From: Denison, Mark
Sent: Tue, 19 Dec 2017 17:54:36 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: P3CO and R01 Ai108197

Hi Erik,
Good to talk yesterday. Seeing the announcement today I can see why you were interested.
To confirm, has our grant already undergone the P3CO review?
I got that sense but I didn't ask directly.
Below are summary of our discussion. We of course are willing to provide more detail if needed and also to present in person if any issues arise that would be considered a test case of the policy and approach.

- The goal of the R01 fundamental discovery of determinants of fidelity and the role of nsp14 in fidelity, replication and immune evasion.
- We may put increased fidelity mutations and adaptive mutations into WT background to recover MERS-ExoN(-) or test whether fidelity can be increased beyond WT

- In other viral systems fidelity enhancing or fidelity impairing mutations are attenuating (picornavirus, alpha virus, influenza)
- To date all fidelity associated mutations we have tested in vitro have been less fit and in vivo have been attenuating.
- We may adapt for increased replication of ExoN mutants but anticipate fitness in vitro and in vivo to be impaired
- We will use MA versions of MERS and SARS for our recombinant experiments, likely less fit in humans due to mouse adaptation
- If we see any unexpected evidence for increased fitness or virulence we would stop and interact with you before proceeding
- We will provide updates of the work (papers, presentations) as it proceeds. We understand the critical importance of this

Hope this helps
Regards
Mark
Mark R. Denison M.D.
Craig-Weaver Professor of Pediatrics
Professor of Pathology, Microbiology & Immunology
Interim Director, Pediatric Infectious Diseases
Vanderbilt University Medical Center
D6217 MCN
Nashville, TN 37232-2581
(b)(6) (office)
(b)(6) (cell)
(b)(6)

From: Baric, Ralph S
Sent: Thu, 7 Dec 2017 16:11:54 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Denison, Mark (NIH)
Subject: RE: Is this good?

Wow---awesome! Fantastic news. Thanks for present!

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, December 7, 2017 9:54 AM
To: Denison, Mark (NIH) (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Is this good?

Already did. You're listed with (b)(4); (b)(6) percentile in our system too.

From: Denison, Mark [mailto:(b)(6)
Sent: Thursday, December 07, 2017 9:39 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: Re: Is this good?

WOO HOO!!
If you would just look at it yourself to be sure I'm not fooling myself! :)

Mark

From: Erik Stemmy (b)(6)
Date: Thursday, December 7, 2017 8:36 AM
To: Mark Denison (b)(6)
Cc: Ralph Baric (b)(6)
Subject: RE: Is this good?

Hi Mark,
Yes, this is great news, (b)(4) percentile from a SEP is still a (b)(4) percentile, so you're well within payline. Not sure when they will start making awards from this council round, but congratulations!

Erik

From: Denison, Mark [mailto:(b)(6)
Sent: Thursday, December 07, 2017 9:31 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: Is this good?

Erik,

I just got my score on AI108197.
It looks good I think but I haven't been in a SEP for a long time.

I'm hoping a (b)(4); percentile is really a (b)(4); percentile, which would be great I think
Do you have any insight on that?

Mark

- **Status:** Scientific Review Group review completed: Council review pending. Refer any questions to Program Official.
  Project Title: Determinants of Coronavirus Fidelity in Replication and Pathogenesis

- **PI Name:** Baric, Ralph S; DENISON, MARK R. (Contact)
  NIH Appl. ID: 9545972
  Application ID: 2 R01 AI108197-06

Application

- **Award Document Number:** RAI108197C
- **FSR Accepted Code:** N
- **Snap Indicator Code:**
- **Impact Score:** (b)(4); (b)(6);
- **Percentile:** (b)(4); (b)(6);
- **For information about next steps:** Click here
- **Early Stage Investigator Eligible:** N
- **New Investigator Eligible:** N
- **Eligible for FFATA Reporting:** Yes

From: Denison, Mark
Sent: Fri, 1 Dec 2017 17:05:17 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: Re: New CETR RFA

Thanks Erik. Yeah i saw it. Appreciate the note. Are you involved with it?
Mark.

Sent from my iPhone

On Dec 1, 2017, at 11:03 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Ralph and Mark,
You've probably already heard, but the new CETR RFA has been released. Thought I'd pass the link on in case you hadn't seen.

Erik

CETR RFA: https://grants.nih.gov/grants/guide/rfa-files/RFA-AI-17-042.html

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Cockrell, Adam
Sent: Thu, 30 Nov 2017 20:32:30 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Baric, Ralph
Cc: Sims, Amy C
Subject: FW: A57 Call
Attachments: AMC report for August 2017.docx

Hi Erik,

This is the email I sent for the rabies vaccine report on September 6. It is attached here.

Best,
Adam

From: Cockrell, Adam
Sent: Wednesday, September 06, 2017 5:23 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]' (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6)
Cc: Baric, Ralph S (b)(6) Sims, Amy C (b)(6)
Subject: RE: A57 Call

Hi Erik and Victor,

Please find the final monthly AMC report attached.

I have started working on the final report, but this will take more time. I have a number of commitments through September, but will try to work this in in the next few weeks.

Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Friday, July 28, 2017 10:00 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6)
Subject: RE: A57 Call

Hi Everyone,
It was nice speaking with you this morning. Based on our discussion, Adam will be wrapping up the final vaccine studies and working on the reports. The contract ends on 8/31, but we can accept the reports after that if you're not able to complete them by then. We also talked about the last monthly report, and I'm fine with you rolling that in to the final technical report as a short section summarizing the final month of the contract. The other reports that are due are the study SOP and the study report for the

vaccine studies. I've pasted below the deliverable information for the final technical report and SOPs, with some comments from me in red.

Let me know if you have any questions. Thanks for all the great work over the course of this contract. I really appreciate your dedication and flexibility getting this work done.

Erik

Standard Operating Procedures
The Contractor shall prepare and deliver the Standard Operating Procedures (SOPs) as described in the Statement of Work in accordance with the Delivery Schedule. For the SOP, include a generic study design and protocol for the studies.

Final Technical Report
This report shall summarize the results of all work completed under the task order and be delivered in accordance with the Delivery Schedule. This report will be in sufficient detail to explain comprehensively the results achieved. The final report shall contain:

a. A title page containing:
- Contract number, task order number and title
- Period of performance being reported
- Contractor's name and address
- Date of submission

b. Introduction covering the purpose and scope of the task order;
c. Description of the overall progress, plus a separate description of each protocol. Descriptions will include pertinent primary and summarized data in tables or graphs as appropriate to present significant results achieved; For this section, just include a brief paragraph for each study outlining design, treatment, challenge, and outcome. No data necessary. If you will include the last monthly report you can add it as a section here.
d. Cumulative list of all evaluations and products tested to date and dates for beginning and completion of evaluations; this can be wrapped into the previous section, if you include the study dates there.
e. Copies of any abstracts, poster presentations, manuscripts, and publications;
f. Copies of raw data as requested by the COR. No raw data necessary for final technical report; study data was included in the individual study reports.
i. For commercially available assay/model components, a list of qualified suppliers including name and contact information, catalog number, and other identifying information needed for purchasing assay/model components. No need to list every commercial product used, limit this list to any unique products that were necessary for the studies.
j. A tech transfer package for assays/models, to include all documentation and reagents required for successful transfer to other facilities. No need to include this tech transfer package.

-----Original Appointment-----
From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, July 25, 2017 4:59 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Accepted: A57 Call

When: Friday, July 28, 2017 9:30 AM-10:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Skype Meeting

MONTHLY REPORT

Contract HHSN272201000019I Task Order HHSN27200003 A57

Mouse Model for Evaluation of Medical Countermeasures Against Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Period of Performance:
August 1, 2017- August 31, 2017

Contractor's Name and Address:
Dr. Peter Palese
Horace W. Goldsmith Professor and ChairDepartment of Microbiology
Professor, Department of MedicineMount Sinai School of Medicine
1 Gustave Levy Pl.
New York, New York 10029-6574
Tel (b)(6)
Fax 212-722-3634
e-mail: (b)(6)

Date of Submission:
September 6, 2017

A. Scope

The objective of this task is to utilize a previously developed, lethal model of MERS-CoV infection to assess the efficacy of therapeutics or vaccine countermeasures against MERS-CoV.

B. Timeline

The timeline will be dependent upon the availability of anti-MERS-CoV therapeutics and vaccines. It is anticipated that four anti-MERS-CoV medical countermeasures will be evaluated over the course of the current contracted period.

C. Progress on Model and Supporting Data

Utilizing the MERS 288-330 Mouse Model to test the BNSP333-S1 Vaccine. Testing of this vaccine is through and agreement with the laboratory of Matthias Schnell at Thomas Jefferson University.

Please see previous reports for a description of the mouse model and viruses. BNSP333-S1 vaccine is derived from a recombinant rabies virus (RABV) vaccine strategy in which the MERS receptor binding domain (RBD) from the S1 region of spike protein is fused to the C-terminal part of the RABV G protein C terminus. The RABV-MERS-S1 particles express the MERS RBD on the surface of the RABV viral particles which are subsequently administered to mice via intramuscular (IM) route. 10ug of chemically inactivated BNSP333-S1, or control RABV vaccine was administered IM. The study outline is depicted in figure 1. Two different Vaccine strategies were executed with BNSP333-S1: 1) a prime, boost at 7 days and boost at 28 days (V1, Figure 1A), or 2) a prime and boost at 28 days (V2, Figure 1B). The RABV control vaccination was administered according to the first vaccine strategy (C1, Figure 1A). All mice were weighed daily and assessed for survival. Three cohorts of 5 mice each (V1 and V2), or 6 mice (C1), were removed at day 3 post-infection to assess gross hemorrhaging in the lungs, viral titer, and samples were removed for histology and RNA. Three additional cohorts of 10 mice each (V1 and V2), and 12 mice (C1), were assessed for respiratory function at day 0, and surviving mice at days 3 and 5 post-infection. Surviving mice at day 6 post-infection were sacrificed to assess gross hemorrhaging and samples were collected for lung titer, histology, and RNA.

Page 010 of 217

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 011 of 217

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 012 of 217

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 013 of 217

Withheld pursuant to exemption

(b)(4)

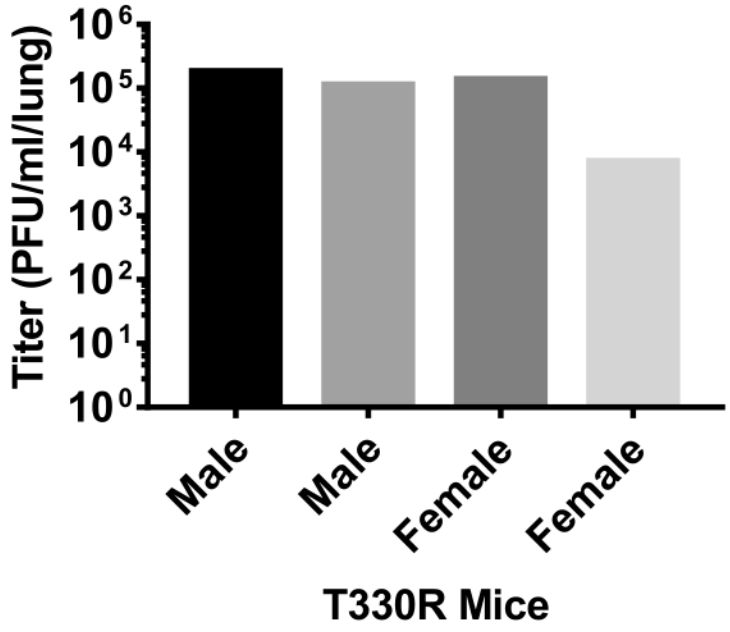
of the Freedom of Information and Privacy Act

Novel MERS-CoV viruses that will be critical for testing anti-MERS vaccines and therapeutics, and understanding how MERS causes respiratory disease.

In the studies presented to date we have used the plaque purified MERS-15 clone 2 virus or the infectious clone of this, icMERSma1. A limitation of this virus, as pointed in our manuscript, is the dose of virus required ($5x10^6$ PFU) to elicit pathogenic phenotypes (as described in the study above) in the mouse. To develop more pathogenic mouse-adapted viruses that can be used in challenge studies that evaluate vaccines and therapeutics, we continued passaging in our mouse model. We have achieved titers that may allow us to reduce our challenge dose in vaccine and therapeutic studies by as much as 100-fold as described in the previous report (April 2017). This virus underwent 35 passages in 288-330 +/- mice. Since this time, we have passaged this virus out to P56, and experiments are ongoing to characterize these viruses. The initial goal in mouse-adapting in the 288-330+/- mice was to select for a MERS virus that would eventually be able to replicate in wild-type mice. In a step toward this direction, we identified that the MERS-35 virus could replicate in the lungs of mice that harbor only the single amino acid humanized at position 330 (we refer to these mice as T330R mice), but not at position 288 (Figure 7). We continued passaging this virus in T330R mice to move closer to a virus that can replicate in wild-type mice. In order sustain a viable titer passaging was alternated between T330R mice and 288-330+/- mice. We are at passage P47. The MERS-35 virus does replicate in wild-type C57Bl/6J or Balb/c mice.

we passaged EMC 2012 in male or female 288-330+/- mice.

Figure 7. MERS-35 replicates in T330R mice.



When we initiated passaging we started with the MERS-0 virus, which harbors a three amino acid insert in the S2 domain of the spike protein. This mutation was previously identified from in vitro passaging on the NIH 3T3 mouse cell line, therefore we assumed that this would provide an advantage during mouse adaptation. Furthermore, we were limited in the number of mice available for passaging therefore chose to start with the MERS-0 virus. To determine if this indeed is the case we initiated three additional independent MERS passaging lines with the EMC 2012 virus. To determine if specific mutations could arise due to gender we passaged EMC 2012 through female 288-330+/- (MERS-F) and a separate MERS line through male 288-330+/- mice (MERS-M). These are at passage P30 for MERS-F and P30 for MERS-M. We expanded the viruses on Vero81 cells, from P20 for each, to test if there are differences in disease for male and female mice. Figures 8 and 9 demonstrate that administration of $5x10^5$ PFU of either MERS-F or MERS-M exhibit similar pathogenesis in both male and female mice. Experiments are ongoing to determine if there are gender difference in other passages, and if there are gender-specific genetic changes in the two MERS lines.

Figure 8. Male mice exhibit similar weight loss from MERS-F and MERS-M.

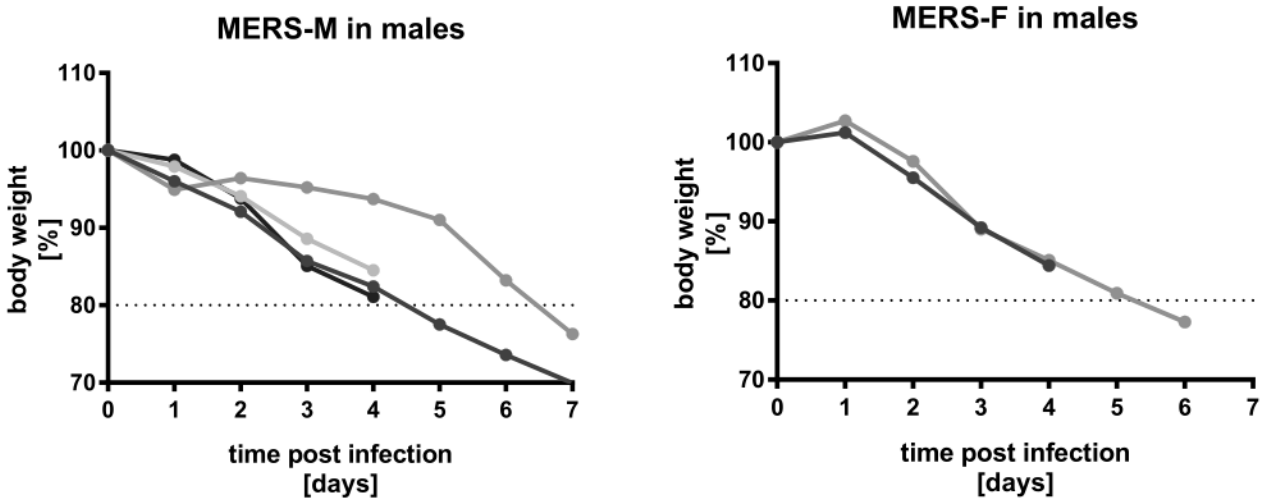
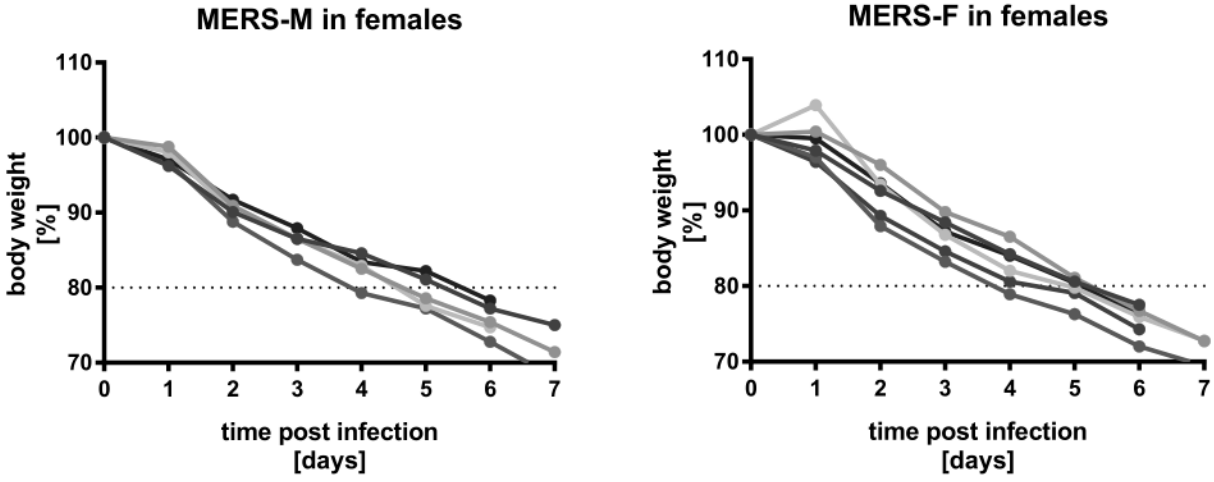


Figure 9. Female mice exhibit similar weight loss from MERS-F and MERS-M.



For the third MERS line we initiated passaging with EMC 2012 in 288-330+/+ mice. All previous passages were initiated, and carried out in heterozygous mice with the understanding that we may be able to facilitate MERS to transition to using mouse DPP4 as the primary receptor. However, we also wanted to adapt to fully homozygous mice to determine if we can achieve a mouse-adapted virus that exhibits pathogenesis at titers in the 10^2-10^3 dose range. We are currently at passage P35. Studies with this MERS line are ongoing to determine the minimum viral dose and the mutations that confer pathogenesis. Overall, having independently adapted MERS lines will allow us to perform comparative genomics to identify common mutations that are associated with enhanced pathogenesis.

Technical/Performance Issues and Proposed Corrective Action

None

D. Expenditures Reporting

Mt. Sinai and UNC have completed a revised subcontract and Option Period Two ends August, 2017.

From: Peter Daszak
Sent: Tue, 21 Nov 2017 19:51:32 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Aleksei Chmura
Cc: Alison Andre
Subject: RE: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01

Hi Erik,

Just letting you know that the paper came back from *Nature* with a request for some more experimental work (SPF pigs). We're setting these up now and hopefully we'll be able to address the comments. It'll take a few weeks, then back to one of the reviewer.

I'll keep you posted….

Cheers,

Peter

Peter Daszak
President

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

Tel. (b)(6)
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 prevent pandemics and promote conservation.

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, November 9, 2017 8:40 AM
To: Peter Daszak; Aleksei Chmura
Cc: Alison Andre
Subject: RE: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01

Hi Peter and Aleksei,

Any news on the paper? Looks like NIAID's OC is planning for a media availability when it is released.

Erik

From: Peter Daszak [mailto:(b)(6)
Sent: Friday, October 20, 2017 5:14 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: RE: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01

I will definitely let you know that minute we hear the news.

Also – I like your positive approach: *When* it gets published, not *If* !! We did meet with the Editor at a DC symposium 3 weeks ago and she was fairly positive about it – just waiting on one reviewer right now..

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Monday, October 2, 2017 11:56 AM
To: Peter Daszak
Cc: Aleksei Chmura; Alison Andre
Subject: RE: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01

Hi Peter,
Glad to see the work is under second review at Nature. I think NIAID's office of communications may be interested in promoting it once it's published. Can you let me know once it's accepted?

Best,
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Peter Daszak [mailto:(b)(6)
Sent: Sunday, October 1, 2017 1:22 PM
To: Fauci, Anthony (NIH/NIAID) [E] (b)(6)
Cc: Morens, David (NIH/NIAID) [E] (b)(6) David Morens (b)(6)
(b)(6) Kurilla, Michael (NIH/NIAID) [E] (b)(6)
(b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Alison Andre
(b)(6) Aleksei Chmura (b)(6)
Subject: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01
Importance: High

Dear Dr Fauci and NIAID colleagues,

It was a pleasure to meet you again today. I've attached an unpublished paper, currently in the second round of review with *Nature* that describes a novel bat-origin Coronavirus (SADS-CoV: Swine Acute Diarrheal Syndrome coronavirus) that recently spilled over into pig farms in Southern China, leading to the death of over 25,000 piglets in 5+ farms in Guandong Province.

The virus originates in the same group of bats as SARS-CoV, and emerged in the same place. It's not known to be zoonotic (we've tested 35+ pig farm workers with an antibody assay and none are positive. The pig farm owners tell us the virus is now under control, thanks to culling and separation of infected herds. It's not yet known if this virus has appeared elsewhere, but we are looking. We're also doing assays to find out if it can infect human cells in the lab – so far no evidence of this.

I hope this paper is of interest. You should know that this work was supported by a NIAID R01 that Erik Stemmy is the Program Officer for, and that I'm PI on, with Zhengli Shi as co-PI.

If you want any other information at all, please don't hesitate to email or call and I'd be happy to come over to NIAID to brief you further. I'll also let you know if/when it will be published so that we can try to foster some publicity as appropriate.

Cheers,

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To: Stemmy, Erik (NIH/NIAID) [E]; Aleksei Chmura
Cc: Alison Andre
Subject: RE: Confidential - A new bat-origin coronavirus emerging in pigs in China discovered under our NIAID R01

Hi Erik – still waiting. One reviewer to go….

Great that NIAID will help with publicity, so I'm keeping my fingers crossed here…

Cheers,

Peter

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Email: (b)(6)

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From: Mathur, Punam (NIH/NIAID) [E]
Sent: Wed, 1 Nov 2017 14:18:27 +0000
To: 'Baric, Toni C'; Baric, Ralph; Graham, Rachel
Cc: Yao, Alison (NIH/NIA/ERP) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Reschedule Nov 7th ORFEOME call

Thank you!

From: Baric, Toni C [mailto:(b)(6)
Sent: Wednesday, November 01, 2017 9:59 AM
To: Mathur, Punam (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Graham, Rachel (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Reschedule Nov 7th ORFEOME call

Wonderful. It is on the calendar.

From: Mathur, Punam (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, November 01, 2017 9:58 AM
To: Baric, Toni C (b)(6) Baric, Ralph S (b)(6) Graham, Rachel (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Reschedule Nov 7th ORFEOME call

Hi Toni,

Friday Nov 17th at 2 pm works for us!

Thanks,
Punam

From: Baric, Toni C [mailto:(b)(6)
Sent: Tuesday, October 31, 2017 12:34 PM
To: Mathur, Punam (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Graham, Rachel (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Reschedule Nov 7th ORFEOME call

Hi Punam,
How about Friday Nov 17 at 2 pm?
Toni

From: Mathur, Punam (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, October 31, 2017 12:09 PM
To: Baric, Ralph S (b)(6) Graham, Rachel (b)(6) Baric, Toni C (b)(6)
Cc: Yao, Alison (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Reschedule Nov 7th ORFEOME call

Dear All,

Since Alison will be on travel next Tuesday, November 7th, we would like to reschedule our call next month. Please let us know if the following time frames might work:

- Thursday, Nov. 9th: 11 am – 12 pm
- Monday, Nov. 13th: 12 – 2 pm
- Tuesday, Nov. 14th: 4 – 5 pm
- Friday, Nov. 17th: 10 -11 am and 1-4 pm

Best,
Punam

From: Peter Daszak
Sent: Thu, 28 Sep 2017 18:14:33 +0000
To: Lu, Kristina (NIH/NIAID) [E]
Cc: Stemmy, Erik (NIH/NIAID) [E]; Hongying Li; Aleksei Chmura; Hume Field
Subject: Re: Invitation to US-Japan 20th Int'l Conference on Emerging Infectious Diseases - NIAID

Hi Kristina,

I would like to recommend Hume Field who is a Senior Science & Policy Advisor for China and Southeast Asia at EcoHealth Alliance for the talk. Hume has long been a collaborator with EcoHealth Alliance and would be excellent to engage with you and the other attendees in discussions around our work.

I've copied Hume on this email.

Cheers,
Peter

Peter Daszak
President
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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 prevent pandemics and promote conservation.

From: Lu, Kristina (NIH/NIAID) [E] (b)(6)
Sent: Monday, September 11, 2017 7:49 PM
To: Peter Daszak
Cc: Stemmy, Erik (NIH/NIAID) [E]; Hongying Li; Aleksei Chmura
Subject: Re: Invitation to US-Japan 20th Int'l Conference on Emerging Infectious Diseases - NIAID

Hi Peter,

Thanks for your response. I'll be sure to keep you in mind the next time we reconvene with a focus on MERS-CoV/viral respiratory infections.

I am planning to extend an invitation to your colleague, Kevin Olival. If he is also unavailable, could you provide additional speaker suggestions with a broad focus on pathogenesis / trends of CoVs in Asia?

Thanks,
Kristina

From: Peter Daszak (b)(6)
Date: Friday, August 25, 2017 at 10:57 AM

To: "Lu, Kristina (NIH/NIAID) [E]" (b)(6)
Cc: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6) Hongying Li (b)(6) Aleksei Chmura (b)(6)
Subject: Re: Invitation to US-Japan 20th Int'l Conference on Emerging Infectious Diseases - NIAID

Dear Kristina,

Apologies for the late reply. I am just back from two weeks in South America and catching up with emails. I would definitely like to attend the Conference, but unfortunately, those dates clash with our PREDICT All-Country Meeting in Belgium from January 9-11 that I need to attend. Good luck with the conference and please do keep me in mind for next time.

Cheers,

Peter

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From: Lu, Kristina (NIH/NIAID) [E] (b)(6)
Sent: Thursday, June 22, 2017 7:31 PM
To: Peter Daszak
Subject: Invitation to US-Japan 20th Int'l Conference on Emerging Infectious Diseases - NIAID

Dear Dr. Daszak,

I would like to invite you to the **U.S.-Japan Cooperative Medical Sciences Program (USJCMSP) 20th International Conference on Emerging Infectious Diseases (EID)** and the **20th Acute Respiratory Infections (ARI) Panel Meeting** in **Shenzhen, China** during **January 8-12, 2018**. I am the Secretariat for the US-Japan ARI Diseases Panel and a Program Officer at NIAID-NIH. I work with Erik Stemmy (NIAID), who highly recommended you for participation and presentation.

The focus of this conference will be on pathogenesis and immunity of viral diseases of importance in the Asia-Pacific region. The conference objectives are to share current research findings and foster existing and potential international research collaborations that engage investigators and institutions in the Asia-Pacific region and the United States.

https://www.niaid.nih.gov/research/us-japan-cooperative-medical-science-program-organization-and-history

During the EID Conference, there will be broad coverage on a number of viral diseases, including influenza, ebola, HIV, dengue, zika, and hepatitis. In conjunction with the EID Conference, the ARI Panel Meeting will convene with a more focused agenda on emerging virus diseases at the animal-human interface, including influenza and coronaviruses.

I am hoping you are willing to give two presentations on the following topics –

1. EID - pathogenesis / trends of CoVs in Asia
2. ARI - there is flexibility for a presentation topic of your choice

We will support your travel expenses.
Please let me know if you are able to participate and present. Many thanks in advance and looking forward to hearing from you!
Kind regards,
Kristina
****

Kristina T. Lu, PhD
Program Officer
Respiratory Diseases Branch
Division of Microbiology & Infectious Diseases
NIAID | NIH | DHHS
Phone: (b)(6)
(b)(6)

From: Peter Daszak
Sent: Thu, 24 Aug 2017 20:47:54 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Hongying Li; Aleksei Chmura
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Hi Erik – we're doing a bunch of experiments to address reviewer's comments. One of our rival groups has already got their (not as significant) paper into EID, so the game is on! I'll keep you updated once we hear back from the next round of review…

Cheers,

Peter

Peter Daszak
President

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, August 2, 2017 12:55 PM
To: Peter Daszak
Cc: Hongying Li; Aleksei Chmura
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Hi Peter,
Just wanted to check in on this SADS-CoV manuscript. Did you get any news from Nature yet?

Erik

From: Peter Daszak [mailto:d(b)(6)
Sent: Thursday, June 29, 2017 2:39 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hongying Li (b)(6)
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Hi Erik,

I just wanted to say thanks for hosting us at NIAD today – it was great to have an interested audience with good questions and nice to have a chance to introduce our collaborators to you personally.

I mentioned the upcoming SADS-CoV paper might get into *Nature*. Obviously, this is touch-and-go right now, but I've attached the draft here so you can forward it to your communications team in case they want to get a release out earlier this time.

By the way – we've had some great publicity from the other paper last week. If you go to the following link we've put some of the stories up on our EHA website here:
http://www.ecohealthalliance.org/updates

Hope you enjoy skimming through them, and thanks again for setting up the talk this morning.

Cheers,

Peter

Peter Daszak
President

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, June 29, 2017 7:22 AM
To: Peter Daszak
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Also, please let me know when you arrive at security and I'll meet you there. My mobile is (b)(6) (b)(6)

Erik

From: Peter Daszak [mailto:(b)(6)
Sent: Thursday, June 29, 2017 12:43 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Hongying Li (b)(6)
Cc: Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Erik,

In case NIAID has issues with USB drives etc., here is a pdf version of our talk for tomorrow morning. I hope you can have that as a backup from your email in case we can't download our talk from our laptops.

Look forward to seeing you.

Cheers,

Peter

Peter Daszak
President

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Monday, June 26, 2017 9:30 AM
To: Hongying Li

Cc: Peter Daszak; Aleksei Chmura; Alison Andre
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Thank you Hongying. I will forward it to security. Looking forward to your visit later this week.

Erik

From: Hongying Li [mailto:(b)(6)
Sent: Monday, June 26, 2017 9:25 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Peter Daszak (b)(6) Aleksei Chmura (b)(6)
Alison Andre (b)(6)
Subject: Re: Potential visit to NIH by our Chinese Co-investigator in June?

Dear Erik,

Not sure if this is too late, but wanted to send you the updated attendee information with Peng Zhou's visa number. Please find it in the attachment. Let me know if there is any question.

Thanks,
Hongying

On Jun 16, 2017, at 11:22 AM, Hongying Li (b)(6) wrote:

Dear Erik,

Please find the security screening information for Zhengli Shi, Peng Zhou, and Hongying Li in the attachment. We don't have the visa No. for Peng Zhou at this moment because his visa application is still under administrative processing at the Embassy. We are not sure if he can obtain his visa on time or not, but will let you know as soon as we have any further confirmed information.

Please let me know if there is any question. Thank you!

Best,
Hongying

<5601 Foreign Visitor Form-China.xlsx>
On May 24, 2017, at 3:16 PM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Peter,
Thanks for this information. I've attached a form that will help expedite security screening for Dr Zhou and Hongying Li. Can you please have them complete the information on the second sheet of the attachment? I'll need to turn it in to our security office at least a week before your visit, so if you could

get it back to me by June 19th or 20th that would be great. Also, please let them know they should bring their passports with them. Everyone else will need a photo ID as well.

Let me know if you need directions to our building. I would suggest planning to arrive between 8:15 and 8:30, as there can be a line at security if there are other public meetings occurring that day. There is no visitor parking at our facilities, but there is a public parking garage on our block that I can get validation stickers for if you'll be driving. We are also a short walk from the Twinbrook Metro stop, if you plan to travel by train.

Erik

From: Peter Daszak [mailto:(b)(6)
Sent: Wednesday, May 24, 2017 3:05 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hongying Li (b)(6) Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?
Importance: High

Hi Erik,

Great to hear from you and looking forward to the talk on June 29th

We're proposing for 4 people to visit NIAID and I've attached bios for all of them to this email. Note that Dr Shi, Dr. Zhou and Hongying Li are all (b)(6) and I'm not sure what sort of clearance you'll need for that, so please let me know and we'll work on getting the relevant documents to you

1. Myself, PI on the NIAID CoV grant, President of EcoHealth Alliance, EHA lead on the USAID PREDICT project
2. Dr. Zhengli Shi, Co-Investigator on the NIAID CoV grant, Director of Center for Emerging Diseases at The Wuhan Institute of Virology
3. Dr. Peng Zhou, Associate Professor at Wuhan Institute of Virology
4. Hongying Li, Research Scientist and Country Liaison for China at EcoHealth Alliance

Re a title for the talk, bearing in mind it should be broader than just SARS-CoV, what about the following:

"SARS, MERS and the risk of novel viral emergence from bats"

Zhengli and I will do a double act, and we'll cover the work we're doing on the NIAID project, as well as the broadscale surveillance of bats for novel viruses in PREDICT.

Cheers,

Peter

Peter Daszak
President

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, May 18, 2017 8:26 AM
To: Peter Daszak
Cc: Hongying Li; Aleksei Chmura; Alison Andre
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Hi Peter,
We've got you on the calendar for June 29th. Can you send me a title for the talk, short summary, and brief bios for the presenters?

Thank you!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Monday, April 24, 2017 4:47 PM
To: Peter Daszak (b)(6)
Cc: Hongying Li (b)(6) Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Ok! I'll see about scheduling you for the slot on June 29th. Can you send me a title and short synopsis? Since our whole division would be attending it would be great if you could cover some of the collaborative work with PREDICT and not solely focus on the MERS work.

Erik

From: Peter Daszak [mailto:(b)(6)
Sent: Monday, April 24, 2017 4:44 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hongying Li (b)(6) Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

That would be perfect. The conference that Zhengli's attending starts on the evening of the 29th in Colorado so she could get a midday plane and still make it.

We'll plan to come to DC the afternoon or evening before and then do the symposium and meet with you.

Cheers,

Peter

Peter Daszak
President

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Monday, April 24, 2017 4:35 PM
To: Peter Daszak
Cc: Hongying Li; Aleksei Chmura; Alison Andre
Subject: RE: Potential visit to NIH by our Chinese Co-investigator in June?

Hi Peter,

I would be happy to have you visit us in June. I am available on the 28th. If there is any flexibility in your schedule, Thursday mornings we have a division-wide seminar from 9-10am, and that would be an ideal time to have you present on your work to the larger audience. I understand if that's not possible, thought, but thought I would check to see. Please let me know.

Thanks,
Erik

From: Peter Daszak [mailto(b)(6)
Sent: Monday, April 24, 2017 4:11 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Hongying Li (b)(6) Aleksei Chmura (b)(6) Alison Andre (b)(6)
Subject: Potential visit to NIH by our Chinese Co-investigator in June?
Importance: High

Dear Erik,

Our Chinese Co-investigator, Zhengli Shi from the Wuhan Institute of Virology, will be visiting the US in June to give a talk at a conference here. I'd really like to come and visit you and your colleagues at NIH with her while she's here. We could have a meeting to talk about progress on the project and could even do a seminar if there is a format for these.

Zhengli's timeline is fixed, and I wondered if you and your colleagues would be available on Wednesday June 28th? If not, we can look at alternative dates…

Cheers,

Peter

Peter Daszak
President

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<5601 Foreign Visitor Form.xlsx>

Hongying Li, MPH 李泓萤
China Programs Coordinator

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

(b)(6) (U.S. mobile)
(b)(6) (China mobile)
(b)(6) (Skype)
(b)(6) (WeChat)

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: Cockrell, Adam
Sent: Sat, 19 Aug 2017 00:24:48 +0000
To: Matthias Schnell
Cc: Stemmy, Erik (NIH/NIAID) [E]; Johnson, Reed (NIH/NIAID) [E]; Baric, Ralph; Matthew Frieman
Subject: RE: Update on Rabies Vaccine Study

Sorry for the confusion. The bleeds were done prior to infection, and prior to moving the mice into the BSL3 for challenge. Therefore, no need for deactivating prior to shipment.
Best,
Adam

From: Matthias Schnell [mailto:(b)(6)
Sent: Friday, August 18, 2017 8:12 PM
To: Cockrell, Adam (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Johnson, Reed (NIH/NIAID) [E] (b)(6) Baric, Ralph S (b)(6) Frieman, Matthew (b)(6)
Subject: Re: Update on Rabies Vaccine Study

You - send us the left over samples so Chris could do the VNA. guess you have protocols in place to get them deactivated- right? We do have a BLSB3 but no approval for MERS-CoV
Matthias

On Aug 18, 2017, at 18:10, Cockrell, Adam (b)(6) wrote:

Hi Matthias,

We will definitely have histology for this manuscript, with a number of disease parameters. I am submitting histology this coming week. It will take a few weeks for processing and analysis.

I have all the serum from the prebleed, bleed two (about 3 weeks after prime and day 7 boost), and bleed three (about 3 weeks after the day 28 boost). We have not done the neut. assays with MERS yet. I would be happy to send some serum your way.

Antiviral research or vaccine sounds good. I was also considering Scientific Reports, which seems on par with antiviral research.

Best Regards,

Adam

From: Matthias Schnell [mailto:(b)(6)
Sent: Thursday, August 17, 2017 8:22 PM

To: Cockrell, Adam (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Johnson, Reed (NIH/NIAID) [E]
(b)(6) Baric, Ralph S (b)(6) Frieman, Matthew
(b)(6)
Subject: Re: Update on Rabies Vaccine Study

Hi Adam:
That really depends - with the current data I think these journals are out of reach because the vaccine itself has already been published. I do agree your system is better than what we previously used. Are you planning on doing histology or other experiments? Also are there sera left for some RABV VNA? We could do them. With the data you have right now I think antiviral research or vaccine would be a better target. However if you want to start higher I have no problem with trying. My two cents
Matthias

On Aug 17, 2017, at 17:23, Cockrell, Adam (b)(6) wrote:

Thanks Matthias and Ralph,

If everyone agrees I will communicate with Chris about writing the manuscript.

Based on the previous JV manuscript, I believe our target would be JV, MBio, MSphere, or something similar? Thoughts?

Best,

Adam

From: Matthias Schnell [mailto:(b)(6)
Sent: Wednesday, August 16, 2017 8:45 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Johnson, Reed (NIH/NIAID) [E] (b)(6) Cockrell, Adam
(b)(6) Baric, Ralph S (b)(6) Frieman, Matthew
(b)(6)
Subject: Re: (b)(4)

Dear all
Adam did most of the work so he should be the first author, Chris made the vaccine so he should be second. The other authors we need to determine. I am fine with whatever we come up with. It's a collaboration so I am happy with all feel is right.
Matthias

On Aug 16, 2017, at 15:27, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

That's great. Publication shouldn't need clearance from our office. The NCEA publication requirements are really to be sure that both the submitter and test site are aware of publications and can

review/comment. If you are working collaborative on a publication, you should just need to keep me in the loop with the drafts.

Erik

From: Johnson, Reed (NIH/NIAID) [E]
Sent: Wednesday, August 16, 2017 2:37 PM
To: Matthias Schnell (b)(6) Cockrell, Adam (b)(6)
Cc: Baric, Ralph (b)(6) Frieman, Matthew (b)(6)
(b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Update on Rabies Vaccine Study

Guys,

When do we want to discuss writing this up?

Erik, do we need clearance through your group to do so?

Thanks,

Reed

From: Matthias Schnell [mailto:(b)(6)
Sent: Tuesday, August 15, 2017 5:24 PM
To: Cockrell, Adam (b)(6)
Cc: Matthias Schnell (b)(6) Baric, Ralph (b)(6) Johnson, Reed (NIH/NIAID) [E] (b)(6) Frieman, Matthew
(b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6) Beall, Anne Elizabeth (b)(6)
Subject: Re: Update on Rabies Vaccine Study

Terrific! Thanks Adam
Matthias

On Aug 15, 2017, at 16:59, Cockrell, Adam (b)(6) wrote:

Everyone,

This is the same update as last week with titers included.

Adam

From: Matthias Schnell [mailto:(b)(6)
Sent: Wednesday, August 09, 2017 11:42 AM
To: Cockrell, Adam (b)(6)
Cc: Matthias Schnell (b)(6) Baric, Ralph S (b)(6)

Johnson, Reed (NIH/NIAID) [E] (b)(6) Frieman, Matthew
(b)(6) Erik [E] Stemmy
(b)(6) Beall, Anne Elizabeth (b)(6)
Subject: Re: Update on Rabies Vaccine Study

Adam:
thanks a lot for all the work. Yes looks very nice.
Thanks again
Matthias
On Aug 9, 2017, at 11:23, Cockrell, Adam (b)(6) wrote:

Hi all,

Please find an update of the data attached for the MERS Rabies vaccine in the our 288-330+/+ mouse model. I think it looks really nice!

I am in the process of titering viruses (should have sometime next week), and will submit tissue for histology next week. This will probably take a few weeks for processing and analysis.

For the respiratory function data. Penh is a unit less measure that reflects airway obstruction/restriction due to debris in the airway. On day 0 and day 5 there was an issue with one of the Buxco chambers so we do not have a single data point for one mouse in the MERS-Rabies Vaccine Prime/28 cohort on day 0 and one mouse from the Rabies Ctrl. cohort on day 5.

Best,
Adam
<Summary of Data.pdf>

<Summary of Data.pdf>

From: Peter Daszak
Sent: Fri, 28 Jul 2017 21:37:02 +0000
To: Chen, Ping (NIH/NIAID) [E]
Cc: Stemmy, Erik (NIH/NIAID) [E]; Hongying Li; Aleksei Chmura; Alison Andre
Subject: Meeting in Beijing on September 4-5?

Hi Ping,

Hope everything is well.

(b)(6) and I will be in Beijing on September the 4th and 5th for the Global Virome Project initiate in China.

There has been progress since the committee meeting in Beijing this February, and we wanted to meet with the Chinese Academy of Sciences and other stakeholders at the US Embassy for more discussions. Would you be in Beijing and available to join some of our meetings.

I've cc'd my NIAID program officer, Erik Stemmy, as well to keep him in the loop.

I look forward to hopefully seeing you in Beijing.

Cheers,

Peter

Peter Daszak
President

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From: Peter Daszak
Sent: Fri, 28 Jul 2017 21:37:02 +0000
To: Kurilla, Michael (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Cassetti, Cristina (NIH/NIAID) [E]; Aleksei Chmura
Subject: Re: Potential (b)(4) overlap projects - can we discuss?

Good to chat with you both the other week.

I'd mentioned that I would update you with the five priority viral families under our USAID PREDICT award are Flaviviruses, Filoviruses, Coronaviruses, Paramyxoviruses and Orthomyxoviruses. Call or email anytime, if you want to chat more about collaboration under (b)(4) projects in Egypt or elsewhere. There is an opportunity get at some very interesting questions.

Also, we are planning on launching the GVP at the upcoming PMAC in Thailand from 29 Jan - 3 Feb 2018:

http://www.pmaconference.mahidol.ac.th/index.php

It would be very good to see you both there.

Cheers,

Peter

Peter Daszak
President

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

Tel. (b)(6)
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 prevent pandemics and promote conservation.

From: Kurilla, Michael (NIH/NIAID) [E] (b)(6)
Sent: Monday, July 10, 2017 3:16 PM
To: Aleksei Chmura
Cc: Peter Daszak; Stemmy, Erik (NIH/NIAID) [E]; Cassetti, Cristina (NIH/NIAID) [E]
Subject: RE: Potential (b)(4) overlap projects - can we discuss?

Raynita had to leave early today.

Let's use: (b)(6)

Passcode: (b)(6)

Michael G Kurilla, MD-PhD
Director, Office of BioDefense, Research Resources, and Translational Research
Associate Director for BioDefense Product Development
DMID, NIAID, NIH, DHHS
5601 Fishers Lane 8G61
Rockville, MD 20852
(b)(6)

Death: "Humans beings make life so interesting. Do you know, that in a universe so full of wonders, they have managed to invent boredom."
- *Terry Pratchett, from Hogfather*

From: Aleksei Chmura [mailto (b)(6)
Sent: Saturday, July 08, 2017 6:05 PM
To: Kurilla, Michael (NIH/NIAID) [E] (b)(6)
Cc: Dr. Peter Daszak (b)(6) Addison, Raynita (NIH/NIAID) [E] (b)(6)
Subject: Re: Potential (b)(4) overlap projects - can we discuss?

That will be super! I will set up the call with Raynita.

Cheers,

-Aleksei

On Jul 8, 2017, at 17:59, Kurilla, Michael (NIH/NIAID) [E] (b)(6) wrote:

Monday after 3:30PM my time works.

Raynita can arrange for me.

Michael G Kurilla, MD-PhD
Director, Office of BioDefense, Research Resources, and Translational Research
Associate Director for BioDefense Product Development
DMID, NIAID, NIH, DHHS
5601 Fishers Lane 8G61

Rockville, MD 20852
(b)(6)

Death: "Humans beings make life so interesting. Do you know, that in a universe so full of wonders, they have managed to invent boredom."
- *Terry Pratchett, from Hogfather*

From: Aleksei Chmura [mailto:(b)(6)
Sent: Friday, July 07, 2017 10:14 PM
To: Kurilla, Michael (NIH/NIAID) [E] (b)(6)
Cc: Dr. Peter Daszak (b)(6)
Subject: Re: Potential (b)(4) overlap projects - can we discuss?
Importance: High

Dear Michael,

Would any blocks of time from the following US (East Coast) times work for you?

Monday 10th July: 12:00pm - 5:00pm
Tuesday 11th July: 3:00pm - 4:00pm

Once you confirm, I will send around call-in details.

Sincerely,

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

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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: Peter Daszak
Sent: Friday, July 7, 2017 8:19 PM

To: Kurilla, Michael (NIH/NIAID) [E]
Subject: RE: Potential (b)(4) overlap projects - can we discuss?

Definitely. I'm traveling but am only 4 hours ahead and can set up a time. I've cc'd Aleksei who will be able to coordinate based on my flights etc. and when you're available. Monday or Tuesday would be good…

I've also been thinking about (b)(4) given our recent findings of SARS-like viruses from bats that are so close to SARS-CoV that they cause similar clinical signs in the humanized mouse model, but when you treat with a monoclonal that knocks SARS-CoV, it has zero effect on the bat virus….It implies that (b)(4) could lay out funds for vaccine development that might not be effective against the broader array of undiscovered viruses out there.

Anyway – look forward to talking with you..

Cheers,

Peter

Peter Daszak
President

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

Tel. (b)(6)
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 prevent pandemics and promote conservation.

From: Kurilla, Michael (NIH/NIAID) [E] (b)(6)
Sent: Friday, July 7, 2017 6:28 PM
To: Peter Daszak
Subject: Potential (b)(4) overlap projects - can we discuss?

Peter,

For a couple of reasons, I'm looking to develop some small scale projects related to (b)(4) that might have some overlap with ongoing or planned GVP activities.

For example, we are discussing some surveillance and screening activities in eastern Africa for MERS-like coronaviruses and Nipah viruses in southeast Asia. The idea would be to collect various environmental samples as well as human blood specimens to look for viruses and serologic evidence of exposure, respectively with a longer term goal of perhaps isolating human MAbs.

Would you have time to discuss early next week?

Michael G Kurilla, MD-PhD
Director, Office of BioDefense, Research Resources, and Translational Research
Associate Director for BioDefense Product Development
DMID, NIAID, NIH, DHHS
5601 Fishers Lane 8G61
Rockville, MD 20852
(b)(6)

Peace is not found in a calmer storm; it's found in a better boat.

- *Travis Meadows*

From: Baric, Ralph S
Sent: Thu, 27 Jul 2017 14:33:57 +0000
To: Lyons, Kelvin (NIH/NIAID) [E]; Burkhart, Carol J.; Chipps, Kati
Cc: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Dear Kelvin, Thank you for the wonderful news. We will provide the information shortly. Ralph

---

From: Lyons, Kelvin (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, July 27, 2017 9:34 AM
To: Burkhart, Carol J. (b)(6) Chipps, Kati (b)(6)
Cc: Baric, Ralph S (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hello,

The request to increase funds has been approved. With this please provide the latest F&A agreement for each consortium, as well as a revised detailed budget reflecting the revised direct cost amount(Vanderbilt $200,000 and UTMB $100,00).

Please provide this information by COB tomorrow 7/28/2017.

Thanks,
Kelvin Lyons
Grants Management Specialist
Office: (b)(6)
Email: (b)(6)

From: Umerah, Nina
Sent: Wed, 26 Jul 2017 20:14:35 +0000
To: Appavu Raj; Kasparian, Sevag (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Bragg, Jordan; Zhang, Jingjiao (MSH); Lau, Hoi Ling (MSH); 'Amy Sims'
Subject: RE: Contract #HHSN272201000019I; Task# HHSN27200003; Task A57 - Option 2; Request for COA for subaward amendment to UNC

Hi Raj,

Can you please give UNC an update on this agreement?

Nina

Nina Umerah
Manager, Grants and Contracts
Department of Microbiology
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, Box 1124
New York, NY 10029
Tel.: (b)(6)
Fax: 212-534-1684
Email: (b)(6)

From: Appavu, Raj [mailto:(b)(6)
Sent: Friday, July 21, 2017 10:34 AM
To: Kasparian, Sevag (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Umerah, Nina; Bragg, Jordan; Zhang, Jingjiao (MSH); Lau, Hoi Ling (MSH)
Subject: FW: Contract #HHSN272201000019I; Task# HHSN27200003; Task A57 - Option 2; Request for COA for subaward amendment to UNC

Dear Sevag :

Attached is the DRAFT of the sub award amendment No. 9 between Icahn School of Medicine at Mount Sinai and University of North Carolina at Chapel Hill (UNC) under Contract No. HHSN272201000019I / HHSN27200003 to provide for the no cost extension under the Option 2 period; please approve and provide us a COA to issue the Amendment to UNC.

Thank you,

Raj

Raj Appavu
Director of Finance
Sponsored Projects Finance
Mount Sinai Hospital
Icahn School of Medicine at Mount Sinai
Financial Division, Box 3500

One Gustave L Levy Place
New York NY 10029
Phone: (b)(6)
E Mail: (b)(6)

From: Leyva-Grado, Victor
Sent: Tue, 25 Jul 2017 19:09:18 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Toni C; Baric, Ralph
Cc: Kasparian, Sevag (NIH/NIAID) [E]
Subject: RE: Scheduling A57 Call

Hi everybody,

Just let me know the time and I will attend. If you think Nina's presence will be important for this meeting, you may want to schedule it at 11 or so. Otherwise, I'm ok with any time that day.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, July 25, 2017 1:18 PM
To: Cockrell, Adam; Baric, Toni C; Baric, Ralph; Leyva-Grado, Victor
Cc: Kasparian, Sevag (NIH/NIAID) [E]
Subject: RE: Scheduling A57 Call

Friday 7/28 I can do any time before 1pm.

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, July 25, 2017 1:10 PM
To: Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6)
Cc: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Subject: RE: Scheduling A57 Call

I will not be available 7/31-8/3.

Adam

From: Baric, Toni C
Sent: Tuesday, July 25, 2017 1:09 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph S (b)(6)
Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Subject: RE: Scheduling A57 Call

Hi Erik,
Ralph's availability is below:

7/28 open

7/31 open
8/1 between 2-3
8/2 after 10 am
8/3 between 2-3

Thanks
Toni

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, July 25, 2017 1:05 PM
To: Baric, Ralph S (b)(6) Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Baric, Toni C (b)(6) Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Subject: Scheduling A57 Call

Hi Everyone,
It's been a little while since we've had a status call, so I'd like to schedule one in the next week or so. This TO will end at the end of next month, so I want to be sure we're on track to meet the deadlines for the final deliverables. Please send me a few dates/times that work, and I'll arrange the call.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Baric, Ralph S
Sent: Tue, 18 Jul 2017 17:52:17 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Ok, talk with you soon.

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, July 18, 2017 1:36 PM
To: Baric, Ralph S (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: Re: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Thanks Ralph. We'll do our best to work it out. I'll let you know if we need anything else.

Erik

Sent from my iPhone

On Jul 18, 2017, at 12:31 PM, Baric, Ralph S (b)(6) wrote:

Hi Erik, thanks for your email…but this is my fault and I greatly appreciate your going the extra mile for me. I have attached the updated budget spreadsheet and the JIT information that was submitted last Friday (we weren't sure what to do so we submitted it with the Indirect costs added to the bottom line. I've also been in contact with **Kelvin Lyons,** Grants Management Specialist at NIH (Office: (b)(6) (b)(6) Email: (b)(6) who is working on this grant to explain the budget dollar discrepancy ($1,267,157 vs **$1,438,157)** that now includes the indirect costs for the partner institutions (Vanderbilt, UTMB) that was accidently left out of the original revised budget that we sent you. There is no change in scope of work. He has flagged the JIT for a few days to hear the final resolution of the matter from you and the appropriate NIH decision makers. I appreciate your checking into this and if the decision is to stay within the first set of numbers, we can revise and resubmit to NIH immediately. Again, I apologize for our error and for the extra work its causing you and others at NIH. I know that the hiring freeze is layering on all kinds of additional work for program. Let me know if there is anything I or Toni can do to assist in this process.
Thanks,
Ralph

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, July 18, 2017 11:42 AM
To: Baric, Ralph S (b)(6)
Subject: Re: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hi Ralph,

Sorry for being slow, I'm at a meeting this week and doing triple duty! Our grant folks are still checking on this. I haven't seen your updated JIT come through yet, so can you send me the exact figure for the omitted F&A and what the updated final total costs would be?

Erik

Sent from my iPhone

On Jul 17, 2017, at 2:41 PM, Baric, Ralph S (b)(6) wrote:

Hi Erik, hope your doing well. I was wondering if you have any feedback for us regarding this issue. Really sorry to be a problem on this. Got in a bind on Friday, so to make the timeline we put in the budget with the indirect costs added (likely caused all kinds of problems). Do you have some time for a quick call? ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Friday, July 14, 2017 11:57 AM
To: Baric, Ralph S (b)(6) Lyons, Kelvin (NIH/NIAID) [E] (b)(6)
Cc: Baric, Toni C (b)(6) Sheahan, Timothy Patrick
(b)(6)
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hi Ralph,
I'll have to check and will get back to you soon.

Erik

From: Baric, Ralph S [mailto:(b)(6)
Sent: Friday, July 14, 2017 11:34 AM
To: Lyons, Kelvin (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Toni C
(b)(6) Sheahan, Timothy Patrick (b)(6)
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hi Kelvin and Erik, As we were putting together this budget (number below), we noticed that we had inadvertently left off the consortium F&A for the Denison and Tseng subcontracts of the revised budget, which total about ~$150,000. Would it be okay for us to increase this $1,267,157 by the consortium F&A costs as absorbing these costs will impact our work performance. Please excuse our error here. Thank you for your assistance in this matter. Ralph

---

From: Lyons, Kelvin (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, July 11, 2017 2:51 PM
To: Burkhart, Carol J. (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hello Again,

Please provide a revised budget reflecting a budget reduction to $1,267,157, in addition to the original information requested. This was also addressed in some of the SRG concerns as well.

Thanks,
Kelvin Lyons
Grants Management Specialist
NIH – NIAID – DEA – GMP
5601 Fishers Lane, Room 4G26
Rockville, Maryland 20852
Office: (b)(6)
Email: (b)(6)

From: Lyons, Kelvin (NIH/NIAID) [E]
Sent: Tuesday, July 11, 2017 1:43 PM
To: (b)(6)
Cc: Baric, Ralph (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hello,

The above referenced application is being considered for funding by the National Institute of Allergy and Infectious Diseases. Please note that this request is not a guarantee of funding. Official notification of funding is only made by issuance of a Notice of Award (NoA).
The following Just-In-Time information (JIT) identified is requested:

_____ Current Other Support - Provide active and pending support information for ALL individuals designated in an application as key personnel.

There is no form page for providing other support, although a sample format page is available at http://grants.nih.gov/grants/funding/2590/non-competing_othersupport.pdf

_____ IRB approval date *(NIH does not require a copy of the IRB certification/approval).* Pending or out-of-date approvals are not acceptable. **If IRB has not met, provide anticipated meeting date.**
Information regarding the Federal Wide Assurance website: http://grants.nih.gov/grants/policy/hs/faqs_aps_assurances.htm

_____ Documentation of the required education in the Protection of Human Subject Research Participants for all key personnel involved in HS research.
Information regarding this requirement can be found at the following website: http://phrp.nihtraining.com/users/login.php

_____ IACUC approval date *(NIH does not require a copy of the IACUC certification/approval).* Pending or out-of-date approvals are not acceptable**. If IACUC has not met, provide anticipated meeting date.**
Information regarding IACUCs can be found at http://grants.nih.gov/grants/olaw/faqs.htm

_____ Other

1. Confirm your institutions Entity Identification Number (EIN) is 1566001393A1.
2. **Include a copy of your latest F&A rate agreement as well as the most recent agreement for each consortium in this application.**
3. Please provide a detailed response to the concerns listed at the end of the Summary Statement.

The requested Just In Time (JIT) information must be submitted via eRA Commons (NIH Guide Notice NOT-OD-12-101) by **07/15/2017**. If you are unable to submit the requested information through eRA Commons, please contact your Grants Management Specialist. Timely submission of the above information will enable us to expedite the issuance of an award should the application be identified for funding.

Thanks,

Kelvin Lyons
Grants Management Specialist
NIH – NIAID – DEA – GMP
5601 Fishers Lane, Room 4G26
Rockville, Maryland 20852
Office: (b)(6)
Email: (b)(6)

<Copy of R01 AI132178 revised budget.xlsx>
<R01 AI132178 JIT.pdf>
<R01 AI132178 revised budget.pdf>

From: Baric, Ralph S
Sent: Wed, 5 Jul 2017 13:34:50 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV
Attachments: eaal3653.full.pdf

Hi Erik, Nice talking with you today. I've appended a copy of our latest science translational paper describing the activity of GS5734 against sars, mers and related viruses in primary human airway epithelial cells and its ability to protect against lethal SARS-CoV challenge. The challenge studies with MERS also look very promising (new paper under development). Ralph

EMERGING INFECTIONS

Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses

Timothy P. Sheahan,[1]* Amy C. Sims,[1]* Rachel L. Graham,[1] Vineet D. Menachery,[1] Lisa E. Gralinski,[1] James B. Case,[2] Sarah R. Leist,[1] Krzysztof Pyrc,[3] Joy Y. Feng,[4] Iva Trantcheva,[4] Roy Bannister,[4] Yeojin Park,[4] Darius Babusis,[4] Michael O. Clarke,[4] Richard L. Mackman,[4] Jamie E. Spahn,[4] Christopher A. Palmiotti,[4] Dustin Siegel,[4] Adrian S. Ray,[4] Tomas Cihlar,[4] Robert Jordan,[4] Mark R. Denison,[5†] Ralph S. Baric[1†]

Emerging viral infections are difficult to control because heterogeneous members periodically cycle in and out of humans and zoonotic hosts, complicating the development of specific antiviral therapies and vaccines. Coronaviruses (CoVs) have a proclivity to spread rapidly into new host species causing severe disease. Severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) successively emerged, causing severe epidemic respiratory disease in immunologically naïve human populations throughout the globe. Broad-spectrum therapies capable of inhibiting CoV infections would address an immediate unmet medical need and could be invaluable in the treatment of emerging and endemic CoV infections. We show that a nucleotide prodrug, GS-5734, currently in clinical development for treatment of Ebola virus disease, can inhibit SARS-CoV and MERS-CoV replication in multiple in vitro systems, including primary human airway epithelial cell cultures with submicromolar IC_{50} values. GS-5734 was also effective against bat CoVs, prepandemic bat CoVs, and circulating contemporary human CoV in primary human lung cells, thus demonstrating broad-spectrum anti-CoV activity. In a mouse model of SARS-CoV pathogenesis, prophylactic and early therapeutic administration of GS-5734 significantly reduced lung viral load and improved clinical signs of disease as well as respiratory function. These data provide substantive evidence that GS-5734 may prove effective against endemic MERS-CoV in the Middle East, circulating human CoV, and, possibly most importantly, emerging CoV of the future.

INTRODUCTION

The genetically diverse coronavirus (CoV) family, currently composed of four genogroups [1 (alpha), 2 (beta), 3 (gamma), and 4 (delta)], infects birds and a variety of mammals. Thus far, only CoV groups 1 and 2 are known to infect humans. Although CoV replication machinery exhibits substantial proofreading activity, replication of viral genomic RNA is inherently error-prone, driving the existence of genetically related yet diverse quasi-species (*1*). Most CoV strains are narrow in their host range, but zoonotic CoVs have a proclivity to jump into new host species (*2*). Severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) are recent examples of newly emerging CoV that caused severe disease in immunologically naïve human populations. SARS-CoV emerged in Guangdong, China in 2002 and, with the aid of commercial air travel, spread rapidly throughout the globe, causing more than 8000 cases with 10% mortality (*2*). In 2012, it was discovered that MERS-CoV evolved to infect humans through bats by way of an intermediate camel host, causing more than 1700 cases with almost 40% mortality and, like SARS-CoV, air travel has fueled global spread to 27 countries (*2*). MERS-CoV is endemic in the Middle East, and serologic studies in the Kingdom of Saudi Arabia and Kenya suggest fairly frequent infections in humans (>45,000 persons) (*3*, *4*). The SARS-CoV epidemic ended over a decade ago, but several SARS-like CoVs have been isolated from bats that efficiently use the human angiotensin-converting enzyme 2 receptor, replicate to high titer in primary human airway cells, and are resistant to existing therapeutic antibodies and vaccines (*5*, *6*). With increasing overlap of human and wild animal ecologies, the potential for novel CoV emergence into humans is great (*2*). Broad-spectrum CoV therapies capable of inhibiting known human CoV would address an immediate unmet medical need and could be an invaluable treatment in the event of novel CoV emergence in the future.

Currently, there are no approved specific antiviral therapies for CoV in humans. Attempts made to treat both SARS-CoV and MERS-CoV patients with approved antivirals (that is, ribavirin and lopinavir-ritonavir) and immunomodulators (that is, corticosteroids, interferons, etc.) have not been effective in randomized controlled trials (*7*). Clinical development of effective CoV-specific direct-acting antivirals (DAAs) has been elusive, although there are several conserved druggable CoV enzyme targets including 3C-like protease, papain-like protease, and nonstructural protein 12 (nsp12) RNA-dependent RNA polymerase (RdRp) (*7*). In 2016, Warren *et al.* reported the in vivo antiviral efficacy of a small-molecule monophosphoramidate prodrug of an adenosine analog, GS-5734, against Ebola virus in nonhuman primates (*8*). Because the mechanism of action of GS-5734 for Ebola virus is the inhibition of the viral RdRp and previous work had suggested weak activity of the nucleoside component of GS-5734 against SARS-CoV (*9*), we sought to assess the antiviral potency and breadth of activity of GS-5734 against a diverse panel of human and zoonotic CoV.

RESULTS

GS-5734 prevents SARS-CoV and MERS-CoV replication in human airway epithelial cells

GS-5734 is a prodrug that requires metabolism by the host cell to the pharmacologically active triphosphate (TP) to inhibit virus replication

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA. [2]Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232, USA. [3]Department of Microbiology, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University, Krakow, Poland. [4]Gilead Sciences Inc., Foster City, CA 94404, USA. [5]Division of Infectious Diseases, Department of Pediatrics and Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN 37232, USA.
*These authors contributed equally to this work.
†Corresponding author. Email: mark.denison@vanderbilt.edu (M.R.D.); rbaric@email.unc.edu (R.S.B.)

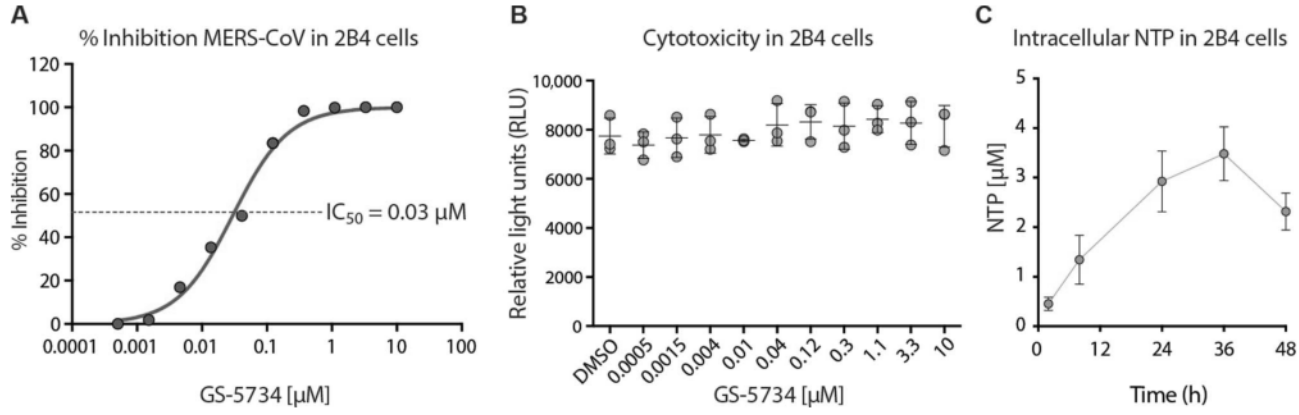

Fig. 1. MERS-CoV antiviral efficacy, toxicity, and metabolism of GS-5734 in 2B4 cells. (**A**) Mean percent inhibition of MERS-CoV replication by GS-5734. 2B4 cells were infected in triplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of varying concentrations of GS-5734 for 48 hours, after which replication was measured through quantitation of MERS-CoV–expressed nLUC. (**B**) Cytotoxicity in 2B4 cells treated similarly to that in (A). Viability was measured via CellTiter-Glo. Data for (A) and (B) are representative of three independent experiments. DMSO, dimethyl sulfoxide. (**C**) Measurement of intracellular nucleotide triphosphate (NTP) in 2B4 cells. In three independent experiments, triplicate wells of cells were treated with 1 μM GS-5734 and harvested over time to measure NTP via liquid chromatography–mass spectrometry (LC-MS).

(*9*). To determine whether GS-5734 could inhibit replication of highly pathogenic human CoV, we first evaluated antiviral activity and cytotoxicity in the continuous human lung epithelial cell line Calu-3 2B4 (2B4) (*10*). GS-5734 inhibited MERS-CoV replication in 2B4 cells with an average half-maximum inhibitory concentration (IC_{50}) value of 0.025 μM (Fig. 1A and fig. S1). We did not observe any measureable cytotoxicity at concentrations of up to 10 μM (Fig. 1B and fig. S1), thus demonstrating that the 50% cytotoxic concentration (CC_{50}) for GS-5734 is in excess of 10 μM (CC_{50}/IC_{50} = therapeutic index, >400) in 2B4 cells. With incubation of 1 μM GS-5734, the average intracellular concentration of the pharmacologically active TP of GS-5734 in 2B4 was 2.79 μM during the 48-hour treatment (Fig. 1C). Together, these results suggest that substantial inhibition of CoV replication will be achieved at low micromolar concentrations of the TP in the lung.

Primary human airway epithelial (HAE) cell cultures are among the most biologically relevant in vitro models of the lung, recapitulating the cellular complexity and physiology of the human conducting airway (*11*). We assessed the antiviral activity of GS-5734 against SARS-CoV and MERS-CoV in HAE cultures. A dose-dependent reduction in replication approaching 1 $\log_{10}$ was observed at 0.1 μM and exceeded 2 $\log_{10}$ at 1 μM GS-5734 as compared to untreated controls (Fig. 2, A and B), with average IC_{50} values of 0.069 μM (SARS-CoV) and 0.074 μM (MERS-CoV). In parallel, we assessed the abundance of intracellular genomic [open reading frame 1a (ORF1a)] and subgenomic viral RNA [open reading frame nucleocapsid (ORFN)] via quantitative reverse transcription polymerase chain reaction (qRT-PCR). A dose-dependent reduction in both ORF1a and ORFN was observed for both SARS-CoV and MERS-CoV (Fig. 2, C and D, and table S1), consistent with titer reduction. The number of MERS-CoV–infected HAE cells also diminished with increasing dose of GS-5734, as observed by microscopy (Fig. 2E). To assess cytotoxicity of GS-5734 in HAE, we first measured the transcript levels of multiple proapoptotic and antiapoptotic factors within the signaling cascades of two different death receptors, TNF (tumor necrosis factor) and FAS (Fas cell surface death receptor) (fig. S2, A and B, and table S2). Unlike the positive control drug staurosporine, which uniformly up-regulated the transcription of all apoptosis factors measured, we did not observe a dose-dependent effect with GS-5734 treatment at concentrations that inhibit CoV replication. We then measured cytotoxicity via CellTiter-Glo assay in HAE treated with 10 or 0.1 μM GS-5734 or DMSO for 48 hours. As expected, GS-5734 treatment was similar to that of DMSO (CC_{50} in HAE > 10 μM; therapeutic index, >100; fig. S2C). To assess cytotoxicity of GS-5734 in an additional primary human lung cell type, we exposed normal human bronchiolar epithelial (NHBE) cell cultures to dilutions of GS-5734 or two known cytotoxic compounds, puromycin or staurosporine (fig. S3). In NHBE, the average CC_{50} for GS-5734 was determined to be 45 μM, which is 1800-fold above the observed IC_{50} value for MERS-CoV in 2B4 cells (0.025 μM) and 600-fold above the observed IC_{50} value for MERS-CoV in HAE cells (0.074 μM) (fig. S3, A and B). Together, we demonstrate antiviral efficacy in HAE against both SARS-CoV and MERS-CoV at concentrations that are at least 100-fold lower than those with observable cytotoxicity.

GS-5734 is effective against a diverse array of human and zoonotic CoV in HAE

CoV host specificity and entry into host cells are guided by the viral spike glycoprotein whose extensive genetic variation is a reflection of host species diversity and variation in virus receptor usage (Fig. 3A). Conversely, the CoV RdRp nsp12 is highly conserved between CoVs especially within genogroups (Fig. 3A), making it a potentially broadly applicable drug target.

Because we observed an antiviral effect against the two members of genogroup 2 (SARS-CoV and MERS-CoV), we sought to assess the breadth of antiviral activity against a genetically diverse array of human and zoonotic bat CoV in HAE cells. Treatment of HAE cultures with GS-5734 infected with human CoV NL63, a circulating group 1 human CoV that typically causes bronchitis (*12*), resulted in a pronounced 3 $\log_{10}$ reduction in virus production at 0.1 μM and undetectable virus at higher concentrations (Fig. 3B). Likewise, GS-5734 treatment inhibited replication of very diverse SARS-CoV–like group 2b (HKU3, WIV1, and SHC014) and MERS-CoV–like group 2c (HKU5) bat CoVs. Among these, WIV1 and SHC014 pose particular concern as "prepandemic strains," which can infect HAE cultures without adaptation and are thus poised for emergence in humans (*5*, *6*). With 1 μM GS-5734, infectious virus production of bat CoV was reduced by 1.5 $\log_{10}$ to 2 $\log_{10}$, and levels of viral genomes and subgenomic transcripts were reduced by 1 $\log_{10}$ to 2 $\log_{10}$ (Fig. 3B). Together, these data suggest that

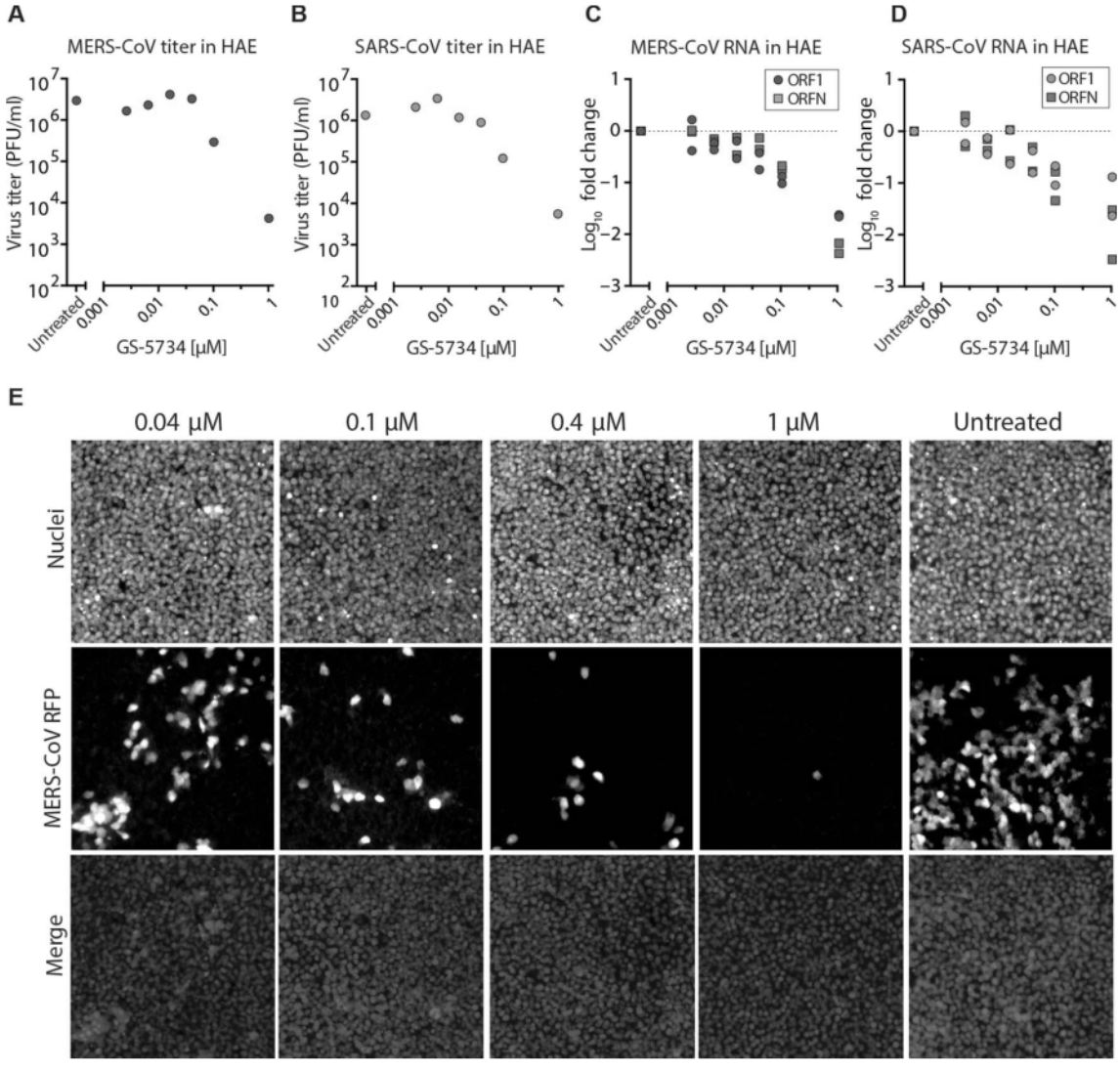

Fig. 2. GS-5734 prevents SARS-CoV and MERS-CoV replication in HAE cells. (**A**) Antiviral efficacy of GS-5734 against MERS-CoV in primary HAE cell cultures. HAE cells were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of GS-5734 for 48 hours, after which apical washes were collected for virus titration. Representative data from two separate experiments with three different cell donors are displayed. PFU, plaque-forming units. (**B**) Antiviral efficacy of GS-5734 against SARS-CoV in HAE cells. Cultures were infected with SARS-CoV green fluorescent protein (GFP), treated, and analyzed as described in (A). (**C**) qRT-PCR for MERS-CoV ORF1 and ORFN mRNA. Total RNA was isolated from cultures in (A) for qRT-PCR analysis. (**D**) qRT-PCR for SARS-CoV ORF1 and ORFN in cells from (C), as described in (B). (**E**) HAE cells were infected with MERS-CoV RFP and treated with GS-5734 as in (A). Nuclei were stained with Hoechst 33258 before fluorescent imaging.

GS-5734 can inhibit a broad range of diverse CoV including circulating human CoV, zoonotic bat CoV, and prepandemic zoonotic CoV.

Prophylactic treatment with GS-5734 reduces SARS-CoV disease

GS-5734 has relatively poor plasma stability in mice (that is, half-life, <5 min) due to expression of a secreted carboxylesterase 1c (*Ces1c*) absent in humans (*13*). Plasma stability of GS-5734 was markedly increased (half-life, ~25 min; fig. S4) in mice genetically deleted for *Ces1c* (*Ces1c*$^{-/-}$). We confirmed that SARS-CoV pathogenesis as measured by weight loss and lung viral titers was similar in wild-type (WT) C57BL/6J and *Ces1c*$^{-/-}$ mice through the infection of age- and sex-matched mice from both strains (fig. S4). We then assessed the pharmacokinetic (PK) profile in *Ces1c*$^{-/-}$ mice dosed subcutaneously with 50 mg/kg once daily (QD) or 25 mg/kg twice daily (BID). Plasma concentrations of prodrug diminished rapidly, accompanied by transient exposure to the alanine metabolite (Ala-Met) and more persistent exposure to the nucleoside analog (Fig. 4A). The plasma PK profile in esterase-deficient mice was similar to that reported previously in monkeys (*8*), but tissue accumulation of metabolites was ~10-fold less efficient in mice, suggesting that high doses and corresponding plasma exposures are necessary to obtain lung TP levels similar to those predicted in human. The metabolite profile in the lung showed the TP to be the dominant intracellular metabolite, establishing the less technically challenging assessment of total lung metabolite levels as a close approximation of TP (Fig. 4B). Although both 50 mg/kg QD and 25 mg/kg BID resulted in target maximal lung levels, tissue activation was not only less efficient in mouse but also the TP had a substantially shorter half-life in the mouse lung (~3 hours) relative to that observed in human lung cells in vitro or the nonhuman primate lung in vivo (half-life, ~20 hours; fig. S5). Therefore,

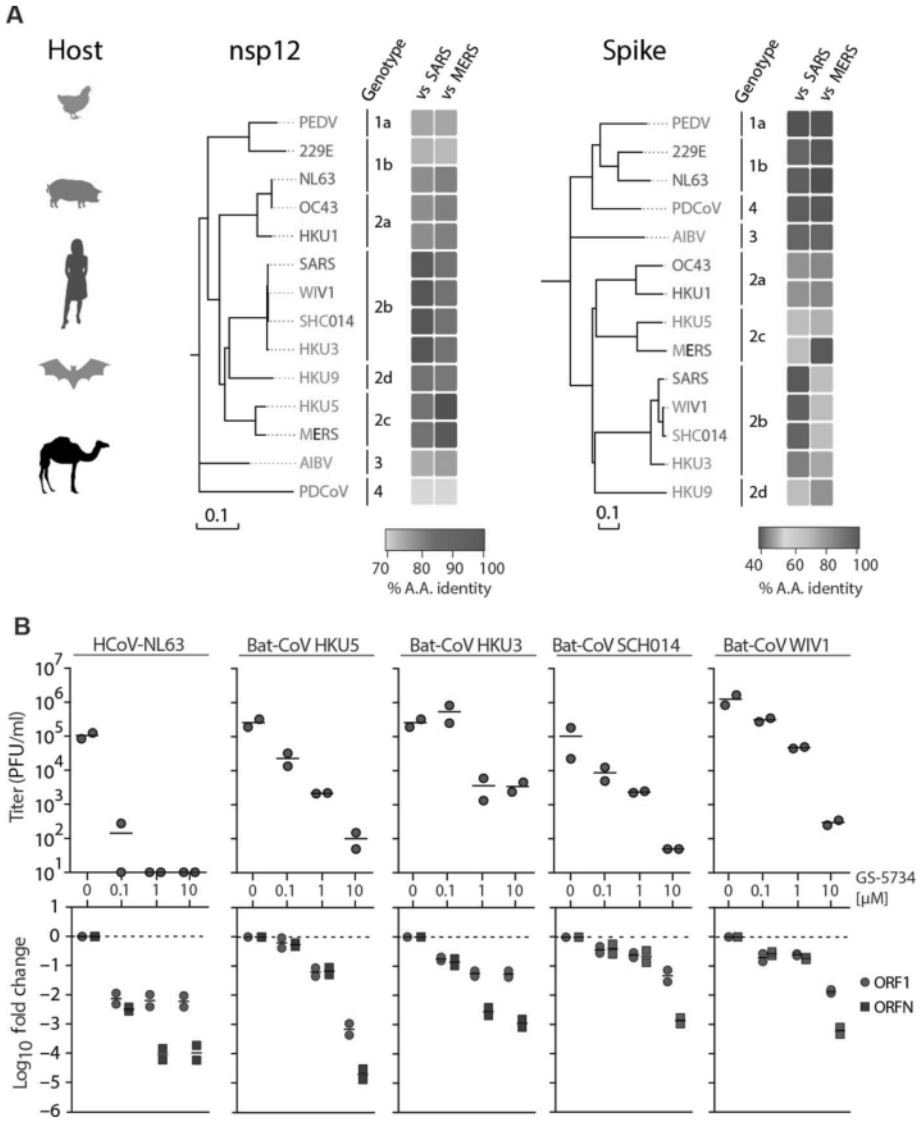

Fig. 3. GS-5734 is effective against a diverse array of human and zoonotic CoV in HAE. (**A**) Neighbor-joining trees created with representatives from all four CoV genogroups showing the genetic similarity of CoV nsp12 (RdRp) and CoV spike glycoprotein, which mediates host tropism and entry into cells. Text color of the virus strain label corresponds to virus host species on the left. The heatmap adjacent to each neighbor-joining tree depicts percent amino acid identity (% A.A. identity) against SARS-CoV or MERS-CoV. (**B**) Top: Antiviral efficacy of GS-5734 in HAE cells against circulating group 1 human CoV (HCoV-NL63) and bat CoV from group 2b (HKU3, SHC014, and WIV1) and 2c (HKU5). HAE cells were infected at an MOI of 0.5 in the presence of GS-5734 in duplicate. After 48 hours, virus produced was titrated via plaque assay. Each data point represents the titer per culture. Bottom: qRT-PCR for CoV ORF1 and ORFN mRNA in total RNA from cultures in the top panel.

only the BID-dosing regimen was able to maintain lung levels between 12 and 24 hours, consistent with those anticipated in humans and sufficient to maintain CoV inhibition over the dosing interval (Fig. 4C).

Mouse models of SARS-CoV disease faithfully recapitulate many aspects of SARS-CoV pathogenesis in humans including anorexia, high titers of virus replication in the lung, and the development of acute respiratory distress syndrome (ARDS) as well as an age-related exacerbation of disease (*14*). As shown in Fig. 5A, prophylactic administration at 50 mg/kg QD or 25 mg/kg BID ameliorated SARS-CoV–induced weight loss seen with vehicle treatment. Virus titers in the lung were significantly reduced ($P < 0.05$) on both 2 and 5 days post-infection (dpi) in GS-5734–treated mice as compared to vehicle-treated animals (Fig. 5B). In addition, levels of viral antigen staining in lung sections of GS-5734–treated animals were significantly lower ($P < 0.05$) as compared to vehicle-treated animals (Fig. 5, C and D). Treatment with GS-5734 also reduced SARS-CoV–induced lung pathology, including denuding bronchiolitis, perivascular accumulation of inflammatory infiltrates (that is, "cuffing"), and intra-alveolar edema associated with diffuse alveolar damage as compared to vehicle-treated animals (Fig. 5E and fig. S6).

Prophylactic treatment with GS-5734 prevented defects in pulmonary function seen in SARS-CoV–infected, vehicle-treated animals, as measured by whole-body plethysmography (WBP), an extremely sensitive means of quantitating pulmonary function (*15*). Penh, a surrogate measure of airway resistance or accumulation of debris in the airway, was significantly ($P < 0.05$) elevated in vehicle-treated animals as compared to those treated with GS-5734 (Fig. 5F). Metrics of labored breathing, such as increased exhalation time and extended pause in between the end of one breath and the beginning of the next, were increased in vehicle-treated animals as compared to those administered with GS-5734 (Fig. 5F).

Therapeutic postexposure administration of GS-5734 mitigates disease

Because prophylactic administration of GS-5734 reduced virus lung titers, improved lung function, and ameliorated symptoms of SARS-CoV disease, it was of interest to determine whether therapeutic treatment would also be effective. First, we compared the antiviral efficacy of GS-5734 (25 mg/kg, BID) beginning at −1 dpi (that is, prophylactic) or +1 dpi (that is, therapeutic). Therapeutic GS-5734 substantially reduced the SARS-CoV–induced weight loss in infected animals (Fig. 6, A and B) and significantly suppressed virus lung titers ($P = 0.0059$), thus demonstrating that therapeutic administration of GS-5734 can reduce disease and suppress replication during an ongoing infection (Fig. 6C). Therapeutic treatment significantly ($P = 0.003$) improved pulmonary function (that is, reduced Penh scores) as compared to vehicle-treated controls (Fig. 6D). We then explored the therapeutic potential of GS-5734 given at 2 dpi, which is after virus replication and lung airway epithelial damage have peaked (fig. S7). Disease severity and survival did not differ with treatment, but we observed a significant reduction ($P < 0.05$) in SARS-CoV lung titers of GS-5734–treated animals at 6 dpi. These data suggest that reductions in viral load after peak lung titers were achieved were insufficient to improve outcomes after the immunopathological phase of disease had been initiated. Thus, in the mouse, if given before the peak of SARS-CoV replication and peak damage to the airway epithelium,

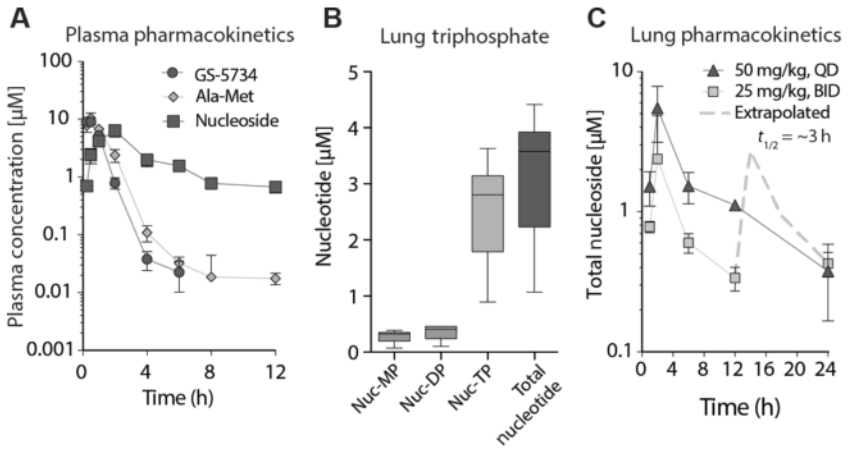

Fig. 4. Pharmacokinetics of GS-5734 in *Ces1c*$^{-/-}$ mice. (**A**) Pharmacokinetics in *Ces1c*$^{-/-}$ mouse plasma after subcutaneous administration of GS-5734 (25 mg/kg). Longitudinal plasma samples were taken to measure prodrug GS-5734, intermediate metabolites Ala-Met, and nucleoside by LC-MS. (**B**) Lung TP in *Ces1c*$^{-/-}$ mouse lung 4 hours after subcutaneous administration of GS-5734 (50 mg/kg). Nucleotide monophosphate (Nuc-MP), diphosphate (Nuc-DP), triphosphate (Nuc-TP), and total nucleotide (sum of Nuc-MP, Nuc-DP, and Nuc-TP) are displayed. (**C**) Pharmacokinetics of total nucleotide in *Ces1c*$^{-/-}$ mouse lung after subcutaneous administration of GS-5734 at 25 mg/kg BID or 50 mg/kg QD.

GS-5734 can improve pulmonary function, reduce viral loads, and diminish disease.

DISCUSSION

Emerging viral infections represent a critical global health concern because specific antiviral therapies and vaccines are usually lacking. To maximize the potential public health benefit of therapeutics against emerging viruses, they should be efficacious against past (that is, SARS-CoV), current (that is, MERS-CoV), and future emerging viral threats. Knowledge of the spectrum of therapeutic efficacy is essential for making informed clinical decisions, especially in the early stages of an outbreak. Because zoonotic CoV emergence is driven by an amalgamation of human, wild animal, and viral factors, it is difficult to gauge zoonotic CoV emergence potential based on viral genome sequences alone (*2*). Here, we provide an example of a successful public-private partnership that combines metagenomics, synthetic biology, primary human cell culture models, drug metabolism, PKs, and in vivo models of viral pathogenesis to demonstrate broad-spectrum activity of a drug candidate against a virus family prone to emergence (fig. S8). Although we demonstrated broad-spectrum efficacy against human and zoonotic CoV from multiple CoV genogroups, we have not yet assessed antiviral efficacy for all CoV genogroups, which is a limitation of our current study. Nevertheless, our panel of reconstructed human and zoonotic bat CoV was essential to determine whether GS-5734 would be efficacious against highly divergent emerged (SARS-CoV), emerging (MERS-CoV), and circulating zoonotic strains with pandemic potential (that is, WIV1 and SHC014) (*5*, *6*, *16*, *17*). In the future, the rapid development of vaccines, therapies, and diagnostics for emerging viruses will be dependent on the reconstruction and the in vitro and in vivo adaptation of these viruses in the laboratory.

Here, we report the broad-spectrum antiviral efficacy of a small molecule against multiple genetically distinct CoV in vitro and in vivo. Current vaccine and human monoclonal antibody approaches have proven to be effective but typically have limited breadth of protection due to antigenic diversity in the CoV spike glycoprotein (*5*, *6*). Conversely, RdRp-targeting therapies such as GS-5734 are more likely to be broadly active against past, current, and future CoV due to the inherent genetic conservation of the CoV replicase. As evidenced by the failure of the nucleoside prodrug balapiravir to translate in vitro efficacy into in vivo efficacy in mice and humans, antiviral drug candidates should be thoroughly evaluated in the most biologically relevant models of pathogenesis to maximize clinical translatability (*18*). Cell type–specific differences in the active transport and/or metabolism of nucleoside analogs may affect the antiviral profile (*19*). Thus, we aimed to expand on previous in vitro studies of SARS-CoV and MERS-CoV antiviral efficacy that were limited to monkey kidney cancer cell lines (*8*, *9*). Similar in cellular complexity and physiology to the human conducting airway, the HAE cell culture contains mucus-secreting cells, basolateral cells, and some of the main target cells of SARS-CoV (ciliated epithelial cells) and MERS-CoV (nonciliated epithelial cells) in vivo (*11*, *20*). With our HAE cell antiviral efficacy data, we provide strong evidence that GS-5734 will be taken up and metabolized in cells targeted by multiple human and zoonotic CoV in the human lung.

Preclinical in vivo antiviral efficacy studies provide insight into the PK/pharmacodynamic (PD) relationship of a drug from which effective dosing regimens can be extrapolated for human clinical trial. To maximize the utility of preclinical PK/PD studies, the use of animal models that accurately recapitulate human disease is essential. Multiple aspects of the human disease are captured by the mouse-adapted SARS-CoV (SARS-CoV MA15) model used herein, including high-titer virus replication limited to the lung, the development of ARDS, age-related exacerbation of disease, and death. In contrast to humans infected with SARS-CoV where viral titers peak 7 to 10 days after the onset of symptoms, virus titers in the lungs of SARS-CoV MA15–infected C57BL/6 mice rapidly increase 4 to 5 logs and peak at 2 dpi, concurrent with maximal damage to the conducting airway epithelium and alveoli (*14*). After 2 dpi, virus titers wane, and the remainder of the disease course is driven by immunopathology. Thus, the 7 to 10 days before peak replication in humans is compressed into the first 48 hours of our mouse model. Similar to humans, disease severity in SARS-CoV–infected mice is directly correlated with lung viral load, which can be modulated through increasing dose of input virus (*14*, *21*). With both prophylactic (−1 dpi) and therapeutic (+1 dpi) dosing of GS-5734, we demonstrate a reduction in replication below a disease-causing threshold. Therapeutic treatment beginning at 2 dpi reduced lung viral loads yet did not improve disease outcomes, suggesting that antivirals initiated after virus replication and immunopathology have reached their tipping point were not clinically beneficial. This result is not surprising given the precedent set by the influenza antiviral oseltamivir, where treatment efficacy diminishes with time after the onset of symptoms (*22*). Like SARS-CoV, MERS-CoV titers in the respiratory tract peak in the second week after the onset of symptoms (*23*). Thus, the window in which to administer antiviral treatment after the onset of symptoms but before achieving peak virus titers should be prolonged in humans as compared to experimentally infected mice. Unfortunately, the differences in SARS-CoV pathogenesis among mice and humans noted above limit our ability to determine the time at which treatment no longer will provide a clinical benefit in humans. Nevertheless, our studies provide data that strongly support the testing of GS-5734 in nonhuman primates and suggest that therapeutic treatment of MERS-CoV–infected

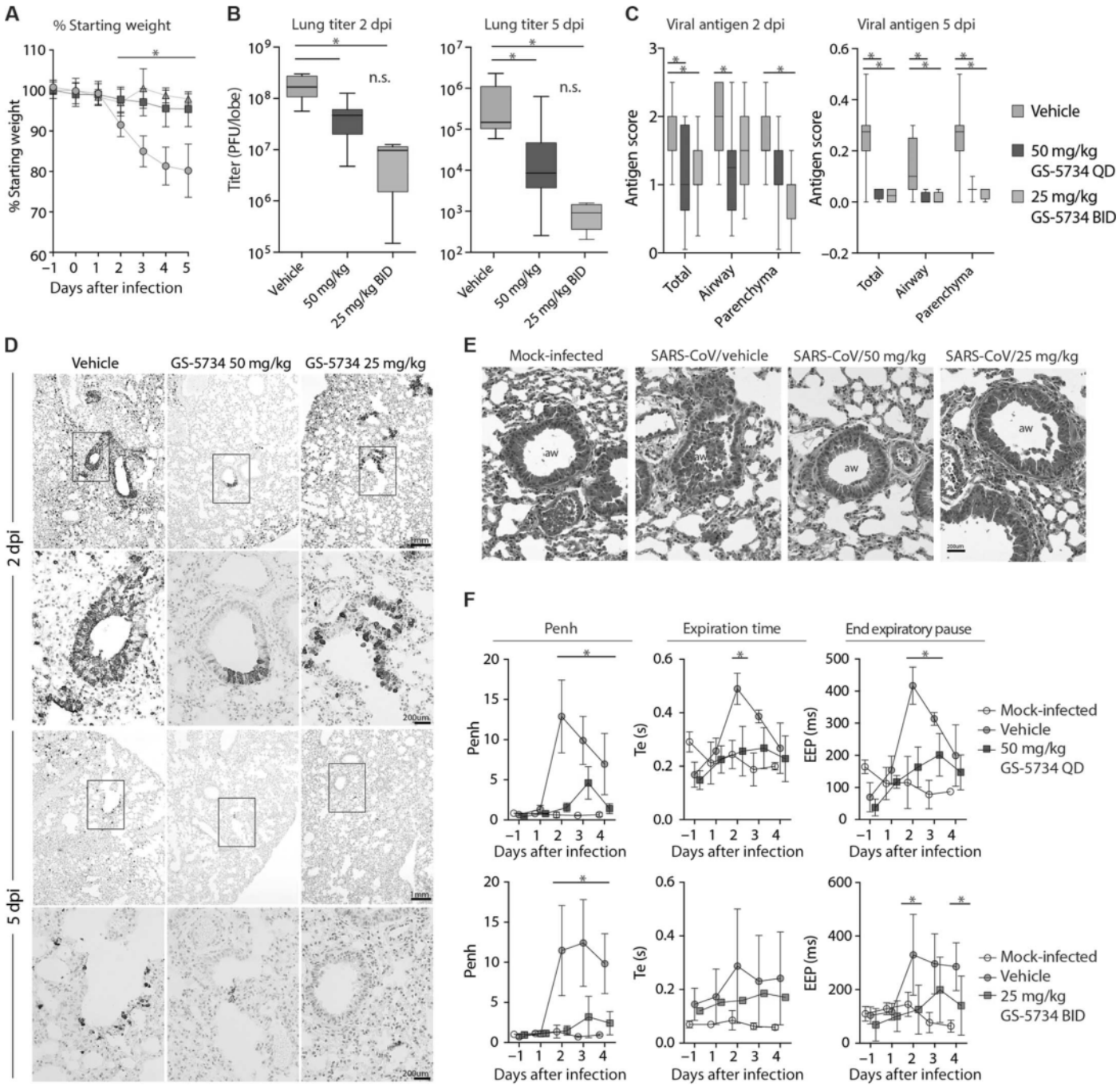

Fig. 5. Prophylactic treatment with GS-5734 reduces SARS-CoV disease. (**A**) Percent starting weight of *Ces1c*$^{-/-}$ mice infected with 10^4 PFU SARS-CoV MA15 treated beginning at −1 dpi with either vehicle (n = 42) or GS-5734 [25 mg/kg BID (n = 25) or 50 mg/kg QD (n = 28)]. (**B**) SARS-CoV lung titer of mice in (A) at 2 dpi (vehicle, n = 11; 50 mg/kg, n = 11; 25 mg/kg, n = 5) (left) or 5 dpi (vehicle, n = 13; 50 mg/kg, n = 13; 25 mg/kg, n = 4) (right). n.s., not significant. (**C**) Quantitation of SARS-CoV antigen in lung sections of mice in (A) at 2 dpi (left) (vehicle, n = 15; 50 mg/kg, n = 12; 25 mg/kg, n = 7) (left) or 5 dpi (vehicle, n = 10; 50 mg/kg, n = 12; 25 mg/kg, n = 4) (right). (**D**) Photomicrographs of SARS-CoV antigen staining (brown) and nuclei (blue) in lung sections from 2 and 5 dpi. (**E**) Photomicrographs of hematoxylin and eosin–stained mouse lung sections from 2 dpi highlighting the conducting airway lumen (aw). (**F**) WBP was used to measure the pulmonary function of mice in (A). Penh is a surrogate measure of bronchoconstriction. Expiration time (t_e) is the time taken to release one breath. End of expiratory pause (EEP) is the time between breaths. Symbols and error bars for (A), (B), (D), and (I) represent the mean and SD. The boxes encompass the 25th to 75th percentile, whereas the whiskers represent the range in (C), (E), and (F). Asterisk indicates statistical significance ($P < 0.05$) by two-way analysis of variance (ANOVA) with Tukey's multiple comparison test for (D), (F), and (I) and with Kruskal-Wallis test for (E).

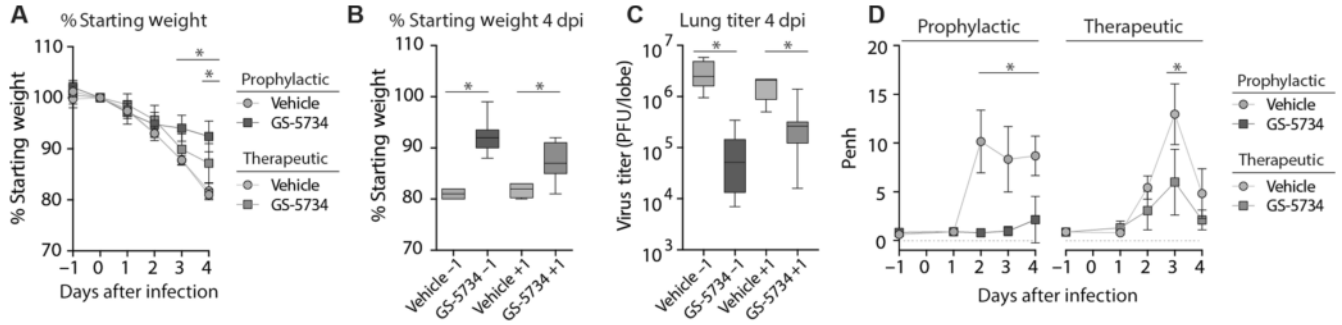

Fig. 6. Therapeutic postexposure administration of GS-5734 mitigates disease. (**A**) Percent starting weight of 27- to 28-week-old female *Ces1c*$^{-/-}$ mice infected with 10^3 PFU SARS-CoV MA15 and treated BID with vehicle or GS-5734 (25 mg/kg) beginning on either −1 dpi (vehicle, $n = 5$; GS-5734, $n = 10$) or +1 dpi (vehicle, $n = 4$; GS-5734, $n = 11$). Weights of GS-5734–treated animals were statistically different ($P < 0.05$) from those of vehicle-treated animals at 3 and 4 dpi for prophylactic groups and at 4 dpi for therapeutic groups by two-way ANOVA with Tukey's multiple comparison test. (**B**) Percent starting weights of mice in (A) at 4 dpi. (**C**) SARS-CoV lung titer in mice infected and treated as described in (A). Asterisks indicate statistical significance ($P < 0.05$) by Mann-Whitney test for (B) and (C). (**D**) WBP was used to measure the pulmonary function in mice infected and treated as described in (A). Penh is a surrogate measure of bronchoconstriction or airway obstruction. Asterisks indicate statistical significance by two-way ANOVA with Šidák's multiple comparison test.

humans with GS-5734 will help diminish virus replication and disease if administered early enough during the course of infection.

Currently, there are no approved antiviral treatments for SARS-CoV or MERS-CoV that specifically target the virus. Multiple therapeutic approaches against SARS-CoV and MERS-CoV are currently in development including immunomodulation, vaccination, DAAs, and host-targeted antivirals (*7*). Known antivirals, such as ribavirin and lopinavir-ritonavir, and immunomodulators, such as interferon and corticosteroids, have been used to treat both SARS-CoV and MERS-CoV patients, but none were proven effective in randomized controlled trials (*7*). Cell culture studies in multiple cell lines have demonstrated antiviral effects of several U.S. Food and Drug Administration–approved drugs (ritonavir, lopinavir, nelfinavir, mycophenolic acid, and ribavirin), but contradictory results and experimental incongruities make the interpretation difficult (*24*–*29*). Small molecules targeting SARS-CoV and MERS-CoV have been assessed in cancer cell lines in vitro, but their antiviral efficacy against other human or zoonotic CoV remains unknown (*16*, *30*). Very few small molecules have been assessed in CoV animal models of viral pathogenesis, and some have even been shown to exacerbate disease (for example, ribavirin and mycophenolic acid) (*31*, *32*). Although the *Ces1c*$^{-/-}$ mice used herein foster increased drug stability, they are not suitable for MERS-CoV efficacy studies because the murine ortholog of the MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), does not facilitate MERS-CoV infection (*33*). Thus, our in vivo studies were limited to SARS-CoV, and future studies assessing MERS-CoV efficacy in double-transgenic humanized DPP4/*Ces1c*$^{-/-}$ mice are planned. Human safety testing for GS-5734 is ongoing, and the drug has already been used to treat a small number of Ebola virus–infected patients under the "compassionate use" clause (*34*). Overall, our work provides evidence that GS-5734 may protect CoV-infected patients from progression to severe disease and could prophylactically protect health care workers in areas with existing endemic MERS-CoV and that its broad-spectrum activity may prove valuable when a novel CoV emerges in the future.

MATERIALS AND METHODS

Study design

The primary goal of this study was to determine whether the small-molecule nucleoside analog GS-5734 exhibited broad-spectrum antiviral activity against the CoV family. Using multiple in vitro models including human primary cells, we measured the antiviral effect of GS-5734 on multiple CoV, encompassing much of the inherent family-wide genetic diversity. Data presented for studies in human primary cultures are representative of those from three human donors. Cytotoxicity was assessed in the 2B4 cell line and in two human primary lung cell types. Experiments were performed in triplicate unless otherwise stated. Drug effects were measured relative to vehicle controls. The secondary goal of this study was to assess antiviral efficacy in vivo within mouse models of severe CoV disease. The in vivo efficacy studies were intended to gain the data required to justify further testing in nonhuman primates and collectively inform future human clinical trials. Mice were age- and sex-matched and randomly assigned into groups before infection and treatment. The prophylactic and therapeutic in vivo studies presented in the main text were repeated at least once. Pathology and SARS-CoV antigen scoring were performed in a blinded manner. Exclusion criteria for in vivo studies were as follows: If a given mouse unexpectedly did not lose weight after infection and their virus lung titers were more than 2 $\log_{10}$ lower the mean of the group, this indicated that infection was inefficient and all data related to that mouse were censored. Primary data are located in table S3.

Viruses

SARS-CoV expressing GFP (GFP replaces ORF7) and MERS-CoV expressing RFP (RFP replaces ORF3) were created from molecular complementary DNA clones as described (*11*, *20*). To create SARS-CoV and MERS-CoV expressing nLUC, the genes for GFP and RFP were replaced with nLUC and isolated as referenced above. Recombinant human CoV NL63 and recombinant bat CoV for strains HKU3, HKU5, WIV1, and SHC014 were created as described (*5*, *6*, *12*, *16*, *17*).

GS-5734

GS-5734 was synthesized at Gilead Sciences Inc., and its chemical identity and purity were determined by nuclear magnetic resonance, high-resolution mass spectrometry, and high-performance liquid chromatography (HPLC) analysis (*9*). GS-5734 was solubilized in 100% DMSO for in vitro studies and in vehicle containing 12% sulfobutylether-β-cyclodextrin in water (with HCl/NaOH) at pH 5 for in vivo studies. GS-5734 was made available to the University of North Carolina (UNC) at Chapel Hill under a materials transfer agreement with Gilead Sciences.

In vitro efficacy and cytotoxicity in 2B4 cells

The human lung epithelial cell line 2B4 was maintained in Dulbecco's modified Eagle's medium (Gibco), 20% fetal bovine serum (HyClone), and 1× antibiotic-antimycotic (Gibco) (*10*). Twenty-four hours after plating 5×10^4 cells per well, fresh medium was added. In triplicate, cells were infected for 1 hour with MERS-nLUC diluted in growth medium (MOI of 0.08), after which virus was removed, cultures were rinsed once, and fresh medium containing dilutions of GS-5734 or vehicle was added. DMSO (0.05%) was constant in all conditions. At 48 hours postinfection (hpi), virus replication was measured by nLUC assay (Promega), and cytotoxicity was measured via CellTiter-Glo (Promega) assay and then read on a SpectraMax plate reader (Molecular Devices). The IC_{50} value was defined in GraphPad Prism 7 (GraphPad) as the concentration at which there was a 50% decrease in viral replication using ultraviolet-treated MERS-nLUC (100% inhibition) and vehicle alone (0% inhibition) as controls. CC_{50} value was determined through comparison of data with that from cell-free (100% cytotoxic) and vehicle-only (0% cytotoxic) samples.

In vitro efficacy and toxicity in HAE cells

HAE cell cultures were obtained from the Tissue Procurement and Cell Culture Core Laboratory in the Marsico Lung Institute/Cystic Fibrosis Research Center at UNC. Before infection, HAE were washed with phosphate-buffered saline (PBS) and moved into air-liquid interface medium containing various doses of GS-5734 ranging from 10 to 0.00260 μM (final DMSO, <0.05%) (*11*). HAE cultures were infected at an MOI of 0.5 for 3 hours at 37°C, after which virus was removed, and cultures were washed with PBS and then incubated at 37°C for 48 hours. Fluorescent images of MERS-RFP were taken at 48 hpi after nuclear staining with Hoechst 33258. Virus replication/titration was performed as previously described (*11*). Similar data were obtained using cells from three different patient donors. Cytotoxicity was measured via CellTiter-Glo (Promega) in duplicate HAE cell cultures treated with 10 or 0.1 μM GS-5734 or DMSO at 0.05%.

In vivo pharmacokinetic analysis in plasma after GS-5734 administration in *Ces1c*$^{-/-}$ mice and marmosets

Mice were subcutaneously administered with GS-5734 (25 mg/kg), after which plasma was isolated from triplicate mice at 0.25, 0.5, 1, 2, 4, 6, 8, and 12 hours after administration. Three male marmosets were administered a single dose of GS-5734 intravenously at 10 mg/kg, after which plasma was isolated at 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours after administration. For both mouse and marmoset, 25 μl of plasma was treated and analyzed as described in the Supplementary Materials and Methods "Stability of GS-5734 in WT or *Ces1c*$^{-/-}$ mouse plasma." Plasma concentrations of GS-5734, alanine metabolite (Ala-Met), and nucleoside monophosphate were determined using 8- to 10-point calibration curves spanning at least three orders of magnitude with quality control samples to ensure accuracy and precision and prepared in normal mouse plasma. Analytes were separated by a 75 × 2 mm (4-μm) Synergi Hydro-RP 30A column (Phenomenex) using a multistage linear gradient from 0.2 to 99% acetonitrile in mobile phase A at a flow rate of 260 μl/min.

Quantitation of GS-5734 metabolites in the lung after GS-5734 administration in *Ces1c*$^{-/-}$ mice and marmosets

Mice were dosed with GS-5734 (25 or 50 mg/kg), as described above. Lungs from triplicate mice were isolated at 1, 2, 6, 12, and 24 hours after administration and snap-frozen. Four male marmosets were dosed with GS-5734, as described above, and lungs were isolated at 2 and 24 hours after administration and were snap-frozen. On dry ice, frozen lung samples were pulverized and weighed. Dry ice–cold extraction buffer containing 0.1% potassium hydroxide and 67 mM EDTA in 70% methanol and containing 0.5 μM chloroadenosine triphosphate as internal standard was added and homogenized. After clarifying centrifugation at 20,000*g* for 20 min, supernatants were dried in a centrifuge evaporator. Dried samples were then reconstituted with 60 μl of mobile phase A, containing 3 mM ammonium formate (pH 5) with 10 mM dimethylhexylamine in water, and centrifuged at 20,000*g* for 20 min, with final supernatants transferred to HPLC injection vials. An aliquot of 10 μl was subsequently injected onto an API 5000 LC/MS/MS system for analysis performed using a similar method, as described for intracellular metabolism studies.

Prophylactic and therapeutic efficacy of GS-5734 against SARS-CoV in *Ces1c*$^{-/-}$ mice

Male and female (25- to 28-week-old) mice genetically deleted for carboxylesterase 1C (*Ces1c*$^{-/-}$) (stock 014096, The Jackson Laboratory) were anesthetized with ketamine/xylazine and infected with 10^4 PFU/50 μl (prophylactic studies) or 10^3 PFU/50 μl (therapeutic studies) SARS-CoV MA15. Animals were weighed daily to monitor virus-associated weight loss and to determine the appropriate dose volume of GS-5734 or vehicle. GS-5734 or vehicle was administered subcutaneously BID, 12 hours apart. On 2 and 5 dpi (prophylactic) or 2 and 4 or 6 dpi (therapeutic), animals were sacrificed by isoflurane overdose, and the large left lobe was frozen at −80°C for viral titration via plaque assay, as described (*14*). The inferior right lobe was placed in 10% buffered formalin and stored at 4°C until histological analysis. Aberrations in lung function were determined by WBP (Data Sciences International), as described (*15*).

Biocontainment and biosafety

Reported studies were initiated after the UNC Institutional Biosafety Committee approved the experimental protocols under the Baric Laboratory Safety Plan (20167715). SARS-CoV is a select agent. All work for these studies was performed with approved standard operating procedures for SARS-CoV, MERS-CoV, and other related CoVs in facilities conforming to the requirements recommended in the Biosafety in Microbiological and Biomedical Laboratories, the U.S. Department of Health and Human Services, the U.S. Public Health Service, the U.S. Centers for Disease Control and Prevention, and the National Institutes of Health.

Animal care

Efficacy studies were performed in animal biosafety level 3 facilities at UNC Chapel Hill. All works were conducted under protocols approved by the Institutional Animal Care and Use Committee at UNC Chapel Hill (protocol #13-288; continued on #16-284) according to guidelines set by the Association for the Assessment and Accreditation of Laboratory Animal Care and the U.S. Department of Agriculture.

Statistics

All statistical calculations were performed in GraphPad Prism 7. Specific tests to determine statistical significance are noted in each figure legend.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/9/396/eaal3653/DC1

Materials and Methods

Fig. S1. In vitro toxicity and efficacy of GS-5734 in 2B4 cells.

Fig. S2. In vitro toxicity of GS-5734 in primary HAE cell cultures.

Fig. S3. In vitro toxicity of GS-5734 in primary NHBE cell cultures.
Fig. S4. SARS-CoV in vivo pathogenesis is similar in WT and *Ces1c*$^{-/-}$ mice.
Fig. S5. Metabolism in NHBE cells and pharmacokinetic analysis in nonhuman primates.
Fig. S6. GS-5734 diminishes SARS-CoV–induced lung pathology.
Fig. S7. Therapeutic administration of GS-5734 beginning at 2 dpi does not provide a therapeutic benefit.
Fig. S8. A comprehensive platform approach to evaluate therapeutics against emerging viral infections.
Table S1. CoV genomic and subgenomic real-time primer sets.
Table S2. Primer/probe sets for indicators of cellular apoptosis/toxicity qRT-PCR.
Table S3. Primary data.

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Science Translational Medicine

Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses

Timothy P. Sheahan, Amy C. Sims, Rachel L. Graham, Vineet D. Menachery, Lisa E. Gralinski, James B. Case, Sarah R. Leist, Krzysztof Pyrc, Joy Y. Feng, Iva Trantcheva, Roy Bannister, Yeojin Park, Darius Babusis, Michael O. Clarke, Richard L. Mackman, Jamie E. Spahn, Christopher A. Palmiotti, Dustin Siegel, Adrian S. Ray, Tomas Cihlar, Robert Jordan, Mark R. Denison and Ralph S. Baric

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Antiviral gets the jump on coronaviruses

Like other emerging infections, coronaviruses can jump from animal reservoirs into the human population with devastating effects, such as the SARS or MERS outbreaks. Sheahan *et al*. tested a small-molecule inhibitor that has shown activity against Ebola virus as a potential agent to be used to fight coronaviruses. This drug was effective against multiple types of coronaviruses in cell culture and in a mouse model of SARS and did not seem to be toxic. Given its broad activity, this antiviral could be deployed to prevent spreading of a future coronavirus outbreak, regardless of the specific virus that jumps over.

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From: Peter Daszak
Sent: Fri, 16 Jun 2017 17:17:28 +0000
To: Park, Eun-Chung (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Kevin Olival, PhD; Anthony Ramos; Coleman, Amanda (NIH/NIAID) [C]
Subject: RE: Potential media interest from a Nature paper in press based on our work funded by two NIAID R01s
Attachments: Olival et al. Host and viral traits predict zoonotic spillover from mammals Nature 2017 proofs.pdf

I've attached the final proofs of the paper, so you can see what it's going to look like.

It's scheduled for publication at 1pm EST on Wednesday June 21st online, then the 29th in paper, and of course is embargoed until then.

Also, to let you know that we used your comments in our updated press release which we're circulating to journalists now, and already fielding calls on.

Cheers,

Peter

Peter Daszak
President

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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 prevent pandemics and promote conservation.

From: Park, Eun-Chung (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, June 14, 2017 5:19 PM
To: Peter Daszak; Stemmy, Erik (NIH/NIAID) [E]
Cc: Kevin Olival, PhD; Anthony Ramos; Coleman, Amanda (NIH/NIAID) [C]
Subject: RE: Potential media interest from a Nature paper in press based on our work funded by two NIAID R01s

Peter,

I am attaching the document containing comments from our communication office.

Sincerely,
Eunchung

Eun-Chung Park, PhD
Program Officer,
NIAID, NIH
PH: (b)(6)
(b)(6)

From: Peter Daszak [mailto(b)(6)
Sent: Wednesday, June 14, 2017 12:30 PM
To: Park, Eun-Chung (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Kevin Olival, PhD (b)(6) Anthony Ramos (b)(6) Coleman, Amanda (NIH/NIAID) [C] (b)(6)
Subject: RE: Potential media interest from a Nature paper in press based on our work funded by two NIAID R01s
Importance: High

No problem.

Hi Amanda. I've attached the pdf of the final version as accepted – not yet in Nature typesetting. We're just waiting on the corrected proofs from Nature and we'll send these on as soon as we get them.

As you know this is embargoed, but unfortunately right now we don't know the official publication date. We think it might be released online next Wednesday June 21st, but will confirm as soon as we hear back from Nature.

By the way – if you want a quote from me or Kevin, or have any questions – no problem – we're around this week and would be happy to help!

Cheers,

Peter

Peter Daszak
President

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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 prevent pandemics and promote conservation.

From: Park, Eun-Chung (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, June 14, 2017 10:36 AM
To: Peter Daszak; Stemmy, Erik (NIH/NIAID) [E]
Cc: Kevin Olival, PhD; Anthony Ramos; Coleman, Amanda (NIH/NIAID) [C]
Subject: RE: Potential media interest from a Nature paper in press based on our work funded by two NIAID R01s

Peter,
Our communication office asks if you can provide the manuscript. I copy Amanda Coleman here, and if you can send to all of us, that will be helpful. Thank you.

Sincerely,
Eunchung

Eun-Chung Park, PhD
Program Officer,
NIAID, NIH
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Cc: Kevin Olival, PhD (b)(6) Anthony Ramos (b)(6)
Subject: Potential media interest from a Nature paper in press based on our work funded by two NIAID R01s
Importance: High

Hi Erik and Eun-Chung

Good News! I want to give you advance notice about a paper Kevin Olival and I have in press with *Nature* that might generate some publicity. It's called "Host and Viral Traits Predict Zoonotic Spillover from Mammals". We acknowledge the current R01 (R01AI110964) on SARS-like CoVs in China that you're Program Officer for, Erik, as well as the R01 on predicting spillover from bat-origin viruses (R01AI079231) that you were Program Officer for a few years ago Eun-Chung – the work for this paper began under that R01, and it's taken a few years of database building and analysis to get to this stage!

I've inserted the abstract below, as accepted by Nature so you can see the content, as well as a draft Press Release we're working on. I don't know what the current standard is for publicity from NIAID-

funded work, but I wanted to let you know in advance, in case you'd like to put a story up about this on your website, or talk to the media about it prior to the embargo.

The timing is tight. As always, we don't know exactly when Nature will release it, but we expect it will be online next week, maybe as early as **Wednesday 21st June.** We've already had pre-proofs and have corrected these so we're getting our ducks in a row for that date so that we don't miss any publicity. We'll let you know as soon as we hear the final decision.

Host and viral traits predict zoonotic spillover from mammals

Kevin J. Olival1, Parviez R. Hosseini1, Carlos Zambrana-Torrelio1, Noam Ross1, Tiffany L. Bogich1 & Peter Daszak1

The majority of human emerging infectious diseases are zoonotic, with viruses that originate in wild mammals of particular concern (for example, HIV, Ebola and SARS)1–3. Understanding patterns of viral diversity in wildlife and determinants of successful crossspecies transmission, or spillover, are therefore key goals for pandemic surveillance programs4. However, few analytical tools exist to identify which host species are likely to harbour the next human virus, or which viruses can cross species boundaries5–7. Here we conduct a comprehensive analysis of mammalian host–virus relationships and show that both the total number of viruses that infect a given species and the proportion likely to be zoonotic are predictable. After controlling for research effort, the proportion of zoonotic viruses per species is predicted by phylogenetic relatedness to humans, host taxonomy and human population within a species range—which may reflect human–wildlife contact. We demonstrate that bats harbour a significantly higher proportion of zoonotic viruses than all other mammalian orders. We also identify the taxa and geographic regions with the largest estimated number of 'missing viruses' and 'missing zoonoses' and therefore of highest value for future surveillance. We then show that phylogenetic host breadth and other viral traits are significant predictors of zoonotic potential, providing a novel framework to assess if a newly discovered mammalian virus could infect people.

Cheers,

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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 prevent pandemics and promote conservation.

LETTER

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Host and viral traits predict zoonotic spillover from mammals

Kevin J. Olival[1], Parviez R. Hosseini[1], Carlos Zambrana-Torrelio[1], Noam Ross[1], Tiffany L. Bogich[1] & Peter Daszak[1]

The majority of human emerging infectious diseases are zoonotic, with viruses that originate in wild mammals of particular concern (for example, HIV, Ebola and SARS)[1–3]. Understanding patterns of viral diversity in wildlife and determinants of successful cross-species transmission, or spillover, are therefore key goals for pandemic surveillance programs[4]. However, few analytical tools exist to identify which host species are likely to harbour the next human virus, or which viruses can cross species boundaries[5–7]. Here we conduct a comprehensive analysis of mammalian host–virus relationships and show that both the total number of viruses that infect a given species and the proportion likely to be zoonotic are predictable. After controlling for research effort, the proportion of zoonotic viruses per species is predicted by phylogenetic relatedness to humans, host taxonomy and human population within a species range—which may reflect human–wildlife contact. We demonstrate that bats harbour a significantly higher proportion of zoonotic viruses than all other mammalian orders. We also identify the taxa and geographic regions with the largest estimated number of 'missing viruses' and 'missing zoonoses' and therefore of highest value for future surveillance. We then show that phylogenetic host breadth and other viral traits are significant predictors of zoonotic potential, providing a novel framework to assess if a newly discovered mammalian virus could infect people.

Viral zoonoses are a serious threat to public health and global security, and have caused the majority of recent pandemics in people[4], yet our understanding of the factors driving viral diversity in mammals, viral host range, and cross-species transmission to humans remains poor. Recent studies have described broad patterns of pathogen host range[1,3] and various host or microbial factors that facilitate cross-species transmission[5,7,8], or have focused on factors promoting pathogen and parasite sharing within specific mammalian taxonomic groups including primates[9–11], bats[12–14], and rodents[12,15]—but to date there has been no comprehensive, species-level analysis of viral sharing between humans and all mammals. Here we create, and then analyse, a database of 2,805 mammal–virus associations, including 754 mammal species (14% of global mammal diversity) from 15 orders and 586 unique viral species (every recognized virus found in mammals[16]) from 28 viral families (Methods). We use these data to test hypotheses on the determinants of viral richness and viral sharing with humans. We fit three inter-related models to elucidate specific components of the process of zoonotic spillover (Extended Data Fig. 1). First, we identify factors that influence total viral richness (that is, the number of unique viral species found in a given host, including those which may have the potential to infect humans). Second, we identify and rank the ecological, phylogenetic and life-history traits that make some species more likely hosts of zoonoses than others. Third, recognizing that not all mammalian viruses will have the biological capacity to infect humans, we identify and rank viral traits that increase the likelihood of a virus being zoonotic.

In examining the raw data, we found that observed viral richness within mammals varies at a host order and viral family level, and is highest for Bunya-, Flavi- and Arenaviruses in rodents; Flavi-, Bunya- and Rhabdoviruses in bats; and Herpesviruses in non-human primates (Extended Data Fig. 2). Of 586 mammalian viruses in our dataset, 263 (44.9%) have been detected in humans, 75 of which are exclusively human and 188 (71.5% of human viruses) zoonotic—defined operationally here as viruses detected at least once in humans and at least once in another mammal species (Methods). The proportion of zoonotic viruses is higher for RNA (159 of 382, 41.6%) than DNA (29 of 205, 14.1%) viruses. The observed number of viruses per wild host species was comparable when averaged across orders, but bats, primates, and rodents had a higher proportion of observed zoonotic viruses compared to other groups of mammals (Fig. 1). Species in other orders (for example, Cingulata, Pilosa, Didelphimorphia, Eulipotyphla) also shared a majority of their observed viruses with humans, but data were limited in these less diverse and poorly studied orders. Several species of domesticated ungulates (orders Cetartiodactyla and Perissodactyla) are outliers for their number of observed viruses, but these species have a relatively low proportion of zoonotic viruses (Fig. 1; Supplementary Discussion).

Previous analyses show that zoonotic disease emergence events and human pathogen species richness are spatially correlated with mammal and bird diversity[2,17]. However, these studies weight all species equally. In reality, the risk of zoonotic viral transmission, or spillover, probably varies among host species owing to differences in underlying viral richness, opportunity for contact with humans, propensity to exhibit clinical signs that exacerbate viral shedding[18], other ecological, behavioural and life-history differences[5,12,15], and phylogenetic proximity to humans[10]. We hypothesize that the number of viruses a given mammal species shares with humans increases with phylogenetic proximity to humans and with opportunity for human contact. We used generalized additive models (GAMs) to identify and rank host-specific predictors (ecological, life history, taxonomic, and phylogenetic traits, and a control for research effort) of the number of total and zoonotic viruses in mammals (Methods; Supplementary Table 1).

The best-fit model for total viral richness per wild mammal species explained 49.2% of the total deviance, and included a per-species measure of disease-related research effort, phylogenetically corrected body mass, geographic range, mammal sympatry, and taxonomy (order) (Fig. 2a–e). Not surprisingly, research effort had the strongest effect on the total number of viruses per host, explaining 31.9% of the total deviance for this model (Extended Data Table 1). The remaining 17.3% can be explained by biological factors, a value greater than or comparable to studies examining much narrower groups of mammal hosts[10,12,15] (Supplementary Discussion). Mammal sympatry was the second most important predictor of total viral richness (Fig. 2d). Our model selection consistently identified mammal sympatry calculated at a $\geq$20% area overlap over other thresholds explored (Methods), providing insight into the minimum geographic overlap needed to facilitate viral sharing between hosts. Host geographic range was also significantly associated with increasing total viral richness, although the strength of this effect was low (Fig. 2c). Several

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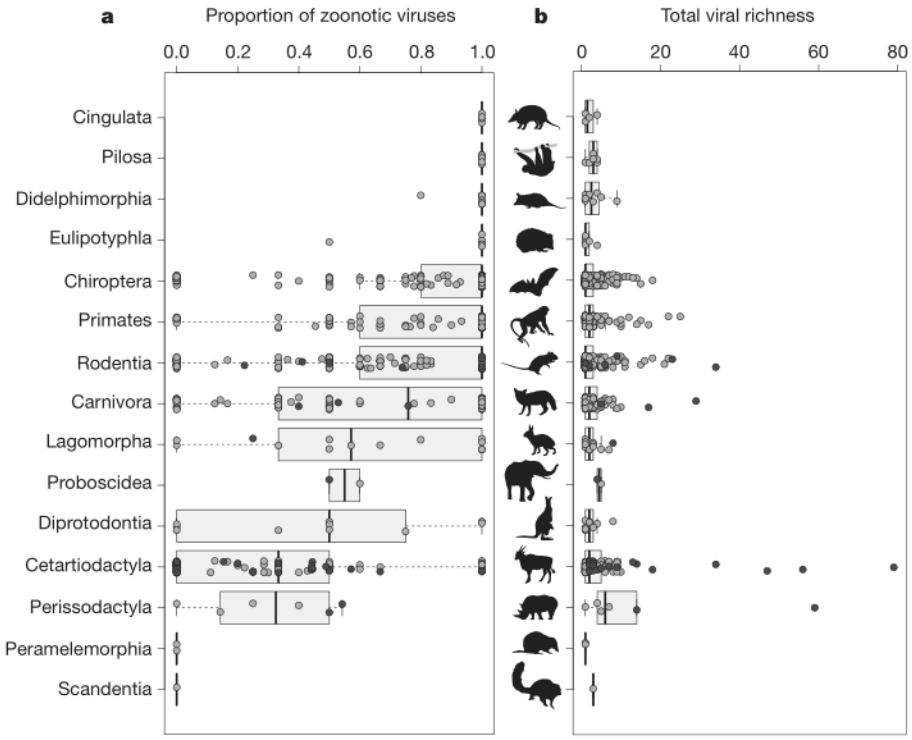

Figure 1 | Observed viral richness in mammals. a, **b**, Box plots of proportion of zoonotic viruses (**a**) and total viral richness per species (**b**), aggregated by order. Data points represent wild (light grey, $n = 721$) and domestic (dark red, $n = 32$) mammal species; lines represent median, boxes, interquartile range. Animal silhouettes from PhyloPic. Data based on 2,805 host–virus associations. See Methods for image credits and licensing.

mammalian orders, Chiroptera (bats), Rodentia (rodents), Primates, Cetartiodactyla (even-toed ungulates), and Perissodactyla (odd-toed ungulates) listed here in order of relative deviance explained, had a significantly greater mean viral richness than predicted by the other variables (Fig. 2e). This finding highlights these taxa as important targets for global viral discovery in wildlife[4], and suggests that traits not captured in our analysis (for example, immunological function, social structure, and other life-history variables) may underlie their capacity to harbour a greater number of viral species. Our models to predict total viral richness were comparable when excluding virus–host associations detected by serology, that is, using the 'stringent data', and were robust when validated with random cross-validation tests (Extended Data Table 1; Supplementary Table 2). However, we identified several regions that showed significant bias when cross-

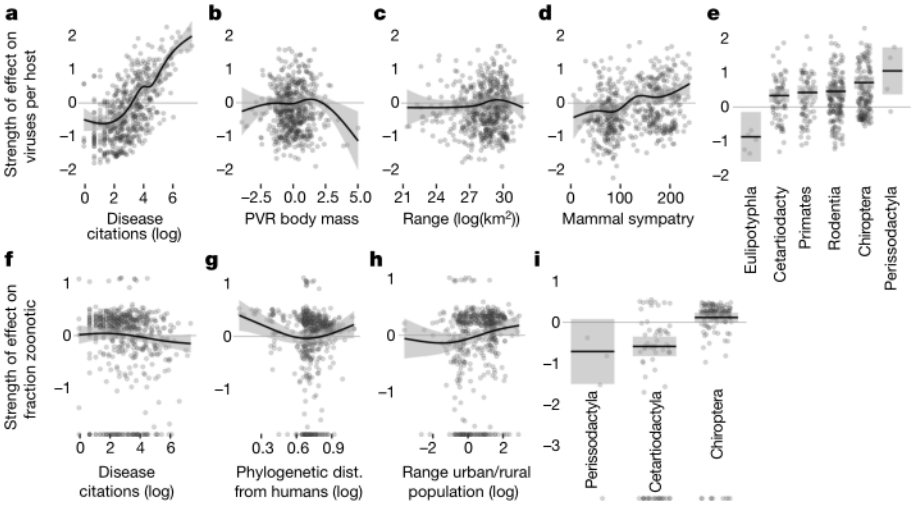

Figure 2 | Host traits that predict total viral richness (top row) and proportion of zoonotic viruses (bottom row) per wild mammal species. Partial effect plots show the relative effect of each variable included in the best-fit GAM, given the effect of the other variables. Shaded circles represent partial residuals; shaded areas, 95% confidence intervals around mean partial effect. **a**–**e**, Best model for total viral richness includes: **a**, number of disease-related citations per host species (research effort, log); **b**, phylogenetic eigenvector regression (PVR) of body mass (log); **c**, geographic range area of each species (log km^2); **d**, number of sympatric mammal species overlapping with at least 20% area of target species range; and **e**, mammalian orders. **f**–**i**, Best model for proportion of zoonoses includes: **f**, research effort (log); **g**, phylogenetic distance from humans (cytochrome *b* tree constrained to the topology of the mammal supertree[28]); **h**, ratio of urban to rural human population within species range; and **i**, three mammalian orders. Bats are the only order with a significantly larger proportion of zoonotic viruses than would be predicted by the other variables in the all-data model. Three additional mammalian orders, and whether or not a species is hunted, improved the overall predictive power of the best zoonotic virus model but were non-significant and are not shown (see Extended Data Table 1).

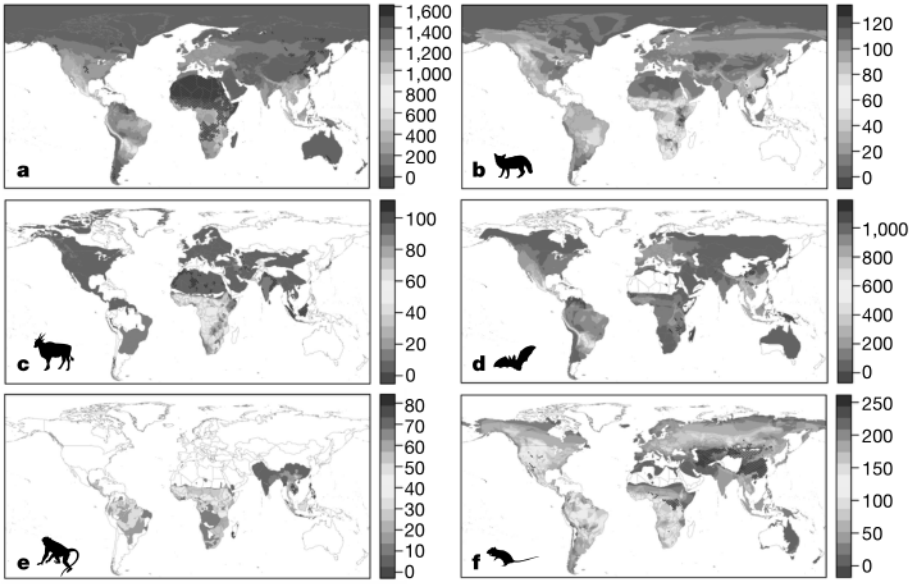

Figure 3 | Global distribution of the predicted number of 'missing zoonoses' by order. Warmer colours highlight areas predicted to be of greatest value for discovering novel zoonotic viruses. **a**, All wild mammals ($n = 584$ spp. included in the best-fit model). **b**, Carnivores (order Carnivora, $n = 55$). **c**, Even-toed ungulates (order Cetartiodactyla, $n = 70$). **d**, Bats (order Chiroptera, $n = 157$). **e**, Primates (order Primates, $n = 73$). **f**, Rodents (order Rodentia, $n = 183$). Hatched regions represent areas where model predictions deviate systematically for the assemblage of species in that grid cell (approximately 18 km × 18 km, see Methods). Animal silhouettes from PhyloPic.

validated by excluding mammals from zoogeographic areas, suggesting that there are location-specific factors that remain unexplained in our models (Methods; Supplementary Table 3).

Our best model to predict the number of zoonotic viruses per wild mammal species explained 82% of the deviance, and included phylogenetic distance from humans, the ratio of urban to rural human population across a species range, host order, whether or not a species is hunted, disease-related research effort, and total viral richness (Extended Data Table 1). A large fraction of the deviance explained is driven by the observed total viral richness per host, supporting the biological assumption that the number of viruses that infect humans scales positively with the size of the potential 'zoonotic pool'[19] in each reservoir host. Removing this contribution by including observed total viral richness per host as an offset, the model explains 33% of the total deviance in the proportion of viruses that are zoonotic (Methods), with 30% of total deviance explained by biological factors (Fig. 2f–i). Some mammalian orders had a significant positive (bats) or negative (two ungulate orders) effect on the proportion of zoonotic viruses (Fig. 2i). A number of previous studies have proposed that bats are special among mammals as reservoir hosts of a large number of recently emerging high-profile zoonoses (for example, SARS, Ebola virus, MERS)[12,13,20]. Our study tests this hypothesis in the context of all known mammalian viruses and hosts. While other mammalian orders have relatively high proportions of observed zoonoses and others have been poorly studied (Fig. 1a), our model results show that bats are host to a significantly higher proportion of zoonoses than all other mammalian orders after controlling for reporting effort and other predictor variables.

We found that the proportion of zoonotic viruses per species increases with host phylogenetic proximity to humans, and that this relationship is significant even when we removed 'reverse zoonoses' primarily associated with transmission from humans to primates (Methods). This is the first time this relationship has been demonstrated using data for all mammals and specifically as a determinant of zoonotic spillover, and is supported by previous taxon-specific studies that have examined host relatedness and parasite/pathogen sharing in primates[9,10], bats[14] and plants[21]. The proportion of zoonotic viruses shows some upward drift for mammals that are very phylogenetically distant from humans (Fig. 2g) that may represent an artefact of preferentially screening marsupials for human viruses. While primate species largely drive the phylogenetic effect, our best-fit model excluded the effect of the order Primates as a discrete variable (Fig. 2i), suggesting that continuous variation in phylogenetic distance across primate species is more important, and is significant even when all mammals are included. This finding highlights the need to uncover the mechanism by which phylogeny affects spillover risk, for example, evolutionarily related species sharing host cell receptors and viral binding affinities[22,23] and specific viral mutations that may expand host range in related mammal species[24].

We tested several measures to estimate human–wildlife contact at a global scale for the 721 wild mammals in our dataset, but only the ratio of urban to rural human population (all data model), the change in human population density, and the change in urban to rural population ratio from 1970–2005 across a species range (stringent data model) were included (Extended Data Table 1). The response curve for urban to rural population suggests that increasing urbanization raises the risk of zoonotic spillover (Fig. 2h), as does increasing human population density and the change in urban to rural population ratio over time. A single global metric of human–wildlife ecological contact did not emerge across models. However, the alternate inclusion of these related variables points to the importance of human–animal contact in defining per-species spillover risk globally, and the need for controlled field experiments and human behavioural risk studies to uncover the mechanisms underlying this risk. Overall, the strength of the effect of phylogenetic proximity was stronger than our proxies for animal–human contact in predicting proportion of zoonoses (30–44% stronger explanatory factor), but both remained significant after controlling for research effort (Extended Data Table 1).

The predominance of zoonoses of wildlife origin in emerging diseases has led to a series of programs to sample wildlife, discover novel viruses, and assess their zoonotic potential[4,23,25,26]. To inform their scale and scope we calculate the expected number of as-yet undiscovered viruses and zoonoses per host species using our best-fit GAMs and a scenario of increased research effort (Methods, Supplementary Table 4). We then project these 'missing viruses' and 'missing zoonoses' geographically (Fig. 3, Extended Data Figs 3–8) to identify regions of the world where targeted, future surveillance to find new viruses and zoonoses will be most effective. In the process of translating our non-spatial, species-level predictions to geographic space, we identified several regions where our model predictions of the number of total

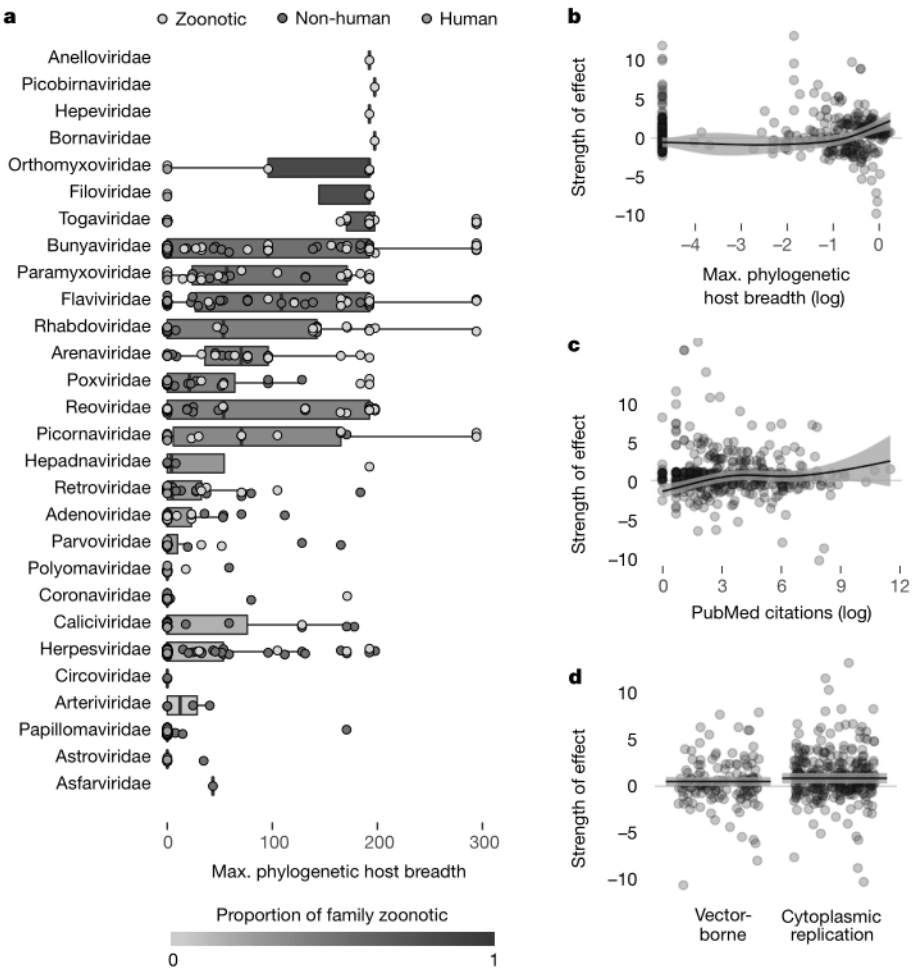

Figure 4 | Traits that predict zoonotic potential of a virus. a, Box plot of maximum phylogenetic host breadth per virus (PHB, see methods) for each of 586 mammalian viruses, aggregated by 28 viral families. Individual points represent viral species, colour-coded by zoonotic status. Box plots coloured and sorted by the proportion of zoonoses in each viral family. **b**–**d**, Partial effect plots for the best-fit GAM to predict the zoonotic potential of a virus. **b**, Maximum PHB. Viruses that infect a phylogenetically broader range of hosts are more likely to be zoonotic. **c**, Research effort (log, number of PubMed citations per viral species). **d**, Whether or not a virus replicates in the cytoplasm or is vector-borne. Viral genome length and whether or not a virus is enveloped improved the overall predictive power but were non-significant and are not shown (see Extended Data Table 1).

and zoonotic viruses were systematically biased (hatched regions in Fig. 3 and Extended Data Figs 3–8; Methods). Local factors contributing to this bias may include geographic variation in the detection probability of human and/or wildlife viruses, indicating areas where additional research and capacity strengthening for viral detection are most needed. Our model predictions were not systematically biased or clustered across host phylogeny (Extended Data Fig. 9).

Geographic hotspots of 'missing zoonoses' vary by host taxonomic order, with foci for carnivores and even-toed ungulates in eastern and southern Africa, bats in South and Central America and parts of Asia, primates in specific tropical regions in Central America, Africa, and southeast Asia; and rodents in pockets of North and South America and Central Africa. Areas where 'missing zoonoses' predictions were systematically biased varied by taxonomic order, but included large parts of Africa for the all-mammal dataset (Fig. 3a, Extended Data Figs 3–8f). By contrast, the distribution of bias in predicting the 'missing viruses' for all mammals was limited to patches of northeastern Asia, Greenland, peninsular Malaysia, and scattered grid cells in western Asia and Patagonia (Extended Data Fig. 3c). We also identify geographic regions with large numbers of mammal species currently lacking any information regarding their viral diversity (Extended Data Figs 3i–8i). In combination, these maps can be used for cost-effective allocation of resources for viral discovery programs, such as the Global Virome Project (D. Carroll *et al.*, submitted).

Finally, a significant challenge to preventing future disease emergence is estimating the zoonotic potential of a newly discovered viral species or strain based on viral traits[4–6,27]. The best model for determining whether or not a known virus ($n = 586$ mammalian viruses) has been observed as zoonotic explained 27.2% of total deviance and included maximum phylogenetic host breadth (PHB—a virus-specific trait that measures the phylogenetic range of known hosts, excluding humans), research effort, whether or not a virus replicates in the cytoplasm, is vector-borne, or is enveloped, and average genome length (Fig. 4). Using the 'stringent' dataset to define whether a virus is zoonotic resulted in a reduced model that excluded enveloped status and genome length (Extended Data Table 1). Our findings confirm a positive relationship between zoonotic potential and ability to replicate in the cytoplasm[7], and that viruses with arthropod vectors may be able to infect a wider range of mammalian hosts[5]. Our phylogenetically explicit measure of host breadth, PHB, can be used at various hierarchical taxonomic levels to quantify and rank viruses from specialist to generalist, and was the strongest predictor of zoonotic potential (12.4% of total deviance explained). This highlights the value of field programs to identify the natural host range of newly discovered pathogens in order to develop early proxies for their zoonotic potential[4]. Significant variation in PHB across viral families is suggestive of intrinsic differences in the ability of a virus to infect diverse hosts, and this relates to the proportion of observed zoonoses in each family (Fig. 4a).

We acknowledge several important caveats in this study. First, our estimates of missing viruses and missing zoonoses per species are based on the current maximum observed research effort from the literature, and these estimates should be viewed as relative, not absolute. The true size of the undiscovered mammalian virome will probably increase with new genetic tools for unbiased viral discovery and in-depth studies that repeatedly sample wildlife populations over time[25]. Second, our ecological and biological predictor variables only explain a portion of the total variation in viral richness per host and zoonotic potential based on viral traits, although this is greater than that reported in comparable order-specific studies[10,12]. Third, while we control for research effort we cannot account for viruses or host associations that have completely evaded human detection to date, nor those identified but not published. Additional resources to support better data sharing and on-the-ground viral surveillance in the species and regions we identify would help validate predictive models to identify zoonotic viral hotspots, and streamline costly efforts to develop measures to prevent their future emergence.

The analyses reported herein have broad potential to assist in expediting viral discovery programs for public health. Our host-specific analyses and estimates of missing zoonoses allow us to identify which species and regions should be preferentially targeted to characterize the global mammalian virome. Our viral trait framework then allows prioritization of newly discovered wildlife viruses for detailed characterization (for example, by sequencing receptor-binding domains, and conducting *in vitro* and *in vivo* infection experiments[23]) to assess their potential to threaten human health.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Supplementary Information is available in the online version of the paper.

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Author Contributions K.J.O., T.L.B. and P.D. designed the study and supervised the collection of data. N.R., P.R.H. and K.J.O. designed the statistical approach, wrote the code, and generated figures. K.J.O. performed phylogenetic analyses. C.Z.-T. performed spatial analyses. All authors were involved in writing the manuscript.

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METHODS

No statistical methods were used to predetermine sample size. The experiments were not randomized and the investigators were not blinded to allocation during experiments and outcome assessment.

Database. To construct the mammal–virus association database we initially extracted all viruses listed as occurring in any mammal from the International Committee on Taxonomy of Viruses database (ICTVdb), and further individually went through each virus listed in the ICTV 8th edition master list and searched the literature for mammalian hosts. All viral species names were synonymized to ICTV 8th edition, which was the global authority on viral taxonomy at the start of our data collection in 2010 (ref. 16). From 2010–15 the authors and a team of research assistants and interns at EcoHealth Alliance compiled mammal species associations for each of 586 unique viruses published in the literature between 1940–2015 initially by using the virus name and synonyms as the search keywords in the major online reference databases (Web of Science, PubMed, and Google Scholar) in addition to searching in books, reviews, and literature cited in sources we had already obtained. To narrow the search for hosts for well-researched viruses, we additionally included the terms 'host(s)', 'reservoir', 'wildlife', 'animals', 'surveillance', and other relevant terms to find publications related to host range. Associations were cross-checked for completeness with the Global Mammal Parasite Database for primate, carnivore and ungulate viruses, version as of Nov 2006 (GMPD, http://www.mammalparasites.org)[29] and other published reviews specific to bats and rodents[12,30,31]. We excluded all records without species-level host information, and those where we could not track down the primary references. Records of mammal–virus associations from experimental infection studies, zoological parks or captive breeding facilities, or cell culture discoveries were excluded. Host species were defined as domestic or wild following the list of domestic animal species from the Food and Agriculture Organization (FAO)[32], and we removed the black rat (*Rattus rattus*) and domestic mouse (*Mus musculus*) from the domesticated list as these two species make up their own 'peri-domestic' category. Host species were categorized as either occurring in human modified habitats or being hunted by humans—both estimates for human contact—according to the IUCN Red List species descriptions[33].

To control for the fact that some detection methods are more reliable than others in identifying the pathogen of interest, we recorded the detection method used for each host–virus association and scored these as 0, 1, or 2 according to the reliability of detection method used. Viral isolation and PCR detection with sequence confirmation were scored as a 2 (=stringent data); and serological methods were scored as a 0 or 1, with viral or serum neutralization tests (=1), and enzyme-linked immunoassays (ELISA), antigen detection assays, and other serological assays scored as (=0). 'Stringent data' were analysed separately to remove potential uncertainty owing to cross-reactivity with related viruses. We exhaustively searched the literature to identify a stringent detection for each mammal–virus pair, and only included the serological finding for that pair if no molecular or viral isolation studies were available. We partitioned data and conducted separate analyses for the entire data set ($0+1+2$ detection quality) and the stringent data (score of 2) to reduce the noise from potential serological cross-reactivity. Full list of host–virus associations, detection methods, and associated references are provided in our data and code repository at http://doi.org/10.5281/zenodo.596810.

Our operational definition of a zoonotic virus includes any virus that was detected in humans and at least one other mammalian host in at least one primary publication, and does not imply directionality. Our complete dataset of mammalian viral associations demonstrates evidence of past or current viral infection which we believe is a reasonable proxy for measuring spillover, and our stringent dataset specifically is more robust to exclude species that may have been exposed to a given virus versus those that show some evidence for replication within the host species. Our bi-directional definition of spillover follows a proposal by the WHO that defines a zoonosis as "any disease or infection that is naturally transmissible from vertebrate animals to humans and vice-versa" (http://www.who.int/zoonoses/en/) and excludes any human pathogens that recently evolved from nonhuman pathogens (for example, HIV in primates), as per Woolhouse and Gowtage-Sequeria (2005) (ref. 1).

In order to address influence of transmission from humans to wildlife in our models, we also ran our GAM model fitting and selection procedure (see below) on a subset of data that excluded any probable 'reverse zoonotic' viruses. We first searched our entire dataset and removed any clear instances of transmission from humans to primates, for example, including records from zoological parks and wildlife rehabilitation centres (as previously noted). We then additionally removed several human viruses most commonly transmitted from humans back to non-human primates to create a subset of data without the most common reverse zoonotic viruses (adeno-associated virus-2; human adenovirus D; human herpesvirus 4; human metapneumovirus; human respiratory syncytial virus; measles virus; mumps virus)[34,35]. We present these additional analyses excluding reverse zoonoses and associated code at http://doi.org/10.5281/zenodo.596810.

Total viral richness was calculated as the number of unique ICTV-recognized viruses found in a given host species, and zoonotic viral richness was defined as the number of unique ICTV-recognized viruses in a given host species that were also detected in humans in our database.

To assess research bias for both host and virus, we searched ISI Web of Knowledge, including Web of Science and Zoological Record, and PubMed for the number of research publications for a given host or pathogen. We recorded two values for the number of research papers for a host. The first was a simple search by scientific binomial in Zoological Abstracts where we recorded the number of papers published between 1940–2013 for each host species. We also recorded the number of disease-related publications for each species using the scientific binomial AND topic keyword: disease* OR virus* OR pathogen* OR parasit*. The * operator was used in our search criteria to capture all words that begin with each term, for example, 'parasit*' would return hits for 'parasite', 'parasites', and 'parasitic'. These search criteria broadly included papers that examined disease or diseases, virus or viruses, pathogen or pathogens, parasite parasites, or parasitology, for each species. Only one measure of per-host research effort was included at a time in model selection. As these metrics are highly correlated and the number of disease related citations per host outperformed the total number of publications per host in all but one model (all-data zoonoses), we decided to use disease-related publications as our per-species research effort measure for all models to improve interpretability. We also recorded the number of publications for each of 586 virus species using a keyword search by virus name in PubMed and Web of Science. Only one measure of per virus research effort was included at a time in model selection.

We used a phylogenetically corrected measure of body mass (see details below under 'Phylogenetic signal') as our main life history predictor variable, because it was the only one for which a nearly complete dataset existed for the species in our dataset. We used the body mass recorded in the PanTHERIA database[36] for 709 species. For 3 species, we used the second choice option, body mass recorded in the AnAge database[37]. For 11 species, we used the third choice option of the extrapolated body mass recorded in PanTHERIA, which is based on body length or forearm length, depending on species. For 36 species, we used the average body mass for members of the genus that had a recorded body mass. We explored other life-history variables related to longevity[38], reproductive success, and basal metabolic rate but these were ultimately excluded owing to the high number of missing records.

Phylogenetic signal. We address the issue of non-independence of host species traits owing to shared ancestry[39] in our analyses by first quantifying the phylogenetic signal for each variable in our model using Blomberg's K[40]. Blomberg's K measures phylogenetic signal in a given trait by quantifying trait variance relative to an expectation under a Brownian motion null model of evolution using a phylogenetic tree with varying branch lengths. Blomberg's K-values are scaled from 0 to infinity, with a value of 0 equal to no phylogenetic signal and values greater than 1 equal to strong phylogenetic signal for closely related species that share more similar trait values. While there is no clearly defined K value cut-off in which to apply phylogenetic comparative methods, non-significant value of <1, or more conservatively <0.5, are typical for traits that are phylogenetically independent. The only host variables we examined with significant K values >0.5 were host body mass, and our direct measure of phylogenetic distance to humans. While there are several tools available to control for phylogeny in multivariate analyses, for example, using phylogenetic generalized least square models (for example, PGLS)[41], there is currently no modelling approach to control for phylogeny using GAMs. More importantly, a wholesale effort to control for phylogeny across all variables in our analysis was not appropriate here, as we are explicitly testing the relative importance of phylogenetic distance to humans versus other host traits including measures of human–wildlife contact to predict the proportion of zoonotic viruses for a given host species. This left body mass as the only variable in our models, excluding our direct measures of phylogenetic distance, with a significant Blomberg K value that was greater than 1. We controlled for the significant effect of shared evolutionary history using a phylogenetic eigenvector regression (PVR)[42,43] on body mass. The PVR approach allowed us to remove phylogenetic signal for any phylogenetically non-independent variables and then include the corrected values back in our GAMs, while retaining predictor variables like phylogenetic distance to humans as unmodified. We calculated PVR for body mass using the R package PVR and our custom-build maximum likelihood host phylogeny using cytochrome *b* sequences constrained to the order-level topology of the mammalian supertree[28,44]. Our new variable for body mass that controls for phylogenetic signal (PVRcytb_resid) removed most of the phylogenetic signal, with $K = 3.5$ unadjusted, and $K < 0.5$ after PVR correction. Our new metric of body mass scales in the same way, with larger values equal to

species with larger body mass. PVR body mass was included in our GAM model selection for the total viral richness and zoonotic virus models.

Host phylogenetic analysis and phylogenetic host breadth. We used two different mammal phylogenetic trees in our analyses and used a model selection framework to determine which best explained our observed association with zoonotic viral richness. First the mammal supertree was pruned in R (package ape, function drop.tips) to include only synonymous species for the 753 species in our database[28,45]. We synonymized all host species names between the mammal supertree and the host associations in our database using the IUCN Red List[33]. If the species was listed as 'cattle' it was assumed to be *Bos taurus*, all other records were excluded if there was ambiguity as to the scientific name for the host species. Second, a maximum likelihood cytochrome *b* tree was generated using the constraint of a multifurcating tree with taxa constrained to their respective orders and the order-level topology matching that of the mammal supertree[6], as per this Newick tree file: (MONOTREMATA,((DIDELPHIMORPHIA,(DIPROTODONTIA,PERAMELEMORPHIA)),(PROBOSCIDEA,((PILOSA,CINGULATA),((((RODENTIA,LAGOMORPHA),(PRIMATES,SCANDENTIA)),((((CETARTIODACTYLA,PERISSODACTYLA),CARNIVORA),CHIROPTERA),EULIPOTYPHLA)))))));). This generated a higher-resolution species-level mammal tree using cytochrome *b* data, with more reliable positioning of the higher-level taxonomic relationships than was obtained in exploratory phylogenetic analyses using cytochrome *b* data alone. GenBank accession numbers and cytochrome *b* sequence lengths for each species are provided in in our data and code repository. Cytochrome *b* gene fragments ranged from 143 to 1,140 bp, with >1,000 bp available for 558/665 (84%) of the taxa. Data derived from the cytochrome *b* tree constrained to the topology of the mammal supertree was selected as the best option in all best-fit GAMs.

Sequences were aligned using MUSCLE with default setting in Geneious R6, and checked visually for errors[46]. The best maximum likelihood tree with and without the constraint tree were generated using RAxML-HPC2 on XSEDE via the CIPRES Science Gateway server v.3.1 (ref. 47) using a GTR model with parsimony seed, 1.000 bootstrap replicates, and the following, specific parameters (raxmlHPC-HYBRID -s infile -n result -x 12345 -g constraint.tre -N 1000 -c 25 -p 12345 -f a -m GTRCAT).

Matrices of pairwise patristic distances between all species, including *Homo sapiens*, were calculated from the two phylogenies using the 'cophenetic' function in the R package ape[45]. Phylogenetic trees (Newick format for pruned supertree and cytochrome *b* tree) and matrices of phylogenetic distance from humans are provided in the data and code repository.

We calculated mean, median, max., min., IQR, and standard deviation (represented as generic function F in equation (1) of phylogenetic host breadth (PHB) from all known mammalian hosts for each virus using the pairwise patristic distances ($d_{i,j}$) for each mammal–mammal association for all hosts of a given virus excluding humans, where i indexes each mammal in the database, as does j, and J represents the total mammals in the database. We aggregated these PHB values using mean, median, or maximum values at a viral species, genus and viral family level to generate higher-level taxonomic variables of host breadth per viral group. Our measure is similar to those developed by previous studies to understand parasite host specificity[48–50], but here we create a generalizable variable to measure viral host breadth that can be aggregated at different viral taxonomic levels.

$$PHB_i = F^{J}_{j=0}\, d_{i,j} \quad (1)$$

To make Extended Data Fig. 9, taxon names and terminal branches of cytochrome *b* tree constrained to supertree were colour-coded using residual from the best-fit zoonotic virus GAM (predicted minus observed zoonotic viral richness) for wildlife species, and plotted using the plot.phylo function in the R package ape[45]. Symbols (circles) at terminal taxa additionally added to better visualize residual value colours were added using willeerd.nodelabels function (http://dx.doi.org/10.5281/zenodo.10855). All marine mammals, domestic animals, and other taxa with missing data were coded as grey for missing data.

Viral richness heat map (Extended Data Fig. 2) was generated using the R package pheatmap, and the 'complete' hierarchical clustering algorithm to sort cells across rows and columns by similar values of viral richness. All box plots, histograms and all other figures generated in R v.3.3.0 (ref. 51). R code for primary figure generation is provided in the code repository.

GAM fitting and selection. We fit a set of generalized additive models (GAMs) that included all of our selected potential variables explaining the number of total viruses or number of zoonoses in hosts, as well as whether viruses were zoonotic (for conceptual framework and summary of each GAM see Extended Data Fig. 1; for full variable list and data sources see Supplementary Table 1). Our use of GAMs, an incorporation of smooth spline predictor functions into the generalized linear model (GLM) framework, allowed us to examine the functional form of our predictor variables (for example, Figs 2 and 4). Categorical and binary variables (for example, host order, IUCN status of hunted or not, and certain viral traits) were fit as random effects of each variable level. We used automated term selection by double penalty smoothing[52] to eliminate variables from the models. This method removes variables with little to no predictive power and has been shown to be comparable or superior to comparing alternate models with and without variables. We did use the model comparison method for domestic animals, where the sample size was not sufficient for fitting all variables. In this case dropping variables by double penalty smoothing still allowed pruning the model list to eliminate redundant models. Where there were competing variables measuring the same mechanistic effect, we fit alternate GAMs using only one of each of these variables (as specified in below and in the Extended Data Fig. 1). These included phylogenetic variables, citation counts from alternate databases, and different measures of human population/host overlap. For example, to capture host phylogeny we used phylogenetic distance based on either the mammal supertree[20] or a purpose-built cytochrome *b* constrained by the topology of the mammal supertree, but never both in the same model. For human population variables, we looked at either variables measuring overlap of species range with human-occupied areas, or human population in those areas, as area- and population-based measures were highly co-linear. For citation variables, we looked at either all citations or the number of disease-related citations for each host species, not both, and similarly citations in either PubMed or Web of Knowledge. We used a binomial GAM to analyse the 586 mammalian viruses in our database and identify viral traits that may serve as predictors of zoonotic potential. Co-linearity was not a major issue among variables included in the same model.

We inspected models within 2 AIC units of the model with the lowest AIC, and present the outputs of the best-fit and all other top models (<2 ΔAIC) in our data and code repository. In general, variable effects retained the same functional form and effect size across models within 2 ΔAIC—differences were limited to the adding or dropping of very weak, insignificant effects, or switching between highly correlated competing variables such as citation counts from different databases.

For our model of number of zoonoses per host, we used the total number of observed viruses per host as an offset, effectively fitting a model of proportion of zoonotic viruses per host. We found this variable had a coefficient near to one when it was used as a linear predictor, indicating its appropriateness as an offset.

We repeated the model selection process for all models using the more stringent set of data that used only virus identified in mammal hosts using viral isolation, PCR, or other methods of nucleic acid sequence confirmation, that is, that excluded all associations detected via serology.

All models were fit using the MGCV package for R (version 1.8-12.). We used the model with the lowest AIC to predict the number of expected zoonotic viruses for each host species, using all the data from our database that had complete observations for the best model. Our top models consistently outperform the alternatives by wide margins, as measured by AIC. We used standard methods in the R package MGCV to calculate deviance explained, which is defined as (D_null – D_model)/D_null. In this formula, D_null is the deviance ($-2\times$likelihood) of an intercept-only, (or, in the case of the zoonoses model, offset-only), model, while D_model is the deviance of our best-fit model.

Analyses were limited to terrestrial mammal species as defined by the IUCN Red List (marine mammals were excluded) and we ran separate analyses for wild and domestic animals. As domestic animals made up a much smaller dataset ($n = 32$ species) with a unique set of explanatory variables that differed from the wild species analyses, these models were fit separately. Domestic species results are also discussed separately (see Supplementary Discussion) as they are tangential to the primary findings.

Model cross-validation. We used k-fold cross-validation to evaluate goodness of fit for all models. The data was divided into ten folds, selected randomly. For each fold, the model was re-fit based on the other nine folds, and goodness of fit was assessed by conducting a nonparametric permutation test comparing the predicted values versus the real values for the kth fold, where a non-significant result indicates that predictions are unbiased. Poisson models goodness-of-fit may be compared via a parametric χ^2 permutation test on deviance values, but this test is inappropriate in the case of models with low mean values, as is our case for some of our GAMs[53]. The k-fold cross-validation confirmed the robustness of our model predictions for wild mammals, code and outputs from these tests for each best-fit GAM are provided in Supplementary Table 2.

In addition to randomly selected k-fold cross-validation, we evaluated the robustness of our models via a non-random geographic cross-validation, code and summary document provided in our code and data repository. In order to meaningfully organize species in our dataset by geographic areas, we used the 34 zoogeographic regions for terrestrial mammals recently redefined by Holt *et al.*[54]. Using QGIS[55], a mammal-specific zoogeographical shapefile provided by Holt's group

at the University of Copenhagen (http://macroecology.ku.dk/resources/wallace) was intersected (using QGIS Vector > Geoprocessing Tools > Intersect) with a shapefile of IUCN's host ranges for all mammals in our database. Areas of these intersections were then calculated using an equal-area projection (Mollweide), and each host was assigned to only the region that contained the greatest proportion of its range. We systematically removed all observations (species) from each given zoogeographical region, re-fit the model using all observations from outside the region, then performed a non-parametric permutation test comparing the predicted values to the observed values for that region. Non-significant results indicate that model predictions are unbiased. Significant results for a given zoogeographic region suggest that there are location-specific biases that remain unexplained. This systematic zoogeographic cross-validation supported the overall robustness of our model predictions for several models, that is, all-data zoonoses, all-data total viral richness, and stringent-data total viral richness models. For these models, even though a majority of zoogeographic regions were unbiased, we still identified several zoogeographic regions that showed significant bias. Our zoogeographic cross-validation was equivocal for the stringent-data zoonoses model, with eight regions that showed evidence of bias and seven regions which showed no evidence of bias (Supplementary Table 3).

The presence of biased regions in our zoogeographic cross-validation suggested the possibility that there is a systematic bias associated with geography not captured by the predictor variables in our models. To further investigate this, we added zoogeographical region as a categorical random effect to each of our best-fit models. For three of our best-fit GAMs (all-data total viruses, stringent-data total viruses, and stringent-data zoonoses) the addition of zoogeographical region as a categorical random effect decreased the model AIC and increased the total deviance explained by 3–5%. The all-data zoonoses model, which was used to create the series of maps in the main manuscript, does not improve with the inclusion of zoogeographical region. However, the improved predictive power of models using region-specific terms is offset by the increase in degrees of freedom (that is, if we included 31 zoogeographic regions as separate terms) and, more importantly, a decreased interpretability of our models—especially when compared to the geographical variables we used, such as host area or species range overlap with human modified habitat. We opted not to include these random effects in our final GAMs in favour of keeping only variables interpretable in the context of our host trait-specific framework. Instead, we indicate areas of geographic bias directly on our spatially mapped outputs. (See 'Calculating and visualizing missing viruses and missing zoonoses', below.) Summaries of these models, along with changes in relative deviance explained for the other explanatory variables when zoogeographic region is added as a random effect, are provided in our code and data repository.

Spatial variables. For all the wildlife hosts we used the geographic range information obtained from the IUCN spatial database version 2015.2. Wildlife host species shapefiles needed to replicate analysis are hosted on our Amazon S3 storage (https://s3.amazonaws.com/hp3-shapefiles/Mammals_Terrestrial.zip)[33]. IUCN depict species' range distributions as polygons based on the extent of occurrence (EOO), which is defined as the area contained within a minimum convex hull around species' observations or records. This convex hull or polygon is further improved by including areas known to be suitable or by removing unsuitable or unoccupied areas based on expert knowledge. To accurately calculate the area in km^2 of each host species we projected the polygons to an equal area projection (Mollweide).

We calculated various thresholds of mammal sympatry based on percentage of range overlap for each wild species in our database using IUCN shape files for all mammals globally. We define mammal sympatry as the number of mammalian species that overlap with the target species' geographic range. We calculated mammal sympatry for each wild species in our database at six different thresholds based on the percentage area overlap with the target species geographic range, that is, the number of other wild mammal species with any (>0%), ≥ 20%, ≥ 40%, ≥ 50%, ≥ 80%, or 100% range overlap. The six different thresholds for mammal sympatry were included as competing terms in our model selection for the total viral richness models.

We derived and tested several global measures to estimate the level of human contact with each wild species in our database. To estimate the area of host geographic range covered by crops, pastures, rural and urban areas—as measures of global human contact with a given wildlife species—each species polygon was intersected (overlapped) with spatial data representing those land cover types. Additionally, we calculated the total number of people within each host geographic range using data from HYDE database[56], and also separately totalled the number of people in rural and urban populations. We obtained data on the distribution of cropland, pastures, rural and urban areas also from the HYDE database[56] for the years 1970, 1980, 1990, 2000 and 2005 with a spatial resolution of 5 × 5 arc minutes, equivalent to 10 km by 10 km at the equator. These datasets were created by combining information from satellite imagery and sub-national crop and pasture statistics[56]. In our GAMs, we used several transformations of these variables as competing proxies for human–wildlife contact: the log-transformed area of host range that overlapped each type of human-modified land cover, log-transformed human population in the host range, log-transformed human population density in the host range, and the log-ratio of urban and rural human populations in the host range. For each of these, we also included as a variable the change in value from 1970 to 2005. Human–wildlife contact variables that significantly covaried were excluded (set as competing terms) during the model selection process. The ratio of urban to rural human population was used to disentangle variables of human–wildlife contact that significantly covaried. For example, the total area of a species range that overlapped with urban and rural areas was highly correlated with the total geographic area variables we examined (for example, total area, and area in crop, pasture, rural, and urban). The ratio of urban to rural population allowed us to separate these signals and best represent this proxy of per-species human–wildlife contact. All spatial analyses were performed in R (3.3.2)[51], using the following R libraries: raster[57], rgdal[58], and sp[58].

Calculating and visualizing missing viruses and missing zoonoses. We used each respective best-fit, all-data GAM from the total viral richness and proportion zoonoses models to calculate the estimated number of viruses that would be observed if the research effort variable for each species was equal to that of the most-studied wild species in our database (*Vulpes vulpes* with 4,433 total publications and 1,477 disease-related publications). We used the prediction of the total virus richness GAM as the offset for the zoonoses GAM. We then calculated the missing viruses and missing zoonoses by subtracting the observed number of viruses and zoonoses from the predictions based on maximum research for each wild mammalian species.

We used geographic range maps from the IUCN spatial database (2015.2) to visualize the spatial distribution of observed host–virus associations, observed host–zoonoses associations, these associations as predicted under maximum research, and the maximum predicted minus the observed viruses, or the missing viruses and missing zoonoses (for example, Fig. 3; Extended Data Figs 3–8; Supplementary Table 4). We also generated maps comparing species richness of all species in the IUCN database against those with viral associations in our database. For each species, the distribution range was converted to a grid system with cells 1/6 of a geographic degree (approximately 18 km × 18 km at the equator line). Each grid cell was assigned a value of one to indicate presence. We repeated this process and assigned the observed and predicted-under-maximum-effort number of zoonotic viruses to their correspondent grid cells. Viral and host species richness maps, and both the missing viruses and missing zoonoses maps were calculated by overlying individual grids. Each richness map represents the sum of all values for a given grid cell. We repeated the process for all the host species in our database and created viral and species richness maps for the following orders: Carnivora, Cetartiodactyla, Chiroptera, Primates and Rodentia. These taxa were selected because they represent 681/736 (92.5%) of wild mammal species in our database.

In the process of translating our non-spatial, species-level predictions to geographic space (that is, layered raster maps), we identified several geographic areas where our model predictions of the number of total and zoonotic viruses were systematically biased, that is, $P < 0.05$ (Supplementary Table 3). In order to visualize the geographic biases of our non-spatial model predictions in our maps (see above regarding zoogeographic cross-validation), we demarcate regions with significant bias with hatching. Hatched regions represent areas where model predictions of total or zoonotic viral richness deviate systematically for the collection of species in that grid cell. For each grid cell we calculated whether the bias exceeded that expected from a random sampling of hosts. This was accomplished by summing the residuals from 100,000 random draws of species in our dataset that was equal to the number of species present in that grid cell, then identifying grid cells where the observed bias was outside the middle 95% of the randomly drawn distribution. We calculated this for all mammals, and separately for each order across all grid cells. Areas with observed bias (outside of 95% of the randomly drawn distribution) are shown with hatched regions on each missing virus and missing zoonoses map.

Animal images used in figures. Animal silhouettes added to Figs 1 and 3 and Extended Data Figs 1 and 2 to visually represent each mammalian order were downloaded from PhyloPic (http://www.phylopic.org). Images used to represent the orders Chiroptera, Cingulata, Diprotodontia, Lagomorpha, Peramelemorphia and Primates were available for use under the Public Domain Dedication license. Images used to represent the orders Carnivora and Rodentia (by R. Groom), Didelphimorphia, Pilosa, and Probscidea (by S. Werning), Eulipotyphyla (by C. Rebler), Certartiodactyla and Perissodactyla (by J. A. Venter, H. H. T. Prins, D. A. Balfour & R. Slotow and vectorized by T. M. Keesey) were provided under a Creative Commons license (https://creativecommons.org/licenses/by/3.0/). We created the silhouette used to represent the order Scandentia.

Data availability. All datasets (host traits, viral traits, full list of host–virus associations and associated references, phylogenetic trees, and phylogenetic distance matrices) needed to fully replicate and evaluate these analyses are provided at http://doi.org/10.5281/zenodo.596810. The top-level README.txt file in the directory details the file structure and metadata provided.

Code availability. All R code and R package dependencies needed to fully replicate and evaluate these analyses are provided at http://doi.org/10.5281/zenodo.596810.

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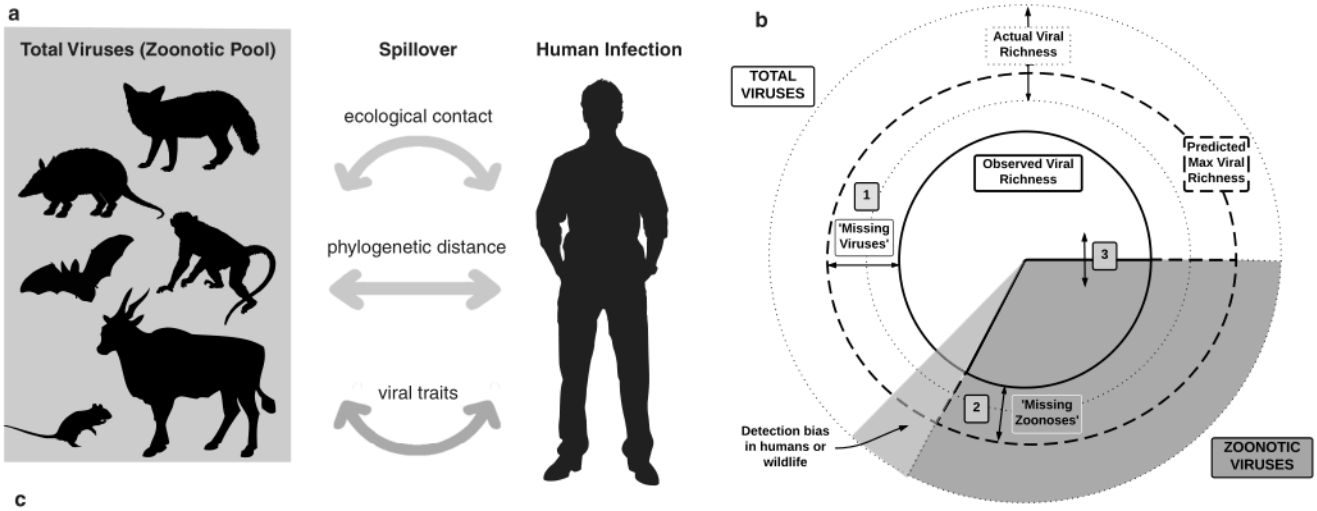


c

Host Species GAMs

1 Total Viruses Per Host Species

host order*

host range area*

change in host range area (1970 - 2005)

mammal sympatry (any, **20***, 40, 50, 80, or 100%)

body mass (phylogenetically corrected)*

disease-related citations per host*

age of domestication (domestic only)

continents inhabitated (domestic only)

production type (domestic only)*

Data subsets:
- all observed wild host-virus associations
- stringent observed wild host-virus associations
- all observed domestic host-virus associations
- stringent observed domestic host-virus associations

2 Zoonotic Viruses Per Host Species

% host habitat range urban, crop, or pasture

change in % host habitat range urban, crop, or pasture (1970 - 2005)

urban to rural human population ratio in host range* or human population density in host range

change in urban to rural human population ratio in host range or change in human population density in host range or total human population in host range (1970 - 2005)

host order*

phylogenetic distance from humans (**CytB*** or Supertree)

IUCN artificial habitat use

IUCN hunted

disease-related citations per host*

age of domestication (domestic only)

continents inhabitated (domestic only)

production type (domestic only)*

+ Offset Variable: Observed total viral richness per host species

Proportion of zoonotic viruses per host = predicted number of zoonoses ÷ total viral richness (offset)

Data subsets:
- all observed wild host-zoonotic virus associations
- stringent observed wild host-zoonotic virus associations
- all observed wild host-zoonotic virus associations without reverse zoonoses
- all observed domestic host-virus associations
- stringent observed domestic host-virus associations

Viral Traits GAMs

3 Probability of a Virus Being Zoonotic

PubMed or **Web of Science citations per virus**

vector-borne*

enveloped

average genome length

nucleic acid type (RNA vs DNA) or strand count

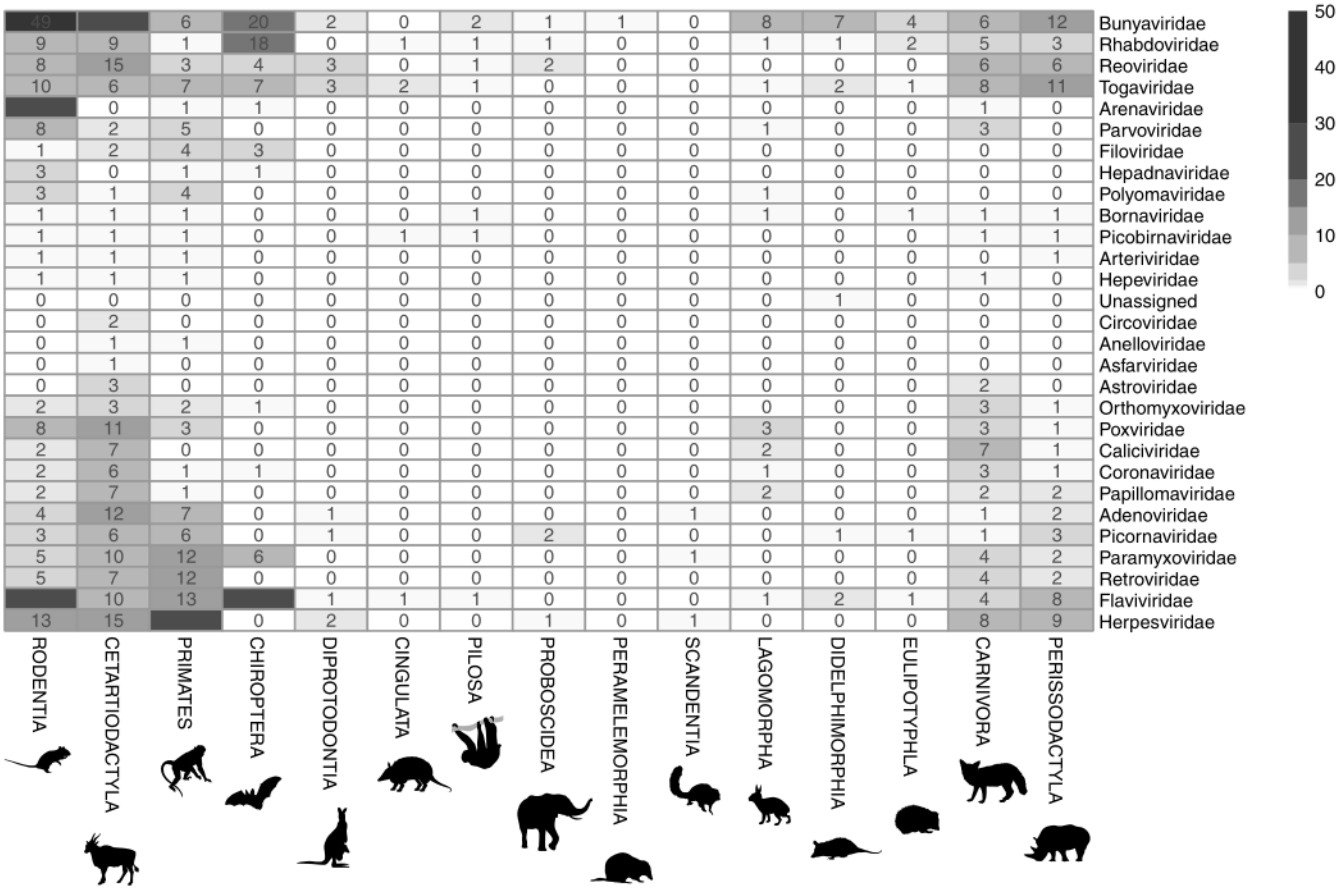
replication in cytoplasm*

median, mean, or **max*** **non-human phylogenetic host breadth** calculated from Supertree or **cytB**

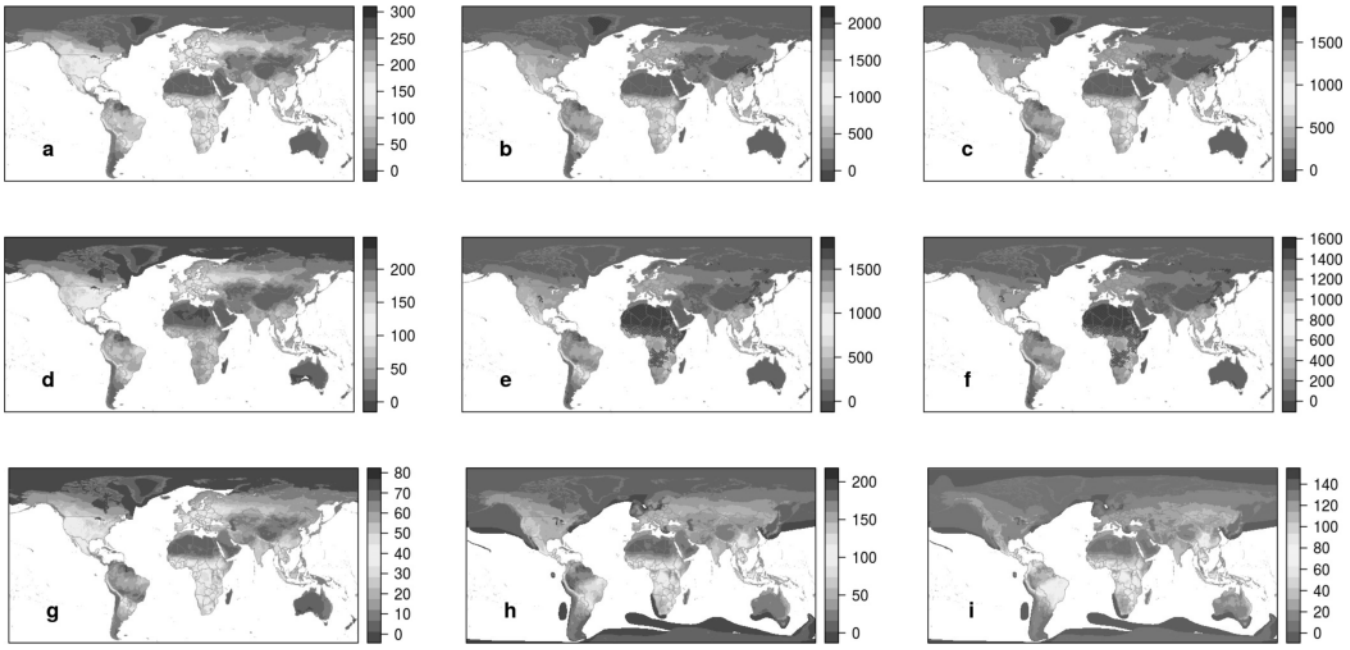
Data subsets:
- observed host-viral associations
- stringent observed host-viral associations

Extended Data Figure 1 | See next page for caption.

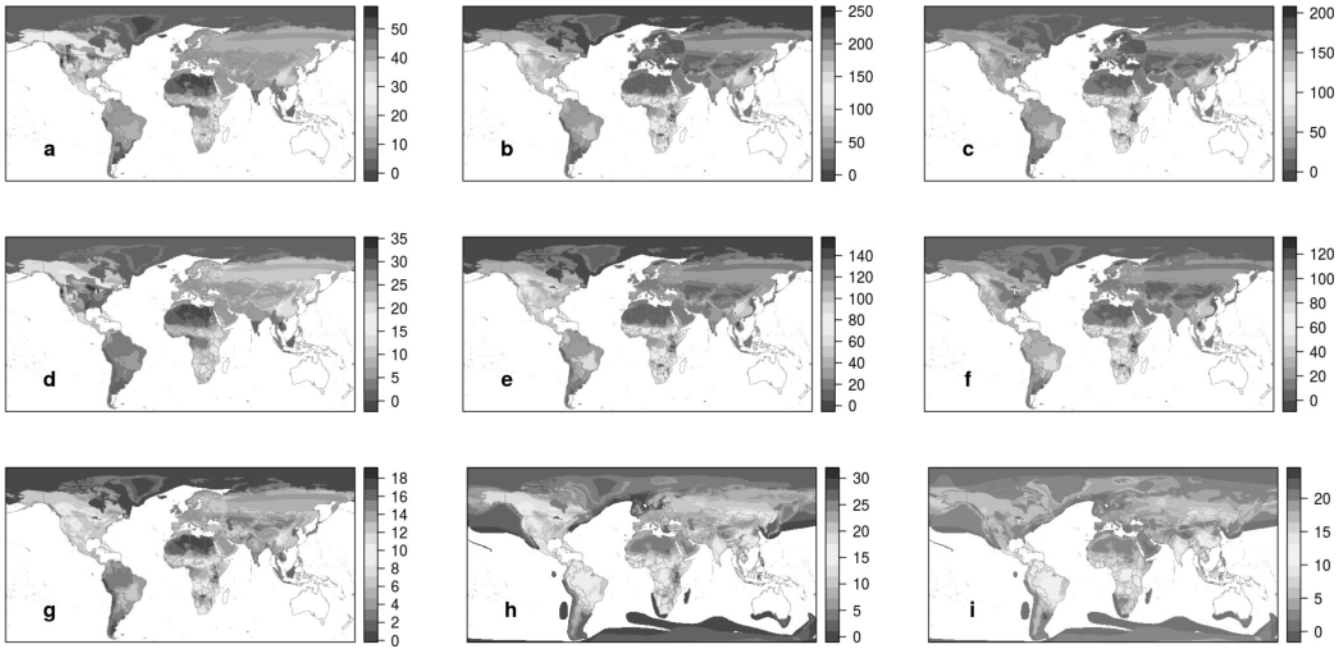
Extended Data Figure 1 | Conceptual model of zoonotic spillover, viral richness, and summary of models. a, Conceptual model of zoonotic spillover showing primary risk factors examined, colour-coded according to generalized additive models used. **b**, Conceptual model of observed, predicted, and actual viral richness in mammals. **c**, GAMs used in our study to address specific components of **a** and **b**, colour-coded by model. Variables listed with 'or' under each GAM covaried and were provided as competing terms in model selection, and those in bold were included in the best-fit model using all host–virus associations. Significant variables from each best-fit GAM are noted with an asterisk. Zoonotic viral spillover first depends on the underlying total viral richness in mammal populations and the ecological, taxonomic, and life-history traits that govern this diversity (GAM 1). Second, host- and virus-specific factors may facilitate viral spillover. We examine the relative importance of host phylogenetic distance to humans, ecological opportunity for contact, or other species-specific life-history and taxonomic traits (GAM 2), and identify viral traits associated with a higher likelihood of an observed virus being zoonotic (GAM 3). We estimate the total and zoonotic viral richness per host species using GAMs 1 and 2, and calculate the missing viruses and missing zoonoses under a scenario of increased research effort (**b**, Methods). Owing to imperfect surveillance in both humans and wildlife and biases in viral detection, there may be uncertainty in the exact proportion of viruses that are zoonotic (**b**, light grey), and also between the actual, or true, viral richness (dotted lines) and the predicted maximum viral richness per host (dashed line).



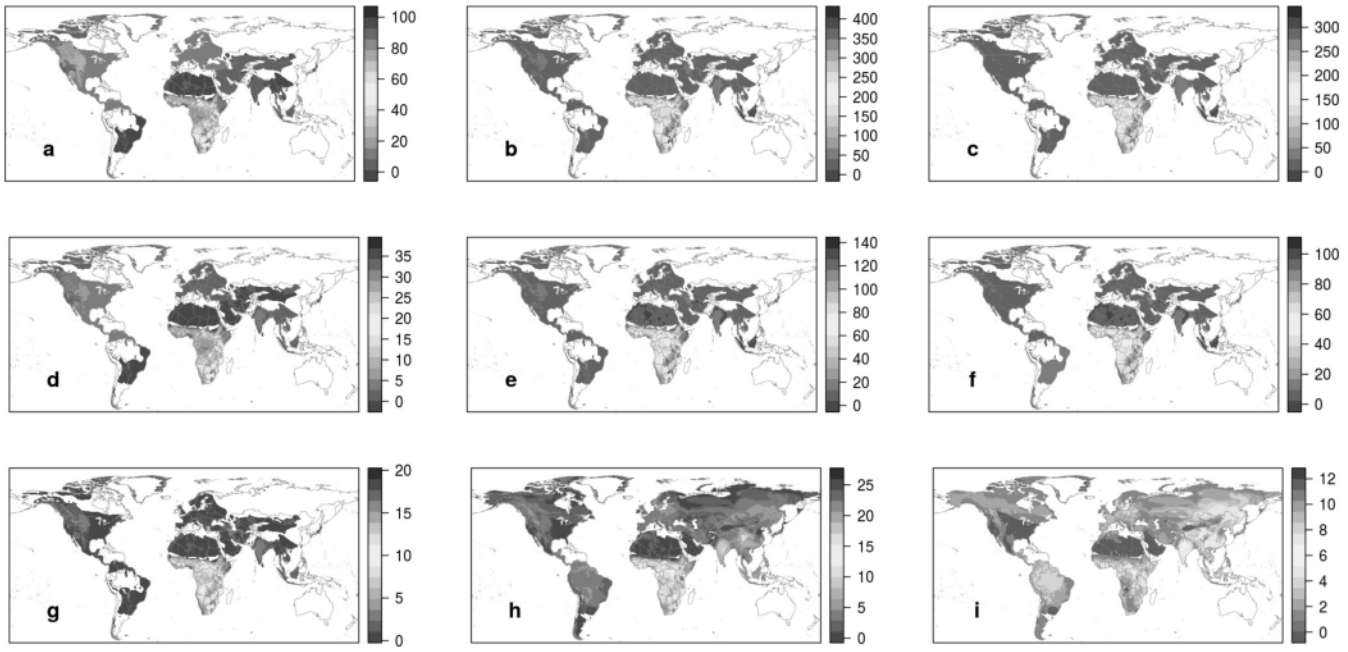
Extended Data Figure 2 | Heat map of observed total viral richness by mammalian order and viral family. Dataset includes 754 mammalian species and 586 unique ICTV recognized viral species. Heat map aggregated by rows and columns to group taxa with similar levels of observed viral richness.



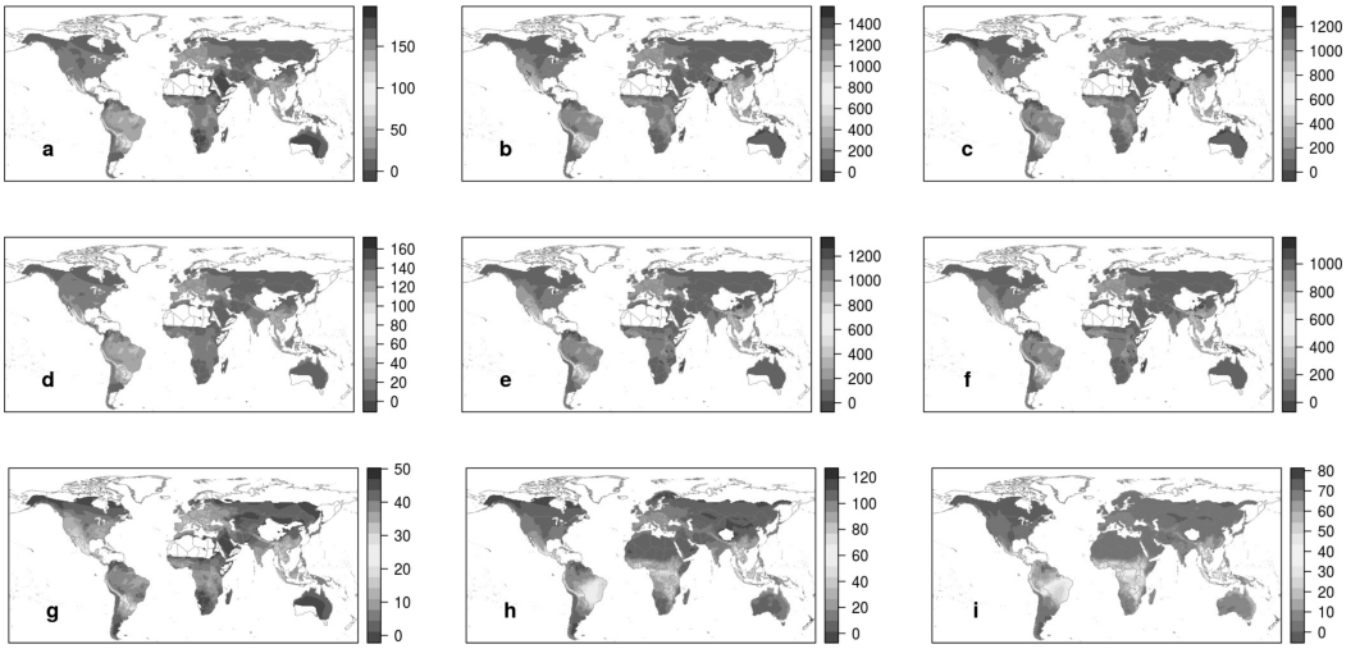
Extended Data Figure 3 | Global distribution of viral and host species richness for all wild mammals. a, Observed total viral richness (for $n = 576$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 584$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3a); **g**, global mammal species richness ($n = 5{,}290$); **h**, mammal richness for species in our database ($n = 753$); **i**, mammal species with no described viruses in the literature. Warmer colours (larger values) in panels **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in mammals. Red/pink colours in panel **i** highlight areas with poor viral surveillance in mammal species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



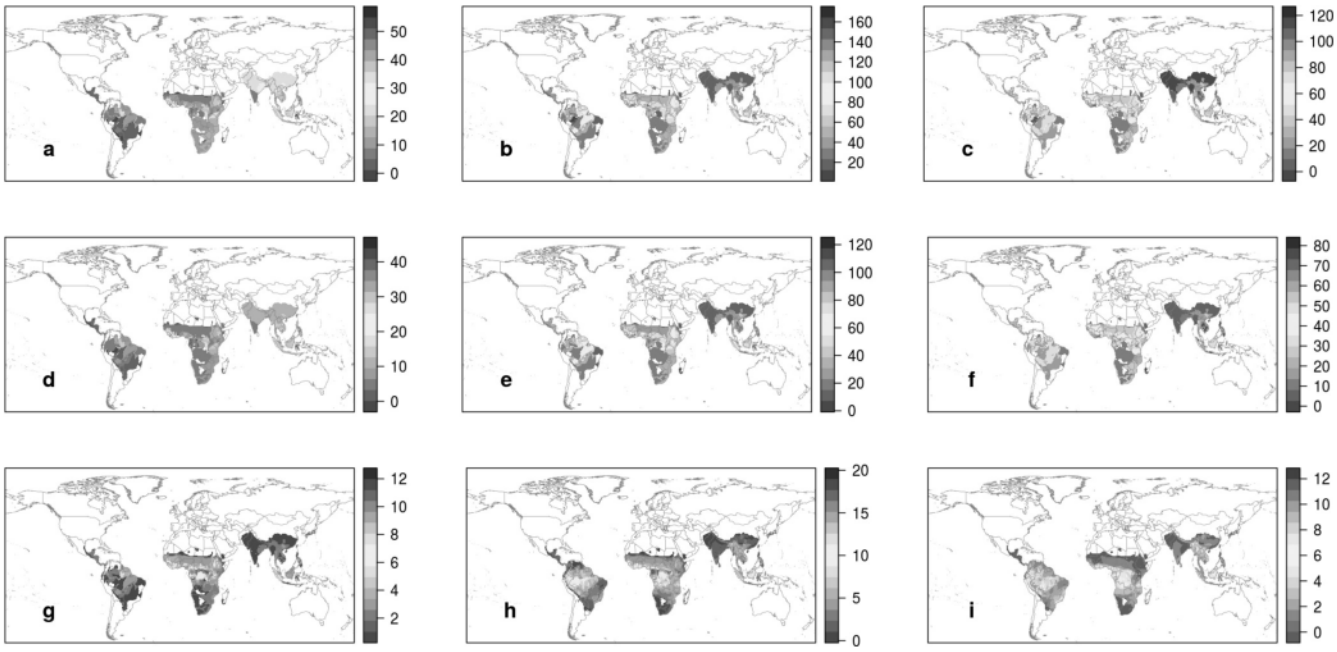
Extended Data Figure 4 | Global distribution of viral and host species richness for wild carnivores (order Carnivora). a, Observed total viral richness (for $n = 55$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 55$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3b); **g**, global host species richness for Carnivora ($n = 276$); **h**, host species richness for Carnivora in our database ($n = 79$); **i**, species of the order Carnivora with no described viruses in the literature. Warmer colours (larger values) in **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in carnivores. Red/pink colours in panel **i** highlight areas with poor viral surveillance in carnivore species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



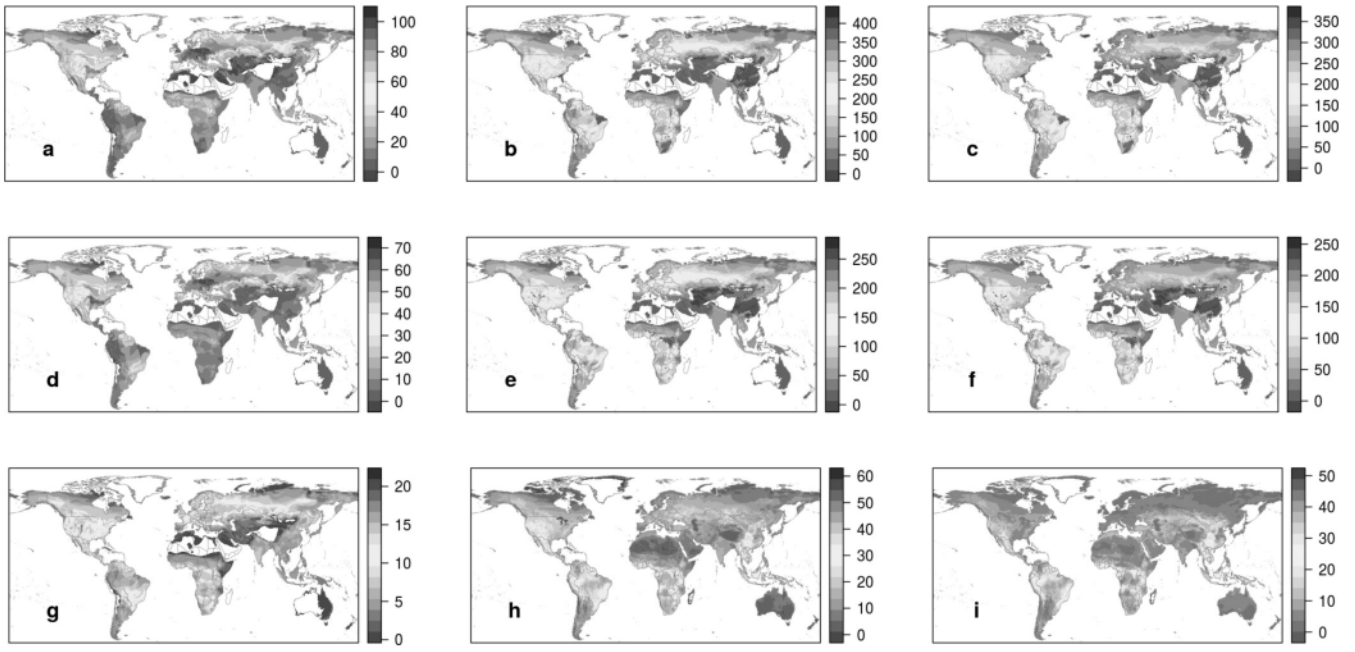
Extended Data Figure 5 | Global distribution of viral and host species richness for wild even-toed ungulates (order Cetartiodactyla). **a**, Observed total viral richness (for $n = 70$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 70$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3c); **g**, global host species richness for Cetartiodactyla ($n = 229$); **h**, host species richness for Cetartiodactyla in our database ($n = 105$); **i**, species of the order Cetartiodactyla with no described viruses in the literature. Warmer colours (larger values) in **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in even-toed ungulates. Red/pink colours in panel **i** highlight areas with poor viral surveillance in even-toed ungulates species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



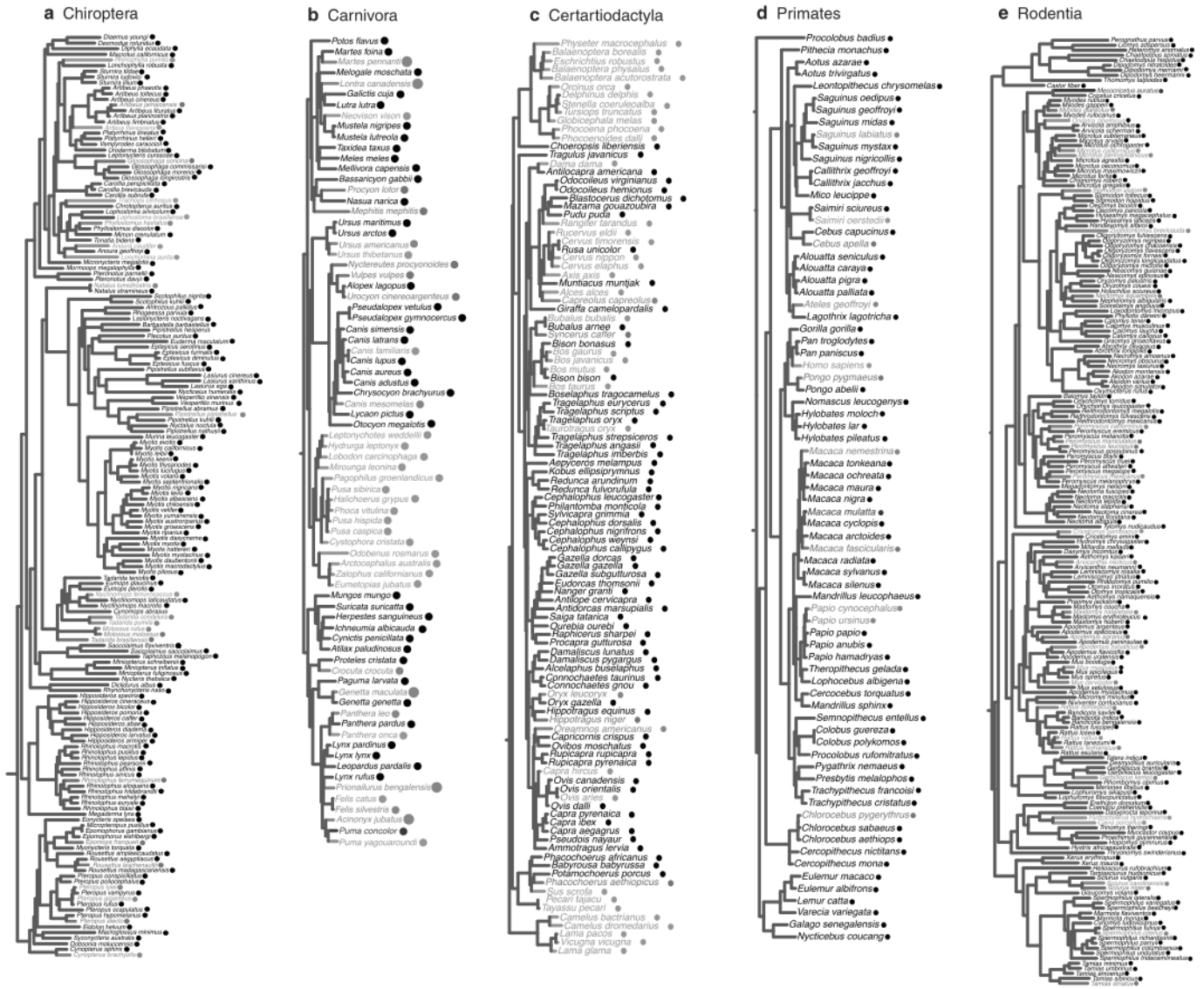
Extended Data Figure 6 | Global distribution of viral and host species richness for bats (order Chiroptera). a, Observed total viral richness (for $n = 156$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 157$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3d); **g**, global host species richness for Chiroptera ($n = 1117$); **h**, host species richness for Chiroptera in our database ($n = 192$); **i**, species of the order Chiroptera with no described viruses in the literature. Warmer colours (larger values) in **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in bats. Red/pink colours in panel **i** highlight areas with poor viral surveillance in bat species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



Extended Data Figure 7 | Global distribution of viral and host species richness for primates (order Primates). **a**, Observed total viral richness (for $n = 71$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 73$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3e); **g**, global host species richness for Primates ($n = 400$); **h**, host species richness for Primates in our database ($n = 98$); **i**, primate species with no described viruses in the literature. Warmer colours (larger values) in **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in primates. Red/pink colours in panel **i** highlight areas with poor viral surveillance in primate species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



Extended Data Figure 8 | Global distribution of viral and host species richness for rodents (order Rodentia). **a**, Observed total viral richness (for $n = 178$ host spp.); **b**, predicted total viral richness given maximum research effort; **c**, missing viruses or predicted minus observed total viral richness; **d**, observed zoonotic viral richness ($n = 183$); **e**, predicted zoonotic viral richness given maximum research effort; **f**, missing zoonoses or predicted minus observed zoonotic viral richness (same as included in Fig. 3f); **g**, global host species richness for Rodentia ($n = 2206$); **h**, host species richness for Rodentia in our database ($n = 221$); **i**, rodent species with no described viruses in the literature. Warmer colours (larger values) in **c** and **f** highlight areas predicted to be of greatest value for discovering novel viruses or novel viral zoonoses, respectively, in wild rodents. Red/pink colours in panel **i** highlight areas with poor viral surveillance in rodent species to date. Hatched regions represent areas where model predictions deviate systematically for the collection of species in that grid cell (see Methods).



Extended Data Figure 9 | Order-level phylogenies showing residuals from zoonoses model. a–e, Subtrees from cytochrome *b* maximum likelihood phylogeny for 558 mammal species (constrained to order-level topology of mammal supertree) for bats (**a**), carnivores (**b**), even-toed ungulates (**c**), rodents (**d**) and primates (**e**). Species included have at least one described virus association and available genetic data. Wildlife species names and terminal branches are colour-coded by the residuals (predicted minus observed) from the best-fit GAM to predict the number of zoonotic viruses using all data. Species with residual values between −1 and 1 (black) are accurately predicted within one virus. Warm colours represent species with positive residuals (orange >1 to 3; red >3). Cool colours represent species with negative residuals (green <−1 to −3; blue <−3). Marine mammals, domestic animals, and species with missing data and not included in the best-fit models are shown in grey.

Extended Data Table 1 | Summary of best-fit GAMs for total and zoonotic viral richness per wild mammal species, and probability of a virus being zoonotic

Term	Value	Z statistic	Chi-sq statistic	P-value	Effective Degrees of Freedom	Total Dev. Explained	Relative Dev. Explained
Total Viral Richness Model (all data, n=576 species)						**49.2%**	
Intercept	0.52	7.43		**<0.001**			
Disease-related publications (log)			1846.57	**<0.001**	5.55		64.8%
Mammal sympatry (>20% range overlap)			301.38	**<0.001**	5.16		10.1%
Order CHIROPTERA			155.12	**<0.001**	1		9.9%
Order RODENTIA			95.49	**<0.001**	1		4.8%
Order PRIMATES			34.4	**<0.001**	0.94		2.5%
Phylogenetically-corrected body mass			216.42	**0.009**	3.82		1.9%
Order CETARTIODACTYLA			24.37	**<0.001**	0.94		1.8%
Geographic range (log)			18.93	**0.025**	3.58		1.6%
Order PERISSODACTYLA			9.95	**0.001**	1		1.4%
Order EULIPOTYPHLA			5.87	**0.009**	0.85		1.1%
Total Viral Richness Model (stringent data, n=575 species)						**35.8%**	
Intercept	-0.47	-5.31		**<0.001**			
Disease-related publications (log)			923.02	**<0.001**	4.98		53.6%
Order RODENTIA			129.28	**<0.001**	0.98		12.6%
Order CHIROPTERA			109.23	**<0.001**	1		12.2%
Order PRIMATES			85.12	**<0.001**	1		11.8%
Mammal sympatry (>20% range overlap)			44.96	**<0.001**	4.69		3.9%
Phylogenetically-corrected body mass			9.65	**0.036**	3.51		2.8%
Geographic range (log)			11.14	0.079	2.66		1.5%
Order CINGULATA			0.87	0.286	0.76		0.6%
Order EULIPOTYPHLA			1.21	0.151	0.59		0.4%
Order PERAMELEMORPHIA			0.74	0.307	0.7		0.4%
Order SCANDENTIA			0.94	0.13	0.41		0.3%
Proportion Zoonoses Model (all data, n=584 species)						**82.0%** (*number* of zoonoses) **33.0%** (*proportion*, w/offset)	
Intercept	-0.34	-8.57		**<0.001**			
Order CETARTIODACTYLA			27	**<0.001**	0.88		36.3%
Phylog. dist. from humans (log, cytb tree)			12.7	**0.002**	1.88		17.0%
Urban to rural human population ratio in species range (log)			10.01	**0.002**	1.25		13.0%
Disease-related publications (log)			5.81	**0.017**	1.2		7.7%
Order CHIROPTERA			4.43	**0.015**	0.71		6.5%
Order PERISSODACTYLA			3.28	**0.039**	0.76		6.4%
Order SCANDENTIA			0.81	0.311	0.79		5.3%
Order PERAMELEMORPHIA			0.76	0.323	0.78		4.8%
Order DIPROTODONTIA			0.72	0.194	0.43		1.7%
Hunted species, IUCN			0.75	0.167	0.36		1.3%
Proportion Zoonoses Model (stringent data, n=576 species)						**23.6%**	
Intercept	-1.35	-22.66		**<0.001**			
Phylog. dist. from humans (log, cytb tree)			56.13	**<0.001**	2.36		34.5%
Order CETARTIODACTYLA			22.93	**<0.001**	0.94		28.0%
Urban to rural human population ratio change, 1970-2005			16.88	**0.002**	4.05		19.6%
Order PERISSODACTYLA			0.86	0.308	0.83		5.0%
Change in human population density in range, 1970-2005			3.16	0.132	1.47		4.3%
Disease-related publications (log)			5.03	**0.014**	1.21		3.8%
Order DIPROTODONTIA			2.39	0.066	0.71		2.8%
Phylogenetically-corrected body mass			0.12	0.294	0.12		1.1%
Order LAGOMORPHA			0.7	0.196	0.42		0.9%
Order PRIMATES			0.62	0.097	0.28		0.1%
Viral Traits Model (all data, n=464 viruses)						**27.2%**	
Intercept	-1.59	-5.69		**<0.001**			
Max phylogenetic host breadth w/out humans, (log, cytb tree)			44.91	**<0.001**	2.94		45.6%
Number of publications (log)			35.83	**<0.001**	3.28		37.4%
Cytoplasmic replication			10.96	**<0.001**	0.86		9.2%
Vector-borne			4.9	**0.014**	0.75		4.6%
Envelope			0.88	0.166	0.46		2.3%
Average genome length (log)			0.12	0.266	0.09		0.9%
Viral Traits Model (stringent data, n=408 viruses)						**21.1%**	
Intercept	-2.23	-7.51		**<0.001**			
Number of publications (log)			29.51	**<0.001**	2.64		53.1%
Max phylogenetic host breadth w/out humans, (log, cytb tree)			15.75	**<0.001**	2.53		25.5%
Cytoplasmic replication			10.33	**0.001**	0.88		17.5%
Vector-borne			1.87	0.085	0.6		3.9%

Models were selected separately using the entire dataset and a stringent dataset that excluded host–virus associations detected by serology. Variables are sorted by relative per cent deviance explained with in each model.

From: Aleksei Chmura
Sent: Wed, 31 May 2017 10:59:02 -0400
To: Normil, Carine (NIH/NIAID) [C]
Cc: Stemmy, Erik (NIH/NIAID) [E]; Dr. Peter Daszak; Smith, Philip (NIH/NIAID) [E]; Alison Andre
Subject: Re: Publication compliance for Grant Number: 5R01AI110964 - 04 PI Name: DASZAK, PETER
Attachments: bib.pdf
Importance: High

Dear Carine,
Please find the attached documentation of this publication being in compliance with NIH Public Access Policy.
Many thanks most,
Sincerely,
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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

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On 23 May 2017, at 13:12, Normil, Carine (NIH/NIAID) [C] (b)(6) wrote:

Good afternoon:
Your progress report for the above referenced award has a non-compliant publication. Please take the necessary steps to bring "*Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Crameri G, Zhang SY, Wang LF, Daszak P, Shi ZL. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. 2013 November 28;503(7477):535-8. PubMed PMID: 24172901*" into compliance with the NIH Public Access Policy.
To comply with the policy, please reply to this email and provide a PDF generated report from My NCBI that includes evidence of compliance (PMCID number) for this publication. If you believe the above referenced publication does not fall under the Public Access Policy, please provide a brief explanation. A response is appreciated by **June 15, 2017**.
If you have questions about the Policy, feel free to contact me via email at (b)(6) or send a note toPublicAccess@nih.gov.
Best regards,

Carine

Carine Normil

Grants Management Specialist (Contractor)

Grants Management Program, DEA, NIAID, NIH, HHS
5601 fishers Lane, Rm 4G46, Bethesda , Maryland 20892

Phone: (b)(6)

Fax: (301)-493-0597
Email: (b)(6)

Publications Reported for this Reporting Period

NIH Public Access Compliance	Citation
Complete	Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Crameri G, Zhang SY, Wang LF, Daszak P, Shi ZL. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. 2013 Nov 28;503(7477):535-8. doi: 10.1038/nature12711. Epub 2013 Oct 30. PubMed PMID: 24172901; PubMed Central PMCID: PMC5389864.

From: Aleksei Chmura
Sent: Sun, 7 May 2017 16:32:41 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Smith, Philip (NIH/NIAID) [E]
Cc: Dr. Peter Daszak; ???
Subject: Re: eRA Commons: RPPR for Grant 5R01AI110964-04 Submitted to NIH with a Non-Compliance warning

Dear Erik and Philip,
We just received our amended Y3 notice of award.
Many thanks for your help with this!
Cheers,
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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

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On 17 Apr 2017, at 13:37, Aleksei Chmura (b)(6) wrote:

Dear Erik,
As per Peter, the work is planned to supplement that done by PREDICT and hopefully to collaborate with the PREDICT team if possible. The aim is for the Co-investigator (Zhengli Shi) and her field team to coordinate with the PREDICT Myanmar field team and co-leads to ensure that there is no duplication of effort (the NIAID group will not use the PREDICT protocols), and that there is the opportunity for cross-training. Samples will be collected from bats and tested by PCR for SARS-like Coronaviruses, then for positive samples, to do a series of further characterization of the viruses using the techniques Zhengli has developed in her lab (spike protein binding assays etc.).
Samples collected will also be made available to the Myanmar lab so that the PREDICT protocols can be run in-country.
Please let me know, if you have any further questions.
Cheers,

Aleksei Chmura
Senior Coordinator of Operations

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New York, NY 10001

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On 13 Apr 2017, at 12:26, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Thanks Aleksei!
One additional item. In processing the foreign clearance for Myanmar, the State Department requested a little bit more information on how the project relates to the PREDICT work. Specifically, they've asked: "could you ask the PI to clarify how they are working with the USAID funded PREDICT Project – it is our understanding that ECO-Health is a partner in PREDICT and the sampling methods, etc. described are similar to activities in PREDICT (it may be that the PR is going to be doing additional testing on already collected samples, but that is not clear from the information provided)."
It sounds like they just want to clarify whether the sampling work is in addition to the PREDICT work. Will this be specific sampling for MERS beyond what is already being done?
Best,
Erik
From: Aleksei Chmura [mailto:(b)(6)
Sent: Wednesday, April 12, 2017 7:42 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Normil, Carine (NIH/NIAID) [C] (b)(6) Peter Daszak (b)(6) Smith, Philip (NIH/NIAID) [E] (b)(6)
Subject: Re: eRA Commons: RPPR for Grant 5R01AI110964-04 Submitted to NIH with a Non-Compliance warning
Dear Erik,
The non-compliant paper referenced above has been uploaded in NIHMS and should be updated in Peter's My NCBI as soon as NIHMS approves it.
Many thanks!
-Aleksei

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 Thu, Apr 13, 2017 at 12:10 AM, <era-notify@mail.nih.gov> wrote:

*** This is an automated notification - Please do not reply to this message. ***

Dear Grantee,

The progress report for the above-reference award includes citation(s) that are out of compliance with the NIH Public Access Policy. Compliance with the NIH Public Access Policy is a legal requirement and a term and condition of all NIH awards. This award will be delayed until all publications arising from it are in compliance with the policy.
The Authorized Organization Representative (AOR) or PD/PI with delegated Progress Report Submit Authority must provide verification that all publications are in compliance with the NIH Public Access Policy, to the Grants Management Specialist (GMS). The Public Access compliance verification may be submitted either using the new Progress Report Additional Material (PRAM) link on the eRA Commons Status page or via email.

Instructions for SO/AOR verification:

- Verify that the PD/PI has used My NCBI to enter publications and/or update compliance status.
- Include a My NCBI PDF report demonstrating all the formerly non-compliant public access citations are now compliant. To process your award, every citation in the report should be either complete, in process or exempt N/A). Please see http://publicaccess.nih.gov/citation_methods.htm for more information about acceptable compliance statuses for public access papers. We have more information about My NCBI athttp://publicaccess.nih.gov/communications.htm.
- If unable to provide verification, provide a justification for why the specific publication(s) cannot be brought into compliance.

NIH awardees are responsible for ensuring that evidence of compliance is included in all NIH applications, proposals and reports. If you have questions about the Policy, please check the NIH Public Access Website or send an email to PublicAccess@nih.gov.

For any further questions about this email, call the eRA Help Desk at 1-866-504-9552 or refer to http://grants.nih.gov/support for additional methods of contact. Please access Commons at http://public.era.nih.gov/commons/.
For more information please visit http://era.nih.gov/

From: Cockrell, Adam
Sent: Fri, 5 May 2017 16:05:35 +0000
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor
Cc: Baric, Ralph; Umerah, Nina
Subject: RE: Study with Planet Biotech.

Sounds good.
Adam

From: Baric, Toni C
Sent: Friday, May 05, 2017 10:13 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Leyva-Grado, Victor (b)(6)
Cc: Baric, Ralph S (b)(6) Umerah, Nina (b)(6)
Subject: RE: Study with Planet Biotech.

Yes Ralph said go ahead.

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, May 05, 2017 10:07 AM
To: Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph S; Umerah, Nina; Baric, Toni C
Subject: RE: Study with Planet Biotech.

Thanks Adam. Are we ok to proceed without Ralph for this call, or should we reschedule for a time that works for him?

From: Cockrell, Adam (b)(6)
Sent: Thursday, May 04, 2017 3:53 PM
To: Leyva-Grado, Victor (b)(6) Stemmy, Erik (NIH/NIAID) [E]
(b)(6) Keith Wycoff (b)(6)
Cc: Baric, Ralph (b)(6) Umerah, Nina (b)(6) Baric, Toni C
(b)(6)
Subject: RE: Study with Planet Biotech.

Hi Erik,

I will be available for the call at 1 on Tuesday.

Adam

From: Leyva-Grado, Victor (b)(6)
Sent: Thursday, May 04, 2017 3:40 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]' (b)(6) Cockrell, Adam (b)(6)
Keith Wycoff (b)(6)
Cc: Baric, Ralph S (b)(6) Umerah, Nina (b)(6) Baric, Toni C

(b)(6)
Subject: RE: Study with Planet Biotech.

Hi Erick,

I can attend the conference call. Just let me know.

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, May 04, 2017 2:55 PM
To: Cockrell, Adam; Keith Wycoff
Cc: Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina; Baric, Toni C
Subject: RE: Study with Planet Biotech.

Thanks Adam. Are you and/or Ralph free next week for a call with Keith on Tuesday 5/9 at 1pm?

Erik

From: Cockrell, Adam (b)(6)
Sent: Friday, April 21, 2017 5:16 PM
To: Keith Wycoff (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6)
Subject: RE: Study with Planet Biotech.

Hi Keith,

I attached the report again here. I agree with you it is difficult to know if the treated mice would have kept losing weight, or not.

Best,
Adam

From: Keith Wycoff (b)(6)
Sent: Friday, April 21, 2017 3:11 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

Thank you for sending me the report on your results. This seems pretty promising, though it leads me to wonder what might have happened after 6 days. Somehow I have lost the email you sent. Could you please send it again?

Thanks,
Keith

On Feb 28, 2017, at 7:41 PM, Cockrell, Adam (b)(6) wrote:

Hi Keith.

Yes. Homozygous mice develop severe disease and death at high virus dose ($5x10^6$ PFU). Whereas, the heterozygous mice still get sick (weight loss and hemorrhaging), but do not die. MERS replicates to higher titers in homozygous mice, which is most likely due to availability of more receptor. Our current evidence indicates less severe disease in heterozygous mice. This comparison is in figure 2 of the Nature Micro manuscript.

We will only be using homozygous mice for the study with your (b)(4)

Best,
Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Tuesday, February 28, 2017 9:59 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

A quick question for you. Does it make any difference whether your mice are homozygous or hemizygous for the human DPP4 transgene?

Thanks,
Keith

On Feb 24, 2017, at 12:27 PM, Cockrell, Adam (b)(6) wrote:

Probably not until late March.

Best,
Adam

From: Keith Wycoff (b)(6)
Sent: Friday, February 24, 2017 3:25 PM
To: Cockrell, Adam
Subject: Re: Study with Planet Biotech.

Hi Adam,

That's great. Let me know if any problems crop up. At what point do you expect to have interim/preliminary efficacy data that you can share with us?

Thanks,
Keith

On Feb 24, 2017, at 12:08 PM, Cockrell, Adam (b)(6) wrote:

Hi Keith,

We received the package.

Best,
Adam

From: Keith Wycoff (b)(6)
Sent: Thursday, February 23, 2017 5:22 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

I called FedEx and they claim it was delayed because of flooding in San Jose. That doesn't square with the fact that it's been in Raleigh, NC since 5:36 this morning. In any case, they told me it will be delivered first thing tomorrow morning.

Keith

On Feb 23, 2017, at 2:12 PM, Cockrell, Adam (b)(6) wrote:

Hi Keith,

No sign of FedEx today.

Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Thursday, February 23, 2017 1:33 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

We sent it frozen, so I recommend storage at -80C until ready to use. My suggestion is to put the tubes you'll need in the fridge the day before needed. Once thawed you can keep it at 4C. It has been sterile filtered.

Keith

On Feb 23, 2017, at 10:27 AM, Cockrell, Adam (b)(6) wrote:

Thanks Keith,

Is storage at 4C?

Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Thursday, February 23, 2017 1:22 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

We decided to send twice the amount of protein promised, just in case of a spill or if you need to repeat the experiment. Should arrive by 3:00 today. The FedEx tracking number is 7784 9010 2170.

Keith

On Feb 20, 2017, at 7:36 AM, Cockrell, Adam (b)(6) wrote:

Thanks Keith,

That sounds great.

Adam

From: Keith Wycoff (b)(6)
Sent: Monday, February 20, 2017 10:18 AM
To: Cockrell, Adam (b)(6)
Cc: Erik [E] Stemmy (b)(6) Leyva-Grado, Victor (b)(6)
Baric, Ralph S (b)(6)
Subject: Re: Study with Planet Biotech.

OK, so you will need a minimum of 12 mg of protein at 2 mg/ml. To account for potential losses of volume, I will send 15 mg. I will also send 7.5 ml of control (PBS). Does that sound good?

Thanks,
Keith

On Feb 20, 2017, at 7:12 AM, Cockrell, Adam (b)(6) wrote:

Hi Keith,

You are correct. We are definitely going with 400ug/mouse. I just did not change it on the outline. Corrected outline is attached.

Thanks,
Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Monday, February 20, 2017 10:09 AM
To: Cockrell, Adam (b)(6)
Cc: Erik [E] Stemmy (b)(6) Leyva-Grado, Victor (b)(6)
Baric, Ralph S (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

I just want to make sure I understand the doses, and thus how much drug we need to supply. Our original discussion contemplated administering an amount, on a molar basis, equivalent to antibodies you have tested before. I had understood that 250 µg of antibody had been administered, and due to the greater molar mass of our protein the equivalent amount of DPP4-Fc would be 380 µg, which you suggested rounding up to 400 µg. Did you intend to divide the 400 µg into two doses (of 200 µg each) or administer two doses of 400 µg each? In any case, the numbers differ from the two 250 µg doses on the study design you sent. Please confirm how much protein you want to administer at -12 and +12 hours. Also, please confirm that you wanted the concentration to be 2 mg/ml (if that is the case).

Thanks,
Keith

On Feb 20, 2017, at 6:40 AM, Cockrell, Adam (b)(6) wrote:

Hi everyone,

We have approval to begin the study with Planet Biotech. I would like to schedule this to begin on Friday March 10. I have included the study time line in this email just as a reminder. Also, I bumped the mouse numbers for the Day 6 time point to 20 (10 for each of the therapeutic and control). Want to make sure that we have enough mice by day 6.

Keith: The address to send S2320-Gal-SF, and control, to is as follows:

Attn: Adam Cockrell
University of North Carolina at Chapel Hill
Department of Epidemiology/#4635
135 Dauer Dr.
Room 3105 MHRC
Chapel Hill, NC

27599

Phone number is below.

Adam Cockrell
Research Associate
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Office Phone: (b)(6)

<Timeline for initial study.pdf>

<Timeline for initial study.pdf>

From: Matthias Schnell
Sent: Fri, 28 Apr 2017 13:20:28 +0000
To: Cockrell, Adam; Christoph Wirblich
Cc: Matthias Schnell; Baric, Ralph; Johnson, Reed (NIH/NIAID) [E]; Matthew Frieman; Stemmy, Erik (NIH/NIAID) [E]
Subject: Re: anti-MERS rabies-derived vaccine

Hi Adam:
this will be shipped coming Monday or Tuesday on dry ice.

1) To make sure that we have plenty of antigen can you please provide double the above amounts….900ug chemically inactivated rabies and 1500ug chemically inactivated rabies-MERS vaccine?

I discuss with Chris the amount and we will add this info later

2) To meet the vaccination volumes indicated can the concentration be set at 10ug/100ul (50ul injection/leg)?

Yes that what we normally do 10 micrograms total in a volume of 100 microliter (PBS) and vaccinate with 50 microliter each leg. We use insulin syringes.

3) Can you ship the vaccine on a Monday or Tuesday and provide all necessary information for storage? (e.g. How will it be shipped…frozen/refrigerated? as one large aliquot that needs to be aliquoted and stored?...etc)

I think we will send you aliquots for each vaccination - the should be stored at -80 C and thawed before use. Just briefly vortex to resuspend any precipitated vaccine. Discard the rest.

Best Regards,
Adam

On Apr 28, 2017, at 00:16, Cockrell, Adam (b)(6) wrote:

Dear Matthias,
Since we are approaching the time to initiate this experiment I wanted to send out a reminder regarding the vaccine reagents.
There are a few logistical issues I wanted to confirm in advance of starting. These are indicated below.
Best Regards,
Adam

From: Cockrell, Adam
Sent: Friday, April 14, 2017 10:03 AM
To: 'Matthias Schnell' (b)(6) Christoph Wirblich (b)(6)
Cc: Johnson, Reed (NIH/NIAID) [E] (b)(6) Frieman, Matthew (b)(6) Baric, Ralph S (b)(6) Erik [E] Stemmy (b)(6)
Subject: RE: anti-MERS rabies-derived vaccine

Thanks Matthias,

We can receive anytime.
Based on the protocol I calculate that we need the following minimal amounts:
Prime Injection: 150ug (15mice) chemically inactivated rabies ctrl. and 300ug (30 mice) chemically inactivated rabies-MERS vaccine.
7 Day boost injection: 150ug (15mice) chemically inactivated rabies ctrl. and 150ug (15 mice) chemically inactivated rabies-MERS vaccine.
28 Day boost injection: 150ug (15mice) chemically inactivated rabies ctrl. and 300ug (30 mice) chemically inactivated rabies-MERS vaccine.
Minimum total: 450ug chemically inactivated rabies ctrl. and 750ug chemically inactivated rabies-MERS vaccine.
A few logistical issues:

1) To make sure that we have plenty of antigen can you please provide double the above amounts….900ug chemically inactivated rabies and 1500ug chemically inactivated rabies-MERS vaccine?
2) To meet the vaccination volumes indicated can the concentration be set at 10ug/100ul (50ul injection/leg)?
3) Can you ship the vaccine on a Monday or Tuesday and provide all necessary information for storage? (e.g. How will it be shipped…frozen/refrigerated? as one large aliquot that needs to be aliquoted and stored?...etc)

Best Regards,
Adam
From: Matthias Schnell [mailto:(b)(6)
Sent: Tuesday, April 11, 2017 9:53 AM
To: Cockrell, Adam (b)(6) Christoph Wirblich (b)(6)
Cc: Johnson, Reed (NIH/NIAID) [E] (b)(6) Matthias Schnell (b)(6) Frieman, Matthew (b)(6) (b)(6) Baric, Ralph S (b)(6) Erik [E] Stemmy (b)(6)
Subject: Re: anti-MERS rabies-derived vaccine

Great - let us know when to send the vaccine.
Matthias
Matthias J. Schnell, Ph.D.
Professor and Chair Department of Microbiology and Immunology
Director Jefferson Vaccine Center
Sidney Kimmel Medical College
Director WHO Collaborating Centre for Neurovirology
Thomas Jefferson University
233 South 10th St, 531 BLSB
Philadelphia PA, 19107
email: (b)(6)
phone: (b)(6)
fax: 215-923-9248
lab phone: (b)(6)
Administrative Coordinator:
Lisa Peeler
(b)(6)
phone: (b)(6)
On Apr 11, 2017, at 09:03, Cockrell, Adam (b)(6) wrote:
Hi everyone,
We have been approved to carry out the anti-MERS rabies-derived vaccine study.
Due to meetings throughout June I have assembled a suitable time line as follows:

Prebleed of all mice: May 15th (Day -4)

Vaccine Prime of all mice: May 19th (Day 0)

Vaccine Boost of Day 7 cohort: May 26th (Day 7)

Bleed of all mice: June 12th (Day 24)

Vaccine Boost at Day 28, all mice: June 16th (Day 28)

Bleed of all mice: July 10th (Day 52)

Challenge with icMERSma1: July 14th (Day 56)

Complete study on July 20th.

I am in the process of transferring mice to our facilities for the study. I am including 3 additional mice in the event there is a problem.

There are a total of 48 mice for this study. All mice have DOB's of 02/09/17 – 02/13/17. There are 23 males and 25 females.

As a reminder I have attached the time line that was approved by everyone.

Adam Cockrell
Research Associate
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Office Phone: (b)(6)

<Summary of Vaccination Protocol.pdf>

From: Peter Daszak
Sent: Tue, 11 Apr 2017 18:52:15 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: Automatic reply: Year 3 report for 5R01AI110964 - Bat Coronaviruses in China and SE Asia.

I'll be out of the office until Tuesday, April 18th and will not have access to email.

Please cc Alison (b)(6) on all emails and I'll respond as soon as possible when I'm back on the 18th.

Cheers,

Peter

From: Cockrell, Adam
Sent: Tue, 11 Apr 2017 15:22:49 +0000
To: Leyva-Grado, Victor; Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Sims, Amy C; Umerah, Nina
Subject: RE: Report describing planet biotech study and novel mouse-adapted MERS clones

Thanks Victor.

From: Leyva-Grado, Victor [mailto:(b)(6)
Sent: Tuesday, April 11, 2017 11:03 AM
To: Cockrell, Adam (b)(6) Erik [E] Stemmy (b)(6)
Cc: Baric, Ralph S (b)(6) Sims, Amy C (b)(6) Umerah, Nina (b)(6)
Subject: RE: Report describing planet biotech study and novel mouse-adapted MERS clones

Thanks Adam.

Very interesting work with the compound and specially with the improved mouse adapted strain.

V

Victor H Leyva-Grado DVM, PhD
Instructor Scientist
Microbiology Department
Global Health and Emerging Pathogens Institute
Icahn School of Medicine at Mount Sinai
One Gustave L Levy Place
Box 1124 Annenberg 16-15
New York, NY 10029
Phone (b)(6)
Fax 1-212-534-1684

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, April 11, 2017 8:29 AM
To: Erik [E] Stemmy; Leyva-Grado, Victor
Cc: Baric, Ralph S; Sims, Amy C
Subject: Report describing planet biotech study and novel mouse-adapted MERS clones

Hi Erik and Victor,

The report for the study with planet biotech is attached. In addition to information for the planet biotech study I have included novel data for new mouse-adapted MERS viruses (figures 7-10) that

overcome a previous limitation of the model (i.e. severe pathology that required high dose virus at 5x10^6 PFU). We can reduce the infectious dose by 100-fold with our novel mouse-adapted MERS.

Best Regards,
Adam

Adam Cockrell
Research Associate
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Office Phone: (b)(6)

From: Normil, Carine (NIH/NIAID) [C]
Sent: Thu, 30 Mar 2017 11:18:37 -0400
To: Chipps, Kati; Hobbs, Ron Lee
Cc: Baric, Ralph; Caldwell, Chandra; Stemmy, Erik (NIH/NIAID) [E]; Cyr, Robin L
Subject: RE: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S

Thank you for concurring!

Have a good day!
Carine

Carine Normil

Grants Management Specialist (Contractor)

Grants Management Program, DEA, NIAID, NIH, HHS
5601 fishers Lane, Rm 4G46, Bethesda , Maryland 20892

Phone: (b)(6)

Fax: (301)-493-0597
Email: (b)(6)

NIH National Institute of Allergy and Infectious Diseases

***Effective January 1, 2017**, NIH closeout policy has changed (see NOT-OD-17-022). NIH is no longer accepting Final Progress Reports (FPR). Grantees must now report final project outcomes using the new F-RPPR. For instructions on how to submit the new F-RPPR please see instructions on the NIH RPPR Page.*

From: Chipps, Kati (b)(6)
Sent: Thursday, March 30, 2017 10:59 AM
To: Normil, Carine (NIH/NIAID) [C] (b)(6) Hobbs, Ron Lee (b)(6)

Cc: Baric, Ralph (b)(6) Caldwell, Chandra (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cyr, Robin L (b)(6)
Subject: RE: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S

Good morning,

I concur with the Dr. Li's Other Support and MYNCBI report.

Thank you,

Kati

Kati Chipps, MPA
Research Administration Manager (RAM)
Office of Sponsored Research (OSR)
The University of North Carolina at Chapel Hill
104 Airport Drive, Suite 2200, CB# 1350
Chapel Hill, NC 27599-1350
(b)(6)
(b)(6)

It's a beautiful day. Don't let it get away!

From: Normil, Carine (NIH/NIAID) [C] [mailto:(b)(6)
Sent: Wednesday, March 29, 2017 9:54 AM
To: Hobbs, Ron Lee (b)(6)
Cc: Baric, Ralph S (b)(6) Caldwell, Chandra (b)(6) Chipps, Kati (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cyr, Robin L (b)(6)
Subject: RE: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S
Importance: High

Hi Ron,

One last think is needed before we can complete our review; please have the SO on this award Kati Chipps concur with the reporting of Dr. Li's other support and MYNCBI report.

Thanks,
Carine

Carine Normil

Grants Management Specialist (Contractor)

Grants Management Program, DEA, NIAID, NIH, HHS
5601 fishers Lane, Rm 4G46, Bethesda , Maryland 20892

Phone: (b)(6)

Fax: (301)-493-0597
Email:(b)(6)

National Institute of Allergy and Infectious Diseases

From: Hobbs, Ron Lee [mailto:(b)(6)
Sent: Wednesday, March 22, 2017 2:38 PM
To: Normil, Carine (NIH/NIAID) [C] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Caldwell, Chandra (b)(6)
Subject: FW: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S

Carine,

Attached, please find the requested publication compliance for Grant Number: 5R01AI110700 – 03. At any time, please feel free to inform us if additional documentation is required. Thanks in advance.

Ronald L. Hobbs Sr.
Contracts and Grants Specialist
The University of North Carolina at Chapel Hill
Office of Sponsored Research
104 Airport Drive, Suite 2200
CB#1350
Chapel Hill, NC 27599-1350
(b)(6) (Tel)
(b)(6)

From: "Normil, Carine (NIH/NIAID) [C]" (b)(6)
Date: March 17, 2017 at 5:14:41 PM EDT
To: (b)(6)
Cc: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6) "Baric, Ralph" (b)(6)
Subject: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S

Dear Authorized Organization Representative,

NIAID has found publication compliance issues on the RPPR for this award because three publications listed in Section B., were not reported in Section C. Public Access MyNCBI report.

The publications below are funded from this award and must to be reported for compliance with NIH public access. The publications below will need to be submitted via email in pdf copy from MyNCBI.

- Structure, Function, and Evolution of Coronavirus Spike Proteins. Li F. Annu Rev Virol. 2016 Sep 29;3(1):237-261.PMID: 27578435
- MERS-CoV spike protein: a key target for antivirals. Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. Expert Opin Ther Targets. 2017 Feb;21(2):131-143. doi: 10.1080/14728222.2017.1271415. PMID: 27936982
- Recombinant Receptor-Binding Domains of Multiple Middle East Respiratory Syndrome Coronaviruses (MERS-CoVs) Induce Cross-Neutralizing Antibodies against Divergent Human and Camel MERS-CoVs and Antibody Escape Mutants.Tai W, Wang Y, Fett CA, Zhao G, Li F, Perlman S, Jiang S, Zhou Y, Du L.J Virol. 2016 Dec 16;91(1). pii: e01651-16. PMID: 27795425

Additionally, please provide an updated other support document for Fr. Fang Li which includes the level of effort for each active support.

Submission deadline for the above documents is **March, 22, 2017**.

Thank you,
Carine

Carine Normil

Grants Management Specialist (Contractor)

Grants Management Program, DEA, NIAID, NIH, HHS
5601 fishers Lane, Rm 4G46, Bethesda , Maryland 20892

Phone: (b)(6)

Fax: (301)-493-0597
Email: (b)(6)

NIH National Institute of Allergy and Infectious Diseases

From: Peter Daszak
Sent: Mon, 20 Mar 2017 18:32:16 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Alison Andre
Cc: Aleksei Chmura; Smith, Philip (NIH/NIAID) [E]; Evelyn Luciano
Subject: Re: Out of Office RE: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER
Importance: High

Hi Erik,

Here are the answers to your questions:

1. Will Dr Daszak (or other EcoHealth staff) plan to spend time directly in country in Myanmar? If so, please provide an approximate % of time.

We are in initial planning of approach with these countries including Myanmar and time spent this year in Myanmar would primarily be by our collaborators and *not* EHA staff. In Yr 4, we will probably need to budget one site visit conducted by Dr. Peter Daszak and Senior Personnel Dr. Olival and/or by our field veterinarian. Please let us know what restrictions there might be for this..

2. How long do you anticipate the sampling will continue? That is, through the remainder of the R01, or a shorter amount of time?
Sampling will be conducted a minimum of four times over then remainder of the R01.

3. Can you confirm the total amount of US$ to be sent to Myanmar for the work?
No funds are presently planned to be sent to Myanmar. We plan to coordinate collaborative transfer of samples from Myanmar to our partner Lab in China.

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, March 16, 2017 2:11 PM
To: Peter Daszak; Alison Andre
Cc: Aleksei Chmura; Smith, Philip (NIH/NIAID) [E]; Evelyn Luciano
Subject: RE: Out of Office RE: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Thank you Peter!

Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Peter Daszak [mailto:(b)(6)
Sent: Thursday, March 16, 2017 2:10 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Alison Andre (b)(6)
Cc: Aleksei Chmura (b)(6) Smith, Philip (NIH/NIAID) [E]
(b)(6) Evelyn Luciano (b)(6)
Subject: RE: Out of Office RE: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Hi Erik,

I've just returned from travel and we'll get answers to you on this by Monday COB.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
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www.ecohealthalliance.org

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From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Thursday, March 16, 2017 1:33 PM
To: Alison Andre
Cc: Peter Daszak; Aleksei Chmura; Smith, Philip (NIH/NIAID) [E]
Subject: FW: Out of Office RE: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Hello Alison,
I received an out of office message from Aleksei. I am working on new foreign clearances for the grant referenced above, and need some additional information for the site in Myanmar. Would you be able to help address the questions below?

Thank you,
Erik

-Will Dr Daszak (or other EcoHealth staff) plan to spend time directly in country in Myanmar? If so, please provide an approximate % of time.
-How long do you anticipate the sampling will continue? That is, through the remainder of the R01, or a shorter amount of time?
-Can you confirm the total amount of US$ to be sent to Myanmar for the work?

From: Aleksei Chmura [mailto:(b)(6)
Sent: Thursday, March 16, 2017 1:23 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Out of Office RE: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Thank you for your email.

I will be out of the office and traveling until 20 March 2017. During this time, I may not have regular access to emails and voice messages. If you should need immediate assistance, please contact Alison Andre at (b)(6) Otherwise, I will respond to your message as soon as possible.

Sincerely,

--
Aleksei Chmura
Senior Coordinator of Operations

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From: Aleksei Chmura
Sent: Wed, 1 Mar 2017 17:54:38 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Smith, Philip (NIH/NIAID) [E]
Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Fantastic to hear, Erik!
I quite understand and no rush.
Much appreciated,
-Aleksei

On Mar 1, 2017, at 17:51, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Aleksei,
Very sorry for my slow response, I've been swamped lately. I think I have everything I need to finish with the foreign clearance, and will let you know if I need anything else.
Erik
Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)
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From: Aleksei Chmura [mailto:(b)(6)
Sent: Wednesday, March 1, 2017 12:31 PM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Smith, Philip (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER
Thanks, Jenny!
Apologies. I will chase up with Philip and Erik.
Cheers,
-Aleksei
On Mar 1, 2017, at 17:28, Greer, Jenny (NIH/NIAID) [E] (b)(6) wrote:

Aleksei,
Thanks for your email. It looks like I did receive your email of February 18. However, as I mentioned, I am no longer the GMS assigned to this grant. You will need to touch base with Philip Smith for any updates on your request. I've copied him on this email for your convenience.
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)
***Effective January 1, 2017**, NIH closeout policy has changed (see NOT-OD-17-022). NIH is no longer accepting Final Progress Reports (FPR). Grantees must now report final project outcomes using the new F-RPPR. For instructions on how to submit the new F-RPPR please see instructions on the NIH RPPR Page.*

From: Aleksei Chmura [mailto:(b)(6)
Sent: Wednesday, March 01, 2017 5:07 AM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: Fwd: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Hi, Jenny.
I received an out-of-office message from Erik last month, so just wanted to see if you also received my email and PDF attachment (below) to Erik and if there were anything else required for now. No rush - I am just checking-in.
Cheers!
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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Begin forwarded message:
From: Aleksei Chmura (b)(6)
Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER
Date: February 18, 2017 at 03:18:23 GMT
To: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6)
Cc: "Greer, Jenny (NIH/NIAID) [E]" (b)(6) "Smith, Philip (NIH/NIAID) [E]" (b)(6)

Dear Erik,
Please find our responses in the attached PDF. If you need any additional details, please let me know.
Many thanks!
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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On Feb 15, 2017, at 08:52, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Aleksei,
I know you said nothing will be changing from your currently approved animal studies, but it would be helpful for me in preparing the foreign clearance request if you could write a few concise sentences about the new animal work addressing the following points:

- Kind or species of animal and number to be used
- Location of the source of the animals, if known
- A brief description of the sampling (blood draw, swab, etc)
- Location from where the animals will be obtained (source)
- If possible, what will be done with the animals after the project ends (e.g., euthanized)

Let me know if you have any questions.
Thanks!
Erik

From: Aleksei Chmura [mailto:(b)(6)
Sent: Monday, February 13, 2017 4:23 PM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Smith, Philip (NIH/NIAID) [E]

(b)(6)

Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Super! Thanks, Jenny.

Erik and Philip - please let me know, if you have any questions or require additional details. We look forward to your responses.

Sincerely,

-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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On Feb 13, 2017, at 16:18, Greer, Jenny (NIH/NIAID) [E] (b)(6) wrote:

Aleksei,

Thank you for your email. I am copying Erik on this response so he can make sure he has everything needed to initiate a request for each of these foreign sites. I am also copying Philip Smith, the grants management specialist assigned to this grant for this fiscal year. Please don't hesitate to contact either of them with any questions you may have.

Please note that this response does not constitute approval and it will take at least 3 weeks for a final determination to be made.

Thanks again! And have a great afternoon!

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)

***Effective January 1, 2017**, NIH closeout policy has changed (see NOT-OD-17-022). NIH is no longer accepting Final Progress Reports (FPR). Grantees must now report final project outcomes using the new F-RPPR. For instructions on how to submit the new F-RPPR please see instructions on the NIH RPPR Page.*

From: Aleksei Chmura (b)(6)
Sent: Friday, February 10, 2017 2:54 PM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Dear Jenny,

I am just following up with item 1 and 1a from your email below. As per Peter's email (also below), we would like to request prior approval for collecting non-human animal samples in 7 countries: Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Thailand, and Vietnam.

No new animals will be introduced nor any new field procedures, we have submitted IACUC protocol modification - for geographic locations only - and will provide approval dates as soon as they are available.

No work will be conducted until we have your approval and IACUC approval.

Testing would be conducted locally and if any samples were to be transferred to China these would be only extracted viral DNA - and not the original sample material.

Samples will be collected by either our current China field team personnel working directly with our collaborators in these countries or by respective in-country personnel and require no more than 10% budget modification total (from already budgeted China fieldwork) for any non-China in-country work.

Here is the list of our local in-country contacts and institutions:

Cambodia

(b)(6)

Indonesia

(b)(6)

Lao People's Democratic Republic

(b)(6)

Malaysia

(b)(6)

(b)(6)

Myanmar

(b)(6)

Thailand

(b)(6)

Vietnam

(b)(6)

If it will be easier to have a quick chat about this, I am happy to call anytime. Also, if this request should be sent more formally as a letter attachment, we can do that rapidly as well.
I hope you and yours had a lovely Holiday and are surviving the blizzard!
Cheers,
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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On Aug 1, 2016, at 12:39, Greer, Jenny (NIH/NIAID) [E] (b)(6) wrote:

Thank you for your email. To answer your questions:

1. To do any work in countries other than China, you will need to request prior approval from NIH. To do so, submit a formal request, including the names, institutions, and full contact information of any institutions with which you will collaborate for such activities. Be sure to indicate whether animal or human research will be conducted and what funds, if any, will be going into these countries. The approval process for new foreign sites takes at least 3 weeks.

1a . If you are introducing new animals into the project, then there may be additional requirements from the Office of Laboratory Animal Welfare (OLAW). Again, you would need to submit a formal request, providing a scientific justification for the inclusion of new species on the project, and, if appropriate, a new Vertebrate Animal Section. If additional IACUC approvals are required, you will need to provide us with the IACUC approval dates (but **not** a copy of the actual approval).

2. These individuals are not listed in the Notice of Award as key personnel, so, from a grants management perspective, you do not need to get prior approval for this change. That said, if this change or other such personnel changes would have a significant impact on the scope of the project or the science itself, you would need to at least run it by your Program Officer. And if it is determined that personnel changes would cause a scope change, then you would need grants management approval as well.
3. I do not know what you are asking here. It looks like we have approved both the Wuhan University and ECNU for work on this project. Therefore, no additional prior approval is required for changes unless otherwise specified in the NIH Grants Policy Statement (eg, a change of scope).

Please don't hesitate to contact me with any additional questions. I will be available until 2:30 eastern and then again on Wednesday.

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 MacDurian [mailto:(b)(6)
Sent: Sunday, July 31, 2016 6:06 AM
To: Greer, Jenny (NIH/NIAID) [E] (b)(6)
Subject: Re: Year 2 Report for 5R01AI110964 - 02 PI Name: DASZAK, PETER

Dear Jenny,

Since you were not cc'ed on the original email, I wanted to follow up with you on three things from Dr. Daszak's email to Erik (included below):

1) Do we need to formally request permission to sample species of bats and other high-risk [rodents and carnivore] hosts in countries that neighbor China (Myanmar, Vietnam, Cambodia, Lao PDR) and others that supply wildlife to the international trade to China (Thailand, Malaysia, Indonesia). Under this award our current US and China IACUC approved protocol via Tufts University and Wuhan Institute of Virology permits us to sample these species in these regions.

2) We provided Dr. Noam Ross' CV with our Year 2 Report. Dr. Ross has replaced Dr. Hosseini who is no longer working on this project. Do we need to do anything else for this? I have attached his Biosketch here for reference.
3) Our Human surveillance work and local IRB approval have all been through the Wuhan University School of Public Health (WUSPH) in China (DUNS No. 529049295). We would like now - in Years 3 - 5 of our award to subcontract directly with them rather than with the institution on our current budget: East China Normal University (ECNU) School of Life Sciences. The Wuhan University School of Public Health budget amount would be the same annual amount as currently budgeted for East China Normal University in these same years.
It may be easier to briefly chat about these questions via telephone. If so, you may reach me at (b)(6) anytime.
Many thanks!
-Aleksei

Aleksei Chmura
Senior Coordinator of Operations

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On Fri, May 13, 2016 at 5:55 PM, Peter Daszak (b)(6) wrote:
Dear Erik,
I just wanted to let you know that we submitted our Year 2 Report yesterday (attached as a pdf).

It's been a pretty productive year, and some of the highlights include: collecting samples from 15 bat genera in southern China with 280 (12%) testing positive for coronaviruses; SARS-like coronaviruses being detected in*Rhinolophus* spp. bats in both Yunnan and Guangdong provinces; 7 published papers from work under our award (including one in *J. Virol.* and one in press at *J. Virol*); 218 quantitative interviews with samples and 47 qualitative coded interviews conducted transcribed and translated.

In the report, I highlight the reduced amount of wildlife in the local markets within Southern China compared to that we've seen before, as well as the continued expansion of the Chinese wildlife trade within SE Asia so that it is now a largescale international activity. It means that SL-CoVs we find in the wildlife trade would likely have an origin in adjacent countries. Given that our collaborators and field team in China have great contacts in these countries, and EHA also has field teams in many of them, we would like to conduct short field trips to assess markets, identify wildlife in them, and sample species of bats and other high-risk hosts in countries that neighbor China (Myanmar, Vietnam, Cambodia, Lao PDR)

and others that supply wildlife to the international trade to China (Thailand, Malaysia, Indonesia). All samples collected would still be tested at the Wuhan Institute of Virology in China. Is there a formal process to ask for permission for this, or is the report and this email appropriate?

I also wanted to let you know about a recent personnel change. Since Dr. Parviez Hosseini has moved to the US Department of State as an Information Advisor earlier this year, we hired another senior researcher Noam Ross to conduct data analysis and spatial mapping. Our Year 2 report includes his CV. Noam has great enthusiasm and I am eager to see his work on our data collected to date. He has already been out to China is hitting the ground running!

We have had great successes this past year and I'd be happy to discuss any of them with you, if you'd like.

Cheers,
Peter

Peter Daszak
President
EcoHealth Alliance
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<NIH-NIAID_5R01AI110964 Additional Site Q and A.PDF>

From: Johnson, Reed (NIH/NIAID) [E]
Sent: Fri, 10 Feb 2017 15:21:52 -0500
To: Cockrell, Adam
Cc: Matthew Frieman; Matthias Schnell; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Subject: Re: Rabies vaccine protocols

Sorry everyone for the late response. I agree with the experimental design lab.
Reed

Sent from my iPhone

On Feb 10, 2017, at 3:15 PM, Cockrell, Adam (b)(6) wrote:

Hi everyone,

Matthias and Matt are in agreement with the proposed protocol. Once I hear back from Reed I will be able to move forward with putting together the amendment for IACUC at UNC.

Best,
Adam

From: Frieman, Matthew [mailto:(b)(6)
Sent: Monday, February 06, 2017 9:55 AM
To: Cockrell, Adam (b)(6)
Cc: Matthias Schnell (b)(6) Erik [E] Stemmy (b)(6) Reed [E] Johnson (b)(6) Baric, Ralph S (b)(6)
Subject: Re: Rabies vaccine protocols

This looks fine to me.

One question which we didnt discuss is the age of the mice in past experiments. You mention that you are going to start at 16 week old for the vaccination. Then they will be another 8 weeks or so older by the time of challenge. Have you infected mice that old in your model before? Just wondering how the severity of infection in older mice corresponds to what you reported already.

Matt

On Feb 6, 2017, at 9:49 AM, Cockrell, Adam (b)(6) wrote:

Corrected version.

From: Matthias Schnell [mailto:(b)(6)
Sent: Monday, February 06, 2017 9:42 AM
To: Cockrell, Adam (b)(6)

Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Frieman, Matthew (b)(6) Johnson, Reed (NIH/NIAID) [E] (b)(6) Matthias Schnell (b)(6) Baric, Ralph S (b)(6)
Subject: Re: Rabies vaccine protocols

Dear Adam:
you have in both immunization 0, 7, 28 but we did want to do 0, 7, 28 (prime, boost, boost) and 0, 28 (prime, boost). I also think you don't need to include two control groups with the same immunization schedule - I would do only 0, 7, 28 with the vector as a control.
My two cents
Matthias

Matthias J. Schnell, Ph.D.
Professor and Chair Department of Microbiology and Immunology
Director Jefferson Vaccine Center
Sidney Kimmel Medical College
Director WHO Collaborating Centre for Neurovirology
Thomas Jefferson University
233 South 10th St, 531 BLSB
Philadelphia PA, 19107
email: (b)(6)
phone: (b)(6)
fax: 215-923-9248
lab phone: (b)(6)

On Feb 6, 2017, at 09:29, Cockrell, Adam (b)(6) wrote:

<Summary of Vaccination Protocol.pdf>

<Summary of Vaccination Protocol.pdf>

Matthew Frieman, PhD
University of Maryland School of Medicine
685 West Baltimore St
Room 380
Baltimore, MD 21201

office: (b)(6)
cell: (b)(6)

From: Umerah, Nina
Sent: Tue, 7 Feb 2017 17:09:56 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Kasparian, Sevag (NIH/NIAID) [E]
Cc: PETERPALESE; Knight, Stanley (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph
Subject: RE: Formal request for an extension to Option 2 of contract HHSN272201000019I HHSN27200003 Task A57

Will do.

Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, February 07, 2017 12:07 PM
To: Umerah, Nina; Kasparian, Sevag (NIH/NIAID) [E]
Cc: Palese, Peter; Knight, Stanley (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph
Subject: RE: Formal request for an extension to Option 2 of contract HHSN272201000019I HHSN27200003 Task A57

Hi Nina,
Ralph indicated that after the planning call for the last two studies it would be good to add an additional month to be sure they have enough time to finish the analysis of the vaccine. Can you please confirm this and update the NCE request with the new date?

Thanks!
Erik

From: Umerah, Nina [mailto:(b)(6)
Sent: Monday, February 06, 2017 11:34 AM
To: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) PETERPALESE (b)(6)
Knight, Stanley (NIH/NIAID) [E] (b)(6)
Subject: RE: Formal request for an extension to Option 2 of contract HHSN272201000019I HHSN27200003 Task A57

Good morning Sevag,

I'll contact UNC right now.

Thanks,
Nina

Nina Umerah
(b)(6)

From: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Sent: Monday, February 06, 2017 11:33 AM
To: Umerah, Nina
Cc: Stemmy, Erik (NIH/NIAID) [E]; Palese, Peter; Knight, Stanley (NIH/NIAID) [E]
Subject: RE: Formal request for an extension to Option 2 of contract HHSN272201000019I HHSN27200003 Task A57

Dear Nina,

Thank you for the extension request. I am the current Contracting Officer administering the subject task order.

In order for NIAID to review and approve this request in regards to the costs breakdown, please have the subcontractor (UNC) edit the summary of proposed costs to include a column for costs spent to date as well as a column for the total approved budget (in additional to the column of NCE proposed costs: a total of 3 columns). Also, I did not see a costs breakdown/justification submitted for Mt. Sinai, please submit as well.

If you have any questions please let me know.

Thank you,

Sevag Kasparian
Contracting Officer, Microbiology and Infectious Diseases
Research Contracts Branch A
Office of Acquisitions, DEA, NIAID, NIH, DHHS
5601 Fishers Lane, Room 3D46
Rockville, Maryland 20852-9821
Phone: (b)(6)
(b)(6)

From: Umerah, Nina (b)(6)
Sent: Friday, February 03, 2017 11:26 AM
To: Knight, Stanley (NIH/NIAID) [E] (b)(6)
Cc: Kasparian, Sevag (NIH/NIAID) [E] (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) PETERPALESE (b)(6)
Subject: Formal request for an extension to Option 2 of contract HHSN272201000019I HHSN27200003 Task A57
Importance: High

Dear Mr. Knight,

On behalf of Dr. Peter Palese, please find attached a request for an extension of option 2 for Task A57. Please feel to contact me with any questions or concerns.

Sincerely,
Nina

Nina Umerah
Manager, Grants and Contracts
Department of Microbiology
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, Box 1124
New York, NY 10029
Tel.: (b)(6)
Fax: 212-534-1684
Email: (b)(6)

From: Baric, Ralph S
Sent: Mon, 6 Feb 2017 15:38:30 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Likely better to add on another month if possible. ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, February 06, 2017 10:27 AM
To: Cockrell, Adam; Baric, Ralph S
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi Adam and Ralph,

The NCE request came in requesting extension to July 31st. Is that still accurate after our call with Matt last week?

Erik

From: Umerah, Nina (b)(6)
Sent: Thursday, February 2, 2017 9:52 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Sims, Amy C (b)(6) PETERPALESE (b)(6) Lim, Jean (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi everyone,

It should be approved by tomorrow at the latest. I'll call our grants office now.

Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, February 02, 2017 8:14 AM
To: Umerah, Nina; Baric, Ralph; Sims, Amy C; Palese, Peter; Lim, Jean; Leyva-Grado, Victor
Cc: Kasparian, Sevag (NIH/NIAID) [E]
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi Everyone,

Can you please update me on the NCE request? I don't think I've seen it come in from MSSM yet. We need to begin processing it this week.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Umerah, Nina (b)(6)
Sent: Thursday, January 26, 2017 1:06 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Sims, Amy C (b)(6) PETERPALESE (b)(6) Lim, Jean (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Kasparian, Sevag (NIH/NIAID) [E] (b)(6)
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Thanks Erik!

Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, January 26, 2017 12:05 PM
To: Umerah, Nina; Baric, Ralph; Sims, Amy C; Palese, Peter; Lim, Jean; Leyva-Grado, Victor

Cc: Kasparian, Sevag (NIH/NIAID) [E]
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi Nina,
Not sure if you know, but Miranda is no longer the contract specialist for this TO. When you submit the request from MSSM please be sure to copy the new CS Sevag Kasparian (copied here too). The NCE request should also include a cost to complete breakdown. It looked like UNC included their costs, but I'm not sure if MSSM would need to add on to that as well.

Let us know if you have any questions.

Thanks!
Erik

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

From: Umerah, Nina (b)(6)
Sent: Wednesday, January 25, 2017 2:05 PM
To: Baric, Ralph (b)(6) Sims, Amy C (b)(6) PETERPALESE (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Lim, Jean (b)(6) Leyva-Grado, Victor (b)(6)
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi Dr. Baric,

Will do.

Nina

Nina Umerah
(b)(6)

From: Baric, Ralph S (b)(6)
Sent: Wednesday, January 25, 2017 3:05 PM
To: Sims, Amy C; Umerah, Nina; Palese, Peter; Erik Stemmy; Lim, Jean; Leyva-Grado, Victor
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Hi Nina, let us know how this request is proceeding through the system. Thanks, ralph

---

From: Sims, Amy C
Sent: Tuesday, January 24, 2017 11:48 AM
To: (b)(6) Palese, Peter; Erik Stemmy; Baric, Ralph S; (b)(6)
(b)(6)
Subject: Fwd: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

All,

The official NCE request from UNC was sent to MSSM this morning.

I just wanted to keep everyone in the loop.

Nina, please let me know if you need anything else from us.

Thank you, Amy

Begin forwarded message:

From: "Baric, Ralph S" (b)(6)
Subject: FW: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request
Date: January 24, 2017 at 10:27:29 AM EST
To: "Sims, Amy C" (b)(6)

From: Farrell, Ronda Lee
Sent: Tuesday, January 24, 2017 9:17 AM
To: (b)(6)

Cc: Musty, Kelly S; Moore, Victoria L; Baric, Ralph S
Subject: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Good Morning,

On behalf of The University of North Carolina at Chapel Hill and Dr. Baric, please see the attached no cost extension request for contract 0258-3962 / HHSN272201000019I / NIH Task Order No. A57 / HSN27200003. If you have any questions, please feel free to contact me. Thank you.

Kind regards,
Ronda

Ronda Farrell

Sponsored Project Specialist
Office of Sponsored Research
The University of North Carolina at Chapel Hill
104 Airport Drive, CB#1350, Chapel Hill, NC 27599-1350
Phone: (b)(6)
Fax: 919-962-5011
(b)(6)

From: Leyva-Grado, Victor
Sent: Tue, 31 Jan 2017 19:38:25 +0000
To: 'Baric, Toni C'; Stemmy, Erik (NIH/NIAID) [E]; Matthew Frieman
Cc: Baric, Ralph; Cockrell, Adam; Johnson, Reed (NIH/NIAID) [E]
Subject: RE: MERS Vx Call with UNC

Yes I will attend.

Cheers,

V

From: Baric, Toni C [mailto:(b)(6)
Sent: Tuesday, January 31, 2017 8:27 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Frieman, Matthew
Cc: Baric, Ralph S; Cockrell, Adam; Leyva-Grado, Victor; Johnson, Reed (NIH/NIAID) [E]
Subject: RE: MERS Vx Call with UNC

Hi Erik,
How about 9 am on Friday 2/3? Does this work for everyone else?
Toni

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, January 31, 2017 7:20 AM
To: Frieman, Matthew; Baric, Toni C
Cc: Baric, Ralph S; Cockrell, Adam; Leyva-Grado, Victor; Johnson, Reed (NIH/NIAID) [E]
Subject: RE: MERS Vx Call with UNC

This Friday I can do before 10am, otherwise I'm booked through the rest of the day. Next week I can do 2/6 any time before 2pm, Tuesday 2/7 before 10:30 am or between 1-3pm, or Wednesday 2/8 between Noon and 3pm.

Toni, will any of those times work?

Erik

From: Frieman, Matthew [mailto:(b)(6)
Sent: Monday, January 30, 2017 12:44 PM
To: Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6)
Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6)
Subject: Re: MERS Vx Call with UNC

I can't do Wednesday afternoon, but I can do Friday morning.

Matt

On Jan 30, 2017, at 11:33 AM, Baric, Toni C (b)(6) wrote:

Hi All
Ralph can't make this call. Can we reschedule for Wednesday afternoon or Friday morning?
Toni

-----Original Appointment-----
From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Monday, January 30, 2017 8:05 AM
To: Frieman, Matthew; Baric, Ralph S; Cockrell, Adam; Leyva-Grado, Victor; Baric, Toni C
Subject: MERS Vx Call with UNC
When: Thursday, February 02, 2017 2:00 PM-3:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:

HI Everyone,
Please see below for dial in details.

Erik

Please join my meeting from your computer, tablet or smartphone.
https://global.gotomeeting.com/join(b)(6)

You can also dial in using your phone.
United States (Toll Free): 1 877 568 4106
United States: +1 (646) 749-3129

Access Code: (b)(6)

Matthew Frieman, PhD
University of Maryland School of Medicine
685 West Baltimore St
Room 380
Baltimore, MD 21201

office: (b)(6)
cell: (b)(6)

From: Cockrell, Adam
Sent: Fri, 27 Jan 2017 00:01:17 +0000
To: Keith Wycoff
Cc: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Subject: RE: timeline for testing anti-MERS therapeutic in MERS mouse model

Thanks Keith.

That sounds great. I will use this information in our IACUC amendment. Hopefully we will be able to get this submitted early next week. At that point it will be out of our hands. Hopefully approval will be within a few weeks. I will be certain to let you know as soon as we know. Nonetheless, we can receive the therapeutic anytime you are ready. Just give me a heads-up and let me know what the exact storage conditions are. Also, please provide the vehicle. We have sterile 1XPBS that I am happy to use, however I prefer that I use the vehicle as provided by yourselves, and shipped and stored how you prefer. I am not sure of the concentration you would be providing but it would be helpful if it was at 400ug/200ul. This way I would not have to perform any manipulation of the drug. I would administer 200ul IP to each mouse directly from what you provide. With 11mg this should leave enough volume to account syringe dead volumes. Also, it would be helpful if you could provide an excess of the vehicle in shipping.

Look forward to testing this out!

Best,
Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Thursday, January 26, 2017 6:41 PM
To: Cockrell, Adam (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph S (b)(6)
Subject: Re: timeline for testing anti-MERS therapeutic in MERS mouse model

Hi Adam,

I think you are right. Please go with the two doses. If it gives 100% protection we have a better chance of convincing NIH to pay for testing one dose. We can easily send 11 mg. When are you thinking of starting this?

Keith

On Jan 26, 2017, at 3:08 PM, Cockrell, Adam (b)(6) wrote:

Trying again. The first email I replied to said it failed to send to Keith.

Thanks for the pK info.

The time line I sent is for the initial study only. However, we can go with a single prophylactic dose if you like.

In the animal studies you presented to us, in the summary, none of the studies indicate a single prophylactic dose. I would be happy to do it this way, however if we do not see therapeutic efficacy it might be more difficult to consider a second study. We may have a better shot at showing initial efficacy with two doses bracketing infection.

I would recommend that we keep the animal numbers I propose, which indicates that a total of 12 mice will receive the therapeutic and 12 mice will receive the vehicle (6 mice, from each group, will be euthanized for the indicated data collection at day 3 and day 6). Based on the dose you indicate I would suggest we round it up to an even 400ug/mouse to make calculations easy. Using the 400ug/mouse, if we dose one time at 12 prior to infection, this would require a minimum of 4800ug. Accounting for dead volumes in the syringe, etc., we would need at least 6mg. So the 7mg would be sufficient. However, if we also go with the additional administration at 12 hours post-infection this would require a minimum of 9600ug, so we would probably need ~11mg.

Look forward to hearing from you.

Best,
Adam

From: Keith Wycoff [mailto:(b)(6)
Sent: Thursday, January 26, 2017 5:28 PM
To: Cockrell, Adam (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph S (b)(6)
Subject: Re: timeline for testing anti-MERS therapeutic in MERS mouse model

Hi Adam,

Thanks for working this up. The timeline seems fine to me. Just to be clear, are you proposing a single dose 12 hr prior to infection, with a second dose to be added in a potential follow-up study?

The predicted size of our molecule is 222 kDa, based on amino acid sequence, which would suggest that we aim for a dose of 370 µg/mouse (typical human IgG ~150 kDa). For one dose and 5 mice I would propose sending you 7 mg of protein which should be more than enough

I am attaching the results of the small mouse PK experiment we did, using another DPP4-Fc variant that differs by only a single amino acid from S2320-Gal (by the way, the SF just indicates that the sample is sterile filtered). I'd be interested in knowing how this compares to anything you've done with human IgG.

Thanks,
Keith

From: Leyva-Grado, Victor
Sent: Thu, 26 Jan 2017 21:57:06 +0000
To: 'Baric, Toni C'; Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph
Cc: Umerah, Nina
Subject: RE: Rabies vaccine for MERS

Hi Erik,

I can do the times that Dr. Baric is available.

V

From: Baric, Toni C (b)(6)
Sent: Thursday, January 26, 2017 4:43 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph S
Cc: Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Rabies vaccine for MERS

Hi Erik and Adam,
Ralph is free 2/1 2:30-3
2/2 between 2-3
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, January 26, 2017 4:33 PM
To: Cockrell, Adam; Baric, Ralph S
Cc: Baric, Toni C; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Rabies vaccine for MERS

Sure. Can you give me a few dates/times after Jan 30th? I can do:

1/31 – between 12:30 and 3pm
2/1 – between 1 and 3 pm
2/2 – between 11 and 3pm

Let me know if any of those times work and I can get in touch with the external folks.

Erik

From: Cockrell, Adam (b)(6)
Sent: Thursday, January 26, 2017 3:28 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6)
Subject: Rabies vaccine for MERS

Hi Erik,

Thank you for also sending the information regarding a description of anti-MERS rabies based vaccine approach. I would submit a separate amendment for this. However, I will need to know the details of the experimental plan to test the vaccine prior to submitting anything to IACUC.

Can we arrange a conference call in the next week to discuss the details of this approach?

Best,

Adam Cockrell
Research Associate
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Office Phone: (b)(6)

From: Sims, Amy C
Sent: Tue, 17 Jan 2017 19:07:55 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor; Nina Umerah; Jean Lim; Musty, Kelly S
Subject: UNC A57 Second NCE for Option Period II

Hi Erik,
I provided all the necessary documents for the NCE (extending the end date of Option Period II to July 31, 2017 as recommended below) to our fiscal office this morning and we should be able to get this information to our Office of Sponsored Research for signature no later than tomorrow. I will let you know when the signed version is sent to MSSM.
Please let me know if you have any additional questions or concerns.
Thank you, Amy
Amy Sims, Ph.D.
UNC Chapel Hill
2107 McGavran-Greenberg Hall
CB7435
Chapel Hill, NC 27599-7435

(b)(6) office
(b)(6)

On Jan 17, 2017, at 9:02 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Thanks Adam! For the NCE we need UNC to submit the request through MSSM. Will need a short justification, also including the time needed for IACUC approval. It should also have an estimated timeline for the studies/analysis as well as acknowledging that no additional funds will be needed to complete the work.
Let me know if you need help.
Erik

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, January 17, 2017 8:59 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6) Sims, Amy C (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: A57 Calls
Sorry for sending again. I forgot to add Amy to email on the first one.
Best,
Adam

From: Cockrell, Adam
Sent: Tuesday, January 17, 2017 8:58 AM
To: 'Stemmy, Erik (NIH/NIAID) [E]' (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)

Cc: Baric, Toni C (b)(6)
Subject: RE: A57 Calls
Thanks Erik.
I am good for Thursday at 2:30. Which therapeutic does Planet Biotech have?
I think an extension to July 31 would suffice. Provided we get the names of the therapeutics/vaccines soon I should be able to get the paper submitted with IACUC to get these studies moving once we have therapeutics in hand.
I am not sure what to do regarding the NCE from our end. I have included Amy to assist with this.
Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto: (b)(6)
Sent: Tuesday, January 17, 2017 8:48 AM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: A57 Calls
Importance: High
Hi Everyone,
Apologies for the delay. I was out of the office at a site visit for the first part of last week, and then had a couple urgent issues to work though after I returned. If you're all still available can we schedule the call with Planet Biotech this Thursday 1/19 at 2:30pm? I'll send an appointment and dial in details if that time still works.
We are also getting close to the deadline for requesting a no cost extension for the final studies. Ideally we'll need to get this to OA this week so we can process the request in time. Adam, do you think you could provide a rough estimate to Victor/Nina for the time required for 2 therapeutic and 1 vaccine studies? For the justification we say that were unexpected toxicity issues with the GSK compounds and after troubleshooting with the submitter we decided to test other compounds instead.
Thanks!
Erik

From: Cockrell, Adam [mailto: (b)(6)
Sent: Friday, January 13, 2017 11:33 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: A57 Calls
Hi Erik.
Hope all is well. I was taking a look at my calendar for the next couple weeks and remembered that you had wanted to get some calls on the schedule for the three therapeutics/vaccine being considered for the contract grant.
Checking in to see if you had some times for the meetings. All of these will require me to make amendments to our IACUC protocols, and obtain approvals, so it would be best to get the names, concentrations, etc…to be used for these therapeutics/vaccine ASAP.
Best Regards,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, January 06, 2017 3:16 PM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado,

Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: A57 Calls
Hi Everyone,
Hope you all had nice holidays! I'd like to try to schedule calls with the submitters for the remaining studies. Could you please provide a few times over the next two weeks when you're available? I will be out of the office at a site visit on Monday and Tuesday next week, but mostly around after that.
Thanks!
Erik
Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Baric, Toni C
Sent: Tue, 17 Jan 2017 14:06:24 +0000
To: Cockrell, Adam; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: A57 Calls

Hi Erik,
Ralph is available at 2:30 on Thursday.
Toni

From: Cockrell, Adam
Sent: Tuesday, January 17, 2017 8:58 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Cc: Baric, Toni C
Subject: RE: A57 Calls

Thanks Erik.

I am good for Thursday at 2:30. Which therapeutic does Planet Biotech have?

I think an extension to July 31 would suffice. Provided we get the names of the therapeutics/vaccines soon I should be able to get the paper submitted with IACUC to get these studies moving once we have therapeutics in hand.

I am not sure what to do regarding the NCE from our end. I have included Amy to assist with this.

Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, January 17, 2017 8:48 AM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: A57 Calls
Importance: High

Hi Everyone,
Apologies for the delay. I was out of the office at a site visit for the first part of last week, and then had a couple urgent issues to work though after I returned. If you're all still available can we schedule the call with Planet Biotech this Thursday 1/19 at 2:30pm? I'll send an appointment and dial in details if that time still works.

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studies? For the justification we say that were unexpected toxicity issues with the GSK compounds and after troubleshooting with the submitter we decided to test other compounds instead.

Thanks!
Erik

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, January 13, 2017 11:33 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(4); (b)(5)
Subject: RE: A57 Calls

Hi Erik.

Hope all is well. I was taking a look at my calendar for the next couple weeks and remembered that you had wanted to get some calls on the schedule for the three therapeutics/vaccine being considered for the contract grant.

Checking in to see if you had some times for the meetings. All of these will require me to make amendments to our IACUC protocols, and obtain approvals, so it would be best to get the names, concentrations, etc…to be used for these therapeutics/vaccine ASAP.

Best Regards,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Friday, January 06, 2017 3:16 PM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: A57 Calls

Hi Everyone,
Hope you all had nice holidays! I'd like to try to schedule calls with the submitters for the remaining studies. Could you please provide a few times over the next two weeks when you're available? I will be out of the office at a site visit on Monday and Tuesday next week, but mostly around after that.

Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)

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: Jeff Pouliot
Sent: Mon, 16 Jan 2017 14:49:36 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Feng Wang
Cc: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Follow-up Meeting

Hi Erik,

I hope everybody had a Happy New Year. Now that we're into 2017, we would like to start a discussion of next steps for the GSK MERS study. Can we find a convenient time for a meeting, or should we discuss by email?

Best Regards,

Jeff

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Friday, December 16, 2016 12:45 PM
To: Jeff Pouliot; Cockrell, Adam; Feng Wang
Cc: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study Follow-up Meeting

EXTERNAL

Understood. We're in the same boat as well. I'll plan to update you all via email, and then we can schedule a call in the new year if necessary.

Happy Holidays!
Erik

From: Jeff Pouliot [mailto:(b)(6)
Sent: Friday, December 16, 2016 12:37 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6) Baric, Ralph (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study Follow-up Meeting

Hi Erik,

Thank you for the update, we look forward to hearing from you. FYI some of our team members will be traveling next week so it will be difficult to schedule a discussion between the groups until the new year.

Best,

Jeff

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Friday, December 16, 2016 9:14 AM
To: Jeff Pouliot; Cockrell, Adam; Feng Wang
Cc: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study Follow-up Meeting

EXTERNAL

Hi Jeff,
Apologies for my delayed response. I tried to get our internal call scheduled this week, but was unable due to conflicting travel schedules. Our internal group will be speaking on Monday, and I'll follow up with you shortly after.

Best,
Erik

From: Jeff Pouliot [mailto:(b)(6)
Sent: Thursday, December 08, 2016 12:22 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Feng Wang (b)(6)
Cc: Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Baric, Ralph (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study Follow-up Meeting

Hi Erik,

Our schedules are filling as we get to the end of the year. We're available 8:30-10:00 am on the 14th and 15th, and 3:00-4:30 pm on the 15th and 16th. Hope one of these works out.

Best,

Jeff

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, December 06, 2016 2:50 PM
To: Jeff Pouliot; Cockrell, Adam; Feng Wang
Cc: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study Follow-up Meeting

EXTERNAL

Hi Jeff,
I've been traveling quite a bit this month, and haven't been able to connect with the team. I'd like to touch base with them before scheduling a follow-up call with your group. Let's aim for a time after the middle of next week; that will give me time to discuss with Adam's group. Could you provide a few times your group is available Weds-Friday next week?

Erik

From: Jeff Pouliot [mailto:(b)(6)
Sent: Tuesday, December 06, 2016 2:45 PM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) Umerah, Nina (b)(6) Baric, Ralph (b)(6)
Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr
(b)(6)
Subject: RE: GSK A57 Study Follow-up Meeting

Hi Adam,

Thank you for the update. It sounds like a follow-up session would be premature at this time.

Eric: What are your thoughts on next steps?

Best Regards,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Monday, December 05, 2016 10:28 AM
To: Jeff Pouliot; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study Follow-up Meeting

EXTERNAL

Hi Jeff,

I hope things are well. Our group has not had a chance to meet and discuss due to busy travel schedules and the holiday. I believe we will be scheduling a meeting time within the next week, or so.

Until we perform another experiment I will not be able to parse the repeated dosing of anesthetic, the repeated use of tween, and/or the short time-frame (12hours) between drug/vehicle delivery.

I think Erik will have the best idea for when we can organize a meeting.

Best Regards,

Adam

From: Jeff Pouliot [mailto (b)(6)
Sent: Monday, December 05, 2016 9:26 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6)
Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr
(b)(6)
Subject: GSK A57 Study Follow-up Meeting

Hi Adam,

Has your group been able to pin down the reason for the greater virus replication in the MERS experiment? The two theories were that either the repeated anesthesia or the Tween in the vehicle were exacerbating the disease.

We would like to discuss next steps in order to arrange a follow up study. Can we have a telecon this Wednesday (12/8) at 10 am to form a plan?

Erik: Do you need to organize the meeting from your end? We'll send out telecon information if not.

Best,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States

Email (b)(6)
Tel (b)(6)

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From: Jeff Pouliot
Sent: Thursday, November 10, 2016 5:57 PM
To: 'Cockrell, Adam'; Feng Wang
Cc: 'Stemmy, Erik (NIH/NIAID) [E]'; 'Leyva-Grado, Victor'; 'Umerah, Nina'; 'Baric, Ralph S'; Deborah Butler; Neil Pearson; 'Yount, Boyd L Jr'
Subject: RE: GSK A57 Study control

Hi Adam,

The team has read the report but without quantifiable viral load is unable to make any conclusion. The simplest way forward at this point is to plan a follow up study as you suggest. We should arrange a planning discussion so that we can move ahead in a timely way.

Who is responsible for scheduling the meeting? Is it Eric, or should I just suggest a date and time?

Best,

Jeff

From: Jeff Pouliot
Sent: Friday, November 04, 2016 3:50 PM
To: 'Cockrell, Adam'; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,

Thank you very much. We'll review it and get back to you early next week.

One question for now: if I understand, you could not differentiate the virus load in the lungs between compound treated and control because the titer was so high. Is it possible to repeat the plaque assays with a higher initial dilution to see if compound caused any reduction in titer? A large reduction in virus

particles might not have a detectable physiological effect if the remaining titer is still more than you've ever seen.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, November 04, 2016 2:18 PM
To: Jeff Pouliot; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

I am attaching our report of the first study for your group to review.

It appears that delivery of the vehicle and/or anesthetic enhance viral replication, which may be augmenting disease phenotypes. In addition, anesthetizing with ketamine/xylazine and intranasal delivery every 12 hours may also be contributing to significant weight loss early on, and enhanced mortality of the mice. It is important to note that the titers were increased in both the vehicle treated and drug treated, well above (>10-fold) those I have ever observed with this model. Two control animals (no drug/vehicle treatment) had lung titers similar to what we have observed previously with this model. This may be an initial indication that the drug is not reducing the viral load in the lungs.

Suggestions for a second study: I think altering the dose schedule to 24 hour increments, using ketamine/xylazine for viral administration, and using isoflurane for subsequent drug administration may result in a more effective second study. However, these are only suggestions.

We look forward to discussing the follow-up study.

Best Regards,

Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Monday, October 31, 2016 9:17 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6)
Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr

(b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Any news on the viral titers? We'd like to schedule another study, but have been waiting to hear whether viral inhibition was detectable from the first run.

Nobody on this end has previously seen toxicity from intranasal dosing with a Tween formulation, so the tox we saw may be related to the infection. Do you know of any literature that suggests detergents of that sort can exacerbate MERS?

Best,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 4:23 PM
To: Jeff Pouliot; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Erik and Jeff.

At this time we have lost 3 vehicle treated and 1 drug treated.

Hopefully we will have the titer data by late next week, and at the latest by the following week.

Best,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 4:09 PM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) (b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Adam,

How unfortunate, we had hoped the mice would respond better to the regimen. We'll defer to your experience in deciding terminate the experiment early. As you suggest, measurement of the viral load in the lungs seems the most likely way to make a conclusion at this point.

What is the distribution of the mice we lost between the control and compound groups? It will be easier to interpret the experiment if the same number of mice remain in each.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 3:49 PM
To: Feng Wang
Cc: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi everyone,

Unfortunately, at this time it appears we have lost 4 of the 12 mice in the study. Most likely due to a combination of repeated anesthetic and repeated intranasal administration. I gave the fourth dose this morning, but so not think the mice will tolerate another dose. I am going to terminate the study at this time to collect the lungs for titering in an attempt to salvage some data from this experiment.

Due to the issues we are having with the dosing regimen titering may be the most telling endpoint at this time.

Please let me know ASAP if everyone is in agreement with this.

Best,

Adam

From: Feng Wang [mailto (b)(6)
Sent: Tuesday, October 11, 2016 3:28 PM
To: Cockrell, Adam (b)(6)
Cc: Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: Re: GSK A57 Study control

Hi Adam,

Thanks for the update! Let's see how those mice hold on.

Best wishes,
Feng

Sent from my iPhone

On Oct 11, 2016, at 11:03 AM, Cockrell, Adam (b)(6) wrote:

EXTERNAL

Thanks Feng,

Just wanted to provide a small update on the current status. After this we will wait until we have all the data for a subsequent update.

The mice have been anesthetized three times at this point. Once for intranasal administration of virus, and twice for intranasal drug/vehicle delivery. Due to the short duration between intranasal delivery times (6 hours between virus and first drug administration, and 12 hours between drug re-administration) it appears that the mice have a difficult time recovering from repeated anesthetic. Due to this fact they do not appear to be eating/drinking. In less than 24 hours the average weight loss has been 8-9% of body weight for both vehicle and drug treated. This is most likely due to lack of recovery from repeated anesthetic administration since we do not observe this in less than 24 hours after virus administration. Therefore, it may be difficult to utilize weight loss as a measure of disease outcome under this circumstance.

Mice may have tolerated 24 hour time points much better.

Best,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Monday, October 10, 2016 3:59 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

How is the first dose going? Just a reminder, please use fresh formulation and vehicle for each dose.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Thursday, October 06, 2016 12:01 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Yes 50ul/mouse intranasal. It is part of the protocol to collect weight information. I attached the agreed upon protocol/time line.

Adam

From: Feng Wang [mailto:(b)(6)
Sent: Thursday, October 06, 2016 11:55 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Great! Let me know if you need anything else. You give 50uL intranasal dose per mouse, right? Is it possible to collect weight info?

Good luck with the study!
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Thursday, October 06, 2016 11:50 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,

I received the drug/vehicle this morning.

Best,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Wednesday, October 05, 2016 2:11 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control
Importance: High

Hi Adam,

Just an update that drugs and vehicles are to be shipped out today and they should arrive at UNC tomorrow morning. There are 7 vials of the drug solution labeled as GSKXXX and another 7 vials labeled as the blank vehicle. Since each vial has about 1.5mL solution, you would pull out one fresh vial of the drug and one fresh vial of the vehicle for each dose. If possible, please save the leftovers. Please refrigerate (i.e. 4°C) all vials upon arrival. At each dosing time, please take out vials, equilibrate them to the room temperature and mix them a little bit prior to the dosing. As we worry about the leakage and the extractable, we used HPLC (glass) vials for the formulation.
Let me know if you need additional information.

Thanks and good luck with the study!
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, October 04, 2016 5:39 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,
The plan is to begin Monday.
Adam

Sent via the Samsung Galaxy S®6 active, an AT&T 4G LTE smartphone

-------- Original message --------
From: Feng Wang (b)(6)
Date: 10/4/2016 5:30 PM (GMT-05:00)
To: "Cockrell, Adam" (b)(6) Jeff Pouliot (b)(6)
"Stemmy, Erik (NIH/NIAID) [E]" (b)(6) '"Leyva-Grado, Victor"'
(b)(6) '"Umerah, Nina"' (b)(6) "Baric, Ralph
S" (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6)
Cc: "Yount, Boyd L Jr" (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Just like to know when you are to give the first dose?

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, October 04, 2016 11:13 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Feng. I will hold on to it.

From: Feng Wang [mailto:(b)(6)
Sent: Tuesday, October 04, 2016 11:11 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Would you please keep the powder and the vehicle for now? Feel free to dispose the suspensions.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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Tel (b)(6)

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, October 04, 2016 11:01 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,

I kept what remained of the previous lot of drug and vehicle. Do you mind if I discard the previous batch of drug and vehicle that you sent? At least, the vials that remain from the suspension trials.

Thanks,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Monday, October 03, 2016 2:26 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Thanks Adam! As it stands now, it only needs refrigerated (i.e. 4°C). I will keep you updated with the shipment.

Best wishes,

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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From: Cockrell, Adam [mailto(b)(6)
Sent: Monday, October 03, 2016 2:21 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Feng,

Just in case it was lost in the shuffle, the following is the information for delivery.

What temperature should the drug be stored at?

Adam Cockrell/Boyd Yount
University of North Carolina at Chapel Hill
Department of Epidemiology
135 Dauer Drive
Hooker Bldg./Room 3105
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Cell #: (b)(6)

Best,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Monday, October 03, 2016 1:56 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Yes, we are on schedule to deliver the formulation to you by this Friday.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Monday, October 03, 2016 1:27 PM

To: Jeff Pouliot; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

Thanks for asking. I think for this experiment we should test for efficacy, and consider this possibility for future experiments.

Should I anticipate the drug to be delivered by this Friday?

Cheers,
Adam

From: Jeff Pouliot [mailto(b)(6)
Sent: Monday, October 03, 2016 11:29 AM
To: Cockrell, Adam(b)(6) Feng Wang(b)(6) Stemmy, Erik (NIH/NIAID) [E](b)(6) 'Leyva-Grado, Victor'(b)(6) 'Umerah, Nina'(b)(6) Baric, Ralph S(b)(6) Deborah Butler(b)(6) Neil Pearson(b)(6)
Cc: Yount, Boyd L Jr(b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Have you decided whether you'll be able to include our proposal to test satellite animals to ensure compound is on board during the study? If so, I can arrange for the sample shipping to GSK. If not we can reconsider while we plan the next round of experiments.

Best Regards,

Jeff

From: Jeff Pouliot
Sent: Thursday, September 08, 2016 3:48 PM
To: 'Cockrell, Adam'; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,

We were thinking of three mice to be dosed identically to those in the study. Dosing simultaneous to the infected animals won't be possible because it will be done under BSL2 conditions, but the compound dose and dosing methodology should be the same as what will be done with the infected animals.

The animals would be euthanized at T=15 minutes after dose, with blood samples and lungs to be frozen on dry ice and shipped to GSK. We can analyze them to determine amount of compound on board and can match those values to the efficacy.

Let me know if this is sufficient detail.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Thursday, September 08, 2016 12:15 PM
To: Jeff Pouliot; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

When you have a chance can you please provide the exact details of what the controls might entail? Exact time point post-drug administration, exactly how to collect/prepare samples, and ship samples?

This will help provide a clearer picture for us of the extent of the work necessary for collecting/preparing these controls.

Best Regards,

Adam

From: Jeff Pouliot [mailto(b)(6)
Sent: Tuesday, September 06, 2016 10:46 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

It's great to hear the compound is en route. Have you had time to consider the inclusion of satellite uninfected animals in the study? We believe adding animals in parallel to test compound delivery at your site would be critical to interpretation if the efficacy is lower than we expect.

Best,

Jeff

From: Jeff Pouliot
Sent: Tuesday, August 30, 2016 12:08 PM
To: 'Cockrell, Adam'; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: GSK A57 Study control

Hi Adam,

We would like to ask if a control can be added to this study. Would you be able to treat 2-3 satellite uninfected animals to test whether your dosing methodology is delivering the same amount of compound we've seen in our studies? This would entail treating uninfected mice, sacrificing them 5-15 minutes after dose and shipping blood samples and terminal lungs to GSK.

This control would provide information on compound delivery without the BSL-3 complications we discussed previously. Apologies for the late addition but this was a recent suggestion. Please let us know your thoughts.

Best Regards,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

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Tel (b)(6)

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<image002.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, August 30, 2016 10:41 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Feng,

I received the vehicle this morning. However, the address on the package had it shipped to a lab in a different building in the pharmacy department. Fortunately, they were able to find our number and let us know.

Also, I stored it at 4C, but it was shipped at ambient temperature.

I will test the formulation late next week when I return.

For shipping of the test compound please use the following address:

Boyd Yount/Adam Cockrell
UNC-CH
135 Dauer Drive
Hooker Bldg./Room 3105
Chapel Hill, NC
27599
Phone#(b)(6)

Best Regards,
Adam

From: Feng Wang [mailto(b)(6)
Sent: Tuesday, August 30, 2016 9:39 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study

Hi Adam,

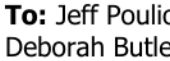
We shipped out study vehicle (i.e. 0.5%Tween80) yesterday and should arrive at your lab today. Please watch out and store it at 4-8°C. Due to some paper work delay, I do not think that the test compound will arrive before you leave for vacation. Is it possible that your coworker could do the formulation test in your absence? In addition, the test compound should also be stored at 4-8°C prior to use.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
Email (b)(6)
Tel (b)(6)

gsk.com | Twitter | YouTube | Facebook | Flickr



From: Cockrell, Adam [mailto:(b)(6)
Sent: Monday, August 29, 2016 9:25 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Jeff,

Contact numbers are (b)(6) (Adam) and (b)(6) (Boyd)

Thanks,

Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Friday, August 26, 2016 4:09 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)

Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study

Hi Adam

Thank you very much. Can you supply a contact phone number for shipping?

We will send the 0.5% Tween in saline with our compound. Everything should arrive by midweek.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, August 26, 2016 10:54 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang; Barb Carter
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Jeff,

Thanks for the update. I have addressed your questions below in red.

I will be out of town September 1st-september 7th, but Boyd Yount will be available to receive the package if I'm not here. Please advise on any special storage conditions.

Would it be possible for you ship a sample for early arrival next week, with all the components, so that I can test out the resuspension of the drug?

Also, I have attached a copy of the study as we discussed. As you suggested I eliminated the time point for drug delivery 6 hours prior to infection.

Best Regards,
Adam

From: Jeff Pouliot [mailto (b)(6)
Sent: Thursday, August 25, 2016 6:38 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)

'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6)
Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6) Feng Wang (b)(6) Barb Carter
(b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

We'd like to update you on the status of the test compound shipping for the study and your formulation pre-work. We have the patent nearly completed and will be able to send the compound early next week, targeting shipping for Tuesday 8/30 with arrival by the end of the week. Please let us know if this does not agree with your planned work schedule. We also have a few shipping questions to be certain everything goes smoothly:

- Can you advise on the planned start date for the in vivo study? If you need compound on the morning of September 6 we will try to send it earlier in the week to reduce the chance of shipping delays. I have reserved time in our BSL3 facility to initiate the experiment on Monday September 12th. Therefore, we would need to have the compound by Friday September 9th.

- Will your shipping group be receiving packages next Thurs-Fri (Sep 1-2)? If I am not here when the package arrives Boyd Yount in the lab will be available to receive the package. Please advise on any special storage conditions. I have included Boyd on this email.

- Could you please confirm the shipping address we should use for the test compound? Adam Cockrell/Boyd Yount, UNC-CH, 135 Dauer Dr., Chapel Hill, NC, 27599

- Do you have 0.5% Tween-80 in saline available for the formulation or should we plan to ship some? It would be simpler if you had some on hand as it necessitates a second package, but we're happy to arrange it if you prefer. I would prefer that the GSK group provides everything relevant to the drug.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Sunday, August 14, 2016 10:48 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Thanks Jeff,

Sounds great!

Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Saturday, August 13, 2016 5:27 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Hi Adam,

We can send you a sample as soon as legal tells us the patent is filed. This should take roughly another week, so we should be able to get the sample to you by the end of two weeks. We will let you know if there are any unexpected delays.

Thanks for the info on dose groups. We can plan in more detail once the pilot run is complete.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Saturday, August 13, 2016 7:43 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Thanks Jeff,

Would you guys mind sending me a sample of the drug (exactly how I will receive it for the mouse studies) in the next week, or two, so that I can validate the resuspension process in my hands?

If we see efficacy with the initial study, I believe 2-3 dose groups, with a 24 hour delivery window, would be feasible.

Thanks,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Thursday, August 11, 2016 3:45 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6)
Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

You should be able to formulate the compound either way. It should easily go into solution in 3-5 min with a 37C water bath. Otherwise, you can vortex and leave it on a heated plate (low setting, warm) with stirring for a couple minutes.

We suggested a 24h dosing schedule for the first study, but your counterproposal of BID dosing to have the greatest chance of efficacy was a good one. A 12-hour doing schedule for the initial study is fine.

For the follow-up study we can modify dosing to qd from 6-hours post infection, presuming the initial results are robust. We can plan this in more detail once the initial test is complete. To help us think it through, though, can you let us know if it is technically feasible to run 2-3 dose groups in parallel?

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, August 10, 2016 6:39 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Dear Jeff,

Please see responses to comments/questions below.

Regards,
Adam

From: Jeff Pouliot [mailto(b)(6)
Sent: Tuesday, August 09, 2016 5:51 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6)

Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

Thanks for the note. Your research plan nicely reflects our discussion last week. We have some information below to fill in the details and a few questions for you.

- The predosing of compound is not needed as these are direct acting antivirals. In addition, only a suboptimal amount of compound would remain at the time of infection given the short T1/2 of this compound. A therapeutic model with the first dose following infection is our preferred choice. Is this acceptable? Starting with a therapeutic dose at 6 hours post-infection sounds great.
- BID dosing starting at 6 hours post infection seems the better plan. Do you know how long robust viral replication continues in an untreated test subject? Our model exhibits robust replication through day 6 post-infection with peak replication at days 2-3.
- We recommend intranasal dosing at 1 mg/kg, 50 uL volume per mouse, at a concentration of 0.5 mg/mL. This should deliver a compound concentration at Tmax of 100x EC50 to the lung. IN sounds good.
- We will plan to ship you the compound as dry powder. We're exploring stability but until we have firm data we can't guarantee that a solution prepared here would be stable long enough for the experiment. You will need to suspend by brief sonication in a dosing solution of 0.5% Tween-80 in saline. Is this acceptable? This is acceptable, however can you please define sonication? Is a water sonicator necessary for this? Or, will vortexing suffice? Does this compound readily go into solution? The 12 hour dosing schedule is quite rigorous, especially in a BSL3, therefore I am trying to get an understanding of how much additional time I will have to spend suspending the drug prior to each 12 hour administration.

We would like also to think ahead to the second round of the experiment. Presuming the outcome shows positive results, we propose a similar experiment at successive 3-fold lower drug concentrations to clarify the PK/PD relationship. If the follow up allows more than one dose group, we would dose at 0.3 mg/kg and 0.1 mg/kg (30x and 10x EC50). Does this sound reasonable to you? A dosing experiment sounds reasonable. Provided the initial study is successful, In follow-up experiments we discussed moving to a 6-7 day time course. In doing this I will have to move to delivering the drug every 24 hours. Is this reasonable to you? Would you prefer that the initial study use a 24 hour repeated dosing time course? The 24 hour time course would begin after the initial delivery of the drug at 6 hours post-infection.

Best,

Jeff

From: Cockrell, Adam [mailto (b)(6)
Sent: Wednesday, August 03, 2016 5:20 PM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S;

Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Hi everyone. It was good to meet everyone in the gsk group.

In putting together the time line (attached to email) I had some additional thoughts.

1) There are two slides. The first is the initial time line that we discussed on the phone. The second slide takes into account the fact that the half-life of drug is really short, therefore we can adjust the drug delivery time line to bracket the initial viral delivery to be -6 hours and +6 hours if you guys would prefer. This would shorten the study on the back end by 6 hours, which should be of no consequence regarding the data we will capture.
2) This is just a thought, and not sure if this is a viable possibility given the half-life of the drug, but we could eliminate any confounding issues with repeated anesthetic administration if there was an option to deliver drug by the IP route. Thoughts?

That said I look forward to working with everyone.

Best Regards,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Wednesday, August 03, 2016 2:13 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Cockrell, Adam (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Thank you all for the productive discussion. We look forward to working together.

I've added one person to the email list above. Please include Feng Wang on the experimental planning communications.

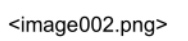
Best,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
Email (b)(6)
Tel (b)(6)

gsk.com | Twitter | YouTube | Facebook | Flickr



From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, August 03, 2016 1:59 PM
To: 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson; Jeff Pouliot; 'Cockrell, Adam'
Subject: GSK A57 Study

EXTERNAL

Hi Everyone,
Thanks for your time today, it was a productive call. Please feel free to email directly to work out the protocol/dosing and other study details, but be sure to CC everyone on this message.

Erik

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

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From: Frieman, Matthew
Sent: Tue, 13 Dec 2016 23:15:45 +0000
To: Baric, Ralph; Stanley Perlman; Susan Baker; (b)(6) Paul Duprex; Vineet D. Menachery; Ryan A. Langlois; Nicholas Heaton; Denison, Mark (NIH); Racaniello, Vincent R. (b)(6) Michael Imperiale; Susan Weiss; Feldmann, Heinrich (NIH/NIAID) [E]; Munster, Vincent (NIH/NIAID) [E]; Johnson, Reed (NIH/NIAID) [E]; PETERPALESE; Adolfo García-Sastre; Benjamin tenOever; (b)(6) Hensley, Lisa (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Mark Heise; Michael Buchmeier; (b)(6) Amy Sims
Subject: Gain of Function Policy Input
Importance: High

Dear all,
Sorry for the mass email, but I met with Jo Handelsman today at the White House Office of Science and Technology Policy, with Stacey Shultz Cherry conferencing in. We discussed the current draft of the NSABB report on Gain of Function Research Oversight.
I wanted to reach out to the Coronavirus community and others who I have talked to about GOF work. I have been asked to compile as much information ASAP (as in tonight!) on how the moratorium has impacted the virology community. They have had very little outside interactions and have no data on how many projects and people are affected by their policy. They can't show us the current format of the policy but they said that it includes several hurdles that they have no problem having when it only affects 5 projects a year. We all know that our work has been impacted in grants but also in projects that were stalled, or didn't pursue because of the moratorium.
Specifically, I need examples of people that have been impacted and a brief description of the experiment(s). It is especially important to include if you had entire lines of work halted, redirected, or unable to be completed or experiments/projects that could never be pursued because of the moratorium. Definitely state if trainees were impacted. The information can be brief and names will not be included but this is really important.
WHY?
Because the perception is that only 5 projects per year are impacted by the moratorium so there is no rush to lift it. Please send me your stories. And please send this to anyone I have left off this list (I am compiling this list while I wait for the train in DC).
Thank you in advance for your assistance.

Matthew Frieman, PhD
University of Maryland School of Medicine
685 West Baltimore St
Room 380
Baltimore, MD 21201

office: (b)(6)
cell: (b)(6)

From: Baric, Toni C
Sent: Wed, 7 Dec 2016 21:53:12 +0000
To: Cockrell, Adam; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Reschedule A57 Call

Ralph can do anytime on 12/19 except 12-1.

Toni

From: Cockrell, Adam
Sent: Wednesday, December 07, 2016 4:52 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Toni C; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Reschedule A57 Call

I can go early on 12/19, like 9am, or the 2-3 time slot.

Thanks Erik,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, December 07, 2016 4:33 PM
To: Baric, Toni C (b)(6) Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Subject: RE: Reschedule A57 Call

Ok! How about Monday 12/19? I can do any time before 3pm except 12-2pm.

Erik

From: Baric, Toni C [mailto:(b)(6)
Sent: Wednesday, December 7, 2016 4:21 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Subject: RE: Reschedule A57 Call

He can't. Our meeting lasts all day.

From: Cockrell, Adam
Sent: Wednesday, December 07, 2016 4:17 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Cc: Baric, Toni C
Subject: RE: Reschedule A57 Call

I'm good for either of those times next Wednesday. If Ralph can meet while up there, I can call in from here.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, December 07, 2016 4:14 PM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: Reschedule A57 Call

Hi Everyone,
Doesn't seem like those times worked. How about Wednesday next week (12/14) between 11am and 12:30pm, or 2-3pm?

Erik

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, December 7, 2016 1:35 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: Reschedule A57 Call

Since tomorrow was one of the times I wanted to check if a time was settled on.

Thanks,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, December 06, 2016 12:16 PM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: Reschedule A57 Call

Hi Everyone,
I'd like to reschedule our A57 call from last week. Please let me know if any of the times below work for you. Once we settle on a time I'll send dial in details.

Thanks!
Erik

Thursday 12/8: between 1-2pm
Friday 12/9: before 10am
Monday 12/12: before 11am or between 1:30-2:30pm

Thursday 12/15: between 12-2pm

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, (b)(6)
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: Cockrell, Adam
Sent: Tue, 22 Nov 2016 19:18:14 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: RE: GSK A57 Study control

Hi Erik,

A meeting the week of December 5th sounds like a good idea.

I have not redone the titers on the GSK stuff. I can, but freeze/thawing samples results in loss of titer. We typically do not do this, but I can still try it. That said, although we could not get an exact titer it was clearly much higher than what I have seen in the past, and more than likely at least 10-fold higher than the two control animals I had in that particular experiment. The exact titer might reveal differences between drug and vehicle only animals, but these are both still much higher than what was observed with controls. Not sure of the value in tittering again.

I think we should discuss performing a second study. However, if the drug does not reduce titers below the controls that did not receive vehicle, or drug, I'm not certain of the value in a second study. The instability of the drug is also a problem.

The antibody, receptor decoy, and vaccine studies sound intriguing.

Look forward to discussing these items when you return from your site visit. Have a safe trip.

Best Regards,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Tuesday, November 22, 2016 1:20 PM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,
Sorry for the delay. I was out on travel last week for a meeting, and then was a bit under the weather after I got back. I haven't heard anything from MSSM to schedule a call, so we may have missed our window. I'm heading out again on a site visit to Hong Kong on Sunday and won't be back until Dec 3rd. I think we'll have to shoot for after the 3rd.

For GSK: Were you able to get the final titer data? I don't recall seeing it, but may have missed it. Let me know if you have a recommendation on whether it's worth it to go ahead with a second study, given the issues from the first.

For the remaining studies: I have a several potential tests, depending on whether we do a second GSK study. One is another antibody, one is a receptor decoy, and there are two vaccines to consider. My priority would be to try to get at least one vaccine tested in the model, but I'm flexible on the other studies. I will plan to circulate updated information sheets on the potential candidates and then we can all discuss once I'm back from my site visit.

Erik

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

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, November 11, 2016 5:59 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: FW: GSK A57 Study control

Hi Erik,

Since we have not had a chance to discuss the next 3 therapeutics for the contract I thought it would be best to get your opinion before responding to Jeff's request to schedule a meeting for a follow-up study.

Are we still planning to have a teleconference as you suggested last week?

Best,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Thursday, November 10, 2016 5:57 PM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) (b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

The team has read the report but without quantifiable viral load is unable to make any conclusion. The simplest way forward at this point is to plan a follow up study as you suggest. We should arrange a planning discussion so that we can move ahead in a timely way.

Who is responsible for scheduling the meeting? Is it Eric, or should I just suggest a date and time?

Best,

Jeff

From: Jeff Pouliot
Sent: Friday, November 04, 2016 3:50 PM
To: 'Cockrell, Adam'; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,

Thank you very much. We'll review it and get back to you early next week.

One question for now: if I understand, you could not differentiate the virus load in the lungs between compound treated and control because the titer was so high. Is it possible to repeat the plaque assays with a higher initial dilution to see if compound caused any reduction in titer? A large reduction in virus particles might not have a detectable physiological effect if the remaining titer is still more than you've ever seen.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, November 04, 2016 2:18 PM

To: Jeff Pouliot; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

I am attaching our report of the first study for your group to review.

It appears that delivery of the vehicle and/or anesthetic enhance viral replication, which may be augmenting disease phenotypes. In addition, anesthetizing with ketamine/xylazine and intranasal delivery every 12 hours may also be contributing to significant weight loss early on, and enhanced mortality of the mice. It is important to note that the titers were increased in both the vehicle treated and drug treated, well above (>10-fold) those I have ever observed with this model. Two control animals (no drug/vehicle treatment) had lung titers similar to what we have observed previously with this model. This may be an initial indication that the drug is not reducing the viral load in the lungs.

Suggestions for a second study: I think altering the dose schedule to 24 hour increments, using ketamine/xylazine for viral administration, and using isoflurane for subsequent drug administration may result in a more effective second study. However, these are only suggestions.

We look forward to discussing the follow-up study.

Best Regards,

Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Monday, October 31, 2016 9:17 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6)
Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr
(b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Any news on the viral titers? We'd like to schedule another study, but have been waiting to hear whether viral inhibition was detectable from the first run.

Nobody on this end has previously seen toxicity from intranasal dosing with a Tween formulation, so the tox we saw may be related to the infection. Do you know of any literature that suggests detergents of that sort can exacerbate MERS?

Best,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

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1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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Tel (b)(6)

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 4:23 PM
To: Jeff Pouliot; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Erik and Jeff.

At this time we have lost 3 vehicle treated and 1 drug treated.

Hopefully we will have the titer data by late next week, and at the latest by the following week.

Best,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 4:09 PM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6)

Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Adam,

How unfortunate, we had hoped the mice would respond better to the regimen. We'll defer to your experience in deciding terminate the experiment early. As you suggest, measurement of the viral load in the lungs seems the most likely way to make a conclusion at this point.

What is the distribution of the mice we lost between the control and compound groups? It will be easier to interpret the experiment if the same number of mice remain in each.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, October 12, 2016 3:49 PM
To: Feng Wang
Cc: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi everyone,

Unfortunately, at this time it appears we have lost 4 of the 12 mice in the study. Most likely due to a combination of repeated anesthetic and repeated intranasal administration. I gave the fourth dose this morning, but so not think the mice will tolerate another dose. I am going to terminate the study at this time to collect the lungs for titering in an attempt to salvage some data from this experiment.

Due to the issues we are having with the dosing regimen titering may be the most telling endpoint at this time.

Please let me know ASAP if everyone is in agreement with this.

Best,

Adam

From: Feng Wang [mailto:(b)(6)
Sent: Tuesday, October 11, 2016 3:28 PM

To: Cockrell, Adam (b)(6)
Cc: Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: Re: GSK A57 Study control

Hi Adam,

Thanks for the update! Let's see how those mice hold on.

Best wishes,
Feng

Sent from my iPhone

On Oct 11, 2016, at 11:03 AM, Cockrell, Adam (b)(6) wrote:

EXTERNAL

Thanks Feng,

Just wanted to provide a small update on the current status. After this we will wait until we have all the data for a subsequent update.

The mice have been anesthetized three times at this point. Once for intranasal administration of virus, and twice for intranasal drug/vehicle delivery. Due to the short duration between intranasal delivery times (6 hours between virus and first drug administration, and 12 hours between drug re-administration) it appears that the mice have a difficult time recovering from repeated anesthetic. Due to this fact they do not appear to be eating/drinking. In less than 24 hours the average weight loss has been 8-9% of body weight for both vehicle and drug treated. This is most likely due to lack of recovery from repeated anesthetic administration since we do not observe this in less than 24 hours after virus administration. Therefore, it may be difficult to utilize weight loss as a measure of disease outcome under this circumstance.

Mice may have tolerated 24 hour time points much better.

Best,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Monday, October 10, 2016 3:59 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)

Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

How is the first dose going? Just a reminder, please use fresh formulation and vehicle for each dose.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Thursday, October 06, 2016 12:01 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Yes 50ul/mouse intranasal. It is part of the protocol to collect weight information. I attached the agreed upon protocol/time line.

Adam

From: Feng Wang [mailto (b)(6)
Sent: Thursday, October 06, 2016 11:55 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Great! Let me know if you need anything else. You give 50uL intranasal dose per mouse, right? Is it possible to collect weight info?

Good luck with the study!
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Thursday, October 06, 2016 11:50 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,

I received the drug/vehicle this morning.

Best,
Adam

From: Feng Wang [mailto(b)(6)
Sent: Wednesday, October 05, 2016 2:11 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control
Importance: High

Hi Adam,

Just an update that drugs and vehicles are to be shipped out today and they should arrive at UNC tomorrow morning. There are 7 vials of the drug solution labeled as GSKXXX and another 7 vials labeled as the blank vehicle. Since each vial has about 1.5mL solution, you would pull out one fresh vial of the drug and one fresh vial of the vehicle for each dose. If possible, please save the leftovers. Please refrigerate (i.e. 4°C) all vials upon arrival. At each dosing time, please take out vials, equilibrate them to the room temperature and mix them a little bit prior to the dosing. As we worry about the leakage and the extractable, we used HPLC (glass) vials for the formulation.
Let me know if you need additional information.

Thanks and good luck with the study!
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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<image001.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, October 04, 2016 5:39 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,
The plan is to begin Monday.
Adam

-------- Original message --------
From: Feng Wang (b)(6)
Date: 10/4/2016 5:30 PM (GMT-05:00)
To: "Cockrell, Adam" (b)(6) Jeff Pouliot (b)(6)
"Stemmy, Erik (NIH/NIAID) [E]" (b)(6) "'Leyva-Grado, Victor'"
(b)(6) "'Umerah, Nina'" (b)(6) "Baric, Ralph
S" (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6)
Cc: "Yount, Boyd L Jr" (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Just like to know when you are to give the first dose?

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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From: Cockrell, Adam [mailto (b)(6)
Sent: Tuesday, October 04, 2016 11:13 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Feng. I will hold on to it.

From: Feng Wang [mailto (b)(6)
Sent: Tuesday, October 04, 2016 11:11 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik
(NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6)

'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Would you please keep the powder and the vehicle for now? Feel free to dispose the suspensions.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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From: Cockrell, Adam [mailto (b)(6)
Sent: Tuesday, October 04, 2016 11:01 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Feng,

I kept what remained of the previous lot of drug and vehicle. Do you mind if I discard the previous batch of drug and vehicle that you sent? At least, the vials that remain from the suspension trials.

Thanks,
Adam

From: Feng Wang [mailto (b)(6)
Sent: Monday, October 03, 2016 2:26 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6)

'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Thanks Adam! As it stands now, it only needs refrigerated (i.e. 4°C). I will keep you updated with the shipment.

Best wishes,

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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From: Cockrell, Adam [mailto (b)(6)
Sent: Monday, October 03, 2016 2:21 PM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Thanks Feng,

Just in case it was lost in the shuffle, the following is the information for delivery.

What temperature should the drug be stored at?

Adam Cockrell/Boyd Yount
University of North Carolina at Chapel Hill
Department of Epidemiology
135 Dauer Drive
Hooker Bldg./Room 3105
Chapel Hill, NC, 27599
Lab Phone: (b)(6)
Cell #: (b)(6)

Best,
Adam

From: Feng Wang [mailto(b)(6)
Sent: Monday, October 03, 2016 1:56 PM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Yes, we are on schedule to deliver the formulation to you by this Friday.

Thanks,
feng

Feng Wang
Investigator
Host Defense DPU
RD Infectious Disease R&D

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<image001.png>

From: Cockrell, Adam [mailto(b)(6)
Sent: Monday, October 03, 2016 1:27 PM
To: Jeff Pouliot; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

Thanks for asking. I think for this experiment we should test for efficacy, and consider this possibility for future experiments.

Should I anticipate the drug to be delivered by this Friday?

Cheers,
Adam

From: Jeff Pouliot [mailto(b)(6)
Sent: Monday, October 03, 2016 11:29 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

Have you decided whether you'll be able to include our proposal to test satellite animals to ensure compound is on board during the study? If so, I can arrange for the sample shipping to GSK. If not we can reconsider while we plan the next round of experiments.

Best Regards,

Jeff

From: Jeff Pouliot
Sent: Thursday, September 08, 2016 3:48 PM
To: 'Cockrell, Adam'; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,

We were thinking of three mice to be dosed identically to those in the study. Dosing simultaneous to the infected animals won't be possible because it will be done under BSL2 conditions, but the compound dose and dosing methodology should be the same as what will be done with the infected animals.

The animals would be euthanized at T=15 minutes after dose, with blood samples and lungs to be frozen on dry ice and shipped to GSK. We can analyze them to determine amount of compound on board and can match those values to the efficacy.

Let me know if this is sufficient detail.

Best,

Jeff

From: Cockrell, Adam [mailto(b)(6)
Sent: Thursday, September 08, 2016 12:15 PM
To: Jeff Pouliot; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

EXTERNAL

Hi Jeff,

When you have a chance can you please provide the exact details of what the controls might entail? Exact time point post-drug administration, exactly how to collect/prepare samples, and ship samples?

This will help provide a clearer picture for us of the extent of the work necessary for collecting/preparing these controls.

Best Regards,

Adam

From: Jeff Pouliot (b)(6)
Sent: Tuesday, September 06, 2016 10:46 AM
To: Cockrell, Adam (b)(6) Feng Wang (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,

It's great to hear the compound is en route. Have you had time to consider the inclusion of satellite uninfected animals in the study? We believe adding animals in parallel to test compound delivery at your site would be critical to interpretation if the efficacy is lower than we expect.

Best,

Jeff

From: Jeff Pouliot
Sent: Tuesday, August 30, 2016 12:08 PM
To: 'Cockrell, Adam'; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: GSK A57 Study control

Hi Adam,

We would like to ask if a control can be added to this study. Would you be able to treat 2-3 satellite uninfected animals to test whether your dosing methodology is delivering the same amount of compound we've seen in our studies? This would entail treating uninfected mice, sacrificing them 5-15 minutes after dose and shipping blood samples and terminal lungs to GSK.

This control would provide information on compound delivery without the BSL-3 complications we discussed previously. Apologies for the late addition but this was a recent suggestion. Please let us know your thoughts.

Best Regards,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

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1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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Tel (b)(6)

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<image002.png>

From: Cockrell, Adam [mailto:(b)(6)
Sent: Tuesday, August 30, 2016 10:41 AM
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Feng,

I received the vehicle this morning. However, the address on the package had it shipped to a lab in a different building in the pharmacy department. Fortunately, they were able to find our number and let us know.

Also, I stored it at 4C, but it was shipped at ambient temperature.

I will test the formulation late next week when I return.

For shipping of the test compound please use the following address:

Boyd Yount/Adam Cockrell
UNC-CH
135 Dauer Drive
Hooker Bldg./Room 3105
Chapel Hill, NC
27599
(b)(6)

Best Regards,
Adam

From: Feng Wang [mailto:(b)(6)
Sent: Tuesday, August 30, 2016 9:39 AM
To: Cockrell, Adam (b)(6) Jeff Pouliot (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study

Hi Adam,

We shipped out study vehicle (i.e. 0.5%Tween80) yesterday and should arrive at your lab today. Please watch out and store it at 4-8°C. Due to some paper work delay, I do not think that the test compound will arrive before you leave for vacation. Is it possible that your coworker could do the formulation test in your absence? In addition, the test compound should also be stored at 4-8°C prior to use.

Thanks,
feng

Feng Wang

Investigator
Host Defense DPU
RD Infectious Disease R&D

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Tel (b)(6)

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From: Cockrell, Adam [mailto:(b)(6)
Sent: Monday, August 29, 2016 9:25 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Jeff,

Contact numbers are (b)(6) (Adam) and (b)(6) (Boyd)

Thanks,

Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Friday, August 26, 2016 4:09 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)
Cc: Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study

Hi Adam

Thank you very much. Can you supply a contact phone number for shipping?

We will send the 0.5% Tween in saline with our compound. Everything should arrive by midweek.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Friday, August 26, 2016 10:54 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang; Barb Carter
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

EXTERNAL

Hi Jeff,

Thanks for the update. I have addressed your questions below in red.

I will be out of town September 1st-september 7th, but Boyd Yount will be available to receive the package if I'm not here. Please advise on any special storage conditions.

Would it be possible for you ship a sample for early arrival next week, with all the components, so that I can test out the resuspension of the drug?

Also, I have attached a copy of the study as we discussed. As you suggested I eliminated the time point for drug delivery 6 hours prior to infection.

Best Regards,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Thursday, August 25, 2016 6:38 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6) Barb Carter (b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

We'd like to update you on the status of the test compound shipping for the study and your formulation pre-work. We have the patent nearly completed and will be able to send the compound early next week,

targeting shipping for Tuesday 8/30 with arrival by the end of the week. Please let us know if this does not agree with your planned work schedule. We also have a few shipping questions to be certain everything goes smoothly:

- Can you advise on the planned start date for the in vivo study? If you need compound on the morning of September 6 we will try to send it earlier in the week to reduce the chance of shipping delays. I have reserved time in our BSL3 facility to initiate the experiment on Monday September 12th. Therefore, we would need to have the compound by Friday September 9th.

- Will your shipping group be receiving packages next Thurs-Fri (Sep 1-2)? If I am not here when the package arrives Boyd Yount in the lab will be available to receive the package. Please advise on any special storage conditions. I have included Boyd on this email.

- Could you please confirm the shipping address we should use for the test compound? Adam Cockrell/Boyd Yount, UNC-CH, 135 Dauer Dr., Chapel Hill, NC, 27599

- Do you have 0.5% Tween-80 in saline available for the formulation or should we plan to ship some? It would be simpler if you had some on hand as it necessitates a second package, but we're happy to arrange it if you prefer. I would prefer that the GSK group provides everything relevant to the drug.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Sunday, August 14, 2016 10:48 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Thanks Jeff,

Sounds great!

Adam

From: Jeff Pouliot [mailto (b)(6)
Sent: Saturday, August 13, 2016 5:27 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6)

Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Hi Adam,

We can send you a sample as soon as legal tells us the patent is filed. This should take roughly another week, so we should be able to get the sample to you by the end of two weeks. We will let you know if there are any unexpected delays.

Thanks for the info on dose groups. We can plan in more detail once the pilot run is complete.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Saturday, August 13, 2016 7:43 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Thanks Jeff,

Would you guys mind sending me a sample of the drug (exactly how I will receive it for the mouse studies) in the next week, or two, so that I can validate the resuspension process in my hands?

If we see efficacy with the initial study, I believe 2-3 dose groups, with a 24 hour delivery window, would be feasible.

Thanks,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Thursday, August 11, 2016 3:45 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

You should be able to formulate the compound either way. It should easily go into solution in 3-5 min with a 37C water bath. Otherwise, you can vortex and leave it on a heated plate (low setting, warm) with stirring for a couple minutes.

We suggested a 24h dosing schedule for the first study, but your counterproposal of BID dosing to have the greatest chance of efficacy was a good one. A 12-hour doing schedule for the initial study is fine.

For the follow-up study we can modify dosing to qd from 6-hours post infection, presuming the initial results are robust. We can plan this in more detail once the initial test is complete. To help us think it through, though, can you let us know if it is technically feasible to run 2-3 dose groups in parallel?

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, August 10, 2016 6:39 AM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Dear Jeff,

Please see responses to comments/questions below.

Regards,
Adam

From: Jeff Pouliot [mailto:(b)(6)
Sent: Tuesday, August 09, 2016 5:51 PM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
'Leyva-Grado, Victor' (b)(6) 'Umerah, Nina' (b)(6)
Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Dear Adam,

Thanks for the note. Your research plan nicely reflects our discussion last week. We have some information below to fill in the details and a few questions for you.

- The predosing of compound is not needed as these are direct acting antivirals. In addition, only a suboptimal amount of compound would remain at the time of infection given the short T1/2 of this compound. A therapeutic model with the first dose following infection is our preferred choice. Is this acceptable? Starting with a therapeutic dose at 6 hours post-infection sounds great.
- BID dosing starting at 6 hours post infection seems the better plan. Do you know how long robust viral replication continues in an untreated test subject? Our model exhibits robust replication through day 6 post-infection with peak replication at days 2-3.
- We recommend intranasal dosing at 1 mg/kg, 50 uL volume per mouse, at a concentration of 0.5 mg/mL. This should deliver a compound concentration at Tmax of 100x EC50 to the lung. IN sounds good.
- We will plan to ship you the compound as dry powder. We're exploring stability but until we have firm data we can't guarantee that a solution prepared here would be stable long enough for the experiment. You will need to suspend by brief sonication in a dosing solution of 0.5% Tween-80 in saline. Is this acceptable? This is acceptable, however can you please define sonication? Is a water sonicator necessary for this? Or, will vortexing suffice? Does this compound readily go into solution? The 12 hour dosing schedule is quite rigorous, especially in a BSL3, therefore I am trying to get an understanding of how much additional time I will have to spend suspending the drug prior to each 12 hour administration.

We would like also to think ahead to the second round of the experiment. Presuming the outcome shows positive results, we propose a similar experiment at successive 3-fold lower drug concentrations to clarify the PK/PD relationship. If the follow up allows more than one dose group, we would dose at 0.3 mg/kg and 0.1 mg/kg (30x and 10x EC50). Does this sound reasonable to you? A dosing experiment sounds reasonable. Provided the initial study is successful, In follow-up experiments we discussed moving to a 6-7 day time course. In doing this I will have to move to delivering the drug every 24 hours. Is this reasonable to you? Would you prefer that the initial study use a 24 hour repeated dosing time course? The 24 hour time course would begin after the initial delivery of the drug at 6 hours post-infection.

Best,

Jeff

From: Cockrell, Adam [mailto:(b)(6)
Sent: Wednesday, August 03, 2016 5:20 PM
To: Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph S; Deborah Butler; Neil Pearson; Feng Wang
Subject: RE: GSK A57 Study

EXTERNAL

Hi everyone. It was good to meet everyone in the gsk group.

In putting together the time line (attached to email) I had some additional thoughts.

1) There are two slides. The first is the initial time line that we discussed on the phone. The second slide takes into account the fact that the half-life of drug is really short, therefore we can adjust the drug delivery time line to bracket the initial viral delivery to be -6 hours and +6 hours if you guys would prefer. This would shorten the study on the back end by 6 hours, which should be of no consequence regarding the data we will capture.
2) This is just a thought, and not sure if this is a viable possibility given the half-life of the drug, but we could eliminate any confounding issues with repeated anesthetic administration if there was an option to deliver drug by the IP route. Thoughts?

That said I look forward to working with everyone.

Best Regards,
Adam

From: Jeff Pouliot [mailto(b)(6)
Sent: Wednesday, August 03, 2016 2:13 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) 'Leyva-Grado, Victor' (b)(6) (b)(6) 'Umerah, Nina' (b)(6) Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Cockrell, Adam (b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

Thank you all for the productive discussion. We look forward to working together.

I've added one person to the email list above. Please include Feng Wang on the experimental planning communications.

Best,

Jeff

Jeffrey Pouliot, Ph.D.
Investigator
Biology Host Defense DPU
R&D Infectious Disease

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
Email (b)(6)
Tel (b)(6)

gsk.com | Twitter | YouTube | Facebook | Flickr

<image002.png>

From: Stemmy, Erik (NIH/NIAID) [E] [mailto:(b)(6)
Sent: Wednesday, August 03, 2016 1:59 PM
To: 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson; Jeff Pouliot; 'Cockrell, Adam'
Subject: GSK A57 Study

EXTERNAL

Hi Everyone,
Thanks for your time today, it was a productive call. Please feel free to email directly to work out the protocol/dosing and other study details, but be sure to CC everyone on this message.

Erik

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

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