABLE

INCLUSION OF CHILDREN PLAN: ACCEPTABLE (CODE 3A)

Project 1: ACCEPTABLE. Children are excluded from leukocyte/LRS cone studies, as they are not eligible to serve as anonymous donors.

Project 2: NOT APPLICABLE

Project 3: ACCEPTABLE. Children are excluded from leukocyte/LRS cone studies, as they are not eligible to serve as anonymous donors.

Project 4: ACCEPTABLE. Children are excluded from leukocyte/LRS cone studies, as they are not eligible to serve as anonymous donors.

Admin Core-001/Administrative Core: NOT APPLICABLE

Core-001 / Animal/Virology Core: NOT APPLICABLE

VERTEBRATE ANIMAL: UNACCEPTABLE (CODE 44)

Project 1: ACCEPTABLE. Procedures for the care and use of the mice were evaluated and are acceptable. Comment: The application states that mice that experience 30% weight loss will be euthanized. 25% percent weight loss is the more standard indication for euthanasia in mice.

Project 2: NOT APPLICABLE. No live vertebrate animals will be used in the proposed study. The Animal/Virology Core will be responsible for all mouse-based experiments.

Project 3: NOT APPLICABLE. No live vertebrate animals will be used in the proposed study. The Animal/Virology Core will be responsible for all mouse-based experiments.

Project 4: UNACCEPTABLE. While the use of animals at the University of Iowa is well described and acceptable, Project 4 states that (b)(4) (b)(6); (b)(4); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and and utilized for vaccine and virulence studies, but no detailed information is provided regarding the care of these animals. This is unacceptable.

Admin Core-001/Administrative Core: NOT APPLICABLE. No live vertebrate animals will be used in the proposed study.

Core-001 / Animal/Virology Core: ACCEPTABLE. Procedures for the care and use of the mice were evaluated and are acceptable. Comment: The application states that mice that experience 30% weight loss will be euthanized. 25% percent weight loss is the more standard indication for euthanasia in mice.

BIOHAZARDS COMMENT: ACCEPTABLE.

Project 1: ACCEPTABLE. The plan to prevent risks during handling of biohazard materials or samples is adequate. All work with SARS-CoV and MERS-CoV will be carried out under BSL-3 conditions at the University of Iowa. Possession and use is monitored by responsible officials and biosafety officers. Access is restricted to employees with appropriate government clearance and BSL-3 training. All relevant federal guidelines are followed.

Project 2: ACCEPTABLE. The plan to prevent risks during handling of biohazard materials or samples is adequate. Comment: It is unclear if the MERS-CoV cloning proposed in Project 2 is adequately covered by the BSL2 facilities at Loyola University.

Project 3: ACCEPTABLE. The plan to prevent risks during handling of biohazard materials or samples is adequate. All work with MERS-CoV will be carried out under BSL-3 conditions at the University of Iowa. Possession and use is monitored by responsible officials and biosafety officers. Access is restricted to employees with appropriate government clearance and BSL-3 training. All relevant federal guidelines are followed.

Project 4: ACCEPTABLE. The plan to prevent risks during handling of biohazard materials or samples is adequate. All work with SARS-CoV and MERS-CoV will be carried out under BSL-3 conditions at the (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Preparedness and Response Act). Possession and use is monitored by responsible officials and biosafety officers. Access is restricted to employees with appropriate government clearance and BSL-3 training. All relevant federal guidelines are followed. Comment: Additional information regarding international shipment of highly pathogenic recombinant viruses is needed.

Admin Core-001/Administrative Core: NOT APPLICABLE

Core-001 / Animal/Virology Core: ACCEPTABLE. The plan to prevent risks during handling of biohazard materials or samples is adequate. All work with SARS-CoV and MERS-CoV will be carried out under BSL-3 conditions at the University of Iowa. Possession and use is monitored by responsible officials and biosafety officers. Access is restricted to employees with appropriate government clearance and BSL-3 training. All relevant federal guidelines are followed.

FOREIGN INSTITUTION: JUSTIFIED. Dr. Luis Enjuanes, of Centro Nacional de Biotecnologia in Madrid, Spain, made many contributions to the PPG in the previous funding cycle. His unique expertise in developing recombinant CoV, vaccine development and evaluation, and modulation of the innate immune response is critical to the success of Project 4.

SELECT AGENTS: UNACCEPTABLE.

Project 1: ACCEPTABLE. The plan to monitor and contain select agents is adequate. All work with SARS-CoV will be carried out at University of Iowa within BSL-3 laboratories registered with, inspected and approved by CDC. The PL, Dr. Perlman, is Select Agent approved. Access is restricted to employees with FBI and CDC clearance and appropriate BSL-3 training. Safety, containment and security of Select Agents are governed by procedures based upon CDC protocols and approved by the Institutional Biosafety Committee. Federal guidelines are followed for transfer, including filing of appropriate permits.

Project 2: NOT APPLICABLE.

Project 3: NOT APPLICABLE.

Project 4: ACCEPTABLE. The plan to monitor and contain select agents is adequate. All work with SARS-CoV will be carried out at the (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Preparedness and Response Act) (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Preparedness and Response Act) (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Preparedness and Response Act). Facilities meet all European regulations on biosafety with infectious and recombinant antigens. Drs. Enjuanes (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and Bioterrorism Select Agent approved. Safety, containment and security of select agents are governed by procedures approved by the Institutional Biosafety Committee and the European Commission. Access is limited to employees with appropriate BSL-3 training and evaluation. Federal guidelines are followed for transfer, including filing of appropriate permits.

Admin Core-001/Administrative Core: NOT APPLICABLE.

Core-001 / Animal/Virology Core: UNACCEPTABLE. SARS-CoV is a Select Agent which will be handled in the Core, but no Select Agent section is included in this section of the application.

DATA SHARING PLAN: ACCEPTABLE

MODEL ORGANISMS SHARING PLANS: NOT APPLICABLE

GENOME WIDE ASSOCIATION STUDIES: NOT APPLICABLE

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: ACCEPTABLE

BUDGETARY OVERLAP: None noted

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested. Comment: There appears to be a discrepancy in the budget request for Dr. Enjuanes' salary, between the budget pages themselves and the budget justification. This may be an administrative error.

Footnotes for 2 P01 AI060699-11; PI Name: Perlman, Stanley

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual

reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

The roster for this review meeting is displayed as an aggregated roster that includes reviewers from multiple AI Special Emphasis Panels of the Investigator Initiated Program Project Grant Applications for the 2016/10 council round.
This roster for AI is available at:
http://public.era.nih.gov/pubroster/Reports?DOCTYPE=SEP&DESFORMAT=PDF&AGENDA_SEQ_NUM_P=308103

Year 1

	Proj 1	Proj 2 (Loyola)	Proj 3 (McCray)	Proj 4 (Spain)	Admin	Animal	Total
Direct Cost	262,000	375,000	250,000	270,000	100,000	200,000	1,457,000
F&A (52.5%)	150,675	-	131,250	-	52,500	105,000	439,425
Total Cost	412,675	375,000	381,250	270,000	152,500	305,000	1,896,425

Year 2

	Proj 1	Proj 2 (Loyola)	Proj 3 (McCray)	Proj 4 (Spain)	Admin	Animal	Total
Direct Cost	269,860	386,250	257,500	278,100	103,000	206,000	1,500,710
F&A (52.5%)	141,677	-	135,188	-	54,075	108,150	439,089
Total Cost	411,537	386,250	392,688	278,100	157,075	314,150	1,939,799

Year 3

	Proj 1	Proj 2 (Loyola)	Proj 3 (McCray)	Proj 4 (Spain)	Admin	Animal	Total
Direct Cost	277,956	397,838	265,225	286,443	106,090	212,180	1,545,731
F&A (52.5%)	145,927	-	139,243	-	55,697	111,395	452,262
Total Cost	423,883	397,838	404,468	286,443	161,787	323,575	1,997,993

Year 4

	Proj 1	Proj 2 (Loyola)	Proj 3 (McCray)	Proj 4 (Spain)	Admin	Animal	Total
Direct Cost	286,294	409,773	273,182	295,036	109,273	218,545	1,592,103
F&A (52.5%)	150,305	-	143,420	-	57,368	114,736	465,830
Total Cost	436,599	409,773	416,602	295,036	166,641	333,282	2,057,933

Year 5

	Proj 1	Proj 2 (Loyola)	Proj 3 (McCray)	Proj 4 (Spain)	Admin	Animal	Total
Direct Cost	294,883	422,066	281,377	303,887	112,551	225,102	1,639,866
F&A (52.5%)	154,814	-	147,723	-	59,089	118,178	479,804
Total Cost	449,697	422,066	429,100	303,887	171,640	343,280	2,119,671

Totals *see below *see below

	Proj 1	Proj 2 (Loyola)*	Proj 3 (McCray)	Proj 4 (Spain)*	Admin	Animal	Total
Direct Cost	1,390,994	1,990,926	1,327,284	1,433,467	530,914	1,061,827	7,735,411
F&A	743,397	-	696,824	-	278,730	557,459	2,276,410
Total Cost	2,134,390	1,990,926	2,024,108	1,433,467	809,643	1,619,286	10,011,820

Direct Cost	1,305,525	1,303,152	Direct Cost	
F&A (52.5%)	685,401	130,315	F&A (10%)	
Total Cost	1,990,926	1,433,467	Total Cost	

OTHER SUPPORT

Perlman, Stanley
ACTIVE

5 R01 NS036592-17 (Perlman) 09/01/1997 - 01/31/2017
NIH/NINDS $218,750
Role of CD4 T cell response in MHV-induced Demyelination. (b)(6); (b)(4)

The major goals of this project are to investigate the differences between pathogenic primary and protective memory T cells responding to a virus epitope and to further characterize regulatory T cells that recognize the same virus epitope.

Overlap: None

5 P01 AI060699-09 (Perlman) 08/01/2004 - 06/30/2017 (NCE)
NIH/NIAID $1,228,721 $1,223,358
SARS-CoV-host cell interactions and vaccine development
Animal Core (Perlman)
Project 1 (Perlman)
Administrative Core (Perlman) (b)(6); (b)(4)

The major goals of Project 1 are: 1. To determine the basis of poor outcomes in young BALB/c mice, 2. To determine if an inefficient T cell response is the basis for severe disease in aged mice; 3. To determine the basis of the poor activation of the innate immune response in aged C57BL/6 mice. This is the grant that is under consideration.

Overlap: The present application is a renewal of this grant.

HHSN272201000013I (Nwoguh) 09/15/2014 - 10/15/2016
NIH/NINDS via Public Health of England $104,973
Adenovirus Mouse Model for Evaluation of Medical Countermeasures against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (b)(6); (b)(4)

The proposed work is to develop a standardised strategy for a small animal model system in which 'proof of concept' between different MERS-CoV countermeasures may be evaluated and comparable data generated to assess efficacy, delivery strategy and utility of countermeasures.

Role: Task PI

Overlap: None.

(b)(6); (b)(4)
Pathogenesis of Demyelination in Mice Infected with a Neurotropic Coronavirus

The major goals of this project are: 1. To determine the role of Treg-expressed cytokines and of memory Tregs in JHMV-infected mice and to use the topoisomerase inhibitor, etoposide to improve disease outcomes. 2. To determine why the absence of PGD_2 signaling results in increased mortality in JHMV-infected mice.

Overlap: None.

PHS 398 OTHER SUPPORT-T. Gallagher

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

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Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

CURRENT:

P01 AI 060699 Perlman, S. (P.I.) 07/01/2011 to 06/30/2016 NCE 07/01/2016 to 06/30/2017
SARS-CoV Host Cell Interactions and Vaccine Development
Gallagher, T., Project 4 P.I.
The major goals of this project are to dissect SARS-CoV and related coronaviruses for their utilization of entry cofactors. This P01 project is in collaboration with laboratories focused on animal models for Middle East Respiratory Syndrome coronavirus – induced disease, immune responses to this virus, and development of virus vaccines. The major goals of project 4 (Gallagher) are to identify host determinants that allow for MERS coronavirus cell entry.

OTHER SUPPORT

McCRAY, Paul B. Jr.

ACTIVE

5 P30 ES 005605 (Thorne) 04/01/07 – 03/31/17 (b)(6); (b)(4)
NIH $15,000
Environmental Health Sciences Research Center
To develop and provide resources and expertise in the application of genetic and genomics analysis approaches for faculty in the EHSRC.

5 P01 HL 091842 (Welsh) 09/01/08 – 06/30/18 (b)(6); (b)(4)
NIH $243,814
Pgm Title: Airway physiology and pathophysiology in a porcine CF model
Project 2: Early lung inflammation in a porcine model of cystic fibrosis
The goals of the project are 1) Does the fetal porcine CF lung exhibit inflammation in the absence of infection? 2) Does the neonatal porcine CF lung develop inflammation spontaneously or in response to infection? 3) How does loss of CFTR function alter specific innate immune functions in the CF pig?

5 P01 AI 060699 (Perlman) 07/19/11 – 06/30/17 (NCE) (b)(6); (b)(4)
NIH $233,312
PPG: SARS-CoV-host cell interactions and vaccine development
Project 3. The aims are: 1. Determine how airway epithelial cell ACE2 expression is affected by SARS-CoV infection. 2. Characterize the physiologic function of airway epithelial ACE2 during SARS-CoV infection. 3. Identify enzyme activity-independent ACE2 functions that modulate host defense responses.
Role: Director, Project 3

5 P01 HL 051670 (McCray) 08/01/15 – 05/31/20 (b)(6); (b)(4)
NIH $1,471,805
Gene Therapy for Cystic Fibrosis Lung Disease
Project 1 – Gene Transfer to Porcine Respiratory Epithelia with Viral Vectors—McCray (PI)
The work from this project is focused on using gene therapy vectors to learn if it is possible to correct key features of cystic fibrosis lung disease. These include mucociliary transport (MCT) and antibacterial activity in airway surface liquid (ASL).

5 R01 HL118000 (McCray) 02/01/14 – 8/31/18 (b)(6); (b)(4)
NIH/NHLBI $1,546,377
Mining a microRNA Regulated Gene Network to Rescue CFTR-DeltaF508 Function
The goals of the project are: 1) Identify the key SIN3A-regulated gene products responsible for CFTR-ΔF508 rescue. 2) Use the genomic signatures of SIN3A-mediated CFTR-ΔF508 rescue to identify therapeutic agents. 3) Use lead compounds to rescue CFTR function in newborn pigs with the ΔF508 mutation.

2 P30 DK 054759 (Engelhardt) 04/01/15 – 03/31/20 (b)(6); (b)(4)
NIH/NIDDK $494,110
Center for Gene Therapy of Cystic Fibrosis and Other Genetic Diseases
The Center's goal has been to provide investigators with the opportunity to improve and/or expand their gene therapy-based research.
The goals of the project are 1) Does the fetal porcine CF lung exhibit inflammation in the absence of infection? 2) Does the neonatal porcine CF lung develop inflammation spontaneously or in response to infection? 3) How does loss of CFTR function alter specific innate immune functions in the CF pig?

(b)(6); (b)(4)

The aims of this project are: 1) Design, test, and select CRISPR-Cas9 sgRNAs that effectively target the *CFTR* locus; 2) Identify the optimal delivery strategy to achieve efficient *CFTR* locus editing; 3) Use CRISPR-Cas9 gene editing to correct the CF defects in airway epithelia. Completion of these proof-of principle studies will provide new information towards the long-term goal of restoring CFTR function airway epithelia.

OVERLAP
None

Program Director/Principal Investigator: Perlman, Stanley / Enjuanes, Luis
(Last, first, middle)

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

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Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL
ACTIVE/PENDING

Project Number (Principal Investigator) Source Title of Project *(or Subproject)* The major goals of this project are…	Dates of Approved/Proposed Project Annual Direct Costs	Person Months (Cal/Academic/ Summer)

OVERLAP *(summarized for each individual)*

ENJUANES, L.

ACTIVE
IMI JU Ref. No 115760 Enjuanes (PI) 01-03-2015 to 28-02-2020 (b)(6); (b)(4)
Founding Agency: European Union, Annual Direct Costs: 70,000 €

Title: "Zoonosis anticipation and preparedness initiative" ZAPI
ZAPI will deliver proof-of-concept on intervention strategies by focusing on three viruses, representative of currently emerging infectious pathogens, SBV, RVFV and MERS-CoV, for the control of future emerging viruses.

(b)(4); (b)(6)

Enjuanes(PI) (b)(4); (b)(6)

(b)(4); (b)(6)

(b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism

ACTIVE
IMI JU Ref. No 115760 Enjuanes (PI) 01-03-2015 to 28-02-2020 (b)(4); (b)(6)
Founding Agency: European Union, Annual Direct Costs: 70,000 €

Title: "Zoonosis anticipation and preparedness initiative" ZAPI
ZAPI will deliver proof-of-concept on intervention strategies by focusing on three viruses, representative of currently emerging infectious pathogens, SBV, RVFV and MERS-CoV, for the control of future emerging viruses.

(b)(4); (b)(6)

Enjuanes(PI) (b)(4); (b)(6)

(b)(4); (b)(6)

(b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism

(b)(4); (b)(6)

Enjuanes(PI) (b)(4); (b)(6)

(b)(4); (b)(6)

Overall response to previous reviews.

We thank the reviewers for their comments and for the substantial time and effort required for the review. The reviewers recognized the collaborative nature of this Program Project grant and that we made substantial progress during the previous funding period. In the summary, it was noted that the reviewers were concerned that data interpretation was complex and that supportive data, technical limitations and data analysis were inadequately discussed. The reviewers also were concerned that the program project was overly ambitious. In response, we note that we largely completed all of the specific projects proposed in the previous rendition of the grant and made substantial progress in research related to the Middle East Respiratory Syndrome. However, we also agree with the reviewers that some of the projects were overly ambitious, and have removed some subaims and even complete aims, to make completion more feasible.

Administrative Core: Response to reviewers.

The reviewers were positive in their comments about the Administrative Core, but were concerned about two specific issues.

1. Monitoring and implementing updated guidelines for select agent research.

Response: We neglected to include this information in the duties of the Administrative Core and will do in the revised application.

2. Describing details of shipping MERS-CoV in sufficient detail.

Response: We successfully shipped SARS-CoV during the last funding period so are well aware of the issues involved. We will make this clearer in the revised application.

Animal/Virology Core:

The reviewers raised two important issues concerning the Animal/Virology Core.

1. *Personnel resources devoted to the Core*.

Response: In the original application, we proposed staffing the Core with a full time research assistant and a senior postdoctoral fellow ((b)(6); effort). We will not change this personnel allocation in the resubmission because of the 1900 mice/year (Project 1-900 mice; Core-1000 mice) used in the project, most will be housed in our (b)(4). In reality, we never have had more than (b)(4 (b)(4) The Core personnel will monitor mice, infect them as required and help develop recombinant viruses (BAC clones used for generating recombinant viruses will be generated by the individual projects). Projects 1 and 3 personnel will process and analyze all of the mice for their proposed experiments. Project 2 proposes a limited number of mouse-based experiments and we anticipate no difficulties in completing these experiments with the core personnel in place. Similarly, the Core will also perform a limited number of experiments for Project 4, mostly involving immune responses to MERS-CoV, with other assays performed at Project 4's home laboratory (b)(6); (b)(3):42 U.S.C. § 262(a)(h); This division of labor will be made more explicit in the revised application.

2. *Pulse oximetry and other measures of respiratory function would enhance the core*.

Response: We agree that additional measures of respiratory function would be useful, but we do not have the appropriate equipment in the BSL3 laboratory at present. Dr. McCray, PL of Project 3, is a pulmonologist and well versed in use of this equipment so data interpretation would not be a problem if the equipment were available.

Human subjects:

We will provide verification that identifying information cannot be derived from the "anonymous numbers of subjects" and/or will not be provided to PPG investigators under any circumstances.

Project 1-S. Perlman-Introduction.

1. A general comment was that the project was over ambitious and that studies of two viruses may dilute efforts and reduce the chance for success. In some cases, insufficient rationale was provided and data interpretation was scanty.

Response*:* In the revised application, we will decrease the number of proposed experiments and provide greater discussion of data interpretation and alternative approaches. The proposal has also been extensively rewritten so that the aims are better integrated and less diffuse.

2. *The investigators have limited expertise in analytical methods and approaches of phospholipid quantification, characterization, data analysis and interpretation.*

Response: We have enlisted [(b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Health Security and Bioterrorism Preparedness and Response Act)] Department of Biochemistry, University of Iowa, as a collaborator with expertise in phospholipid analysis, who will help with experimental design and data interpretation.

3. Rationale for some of the experiments is lacking (e.g., role of oxidized phospholipids (OxPL) and of TLR4 signaling in PLA_2G2D induction; use of attenuated SARS-CoV); consideration of molecules other than OxPL in PLA_2G2D induction.

Response: We have added additional rationale to all of the subaims.

4. *Differences between young B6 and BALB/c mice in terms of disease*.

Response: These differences are very notable, but are unlikely to be due only to differences in PLA2G2D expression. We have clarified this in the resubmission.

5. *Low dose LPS is likely to have both pro- and anti-inflammatory components*.

Response: Several of the reviewers commented on problems with using LPS to induce stress in mice. In response, we have deleted these approaches from the resubmission.

6. *While important to test, much of Aim 3 may not be possible if there is no age-dependent to MERS-CoV infection*.

Response: Since the original submission, the increased susceptibility observed in aged patients has become better documented. We have also found an age-dependent susceptibility to MERS-CoV in our aged human DPP4 KI mice. As a consequence, we modified the proposal to focus more on the role of aging in MERS. It is not known whether the same factors in increased susceptibility are involved in both SARS-CoV and MERS-CoV infected mice and this will be investigated in Aim 3 of the revised proposal. This Aim will be tightly linked with the other projects.

7. *Interactions with other projects are only eluded to in a cursory manner*.

Response: Interactions will be discussed in more detail in the revised submission.

8**.** *Studies of Tiam1/Rac1, ERK1/2 and Akt are of limited feasibility and unlikely to provide meaningful information.*

Response: We agree and will remove these approaches from the revised manuscript.

9. PLA2-induced release of arachidonic acid is an initial step in synthesis of many prostaglandins, thromboxanes and leukotrienes with pro- and anti-inflammatory potential. Role of these products was not discussed.

Response: We chose to focus on PGD_2/DP1 signaling and on PGE_2, for two reasons. First, our published and preliminary results suggest that PGD_2/DP1 signaling is critical for an effective immune response and PGE_2 is also PLA_2G2D-dependent. Second, inclusion of experiments examining the role of other eicosanoids would dilute our efforts and decrease our focus. We recognize that other lipid mediators are important and have included a discussion of our rationale in the revised proposal.

Project 2-T. Gallagher-Introduction

We appreciate the extensive recommendations provided by our reviewers. They have made several valuable comments. Our responses to their concerns are summarized below.

All reviewers asked how a study of MERS-CoV adaptation to mice would reveal information that is relevant to human MERS-CoV infection and human disease. In considering this question, we hold to our central hypothesis that MERS-CoV (and many other CoVs) cause disease in humans and animals because they robustly utilize host cell proteases for their propagation. We hypothesize that CoV adaptations for *in vivo* lung environments, in both mice and humans, involve viral spike protein changes that facilitate utilization of specific cell-surface proteases. By addressing this hypothesis, we suggest that we will further understand the human CoV infections enough to use protease inhibitors as antivirals. To formally address this hypothesis, we have revised aims to adapt MERS-CoVs for either cell-surface or endosomal proteases, and then evaluate the viruses for differential adaptive mutations, and for virulence in mice. To establish relevance to human infection, our aims are to use human airway epithelia (HAE) and alveolar-derived human cell lines as infection hosts. These cells reflecting the human lung environment will be infected to determine whether *in vitro* virulence in relevant cells correlates with virus' preference for cell-surface proteases.

Reviewers requested preliminary data identifying a specific mechanism of viral entry by mouse-adapted MERS-CoV. We are well on the way to satisfying this request, and our revised proposal includes data supporting adaptation for a so-called "early" (cell-surface) cell entry route via mouse-adaptation. The cell-surface proteases utilized during the early entry route are numerous, and therefore we have not yet determined whether MERS-CoVs adapt to preferentially use only one. However, we have aims to determine the breadth of protease utilization by MERS-CoVs. In response to reviewers, we have included more detail about our aim to identify specific proteases utilized by MERS-CoV, and have clarified experiments that account for possible redundant virus-activating proteases in lung cells.

Reviewers considered many of our aims to be worthy, but not feasible, given our limited human and material resources. They specifically requested that we request funds for antiviral research, as described in aim 5, via other sources. We have complied with this request by deleting aim 5. Our revised application now focuses explicitly on the central hypothesis that MERS-CoV lung virulence correlates with host protease utilization during virus secretion and virus entry.

Reviewers appeared to be generally enthusiastic with our plans, but they were, at times, concerned about the depth of our investigations. We have added details in aim 1, such that we can determine whether adapted spike proteins contribute only partially to lung virulence in mice. We have also added details in aims 2 and 3, such that we can systematically and individually evaluate proteases for their virus-activating potential. Of note, we have brought CRISPR/Cas technologies into our evaluations of virus-activating proteases, as described in our revised aim 3, and together with shRNAs and pharmacologic inhibitors, we are positioning our experiments to definitively identify the host proteases used in MERS-CoV entry and their relevance to human disease.

Project 3- P. McCray, Jr.-Introduction
We thank the reviewers for taking the substantial time required to review our program and this project.

One broad criticism of our approach was centered on Aim 2. The focus of this proposed aim was to investigate how adaptive mutations in MERS-CoV might contribute to increased virulence. We have considered the reviewer's criticisms regarding the difficulties that might be encountered in completing these experiments and reaching definitive conclusions. After careful deliberation, we elected to remove Aim 2 from the proposal. We will plan to use the data that we obtain from sequencing the mouse adapted, virulent, and triple plaque purified MERS-CoV to assemble a recombinant mouse adapted strain for our studies. Our PO1 PIs will all provide input on this decision, and the recombinant $MERS_{MA}$ will be generated using the BAC system developed by Dr. Enjuanes and further modified by Dr. Perlman's group. We plan to collaborate with Dr. Gallagher to investigate the contributions of adaptive mutations in the S gene to virulence in mice.

A general criticism of the proposal significance was that "the reliance on a mouse model may make it difficult to generalize results to understand human disease." As noted, we have attempted to complement the mouse studies with experiments in human airway epithelial cell organotypic cultures and human cell models where possible. In addition, it is worth noting that the mouse adapted strain of SARS-CoV developed by Subbarao, Baric and colleagues (termed "MA15") proved to be a substantial resource to the field.

Responses to specific review comments:

- We now propose functional tests to evaluate parameters of lung injury and edema in infected mice. These include Evan's blue dye leakage and lung weights. In addition, histopathologic scoring is performed on lung tissue sections and will assess parameters that include alveolar edema and vascular congestion.

- The chronic LPS administration model of metabolic syndrome was criticized. We have removed this model from the proposal. Our focus will be to use the obesity model first. We also propose additional models of chronic lung disease as co-morbidity factors.

- In the revised proposal, we now include more rationale and plans for investigating the potential mechanisms contributing to the morbidity and mortality associated with MERS infection in the co-morbidity models of obesity/diabetes and chronic lung disease.

- In proposed studies of the possible role of DPP4 to MERS severity, we now include studies of young and middle-aged animals, as used in Aim 1.

- To clarify our hypothesis, we posit that different cell types with different DPP4 expression levels could contribute to disease outcomes by, 1) supporting more or less virus entry and replication, 2) releasing more or less soluble DPP4 that acts as a soluble receptor or as a factor that modulates immune responses and inflammation through its target substrates.

- We acknowledge that only using a single inhibitor of DPP4 enzymatic activity, sitagliptin, may lead to inconclusive results. For this reason, we now include the use of a second inhibitor, linagliptin, in Aim 2 of the revised proposal.

- Regarding the proposed BMT experiment, we have continued to investigate the ability of $MERS_{MA}$ to infect hematopoietic cells in the knock in mouse model. We see viral antigen in alveolar macrophages following infection. In addition, new preliminary data suggest that viral replication is taking place in alveolar macrophages. We also stress that even if the virus infection is not productive, it still could have important effects on the immune response and virulence.

We hope the reviewers share our enthusiasm for this project.

Project 4-L. Enjuanes/ Introduction.
We thank the reviewers for their comments. The reviewers raised several issues that we have addressed in the revised proposal.

1. *Project 4 proposes an ambitious body of work, and there is concern as to the feasibility of completing the project*. We agree with this realistic view of the reviewers and have decided to delete former Aim 2, devoted to studies of non-coding RNAs in order to provide additional time for depth analyses in former Aims 1 and 3. This significant modification will allow us to introduce the requested information on other aspects of the project, and to assemble a tighter proposal.

2. *The reviewers ask why we favor the yeast-2-hybrid approach for the identification of specific cellular proteins binding viral proteins with PBM motifs instead of first selecting in bulk by tandem affinity chromatography*. We reported that SARS-CoV and MERS-CoV each have two proteins that contain PBM motifs and that the E protein of SARS-CoV is a strong virulence factor. We have described E protein's mechanism of action. As there are more than 400 cellular proteins including 1 to 13 PDZ motifs, the study of these interactions has the potential of leading to the identification of signaling pathways involved in coronavirus replication and pathogenesis, as shown in our previous studies. The strategy to identify specific PDZ^+ proteins recognized by these PBM motifs has been chosen because an already well established proteomics system, based on a yeast-2-hybrid platform including approximately 400 cellular PDZ^+ proteins, is available [Belotti et al., Molec. Cell. Proteomics 12.9, 2587 (2013)], and this screening system has been made available to us by Prof. Jean-Paul Borg (Marseille, France). Interactions will be confirmed by complementary methods.

3. *Reviewer 2 questions the feasibility of inhibiting the interaction of the viral PBM with cellular proteins containing PDZ motifs using peptides*. The screening of peptide libraries in search of peptides that inhibit a specific protein-protein interaction presents no technical problem although, in agreement with the reviewer, we acknowledge that *in vivo* applications of inhibitor peptides are being developed at present. New approaches using the coupling of peptides to other molecules facilitating the penetration into cells have been described. In response to the this comment, we will incorporate an alternative approach in the revised proposal, namely, screening available libraries of chemical compounds for those that inhibit interactions of PBM with PDZ motifs.

4. *Reviewer 2 indicates that whereas we identified E protein as a potentially important cause of pulmonary edema, we have not addressed the role of lung inflammation in edema induction, in conjunction with virus mediated ion (i.e., Ca^{++}) transport, and paracellular fluid regulation*. We agree with the reviewer. In the revised application, we will consider the impact of viral proteins containing ion channel activity and PBM motifs on the function of ion transport proteins in the lung epithelium (ENa^+C, CFTR, Na^+/K^+ ATPase), since deregulation of ion transport leads to disruption of the liquid balance in the lung and thus to edema.

5. *Reviewers propose that we expand the description of the evaluation of protection by MERS-CoV vaccine candidates*. Following the reviewer's suggestion we have expanded this section. Vaccine efficacy will be mainly determined by using hDPP4 knock in mice, which are susceptible to MERS-CoV. In addition, mouse adapted MERS-CoV obtained by Project 3 and the Animal/Virology Core by 30 passages through mouse lungs will be used as this virus causes lethal disease in hDPP4-KI mice. In the revised version of the project, studies proposing to examine the nature, magnitude and duration of the protective immune responses, including correlates of protection (antibodies and cell responses) will be incorporated.

6. *Reviewers indicate that the application would be strengthened by additional studies designed to directly implicate human immune and host cell targets for therapeutic intervention*. We fully agree with this suggestion. In fact, we have expanded the analysis of the consequences of the interaction of the selected vaccine candidates with human cells involved in the immune response (macrophages, dendritic cells, B and T cells). It is known that both SARS-CoV and MERS-CoV cause productive and abortive infections, dependent upon cell type, potentially leading to immune suppression or hyper-stimulation of the immune response after vaccine administration, which are relevant issues in the analysis of vaccine safety.

SPECIFIC AIMS – S. Perlman, Project 1

In general, aged individuals handle respiratory infections less well and respond less well to vaccines than younger individuals. The basis for these differences is multi-faceted and not well understood. However, understanding why the immune response becomes less effective during aging is critical, as humans live to older ages and continue to be exposed to pathogens. Coronavirus infections, in particular those caused by the Severe Acute Respiratory Syndrome-coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome-CoV (MERS-CoV) cause highly lethal human respiratory infections, with more severe disease occurring in the elderly. No patients under 24 years died from SARS while the mortality rate in those over 60 years of age was greater than 50%. This age dependence also occurs in mice infected with mouse-adapted SARS-CoV (MA15 strain) or mouse-adapted MERS-CoV. This proposal will largely focus on age-dependent differences in the host response to these viruses.

With aging, the lung is exposed to an increasing number of environmental antigens, resulting in a state of chronic inflammation. Results from the last funding period indicated that anti-inflammatory factors were upregulated in response to this chronic inflammation. This upregulation resulted in delayed responses not only to environmental antigens but also to rapidly replicating viruses such as MA15. A consequence of this delayed initial response was depressed respiratory dendritic cell (rDC) migration to the draining lymph nodes, which resulted in a poor MA15-specific T cell response in aged mice and delayed virus clearance. Most importantly, we also showed that age-dependent decreases in rDC migration occurred because levels of a single prostaglandin (PG), (PGD_2) increased with aging with consequent increased signaling through its receptor on myeloid cells, DP1. Additional studies showed that enhanced expression of PGD_2 was a direct consequence of age-dependent increases in an upstream phospholipase (phospholipase A_2 group IID, PLA_2G2D); PLA_2G2D was produced by lung $CD11c^+$ cells (alveolar macrophages and rDCs). In the genetic absence of PLA_2G2D or after DP1 blockade, survival was greatly increased after MA15 infection. Of note, PLA_2G2D serves to modulate PGD_2 expression but not to completely abrogate PGD_2/DP1 signaling. However, newly obtained data shown that in the complete absence of PGD_2/DP1 signaling, mice succumb to MA15 infection, indicating that DP1 signaling has additional roles in the immune response. These results prompt us to consider our central hypothesis: PGD_2 and PLA_2G2D along with other members of the small lipid mediator pathways have central roles in modulating the inflammatory state of the lung especially during aging. In specific they regulate multiple steps in the innate and subsequent T cell responses in mice infected with SARS-CoV, MERS-CoV and likely other viral respiratory pathogens.

Specific aim 1. To determine the mechanism of PLA_2G2D upregulation and the role of PLA_2G2D in vaccine responses in 12m old mice. The role of oxidized phospholipids, likely induced by aging and MA15 infection, in stimulating PLA_2G2D will be investigated. We will also determine the effect of PLA_2G2D on vaccine responses in 12m old mice and will investigate whether PGE_2, which is also decreased in $Pla_2g_2d^{-/-}$ mice, contributes to suboptimal immune responses in middle-aged mice.

Specific aim 2. **To determine the role of PGD_2-DP1 signaling in the immune response to SARS-CoV in 12 m mice.** Our preliminary results suggest that in addition to inhibiting rDC migration to lymph nodes, PGD_2 signaling through the DP1 receptor is involved in myeloid cell activation and in regulating inflammasome activation. Here, we will investigate how PGD_2/DP1 signaling affects these aspects of the anti-SARS-CoV and MERS-CoV immune responses.

Specific aim 3. To determine the basis of age-dependent increase in severity in MERS-CoV-infected mice. In addition to characterizing the infection, we will determine whether PGD_2 and PLA_2G2D contribute to poorer outcomes in mice infected with MERS-CoV, another infection in which severity is age-dependent. This aim will be performed using mice expressing hDPP4 and our newly isolated virulent mouse-adapted, MERS-CoV ($MERS_{MA}$). This Aim will be performed in conjunction with Projects 3 and 4 and the Animal/Virology Core.

SPECIFIC AIMS – T. Gallagher, Project 2

Coronaviruses (CoVs) are pathogens of humans and animals that exhibit facile zoonotic transmission. The Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS)-CoV outbreaks are the most recent examples of these zoonotic infections. SARS-CoV caused an acute human epidemic, but was rapidly extinguished through effective quarantine measures and has not reentered into humans in over ten years. By contrast, MERS-CoV continues to be more persistent, largely due to its prevalence in domesticated camels and its ongoing transmission to humans. MERS and other as yet unknown CoVs may continue to intrude into humans, raising the chances that they will adapt into forms that more freely transmit and cause human respiratory disease.

Adaptation of MERS and other CoVs to transmissible disease-causing forms may correlate with changes in many viral proteins that operate at many different infection stages. Amongst the selective pressures driving virus adaptation, we are specifically interested in those operating during cell entry. Selections at this stage fix mutations into the viral spike (S) proteins, and potentially adaptive MERS-CoV S mutations have been observed, but their relevance to human transmissibility and pathogenesis are unknown. This proposed research will identify adaptive changes in MERS-CoV S proteins that are responsible for pathogenesis, and will discern the selective pressures driving CoV evolution.

AIM 1: Identify adaptive mutations responsible for MERS-CoV pathogenesis in mice. In conjunction with Projects 1 and 3, we have isolated MERS-CoV variants with enhanced replication and pathogenesis in mice. Relative to wild-type (WT) viruses, the mouse-adapted (MA) viruses have S gene mutations. With the participation of Project 4, we will employ a MERS Bacterial Artificial Chromosome (BAC) and reverse genetics procedures to construct recombinant $MERS_{MA}$-CoVs with or without the MA-specific S mutations, and we will discern the contributions of S mutations to the MA phenotype.

AIM 2: Determine how MA mutations affect spike structure and function. The MA MERS-CoVs are distinguished from wild-type (WT) viruses in domains regulating virus-cell entry. Thus we hypothesize that CoV virulence in lungs correlates with the route that viruses take into susceptible cells. CoV - cell entry routes begin with S protein - cell receptor interactions, and then proceed to S protein proteolysis, with the S cleavages "activating" virus-cell membrane fusion. We will address the hypothesis that the MA mutations promote S protein cleavage-activation. CoV-mediated fusion can take place "early", at plasma membranes, or "late", in endosomes. We will address the hypothesis that the MA changes facilitate an early entry into both human and murine lung-derived cells. Results from AIMS 1 and 2 may reveal the importance of S cleavage in general models of CoV virulence.

AIM 3: Identify the proteases activating MERS-CoV *in vivo*. Some proteases activating MERS-CoV fusion have been identified in cell cultures, but it remains unclear which proteases operate *in vivo*. In conjunction with Projects 1 and 3, we have developed adenovirus-based transducing vectors that co-express the MERS-CoV receptor, human dipeptidyl peptidase 4 (hDPP4), along with silencing RNAs that diminish specific proteases. We will determine whether mice transduced with these vectors are susceptible or resistant to MERS-CoV. In addition, cell cultures, including murine and human airway epithelia (MAE and HAE), will have selected proteases eliminated using CRISPR / Cas vectors, and we will determine whether protease omissions reduce susceptibility to MERS-CoV. Results here will identify activating *in vivo* proteases, which will inform on the use of specific protease inhibitors in antiviral strategies.

AIM 4: Identify host cell factors controlling MERS spike protein evolution. Depending on the host cell type, MERS-CoVs enter cells through "early" fusion at or near plasma membranes, or through "late" fusion within late endosomes. Here we will identify evolutionary pressures driving MERS-CoV to utilize the early or late cell entry pathway. We will select for virus types exclusively utilizing the early or the late entry pathway, and will determine how the two types differ in S protein structure and function, and in mouse virulence. Infections in mice will be performed in conjunction with Projects 1 and 3. AIM 4 results may offer general explanations on how CoVs adapt to their hosts.

SPECIFIC AIMS- P. McCray,Jr., Project 3

Our understanding of MERS pathogenesis has been severely limited by the very small number of reports of surgical pathological specimens or autopsy studies from patients who have died of the disease. In addition, until recently there were no animal models of MERS that recapitulate features of the lung disease phenotype. Mice are restricted to infection at the level of the receptor, dipeptidyl peptidase 4 (DPP4). To overcome this barrier, we developed the first mouse model of MERS-CoV infection by sensitizing animals with pre-administration of an adenoviral vector expressing human (h)DPP4. We developed a second small animal model by expressing hDPP4 transgenically using the cytokeratin 18 (K18) promoter. K18-hDPP4 Tg mice develop lethal disease with infection of the lungs and brain. Most recently, we generated hDPP4 knock-in (KI) mice with exons 10-12 of the mouse dpp4 locus replaced by the human codons. DPP4 expression is regulated by the native promoter. These exons encode residues required for virus binding and entry. Importantly, the KI mice support high levels of virus replication in the lungs without CNS disease. After 30 serial passages of MERS-CoV in KI mice we obtained a mouse adapted (MA) virus ("$MERS_{MA}$") that causes lethal pulmonary disease. We will use the KI mouse, $MERS_{MA}$, along with well-differentiated cultures of airway epithelia and mouse and human cell models to investigate how the mouse adapted virus causes severe lung disease. There are two aims.

Aim 1. **To understand how an *in vivo* evolved MERS-CoV causes lethal lung disease**. The lung disease in KI mice infected with $MERS_{MA}$ is characterized by inflammatory cell infiltration of the lungs with pneumonia, patchy alveolar edema, and microvascular injury and thrombosis. In marked contrast, Ad-hDPP4 sensitized and K18 Tg mice infected with $MERS_{MA}$ do not develop severe disease and survive. This result suggests that infection of different cell populations expressing hDPP4 in these models may determine disease outcomes. The $MERS_{MA}$ provides an opportunity to gain new insights into host-pathogen interactions and how the virus infection results in lung injury and death.

We hypothesize that $MERS_{MA}$ causes increased disease in part through new cell type tropism. In human lung tissue there is abundant DPP4 expression on alveolar epithelia as well as non-epithelial cell types including lymphocytes, macrophages, dendritic cells, lymphatic and vascular endothelia, and pleural mesothelia. To learn how $MERS_{MA}$ causes disease, we will extensively phenotype the course of infection in KI mice and assess $MERS_{MA}$ contributions to the observed epithelial cell damage, vascular endothelial injury, and thrombosis. We will contrast these disease findings with those observed in Ad5-hDPP4-sensitized and K18 Tg mice. Finally, we will model common human MERS co-morbidities in KI mice and assess their impact on disease outcomes.

Aim 2. **To investigate how DPP4 abundance and function influence MERS disease pathogenesis.** In addition to serving as the MERS-CoV receptor, DPP4 has important enzymatic functions. As a surface displayed and soluble dipeptidylpeptidase, DPP4 cleaves dipeptides from many bioactive proteins including cytokines, chemokines, and growth factors, and thereby alters function. DPP4 abundance and activity is increased in many disease states associated with inflammation. Of note, $MERS_{MA}$ infection in hDPP4 KI mice causes a significant acute increase in serum DPP4 levels.

We hypothesize that DPP4 abundance and enzymatic activity contribute to disease. To investigate the role of DPP4 activity on the disease state, we will treat KI mice with a chemical inhibitor of DPP4's enzymatic activity in the setting of MERS-CoV infection. Furthermore, to understand the importance of infection of hematopoietic cells expressing DPP4, we will perform bone marrow chimera studies in KI mice, using WT and DPP4 null mice donor marrow and assess disease outcomes.

Completion of these proposed studies will provide new insights into how MERS-CoV causes lung disease. This knowledge may help inform future therapeutic strategies.

SPECIFIC AIMS, Project 4-L. Enjuanes. (b)(6); (b)(3):42 U.S.C. 262a(h)(1) (Public Heatlh Security and

To prevent and treat deadly human coronavirus (CoV) respiratory infections we will develop antivirals and live attenuated vaccines by studying the molecular basis of CoV-induced lung edema and resolution. Two strategies are considered: (i) To identify signaling pathways involved in CoV-host interaction, and how they result in severe lung disease. Inhibitors of these pathways will inform antiviral candidates; (ii) To identify virus virulence genes. Deletion of these genes will lead to attenuated viruses that represent vaccine candidates. This work will be performed in collaboration with Projects 1 and 3, and the animal Animal/Virology Core.

Aim 1. **To identify host factors involved in edema induction by interacting with CoV proteins including PDZ binding motifs (PBMs).** In the previous PPG funding period, we showed that SARS-CoV E and 3a proteins, and proteins E and 5 of MERS-CoV include sequence domains containing PBMs. Our work showed that SARS-CoV E protein PBM motif is a virulence factor that induces exacerbated inflammation by its binding to syntenin, leading to p38 MAPK activation and acute respiratory distress syndrome (ARDS). PBMs have the capability of binding more than 400 cellular proteins and, consequently, may regulate many cell signaling pathways. In particular, ion transport proteins (CFTR and Na^+/K^+ ATPase) contributing to the liquid balance in the lung are regulated by PBM-PDZ interactions. We propose:

1.1. To study whole proteome interactions between PBMs in MERS-CoV, and cellular PDZs. PBM-PDZ interactions involved in signaling pathways associated with virulence will be the basis for subaims 1.2 and 1.3.

1.2. Identification of antivirals that block selected MERS-CoV PBM-cellular PDZ interactions by using libraries of peptides and of chemical compounds.

1.3. Identification of essential MERS-CoV PBM-PDZ interactions involved in virus virulence. Virus modifications that minimize the activation of these signaling pathways will attenuate the virus and serve to generate novel live vaccine candidates.

Aim 2. To determine host and CoV proteins with ion transport activity involved in edema induction and disease resolution. Both SARS-CoV E and 3a proteins, and proteins E and 5 of MERS-CoV encode ion channel (IC) activities. We demonstrated that E protein IC activity is a virulence factor, leading to Ca^{2+} dependent inflammasome activation.

2.1. To identify antiviral candidates that promote epithelial ion transport and edema resolution. In the previous PPG funding period, we described the binding of SARS-CoV E protein to Na^+/K^+ ATPase, which is a critical component in edema resolution. We postulate that inhibition of E protein binding to Na^+/K^+ ATPase with peptides or chemical compounds may promote Na^+/K^+ ATPase activity and edema resolution.

2.2. Generation of MERS-CoV live-attenuated vaccine candidates by engineering recombinant viruses without IC activity. Our previous data showed that replacing IC^+ E protein by an alternative IC^- transmembrane protein with a PBM motif resulted in a stable and safe SARS-CoV vaccine, which will be applied to MERS-CoV.

Aim 3. **To develop safe live-attenuated vaccines for MERS-CoV.** In the previous PPG funding period, we reported the engineering of an effective and genetically stable SARS-CoV vaccine candidate based on the introduction of attenuating deletions in two viral proteins, E and nsp1. In this application, the engineering of vaccine candidates for MERS-CoV is proposed, by using the mechanisms of virus attenuation indicated in subaims 1.3, 2.2, 3.1 and 3.2. Only 1-2 vaccine candidates will be selected for further studies.

3.1. To construct propagation-defective viruses by deleting MERS-CoV E protein as vaccine candidates.

3.2. To construct vaccine candidates based on replication- and dissemination-competent rMERS-CoVs by the introduction of small deletions in the E protein, based on our previous results with SARS-CoV.

3.3. To increase the biosafety of the vaccine candidate by the introduction of two additional safety modifications in genes nsp1 and N. Complementary strategies to increase attenuation will be engineered by generating rMERS-CoVs including target sites for endogenous miRNAs to limit vaccine cellular tropism. Assessing the biosafety and genetic stability of vaccine candidates is a main goal of the project.

3.4. To evaluate vaccine protection in knock in mice susceptible to mouse-adapted MERS-CoV generated by the consortium. Studies to examine the nature, magnitude and duration of the protective immune responses, including correlates of protection (antibodies and cell response) will be performed, in collaboration with Projects 1 and 3.

3.5. To characterize the interaction of vaccine candidate with human cells of the immune system. MERS-CoV infects key cells involved in the immune response, such as macrophages, dendritic cells, CD4 and CD8 T cells. The effect of infecting these human leukocytes with vaccine candidates will be investigated.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 21 Jul 2016 12:30:15 +0000
To: Glowinski, Irene (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Cc: Powell, Shunetta (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]
Subject: 7/22 DURC/GoF Meeting Agenda
Attachments: 1a-Eurasian swine influenza viruses.pdf, 1b-Generation of (b)(4) flu viruses.pdf, 2-2016 CEIRS annual meeting AGENDA_2016_v11.docx

Hi Everyone,
The agenda for tomorrow's GoF/DURC meeting is below. Attached are documents for items 1 & 2.
Please note the passcode for this call is different:
Call-in number: (b)(6)
Passcode: (b)(6)

Erik

Weekly DURC/GoF Meeting Agenda
Friday, July 22, 2016
3:00-4:30pm
5601/7G31

1. Projects for GoF Review
    a. Yen (CEIRS) – Eurasian swine flu viruses – Diane
    b. Kawaoka (CEIRS) – (b)(4) flu viruses – Diane
2. Overview of CEIRS Meeting – Diane
3. Updates
    a. NSABB WG – Dennis, Diane, Teresa
    b. DURC/BSAT Sub-IPC – Dennis
    c. ISARG – Dennis/Ken/Tricia
    d. Erasmus RMP – Diane/Ken/Tricia
4. Round Robin/Other Items

Hauguel, Teresa (NIH/NIAID) [E]

Subject: FW: Eurasian swine influenza virus

From: Hui-Ling Yen [mailto:(b)(6)]
Sent: Friday, July 01, 2016 3:45 PM
To: Post, Diane (NIH/NIAID) [E] (b)(6)
Cc: (b)(6) Hui-Ling Yen (b)(6)
Subject: Re: Eurasian swine influenza virus

Dear Diane,

It was great to see you and congrats on the successful meeting!

We were previously funded in 2010 by the Health and Medical Research Fund (HMRF) by the Hong Kong government to work on Eurasian swine influenza virus to understand the molecular determinants that may facilitate transmission of the Eurasian swine influenza virus in ferrets. Mutations were introduced into the HA and PB2 proteins through a hypothesis driven approach into the recombinant virus A/Swine/Hong Kong/NS29/2009 (H1N1). The recombinant viruses were generated and most of the transmission experiments in ferrets were performed before the voluntary moratorium in 2012. We performed additional animal experiments when the first moratorium was lifted and stopped all the work after the second moratorium.

We hope to continue and summarise the study by analysing the viral population in the contact ferrets' nasal washes. I would appreciate your comments on the feasibility of this issue.

Thank you so much.

Best regards,
Hui-Ling

Hauguel, Teresa (NIH/NIAID) [E]

Subject: FW: Generation of (b)(4) flu viruses

From: YOSHIHIRO KAWAOKA [mailto: (b)(6)
Sent: Friday, June 24, 2016 8:25 PM
To: Post, Diane (NIH/NIAID) [E] (b)(6)
Cc: GABRIELE NEUMANN (b)(6)
Subject: Generation of (b)(4) flu viruses

Dear Diane,

We recently rescued (b)(4) flu viruses from cloned cDNA, but the titers in cultured cells are relatively low. Are limited (up to 10) passages in cultured cells (to adapt the viruses to mammalian cells) considered GoF?

All the experiments are currently being done in BSL3.

Yours,

Yoshi

Yoshihiro Kawaoka, DVM, Ph.D.
Professor
Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
575 Science Drive
Madison, WI 53711
Tel (b)(6) Fax:(608)265 5622
(b)(6)

From: Hanson, Christopher (NIH/NIAID) [E]
Sent: Thu, 21 Jul 2016 08:30:17 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: 7/22 DURC/GoF Meeting Agenda

Greetings,

I will be out of the office participating in a workshop July 20-21st with intermittent access to email. Any accumulated messages will be addressed upon my return on July 22nd.

If urgent assistance is needed, please call DIR-OD at 301-496-3006. For matters that require my immediate attention, my work cell is listed below.

All the best,

-Chris

Christopher T. Hanson
Biosafety & Scientific Operations Chief
Office of the Scientific Director
NIH-NIAID-DIR-OD
Bldg. 33, Rm. 2N09E
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Bethesda, MD 20892

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(cell) (b)(6)
(fax) 301-480-1878
(b)(6)

From: Ford, Andrew (NIH/NIAID) [E]
Sent: Thu, 21 Jul 2016 08:30:17 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: 7/22 DURC/GoF Meeting Agenda

I am currently out of the office and will be checking email occasionally; any responses will be delayed. For urgent issues, please contact BUGS@niaid.nih.gov.

From: Post, Diane (NIH/NIAID) [E]
Sent: Thu, 21 Jul 2016 09:33:15 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: For review - GoF letters

Thanks Erik. I've been putting these off for a long time ☹

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, July 21, 2016 9:32 AM
To: Post, Diane (NIH/NIAID) [E] (b)(6)
Subject: RE: For review - GoF letters

Hi Diane,
No comments from me; the letters look good!

Erik

From: Post, Diane (NIH/NIAID) [E]
Sent: Tuesday, July 19, 2016 11:46 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: For review - GoF letters

Hi Everyone,

Attached for your review are a couple of GoF letters for the CEIRS investigators. One is a letter to Dr. Kawaoka for experiments that he wanted to conduct now that his preliminary work is finished. The second letter is for Dr. Lowen at Emory for her exception request. I've attached their requests as well for reference.

Please send me any edits/comments by **noon this Friday, July 22nd** if possible.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS

5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

From: Post, Diane (NIH/NIAID) [E]
Sent: Thu, 21 Jul 2016 11:21:15 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: JVI: Reversion of Cold-adapted Live Attenuated Influenza Vaccine into a Pathogenic Virus

No – probably not because they don't do research.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, July 21, 2016 10:36 AM
To: Post, Diane (NIH/NIAID) [E] (b)(6)
Subject: FW: JVI: Reversion of Cold-adapted Live Attenuated Influenza Vaccine into a Pathogenic Virus

Do you think CDC reviewed this for GoF??

From: Folkers, Greg (NIH/NIAID) [E]
Sent: Thursday, July 21, 2016 10:32 AM
Subject: JVI: Reversion of Cold-adapted Live Attenuated Influenza Vaccine into a Pathogenic Virus

1. Accepted manuscript posted online 20 July 2016, doi: 10.1128/JVI.00163-16 *JVI.00163-16*

1. » Abstract
2. PDF

Reversion of Cold-adapted Live Attenuated Influenza Vaccine into a Pathogenic Virus

1. Bin Zhoua#,
2. Victoria A. Meliopoulosb,
3. Wei Wanga,
4. Xudong Lina,
5. Karla M. Stuckera,
6. Rebecca A. Halpina,
7. Timothy B. Stockwella,
8. Stacey Schultz-Cherryb and
9. David E. Wentwortha#

+ Author Affiliations

1. *Virology, J. Craig Venter Institute, Rockville, Maryland, USA*[a]

2. *Departments of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA*[b]

ABSTRACT

The only licensed live attenuated influenza A vaccines (LAIVs) in the United States (FluMist®) are created using internal protein coding gene segments from the cold-adapted temperature sensitive master donor virus A/Ann Arbor/6/1960 and HA/NA gene segments from circulating viruses. During serial passage of A/Ann Arbor/6/1960 at low temperatures to select the desired attenuating phenotypes, multiple cold-adaptive mutations and temperature-sensitive mutations arose. A substantial amount of scientific and clinical evidence has proven that FluMist is safe and effective. Nevertheless, no study has been conducted specifically to determine if the attenuating temperature sensitive phenotype can revert, and if so, the type of substitutions that will emerge (i.e., compensatory substitutions versus reversion of existing attenuating mutations). Serial passage of the monovalent FluMist 2009 H1N1 pandemic vaccine at increasing temperatures *in vitro* generated a variant that replicated efficiently at higher temperatures. Sequencing of the variant identified seven nonsynonymous mutations including PB1-E51K, PB1-I171V, PA-N350K, PA-L366I, NP-N125Y, NP-V186I, and NS2-G63E. None occurred at positions previously reported to affect temperature sensitivity of influenza A viruses. Synthetic genomics technology was used to synthesize the whole genome of the virus, and the role of individual mutations was characterized by assessing their effects on RNA polymerase activity and virus replication kinetics at various temperatures. The revertant also regained virulence and caused significant disease in mice, with severity comparable to that caused by a wild type 2009 H1N1 pandemic virus.

IMPORTANCE The live attenuated influenza vaccine FluMist® has been proven safe and effective and are widely used in the USA. The phenotype and genotype of the vaccine virus are believed to be very stable and mutants that cause disease in animals or humans have never been reported. By propagating the virus under well-controlled laboratory conditions, we found that the FluMist vaccine backbone could regain virulence to cause severe disease in mice. The identification of the responsible substitutions and elucidation of the underlying mechanisms provide unique insights on the attenuation of influenza virus, which is important to basic research on vaccines, attenuation reversion, and replication. In addition, this study suggests that the safety of LAIVs should be closely monitored after mass vaccination and novel strategies to continue to improve LAIV vaccine safety should be investigated.

FOOTNOTES

- #Address correspondence to: David E. Wentworth, (b)(6) or Bin Zhou, (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 22 Jul 2016 14:28:53 +0000
To: Hanson, Christopher (NIH/NIAID) [E]
Subject: RE: 7/22 DURC/GoF Meeting Agenda

Will do. Thanks for letting me know.

Erik

From: Hanson, Christopher (NIH/NIAID) [E]
Sent: Friday, July 22, 2016 10:27 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Re: 7/22 DURC/GoF Meeting Agenda

Erik,

I have another commitment at 3pm today and will miss this meeting. Please let me know if anything discussed will impact DIR before the next meeting.

Thank you!

-Chris

Sent from my iPhone

On Jul 21, 2016, at 8:30 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Everyone,
The agenda for tomorrow's GoF/DURC meeting is below. Attached are documents for items 1 & 2.
Please note the passcode for this call is different:
Call-in number: (b)(6)
Passcode: (b)(6)

Erik

Weekly DURC/GoF Meeting Agenda
Friday, July 22, 2016
3:00-4:30pm
5601/7G31

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c. ISARG – Dennis/Ken/Tricia
d. Erasmus RMP – Diane/Ken/Tricia

4. Round Robin/Other Items

<1a-Eurasian swine influenza viruses.pdf>
<1b-Generation of [b)(4)] flu viruses.pdf>
<2-2016 CEIRS annual meeting AGENDA_2016_v11.docx>

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 22 Jul 2016 15:51:47 +0000
To: Lambert, Linda (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: RE: P01 requests for September 25, 2016 receipt date

Thank you Linda! I will let Carolyn know and upload this to the P01 site.

Erik

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Friday, July 22, 2016 11:48 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: P01 requests for September 25, 2016 receipt date

Hi Erik
Thank you for the nice background on this. I am good with this going forward to the OD for BC review.
L

Linda C. Lambert, Ph.D.
Chief, Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
Room 8E31, 5601 Fishers Lane
Bethesda, MD 20892
Tel: (b)(6)
Fax: 301-496-8030
Email: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 22, 2016 8:47 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6)
Cc: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: P01 requests for September 25, 2016 receipt date

Dear Linda,
This week Stanley Perlman sent me his request to revise and resubmit his P01 for MERS vaccine and therapeutic development. The review of the 01 submission was overall very favorable: the final score of the 01 was (b)(6) with 3 of the 4 projects were scored as (b)(6) and the last (b)(6) The reviewers were enthusiastic about the work and the weaknesses noted should be very addressable in revision (summary statement attached). I had a quick discussion with David and he is supportive of allowing this to come in for BC/management team review. Can you please let me know if you're supportive of this coming in for review? The deadline to let Carolyn know is next Friday (7/29).

As a little bit of a refresher this would be the third renewal of this P01, which originally focused on SARS. The group has been highly productive and shifted focus to MERS after 2012. This award developed the first MERS animal model (adenovirus vector), and was granted a GoF exception to continue the work. Some of the main goals of the renewal will be: 1) refine MERS mouse models; 2) understand the pathogenicity of MERS and use this information to 3) identify novel Tx targets; and 4) develop and test MERS Tx and Vx in vivo.

Let me know if you have any questions.
Thanks!
Erik

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 4:37 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: P01 requests for September 25, 2016 receipt date

Thank you Erik.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, July 08, 2016 4:10 PM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6)
Cc: Spiro, David (NIH/NIAID) [E] (b)(6)
Subject: RE: P01 requests for September 25, 2016 receipt date

Dear Linda,
Stanley Perlman's P01 was reviewed last month and the summary statement just released the other day. It got a score of (b)(6) and he's just asked me about revising and resubmitting. I haven't yet had a chance to speak with David about it in any detail, and Stanley still needs to discuss the summary statement with his Co-PIs, but I wanted to let you know that he may request to submit a revision for Sept 25th. As of now, though, nothing is decided but I'll remind him of the 10-week deadline.

Erik

From: Glasgow, Carolyn (NIH/NIAID) [E]
Sent: Friday, July 8, 2016 2:11 PM
To: NIAID DMIDBC (b)(6)
Cc: DMID GrantOps (b)(6) NIAID DMIDPRO (b)(6)
Subject: P01 requests for September 25, 2016 receipt date

Dear Branch Chiefs,

Investigators interested in submitting a P01 application must contact program staff 10 weeks in advance of the receipt date. In order for a PI to be eligible to submit a P01 for the September 25, 2016 receipt date they should notify you by Friday, July 22, 2016.

Please let us know by Friday, July 29, 2016, if your branch has any P01 requests. If there are only a few requests, we may be able to schedule the P01 discussion during an upcoming Management Team meeting. If there are a large number, we will look at scheduling a separate BC meeting to discuss.

If you have any questions, just let us know.

Thank you

Carolyn

Carolyn Glasgow
Program Analyst
Room 7G46
5601 Fishers Lane MSC7630
Direct Phone: (b)(6)
Fax:
E-mail: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 22 Jul 2016 16:15:23 +0000
To: Santora, Kenneth (NIH/NIAID) [E]
Subject: RE: 7/22 DURC/GoF Meeting Agenda

Hi Ken,
Thanks for letting me know. Have a nice weekend.

Erik

From: Santora, Kenneth (NIH/NIAID) [E]
Sent: Friday, July 22, 2016 12:14 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: 7/22 DURC/GoF Meeting Agenda

Erik,

I have a meeting conflict and will not attending this time.
Thanks,
Ken

Ken Santora, PhD
Acting Director
Office of Extramural Research Policy and Operations
DEA, NIAID, NIH Room 4G20
Phone: (b)(6)
Email: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thursday, July 21, 2016 8:30 AM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6) Hanson, Christopher (NIH/NIAID) [E] (b)(6)
Cc: Powell, Shunetta (NIH/NIAID) [E] <(b)(6)>; Brown, Liliana (NIH/NIAID) [E] <(b)(6)>
Subject: 7/22 DURC/GoF Meeting Agenda

Hi Everyone,
The agenda for tomorrow's GoF/DURC meeting is below. Attached are documents for items 1 & 2.
Please note the passcode for this call is different:
Call-in number: (b)(6)

Passcode: (b)(6)

Erik

Weekly DURC/GoF Meeting Agenda
Friday, July 22, 2016
3:00-4:30pm
5601/7G31

1. Projects for GoF Review
    a. Yen (CEIRS) – Eurasian swine flu viruses – Diane
    b. Kawaoka (CEIRS) – (b)(4) flu viruses – Diane
2. Overview of CEIRS Meeting – Diane
3. Updates
    a. NSABB WG – Dennis, Diane, Teresa
    b. DURC/BSAT Sub-IPC – Dennis
    c. ISARG – Dennis/Ken/Tricia
    d. Erasmus RMP – Diane/Ken/Tricia
4. Round Robin/Other Items

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 25 Jul 2016 13:24:49 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]
Subject: GoF meeting Notes 7-22-2016
Attachments: GoF meeting Notes 7-22-2016.docx

Let me know if you have any questions on the notes.

GoF/DURC Committee Meeting Notes
7/22/2015

Attendees: Diane, David, Linda, Irene, Liliana, Barbara, Dennis, Erik

Weekly DURC/GoF Meeting Agenda
Friday, July 22, 2016
3:00-4:30pm
5601/7G31

1. Projects for GoF Review
    a. Yen (CEIRS) – Eurasian swine flu viruses – Diane
    - Viruses were constructed prior to research moratorium, and some experiments were done between moratorium and GoF pause
    - Work now stopped, but need to complete experiments for paper publication
    - All proposed work would be characterization; no additional GoF work
    - DMID funded generation of the viruses, but it was done before the GoF pause.
    - Group OK with allowing work to proceed, with citation in paper specifying viruses were created prior to pause.
    - Diane will email PI back with response.
    b. Kawaoka (CEIRS) – (b)(4) flu viruses – Diane
    - Proposed work to rescue (b)(4) viruses that don't grow well in culture, because they require extra (b)(4)
    - Proposed work is to passage viruses in culture to get variants that replicate efficiently.
    - Group deems this work GoF. Dennis noted that this "seems like work that was captured under GoF pause, but might not be concerning under the new NSABB guidelines."
    - Diane will email Yoshi and tell him the work can't be done under the GoF pause.
    c. Diane noted these questions came via email pings and not official correspondence through business offices. Question is how to respond: is informal email ok, or better to have determination in formal letter via business office? Group decided that for these informal messages, informal messages back are ok, but to copy Andrew so he can keep a record.
2. Overview of CEIRS Meeting – Diane
    - Diane described GoF session, and noted the PIs like David's presentation
    - US thought is that "the rest of the world is waiting on our example," but Ron noted in his presentation that the EU has already made their decision and work is proceeding.
    - Diane noted that there is still general confusion in CEIRS PIs over what would be covered by GoF/final NSABB recommendations; most PIs think it won't impact their work.
    - Push from CEIRS investigators to encourage the flu community to use caution when communicating work, especially regarding "pandemic potential." Not all zoonotic viruses have high pandemic potential.
    - Call from CEIRS group for more support of modeling work to better understand what contributes to pandemic potential
3. Updates

a. NSABB WG – Dennis, Diane, Teresa
   - No update for this item.
b. DURC/BSAT Sub-IPC – Dennis
   - No update for this item.
c. ISARG – Dennis/Ken/Tricia
   - No update for this item
d. Erasmus RMP – Diane/Ken/Tricia
   - General confusion from CDC/Erasmus on this RMP. CDC had questions that were sent to Erasmus business office, but were never forwarded on to Ron. This was why there was such a large delay. Lesson learned: also CC PI directly and not just the institution business office.
   - After reviewing responses, CDC recommends approving the work to move forward after DMID requests a copy of the respirator fit test protocol from Erasmus.
   - Some confusion exists about what CDC is supposed to send us on these RMP reviews; their determination was just text in an email. They didn't send a formal report or review.
   - Diane will ask Tricia to email Erasmus to request fit test protocol, but request Tricia should also CC Diane, Ron, and MSSM since they're the prime contractor.
   - Dennis noted there is still some disagreement on the inter-governmental DURC working group on the adequacy of foreign background checks. He said that Justice and State don't consider the foreign background check process equivalent to ours, while CDC had no concerns and routinely reviews the select agent laboratories.

4. Round Robin/Other Items
   - Erik brought up GoF in grant reviews: We request that PIs who receive exceptions note in publications that the work received an exception, but no guidance exists for grant applications. Stanley Perlman's P01 renewal was reviewed recently and he described MERS passaging and adaptation work he did under his exception to create his animal model. He didn't note his receipt of an exception and SRG commented that it sounded like it GoF work. SRO reminded group that any GoF issues will be addressed by Program and should affect review. Depending on reviewers, this could change perception of whether GoF work was really paused, so implementation guidelines might want to take this into consideration.
   - Liliana brought up Systems Bio Kickoff meeting: Questions were asked during kickoff whether viral evolution experiments were subject to pause. Currently the pathogens were not ones covered by GoF pause, but it is good that PIs are thinking in this context. Liliana encouraged PIs to always feel free to ask if they have GoF questions on their work.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Mon, 25 Jul 2016 09:46:09 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: GoF meeting Notes 7-22-2016

Thanks!

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

Please consider the environment before printing this e-mail

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Monday, July 25, 2016 9:25 AM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6)
Subject: GoF meeting Notes 7-22-2016

Let me know if you have any questions on the notes.

From: Post, Diane (NIH/NIAID) [E]
Sent: Tue, 26 Jul 2016 14:28:46 -0400
To: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: For review - GoF letters
Attachments: NIAID exception request_Emory.doc, NIAID_GoF Pause_Kawaoka_07_2016.doc, Lowen_GOF_Exemption.pdf, Kawaoka request_GoF Assessment - 03-29-16 (003).pdf

Hi Everyone,

Just wanted to follow up on these. For those who have not responded, if you have any comments can you send them by COB tomorrow? I'd really like to get these out since they have been sitting for quite some time.

One of these is for the Lowen exemption request. This is the first letter we will be sending out that denies an exemption request so it would be good to get your feedback on it.

If I do not hear from you by COB tomorrow I will forward on to Andrew for review.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

From: Post, Diane (NIH/NIAID) [E]
Sent: Tuesday, July 19, 2016 11:46 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E]

(b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: For review - GoF letters

Hi Everyone,

Attached for your review are a couple of GoF letters for the CEIRS investigators. One is a letter to Dr. Kawaoka for experiments that he wanted to conduct now that his preliminary work is finished. The second letter is for Dr. Lowen at Emory for her exception request. I've attached their requests as well for reference.

Please send me any edits/comments by **noon this Friday, July 22nd** if possible.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)
5601 Fishers Lane, MSC 9825
Bethesda, MD 20892

http://www.niaid.nih.gov/

July XX, 2016 Transmitted via e-mail to:

Dr. Anice Lowen
Department of Microbiology and Immunology,
Emory University School of Medicine,
1510 Clifton Road, Atlanta, GA, 30322

Subject: Contract HHSN272201400004C
"NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Lowen:

The U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses announced on October 17, 2014 provides for exceptions from the research funding pause if "…the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security." In accordance with this provision, NIAID considered the request for an exception from the Emory CEIRS influenza research team for proposed experiments to generate viruses with genes or amino acid sequences derived from both avian and human adapted influenza A viruses. NIAID reviewed the information provided and determined that while this work is scientifically important it does not meet the defined requirements for an exception in that the work is not urgently necessary to protect public health or national security. Therefore this work must remain paused while the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses is in place.

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

_____
Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

_____
Diane Post, Ph.D.
Contracting Officer Representative, CEIRS
Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Walt Orenstein, Emory University

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Phone: (b)(6)
Fax: 301-402-0972
http://www.niaid.nih.gov/

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
DEA, Office of Acquisitions

5601 Fishers Lane, Room 3B48, MSC 9821
Rockville, Maryland 20852

July XX, 2016

Transmitted via e-mail to (b)(6)

Dr. Yoshi Kawaoka
Professor, Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison

Subject: Research under contract HHSN272201400008C "NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Kawaoka:

Thank you for your initial correspondence of March 29th, 2016, and subsequent correspondence regarding the research that was re-directed under contract HHSN272201400008C to add the project "Identification of host-specific amino acids in the viral polymerase proteins". NIAID has reviewed your projects progress, your request for the continuation of new experiments under the project and the additional information provided by you, and made the following assessments:

- NIAID considered the request to generate and characterize replicating viruses possessing the mutations identified that increased the polymerase activity of (b)(4) in human 293T cells. Review of the preliminary data provided scientific evidence that the mutations will be anticipated to increase viral pathogenicity in the mammalian model. The proposed experiments were evaluated based on whether they would result in a gain of function as compared to the original wild-type virus isolate of (b)(4)
- NIAID has determined that the work proposed is subject to the current GoF research funding pause and therefore cannot move forward with contract funding at this time.

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

_____
Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

_____
Diane Post, Ph.D.
Contracting Officer Representative, CEIRS

Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Adolfo Garcia-Sastre, Ichan School of Medicine at Mt. Sinai

NIAID Request for Exception from the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses

The U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses announced on October 17, 2014 provides for exceptions from the research funding pause if "…the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security." The following request for exception is being submitted in accordance with this provision.

Date submitted:
May X, 2016

Submitted by:
Dr. Carole Heilman, Division Director DMID/NIAID

Background and description of research for which an Exception is requested:
Influenza A viruses are constantly changing. It is for this reason that they pose a significant and continued challenge to public health. Genetic diversification of influenza viruses arises due to polymerase error during genome copying and reassortment. Reassortment is the exchange of intact gene segments between two viruses that co-infect one cell and it facilitates viral evolution by allowing the coupling of advantageous mutations and the loss of deleterious mutations within a gene constellation. In the field, reassortment has been seen to enable the spread of antiviral resistant and novel epidemic strains. Reassortment between viruses adapted to different host species can occur following zoonotic transmission, e.g. of an avian influenza virus to humans, and can give rise to chimeric viruses with increased potential for spread in the new host. This mechanism underpinned the emergence of the 1957, 1968, and 2009 pandemic strains. There is an urgent unmet need to understand the factors driving reassortment in a host co-infected with two influenza A viruses. We currently have only a superficial understanding of this process and the likelihood that reassortant viruses with pandemic potential will emerge within a co-infected host is therefore unclear.

Recent data generated in the Lowen laboratory suggest that markedly enhanced levels of reassortment accompany cross-species transfer events. When two genetically tagged variants of an avian influenza virus are used to co-inoculate cultured cells, reassortment levels are found to be dose-dependent if the cells are of avian origin. If the cells are of mammalian origin, however, dose dependency is lost and the proportion of progeny viruses with reassortant genotypes is consistently 90-100%. Exceedingly high levels of reassortment are seen in this mis-matched virus-host system because greater than two virus particles are needed to initiate a productive infection (that is, essentially all infected cells are co-infected). We hypothesize that a cytoplasmic host restriction factor, which avian influenza viruses have not adapted to evade, is preventing import of a subset of incoming gene segments into the nucleus and thereby giving rise to incomplete viral genomes within the infected cell. When incomplete genomes are complemented through co-infection with multiple virus particles, however, infection can proceed and will give rise to mainly reassortant viral progeny. Toward testing this hypothesis, we wish to identify the viral target of the putative host restriction. To accomplish this aim, we need to introduce genetic features (whole segments or targeted amino acid changes) of i) an avian influenza virus into the genome of a human influenza virus and ii) a human influenza virus into the genome of an avian influenza virus. For each chimeric virus, we will then test whether an avian-like, high, reassortment phenotype or a human-like, dose-dependent, reassortment phenotype is seen in mammalian cells. The information gained will provide mechanistic insight into how reassortment proceeds, particularly in the context of zoonotic infection, and will reveal genetic markers both of avian-human host adaptation and of reassortment potential.

Knowledge of both the fundamental processes and specific genetic markers will in turn inform efforts to assess the risk of zoonotic influenza A viruses giving rise to pandemic influenza A viruses.

An **Exception** is requested for one project within the NIAID Contract HHSN272201400004C "Centers of Excellence for Influenza Research and Surveillance" (PI: Walt Orenstein, Emory University). This contract is to provide the US government with information regarding emerging pathogens, provide a research response in the event of an influenza emergency, and conduct basic research on influenza strains. The work proposed would be conducted in the laboratory of Dr. Anice Lowen at Emory University, as a co-investigator on contract HHSN272201400004C. In order to improve our ability to interpret surveillance data and anticipate influenza A virus outbreaks, the PI proposes to generate viruses with genes or amino acid sequences derived from both avian and human adapted influenza A viruses. Specific strain backgrounds to be used are all low pathogenicity and comprise A/Panama/2007/99 (H3N2); A/Netherlands/602/2009 (H1N1); A/mallard/Minnesota/199106/99 (H3N8); A/guinea fowl/Hong Kong/WF10/99 (H9N2); and A/duck/Alberta/35/76 (H1N1). We propose to introduce single gene segments (e.g. A/guinea fowl/Hong Kong/WF10/99 (H9N2) carrying the NP segment of A/Netherlands/602/2009 (H1N1)), multiple gene segments and targeted mutations (e.g. A/guinea fowl/Hong Kong/WF10/99 (H9N2) carrying PB2 E627K). As such, this work will require the generation of avian-like influenza A viruses that are anticipated to replicate to higher titers and are therefore anticipated to have increased pathogenicity in mammalian hosts. Since we expect the phenotype to map to components of the vRNP complex, we do not plan to introduce avian HA and/or NA gene segments into the background of a human influenza virus, but we do plan to introduce PB2, PB1, PA and/or NP of human viruses into avian backgrounds.

Requestor's rationale for Exception:
The research proposed will further mechanistic understanding of influenza A virus evolution and therefore the emergence of novel outbreak strains. This knowledge is essential to improving our ability to anticipate influenza pandemics and thereby afford more time to prepare effective countermeasures.

Remarks by Program/Contract staff (Please address the following elements)

- *Is the research in question subject to the funding pause?*
  Yes. The goal of generating influenza A and influenza B viruses with increased viral replication will be reasonably anticipated to enhance pathogenicity in mammals (mice).

- *Is continuation of the research urgently necessary to protect public health or national security? Explain (e.g., what are the anticipated outcomes of continuing, or consequences of pausing, this research?)*
  Yes. The significance of this NIAID-funded research is that improved influenza vaccines and vaccination strategies are urgently needed due to the significant morbidity and mortality from seasonal influenza viruses as well as those that could cause future pandemics. The use of a high-yield influenza vaccine backbone could significantly increase the amount of vaccine that could be produced in an expedited manner.

- *Are there feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach?*
  There are no feasible alternative methods to address the same scientific question in a manner that poses less risk.

References:

NIAID Program/Contract Staff Recommendation:

NIAID recommends that an **Exception** be granted for the above work under NIAID contract HHSN272201400004C such that the work to … may continue.

Recommendation of NIAID Director or Designee:

_____ Date _____
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases

Decision by NIH Director or Designee:

_____ Date _____

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health

Identification of novel host-specific residues in the influenza A virus polymerase complex

We aim to identify contact points between the influenza A viral polymerase subunits which may affect host-adaptation. Additionally, we aim to identify novel host-adaptation markers in the polymerase complex. Based on sequence and structural analyses, we identified more than 30 candidates in PB2, PB1, and PA. Using site-directed mutagenesis, the human virus-like amino acids were introduced into the background of a low pathogenic avian H5N1 virus [A/muscovy duck/Vietnam/NCVD18/2003 ((b)(4) MLD_{50}: 10^4 pfu]. Wild-type and mutant polymerases were then tested in minigenome assays in human 293T cells at 37˚C and 33˚C, and in avian DF-1 cells at 37˚C and 39˚C.

We identified four mutants that increased the polymerase activity of (b)(4) in human 293T cells: (b)(4) (Figure 1). No significant differences were detected in avian DF-1 cells.

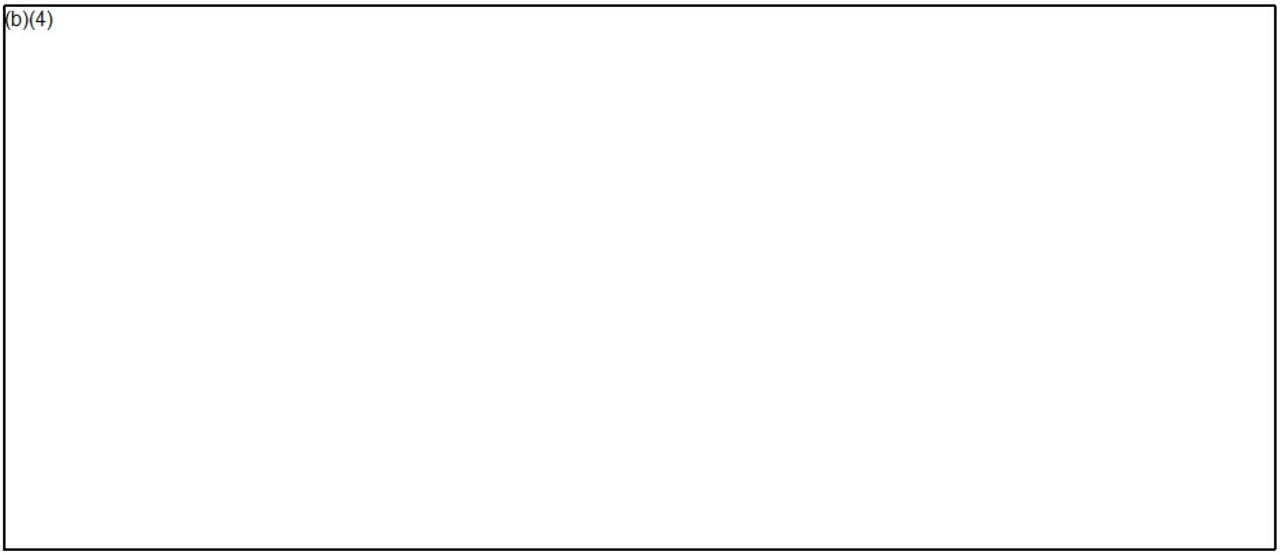

Figure 1. Relative luciferase activity of (b)(4) PB2 and PA mutant proteins encoding human virus-like residues (b)(4) (b)(4)

GoF Assessment: Previously, we received permission to carry out the above-described minireplicon studies. We now propose to test the (b)(4) in the background of replicating (b)(4) virus. Wild-type and mutant viruses will be compared for their growth properties in human and avian cells, and for their virulence in mice. The proposed studies will be carried out in BSL-3 containment. Wild-type (b)(4) virus does not carry known markers of mammalian-adaptation (such as PB2-627K, PB2-D701N, or human-type receptor-binding specificity). Moreover, the virulence of VD18 (MLD_{50}: 10^4 pfu) is substantially lower than that of other H5N1 viruses (for example, the MLD_{50} of A/Vietnam/1203/2004 is ~1 pfu). Thus, (b)(4) viruses possessing the (b)(4) (b)(4) are not reasonably anticipated to be more virulent or transmissible than currently circulating H5N1 viruses.

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tue, 26 Jul 2016 14:53:14 -0400
To: Post, Diane (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: For review - GoF letters
Attachments: NIAID_GoF Pause_Kawaoka_07_2016_lambert.doc, NIAID exception request_Emory_lambert.doc

Hello Diane,
Here are my edits.
L

From: Post, Diane (NIH/NIAID) [E]
Sent: Tuesday, July 26, 2016 2:29 PM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: For review - GoF letters

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Just wanted to follow up on these. For those who have not responded, if you have any comments can you send them by COB tomorrow? I'd really like to get these out since they have been sitting for quite some time.

One of these is for the Lowen exemption request. This is the first letter we will be sending out that denies an exemption request so it would be good to get your feedback on it.

If I do not hear from you by COB tomorrow I will forward on to Andrew for review.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

****

From: Post, Diane (NIH/NIAID) [E]
Sent: Tuesday, July 19, 2016 11:46 AM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: For review - GoF letters

Hi Everyone,

Attached for your review are a couple of GoF letters for the CEIRS investigators. One is a letter to Dr. Kawaoka for experiments that he wanted to conduct now that his preliminary work is finished. The second letter is for Dr. Lowen at Emory for her exception request. I've attached their requests as well for reference.

Please send me any edits/comments by **noon this Friday, July 22nd** if possible.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
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****
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****

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Fax: 301-402-0972
http://www.niaid.nih.gov/

National Institutes of Health (NIH)
National Institute of Allergy and Infectious Diseases (NIAID)
DEA, Office of Acquisitions

5601 Fishers Lane, Room 3B48, MSC 9821
Rockville, Maryland 20852

July XX, 2016

Transmitted via e-mail to (b)(6)

Dr. Yoshi Kawaoka
Professor, Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison

Subject: Research under contract HHSN272201400008C "NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Kawaoka:

Thank you for your initial correspondence of March 29th, 2016, and subsequent correspondence regarding the research that was re-directed under contract HHSN272201400008C to add the project "Identification of host-specific amino acids in the viral polymerase proteins". NIAID has reviewed your ~~projects~~ progress on the redirected project (?Is this what you mean), your request for the continuation of new experiments under thise project and the additional information provided by you, and made the following assessments:

- NIAID considered ~~the~~ your request to generate and characterize replicating viruses possessing the mutations ??that you? identified that increased the polymerase activity of (b)(4) in human 293T cells. It is our assessment that ~~Review of~~ the preliminary data provided scientific evidence that the mutations ~~will b~~are reasonably ~~e~~ anticipated to increase viral pathogenicity in the mammalian model. ~~The~~ Your proposed experiments were also evaluated based on whether they would likely result in a gain of function as compared to the original wild-type virus isolate of (b)(4)
- NIAID has determined that the work proposed is subject to the current GoF research funding pause and therefore cannot move forward with contract funding at this time.

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

Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

Diane Post, Ph.D.

Commented [LL([1]: Can you be more specific? Answers to our questions? Not sure what this refers to.

Commented [LL([2]: Is this a reference to a virus?

Commented [LL([3]: See comment above

Commented [LL([4]: Consider being consistent with Lowen statement:

Therefore this work must remain paused while the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses is in place.

Contracting Officer Representative, CEIRS
Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Adolfo Garcia-Sastre, Ichan School of Medicine at Mt. Sinai

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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National Institute of Allergy and Infectious Diseases (NIAID)
Division of Microbiology and Infectious Diseases (DMID)
5601 Fishers Lane, MSC 9825
Bethesda, MD 20892

http://www.niaid.nih.gov/

July XX, 2016 Transmitted via e-mail to:

Dr. Anice Lowen
Department of Microbiology and Immunology,
Emory University School of Medicine,
1510 Clifton Road, Atlanta, GA, 30322

Subject: Contract HHSN272201400004C
"NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Lowen:

The U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses announced on October 17, 2014 provides for exceptions from the research funding pause if "…the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security." In accordance with this provision, NIAID considered the request for an exception from the Emory CEIRS influenza research team for proposed experiments to generate viruses with genes or amino acid sequences derived from both avian and human adapted influenza A viruses. NIAID reviewed the information provided and determined that while this work is scientifically important it does not meet the defined requirements for an exception in that the work is not urgently necessary to protect public health or national security. Therefore this work must remain paused while the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses is in place.

Commented [LL([1]: Seems to me that this would benefit with one more phrase or sentence which is why she wanted to seek the exception. It's not just to generate these viruses but there's the public health purpose that she wants considered. If there is no specific purpose – let me know then I am okay with this as written.

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

_____
Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

_____
Diane Post, Ph.D.
Contracting Officer Representative, CEIRS
Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Walt Orenstein, Emory University

From: Post, Diane (NIH/NIAID) [E]
Sent: Tue, 26 Jul 2016 15:21:24 -0400
To: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: GOF Letters for review - from last Friday
Attachments: Kawaoka_GoF request_bat viruses.docx, Yen_GoF request.docx

Dear all,

Please find attached here 2 new GoF letters for review. These are for requests that we discussed at our most recent GoF committee meeting last Friday. The first letter for review is from the group at HKU that would like to conduct some phenotypic characterization studies on viruses that were generated prior to the research funding pause. The second letter for review is for Yoshi and his request to adapt the (b)(4) (b)(4) influenza viruses to mammalian cell culture.

Please review and provide any feedback you have for these letters. Note that these will be going out as emails instead of formal letters as we discussed at the meeting.

Thank you!
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

Dear Dr. Kawaoka,

Thank you for your correspondence of June 24th, 2016, regarding experiments involving the recently rescued (b)(4) influenza viruses. These viruses do not grow well in cell culture and require exogenous (b)(4) for efficient growth in mammalian cells. NIAID discussed and reviewed your request to (b)(4) viruses in mammalian cell lines (b)(4) and/or with successively lower concentrations of (b)(4) to isolate variants that replicate efficiently. The intent of the requested experiments are to adapt the (b)(4) influenza viruses to efficiently grow in various mammalian cell lines thereby introducing new properties to the (b)(4) bat viruses. These experiments are reasonably anticipated to increase the pathogenicity and/or transmissibility in mammals via the respiratory route of the (b)(4) nfluenza viruses. Therefore this work must remain paused while the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses is in place.

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

Sincerely,

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

Dear Dr. Yen,

Thank you for your correspondence of July 1st, 2016, regarding the swine influenza studies that are currently on hold due to the Government Research Funding Pause on selected gain-of-function (GoF) research on influenza, MERS and SARS viruses (http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf). NIAID reviewed your request to analyze virus populations recovered from contact ferret nasal washes from a transmission study that was performed prior to the research funding pause.

NIAID recommends that studies to conduct phenotypic characterization of existing laboratory-generated viruses do not fall under the scope of the GoF funding pause because they are not reasonably anticipated to enhance the pathogenicity and/or transmissibility in mammals via the respiratory route of these previously generated viruses any further. However, in the event that the characterization studies unexpectedly result in a virus with further enhanced pathogenicity and/or transmissibility in mammals via the respiratory route, you must immediately stop these research activities and provide the NIAID Program Officer and Contracting Officer with the relevant data and information related to these unanticipated outcomes.

NIAID requests that when you publish the results of the experiments that you place a note in the acknowledgement section that states that the initial generation of viruses with mutations and transmission experiments were conducted prior to the US Government GoF funding pause.

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

Sincerely,

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
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From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Tue, 26 Jul 2016 15:52:05 -0400
To: Post, Diane (NIH/NIAID) [E]
Cc: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: For review - GoF letters
Attachments: NIAID exception request_Emory_lambert-TH.doc, NIAID_GoF Pause_Kawaoka_07_2016_lambert-TH.doc

I added my suggested edits to Linda's.

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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.

Please consider the environment before printing this e-mail

From: Lambert, Linda (NIH/NIAID) [E]
Sent: Tuesday, July 26, 2016 2:53 PM
To: Post, Diane (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: For review - GoF letters

Hello Diane,
Here are my edits.
L

From: Post, Diane (NIH/NIAID) [E]
Sent: Tuesday, July 26, 2016 2:29 PM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik

(NIH/NIAID) [E] (b)(6)
Subject: RE: For review - GoF letters

Hi Everyone,

Just wanted to follow up on these. For those who have not responded, if you have any comments can you send them by COB tomorrow? I'd really like to get these out since they have been sitting for quite some time.

One of these is for the Lowen exemption request. This is the first letter we will be sending out that denies an exemption request so it would be good to get your feedback on it.

If I do not hear from you by COB tomorrow I will forward on to Andrew for review.

Thank you,
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
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Please send me any edits/comments by **noon this Friday, July 22nd** if possible.

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July XX, 2016 Transmitted via e-mail to:

Dr. Anice Lowen
Department of Microbiology and Immunology,
Emory University School of Medicine,
1510 Clifton Road, Atlanta, GA, 30322

Subject: Contract HHSN272201400004C
"NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Lowen:

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

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Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

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Diane Post, Ph.D.
Contracting Officer Representative, CEIRS
Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Walt Orenstein, Emory University

Commented [LL([1]: Seems to me that this would benefit with one more phrase or sentence which is why she wanted to seek the exception. It's not just to generate these viruses but there's the public health purpose that she wants considered. If there is no specific purpose – let me know then I am okay with this as written.

Commented [HT([2R1]: Agree – added sentence from rational section of the exception request

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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National Institutes of Health (NIH)
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DEA, Office of Acquisitions

5601 Fishers Lane, Room 3B48, MSC 9821
Rockville, Maryland 20852

July XX, 2016

Transmitted via e-mail to (b)(6)

Dr. Yoshi Kawaoka
Professor, Influenza Research Institute
Department of Pathobiological Sciences
School of Veterinary Medicine
University of Wisconsin-Madison

Subject: Research under contract HHSN272201400008C "NIAID Centers of Excellence for Influenza Research and Surveillance"

Dear Dr. Kawaoka:

Thank you for your initial correspondence of March 29th, 2016, and subsequent correspondence regarding the research that was re-directed under contract HHSN272201400008C to add the project "Identification of host-specific amino acids in the viral polymerase proteins". NIAID has reviewed your ~~projects~~ progress on the redirected project (?Is this what you mean), your request for the continuation of new experiments under thise project and the additional information provided by you, and made the following assessments:

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Michael C. Finn
Contracting Officer, MID Research Contracts Branch-B
Office of Acquisitions, DEA, NIAID, NIH

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Contracting Officer Representative, CEIRS
Respiratory Disease Branch, DMID, NIAID, NIH

cc: Dr. Irene Glowinski, Deputy Director, DMID, NIAID
Dr. Adolfo Garcia-Sastre, Ichan School of Medicine at Mt. Sinai

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Wed, 27 Jul 2016 10:00:22 -0400
To: Post, Diane (NIH/NIAID) [E]
Cc: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: GOF Letters for review - from last Friday
Attachments: Kawaoka_GoF request_(b)(4 viruses-TH.docx, Yen_GoF request-TH.docx

Hi Diane,

Attached are my suggested edits for your consideration.

Best,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
Phone: (b)(6)
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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.

Please consider the environment before printing this e-mail

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Sent: Tuesday, July 26, 2016 3:21 PM
To: Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: GOF Letters for review - from last Friday

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Please review and provide any feedback you have for these letters. Note that these will be going out as emails instead of formal letters as we discussed at the meeting.

Thank you!
Diane

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
Bethesda, MD 20892
Office: (b)(6)
Cell: (b)(6)
Email: (b)(6)

Dear Dr. Kawaoka,

Thank you for your correspondence of June 24th, 2016, regarding experiments involving the recently rescued (b)(4) influenza viruses. ~~These viruses do not grow well in cell culture and require exogenous (b)(4) for efficient growth in mammalian cells.~~ NIAID discussed and reviewed your request to (b)(4) influenza viruses in mammalian cell lines ~~without (b)(4) and/or with successively lower concentrations of (b)(4) to isolate variants that replicate efficiently. The intent of the requested experiments are~~ with the goal of~~to~~ adapting ~~the~~ (b)((b)(4) ~~influenza~~these viruses to efficiently grow in ~~various~~ mammalian cells~~,~~ ~~lines~~ thereby introducing new properties to the (b)(4) viruses. NIAID's determination is that ~~T~~these experiments are reasonably anticipated to increase the pathogenicity and/or transmissibility in mammals via the respiratory route of the (b)(4) influenza viruses. Therefore this work must remain paused while the Research Funding Pause on Selected GOF Research Involving Influenza, MERS, and SARS Viruses is in place.

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

Sincerely,

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
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Commented [HT([1]: I don't think you need the additional scientific details about growth requirements, but if you think it's necessary to keep them I am not opposed to that.

Dear Dr. Yen,

Thank you for your correspondence of July 1st, 2016, regarding the swine influenza studies that are currently on hold due to the Government Research Funding Pause on selected gain-of-function (GoF) research on influenza, MERS and SARS viruses (http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf). NIAID reviewed your request to analyze virus populations recovered from contact ferret nasal washes from a transmission study that was performed prior to the research funding pause.

Performing ~~NIAID recommends that studies to conduct~~ phenotypic characterization studies of existing laboratory-generated viruses does not fall under the scope of the GoF research funding pause because these studies~~y~~ are not reasonably anticipated to enhance the pathogenicity and/or transmissibility in mammals via the respiratory route beyond what has been~~of these~~ previously generated ~~viruses any further~~. However, further studies beyond characterization or those that would alter the existing virus may be subject to the GoF research funding pause and you should notify NIAID before initiating these experiments. Additionally, in the event that the characterization studies unexpectedly result in a virus with further enhanced pathogenicity and/or transmissibility in mammals via the respiratory route, you must immediately stop these research activities and provide the NIAID Program Officer and Contracting Officer with the relevant data and information related to these unanticipated outcomes.

Commented [HT([1]: Do these previously generated viruses exhibit enhanced path/trans compared to wt?

NIAID requests that when you publish the results of the experiments, ~~that~~ you place a note in the acknowledgement section ~~that~~ which states that the initial generation of these mutant viruses ~~with mutations and~~and the transmission experiments were conducted prior to the US Government GoF research funding pause.

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

Sincerely,

Diane J. Post, Ph.D.
Influenza Program Officer
Contracting Officer Representative (COR), CEIRS
Respiratory Diseases Branch
DMID/NIAID/NIH/DHHS
5601 Fishers Lane Room 8E16, MSC 9825
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From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Mon, 1 Aug 2016 14:11:06 -0400
To: Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Subject: Call for agenda items - 8/5 DURC/GoF meeting

Hi All,

Please let me know if you have any agenda items for this Friday's DURC/GoF meeting by COB Wednesday.

Thanks,
Teresa

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
Phone: (b)(6)
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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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From: Pickett, Thames (NIH/NIAID) [E]
Sent: Wed, 3 Aug 2016 15:48:20 -0400
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: AMoID Question

Got it. Thanks.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, August 03, 2016 3:41 PM
To: Pickett, Thames (NIH/NIAID) [E] (b)(6)
Subject: RE: AMoID Question

Thanks Thames. No, no problem with the work. The first NCEs were delays due to the GoF pause and then breeding the mice. For the option periods, the 4 month window turned out not to be realistic for the studies. Based on the prior performance I'd wanted to build the extension in when we exercised Option 2, but Stan said I had to do a separate mod for that so that's why we'll have another NCE.

Erik

From: Pickett, Thames (NIH/NIAID) [E]
Sent: Wednesday, August 3, 2016 2:42 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: AMoID Question

Hi Erik,

The ordering period under the base contract ends March 21, 2017. I believe that the no-cost extension can go beyond that date, but it couldn't be executed after that date. You can verify with OA

I notice that this task order has had a number of NCEs, is there a problem with the work?

Thames

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wednesday, August 03, 2016 1:57 PM
To: Pickett, Thames (NIH/NIAID) [E] (b)(6)
Subject: AMoID Question

Hi Thames,
I had a call with MSSM/UNC on TOA57 today. We're planning to request an NCE for the rest of the studies, but noted that MSSM's AMoID contract ends Feb 28th, 2017. Will the NCE have to end on that date as well, or is it possible to extend beyond Feb 28th?

Erik

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Thu, 4 Aug 2016 09:49:49 -0400
To: Glowinski, Irene (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Hauguel, Teresa (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]; Delarosa, Patricia (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]
Subject: 8/5 DURC/GoF Meeting Agenda
Attachments: H6N1 receptor paper, 2-NAS DURC Communication Meeting - Agenda.pdf

Hello Everyone,

We will have a short DURC/GoF meeting this Friday.

Attached are documents for agenda items 1 & 2.

Weekly DURC/GoF Meeting Agenda
Friday, August 5, 2016
2:00-3:30pm
5601/7G31
Call in number: (b)(6)
Passcode: (b)(6)

1. Discussion of H6N1 Draft Manuscript – Teresa
2. Overview of NAS DURC Communication Meeting – Teresa
3. Updates
    a. NSABB WG – Dennis/Diane/Teresa
    b. DURC/BSAT Sub-IPC – Dennis
    c. ISARG – Dennis/Ken/Tricia
    d. Erasmus RMP – Diane/Ken/Tricia
4. Round Robin/Other Items

Teresa M. Hauguel, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/DHHS
5601 Fishers Lane, Room 8E19
Bethesda, MD 20892
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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.

From: Jim Paulson
Sent: Mon, 1 Aug 2016 19:37:34 +0000
To: Hauguel, Teresa (NIH/NIAID) [E]
Cc: Anna Crie
Subject: H6N1 receptor paper
Attachments: Fig1to2V080116.pdf, H6N1_mutant_V10_SI.pdf, H6N1_mutant_V10.pdf

Dear Teresa,

I am attaching a near final draft of a paper we are preparing to submit to Science documenting our investigation to switch the receptor specificity of a taiwanese H6N1 HA from avian type to human type. Am sending it to you to both inform you and to ask if you have any concerns about submission. We believe the work does not fall under DURC since we have not worked with viruses. As a further precaution we have requested a review of the MS by our IBC and plan to include a letter from them in our submission to the journal.

Feel free to share this with any of your NIH colleagues.

Best regards,

Jim

The National Academies of
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Committee on Dual Use Research of Concern: Options for Limited Communication
First Meeting

Eventi Hotel
Verdi II Room – 4th Floor
851 Avenue of the Americas
New York, NY 10001

July 11-12, 2016

AGENDA

Monday, July 11

OPEN SESSION

10:00 am	**Welcome and Introductions** Committee Co-chairs: Harold Varmus, Weill Cornell Medical College Richard A. Meserve, Covington & Burling LLP
10:15 am	**Charge from Sponsors** Paula Olsiewski, Alfred P. Sloan Foundation Ed You, Federal Bureau of Investigation
10:30 am	**Overview of Government Policies Influencing Publication of Dual Use Research of Concern** Gerald L. Epstein, White House Office of Science and Technology Policy
10:50 am	**Key Challenges of Current Policy and Possible Options for Limited Dissemination** Elisa D. Harris, University of Maryland
11:15	**Committee Discussion with Drs. Epstein and Harris**
12 noon	**Lunch**

1:00 pm	**Keeping Up with Dual Use Research, Emerging Science, and Publication Concerns: Challenges for Scientific Journals** Phillip Campbell, *Nature – via videoconference* Inder Verma, *Proceedings of the National Academy of Sciences – via videoconference* Randy Schekman, *eLife – via videoconference*
2:30 pm	**Looking Forward: Lessons Learned from the Past and Options for the Future** Michael Imperiale, University of Michigan David Relman, Stanford University
4:00 pm	**Break**
4:15 pm	**National Science Advisory Board for Biosecurity's Current Thinking on Publication of Dual Use Research of Concern** Carrie Wolinetz, National Institutes of Health
5:00 pm	**Adjourn to Closed Session**

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July 11-12, 2016

AGENDA

Tuesday, July 12

OPEN SESSION

8:30 am	**Breakfast**
9:00 am	**Welcome**
	Committee Co-chairs:
	Harold Varmus, Weill Cornell Medical College Richard A. Meserve, Covington & Burling LLP
9:15 am	**Lessons Learned**
	Teresa Hauguel, National Institute of Allergy and Infectious Diseases
10:00 am	**Break**
10:15 am	**Perspectives from Research Institutions**
	Ara Tahmassian, Harvard University David L. Wynes, Emory University
11:15 am	**Considerations for Options for Limiting/Restricting Dissemination**
	Alan Morrison, The George Washington University – *via videoconference*
12:00 noon	**Lunch**
1:00 pm	**Adjourn to Closed Session**

From: Delarosa, Patricia (NIH/NIAID) [E]
Sent: Thu, 4 Aug 2016 15:20:35 -0400
To: Hauguel, Teresa (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Dixon, Dennis M. (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Mulach, Barbara (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Strickler-Dinglasan, Patricia (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]; Santora, Kenneth (NIH/NIAID) [E]
Subject: RE: 8/5 DURC/GoF Meeting Agenda

Teresa, Neither Ken or I will attend tomorrow. (b)(6) (b)(6) I want to thank the DMID team for all your kindness and great science discussions. (b)(6) (b)(6)

(b)(6)
Tricia

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Rockville, MD 20852
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From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Thursday, August 04, 2016 9:50 AM
To: Glowinski, Irene (NIH/NIAID) [E] (b)(6) Dixon, Dennis M. (NIH/NIAID) [E] (b)(6) Lambert, Linda (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Brown, Liliana (NIH/NIAID) [E] (b)(6) Mulach, Barbara (NIH/NIAID) [E] (b)(6) Ford, Andrew (NIH/NIAID) [E] (b)(6) Strickler-Dinglasan, Patricia (NIH/NIAID) [E] (b)(6) Hanson, Christopher

(NIH/NIAID) [E] (b)(6) Delarosa, Patricia (NIH/NIAID) [E]
(b)(6) Santora, Kenneth (NIH/NIAID) [E] (b)(6)
Subject: 8/5 DURC/GoF Meeting Agenda

Hello Everyone,

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Attached are documents for agenda items 1 & 2.

Weekly DURC/GoF Meeting Agenda
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Teresa M. Hauguel, Ph.D.
Program Officer
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From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Fri, 5 Aug 2016 16:09:46 -0400
To: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Paulson H6N1 manuscript
Attachments: H6N1_mutant_V10.pdf

Linda, David, Diane & Erik,

As we discussed at our DURC/GoF meeting this afternoon, I am drafting an email to Dr. Paulson with suggestions to strengthen the communication strategy for his H6N1 receptor binding manuscript (manuscript is attached).

I would appreciate it if you could review the suggestions below and provide me with feedback by **COB Monday** (so that I can get this to BUGS and then back to the PI early next week).

In particular, can you take a look at the last bullet and let me know if you interpreted the manuscript language in the same way that I did?

Thanks!

****

As part of the communication strategy for this manuscript, NIAID recommends the following:

- Considering modifying the title.
- Provide additional details on the single case of human H6N1 infection which describe disease severity and patient outcome.
- Strengthen the explanation of the benefits of this research and the reasons for conducting the experiments.
- Discuss relevant risk mitigation measures or alternative approaches employed, particularly as they relate to the current USG gain-of-function research funding pause. In the last paragraph, this is very briefly discussed in the context of not being able to conduct ferret transmission studies. It would be useful to note here that the HA mutation which conferred alpha 2-6 receptor binding was not placed into a replication-competent virus and studies were restricted to *in vitro* analysis of a single viral protein.
- On lines 164-166, you state: "Thus there is potential for a switch in receptor specificity of H6N1 viruses from a single human infection. In this regard, H6N1 is quite different compared to H5N1, where several mutations are required to attain respiratory droplet transmission between ferrets (25-27)." As written, this statement seems to imply that a single mutation in H6N1 that switches receptor binding specificity could alone confer respiratory droplet transmission in ferrets (i.e., it is different than H5N1 because it doesn't require multiple mutations as has been shown for H5N1). Given that the requirements for H6N1 respiratory droplet transmission in ferrets has not been defined we think that this conclusion is premature and recommend modifying this statement.

Teresa M. Hauguel, Ph.D.

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Only a single mutation in Taiwanese H6N1 influenza hemagglutinin switches binding to human-type receptors

Robert P de Vries[1, 2#], Netanel Tzarum[3#], Wenjie Peng[1#], Iresha N Ambepitiya Wickramasinghe[4], Kim Bouwman[4], Xueyong Zhu[3], Ryan McBride[1], Wenli Yu[3], Monique H Verheije[4], Ian A Wilson[3,5*] and James C Paulson[1*].

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[2] Department of Chemical Biology and Drug Discovery, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3584 CG Utrecht, The Netherlands

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[4] Pathology Division, Department of Pathobiology, Faculty of Veterinary Medicine, Utrecht University, 3584 CL Utrecht, The Netherlands

[5] Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

[#] These authors contributed equally

* To whom correspondence should be addressed. E-mail: (b)(6)

(b)(6)

Main text including references: 2184 words.

One-sentence summary: A single amino-acid substitution in the HA of an avian origin human H6N1 virus switches specificity from avian to human-type receptors

ABSTRACT

In June 2013, the first case of human infection with an avian H6N1 virus was reported in a Taiwanese woman. As with any emerging avian virus that infects humans, there is concern about acquisition of human-type receptor specificity and transmission in humans. We have identified a single mutation of Gly to Asp at position 225 (G225D) that completely switches specificity from avian-type (NeuAcα2-3Gal) to human-type (NeuAcα2-6Gal) receptors. In contrast to wild-type H6N1, the mutant HA now binds the human trachea epithelium. Structural analyses reveal that Asp225 directly interacts with the penultimate Gal of the human-type receptor, stabilizing human receptor binding. Because human-receptor specificity can surprisingly be achieved in H6N1 with only a single nucleotide change, intense surveillance of H6N1 in Taiwanese poultry is warranted. (124 words)

2013 was a remarkable year for influenza A virus (IAV) zoonosis. Multiple avian virus subtypes successfully crossed the species barrier into humans including H5N1, H7N7, H7N9, H9N2 and H10N8 viruses (*1*), as well as a single infection of a novel H6N1 virus in a 20-year-old Taiwanese woman with (*2-4*). Fortunately, none of these viruses has to date acquired the ability to transmit efficiently between humans (*5-10*). All previous human pandemics have been of avian origin and required a shift in receptor specificity from glycans with a sialic acid linked α2-3 to galactose (avian-type receptor) to α2-6 linked sialosides (human-type receptor) (*11*). Thus, understanding the potential for new avian viruses to acquire human receptor specificity is an important factor in assessing potential pandemic threats.

Over the last 100 years, human influenza pandemics have been caused by only three influenza A virus subtypes, H1N1, H2N2 and H3N2. In each case, only two amino acid changes in the HA to were required to change the specificity of the avian virus progenitor to recognition of human-type receptors (*12, 13*). H1N1 viruses did so by introducing E190D / G225D mutations and H2 and H3 viruses by Q226L / G228S, respectively (fig. S1A) (*12*). Analysis of H6 HA isolates from humans and poultry reveals a combination of four amino acids at these positions that are not often seen in avian viruses, namely V190, G225, Q226 and S228. While these residues are not all canonical for avian viruses (V190, S228), the human H6 hemagglutinin retains binding to avian-type receptors (*6, 8, 10*).

To further investigate the potential for human H6 HA to acquire human-type receptor specificity, we employed site-directed mutagenesis of the receptor binding site (RBS) and produced the respective soluble recombinant trimeric HA proteins (*14*). Receptor specificity was assessed on a glycan microarray containing linear and branched O- and N-linked glycans with extended poly-N-acetyl-lactosamine chains, which were found as the preferred receptors of the 2009 H1N1 pandemic virus (A/CA/04/09) and recent human H3N2 viruses (See table S1 for complete list) (*15*). As observed for a reference H5 HA, the wild-type human H6 HA binds solely to avian-type receptors (*6, 16*), but with remarkable specificity towards extended N-linked glycans (#53-67) (Fig. 1A). To assess mutations that confer human-type specificity in H1N1, H2N2, and H3N2 viruses, we introduced such mutations at positions 190, 225, 226 and 228. Although most of these H6 HA mutations caused a significant decrease in receptor binding (fig. S1), a single G225D mutation surprisingly conferred binding to human-type receptors (Fig. 1A). Binding was observed only to α2-6 linked sialosides with preferential binding to selected extended N-linked glycans similar to a recent human H3N2 HA. Similar specificity was observed for the G225D mutant HA produced in insect cells, where binding was observed with even higher avidity, presumably due to the smaller glycans attached by these cells (fig. S2). Because G225D is a hallmark mutation in H1N1 viruses and confers binding to human-type receptors, we tested several other amino acid positions known to influence receptor binding in H1 viruses; L186P/S, A222K and R227A (fig. S3). Although none of the single amino-acid changes resulted in human-type receptor binding,

addition of the G225D in these backbones permitted binding to human-type receptors (fig S3). From this, we conclude that the aspartic acid at position 225 is a significant determinant for human-type receptor binding.

Because binding to the human respiratory epithelium coincides with the ability of viruses to transmit between humans (*17, 18*), we tested the ability of the HAs to bind to airway epithelial cells in tissue sections from chicken and human trachea. Like the HA from the avian reference strain A/Vietnam/1203/04 H5N1, the WT H6 HA binds epithelia sections of chicken trachea, but not human trachea (Fig. 1B). In contrast, the G225D mutant has acquired the ability to bind human trachea epithelium and concomitantly lost binding to chicken trachea. As expected, the human seasonal H3N2 control stains only human but not chicken trachea.

To examine the structural features that underlie the specificity switch of the G225D mutant, we determined its crystal structure in its apo form and in complex with human and avian receptor analogs (table S2). The G225D H6 mutant structure at 2.0 Å is highly similar to wild-type H6 HA [PDB entry 4XKD, Cα root mean squares deviation (RMSD) of 0.13 Å and 0.14 to the HA monomer and the RBS subdomain (amino acid 117-265)] with slight conformational changes in the side chains of RBS N137, L186 and Q226 (Fig. 2A). The 6′-SLN (human-type receptor) analog binds in a cis conformation, extending into the space between the 190-helix and 220-loop (Fig. 2B and C, fig. S4). The phi angle between Sia-1 and Gal-2 (O_6Sia-C_2Sia-O-C_6Gal) is similar to human analogs with other avian

and humans HAs (fig. S5) (*19*), but different from the H6 HA wild-type with 6′-SLN (*6*) (phi of 70 ° for G225D mutant and ~120 ° for wild-type, Fig. 2D). 6′-SLN hydrogen bonds with the main chain and side chain of D225 through the 3-hydroxyl and 4-hydroxyl of Gal-2 and with the Q226 side chain via the 4-hydroxyl of Gal-2. To understand the differential binding to human-type receptors, the G225D mutant in complex with a 50-fold excess of trisaccharide avian receptor analogues 3′-SLN (NeuAcα2-3Galβ1-4GlcNAc) and pentasaccharide LSTa (NeuAcα2-3Galβ1-3GlcNAcβ1-3Galβ1-4Glc) at 2.9 Å and 2.1 Å where three and two glycans could be visualized, respectively (fig. S6A and table S2). 3′-SLN binds in a cis conformation similar to wild type (*6*) with slight changes in Gal-2 and GlcNAc-3 presumably to prevent steric clashes between its Gal-2 6-hydroxyl with the aliphatic part of Asp225 (fig. S6B and C). Consequently, the distance between Asp225 main-chain carbonyl to Gal-2 6-hydroxyl and GlcNAc-3 3-hydroxyl is increased (from 2.6 Å and 3.2 Å respectively in the H6 HA wild-type complex to 4.6 Å and 3.8 Å in the mutant complex) decreasing the hydrogen bond interactions between Gal-2 and GlcNac-3 of 3′-SLN with the G225D mutant RBS. For LSTa, only Sia-1 and Gal-2 displayed any electron density implying very weak interactions between LSTa and the RBS. Similar to the wild type complex, LSTa bind in a cis conformation forming hydrogen interacting between Gal-2 and the carboxyl group of Asp225 (fig. S6D and E). We thus conclude that the single amino-acid mutation, G225D, in HA of H6N1 enables interaction with human-type receptors with a similar binding mode compared to other human HAs

143 despite not having all the canonical residues in human H1 (Val190) or H2/H3
144 (Gln228) HAs (fig S5).
145
146 Although the H6N1 virus remains prevalent in Taiwanese poultry, there has been
147 only one reported infection in humans in contrast to numerous infections from
148 avian H5N1 and H7N9 associated with human exposure to poultry (*20, 21*).
149 Recently, Wang *et al.* compared sequences from the human H6N1 isolate and
150 H6N1 viruses from Taiwanese poultry with a reference duck virus in 1972.
151 Positions 186, 190 and 228 increased avidity to human-type receptors, using
152 assays that employ commonly used fragments of avian and human-type
153 receptors (*22*). However, as shown previously (*6*) and in this report (Fig. 1 and fig.
154 S3), human H6 HA maintains a clear preference to avian-type receptors,
155 especially those that contain extended poly-N-acetyl-lactosamine branches.
156
157 Surprisingly, we found that the H6 HA has the capacity to completely switch to
158 human-type receptor specificity with a single nucleotide change resulting in the
159 G225D mutation previously documented as one of two amino-acid changes that
160 confer switch in receptor specificity in human H1N1 viruses. Single amino-acid
161 changes affecting receptor binding can occur in a single infection as documented
162 for a switch from human- to avian-type specificity in an H3N2 virus from a single
163 passage in eggs (*23*), and from avian- to transmissible human-type specificity for
164 an H1N1 virus after a single passage in ferrets (*24*). Thus, there is potential for a
165 switch in receptor specificity of H6N1 viruses from a single human infection. In

this regard, H6N1 is quite different compared to H5N1, where several mutations are required to attain respiratory droplet transmission between ferrets (*25-27*).

Although it would be optimal to determine if the G225D switch to human-type receptor specificity also supports aerosol droplet transmission in ferrets, such experiments comprise gain-of-function studies that are currently under a moratorium. In fact, while acquisition of human-type receptor specificity is believed to be a prerequisite for transmission of human influenza viruses, it is well known that an influenza polymerase E627K mutation is required for optimal infection (*28*). E627K is not present in avian and human H6N1 isolates but is detected in canine isolates (*22*). Also other as yet to be identified properties may need to be optimized for adaptation of the virus for transmission in man. Thus, new human infections with H6N1 should be closely monitored for any sign of change in receptor specificity or possible gain in human transmissibility.

ACCESSION NUMBERS

Atomic coordinates and structure factors have been deposited in the Protein Data Bank (PDB) under accession codes AAAA for Taiwan2 H6 G225D HA in apo form and BBBB, CCCC and DDDD in complex with 6′-SLN, LSTa and 3′-SLN.

AUTHOR CONTRIBUTIONS

Project design by R.P.dV., N.T., W.P., I.A.W. and J.C.P.; glycan array studies by R.P.dV. and R.M.; tissue staining studies by R.P.dV., I.N.A.W. and M.H.V.; X-ray

188 structure determination, protein production, and analysis by N.T., W.Y., and X.Z.,
189 and manuscript written by R.P.dV., N.T., I.A.W. and J.C.P.
190
191 **ACKNOWLEDGEMENTS**

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FIGURE LEGENDS

Fig. 1. Analysis of mutant human H6N1 HAs on glycan microarrays and binding to chicken and human trachea epithelial cells. (A) Glycan microarray analysis of A/Vietnam/1203/04 H5N1, A/Taiwan/2/13 H6N1, H6N1 G225D mutant and a human seasonal H3N2 control (A/Hong Kong/6934/10). The mean signal and standard error were calculated from four of the six independent replicates on the array after omitting the high and low values. α2-3 linked sialosides in white bars (glycans #11 to 79 on the x axis), α2-6 linked sialosides in black (glycans #80 to 135) and are further grouped by structure type (see top): L, linear; O, O-linked; N, N-linked and Lx, sialyl Lex. Glycans #1 to 10 are non-sialylated controls (see table S1 for complete structures). (B) Binding of the same recombinant HA proteins to chicken and human tracheal tissue. Binding is detected using by HA-antibody complexes containing and anti-StrepTag-HRP and a goat-anti-mouse HRP and developed with AEC.

Fig. 2. Crystal structure of the H6 HA G225D mutant in complex with a human receptor analogue. (A) Structural comparison of the RBS of the G225D mutant HA (gray) and the wild-type HA (green) displaying slight conformation changes in the vicinity of the mutation site Asp225. The conserved secondary

elements of the HA RBS (130-loop, 190-helix and 220-loop) are labeled and shown in cartoon representation. Selected residues and the receptor analogues are labeled and shown in sticks. (B) The glycan structure of human receptor 6′-SLN (Sia is abbreviation for sialic acid, Gal for galactose, GlcNAc for N-acetylglucosamine and Glc for Glucose). (C) Hydrogen bond interactions of the H6 G225D mutant RBS with Gal-2 of human receptor analogue 6′-SLN. The receptor analogue is labeled, colored in yellow and shown in sticks. (D) Superposition of 6′-SLN receptor analog from H6 G225D mutant complex (grey) compared to the H6 wild-type complex (green) indicates conformational changes arising from rotation around the linkage between Sia-1 and Gal-2 (phi changes from 70 ° in mutant structures to 120 ° for wild type). The 6′-SLN receptor analogue and the RBS Asp225 and Gln226 are labeled and shown in sticks.

From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Mon, 8 Aug 2016 08:55:56 -0400
To: Lambert, Linda (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Paulson H6N1 manuscript

Thanks Linda. I like your edits.

If anyone else has any feedback please let me know by COB today.

Teresa M. Hauguel, Ph.D.
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Sent: Friday, August 05, 2016 4:45 PM
To: Hauguel, Teresa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6) Post, Diane (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
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I also took a stab at the title language – moving it to the bottom.
Jump in and edit my comments. If our feedback went public would we be okay with it or would be viewed as heavy handed???
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Thank you all for your continuous work on this!
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Subject: Paulson H6N1 manuscript

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In particular, can you take a look at the last bullet and let me know if you interpreted the manuscript language in the same way that I did?

Thanks!

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As part of the communication strategy for this manuscript, NIAID ~~recommends~~ suggests the following:

- ~~Considering modifying the title.~~
- Provide additional details on the single case of human H6N1 infection which describe disease severity and patient outcome.
- Strengthen the explanation of the benefits of this research and the reasons for conducting the experiments.
- Discuss relevant risk mitigation measures or alternative approaches employed, particularly as they relate to the current USG gain-of-function research funding pause. In the last paragraph, this is very briefly discussed in the context of not being able to conduct ferret transmission studies. It would be useful to note here that the HA mutation which conferred alpha 2-6 receptor binding was not placed into a replication-competent virus and studies were restricted to *in vitro* analysis of a single viral protein.
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Lastly, there was a discussion about the title of the manuscript and that it could evoke significant concern in the public's understanding of/interpretation of these results – including the fact that live viruses with this mutation were not generated.

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From: Hauguel, Teresa (NIH/NIAID) [E]
Sent: Mon, 8 Aug 2016 08:58:23 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Brown, Liliana (NIH/NIAID) [E]; Ford, Andrew (NIH/NIAID) [E]; Hanson, Christopher (NIH/NIAID) [E]
Subject: Call for agenda items - 8/12 DURC/GoF meeting

Hi All,

Hope you had a nice weekend.

Please let me know if you have any agenda items for Friday's DURC/GOF meeting by COB Wednesday.

Thanks,
Teresa

Teresa M. Hauguel, Ph.D.
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From: Lambert, Linda (NIH/NIAID) [E]
Sent: Mon, 8 Aug 2016 12:30:35 -0400
To: Hauguel, Teresa (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Re: Paulson H6N1 manuscript
Attachments: image001.png

Hi all
Just one further comment...
Please note that when I read the draft I put my "conservative" lenses on. Specifically by our word choices were we Telling, recommending, suggesting, and if we don't have the authority to tell...we need to be softer. That said I look to the rest of you for belong to set the tone based on how we should be regarded in the conveying if these points and Teresa you know the situation with the PI and institution better than me...
L

Sent from my iPhone

On Aug 8, 2016, at 8:55 AM, Hauguel, Teresa (NIH/NIAID) [E] (b)(6) wrote:

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Sent: Mon, 8 Aug 2016 13:25:18 -0400
To: Hauguel, Teresa (NIH/NIAID) [E]; Lambert, Linda (NIH/NIAID) [E]; Post, Diane (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Paulson H6N1 manuscript

Hi,
Great job.
Just a single comment below.
My two cents are that we could "recommend" actions (based on our experience with the negative outcomes that can result from use of language in GOFROC publications).
Thanks,
David

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Thanks!

****

As part of the communication strategy for this manuscript, NIAID recommends the following:

- Considering modifying the title and one sentence summary to use less provocative and more scientifically nuanced language making clear that the work was done using recombinant protein not whole virus.
- Provide additional details on the single case of human H6N1 infection which describe disease severity and patient outcome.
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