From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 30 Nov 2017 18:41:04 +0000
To: Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph; Sims, Amy C
Subject: RE: A57 Call

Thanks Adam,
I'm finally getting some time to catch up on the contract work. Going through my records, did you ever send a study report for the last two studies (rabies vector vaccine)? I have the data summary, but don't see a report. I will be filing all these reports and plan to close out the TO soon.

Thanks!
Erik

From: Cockrell, Adam (b)(6)
Sent: Thursday, October 12, 2017 10:52 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) (b)(6)
Cc: Baric, Ralph (b)(6) Sims, Amy C (b)(6)
Subject: RE: A57 Call

Hi Erik,

Please find the final report attached. I believe everything you suggested in your email is there.

Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, October 06, 2017 8:04 AM
To: Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Baric, Ralph S (b)(6) Sims, Amy C (b)(6)
Subject: RE: A57 Call

Hi Adam,
Just wanted to check in, do you have an update for completion of the final report?

Thanks!
Erik

From: Cockrell, Adam (b)(6)
Sent: Wednesday, September 06, 2017 5:24 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6) (b)(6)
Cc: Baric, Ralph (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] (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.

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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

From: Leyva-Grado, Victor
Sent: Thu, 12 Oct 2017 14:52:41 +0000
To: 'Cockrell, Adam'; Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Sims, Amy C
Subject: RE: A57 Call

Thanks Adam.

V

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Sent: Thursday, October 12, 2017 10:52 AM
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Where: Skype Meeting

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Sent: Thu, 12 Oct 2017 14:51:38 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor
Cc: Baric, Ralph; Sims, Amy C
Subject: RE: A57 Call
Attachments: Final Technical Report.docx, Standard Operating Procedures.docx

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FINAL TECHNICAL 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:
January 1, 2014- 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:
October 13, 2017

Page 011 of 775

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Page 012 of 775

Withheld pursuant to exemption

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Page 013 of 775

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Page 021 of 775

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Page 022 of 775

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From: Cockrell, Adam
Sent: Fri, 6 Oct 2017 12:35:17 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor
Cc: Baric, Ralph; Sims, Amy C
Subject: RE: A57 Call

Hi Erik,

I will try to get a copy out by the end of next week.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, October 06, 2017 8:04 AM
To: Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6)
Cc: Baric, Ralph S (b)(6) Sims, Amy C (b)(6)
Subject: RE: A57 Call

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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

From: Baric, Ralph S
Sent: Thu, 17 Aug 2017 12:58:40 +0000
To: Matthias Schnell; Stemmy, Erik (NIH/NIAID) [E]
Cc: Johnson, Reed (NIH/NIAID) [E]; Cockrell, Adam; Frieman, Matthew (b)(6)
Subject: RE: Update on Rabies Vaccine Study

I also think that this is appropriate. Ralph

From: Matthias Schnell (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: Update on Rabies Vaccine Study

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 (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 (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: Johnson, Reed (NIH/NIAID) [E]
Sent: Wed, 16 Aug 2017 00:28:58 +0000
To: Cockrell, Adam; Matthias Schnell
Cc: Baric, Ralph; Frieman, Matthew (b)(6) Stemmy, Erik (NIH/NIAID) [E]; Beall, Anne Elizabeth
Subject: RE: Update on Rabies Vaccine Study

Looks great! Thank you!

Reed

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Sent: Tuesday, August 15, 2017 5:00 PM
To: Matthias Schnell (b)(6)
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Best,
Adam
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From: Frieman, Matthew
Sent: Tue, 15 Aug 2017 21:23:35 +0000
To: Cockrell, Adam
Cc: Matthias Schnell; Baric, Ralph; Johnson, Reed (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Beall, Anne Elizabeth
Subject: Re: Update on Rabies Vaccine Study

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From: Cockrell, Adam
Sent: Fri, 28 Jul 2017 14:25:46 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Leyva-Grado, Victor
Subject: RE: A57 Call

Thanks Erik,

This is really helpful for wrapping up the final technical report.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (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 (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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 25 Jul 2017 19:27:48 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; 'Cockrell, Adam'; Leyva-Grado, Victor; Baric, Toni C
Subject: A57 Call

Hi Everyone,
Let me know if this time doesn't work. Here's a draft agenda for the call:

1. Update on final two Vx studies (UNC)
2. Final report deliverable due dates (Erik)
3. Other closeout questions (all)

Thanks!
Erik

→ Join Skype Meeting
Trouble Joining? Try Skype Web App

Join by phone

(301) 761-5000, access code: (b)(6)	(NIAID)	English (United States)
(406) 802-6000, access code:	(NIAID)	English (United States)

Find a local number

Conference ID: (b)(6) (same as access code above)
Forgot your dial-in PIN? | Help

From: Baric, Toni C
Sent: Tue, 25 Jul 2017 17:19:17 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor
Cc: Kasparian, Sevag (NIH/NIAID) [E]
Subject: RE: Scheduling A57 Call

How about 9 am? Do you want me to send a conferencing line?

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

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

From: Cockrell, Adam (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] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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: Fri, 14 Jul 2017 15:57:48 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Grant Number: 1R01AI132178 - 01 PI Name: Baric, Ralph S

Hi Erik, Thanks, very sorry about this error. My phone number is (b)(6) if you need to call. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (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 (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 (b)(4) Would it be okay for us to increase this (b)(4) 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] (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 (b)(4) 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:

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:

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 6 Jul 2017 17:27:12 +0000
To: Baric, Ralph S
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Thanks Ralph. It was good catching up with you too.

Also, you may get a request from grants management requesting updated JIT and/or updated budget pages for the partnership. When it comes through please go ahead and submit the revision you'd sent me through your business office. Along with anything else they may request.

Erik

From: Baric, Ralph S (b)(6)
Sent: Wednesday, July 05, 2017 9:35 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 5 Jul 2017 13:04:26 +0000
To: Baric, Ralph S
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Sorry, just noticed a typo should be (b)(6)

From: Baric, Ralph S (b)(6)
Sent: Wednesday, July 5, 2017 9:03 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

ok

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, July 5, 2017 9:03 AM
To: Baric, Ralph S (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
Sorry, I neglected to send my number. Can you call me at (b)(6)?

Erik

From: Baric, Ralph S (b)(6)
Sent: Wednesday, July 5, 2017 9:00 AM
To: Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Sheahan, Timothy Patrick (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Is there a number for me to call or Erik are you calling me?

From: Baric, Toni C
Sent: Friday, June 30, 2017 10:18 AM
To: Baric, Ralph S (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Sheahan, Timothy Patrick (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Dear Erik,
Ralph can make a call on Wednesday July 5 at 9 am, if this still works for you.

Best regards,
Toni

From: Baric, Ralph S
Sent: Thursday, June 29, 2017 4:22 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Sheahan, Timothy Patrick (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, Okay, toni can help set up a time next week. I also wanted some updates on the SARS-Uganda virus (b)(4) (b)(4) regarding this study proposal. Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, June 29, 2017 1:47 PM
To: Baric, Ralph S (b)(6) Sheahan, Timothy Patrick (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
Sorry for the delay. I was out of the office last week, and this week most of our group has been helping with a flu vaccine workshop here at NIAID. Since you're out this week, let's set up a time to chat next week. I could do Wednesday morning (7/5), Thursday (7/6) any time before 1pm, or Friday (7/7 between 9am and noon. Let me know if any of those times work.

Erik

From: Baric, Ralph S (b)(6)
Sent: Monday, June 19, 2017 11:57 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Sheahan, Timothy Patrick (b)(6)
Cc: Baric, Toni C (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, hope your doing well. I was wondering if we could set up a brief call to talk about a few issues centering around: 1) current status of the partnership grant-is there still potential for funding, 2) paper updates-our GS5734 paper will come out June 28th, and 3) animal models contract related issues. I'm on vacation next week but have some time this Thursday 3-4:30 block and Friday if your available. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, May 18, 2017 8:28 AM
To: Sheahan, Timothy Patrick (b)(6)
Cc: Baric, Ralph S (b)(6)

Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Thanks Tim. This is good to have. At the moment we're not sure exactly how the budget changes will impact the funding plan for these partnership awards. We'll hopefully have some news soon, so let's hold off on scheduling a call until we have a better handle on things.

Erik

From: Sheahan, Timothy Patrick (b)(6)
Sent: Wednesday, May 17, 2017 11:31 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6) Baric, Ralph (b)(6)
Subject: Re: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Dear Erik,

I hope you are doing well. Ralph and I have drafted a letter highlighting our 20% reduction in budget, reduction in experimental scope and have addressed reviewer critiques of our Partnership R01. See attached. I've also included an Excel Spreadsheet with our reduced 5 year budget details and a Word file containing the new Budget Justification.

The critiques seemed to focus on our lack of mitochondrial toxicity data and potential renal toxicity as noted in the single NHP study mentioned in our application. Our letter summarizes the voluminous mitochondrial toxicity data that Gilead has generated and additional toxicity/safety data from both NHP and healthy human adults. All data at this time point to GS-5734 being a low safety risk.

Given the current state of the NIH budget, we are curious if our reduction in budget and explanation of our application's weaknesses may change our position in funding potential? After perusing the attached information, perhaps we can all speak on the phone about our funding options in the future?

Thanks and have a great day,

Tim

Timothy Patrick Sheahan, Ph.D.
Exploring the host pathogen interface to develop new methods for viral control

Research Assistant Professor
University of North Carolina at Chapel Hill
Department of Epidemiology

Email: (b)(6)
Website: http://sph.unc.edu/adv_profile/timothy-sheahan-phd/
Twitter: https://twitter.com/timothysheahan

LinkedIn: https://www.linkedin.com/pub/tim-sheahan/4/a0b/614

On Mar 6, 2017, at 9:25 AM, Baric, Ralph S (b)(6) wrote:

Hi Erik, Hope you are doing well. Tim and I would like to have a conversation of your impressions of the review of our partnership grant this week if possible. We???re very excited about this application and our partnership with Gilead. Any insight into how competitive this application is with a score of (b)(6) would be much appreciated. Talk with you soon. Ralph

From: Baric, Ralph S
Sent: Fri, 19 May 2017 14:38:53 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Sheahan, Timothy Patrick
Subject: Re: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, Were these cuts along the lines that you were hoping to see? Thanks, ralph
From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, May 18, 2017 8:28:02 AM
To: Sheahan, Timothy Patrick
Cc: Baric, Ralph S
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Thanks Tim. This is good to have. At the moment we're not sure exactly how the budget changes will impact the funding plan for these partnership awards. We'll hopefully have some news soon, so let's hold off on scheduling a call until we have a better handle on things.

Erik

From: Sheahan, Timothy Patrick (b)(6)
Sent: Wednesday, May 17, 2017 11:31 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6) Baric, Ralph (b)(6)
Subject: Re: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

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Timothy Patrick Sheahan, Ph.D.
Exploring the host pathogen interface to develop new methods for viral control

Research Assistant Professor
University of North Carolina at Chapel Hill
Department of Epidemiology

Email: (b)(6)
Website: http://sph.unc.edu/adv_profile/timothy-sheahan-phd/
Twitter: https://twitter.com/timothysheahan
LinkedIn: https://www.linkedin.com/pub/tim-sheahan/4/a0b/614

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From: Sheahan, Timothy Patrick
Sent: Wed, 17 May 2017 15:30:41 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Sheahan, Timothy Patrick; Baric, Ralph
Subject: Re: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV
Attachments: 20170516 Sheahan Baric RFA-AI-16-034 Petition Letter.docx, 20170516 Baric Sheahan Partnership R01 Budget Reduced.xlsx, 20170516 GS5734 R01 Budget Justification Reduced.docx

Dear Erik,

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Tim

Timothy Patrick Sheahan, Ph.D.
Exploring the host pathogen interface to develop new methods for viral control

Research Assistant Professor
University of North Carolina at Chapel Hill
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Twitter: https://twitter.com/timothysheahan
LinkedIn: https://www.linkedin.com/pub/tim-sheahan/4/a0b/614

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UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL
DEPARTMENT OF EPIDEMIOLOGY F 919.966.2089
McGAVRAN-GREENBERG HALL
CAMPUS BOX 7435
CHAPEL HILL, NC 27599-7435

February 21, 2024

Dear Dr. Stemmy:

The purpose of this letter is to summarize the changes to our grant application submitted in response to the Partnerships for Countermeasures Against Select Pathogens (R01, RFA-AI-16-034). Our program titled "Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV" is intended to accelerate the preclinical development of GS-5734 and provide proof of concept data necessary for IND licensure and the origination of human clinical trial. Our application was received well in study section (b)(6) with a few noted weaknesses. Below, we summarize our 20% reduction in budget, and address the weaknesses noted by reviewers.

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

(b)(6)

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

Sincerely,

(b)(6)

Ralph S. Baric
Professor, Department of Epidemiology
University of North Carolina at Chapel Hill
(b)(6)

(b)(6)

Timothy P. Sheahan, Ph.D.
Research Assistant Professor, Department of Epidemiology
University of North Carolina at Chapel Hill
(b)(6)

Start Date: June 1, 2017-May 31, 2018			12 Cal Months				YEAR 2 6/1/18-5/31/19						
NAME	TITLE	SALARY	EFFORT	SALARY	FRINGE	TOTAL	NAME	TITLE	SALARY	EFFORT	Cal Months	SALARY	FRINGE	TOTAL
Baric, Ralph	PI	(b)(4); (b)(6)					Baric, Ralph	PI	(b)(4); (b)(6)					
Sheahan, Timothy	PI						Sheahan, Timothy	PI						
Sims, Amy	Co-Investigator						Sims, Amy	Co-Investigator						
Randell, Scott	Co-Investigator						Randell, Scott	Co-Investigator						
Schaefer, Alexandra	Staff Scientist						Schaefer, Alexand	Staff Scientist						
Kocher, Jacob	Postdoctoral Fello						Kocher, Jacob	Postdoctoral Fellow						
West, Ande	Res. Specialist						West, Ande	Res. Specialist						
Fulcher, Leslie	Res. Specialist						Fulcher, Leslie	Res. Specialist						
Scobey, Trevor	Res. Technician						Scobey, Trevor	Res. Technician						
Begley, Matthew	Technician						Begley, Matthew	Technician						
Lam, Mariam	Res. Specialist						Lam, Mariam	Res. Specialist						
Dinnon III, Kenneth	Res. Assistant Gra						Dinnon III, Kenne	Res. Assistant Grad						
TOTALS:							TOTALS:							
						0	CONSULTANTS							0
SUPPLIES							SUPPLIES							
	Cell Culture, Serum and Media	(b)(4)						Cell Culture, Serum and Media	(b)(4)					
	BSL3 gear PAPR							BSL3 gear PAPR						
	Plasticware							Plasticware						
	Enymes, kits and reagents							Enymes, kits and reagents						
	Misc.							Misc.						
	Computer Supplies	$10,000						Computer Supplies	$10,000					
	RNA Seq	(b)(4)						RNA Seq	(b)(4)					
	Primary Cells	$20,000						Primary Cells	$20,000					
	Bioplex	(b)(4)						Bioplex	(b)(4)					
Total Supplies							Total Supplies							
EQUIPMENT (Itemize) ($300,000 max)						$273,497	EQUIPMENT (Itemize)							$0
SpectraMax M3		$35,646												
Magna lysers		$11,500												
Dual Stack Incubators		$9,989												
Biosafety Cabinet		$9,620												
80C Freezer		$13,942												
Perkin Elemer Lumina Series III		$177,300												
Abaxis Hematology Analyzer		$15,500												
		$273,497												
OTHER (Itemize by category)							OTHER (Itemize by category)							
		$0												
		$0												
Publishing		$2,000					Publishing		$2,000					
Maint. Contracts		$5,000					Maint. Contracts		$5,000					
Tuition		(b)(4); (b)(6)					Tuition		(b)(4); (b)(6)					
Histology		$10,000					Histology		$10,000					
Animal Cost		$1,120					Animal Cost		$0					
Animal per diem		$604					Animal per diem		$604					
		$0												
TOTAL OTHER:		(b)(4)					TOTAL OTHER:		(b)(4)					
TRAVEL							TRAVEL							
	International	$3,000						International	$3,000					
	Domestic	$3,000				$6,000		Domestic	$3,000					$6,000
TOTAL COST:						(b)(4)	TOTAL COST:							(b)(4)
CONSORTIUM DIRECT						300000	CONSORTIUM DIRECT							300000
SUBTOTAL DIRECT COST FOR BUDGET PERIOD						(b)(4)	SUBTOTAL DIRECT COST FOR BUDGET PERIOD							(b)(4)
CONSORTIUM F & A						$0	CONSORTIUM F & A							$0
TOTAL DIRECT COSTS						(b)(4)	TOTAL DIRECT COSTS							(b)(4)
UNC-CH F & A @ 52% MOD							UNC-CH F & A @ 52% MOD							
TOTAL COST							TOTAL COST							

(b)(4)

PERSONNEL

Ralph Baric, Ph.D., Co-Principal Investigator (b)(4); (b)(6) Dr. Baric will lead and supervise the in vitro drug testing for this project and in collaboration with Dr. Sheahan manage the overall direction of this highly interactive proposal. He will interact closely with Gilead, Drs. Sheahan, Denison, Sims, Randell, Kocher, Tseng, and Schaefer and Ms. West and Mr. Scobey to ensure steady progress during the course of the proposal, evaluate results and propose alternative experiments. Drs. Baric and Sheahan will share the responsibility for interacting closely with all research staff, holding regular laboratory meetings, communicating research findings with the Denison and Tseng laboratories, writing progress reports and managing fiscal matters associated with the proposal. Given the extensive interaction and collaboration with Dr. Denison in the past, he will also lead efforts to coordinate and promote research efforts with the groups. Dr. Baric will communicate his findings with Gilead, Dr. Sheahan, Denison, Sims and Tseng on a regular basis via both conference calls and meetings between all laboratories working on this proposal.

Timothy Sheahan, Ph.D. Co-Principal Investigator (b)(4); (b)(6) Dr. Sheahan will lead and oversee the in vivo rodent model drug testing of the project and in collaboration with Dr. Baric manage the overall direction of this highly interactive proposal. He has extensive experience working at BSL3 containment and drug testing in rodent animal models. Dr. Sheahan will oversee Dr. Schaefer, Mr. Scobey and Mr. Dinnon to ensure daily progress on all in vivo rodent drug testing as well as assist with problem solving and experimental design. Drs. Sheahan and Baric will share the responsibility for overseeing all research staff, holding regular laboratory meetings, communicating research findings with Gilead, the Denison, Tseng, and Randell laboratories, writing progress reports and managing fiscal matters associated with the proposal. Dr. Sheahan will interact closely with and meet in regular scheduled conference calls/face to face meetings with Gilead, Drs. Baric, Sims, Denison, and Tseng to communicate all data and results in real time.

Amy Sims, Ph.D. Co-Investigator (b)(4); (b)(6) Dr. Sims has more than a decade experience working at BSL3 with primary human airway cells. She will work closely with Drs. Baric and Randell to design and execute all testing of SARS-CoV, MERS-CoV, and various mutant strains of each virus in primary culture models of the human lung. Drs. Sims and Randell will coordinate with Ms. Fulcher and Lam to ensure that the appropriate numbers of primary human lung cells and lung cell donors are available as needed for this project. (b)(3):42 U.S.C. § 262(a) She will report findings regularly to Drs. Baric and Sheahan as well as interfacing with Gilead to discuss all drug studies.

Scott Randell, Ph.D. Co-Investigator (b)(4); (b)(6) Dr. Randell will interact with Drs. Baric, Sheahan and Sims and Ms. Fulcher and Ms. Lam to ensure that specific project needs regarding primary cell cultures are met, establish standard operating procedures for production of culture substrates and media, and create new protocols as needed. Dr. Randell is expert in airway biology, and has extensive datasets evaluating genomic and metagenomic changes in these cultures following various perturbations. He will supervise Ms. M. Leslie Fulcher and Ms. Mariam Lam in the isolation, culture and distribution of primary cells (human airway epithelium nasal epithelium, type II pneumocytes, and alveolar macrophages) for this proposal, and oversee quality control and troubleshooting. Dr. Randell will consult with Drs. Baric and Sims on experimental design, methods, data analysis and publication, and ensure that all regulatory and reporting requirements are fulfilled for work with the primary cell isolates.

Alexandra Schaefer, Ph.D. Staff Scientist (b)(4); (b)(6) Dr Schaefer has extensive BSL3 experience in the Baric laboratory and is an expert at working with BSL3 pathogens in mice. She will work with Dr. Sheahan to design and execute the in vivo animal drug testing proposed in this project. She will also work

with Mr. Scobey and Mr. Dinnon to ensure there is steady progress on sample processing for viral titrations and histology.

Jacob Kocher, Ph.D. Postdoctoral Fellow (b)(4); (b)(6) Dr. Kocher has completed BSL3 training and is now working independently in the Baric containment laboratories. He will work with Dr. Sims to perform in vitro drug testing in primary cells. He will assist with the isolation and characterization of SARS-CoV and MERS-CoV strains containing resistance mutations as well as testing these mutants in the presence of drugs.

Ms. Ande West, Research Specialist (b)(4); (b)(6) Ms. West has extensive BSL3 experience and will assist with viral titration assays and BSL3 animal husbandry. She will also support Drs. Sheahan, Sims, Schafer, and Kocher's research efforts as needed.

Ms. M. Leslie Fulcher, Research Specialist (b)(4); (b)(6) Ms. Fulcher facilitates the day-to-day operations of the UNC Cystic Fibrosis Center Tissue Procurement and Cell Culture Core. In support of this proposal she will oversee and maintain quality control of cell isolation and culture procedures from human lung specimens and assist Drs. Baric, Sims, and Randell with the design and performance of the primary cell culture experiments.

Mr. D. Trevor Scobey, Research Technician (b)(4); (b)(6) Mr. Scobey has extensive BSL3 experience and will assist with the generation of viral stocks, viral titration assays, daily BSL3 laboratory maintenance and BSL3 animal husbandry. He will also assist with weighing and performing whole body plethysmography measurements for infected mice. Mr. Scobey will also maintain our RAG-/- breeding colony.

Mr. Matthew Begley Research Technician (b)(4); (b)(6) Mr. Matthews will be responsible for preparing tissue culture cells for viral titration and will work closely with Drs. Sims and Kocher to anticipate the needs of the project. Mr. Begley will also be responsible for purchasing supplies and supporting Drs. Sheahan, Baric, Sims, and Kocher's research efforts as needed.

Ms. Mariam Lam, Research Specialist (b)(4); (b)(6) Ms. Lam will perform cell isolation human lungs dedicated to this project per year, following specified procedures. She will maintain inventories of frozen cells, prepare reagents and custom media, order supplies and maintain laboratory records. She is fully trained and highly experienced in the culture methods and will work closely with Drs. Baric, Sims, and Randell to provide the specific number of cultured human airway cells designated in the projects.

Mr. Kenneth Dinnon III Graduate student (b)(4); (b)(6) Mr. Dinnon is a new graduate student in the Baric/Sheahan laboratories and he will work closely with Drs. Sheahan and Kocher to perform drug testing with the resistance mutants in vivo once he had completed his BSL3 training.

Fringe Benefits: Faculty/Staff: 22.883% Social Security and Retirement; $5,659/FTE Health Insurance. Post-doctoral Research Associates: 8.99% Social Security and benefits; $4,310/FTE Health Insurance. Health Insurance for Graduate Research Assistants is $3,399. All fringe rates are prorated for effort.

Dr. Baric's compensation is above the NIH salary cap, the balance of his salary will be covered by departmental funds

EQUIPMENT

Spectra Max M3 ($35,646) Funds are requested to purchase a SpectraMax M3 plate reader/luminometer for our BSL3 laboratory for the SARS-CoV and MERS-CoV nano-luciferase assays. We are currently restricted to preforming these assays in one of our laboratories and this purchase will give us additional flexibility in performing the proposed in vitro experiments in this proposal.

Magna Lysers ($11,500) Processing mouse lung tissue for viral titration assays in the BL3 requires homogenization. The Roche Magna Lyser is the best homogenizer on the market for performing homogenization in a containment laboratory. However, constantly moving the equipment into and out of the

biosafety cabinet and daily decontamination causes key parts inside the machine to break frequently. We are requesting two of Magna Lysers to replace ones that will age and break over the course of the project.

Dual Stack CO2 Incubators ($9,989) Funds are requested to replace the dual stack incubator in one of our two BSL3 laboratories. The current incubators are more than ten years old and have issues with contamination that will be solved by the copper lined units we are requesting. Incubators are required for all in vitro virus studies and viral titration assays proposed in this grant.

Biosafety cabinet ($9,620) All work in the BSL3 laboratories must occur in biological safety cabinets. Funds are requested to add an additional biological safety cabinet to our existing facilities to allow enough space to perform the proposed experiments.

-80C Freezer ($13,942) Funds are requested to store the large number of viral primary cell, mouse and non-human primate samples to be generated over the course of this project.

Perkin Elmer Lumina Series III ($177,300) The IVIS Lumina III is an in vivo imaging instrument capable of measuring bioluminescence and fluorescence in live animals. Viruses can be engineered to express luciferase whose expression can be detected by the IVIS upon injection of luciferase substrate. Not only is this technology exquisitely sensitive, but it also allows for repeated measures in live animals eliminating the need to sacrifice multiple cohorts of mice over time and the traditional evaluation of virus replication in harvested tissues. Virus replication data as measured by IVIS is also obtained instantaneously in real time eliminating the wait time associated with traditional virus titration techniques. Thus, in vivo drug efficacy testing can be done faster with far fewer animals and greater sensitivity thus fulfilling the principles of the 3Rs (reduction, refinement, replacement) that guide humane animal research. This technology will revolutionize in vivo efficacy testing.

Abaxis Hematology Analyzer ($15,500) The Vetscan HM5c is a 5-part differential hematology analyzer displaying a comprehensive 22-parameter complete blood count (CBC). Since similar blood panels are collected in routine human clinical practice, the data obtained from the HM5c is inherently translatable. Accurate measurement of CBC should prove to be a valuable biomarker of antiviral treatment success or failure since blood cell populations in humans and mice infected with SARS and MERS-CoV are modulated during infection.

SUPPLIES

Cell culture, Serum, and media (b)(4) Funds are requested for media, serum and related cell culture supplies to maintain Vero cells (titering) in culture to measure virus growth kinetics and to characterize mutant strains containing potential resistance mutations.

BSL3 protective gear (b)(4) Personnel wear powered air purifying HEPA filtered breathing apparatuses, wear tyvek suits, tyvek aprons, hoods, booties and are double gloved when entering the BSL3 facility. These materials are expensive as the HEPA, organic chemical filters and even batteries must be replaced every ~6 months, and the tyvek suits are disposable. Moreover, the PAPR (powered air breathing apparatus) are expensive and must be replaced every ~2 years from normal wear and tear, and daily contact with EPA disinfectants. Personnel use high quantities of disinfectants like ethanol, Clorox and other EPA approved disinfectants in maintaining a safe working environment in the BSL3. Personnel spray down tyvek suits, etc. with alcohol or related disinfectants in the process of deconing and leaving the BSL3 facility. All materials that leave the BSL3 must be disinfected, packaged in disinfected, sealed containers, which are disinfected prior to removal from the BSL3 facility. In addition, funds are requested to help defray costs associated with the decontamination and maintenance of the BSL3 laboratory each year.

Plasticware (b)(4) Funds are requested to purchase tissue culture flasks, dishes, pipettes, etc. used in day to day virologic and cell culture procedures as well as in growing and titering virus growth in vitro.

Enzymes, kits and reagents (b)(4) Assembling recombinant SARS-CoV and MERS-CoV requires large amounts of highly expensive restriction enzymes (e.g., BsmB1, etc.) and large amounts of DNA ligase. In addition, funds are requested for DNA markers, high quality T7 RNA polymerase, and protein and nucleic

acid markers. As sequence confirmation is critical prior to assembly of full-length genomic cDNA, funds are also requested to sequence modified genomic fragments following introduction of resistance mutations.

Miscellaneous (b)(4) Monies are requested to purchase glassware, pipettes, etc. used in day to day virologic and cell culture procedures as well as in growing, titering and characterizing virus growth in vitro. Funds are also requested to purchase chemicals, reagents, paper products, gloves, micropipetors, autoclave supplies, plastic tips, water baths, and other small equipment items that typically have short half lives in laboratory settings.

Computer supplies ($10,000/year) Funds are requested for project specific computer and software upgrades over the course of the proposal.

RNA Seq (b)(4) RNASeq will be used to identify viral mutations that arise following passage of virus in the presence of GS-5734. Funds are requested for supplies to generate amplicon library and to prepare the library for sequencing as well as for informatics support. As such, we anticipate significant sequencing costs over the duration of this proposal.

Primary Cells ($20,000/year) Funds are requested to acquire up to 8 different primary human cell types (i.e. lung-HAE, FB, MVE, AT2; immune cell-PBMC, etc.) and testing seven different drug concentrations in triplicate. We estimate a total number of 120 wells of primary cells per year at $130 a well.

BioRad Bioplex kits (b)(4) Funds are requested to purchase BioRad Bioplex kits to analyze primary cell and mouse lung cytokine profiles. This data will contribute to understanding how the immune response contributes to the mechanism of action of GS-5734.

OTHER EXPENSES

Publishing ($2,000/year) Funds are requested to cover the publication of manuscripts.

Maintenance Contracts ($5,000/year) The Baric/Sheahan laboratory covers costs for maintenance on the Dracor Water Purifiers and Steris Autoclaves used in the BSL3 laboratories. These are sophisticated instruments, so the repairs require specialists with appropriate tools and particular replacement parts. The funds requested each year will cover a portion of these two sets of maintenance contracts.

Histology ($10,000/year) Histology slides from paraformaldehyde fixed tissues are prepared on a fee for service basis at UNC Chapel Hill. Given the large number of tissues to be analyzed each year, we are requesting funds to cover tissue/slide preparation and staining costs.

Animal Costs ($1,120 Year 1 only) Funds are requested to purchase 8 $RAG^{-/-}$ mice for breeding to generate the $Ces^{-/-}$ mice in Aim 3. All other mice will be sent to us from Jackson Laboratories courtesy of Gilead.

Animal Per Diem ($604/year) We anticipate breeding/acquiring from Jackson laboratory 534 mice for Aim 1, 768 mice for Aim 2, and 390 mice for Aim 3 for a total of 1,692 mice for five years. We estimate using approximately 338 mice a year. These mice will be housed in sets of 4 and will be maintained in UNC DLAM facilities for approximately 10 days prior to being moved to the BL3. 10 days x $0.71 per cage per day x 85 cages (to house 338 mice) =$604 a year.

Tuition (b)(4); (b)(6) In accordance with University policy, funds are requested to cover tuition costs for Mr. Dinnon's graduate studies and are prorated to his effort.

Travel

Funds are requested for the PIs and co-investigators to attend annual meetings at Gilead Sciences and one to two conferences each year. ($3,000 international and $3,000 domestic per year)

INDIRECT COST

In a DHHS agreement dated May 16, 2012, the UNC F&A rate is 52% of MTDC.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 4 May 2017 19:01:33 +0000
To: Baric, Toni C
Cc: Cockrell, Adam; Baric, Ralph
Subject: RE: Study with Planet Biotech.

Thanks Toni.

Adam/Ralph, I'll leave it up to you if you'd like me to reschedule or have Adam on if he's free on Tuesday. Let me know.

Thanks!
Erik

From: Baric, Toni C (b)(6)
Sent: Thursday, May 04, 2017 2:59 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6) Keith Wycoff (b)(6)
Cc: Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Subject: RE: Study with Planet Biotech.

Hi Erik,
Ralph is not in town on Tuesday, but is available any other day next week.
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, May 04, 2017 2:55 PM
To: Cockrell, Adam; Keith Wycoff
Cc: Baric, Ralph S; 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 soluble DPP4 protein.

Best,
Adam

From: Keith Wycoff (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 (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 (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 (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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 25 Apr 2017 12:40:52 +0000
To: Baric, Ralph S
Cc: 'Baric, Toni C'
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
The partnership funding plan is starting to take shape. At the moment your application is outside of it, but I had a couple of questions for you. Let me know if you have some time to chat.

Thanks!
Erik

From: Baric, Ralph S (b)(6)
Sent: Wednesday, April 05, 2017 8:46 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, hope your doing well. We just received our critiques on the partnership grant and were wondering if we could do a call and get an update on the review process and probability of success and failure/likely timeline to decision tree's. Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 06, 2017 9:49 AM
To: Baric, Ralph S (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
I'd be happy to chat with you about your application. Unfortunately I wasn't able to hear the review since I had to juggle a few calls that day. I'm not quite sure how the final awards will be for this partnerships program, but it may be necessary to wait until both the vaccine and therapeutics review sessions have met, possibly not until early next month. I'll look into it and get back to you.

Erik

From: Baric, Ralph S (b)(6)
Sent: Monday, March 6, 2017 9:26 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6)
Subject: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, Hope you are doing well. Tim and I would like to have a conversation of your impressions of the review of our partnership grant this week if possible. We're very excited about this application and our partnership with Gilead. Any insight into how competitive this application is with a score of (b)(6) would be much appreciated. Talk with you soon. Ralph

From: Baric, Ralph S
Sent: Wed, 19 Apr 2017 13:44:43 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam
Subject: RE: Study with Planet Biotech.

Thanks adam and erik. We will proceed.

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, April 19, 2017 7:38 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Study with Planet Biotech.

Hi Adam,
That's great. Please go ahead and draft the study report and send it to Keith (cc me as well).

Thanks!
Erik

From: Cockrell, Adam (b)(6)
Sent: Tuesday, April 18, 2017 8:34 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: FW: Study with Planet Biotech.

Hi Erik,

Keith requested that I share the results with him from the Planet Biotech study. I put this in the report that was submitted to yourself and Victor last Tuesday.

Provided you are alright with us sharing this, I will separate our the data for the planet biotech study from the additional data that I included.

Best,
Adam

From: Keith Wycoff (b)(6)
Sent: Tuesday, April 18, 2017 7:33 PM
To: Cockrell, Adam (b)(6)
Subject: Re: Study with Planet Biotech.

Hi Adam,

Now that we are well into April, I'm wondering if you have any data you can share with us.

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
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Subject: Re: Study with Planet Biotech.

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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 (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: Sheahan, Timothy Patrick
Sent: Wed, 5 Apr 2017 16:40:11 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: Re: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Dear Erik,

How are things? We were wondering if you have any new information regarding our partnership grant we wrote. See the original email thread below. Any insight into what program is thinking would be greatly appreciated. Thanks again!

Tim

Timothy Patrick Sheahan, Ph.D.
Exploring the host pathogen interface to develop new methods for viral control

Research Assistant Professor
University of North Carolina at Chapel Hill
Department of Epidemiology

Email: (b)(6)
Website: http://sph.unc.edu/adv_profile/timothy-sheahan-phd/
Twitter: https://twitter.com/timothysheahan
LinkedIn: https://www.linkedin.com/pub/tim-sheahan/4/a0b/614

On Mar 6, 2017, at 9:48 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Ralph,
I'd be happy to chat with you about your application. Unfortunately I wasn't able to hear the review since I had to juggle a few calls that day. I'm not quite sure how the final awards will be for this partnerships program, but it may be necessary to wait until both the vaccine and therapeutics review sessions have met, possibly not until early next month. I'll look into it and get back to you.

Erik

From: Baric, Ralph S (b)(6)
Sent: Monday, March 6, 2017 9:26 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6)
Subject: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, Hope you are doing well. Tim and I would like to have a conversation of your impressions of the review of our partnership grant this week if possible. We're very excited about this application and our

partnership with Gilead. Any insight into how competitive this application is with a score of (b)(6) would be much appreciated. Talk with you soon. Ralph

From: Hobbs, Ron Lee
Sent: Thu, 23 Mar 2017 17:57:05 +0000
To: Normil, Carine (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Caldwell, Chandra
Subject: RE: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S

Carine,

Yesterday, we submitted requested publication compliance information to you for Grant Number: 5R01AI110700 – 03. After further review, two publications were deemed non-compliant with NIH Public Access Policy which may delay funding to the grant. Earlier today, Dr. Li (another UNC Principal Investigator) received the following email from NIH regarding temporarily waving public access compliance requirements. If possible, can you please advise us on our next course of action? Lastly, thank you again for your continued support of UNC projects.

---------- Forwarded message ----------
From: **nihms-help@ncbi.nlm.nih.gov** <nihms-help@ncbi.nlm.nih.gov>
Date: Thu, Mar 23, 2017 at 9:23 AM
Subject: NIHMS - Ticket #28045-183883 need PMCID number for two publications urgently
To: (b)(6)

Dear Dr. Li,

Thank you for contacting us regarding your NIHMS submissions. Please note that due to a contract issue, the NIHMS is processing manuscripts slower than the standard 2-3 week turnaround.

Our system is currently able to collect manuscripts and issue NIHMS identifiers (NIHMIDs). Papers with an NIHMSID that have not yet been published, or are within 3 months of publication, will retain their provisional compliance status. These delays will impact papers that were published over 3 months ago.

We are working towards a quick resolution. **In the meantime, NIH has temporarily waived public access compliance requirements as a condition of processing awards. When this situation is resolved, you will be again required to ensure full compliance for your papers.**

What you should do:

· Continue to submit manuscripts to the NIHMS as you would normally.

· Link your paper with any applicable award in My Bibliography (see https://www.ncbi.nlm.nih.gov/books/NBK53595/#mybibliography.Managing_Compliance_to_th for instructions)

· Respond to all NIHMS notifications / approval requests in a timely manner

Please contact publicaccess@nih.gov if you have any questions about funding and be sure to include your award number. If you have further questions about your paper or the NIHMS, please reply to this email.

We thank you for your patience and your support of the public access policy. Your work is important to us. We look forward to making it publicly available on PubMed Central.

Kindest regards,
Kathryn
Kathryn O'Neill
User Support, contractor

NIHMS | NCBI | NLM | NIH

Ticket Information:

Summary:	need PMCID number for two publications urgently
Original message:	Original Email Information From: (b)(6) To: nihms-help@ncbi.nlm.nih.gov Cc: _____ Hi, We will need the PMCID number for two publications urgently. Without the PMCID number, NIH won't release funding for our grant. The deadline for getting the PMCID number is Tuesday. The two publications are: (1) Li F. https://www.ncbi.nlm.nih.gov/pubmed/27578435 Annu Rev Virol. 2016 Sep 29;3(1):237-261. PubMed PMID: 27578435. NIHMS ID: http://www.nihms.nih.gov/db/sub.cgi?mid=861907 (2) Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. https://www.ncbi.nlm.nih.gov/pubmed/27936982 Expert Opin Ther Targets. 2017 Feb;21(2):131-143. doi: 10.1080/14728222.2017.1271415. PubMed PMID: 27936982. NIHMS ID: http://www.nihms.nih.gov/db/sub.cgi?mid=861913 I would appreciate your help very much! Fang Li -- ********** Fang Li, Ph.D. Associate Professor Department of Pharmacology University of Minnesota Twin Cities (b)(6) http://www.msi.umn.edu/%7Elifang **********
Original Email To:	nihms-help@ncbi.nlm.nih.gov
CC'ed Customers list:	

--
****
Fang Li, Ph.D.
Associate Professor

Department of Pharmacology
University of Minnesota Twin Cities
(b)(6)
http://www.msi.umn.edu/~lifang
****

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)

From: Normil, Carine (NIH/NIAID) [C] (b)(6)
Sent: Wednesday, March 22, 2017 4:20 PM
To: Hobbs, Ron Lee (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Caldwell, Chandra (b)(6)
Subject: RE: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S
Importance: High

Thank you for submitting the information I requested for Grant Number: 5R01AI110700 – 03. The two publications that are non-compliant with NIH Public Access Policy and will need to be brought to compliance. *Until* these publications are brought to compliance as evidenced by a PMCID number, funding to this grant will be delayed.

Please let me know the status of the publication compliance by Tuesday, March 28, 2017.

If you have questions about the Policy, feel free to contact me via email at (b)(6) or send a note to PublicAccess@nih.gov.

Best,
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 (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)

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: Hobbs, Ron Lee
Sent: Wed, 22 Mar 2017 18:37:51 +0000
To: Normil, Carine (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Caldwell, Chandra
Subject: FW: Publication Compliance for Grant Number: 5R01AI110700 - 03 PI Name: Baric, Ralph S
Attachments: Baric Response_R01AI110700-03.pdf

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)

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

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- 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

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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

UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

DEPARTMENT OF EPIDEMIOLOGY F 919.966.2089
McGAVRAN-GREENBERG HALL
CAMPUS BOX 7435
CHAPEL HILL, NC 27599-7435

March 22, 2017

Carine Normil
Grants Management Specialist (Contractor)
Grants Management Program, DEA, NIAID, NIH, HHS
5601 fishers Lane, Rm 4G46,
Bethesda , Maryland 20892

RE: Publication Compliance for Grant Number: 5R01AI110700-03, PI Name: Baric, Ralph S

Dear Ms. Normil,

Per the email notice you sent on March 17, the updated other support document for Dr. Fang Li including his level of effort is attached. Also, I have attached the PDF file from MyNCBI in regards to the following three publications:

- Structure, Function, and Evolution of Coronavirus Spike Proteins. Li F. Annu Rev Virol. 2016 Sep 29;3(1):237-261.PMID: 27578435 – Undergoing NIHMS submission
- 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 – Undergoing NIHMS submission
- 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 – Publication is compliant per the attached documentation

If you have any other additional questions, please let me know.

Sincerely,

(b)(6)

Ralph Baric, PhD
Professor of Epidemiology
Principal Investigator of Grant No: R01AI110700-03

Other Support

LI, FANG

Active

National Institutes of Health 04/01/15 – 03/31/20
R01AI110700 Annual Direct Costs $245,000 (b)(4); (b)(6)
Role: Co-Principal Investigator (contact Co-PI: Ralph Baric, University of North Carolina)
Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis
Goal: This research investigates genetic pathways regulating MERS coronavirus cross species transmission and receptor homolog usage, establishes robust animal models of human disease, and discovers critical reagents for therapeutic and vaccine testing.

National Institutes of Health 06/07/16 – 05/31/21
R01AI089728 Annual Direct Costs $217,800 (b)(4); (b)(6)
Role: Principal Investigator
Receptor recognition and cell entry of coronaviruses
Goal: This research investigates how coronaviruses recognize their receptors and how they interact with receptors from different hosts. It explores novel principles governing viral evolution, virus-receptor interactions, viral host ranges and cross-species infections, and may lead to new approaches in the prevention and treatment of coronavirus infections in humans and other animals.

AHC Faculty Research Development Grant, 09/01/16 – 08/31/18
University of Minnesota Annual Direct Costs $30,000 (b)(4); (b)(6)
Role: Co Principal Investigator (contact PI: Robert Geraghty, University of Minnesota)
Development of biological and structural approaches to Zika virus drug discovery
Goal: This research develops and implements the tools necessary to identify small molecule inhibitors of Zika virus, and also elucidates the structure/function of the viral RNA-dependent RNA polymerase.

Publications Reported for this Reporting Period

NIH Public Access Compliance	Citation
Non-compliant	Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. MERS-CoV spike protein: a key target for antivirals. Expert Opin Ther Targets. 2017 Feb;21(2):131-143. doi: 10.1080/14728222.2017.1271415. PubMed PMID: 27936982.
Complete	Tai W, Wang Y, Fett CA, Zhao G, Li F, Perlman S, Jiang S, Zhou Y, Du L. 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. J Virol. 2016 Dec 16;91(1). pii: e01651-16. PubMed PMID: 27795425; PubMed Central PMCID: PMC5165220.
Non-compliant	Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016 Sep 29;3(1):237-261. PubMed PMID: 27578435.

Manuscript Summary

Status	Undergoing NIHMS submission review and file preparation
Manuscript Title	Structure, Function, and Evolution of Coronavirus Spike Proteins.
Journal Title	Annual review of virology
NIHMSID	861907
PDF Receipt	PDF Receipt [2017-03-21 15:42:56, 5,416.4 KB]
Release Delay	Set to release to PubMed Central **immediately** after publication in the journal.
Reviewer	Fang Li

Manuscript Summary

Status	Undergoing NIHMS submission review and file preparation
Manuscript Title	MERS-CoV spike protein: a key target for antivirals.
Journal Title	Expert opinion on therapeutic targets
NIHMSID	861913
PDF Receipt	PDF Receipt [2017-03-21 15:49:30, 1,399.9 KB]
Release Delay	Set to release to PubMed Central **immediately** after publication in the journal.
Reviewer	Fang Li

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 9 Mar 2017 13:25:49 +0000
To: Baric, Ralph S
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
No word yet on the partnerships awards, but I wanted to share with you a new BAA in case you hadn't seen it yet. It was announced yesterday under solicitation number HHS-NIH-NIAID-BAA2017-1, for development of therapeutics and vaccines for biodefense and emerging infectious diseases. More info can be found at the link below, and proposals would be due for the DMID areas in July.

Best,
Erik

https://www.fbo.gov/spg/HHS/NIH/NIAID/HHS-NIH-NIAID-BAA2017-1/listing.html

---

From: Baric, Ralph S (b)(6)
Sent: Monday, March 06, 2017 10:29 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6)
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erk, Thanks for helping out. Look forward to talking with you sometime soon. Keep us informed.
Thanks, Ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 06, 2017 9:49 AM
To: Baric, Ralph S
Cc: Sheahan, Timothy Patrick
Subject: RE: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Ralph,
I'd be happy to chat with you about your application. Unfortunately I wasn't able to hear the review since I had to juggle a few calls that day. I'm not quite sure how the final awards will be for this partnerships program, but it may be necessary to wait until both the vaccine and therapeutics review sessions have met, possibly not until early next month. I'll look into it and get back to you.

Erik

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To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Sheahan, Timothy Patrick (b)(6)

Subject: 1 R01 AI132178-01, entitled Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV

Hi Erik, Hope you are doing well. Tim and I would like to have a conversation of your impressions of the review of our partnership grant this week if possible. We're very excited about this application and our partnership with Gilead. Any insight into how competitive this application is with a score of (b)(6) would be much appreciated. Talk with you soon. Ralph

From: Baric, Toni C
Sent: Mon, 6 Mar 2017 20:13:58 +0000
To: Spiro, David (NIH/FIC) [E]; Stemmy, Erik (NIH/NIAID) [E]; Sims, Amy C; 'Vivien Dugan (b)(6)
Subject: Canceled: UNC-NIAID Monthly Conference call
Importance: High

This call has been cancelled.

Phone: 1-800-747-5150
Passcode: (b)(6)

Best regards,
Toni

From: Cockrell, Adam
Sent: Mon, 20 Feb 2017 15:17:45 +0000
To: Keith Wycoff
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Baric, Ralph
Subject: RE: Study with Planet Biotech.

Hi Keith,

I forgot to mention that with the 400ug/mouse dose we will need ~14mg for two doses in 15 mice. This will provide enough extra for syringe dead volumes, etc…

Best,
Adam

From: Keith Wycoff (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>

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 17 Feb 2017 14:01:00 +0000
To: Cockrell, Adam
Cc: Baric, Ralph; Leyva-Grado, Victor
Subject: FW: timeline for testing anti-MERS therapeutic in MERS mouse model

Hi Adam,
Can you send me the shipping address for Keith? Also, do you have an idea when his study will begin?

Thanks!
Erik

From: Keith Wycoff (b)(6)
Sent: Thursday, February 16, 2017 4:25 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Re: timeline for testing anti-MERS therapeutic in MERS mouse model

Hi Erik,

I'm writing to see if you have an update on the timeline for the MERS mouse testing. I sent you the completed SRF on January 31. Any news?

Thanks,
Keith

On Jan 31, 2017, at 11:19 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Keith,
Attached please find a Service Request Form (SRF) to cover the study we discussed with our contractors at UNC. Please complete the highlighted areas, and confirm that the study design is still accurate. Please also include the dosing information in the study description area so all the information is together. Once that's complete, please sign and date the signature block on the first page, and convert the document to a pdf.

External Requestors in NIAID's Antiviral Screening Program are required to register and submit requests at DMID's "Preclinical Services for Researchers Site" (https://dmidservices.niaid.nih.gov/). Please let me know if you are not already registered, and I will send an email invitation with instructions for registering on the website. If you are already registered, you only need to submit your request. When you access the site to create your request please be sure the title is descriptive and includes a reference to the compound(s) being screened. You will also be asked to upload a Description and Justification document. Please upload the signed version of the approved SRF to fulfill that request. Be sure to select me as the Program Officer so I'll be notified when you've completed the request.

Let me know if you have any questions or any trouble with the site.

Erik

From: Keith Wycoff (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 (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 (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

<Planet Biotechnology In vivo SRF 1-31-2017.docx>

From: Cockrell, Adam
Sent: Mon, 6 Feb 2017 15:00:05 +0000
To: Frieman, Matthew
Cc: Matthias Schnell; Stemmy, Erik (NIH/NIAID) [E]; Johnson, Reed (NIH/NIAID) [E]; Baric, Ralph
Subject: RE: Rabies vaccine protocols

Mice will be about 16 weeks. Since they come from our own colony the ages will vary. Probably more like 12-16 weeks depending on what is available. Once I have a better idea of start date I will be able to allocate mice.

We just did an experiment with mice around 22 weeks of age (all females) and they responded as I would have anticipated from previous experiments.

Adam

From: Frieman, Matthew (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 (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: Matthias Schnell
Sent: Mon, 6 Feb 2017 14:50:43 +0000
To: Cockrell, Adam
Cc: Matthias Schnell; Stemmy, Erik (NIH/NIAID) [E]; Frieman, Matthew (b)(6) Johnson, Reed (NIH/NIAID) [E]; Baric, Ralph
Subject: Re: Rabies vaccine protocols

Sound good to me lets see if everybody else agrees.

Matthias J. Schnell, Ph.D.
Professor and Chair Department of Microbiology and Immunology
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email:(b)(6)
phone: (b)(6)
fax: 215-923-9248
lab phone: (b)(6)

On Feb 6, 2017, at 09:44, Cockrell, Adam (b)(6) wrote:

My mistake copy-paste error. Forgot to delete day 7 on the second one.

Sounds good. Will only include one control group as you suggest.

From: Matthias Schnell (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)
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233 South 10th St, 531 BLSB
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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>

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 3 Feb 2017 16:03:48 +0000
To: Leyva-Grado, Victor
Cc: Baric, Ralph; Cockrell, Adam; Umerah, Nina
Subject: RE: MERS Vx Call with UNC

Hi Victor,
No problem, we mainly discussed using the final 2 slots for the rabies virus vector MERS vaccine. One issue that did come up was that Adam and Ralph may need to change the proposed end date for the NCE, given the amount of time needed for the prime/boost strategies for the vaccine. So we will likely need to extend the end data by a couple of months. Do you think it would be possible to get that submitted today? We're less than 30 days from the end of the performance period, so we really need to get this rolling with OA.

Thanks!
Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Friday, February 03, 2017 10:48 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: MERS Vx Call with UNC

Hi Erik,

How are you doing?

I just want to apologize because I was not able to make it this morning to the conference call.

Is there anything from our side we can do to help? I know Nina is looking into the NCE document, have you received it yet?

Once again my apologies.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, January 31, 2017 7:20 AM
To: Frieman, Matthew; Baric, Toni C
Cc: Baric, Ralph; 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 (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] (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: Frieman, Matthew
Sent: Tue, 31 Jan 2017 14:00:28 +0000
To: Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Cockrell, Adam; Leyva-Grado, Victor; Johnson, Reed (NIH/NIAID) [E]
Subject: Re: MERS Vx Call with UNC

Works for me too.

Matt

On Jan 31, 2017, at 8:27 AM, Baric, Toni C (b)(6) wrote:

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

From: Stemmy, Erik (NIH/NIAID) [E] (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

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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: Tue, 31 Jan 2017 13:27:55 +0000
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; Frieman, Matthew
Cc: Baric, Ralph; Leyva-Grado, Victor; Johnson, Reed (NIH/NIAID) [E]
Subject: RE: MERS Vx Call with UNC

Yes

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

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To: Frieman, Matthew; Baric, Toni C
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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: Johnson, Reed (NIH/NIAID) [E]
Sent: Tue, 31 Jan 2017 07:24:17 -0500
To: Stemmy, Erik (NIH/NIAID) [E]; Frieman, Matthew; Baric, Toni C
Cc: Baric, Ralph; Cockrell, Adam; Leyva-Grado, Victor
Subject: RE: MERS Vx Call with UNC

Hi Everyone,

Anytime before 10:00 works for me as well.

Reed

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, January 31, 2017 7:20 AM
To: Frieman, Matthew (b)(6) Baric, Toni C (b)(6)
Cc: Baric, Ralph (b)(6) Cockrell, Adam (b)(6) Leyva-Grado, Victor (b)(6) Johnson, Reed (NIH/NIAID) [E] (b)(6)
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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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 26 Jan 2017 22:02:27 +0000
To: Leyva-Grado, Victor; 'Baric, Toni C'; Cockrell, Adam; Baric, Ralph
Cc: Umerah, Nina
Subject: RE: Rabies vaccine for MERS

Thanks! I'll reach out to the submitters and get back to you all.

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Thursday, January 26, 2017 3:57 PM
To: 'Baric, Toni C' (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6) Baric, Ralph (b)(6)
Cc: Umerah, Nina (b)(6)
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: Cockrell, Adam
Sent: Thu, 26 Jan 2017 21:38:45 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Cc: Baric, Toni C; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Rabies vaccine for MERS

I am good for any of those times.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, January 26, 2017 4:33 PM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6)
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(b)(6) Umerah, Nina (b)(6)
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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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 24 Jan 2017 16:55:24 +0000
To: Sims, Amy C; (b)(6) PETERPALESE; Baric, Ralph; (b)(6)
Subject: RE: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request

Thank you Amy!

Erik

From: Sims, Amy C (b)(6)
Sent: Tuesday, January 24, 2017 11:48 AM
To: (b)(6) PETERPALESE (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (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: SubContractAgreements@mountsinai.org

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: Sims, Amy C
Sent: Tue, 24 Jan 2017 16:48:25 +0000
To: (b)(6) PETERPALESE; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6)
Subject: Fwd: MSSM No. 0258-3962 Contract #HHSN272201000019I; NIH Task Order No. A57 HHSN27200003; Option 2 NCE Request
Attachments: MSSM No. 0258-3962 NCE Request.pdf, ATT00001.htm

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)

UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL
DEPARTMENT OF EPIDEMIOLOGY F 919.966.2089
McGAVRAN-GREENBERG HALL
CAMPUS BOX 7435
CHAPEL HILL, NC 27599-7435

January 17, 2017

Peter Palese, Ph.D.
Horace W. Goldsmith Professor and Chair
Department of Microbiology
Professor, Department of Medicine
Mount Sinai School of Medicine
1 Gustave Levy Pl.
New York, New York 10029-6574

Re: MSSM No. 0258-3962/HHSN272201000019I
NIH Task Order No A57/HSN27200003
Option 2 – Evaluation of Candidate Medical Countermeasures
Mouse Model for Evaluation of Medical Countermeasures against Middle East Respiratory Syndrome (MERS-CoV)

Dear Dr. Palese:

We would like to formally request an additional 5 months of no cost extension until July 31, 2017, under Option Period 2 of the referenced subcontract. Option Period 2 of the program is currently scheduled to end on February 28, 2017. This extension is requested to allow us additional time due to unexpected toxicity with the last batch of compounds, which led to unanticipated time spent trouble shooting with the provider. It was finally decided that other compounds should be evaluated instead of the originally proposed set. The remaining experiments in Option Period 2 will involve 2 therapeutic compounds and one vaccine study and these are slated to begin in April 2017 allowing time for IACUC approvals. This extension will also afford us time to complete the data analyses, determine virus titers in treated and control animals, to evaluate pathologic changes in the lung tissues and to write a final report. Following is an anticipated timeline of the option period if the no-cost extension is approved:

January 2017 through May 2017 breeding of animals
February 2017 through March 2017 IACUC approvals for new compounds
April 2017 through May 2017 testing of compounds A and B
June 2017 through July 2017 vaccine trial, wrap up and data analysis

Costs during the extension period would include effort by Ralph Baric and others in his lab including Adam Cockrell and Trevor Scobey, animal per diem and lab supplies. We anticipate having sufficient funds remaining under the current obligation. Therefore no additional funds are required. A budget and budget justification are attached for the no-cost extension period based on the estimated unobligated funds we believe will be available.

Please let us know if you require any additional information or have any questions. Thank you for your consideration of this request.

Sincerely,

(b)(6)

Ralph S. Baric
Professor
Department of Epidemiology

(b)(6)

Terry Magnuson
Vice Chancellor for Research

SUMMARY OF PROPOSED COSTS

University of North Carolina at Chapel Hill

			OPTION PERIOD I Extension		
*** Period (dates)			3/1/2017 Through 7/31/2017		
Direct Labor - Percent of Effort			$16,030		
Fringe Benefits - Percent of Effort			3,279		
Direct Labor - Hourly			0		
Fringe Benefits - Hourly			0		
Total Direct Labor & Fringe Benefits			$19,309		
☆ **Overhead**	0%	0%	$0	0%	0%
Materials and Supplies			$8,849		
Professional Travel			0		
Equipment			0		
Consultants			0		
Other Direct Costs			2,540		
Patient Care Costs			0		
Subcontracts			0		
Total Other Direct Costs			$11,389		
Subtotal: Direct Labor, Fringe Benefits, Overhead , & Other Directs			$30,697		
Exclusion(s) From Base For G&A			0		
Adjusted Base for G&A			$30,697		
☆ **G&A**	48%	48%	14,735	48%	48%
Total Proposed Cost Excluding Fee			45,432		
Proposed Fee/Profit	0%	0%	0	0%	0%
Total Proposed Cost Plus Fee/Profit			$45,432		

Budget Justification Baric Animal Models for MERS-CoV Option Period II No Cost Extension Through July 31, 2017

Personnel calendar months effort for the base period is based on a 5 month period.

Ralph S. Baric, PhD, Principal Investigator (b)(4); (b)(6) Dr. Baric will supervise the overall direction of the project. He will interact closely with the other co-investigators and research staff to ensure steady progress during the course of the proposal, evaluate results and propose alternative experiments. He also directs ~1,000 sq. ft. of BSL3 space in the School of Public Health, including animal satellite facilities that will be used for all of the proposed studies. Dr. Baric will be responsible for interacting closely with all research staff, holding regular laboratory meetings, communicating research findings between project staff, writing progress reports and managing fiscal matters associated with the project. Dr. Baric will communicate his findings with other program faculty on a regular basis and hold monthly conference calls with NIH to discuss the progress of the project. He will design, edit and submit manuscripts associated with this work.

Adam Cockrell, PhD, Postdoctoral Fellow. (b)(6) Dr. Cockrell has several years experience at BSL3 and has established the lethal mouse model for MERS-CoV infection that will be tested. He will use the Buxco Plethysmography System to assess the impact of highly pathogenic respiratory virus infection on lung function in the presence or absence of therapeutics. Dr. Cockrell will conduct the in vivo animal experiments proposed in the application and he will assist in the production of reports and presentations to NIH and program participants. He will oversee Mr. Yount and Mr. Scobey in conducting in vivo pathogenesis experiments during the duration of the grant. He will report his results to Dr. Baric at regular intervals.

Mr. D. Trevor Scobey, Research Technician (b)(6) Mr. Scobey has over 5 years experience working at BSL3 and was a major contributor in isolating the MERS-CoV infectious clone. As such he is well trained to conduct detailed virologic, immunologic and physiologic testing of MERS-CoV infected mice. He will also be responsible for purchasing supplies, maintaining stocks in the BSL3, and supporting Dr. Cockrell's research efforts. He will report his results to Dr. Baric at regular intervals.

FRINGE BENEFITS:

In accordance with the attached memo, UNC benefits, excluding health insurance are calculated at a composite rate of 22.741% of requested salary. The composite rate includes, but is not limited to, retirement, Social Security, disability, etc. An annual rate of $5,471 prorated based on FTE is budgeted per person to cover health insurance.

SUPPLIES:

Protective Gear and Disinfectants (Items #38-51 under Summary of Materials & Supplies). PAPRs, tyvek suits, gloves and other protective gear **($3,667)**. Personnel wear powered air purifying HEPA filtered breathing apparatuses, tyvek suits, tyvek aprons, hoods, booties and are double gloved when entering the BSL3 facility. These materials are expensive as the HEPA, organic chemical filters and even batteries must be replaced every ~6 months, and the tyvek suits/booties/gloves are disposable. Moreover, the PAPRs are expensive and must be replaced due to normal wear and tear, and daily contact with EPA disinfectants. Personnel use high quantities of EPA approved disinfectants like ethanol alcohol, Cidecon and other EPA approved disinfectants in maintaining a safe working environment in the BSL3. Personnel spray down tyvek suits, etc. with alcohol in the process of deconing and leaving the BSL3 facility. All materials that leave the BSL3 must be

disinfected, packaged in sealed containers, which are disinfected again prior to removal from the BSL3 facility.

Cell Culture Media, Serum, and Supplies (Items # 7, 16-22 under Summary of Materials & Supplies) **($2,384).** Funds are requested for media to maintain VeroE6 cells for determining viral replication titers. The contract is cell culture heavy, requiring considerable supplies to keep up with the workload. In particular, fetal clone II serum, 1X and 2X DMEM are expensive but provide excellent conditions for virus growth and plaque assay conditions.

Plasticware (Items #23-36 under Summary of Materials & Supplies) **($2,213).** Funds are requested for filtered pipette tips, tissue culture plates, pipettes, aerosol tips, plastic pipettes, conical tubes, eppendorf tubes, etc. used commonly in normal BSL2/ BSL3 laboratory settings.

Flow Cytometry Services (Item #72 under Summary of Materials and Supplies) **($585)**. Assessment of MERS-CoV-induced lung pathology will require identifying inflammatory cell infiltrates in a subset of MERS-CoV challenged mice, which is performed on a fee for service basis at UNC.

OTHER DIRECT COSTS

Animal per diem housing costs (Other direct costs**) ($1,300).** Animal housing costs are $0.65/day, usually housing 4 animals/cage. We anticipate housing 104 animals in the Option Period in University Facilities for up to 77 days prior to moving them into the BSL-3 laboratory for MERS-CoV challenge.

Histology Services. ($1,240) Assessment of MERS-CoV-induced lung pathology will require preparation of histology slides, which are performed on a fee for service basis at UNC.

INDIRECT COSTS:

Indirect costs are budgeted at a rate of 48% of MTDC in accordance with the University's cost rate agreement dated November 6, 2007.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 17 Jan 2017 19:14:49 +0000
To: Sims, Amy C
Cc: Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor; Nina Umerah
Subject: RE: UNC A57 Second NCE for Option Period II
Attachments: Rhabdo.MERSVax.NIAIDSheet.docx, NIAID DPP4 FC Product Development Information Sheet from Requestors.docx

Thank you Amy!

Adam, I've attached the information sheets for the two new products (decoy DPP4 and vaccine). Please let me know if there is enough information there for your IACUC review. If not we can get additional details for you. As usual, please consider the information sheets as confidential, for internal TO A57 use only.

Thanks!
Erik

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

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: Sims, Amy C (b)(6)
Sent: Tuesday, January 17, 2017 2:08 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Cockrell, Adam (b)(6) Baric, Ralph (b)(6) Leyva-Grado,

Victor (b)(6) Nina Umerah (b)(6) Jean Lim
(b)(6) Musty, Kelly S (b)(6)
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)

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 (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] (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 (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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.

****

NIAID Respiratory Disease Branch
Product Development
Information Sheet from Requestors

PLEASE PROVIDE THE FOLLOWING INFORMATION:

NAME: Reed Johnson
INSTITUTION: IRF/NIAID
ADDRESS: Ft Detrick, MD
TEL#:
FAX#:
E-MAIL: (b)(6)

NAME: Matthew Frieman
INSTITUTION: University of Maryland School of Medicine
ADDRESS: 685 West Baltimore St, Room 380, Baltimore MD 21201
TEL#: (b)(6)
FAX#: 410 706 6970
E-MAIL: (b)(6)

NAME: Matthias J. Schnell
INSTITUTION: Thomas Jefferson University
ADDRESS: 233 South 10th St, 531 BLSB Philadelphia PA, 19107
TEL#: (b)(6)
FAX#: 215-923-9248
E-MAIL: (b)(6)

If applicable, provide:
NIH GRANT OR CONTRACT:
GRANT OR CONTRACT NUMBER:
GRANT OR CONTRACT START DATE:
GRANT OR CONTRACT END DATE:

NIH GRANT OR CONTRACT FUNDING IS NOT A REQUIREMENT FOR ACCESS TO THESE RESOURCES

1. **SERVICE REQUESTED:**

Evaluation of a RABV-MERS bivalent vaccine (BNSP333-S1) in available MERS-CoV mouse model

2. GENERAL PRODUCT INFORMATION (this information will be kept confidential)

Please be as complete and succinct as possible; indicate if the information is not available or not applicable to your request. References may be cited

a. Candidate name: RABV-MERS bivalent vaccine (BNSP333-S1)

b. Manufacturer/developer: NIAID-DIR, Thomas Jefferson University, University of Maryland

c. Product type (vaccine, adjuvant, therapeutic) and description (e.g. whole cell derived, subunit, vector based, etc.): Vaccine

d. Target: MERS-CoV

e. Candidate composition or active ingredient (e.g. DNA vaccine, recombinant vaccine, enzyme/neuraminidase inhibitor, etc.): Inactivated recombinant RABV vaccine vector virions containing MERS-CoV S1.

f. Formulation (storage buffer, pH, salt conditions, etc.): Sucrose purified inactivated viral particles in 1 x PBS

g. Is the manufacturing process fully developed? (describe the current process):

The manufacturing process is currently developed for a similar vaccine for EBOV, SUDV and MARV by IDT.

The provided material is a laboratory produced vaccine produce as described below:

For large-scale purification of virus particles, 2-stack cell culture chambers were seeded with Vero cells (CCL-81, ATCC) in DMEM supplemented with 5% FCS. Prior to adding virus, the cells were washed with phosphate buffered saline (PBS; Corning, Manassas, VA) and then infected at low multiplicity of infection (0.01-0.05) in serum-free medium at 34 °C. Supernatant was collected at 3- to 4-day intervals and replaced with fresh serum-free medium. Cell culture media were centrifuged at low speed for 10 min to remove debris and filtered through 0.45 μm PES membrane filters (Nalgene). The filtered supernatant was then concentrated by tangential flow filtration in mPES hollow fiber cartridges (Spectrum Labs) followed by ultracentrifugation on 20% sucrose cushions in a SW32Ti rotor (Beckman) for 2 h at 25000 rpm (106000 g). Pelleted virus was resuspended in PBS and protein content measured using a BCA Protein Assay Kit (PIERCE) according to the manufacturers' instructions. Following addition of PBS to adjust the protein concentration to 1 mg/ml, beta-Propriolactone was added at a concentration of 0.05% (v/v) to inactivate virus. After overnight incubation at 4 °C, inactivated particles were incubated at 37 °C for 30 min and subsequently frozen in aliquots at −80 °C. To verify complete inactivation/absence of infectious

virus, 10 µg of inactivated virus was inoculated in a flask seeded with BSR cells (Baby hamster kidney cell clone). Four days after inoculation 1/10th of supernatant was passaged on fresh BSR cells. Four days post inoculation, the cells were fixed and stained with FITC-labeled monoclonal antibody against RABV nucleoprotein (Fujirebio).

h. Is GMP material available? No

i. Amount of candidate available for the requested studies: about 1 mg

j. Stability of candidate; storage and handling conditions: Store at -80^{0}C, stable at 4^{0}C for at least 24 hours

k. Current other support for product development including grants, contracts and private sources of funding: Not for this vaccine but for a similar vaccine for filoviruses. The vaccine platform is at advance development (preclinical). 2013/02/01-2018/01/3, R01 AI105204-03, National Institute of Allergy and Infectious Diseases (NIAID), Schnell, Matthias Johannes (PI), Preclinical characterization of a multivalent killed Filovirus/Rabies vaccine

3. PROVIDE A CONCISE SCIENTIFIC JUSTIFICATION FOR USE OF THIS CANDIDATE (Include a discussion of the mode of action, if applicable):

The RABV-MERS CoV bivalent vaccine has demonstrated efficacy, by viral titer reduction, in the human DPP4 adenovirus transduced murine model of MERS. Further evaluation is warranted in an improved murine model to demonstrate efficacy by reduction of viral titer and reduced lung pathology.

4. PROVIDE A SUMMARY OF EXISTING DATA:

Preclinical data

Provide a brief summary of *in vitro* and *in vivo* experimental results relevant to the candidate including but not limited to safety, immunogenicity, efficacy, pharmacokinetic and pharmacodynamic studies. Indicate if data are not available.

The RABV-MERS candidate have proven immunogenic and safe in murine models.

Efficacy data

Provide a summary of efficacy data to date. Indicate if data are not available.

The RABV-MERS vaccine proved efficacious in the human Ad4 mouse transduction model.

Toxicity data

Provide a summary of existing toxicity data including any IND enabling studies. Identify the cell culture system(s) and animal model(s) and provide results of testing. Include such

information as dose and/or formulations tested, dose schedule, concentration/titer, negative and positive controls, performance lab results, and other relevant details. Indicate if data are not available.
Data not available.

5. DEVELOPMENT PLAN

Please indicate how data obtained via DMID/NIAD contract resources fit into the overall development plan of your product.
In the absence of other animal models that recapitulate MERS, additional experiments to address efficacy in suitable murine models are warranted to further pre-clinical development.
In addition please address:

- Have you filed a patent request? YES, patent filed under NIAID
- Do you have IP rights? If so, please provide the U.S. patent#
- If results warrant, do you plan to pursue licensure of the candidate?

6. REFERENCES

Please list references providing relevant background information on your product. References from peer reviewed publications are preferred.

Wirblich, C., Coleman, C.M., Kurup, D., Shaik, N., Abraham, T.S., Jahrling P.B., Hensley, L.E., Johnson, R.F., Frieman, M.B., Schnell, M.J. (2016) One-Health: A Safe, Efficient Dual-use Vaccine for Humans and Animals against MERS-CoV and Rabies. The Journal of Virology (Accepted manuscript posted online 2 November 2016, doi: 10.1128/JVI.02040-16)

http://jvi.asm.org/content/early/2016/10/27/JVI.02040-16.long

NIAID Respiratory Disease Branch
Product Development
Information Sheet from Requestors

PLEASE PROVIDE THE FOLLOWING INFORMATION:

NAME: **Keith Wycoff**
INSTITUTION: **Planet Biotechnology Inc**
ADDRESS: **20980 Corsair Blvd, Hayward, CA 94545**
TEL#: (b)(6)
FAX#: **(510) 887-1623**
E-MAIL: (b)(6)

If applicable, provide:
NIH GRANT OR CONTRACT: **R44 AI114023**
GRANT OR CONTRACT NUMBER:
GRANT OR CONTRACT START DATE: **06/01/2014**
GRANT OR CONTRACT END DATE: **12/31/2016**

NIH GRANT OR CONTRACT FUNDING IS NOT A REQUIREMENT FOR ACCESS TO THESE RESOURCES

1. SERVICE REQUESTED:

Screening of lead compounds in an adenovirus vectored model of MERS, or, if possible, a non-human primate model of MERS

2. GENERAL PRODUCT INFORMATION (this information will be kept confidential)
Please be as complete and succinct as possible; indicate if the information is not available or not applicable to your request. References may be cited

a. Candidate name: DPP4-Fc

b. Manufacturer/developer: Planet Biotechnology Inc

c. Product type (vaccine, adjuvant, therapeutic) and description (e.g. whole cell derived, subunit, vector based, etc.): recombinant therapeutic human protein expressed in *N. benthamiana* plants

d. Target: MERS coronavirus

e. Candidate composition or active ingredient (e.g. DNA vaccine, recombinant vaccine, enzyme/neuraminidase inhibitor, etc.): fusion of extracellular portion of dipeptidyl peptidase IV (DPP4) with human immunoglobulin Fc

f. Formulation (storage buffer, pH, salt conditions, etc.): phosphate buffered saline

g. Is the manufacturing process fully developed? (describe the current process)

The process is not fully developed. Currently the protein is expressed via agroinfiltration of *N. benthamiana* plants. The plants are homogenized in an aqueous buffer and the extract is clarified by centrifugation and filtration. DPP4-Fc is recovered at 95% purity via Protein A affinity chromatography.

h. Is GMP material available? Not yet

i. Amount of candidate available for the requested studies: Current inventory is at least (b)(4)

j. Stability of candidate; storage and handling conditions: stability studies have not been done. DPP4-Fc appears to be (b)(4)

k. Current other support for product development including grants, contracts and private sources of funding: No other current support besides R44 AI114023

3. PROVIDE A CONCISE SCIENTIFIC JUSTIFICATION FOR USE OF THIS CANDIDATE (Include a discussion of the mode of action, if applicable):

Middle East respiratory syndrome coronavirus (MERS-CoV) is a newly emerging human health threat with a ~35% case fatality rate. MERS-CoV uses dipeptidyl peptidase 4 (DPP4), a cell surface protein, to enter and infect cells (1). We produced fusions of human DPP4 and the Fc sequences of human IgG1, IgA1 and IgA2 using a transient plant expression system and used these "receptor decoys" to block cellular infection with MERS-CoV. We demonstrated that DPP4-Fc binds to the S1 domain of MERS-CoV S protein, and that DPP4-Fc is a more potent inhibitor of MERS-CoV cellular infection than soluble DPP4. We showed that a DPP4-Fc fusion based on IgA1 may be more effective than one based on IgG1. In addition, we demonstrated that S1 binding and virus neutralization were improved more than 10-fold by modifying the human DPP4 amino acid sequence of the fusion. Unlike antibodies against MERS-CoV, a DPP4-Fc decoy will not subject the virus to selection for neutralization escape mutants, as any mutation that decreases binding to the decoy will decrease binding to the native receptor, resulting in an attenuated virus. As a potential therapeutic, DPP4-Fc is expected to have superior pharmacokinetics to soluble DPP4, as Fc will confer a long circulating half-life and the ability to be delivered to airway mucosal surfaces, the site of MERS-CoV infection.

4. PROVIDE A SUMMARY OF EXISTING DATA:

Preclinical data

Sequences encoding the DPP4 extracellular domain (aa 39-766) were PCR-amplified from the human DPP4 sequence (from Bart Haagmans, Erasmus Medical Center, The Netherlands). The DPP4 sequences were cloned into the pTRAkc plant binary vector (2), upstream of and in-frame with a codon-optimized Fc sequence from either human IgG1, IgA1 or IgA2 (listed below). The IgA constructs were truncated to remove the 18-amino acid C-terminal IgA tail-piece. Two DPP4 sequence variants (V1 and V2) were made by substituting amino acids in human DPP4 with corresponding camel residues in the contact region for spike protein.

The expression vectors were introduced into *A. tumefaciens* and transient expression was initiated by vacuum infiltration into whole *N. benthamiana* plants. DPP4-Fc fusions were purified from plant homogenates using affinity chromatography.

The DPP4-Fc proteins were analyzed by size exclusion chromatography (SEC) and SDS-PAGE. The majority of DPP4-Fc was in the expected dimeric form under non-reducing conditions.

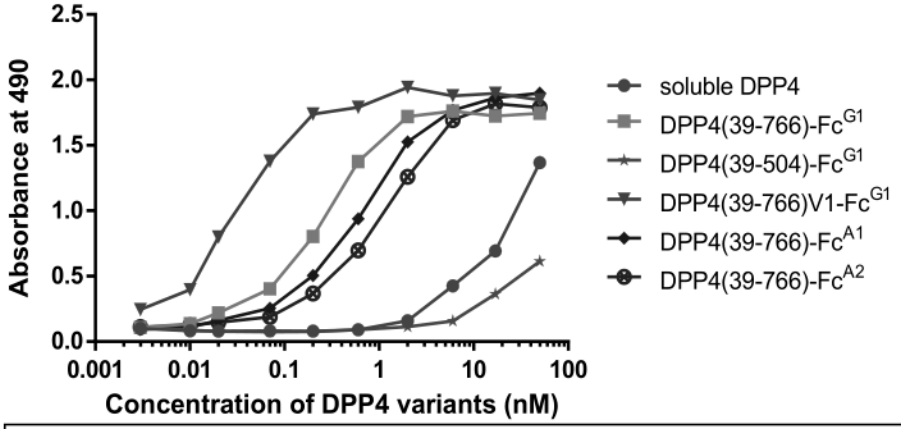


Figure 1. Dose-dependent binding of DPP4-Fc variants to MERS-CoV spike protein.
The ability of the DPP4-Fc variants to bind to the S1 domain of the MERS-CoV S protein was tested using a ligand binding ELISA. Dilutions of DPP4-Fc variants or soluble DPP4 were added to S1 protein coated on microtiter plates. Bound DPP4-Fc was detected using goat anti DPP4 IgG and reported with donkey anti-goat IgG labeled with HRP.

By ELISA we demonstrated that DPP4(39-766)-Fc^{G1} bound the S1 domain of MERS-CoV S protein with an EC_{50} of 0.04 µg/ml, a 30-fold enhanced binding compared to soluble DPP4. DPP4(39-766)V1-Fc^{G1} showed even better binding to Spike S1 protein (**Figure 1**).

Our collaborator, Shibo Jiang at the New York Blood Center, evaluated the virus neutralizing potency of three DPP4-Fc variants using a MERS-CoV pseudovirus. All three neutralized pseudovirus infection, but with different potencies (**Figure 2**). The 50% inhibitory concentrations (IC_{50}) for DPP4(39-766)-Fc^{G1}, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} were 0.46, 0.05 and 0.02 µg/ml, respectively. The 90%

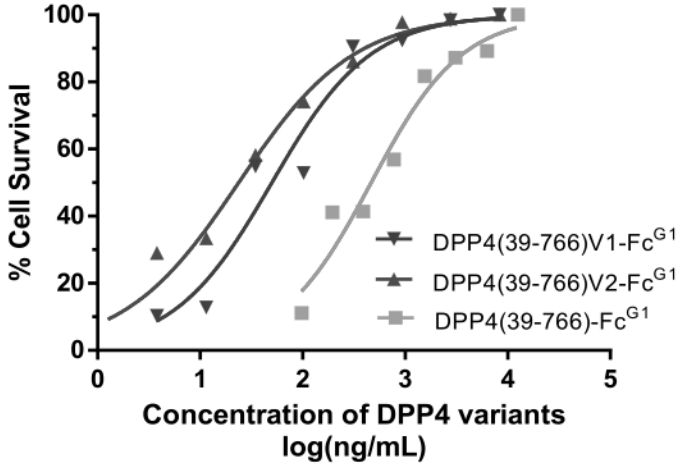


Figure 2. Inhibition of MERS-CoV spike-mediated pseudovirus entry into target cells. Pseudovirus particles expressing MERS-CoV spike protein and luciferase were incubated with dilutions of DPP4-Fc variants. The mixture was added to DPP4-expressing Huh-7 cells and after 72h, the cells were lysed and the luciferase activity was determined and normalized data plotted.

inhibitory concentrations (IC_{90}) were 4.2, 0.45 and 0.21 µg/ml, respectively. This compares to an IC_{90} of 0.039 µg/ml for the most potent mAb against the MERS-CoV S1 protein (3).

Another collaborator, Bart Haagmans at the Erasmus Medical Center, tested some of the DPP4 variants in an assay that measures inhibition of MERS-CoV infection. This assay is a measure of the ability of the different DPP4-Fc variants to block MERS-CoV infection of human cells. In this assay (**Figure 3**) the IC50 for DPP4(39-766)-Fc^{G1}, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} were 0.66, 0.05 and 0.03 µg/ml, respectively. The IC50 for DPP4(39-766)-Fc^{A1} was 0.30 µg/ml, while DPP4(39-766)-Fc^{A2} did not inhibit infection at any concentration.

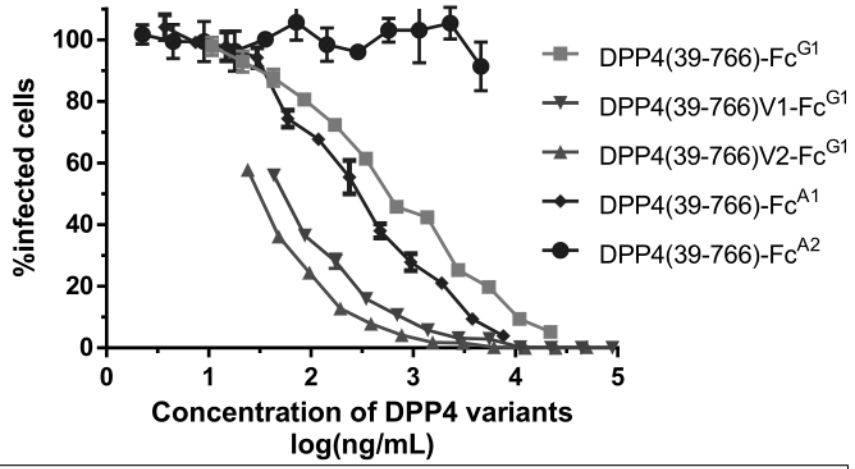


Figure 3. Inhibition of MERS-CoV infection of human cells. MERS-CoV (EMC isolate) was incubated with dilutions of DPP4-Fc variants. The mixture was added to DPP4-expressing Huh-7 cells and after 8 hr, the cells were fixed and synthesized viral proteins were detected by staining the cells with an antiserum against MERS-CoV.

Another collaborator, Matt Frieman at the University of Maryland School of Medicine in Baltimore, tested our DPP4 variants in a cell-based viral neutralization assay with live MERS-CoV (the Jordan strain) (**Figure 4**). As with the binding ELISA and pseudovirus infection experiment, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} performed better than DPP4(39-766)-Fc^{G1}. In this assay the IgA1 fusion variant, DPP4(39-766)-Fc^{A1}, had comparable potency to the IgG1 fusion, DPP4(39-766)-Fc^{G1}, while the IgA2 fusion variant did not protect against cell death at any concentration (not shown).

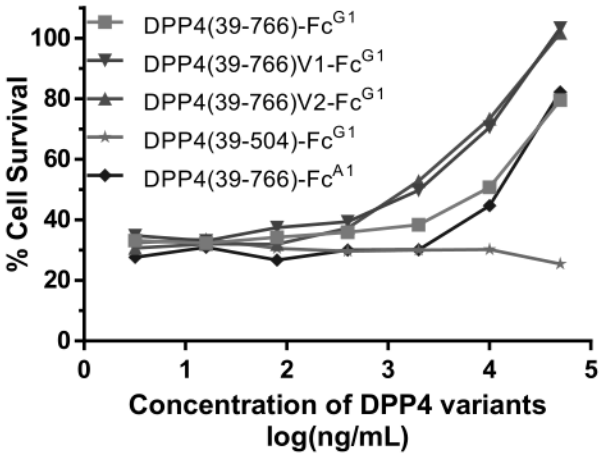
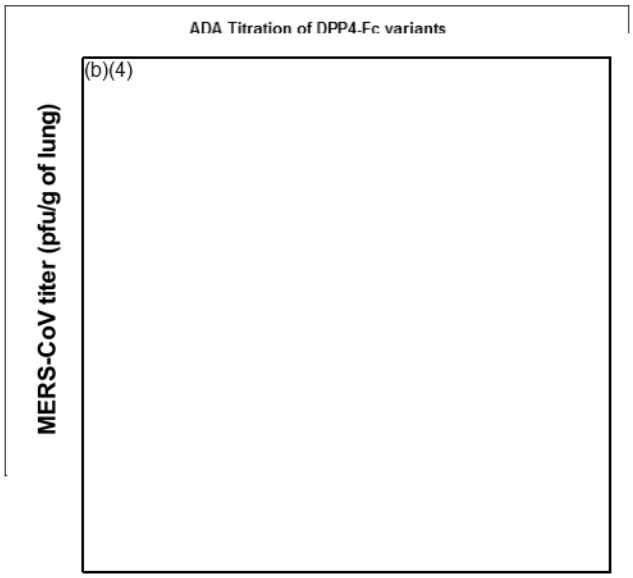


Figure 4. Inhibition of MERS-CoV killing of Vero E6 cells by DPP4-Fc variants. As detailed in Aim#2, in the in vitro cell survival assay, we tested a number of DPP4-Fc variants for their ability to neutralize MERS-CoV infection in susceptible Vero E6 cells.

Modifications of DPP4(39-766)V1-Fc^{G1}

DPP4(39-766)V1- Fc^{G1} is also known by the short-hand designation (b)(4) The peptidase activity of DPP4 represents a potential safety concern for in vivo use, as parenteral administration of large quantities of DPP4(39-766)V1- Fc^{G1} (b)(4) could have unintended deleterious affects due to peptide cleavage. The peptidase activity of DPP4 resides in the catalytic domain, far from the binding site for spike protein. We introduced a single amino acid mutation, S630A, into (b)(4) eliminating the peptidase activity (activity reduced to <0.03% of non-mutant DPP4-Fc) without affecting binding to MERS-CoV Spike. The mutant DPP4-Fc is called (b)(4) and also the short-hand designation (b)(4)

Another concern about the use of DPP4-Fc as an in vivo therapeutic for MERS is that DPP4 binds to extracellular adenosine deaminase (ADA). Binding of ADA to the DPP4 on the cell surface is an important regulatory mechanism of T cell activation, so therapeutic administration of large quantities of DPP4-Fc might have some deleterious affect on T cell activation. We tested (b)(4) (b)(4) variants of DPP4-Fc (b)(4) (b)(4) for ADA binding, using a competition assay. This assay takes advantage of the fact that ADA and MERS-CoV Spike bind to DPP4 at the same site. In this assay, binding of DPP4-Fc to ADA is monitored by the ability of ADA to block binding of DPP4-Fc to Spike protein. We identified one DPP4-Fc variant, (b)(4) (b)(4) whose binding to ADA was (b)(4) (b)(4) (b)(4)



All the new DPP4-Fc constructs were tested for the ability to neutralize MERS-CoV infection of susceptible human cells in the laboratory of our collaborator, Matt Frieman. MERS-CoV is cytolytic to Vero E6 cells, so the assay uses Cell-TiterGlo (Promega) to assay cell survival. In this assay a fixed amount of MERS-CoV is added to Vero E6 cells and cell survival measured by luciferase activity after 4 days of infection. MERS-CoV inhibitory activity of DPP4-Fc variants were assayed by monitoring luciferase activity when added to the MERS-CoV infection. The *in vitro* data showed (b)(4) (b)(4) (b)(4)

Presently, Matt Frieman's group is comparing *in vivo* activity of two versions of DPP4-Fc variant S2320, with and without terminal galactose residues on the N-glycans, in the adenovirus mouse model of MERS.

Efficacy data

Balb/c mice were transduced with an adenovirus vector ($2.5x10^8$ pfu/mouse) by intranasal inoculation and left for 4 days to ensure expression of hDPP4, as has been described previously [1]. Transduced mice were intranasally inoculated at day 0 with 2.5×10^3 pfu of MERS-CoV (Jordan) in 50 µl total volume. Transduced mice were divided into groups receiving (b)(4) doses of purified hDPP4(S2320-Gal-SF) at different time points (before and/or after inoculation) by i.p. injection. Group 1 received (b)(4) at days -1 and 0 (24 hour prior to and just after inoculation), group 2 received (b)(4) at days -1, 0 and +1 and group 3 received a (b)(4) at days 0 and +1. At 3 days post-infection mice were euthanized and MERS-CoV (Jordan) lung titers were determined by plaque assay as described previously [2] (figure to right). MERS-CoV RNA levels were determined by PCR, as described previously [2], except that the endogenous control was mouse transferrin receptor protein 1 (TFRC) using the following forward primer: ATGACGTTGAATTGAACCTGGACTA; reverse primer: GTCTCCACGAGCGGAATACAG; and probe: ABY-

ATCAGGGATATGGGTCTAAGTCTACAGTGG-QSY in triplex with the previously described MERS-CoV primer/probe sets to UpE and membrane (M) protein mRNA [3].

Toxicity data

Toxicity data are not available.

5. DEVELOPMENT PLAN

Please indicate how data obtained via DMID/NIAD contract resources fit into the overall development plan of your product.

MERS, as an emerging disease, does not occur with sufficient frequency to readily allow a phase 1 or more advanced clinical trial for a therapeutic biological. It is likely that development of the product will require establishment of efficacy in animal models that are highly relevant to the mechanism of pathology of MERS-CoV in human beings. So far, models of MERS have been established in mice in an adenovirus-vectored model, in transgenic mice (Regeneron, Inc.; however this model is not generally available), rhesus macaques and marmosets. The adenovirus-vectored mouse model at the University of Maryland will be used pursuant to a consortium agreement if the Company's Phase II SBIR is funded, however we have not requested SBIR funding for NHP studies under that grant application. A MERS therapeutic biological may require development pursuant to the so-called Animal Rule. We anticipate that the marmoset model of the disease will be most relevant for this purpose, as it has been shown to cause a fatal disease syndrome, unlike the rhesus macaque model, which generally does not progress to death in this species.

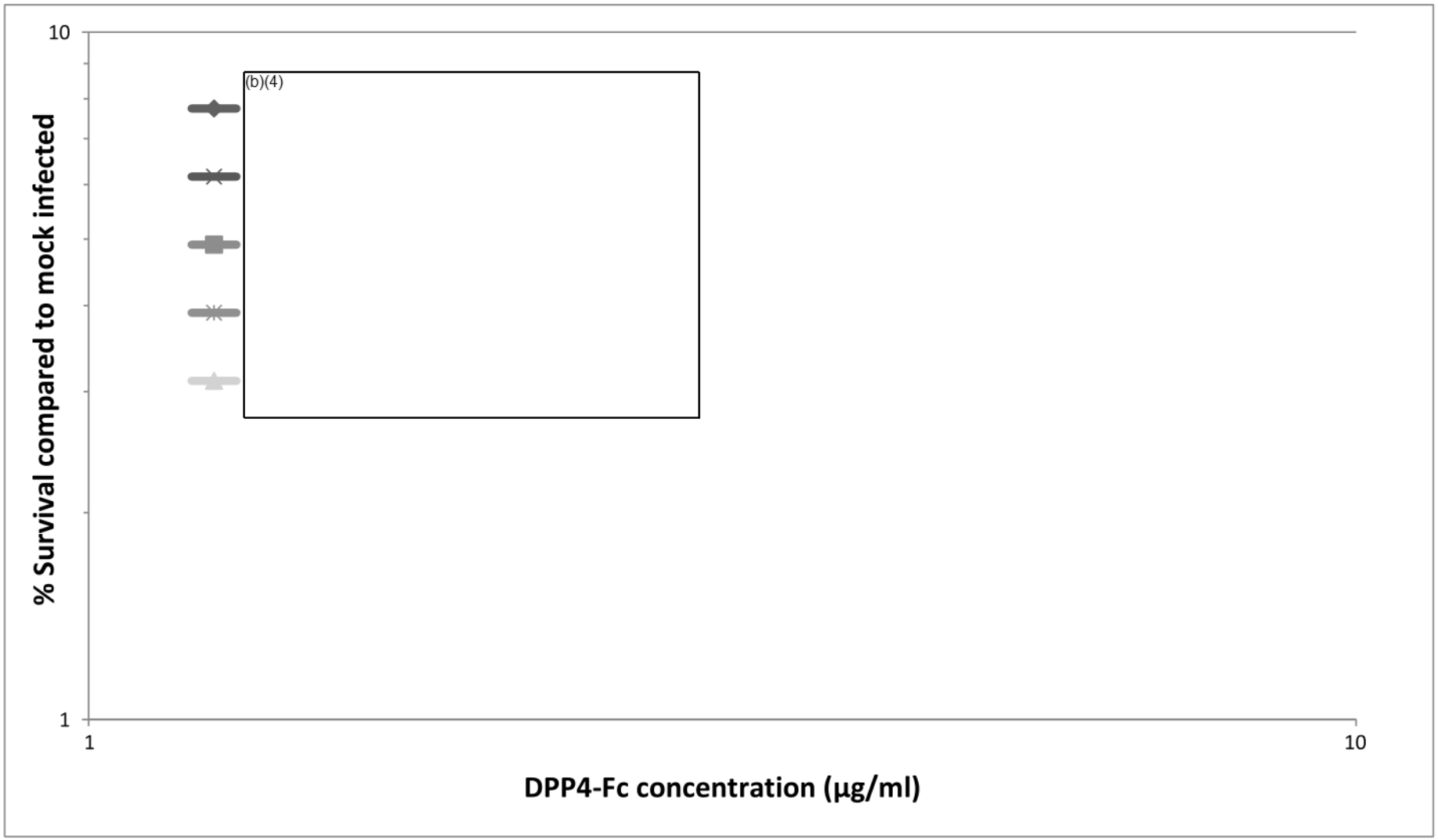
In addition please address:

- Have you filed a patent request?
  We filed a PCT application in December 2015 designating the United States Europe Japan, and several other countries. The PCT application number is PCT/ US 2015/064142
- Do you have IP rights?
  No US Patent has issued at this time.
- If results warrant, do you plan to pursue licensure of the candidate?
  We will pursue further development of the product with Phase II SBIR funding, for which an application is currently pending. We will seek a partner for post-Phase II SBIR development; however we would plan to apply for a clinical trial planning grant (R34) and clinical trial implementation grant if allowed by the NIAID program officers.

6. REFERENCES

Please list references providing relevant background information on your product. References from peer reviewed publications are preferred.

1. **Raj, V.S., H. Mou, S.L. Smits, D.H. Dekkers, M.A. Muller, R. Dijkman, D. Muth, J.A. Demmers, A. Zaki, R.A. Fouchier, V. Thiel, C. Drosten, P.J. Rottier, A.D. Osterhaus, B.J. Bosch, and B.L. Haagmans.** 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature **495:**251-254.
2. **Maclean, J., M. Koekemoer, A.J. Olivier, D. Stewart, Hitzeroth, II, T. Rademacher, R. Fischer, A.L. Williamson, and E.P. Rybicki.** 2007. Optimization of human papillomavirus type 16 (HPV-16) L1 expression in plants: comparison of the suitability of different HPV-16 L1 gene variants and different cell-compartment localization. J Gen Virol **88:**1460-1469. http://vir.sgmjournals.org/content/88/5/1460.long
3. **Ying, T., L. Du, T.W. Ju, P. Prabakaran, C.C. Lau, L. Lu, Q. Liu, L. Wang, Y. Feng, Y. Wang, B.J. Zheng, K.Y. Yuen, S. Jiang, and D.S. Dimitrov.** 2014. Exceptionally potent neutralization of MERS-CoV by human monoclonal antibodies. J Virol http://www.ncbi.nlm.nih.gov/pubmed/24789777


10
1
1
10
% Survival compared to mock infected
DPP4-Fc concentration (µg/ml)
(b)(4)

	Concentration (ug/ul)	50ug (per 100ul)	In 150ul (for first well) DPP4	In 150ul (for first well) Media
1	(b)(4)			
2				
3				
4				
5				

	Stock (TCID50/ml)	10 TCID50	For 500 wells Virus	For 500 wells Media
MERS-CoV(Jordan)	1.25E+04	0.80	400	4600

Plate	DPP4	DPP4 (ug/ml)											
A	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)					
B	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only						
C	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only						

	Concentration (ug/ul)	50ug (per 100ul)	In 150ul (for first well) DPP4	In 150ul (for first well) Media
1	(b)(4)			
2				
3				
4				
5				

	Stock (TCID50/ml)	10 TCID50	For 500 wells Virus	For 500 wells Media
MERS-CoV(Jordan)	1.25E+04	0.80	400	4600

Plate	DPP4	DPP4 (ug/ml)											
A	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)			Empty	Empty	Empty
B	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)			Empty	Empty	Empty
C	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only				Empty	Empty	Empty

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)

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 (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] (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 (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, Room 8E18

Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 17 Jan 2017 14:21:36 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Cockrell, Adam; Leyva-Grado, Victor; Umerah, Nina; Baric, Toni C; Keith Wycoff
Subject: A57 Call to discuss Planet Biotech

Hi Everyone,
Please see below for dial in details for the call later this week.

Best,
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.
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United States: +1 (224) 501-3216

Access Code:(b)(6)

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Italy: +39 0 247 92 13 01
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Uruguay (Toll Free): 000 413 598 4110
Viet Nam (Toll Free): 122 80 481

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_____

From: Cockrell, Adam
Sent: Fri, 6 Jan 2017 20:47:15 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Cc: Baric, Toni C
Subject: RE: A57 Calls

Happy New Year Erik!

I have a large experiment scheduled for the week of the 16th. My best times that overlap with Ralph's schedule would be on the 12th and 19th.

Thanks,
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

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Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
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5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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or any other action based on the contents of this material. If you have received this communication in error, please permanently delete this from your system immediately. Thank you.

From: Leyva-Grado, Victor
Sent: Fri, 6 Jan 2017 20:31:47 +0000
To: 'Baric, Toni C'; Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph; Umerah, Nina
Subject: RE: A57 Calls

Hi Erik,

I can accommodate my time to the ones Dr. Baric is available. For the 1/18 I also can do before 2 but not earlier than 10:30.

Cheers,

V

From: Baric, Toni C (b)(6)
Sent: Friday, January 06, 2017 3:18 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: A57 Calls

Hi Erik,
Ralph's availability is:
1/12 after 3
1/17 before 11
1/18 before 2
1/19 after 2
1/20 any time except 1-2

Best regards,
Toni

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

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Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer

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Email: (b)(6)

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

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 16 Dec 2016 14:08:24 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; 'Baric, Toni C'; Cockrell, Adam; Leyva-Grado, Victor
Subject: A57 Call to Discuss Remaining Studies
Attachments: Rhabdo.MERSVax.NIAIDSheet.docx, NIAID DPP4 FC Product Development Information Sheet from Requestors.docx

Hi Everyone,
Hopefully this time still works for everyone; I know things get crazy leading up to the holidays! Please use the Skype link/dial in below to join the call. I'd like to discuss the ongoing GSK study, and then plan out the remaining 3 slots. Attached are the info sheets for the two other candidates I'm considering. Please keep this information confidential, for internal A57 use only. With the current performance period ending in February, we will also need to request another extension for the work. I'm hoping to schedule calls with the submitters early in the new year. If we can get everything planned out, this should hopefully take us through the end of the contract!

Erik

→

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(406) 802-6000 (NIAID) English (United States)
Find a local number

Conference ID: (b)(6)
Forgot your dial-in PIN? | Help

[!OC([1033])!]

NIAID Respiratory Disease Branch
Product Development
Information Sheet from Requestors

PLEASE PROVIDE THE FOLLOWING INFORMATION:

NAME: Reed Johnson
INSTITUTION: IRF/NIAID
ADDRESS: Ft Detrick, MD
TEL#:
FAX#:
E-MAIL: (b)(6)

NAME: Matthew Frieman
INSTITUTION: University of Maryland School of Medicine
ADDRESS: 685 West Baltimore St, Room 380, Baltimore MD 21201
TEL#: (b)(6)
FAX#: 410 706 6970
E-MAIL: (b)(6)

NAME: Matthias J. Schnell
INSTITUTION: Thomas Jefferson University
ADDRESS: 233 South 10th St, 531 BLSB Philadelphia PA, 19107
TEL#: (b)(6)
FAX#: 215-923-9248
E-MAIL: (b)(6)

If applicable, provide:
NIH GRANT OR CONTRACT:
GRANT OR CONTRACT NUMBER:
GRANT OR CONTRACT START DATE:
GRANT OR CONTRACT END DATE:

NIH GRANT OR CONTRACT FUNDING IS NOT A REQUIREMENT FOR ACCESS TO THESE RESOURCES

1. **SERVICE REQUESTED:**

Evaluation of a RABV-MERS bivalent vaccine (BNSP333-S1) in available MERS-CoV mouse model

2. GENERAL PRODUCT INFORMATION (this information will be kept confidential)

Please be as complete and succinct as possible; indicate if the information is not available or not applicable to your request. References may be cited

a. Candidate name: RABV-MERS bivalent vaccine (BNSP333-S1)

b. Manufacturer/developer: NIAID-DIR, Thomas Jefferson University, University of Maryland

c. Product type (vaccine, adjuvant, therapeutic) and description (e.g. whole cell derived, subunit, vector based, etc.): Vaccine

d. Target: MERS-CoV

e. Candidate composition or active ingredient (e.g. DNA vaccine, recombinant vaccine, enzyme/neuraminidase inhibitor, etc.): Inactivated recombinant RABV vaccine vector virions containing MERS-CoV S1.

f. Formulation (storage buffer, pH, salt conditions, etc.): Sucrose purified inactivated viral particles in 1 x PBS

g. Is the manufacturing process fully developed? (describe the current process):

The manufacturing process is currently developed for a similar vaccine for EBOV, SUDV and MARV by IDT.

The provided material is a laboratory produced vaccine produce as described below:

For large-scale purification of virus particles, 2-stack cell culture chambers were seeded with Vero cells (CCL-81, ATCC) in DMEM supplemented with 5% FCS. Prior to adding virus, the cells were washed with phosphate buffered saline (PBS; Corning, Manassas, VA) and then infected at low multiplicity of infection (0.01-0.05) in serum-free medium at 34 °C. Supernatant was collected at 3- to 4-day intervals and replaced with fresh serum-free medium. Cell culture media were centrifuged at low speed for 10 min to remove debris and filtered through 0.45 μm PES membrane filters (Nalgene). The filtered supernatant was then concentrated by tangential flow filtration in mPES hollow fiber cartridges (Spectrum Labs) followed by ultracentrifugation on 20% sucrose cushions in a SW32Ti rotor (Beckman) for 2 h at 25000 rpm (106000 g). Pelleted virus was resuspended in PBS and protein content measured using a BCA Protein Assay Kit (PIERCE) according to the manufacturers' instructions. Following addition of PBS to adjust the protein concentration to 1 mg/ml, beta-Propriolactone was added at a concentration of 0.05% (v/v) to inactivate virus. After overnight incubation at 4 °C, inactivated particles were incubated at 37 °C for 30 min and subsequently frozen in aliquots at −80 °C. To verify complete inactivation/absence of infectious

virus, 10 µg of inactivated virus was inoculated in a flask seeded with BSR cells (Baby hamster kidney cell clone). Four days after inoculation 1/10th of supernatant was passaged on fresh BSR cells. Four days post inoculation, the cells were fixed and stained with FITC-labeled monoclonal antibody against RABV nucleoprotein (Fujirebio).

h. Is GMP material available? No

i. Amount of candidate available for the requested studies: about 1 mg

j. Stability of candidate; storage and handling conditions: Store at -80^{0}C, stable at 4^{0}C for at least 24 hours

k. Current other support for product development including grants, contracts and private sources of funding: Not for this vaccine but for a similar vaccine for filoviruses. The vaccine platform is at advance development (preclinical). 2013/02/01-2018/01/3, R01 AI105204-03, National Institute of Allergy and Infectious Diseases (NIAID), Schnell, Matthias Johannes (PI), Preclinical characterization of a multivalent killed Filovirus/Rabies vaccine

3. PROVIDE A CONCISE SCIENTIFIC JUSTIFICATION FOR USE OF THIS CANDIDATE (Include a discussion of the mode of action, if applicable):

The RABV-MERS CoV bivalent vaccine has demonstrated efficacy, by viral titer reduction, in the human DPP4 adenovirus transduced murine model of MERS. Further evaluation is warranted in an improved murine model to demonstrate efficacy by reduction of viral titer and reduced lung pathology.

4. PROVIDE A SUMMARY OF EXISTING DATA:

Preclinical data

Provide a brief summary of *in vitro* and *in vivo* experimental results relevant to the candidate including but not limited to safety, immunogenicity, efficacy, pharmacokinetic and pharmacodynamic studies. Indicate if data are not available.

The RABV-MERS candidate have proven immunogenic and safe in murine models.

Efficacy data

Provide a summary of efficacy data to date. Indicate if data are not available.

The RABV-MERS vaccine proved efficacious in the human Ad4 mouse transduction model.

Toxicity data

Provide a summary of existing toxicity data including any IND enabling studies. Identify the cell culture system(s) and animal model(s) and provide results of testing. Include such

information as dose and/or formulations tested, dose schedule, concentration/titer, negative and positive controls, performance lab results, and other relevant details. Indicate if data are not available.
Data not available.

5. DEVELOPMENT PLAN

Please indicate how data obtained via DMID/NIAD contract resources fit into the overall development plan of your product.
In the absence of other animal models that recapitulate MERS, additional experiments to address efficacy in suitable murine models are warranted to further pre-clinical development.
In addition please address:

- Have you filed a patent request? YES, patent filed under NIAID
- Do you have IP rights? If so, please provide the U.S. patent#
- If results warrant, do you plan to pursue licensure of the candidate?

6. REFERENCES

Please list references providing relevant background information on your product. References from peer reviewed publications are preferred.

Wirblich, C., Coleman, C.M., Kurup, D., Shaik, N., Abraham, T.S., Jahrling P.B., Hensley, L.E., Johnson, R.F., Frieman, M.B., Schnell, M.J. (2016) One-Health: A Safe, Efficient Dual-use Vaccine for Humans and Animals against MERS-CoV and Rabies. The Journal of Virology (Accepted manuscript posted online 2 November 2016, doi: 10.1128/JVI.02040-16)

http://jvi.asm.org/content/early/2016/10/27/JVI.02040-16.long

NIAID Respiratory Disease Branch
Product Development
Information Sheet from Requestors

PLEASE PROVIDE THE FOLLOWING INFORMATION:

NAME: **Keith Wycoff**
INSTITUTION: **Planet Biotechnology Inc**
ADDRESS: **20980 Corsair Blvd, Hayward, CA 94545**
TEL#: (b)(6)
FAX#: **(510) 887-1623**
E-MAIL: (b)(6)

If applicable, provide:
NIH GRANT OR CONTRACT: **R44 AI114023**
GRANT OR CONTRACT NUMBER:
GRANT OR CONTRACT START DATE: **06/01/2014**
GRANT OR CONTRACT END DATE: **12/31/2016**

NIH GRANT OR CONTRACT FUNDING IS NOT A REQUIREMENT FOR ACCESS TO THESE RESOURCES

1. SERVICE REQUESTED:

Screening of lead compounds in an adenovirus vectored model of MERS, or, if possible, a non-human primate model of MERS

2. GENERAL PRODUCT INFORMATION (this information will be kept confidential)
Please be as complete and succinct as possible; indicate if the information is not available or not applicable to your request. References may be cited

a. Candidate name: DPP4-Fc

b. Manufacturer/developer: Planet Biotechnology Inc

c. Product type (vaccine, adjuvant, therapeutic) and description (e.g. whole cell derived, subunit, vector based, etc.): recombinant therapeutic human protein expressed in *N. benthamiana* plants

d. Target: MERS coronavirus

e. Candidate composition or active ingredient (e.g. DNA vaccine, recombinant vaccine, enzyme/neuraminidase inhibitor, etc.): fusion of extracellular portion of dipeptidyl peptidase IV (DPP4) with human immunoglobulin Fc

f. Formulation (storage buffer, pH, salt conditions, etc.): phosphate buffered saline

g. Is the manufacturing process fully developed? (describe the current process)

The process is not fully developed. Currently the protein is expressed via agroinfiltration of *N. benthamiana* plants. The plants are homogenized in an aqueous buffer and the extract is clarified by centrifugation and filtration. DPP4-Fc is recovered at 95% purity via Protein A affinity chromatography.

h. Is GMP material available? Not yet

i. Amount of candidate available for the requested studies: Current inventory is at least (b)(4)

j. Stability of candidate; storage and handling conditions: stability studies have not been done. DPP4-Fc appears to be (b)(4)

k. Current other support for product development including grants, contracts and private sources of funding: No other current support besides R44 AI114023

3. PROVIDE A CONCISE SCIENTIFIC JUSTIFICATION FOR USE OF THIS CANDIDATE (Include a discussion of the mode of action, if applicable):

Middle East respiratory syndrome coronavirus (MERS-CoV) is a newly emerging human health threat with a ~35% case fatality rate. MERS-CoV uses dipeptidyl peptidase 4 (DPP4), a cell surface protein, to enter and infect cells (1). We produced fusions of human DPP4 and the Fc sequences of human IgG1, IgA1 and IgA2 using a transient plant expression system and used these "receptor decoys" to block cellular infection with MERS-CoV. We demonstrated that DPP4-Fc binds to the S1 domain of MERS-CoV S protein, and that DPP4-Fc is a more potent inhibitor of MERS-CoV cellular infection than soluble DPP4. We showed that a DPP4-Fc fusion based on IgA1 may be more effective than one based on IgG1. In addition, we demonstrated that S1 binding and virus neutralization were improved more than 10-fold by modifying the human DPP4 amino acid sequence of the fusion. Unlike antibodies against MERS-CoV, a DPP4-Fc decoy will not subject the virus to selection for neutralization escape mutants, as any mutation that decreases binding to the decoy will decrease binding to the native receptor, resulting in an attenuated virus. As a potential therapeutic, DPP4-Fc is expected to have superior pharmacokinetics to soluble DPP4, as Fc will confer a long circulating half-life and the ability to be delivered to airway mucosal surfaces, the site of MERS-CoV infection.

4. PROVIDE A SUMMARY OF EXISTING DATA:

Preclinical data

Sequences encoding the DPP4 extracellular domain (aa 39-766) were PCR-amplified from the human DPP4 sequence (from Bart Haagmans, Erasmus Medical Center, The Netherlands). The DPP4 sequences were cloned into the pTRAkc plant binary vector (2), upstream of and in-frame with a codon-optimized Fc sequence from either human IgG1, IgA1 or IgA2 (listed below). The IgA constructs were truncated to remove the 18-amino acid C-terminal IgA tail-piece. Two DPP4 sequence variants (V1 and V2) were made by substituting amino acids in human DPP4 with corresponding camel residues in the contact region for spike protein.

The expression vectors were introduced into *A. tumefaciens* and transient expression was initiated by vacuum infiltration into whole *N. benthamiana* plants. DPP4-Fc fusions were purified from plant homogenates using affinity chromatography.

The DPP4-Fc proteins were analyzed by size exclusion chromatography (SEC) and SDS-PAGE. The majority of DPP4-Fc was in the expected dimeric form under non-reducing conditions.

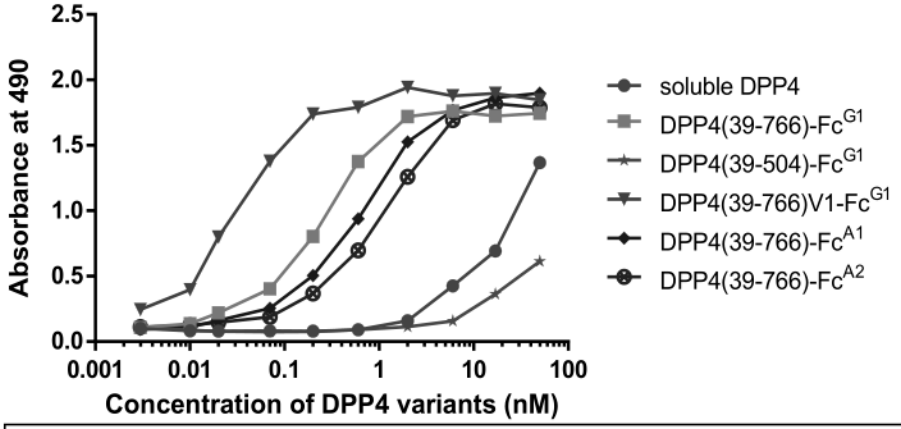


Figure 1. Dose-dependent binding of DPP4-Fc variants to MERS-CoV spike protein.
The ability of the DPP4-Fc variants to bind to the S1 domain of the MERS-CoV S protein was tested using a ligand binding ELISA. Dilutions of DPP4-Fc variants or soluble DPP4 were added to S1 protein coated on microtiter plates. Bound DPP4-Fc was detected using goat anti DPP4 IgG and reported with donkey anti-goat IgG labeled with HRP.

By ELISA we demonstrated that DPP4(39-766)-Fc^{G1} bound the S1 domain of MERS-CoV S protein with an EC_{50} of 0.04 µg/ml, a 30-fold enhanced binding compared to soluble DPP4. DPP4(39-766)V1-Fc^{G1} showed even better binding to Spike S1 protein (**Figure 1**).

Our collaborator, Shibo Jiang at the New York Blood Center, evaluated the virus neutralizing potency of three DPP4-Fc variants using a MERS-CoV pseudovirus. All three neutralized pseudovirus infection, but with different potencies (**Figure 2**). The 50% inhibitory concentrations (IC_{50}) for DPP4(39-766)-Fc^{G1}, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} were 0.46, 0.05 and 0.02 µg/ml, respectively. The 90%

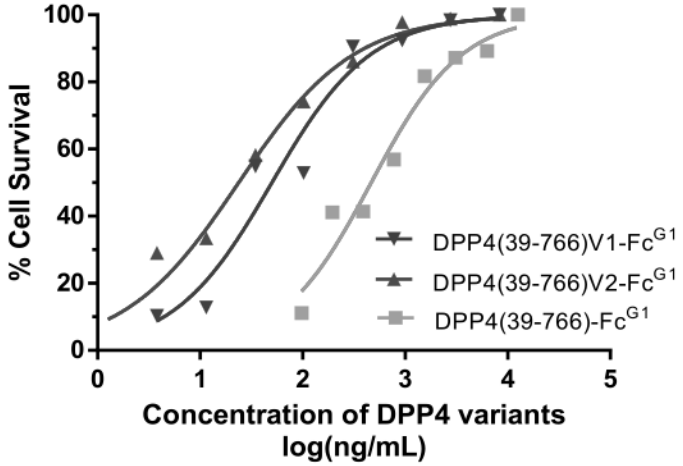


Figure 2. Inhibition of MERS-CoV spike-mediated pseudovirus entry into target cells. Pseudovirus particles expressing MERS-CoV spike protein and luciferase were incubated with dilutions of DPP4-Fc variants. The mixture was added to DPP4-expressing Huh-7 cells and after 72h, the cells were lysed and the luciferase activity was determined and normalized data plotted.

inhibitory concentrations (IC_{90}) were 4.2, 0.45 and 0.21 µg/ml, respectively. This compares to an IC_{90} of 0.039 µg/ml for the most potent mAb against the MERS-CoV S1 protein (3).

Another collaborator, Bart Haagmans at the Erasmus Medical Center, tested some of the DPP4 variants in an assay that measures inhibition of MERS-CoV infection. This assay is a measure of the ability of the different DPP4-Fc variants to block MERS-CoV infection of human cells. In this assay (**Figure 3**) the IC50 for DPP4(39-766)-Fc^{G1}, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} were 0.66, 0.05 and 0.03 µg/ml, respectively. The IC50 for DPP4(39-766)-Fc^{A1} was 0.30 µg/ml, while DPP4(39-766)-Fc^{A2} did not inhibit infection at any concentration.

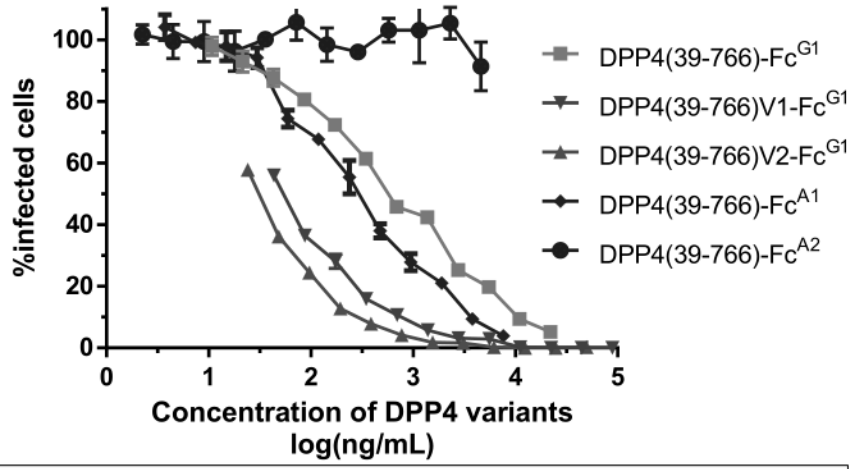


Figure 3. Inhibition of MERS-CoV infection of human cells. MERS-CoV (EMC isolate) was incubated with dilutions of DPP4-Fc variants. The mixture was added to DPP4-expressing Huh-7 cells and after 8 hr, the cells were fixed and synthesized viral proteins were detected by staining the cells with an antiserum against MERS-CoV.

Another collaborator, Matt Frieman at the University of Maryland School of Medicine in Baltimore, tested our DPP4 variants in a cell-based viral neutralization assay with live MERS-CoV (the Jordan strain) (**Figure 4**). As with the binding ELISA and pseudovirus infection experiment, DPP4(39-766)V1-Fc^{G1} and DPP4(39-766)V2-Fc^{G1} performed better than DPP4(39-766)-Fc^{G1}. In this assay the IgA1 fusion variant, DPP4(39-766)-Fc^{A1}, had comparable potency to the IgG1 fusion, DPP4(39-766)-Fc^{G1}, while the IgA2 fusion variant did not protect against cell death at any concentration (not shown).

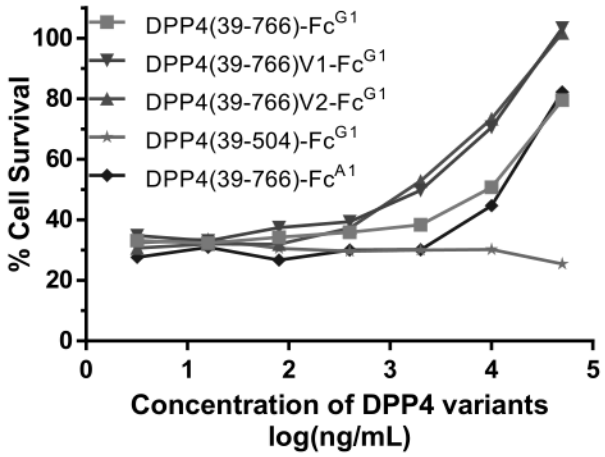


Figure 4. Inhibition of MERS-CoV killing of Vero E6 cells by DPP4-Fc variants. As detailed in Aim#2, in the in vitro cell survival assay, we tested a number of DPP4-Fc variants for their ability to neutralize MERS-CoV infection in susceptible Vero E6 cells.

Modifications of DPP4(39-766)V1-Fc^{G1}

DPP4(39-766)V1- Fc^{G1} is also known by the short-hand designation (b)(4) The peptidase activity of DPP4 represents a potential safety concern for in vivo use, as parenteral administration of large quantities of DPP4(39-766)V1- Fc^{G1} (b)(4) could have unintended deleterious affects due to peptide cleavage. The peptidase activity of DPP4 resides in the catalytic domain, far from the binding site for spike protein. We introduced a single amino acid mutation, S630A, into (b)(4) eliminating the peptidase activity (activity reduced to <0.03% of non-mutant DPP4-Fc) without affecting binding to MERS-CoV Spike. The mutant DPP4-Fc is called (b)(4) and also the short-hand designation (b)(4)

Another concern about the use of DPP4-Fc as an in vivo therapeutic for MERS is that DPP4 binds to extracellular adenosine deaminase (ADA). Binding of ADA to the DPP4 on the cell surface is an important regulatory mechanism of T cell activation, so therapeutic administration of large quantities of DPP4-Fc might have some deleterious affect on T cell activation. We tested (b)(4) (b)(4) variants of DPP4-Fc (b)(4) (b)(4) for ADA binding, using a competition assay. This assay takes advantage of the fact that ADA and MERS-CoV Spike bind to DPP4 at the same site. In this assay, binding of DPP4-Fc to ADA is monitored by the ability of ADA to block binding of DPP4-Fc to Spike protein. We identified one DPP4-Fc variant, (b)(4) (b)(4) whose binding to ADA was (b)(4) (b)(4) (b)(4)

(b)(4)

All the new DPP4-Fc constructs were tested for the ability to neutralize MERS-CoV infection of susceptible human cells in the laboratory of our collaborator, Matt Frieman. MERS-CoV is cytolytic to Vero E6 cells, so the assay uses Cell-TiterGlo (Promega) to assay cell survival. In this assay a fixed amount of MERS-CoV is added to Vero E6 cells and cell survival measured by luciferase activity after 4 days of infection. MERS-CoV inhibitory activity of DPP4-Fc variants were assayed by monitoring luciferase activity when added to the MERS-CoV infection. The *in vitro* data showed that (b)(4) (b)(4) (b)(4)

Presently, Matt Frieman's group is comparing *in vivo* activity of two versions of DPP4-Fc variant S2320, with and without terminal galactose residues on the N-glycans, in the adenovirus mouse model of MERS.

Efficacy data

Balb/c mice were transduced with an adenovirus vector ($2.5x10^8$ pfu/mouse) by intranasal inoculation and left for 4 days to ensure expression of hDPP4, as has been described previously [1]. Transduced mice were intranasally inoculated at day 0 with 2.5×10^3 pfu of MERS-CoV (Jordan) in 50 µl total volume. Transduced mice were divided into groups receiving (b)(4) doses of purified hDPP4(S2320-Gal-SF) at different time points (before and/or after inoculation) by i.p. injection. Group 1 received (b)(4) at days -1 and 0 (24 hour prior to and just after inoculation), group 2 received (b)(4) at days -1, 0 and +1 and group 3 received a (b)(4) at days 0 and +1. At 3 days post-infection mice were euthanized and MERS-CoV (Jordan) lung titers were determined by plaque assay as described previously [2] (figure to right). MERS-CoV RNA levels were determined by PCR, as described previously [2], except that the endogenous control was mouse transferrin receptor protein 1 (TFRC) using the following forward primer: ATGACGTTGAATTGAACCTGGACTA; reverse primer: GTCTCCACGAGCGGAATACAG; and probe: ABY-

ATCAGGGATATGGGTCTAAGTCTACAGTGG-QSY in triplex with the previously described MERS-CoV primer/probe sets to UpE and membrane (M) protein mRNA [3].

Toxicity data

Toxicity data are not available.

5. DEVELOPMENT PLAN

Please indicate how data obtained via DMID/NIAD contract resources fit into the overall development plan of your product.

MERS, as an emerging disease, does not occur with sufficient frequency to readily allow a phase 1 or more advanced clinical trial for a therapeutic biological. It is likely that development of the product will require establishment of efficacy in animal models that are highly relevant to the mechanism of pathology of MERS-CoV in human beings. So far, models of MERS have been established in mice in an adenovirus-vectored model, in transgenic mice (Regeneron, Inc.; however this model is not generally available), rhesus macaques and marmosets. The adenovirus-vectored mouse model at the University of Maryland will be used pursuant to a consortium agreement if the Company's Phase II SBIR is funded, however we have not requested SBIR funding for NHP studies under that grant application. A MERS therapeutic biological may require development pursuant to the so-called Animal Rule. We anticipate that the marmoset model of the disease will be most relevant for this purpose, as it has been shown to cause a fatal disease syndrome, unlike the rhesus macaque model, which generally does not progress to death in this species.

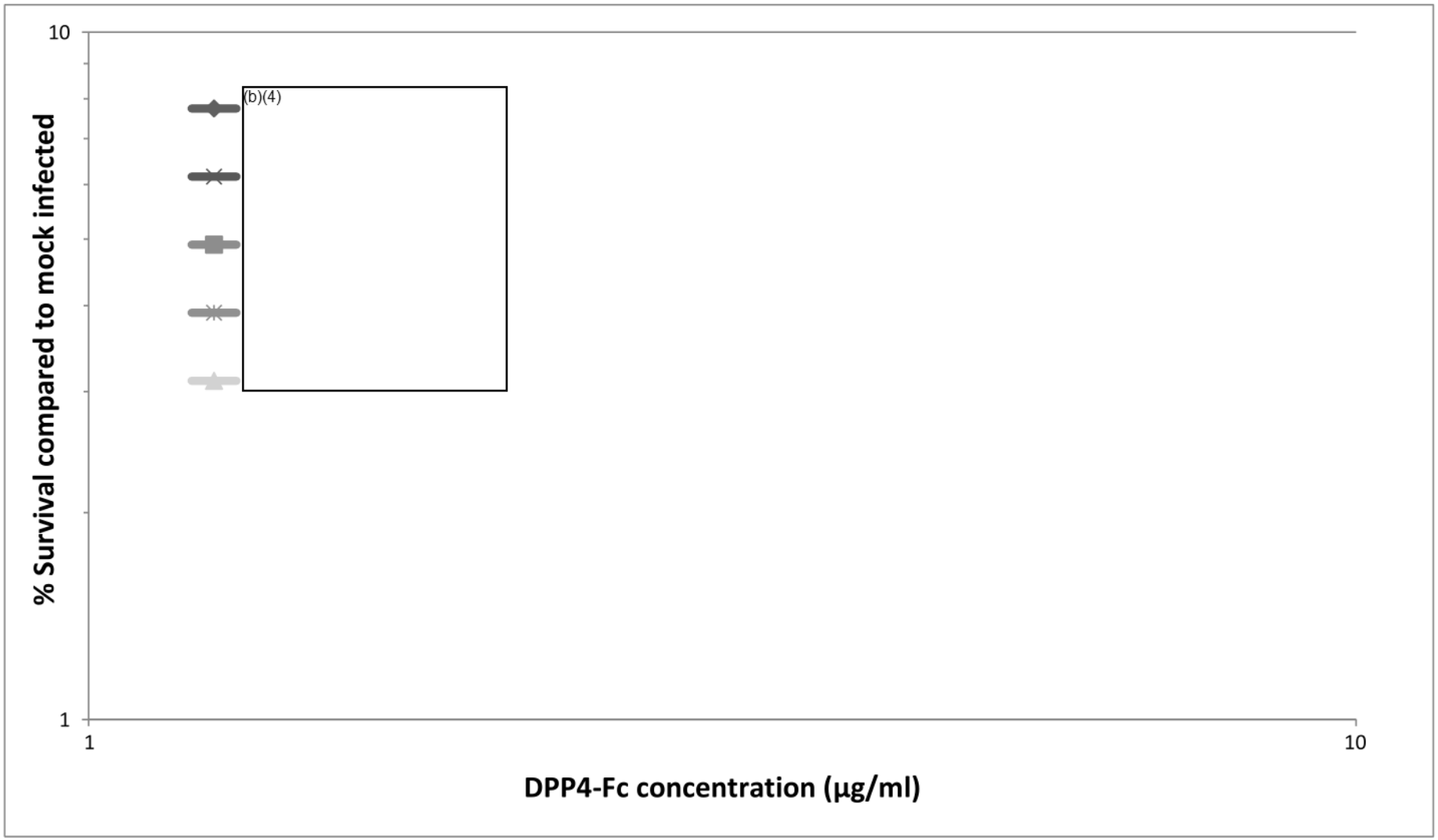
In addition please address:

- Have you filed a patent request?
  We filed a PCT application in December 2015 designating the United States Europe Japan, and several other countries. The PCT application number is PCT/ US 2015/064142
- Do you have IP rights?
  No US Patent has issued at this time.
- If results warrant, do you plan to pursue licensure of the candidate?
  We will pursue further development of the product with Phase II SBIR funding, for which an application is currently pending. We will seek a partner for post-Phase II SBIR development; however we would plan to apply for a clinical trial planning grant (R34) and clinical trial implementation grant if allowed by the NIAID program officers.

6. REFERENCES

Please list references providing relevant background information on your product. References from peer reviewed publications are preferred.

1. **Raj, V.S., H. Mou, S.L. Smits, D.H. Dekkers, M.A. Muller, R. Dijkman, D. Muth, J.A. Demmers, A. Zaki, R.A. Fouchier, V. Thiel, C. Drosten, P.J. Rottier, A.D. Osterhaus, B.J. Bosch, and B.L. Haagmans.** 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature **495:**251-254.
2. **Maclean, J., M. Koekemoer, A.J. Olivier, D. Stewart, Hitzeroth, II, T. Rademacher, R. Fischer, A.L. Williamson, and E.P. Rybicki.** 2007. Optimization of human papillomavirus type 16 (HPV-16) L1 expression in plants: comparison of the suitability of different HPV-16 L1 gene variants and different cell-compartment localization. J Gen Virol **88:**1460-1469. http://vir.sgmjournals.org/content/88/5/1460.long
3. **Ying, T., L. Du, T.W. Ju, P. Prabakaran, C.C. Lau, L. Lu, Q. Liu, L. Wang, Y. Feng, Y. Wang, B.J. Zheng, K.Y. Yuen, S. Jiang, and D.S. Dimitrov.** 2014. Exceptionally potent neutralization of MERS-CoV by human monoclonal antibodies. J Virol http://www.ncbi.nlm.nih.gov/pubmed/24789777


10
1
1
10
% Survival compared to mock infected
DPP4-Fc concentration (µg/ml)
(b)(4)

	Concentration (ug/ul)	50ug (per 100ul)	In 150ul (for first well) DPP4	In 150ul (for first well) Media
1	(b)(4)			
2				
3				
4				
5				

	Stock (TCID50/ml)	10 TCID50	For 500 wells Virus	For 500 wells Media
MERS-CoV(Jordan)	1.25E+04	0.80	400	4600

Plate	DPP4	DPP4 (ug/ml)											
A	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)					
B	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only						
C	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only						

	Concentration (ug/ul)	50ug (per 100ul)	In 150ul (for first well) DPP4	In 150ul (for first well) Media
1	(b)(4)			
2				
3				
4				
5				

	Stock (TCID50/ml)	10 TCID50	For 500 wells Virus	For 500 wells Media
MERS-CoV(Jordan)	1.25E+04	0.80	400	4600

Plate	DPP4	DPP4 (ug/ml)											
A	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)			Empty	Empty	Empty
B	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only	(b)(4)			Empty	Empty	Empty
C	(b)(4)	(b)(4)											
		No virus or serum	No virus or serum	No virus or serum	Virus only	Virus only	Virus only				Empty	Empty	Empty

From: Leyva-Grado, Victor
Sent: Wed, 7 Dec 2016 21:41:27 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Toni C; Cockrell, Adam; Baric, Ralph; Umerah, Nina
Subject: RE: Reschedule A57 Call

Hi everybody,

I can do Monday 12/19 anytime.

Also, if you guys want to do Monday 12/12 before 11:00 I can skip my meeting here and call in.

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, December 07, 2016 4:33 PM
To: Baric, Toni C; Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
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 (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] (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 (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] (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, Room 8E18
Bethesda, MD 20892-9825

Phone: (b)(6)
Email:

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: Wed, 7 Dec 2016 21:15:22 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Reschedule A57 Call

Hi Erik,
Ralph will be up in your building at a DAIT meeting.
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, December 07, 2016 4:14 PM
To: Cockrell, Adam; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Cc: Baric, Toni C
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 (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] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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: Leyva-Grado, Victor
Sent: Tue, 6 Dec 2016 17:34:24 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; 'Cockrell, Adam'; Baric, Ralph; Umerah, Nina
Cc: 'Baric, Toni C'
Subject: RE: Reschedule A57 Call

Hi Erik,

These will work for me:

Friday 12/9: before 10am
Monday 12/12: between 1:30-2:30pm
Thursday 12/15: between 12-2pm

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, December 06, 2016 12:16 PM
To: 'Cockrell, Adam'; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Cc: 'Baric, Toni C'
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
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5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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, 6 Dec 2016 17:20:51 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: Reschedule A57 Call

See Below for Ralph's availability

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, December 06, 2016 12:16 PM
To: Cockrell, Adam; Baric, Ralph S; Leyva-Grado, Victor; Umerah, Nina
Cc: Baric, Toni C
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 Yes
Friday 12/9: before 10am no
Monday 12/12: before 11am or between 1:30-2:30pm Yes before 11 am
Thursday 12/15: between 12-2pm no

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

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 4 Nov 2016 16:41:59 +0000
To: Cockrell, Adam
Cc: Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: GSK A57 Study control

That's great. Please go ahead and update Jeff/GSK and see what they say about your suggested alterations to the treatment schedule.

Victor/Nina, would you mind trying to organize a time in the next week or so to try and have a call. I'd like to briefly discuss the candidates for the remaining studies, and set a timeline for their completion. Then we can use that to request the last extension.

Thank you!
Erik

From: Cockrell, Adam (b)(6)
Sent: Friday, November 04, 2016 11:15 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6)
Umerah, Nina (b)(6)
Subject: RE: GSK A57 Study control

Hi Erik,

Based on the latest email from Jeff I think they are waiting on the data from the first study before planning the second study. It is not clear if there is toxicity. 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.

Regarding the second GSK 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.

Jeff had requested an update of the results on Monday. Would you like me to update him? Or, should we do this after we have a call?

Regarding an extension to complete the studies: I think with the holidays in there it will be difficult to complete the final 3 studies by February 28. That said a final extension would depend on what the last 3 candidates are. For instance, if any of these are vaccine candidates these studies would require a longer

duration. If they are drug/antibody therapeutics I would estimate that we could finish things up by the end of May 2017.

I am available next week for a call. Just let me know a time that is good for everyone's schedules.

Regards,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, November 04, 2016 9:06 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6)
Umerah, Nina (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,
Sorry for the delay. Just circling back around, can you please confirm this is where things stand now: we planned to do 2 studies for GSK, however there was toxicity in the first so we haven't started the second yet. Is that correct? If so do you see a way to salvage the second study, such as altering the dose schedule to reduce the number of times the mice are anesthetized?

The current period of performance for this option will end on Feb 28th, so I'd like to get the remaining studies planned out. I do have a couple other candidates for the final studies, but is it reasonable to be able to finish 3 more studies by then? If not then I think we should plan everything out and request a (hopefully!) final extension.

We missed the last monthly call, and I'm scheduled to be on Travel in Hong Kong for the next one. Can we find a time to chat in the next week or so?

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, October 31, 2016 9:22 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: FW: GSK A57 Study control

Hi Erik,

Would you like to respond to this?

Adam

From: Jeff Pouliot (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
Email (b)(6)
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From: Cockrell, Adam (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 (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 (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 (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 (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

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

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<image001.png>

From: Cockrell, Adam (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 (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 (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 (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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Tel

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From: Cockrell, Adam (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 (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 (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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Email (b)(6)
Tel

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<image001.png>

From: Cockrell, Adam (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 (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 (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 (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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From: Cockrell, Adam (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 (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 (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

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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<image002.png>

From: Cockrell, Adam (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 (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
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Tel

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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

gsk.com | Twitter | YouTube | Facebook | Flickr

<image002.png>

From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 24 Oct 2016 13:20:35 +0000
To: Cockrell, Adam; Umerah, Nina; Baric, Ralph; Leyva-Grado, Victor
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Great. Let's reconnect when you have the data from the GSK studies and we can schedule a call if needed then.

Erik

From: Cockrell, Adam (b)(6)
Sent: Tuesday, October 18, 2016 11:28 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6) Baric, Ralph (b)(6) Heise, Mark T (b)(6) Leyva-Grado, Victor (b)(6)
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Thanks Erik,

I have to be in meetings all Monday morning so would not be able to make it either. Once I have the titers done for the experiment I will assemble a summary of the GSK study, and circulate. Probably by mid-next week.

Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, October 18, 2016 11:23 AM
To: Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Heise, Mark T (b)(6) Leyva-Grado, Victor (b)(6) Cockrell, Adam (b)(6)
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Everyone,
I've had a conflict come up for 11am on Monday 10/24. Do we need to reschedule the call or would you prefer to just update via email? Adam – not sure if you'll have any updates for the GSK study by next week… Any other topics to discuss?

Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 09, 2015 1:48 PM
To: 'Umerah, Nina'; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

When: Monday, October 24, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 18 Oct 2016 15:35:58 +0000
To: Baric, Ralph
Subject: RE: mers model

Thanks Ralph, that's great news. If you don't mind, please let me know when the epub comes out; I'd like to share it with the NIAID communications office.

Erik

From: Baric, Ralph
Sent: Tuesday, October 18, 2016 11:31 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: mers model

Hi Erik, just wanted you to know that the DPP4 paper is now in press in Nature Microbiology. ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, October 12, 2016 4:03 PM
To: Cockrell, Adam; Feng Wang
Cc: Jeff Pouliot; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,
That sounds like the best way to salvage information from the experiment.

Erik

From: Cockrell, Adam (b)(6)
Sent: Wednesday, October 12, 2016 3:49 PM
To: Feng Wang (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 (b)(6) Deborah Butler (b)(6) Neil Pearson (b)(6) Yount, Boyd L Jr (b)(6)
Subject: RE: GSK A57 Study control

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 (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 (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

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

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From: Cockrell, Adam (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 (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

GSK
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Email (b)(6)
Tel

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From: Cockrell, Adam (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 (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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1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
Email (b)(6)
Tel

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From: Cockrell, Adam (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

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

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From: Cockrell, Adam (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 (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

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

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<image001.png>

From: Cockrell, Adam (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 (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

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

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From: Cockrell, Adam (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 (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

GSK
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Email (b)(6)
Tel

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<image001.png>

From: Cockrell, Adam (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 (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 (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

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

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<image002.png>

From: Cockrell, Adam (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 (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

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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

gsk.com | Twitter | YouTube | Facebook | Flickr

<image002.png>

From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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

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From: Leyva-Grado, Victor
Sent: Tue, 18 Oct 2016 15:24:42 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Baric, Ralph; (b)(6) Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

We are ok either way.

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, October 18, 2016 11:23 AM
To: Umerah, Nina; Baric, Ralph; (b)(6) Leyva-Grado, Victor; Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Everyone,
I've had a conflict come up for 11am on Monday 10/24. Do we need to reschedule the call or would you prefer to just update via email? Adam – not sure if you'll have any updates for the GSK study by next week… Any other topics to discuss?

Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 09, 2015 1:48 PM
To: 'Umerah, Nina'; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, October 24, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Jeff Pouliot
Sent: Mon, 17 Oct 2016 16:53:34 +0000
To: Cockrell, Adam; Feng Wang
Cc: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Deborah Butler; Neil Pearson; Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Adam,

Thank you very much. It sounds like you can differentiate by behavior between mice that are sick from MERS and what you observed here. Will you be able to look at the histology to confirm this? In any case it is fortuitous that your separate experimental controls can be a dosing protocol control for our own run.

Best,

Jeff

From: Cockrell, Adam (b)(6)
Sent: Monday, October 17, 2016 10:11 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 control

EXTERNAL

Hi Jeff,

Thanks for the suggestion. Upon death the animals experience rigor mortis in the cage so we do not take the tissue following death.

Nonetheless, I concomitantly infected two additional mice without any treatment or anesthetic. This was being done for another experiment. These mice were infected and collected at the same time and will hopefully help address this point once the lung tittering is complete.

Just to address your suggestion in the event that we do observe an exacerbated infection in drug/vehicle treated mice. Since we cannot rule out that repeated anesthetic might exacerbate disease it is a possibility. However, repeated intranasal administration of the vehicle may also exacerbate infection, especially since the vehicle contains a non-ionic detergent (0.5% Tween-80) that is being directly delivered to the lung. Or potentially, there is some combinatorial effect. If in fact there is enhanced infection I believe these two scenarios might be difficult to dissect from the current experiment.

Once I have the results from the plaque assays we will have a better assessment.

Best Regards,
Adam

From: Jeff Pouliot (b)(6)
Sent: Monday, October 17, 2016 8:58 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 all,

Re-sending because my original message bounced back from the UNC accounts.

Adam: see below - could the mice have died from MERS? It would be great to titer virus in the lungs from the mice we lost.

Jeff

From: Jeff Pouliot
Sent: Thursday, October 13, 2016 10:14 AM
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

Thanks Adam,

Could the mice have died of MERS? The repeated anesthetic might have somehow exacerbated the disease. Is it possible to titer virus from the lungs of the mice we lost?

Best,

Jeff

From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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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From: Cockrell, Adam (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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Tel

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From: Cockrell, Adam (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 (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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<image001.png>

From: Cockrell, Adam (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 (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 (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 (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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From: Cockrell, Adam (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 (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 (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
Email (b)(6)
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<image002.png>

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

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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.
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From: Cockrell, Adam
Sent: Tue, 11 Oct 2016 14:57:21 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: RE: GSK A57 Study control

Hi Erik,

This morning's dose administration was 12 hours after last night's dose and most appeared lethargic. I will see how the rest of the time points go.

I think 24 hour time points would have been better for intranasal administration with repeated anesthetic dosing. Or, IP every 12 hours in the absence of anesthetic might also have been an option. However, I think there was concern from GSK folks that the half-life of the drug may have been too short for IP administration.

Best,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, October 11, 2016 10:43 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: GSK A57 Study control

Hi Adam,
That sounds fine. Do you expect lasting effects of the anesthetic? The later points are every 12h, if I recall correctly. Do you think they will still have the delayed recovery after 12h?

Erik

From: Cockrell, Adam (b)(6)
Sent: Tuesday, October 11, 2016 10:38 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: RE: GSK A57 Study control

Hi Erik,

I would like to provide this as an update for the GSK study as requested by Feng. Is it alright to provide this information now?

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 readministration) 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 (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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From: Cockrell, Adam (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 (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 (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 (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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From: Cockrell, Adam (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 (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 (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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From: Cockrell, Adam (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 (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

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

From: Cockrell, Adam (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 (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

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

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From: Cockrell, Adam (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 (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 (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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From: Cockrell, Adam (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 (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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1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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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: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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

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Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

From: Feng Wang
Sent: Thu, 6 Oct 2016 16:02:09 +0000
To: Cockrell, Adam; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Thanks!

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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From: Cockrell, Adam (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 (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 (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 (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

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

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From: Cockrell, Adam (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

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

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From: Cockrell, Adam (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 (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

GSK
1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States
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From: Cockrell, Adam (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 (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

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

From: Cockrell, Adam (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 (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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From: Cockrell, Adam (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 (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 (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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From: Cockrell, Adam (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 (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
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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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

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From: Feng Wang
Sent: Tue, 4 Oct 2016 21:39:48 +0000
To: Cockrell, Adam; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Great. Thanks!

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
Email (b)(6)
Tel

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From: Cockrell, Adam (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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Tel (b)(6)

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From: Cockrell, Adam (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 (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 (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 (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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Tel (b)(6)

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From: Cockrell, Adam (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 (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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From: Cockrell, Adam (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 (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 (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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From: Cockrell, Adam (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 (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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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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

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From: Cockrell, Adam
Sent: Mon, 3 Oct 2016 18:54:32 +0000
To: Jeff Pouliot; Feng Wang; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Hi Jeff,

You are correct. We are not able to bring tissue samples out of the BSL3.

Looking forward to executing the experiment.

Best,
Adam

From: Jeff Pouliot (b)(6)
Sent: Monday, October 03, 2016 2:47 PM
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,

Thanks for the heads-up. The other way to get the information would be to ship lung/blood samples here, but my recollection is that we can't decontaminate infected samples sufficiently for this to be done. Let me know if my memory is wrong and we can discuss.

Otherwise I'll wish you good luck with the experiment. I'm excited to see the results.

Best Regards,

Jeff

From: Cockrell, Adam (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 (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 (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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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 26 Sep 2016 14:47:21 +0000
To: Cockrell, Adam
Cc: Baric, Ralph; Leyva-Grado, Victor; Umerah, Nina
Subject: RE: AMC Call?

Ok, great. I don't have any other items to discuss so we can go ahead and cancel the call.

Thanks!

From: Cockrell, Adam (b)(6)
Sent: Monday, September 26, 2016 10:22 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Leyva-Grado, Victor (b)(6)
Umerah, Nina (b)(6)
Subject: RE: AMC Call?

Hi Erik.

It looks like GSK will send the drug solubilized and I will initiate the testing October 10th.

Best,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, September 26, 2016 9:34 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Leyva-Grado, Victor (b)(6)
Umerah, Nina (b)(6)
Subject: RE: AMC Call?

Hi Adam,
We can cancel today. The only update I had on my list was the GSK study. Following along on the emails it looks like you're good to go when the BSL3 reopens. You solved all the solubility issues?

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, September 26, 2016 9:25 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: AMC Call?

Hi Erik,

Checking to make sure that we do not have a call today.

Best,

Adam Cockrell
Post-Doctoral Fellow
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Phone: (b)(6)

From: Cockrell, Adam
Sent: Fri, 23 Sep 2016 18:47:39 +0000
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Thanks Feng.

Sounds great.

Adam

From: Feng Wang (b)(6)
Sent: Friday, September 23, 2016 2:12 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,

Thanks for the update! So, let's plan on Oct 10 then. Will aliquot the formulation in plastic vial.

Have a nice weekend,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 23, 2016 2:04 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.

Unfortunately I was informed that we have DLAM inspections in our BSL3 facility the week of Oct. 3rd so I would begin the study **Monday Oct. 10th**, and have reserved space for that week.

I would prefer that the vial is not glass. Other than that as long as a p200 pipet tip can reach the bottom of the tube, any should be alright.

Thanks again,
Adam

From: Feng Wang (b)(6)
Sent: Friday, September 23, 2016 1:57 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,

Just like to confirm the date for the study is still on Oct 03 2016. We will ship the formulation and vehicle control to you no later Sept 30 2016 (Friday). Since the study requires total 5 doses, we will prepare 6 aliquots of ~ 500uL per vial (one extra, just in case) . So, you just need to pull out one vial per dose. Most likely, we will do the same for the vehicle controls. Kindly let me know if you have any preference for the vial.
I will keep you updated with the shipping next week.

Thanks for your patience!
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)

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From: Cockrell, Adam (b)(6)
Sent: Tuesday, September 20, 2016 1:42 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,

Sorry for not responding earlier. How would you provide the sonicator? Also, you mention degassing as part of the procedure, how is this done, for how long, etc?

For me to perform the resuspension here I will need a precise protocol with the exact amount of time required for each step. If the entire process takes longer than 30 minutes it will be difficult to perform 12 hour time points with the drug. So the options would be to suspend drug here and administer at 24 hour intervals, or for your group to suspend the drug and ship to us in that form.

In the case that we suspend the drug here I would still need a detailed protocol. Without this information I will not be able to suspend the drug here.

Best,

Adam

From: Feng Wang (b)(6)
Sent: Monday, September 12, 2016 3:50 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,

Just some updates on the formulation testing. We performed tests with the batch sent to you and some previous batches head to head. We found out that the batch you have did take longer to get into the

solution. With sonication and degassing, it took about 20-30min to get a clear solution without any acidification. So, I am asking whether you could do the formulation if we arrange a sonicator for you? In addition, we are exploring the possibility to send you the formulated solution too. Of cause, the solution stability is a concern here.
I will keep you updated about our decision.

Thanks,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 2:18 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

Will do.

You have a nice weekend also.

Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 2:17 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

Please keep those compounds and vehicles refrigerated for now.

Have a nice weekend,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 2:14 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,

That sounds great. Good luck on optimizing the formulation.

Let us know how things are progressing.

Best Regards,

Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 1:52 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,

Let's delay the study to Oct 03. In next week, we will double check and optimize the formulation procedure and get back to you with our findings. Hopefully, we can find an easy solution.

Much thanks for your efforts and sorry for the inconvenience!

feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 1:18 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.

Looks like the next available slot would be the week of October 3rd. Provided you guys can provide the drug in solution I believe that this would be a more feasible time to initiate the study.

Best,
Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 12:42 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,

If we delay the study, what's the next possible time slot?

Regards,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 10:57 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

5 drops from a p200 pipetman.

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 10:53 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,

A quick question: how much 1N HCl did you add to the solution?
I will reply soon with our recommendation.

Thanks,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 8:59 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 & Jeff,

A few points regarding the drug.

1) I have added the vehicle to 0.5mg/ml. For instance I suspended the 1.24mg vial in 2.48ml of vehicle.

2) I attempted to dissolve a second vial of drug this morning and ran into a similar problem as yesterday. However, after leaving the drug from yesterday, overnight on my benchtop it was dissolved. This required more than leaving the drug overnight. As suggested by Feng I had also added 1N HCl to this batch, and the pH was at 3-4. Is this the correct pH? I also incubated the drug at 37C for 1hour, and then at 55C for an additional hour, and it still was not in solution by this time.

3) The complications in getting the drug dissolved will not allow me to dissolve the drug in a timely manner to execute 12 hour time points as discussed. The drug clearly takes longer than 2 hours to get into solution.

4) I would recommend that I either dissolve the drug overnight at room temperature prior to the study time points, or that we post-pone the study until we can obtain the drug in solution from GSK.

Regards,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:36 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,

Just to check how much vehicle did you add to the vial? Should around 2mL for a dose concentration of 0.5mg/mL.
Hope tomorrow is a better day!

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)

From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 3:29 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,

I added the HCl. The large precipitates continue after addition of HCl and ph appears to be between 3-4.

Before we got started I had mentioned to Jeff that we do not have a water bath sonicator, and I do not know anyone that has one.

I will try to resuspend a second vial tomorrow.

Thanks,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:18 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,

See my comments below:

Good luck!

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

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From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 3:08 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 precipitates settle rapidly so difficult to get a pic. Yes I had just finished mixing/aliquoting and warming the vehicle and drug to room temperature.

What kind of sonicator do I need for that vial? Regular water bath one is fine; just put the vial in a beaker with a little bit water

I can locate some 1N HCl and try adding. However, this volume is too small to measure with our ph meter. Will have to try ph paper if I can find some. Yes, either immerse the pH paper or put a couple of drops on the paper

Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:00 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,

Is it possible for you to send a picture to me? Did you mix or shake the vehicle before you added to the compound vial?
Here are a couple of suggestions:

(1) Is it possible for you to borrow a sonicator?
(2) If you have 1N HCl in the lab, please add 5uL to the solution to see whether it helps
(3) If the acid helps, please measure the pH of the final solution

Thanks for your efforts!
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 2:39 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 Feng,

I have attached a signed copy of the MTA you sent for the drugs.

However, I have attempted to suspend the drug in the vehicle. I have had the drug at 37C for the last 45 minutes, and have vortexed about every 5-10 minutes. There are numerous precipitates that have not gone into solution.

We do not have a sonicator, and the drug is in glass vials. Can you please provide suggestions for resuspension?

Before I commit the mice for the experiment I will have to confirm that we get the drug in solution.

I will continue incubation at 37C with vortexing with the aliquot I am testing.

Thanks,
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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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:(b)(6)

Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.
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From: Cockrell, Adam
Sent: Fri, 9 Sep 2016 18:17:43 +0000
To: Feng Wang; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study control

Will do.

You have a nice weekend also.

Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 2:17 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

Please keep those compounds and vehicles refrigerated for now.

Have a nice weekend,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 2:14 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,

That sounds great. Good luck on optimizing the formulation.

Let us know how things are progressing.

Best Regards,

Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 1:52 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,

Let's delay the study to Oct 03. In next week, we will double check and optimize the formulation procedure and get back to you with our findings. Hopefully, we can find an easy solution.

Much thanks for your efforts and sorry for the inconvenience!

feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 1:18 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.

Looks like the next available slot would be the week of October 3rd. Provided you guys can provide the drug in solution I believe that this would be a more feasible time to initiate the study.

Best,
Adam

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 12:42 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,

If we delay the study, what's the next possible time slot?

Regards,
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)

From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 10:57 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

5 drops from a p200 pipetman.

From: Feng Wang (b)(6)
Sent: Friday, September 09, 2016 10:53 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,

A quick question: how much 1N HCl did you add to the solution?
I will reply soon with our recommendation.

Thanks,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Friday, September 09, 2016 8:59 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 & Jeff,

A few points regarding the drug.

1) I have added the vehicle to 0.5mg/ml. For instance I suspended the 1.24mg vial in 2.48ml of vehicle.

2) I attempted to dissolve a second vial of drug this morning and ran into a similar problem as yesterday. However, after leaving the drug from yesterday, overnight on my benchtop it was dissolved. This required more than leaving the drug overnight. As suggested by Feng I had also added 1N HCl to this batch, and the pH was at 3-4. Is this the correct pH? I also incubated the drug at 37C for 1hour, and then at 55C for an additional hour, and it still was not in solution by this time.

3) The complications in getting the drug dissolved will not allow me to dissolve the drug in a timely manner to execute 12 hour time points as discussed. The drug clearly takes longer than 2 hours to get into solution.

4) I would recommend that I either dissolve the drug overnight at room temperature prior to the study time points, or that we post-pone the study until we can obtain the drug in solution from GSK.

Regards,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:36 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,

Just to check how much vehicle did you add to the vial? Should around 2mL for a dose concentration of 0.5mg/mL.
Hope tomorrow is a better day!

Thanks,
feng

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

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From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 3:29 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,

I added the HCl. The large precipitates continue after addition of HCl and ph appears to be between 3-4.

Before we got started I had mentioned to Jeff that we do not have a water bath sonicator, and I do not know anyone that has one.

I will try to resuspend a second vial tomorrow.

Thanks,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:18 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,

See my comments below:

Good luck!

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

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From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 3:08 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 precipitates settle rapidly so difficult to get a pic. Yes I had just finished mixing/aliquoting and warming the vehicle and drug to room temperature.

What kind of sonicator do I need for that vial? Regular water bath one is fine; just put the vial in a beaker with a little bit water

I can locate some 1N HCl and try adding. However, this volume is too small to measure with our ph meter. Will have to try ph paper if I can find some. Yes, either immerse the pH paper or put a couple of drops on the paper

Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 08, 2016 3:00 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,

Is it possible for you to send a picture to me? Did you mix or shake the vehicle before you added to the compound vial?
Here are a couple of suggestions:

(1) Is it possible for you to borrow a sonicator?
(2) If you have 1N HCl in the lab, please add 5uL to the solution to see whether it helps
(3) If the acid helps, please measure the pH of the final solution

Thanks for your efforts!
feng

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

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

From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 2:39 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 Feng,

I have attached a signed copy of the MTA you sent for the drugs.

However, I have attempted to suspend the drug in the vehicle. I have had the drug at 37C for the last 45 minutes, and have vortexed about every 5-10 minutes. There are numerous precipitates that have not gone into solution.

We do not have a sonicator, and the drug is in glass vials. Can you please provide suggestions for resuspension?

Before I commit the mice for the experiment I will have to confirm that we get the drug in solution.

I will continue incubation at 37C with vortexing with the aliquot I am testing.

Thanks,
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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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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,

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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.

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(b)(6) Feng Wang (b)(6)
Subject: RE: GSK A57 Study

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EXTERNAL

Dear Jeff,

Please see responses to comments/questions below.

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From: Jeff Pouliot (b)(6)
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Baric, Ralph S (b)(6) Deborah Butler (b)(6) Neil Pearson
(b)(6) Feng Wang (b)(6)
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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.

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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

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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: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 8 Sep 2016 12:54:32 +0000
To: Cockrell, Adam
Cc: Baric, Ralph
Subject: RE: GSK A57 Study control

Hi Adam,
Will the addition of the additional controls affect the cost? That's really what is constraining the contract: we can't add additional funds without extra approvals. If it can work within the cost then I'm fine with it. If not then we'll have to skip them. Does that make sense?

Erik

From: Cockrell, Adam (b)(6)
Sent: Thursday, September 08, 2016 8:31 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: FW: GSK A57 Study control

Hi Erik,

Before I respond to this request from the GSK group I wanted to be certain that this is within the terms of the contract.

Thanks,
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

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

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From: Cockrell, Adam (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 (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
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From: Cockrell, Adam (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 (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 (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 (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.

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(b)(6) Feng Wang (b)(6)
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Subject: RE: GSK A57 Study

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Best,

Jeff

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

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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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 6 Sep 2016 14:02:57 +0000
To: Umerah, Nina; Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph; Adams, Miranda (NIH/NIAID) [E]
Subject: RE: A57 NCE?

Thanks Nina. I need to have this NCE mod underway before the end of the week since I will be out of the office on travel starting 9/9.

From: Umerah, Nina (b)(6)
Sent: Tuesday, September 06, 2016 10:01 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Leyva-Grado, Victor (b)(6)
Cc: Baric, Ralph (b)(6) Adams, Miranda (NIH/NIAID) [E] (b)(6)
Subject: RE: A57 NCE?

Hi Erik,

I'm not sure what the holdup is, but I'll make sure it's sent out today.

Thanks,
Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, September 06, 2016 7:20 AM
To: Umerah, Nina; Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph; Adams, Miranda (NIH/NIAID) [E]
Subject: RE: A57 NCE?

Hi Nina,
Any update on the NCE? I still don't think we've received it.

Erik

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

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****

From: Umerah, Nina (b)(6)
Sent: Wednesday, August 31, 2016 1:57 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Leyva-Grado, Victor (b)(6)
Cc: Baric, Ralph (b)(6) Adams, Miranda (NIH/NIAID) [E] (b)(6)
Subject: RE: A57 NCE?

Hi Erik,

The NCE request was sent directly to our finance office last week. I will follow up today.

Thanks,
Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, August 31, 2016 1:40 PM
To: Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph; Umerah, Nina; Adams, Miranda (NIH/NIAID) [E]
Subject: A57 NCE?
Importance: High

Hi Adam,
Any news on the NCE? Technically we need to process the request 30 days before the end of the performance period, which is the end of September. If we don't get it in soon, the contract will end next month.

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, August 22, 2016 11:14 AM
To: Leyva-Grado, Victor (b)(6) Stemmy, Erik (NIH/NIAID) [E]

(b)(6)
Cc: Baric, Ralph (b)(6) Umerah, Nina (b)(6)
Subject: RE: AMC call today?

Hi Victor,

I will speak with Ralph about putting together the NCE and get that over to you.

Best Regards,

Adam

From: Leyva-Grado, Victor (b)(6)
Sent: Monday, August 22, 2016 11:10 AM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Umerah, Nina (b)(6)
Subject: RE: AMC call today?

Hi Adam,

Is Amy still helping you out with the administrative part of the contract? I talked to Nina last week and we haven't received the request from UNC (is this still correct Nina?). The only one we have is the previous NCE for the 5 months.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 2 Sep 2016 19:46:39 +0000
To: Baric, Ralph
Subject: RE: MERS Model Workshop Draft Manuscript

Thanks Ralph!

Erik

Sent with Good (www.good.com)

-----Original Message-----
From: Baric, Ralph
Sent: Friday, September 02, 2016 02:57 PM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: MERS Model Workshop Draft Manuscript

Hi Erik, I'll get my comments to you over the weekend. Hope things are going well. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, August 25, 2016 2:45 PM
To: Baric, Ralph S; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Munster, Vincent (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: MERS Model Workshop Draft Manuscript

Hi Everyone,
I know it's been a while since the MERS Model workshop, but David and I have put together a draft manuscript that we would like to submit to EID for publication. We've put this together based on the detailed summary provided by the science writer. Since you all were part of the organizing committee for the workshop, we thought it would be good to have you as co-authors writing on behalf of the entire group. We're asking for your comments and feedback first, and then we will circulate an updated draft to the larger presenter/panelist group. If possible, we would appreciate it if you could please send any comments back to us by September 12th. Please also let me know if you'd prefer not to be listed as an author, or are otherwise unable to participate in preparing the paper.

In addition to the draft, I've also attached two recent, related, EID papers. Our thought is that this paper would be a follow on to these two. Please let me know if you have any questions.

Thanks!
Erik

Erik J. Stemmy, Ph.D.

Program Officer
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5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-9825
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Email:

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****

From: Feng Wang
Sent: Thu, 1 Sep 2016 20:12:07 +0000
To: Cockrell, Adam; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

Hi Adam,

I will double check my colleague for the stability and get back to you soon. For now, you are free to take a vial for the formulation test and you can use one vial for two doses.

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 (b)(6)
Sent: Thursday, September 01, 2016 4:04 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

EXTERNAL

Hi Feng,

Thanks for the resuspension info.

I was previously informed that the drug is highly unstable, therefore I would have to resuspend the drug prior to every administration. There are five administrations therefore I would need all five bottles you send for the experiment.

That is why I requested a couple extra vials. Please let me know if I can use one vial for more than one administration.

Thanks,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 01, 2016 3:30 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

Hi Adam,

Each bottle would provide more than enough formulations required for one day (BID) dosing. So, for the whole study, you only need three bottles. You could use the 4th bottle for your formulation test and the last bottle as a backup.
Here is the calculation:
To achieve a 1mg/kg IN dose with fixed 50uL dose volume, you need a dose solution of 0.5mg/mL assuming a typical mouse weight of 0.025g. So for one day BID dosing of 6 mice, you only need 0.3mg test compound.

To prepare a dose solution of 0.5mg/mL. You just need to take the weight information from the bottle and calculate the volume of 0.5%Tween 80 needed, and then add that exact volume of vehicle to the bottle. After a couple min sonication or mixing on a warm hotplate, a clear solution will be obtained.

Let me know if you have more questions. We still have time to ship more materials as needed.

Thanks,
feng

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

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Tel (b)(6)

From: Cockrell, Adam (b)(6)
Sent: Thursday, September 01, 2016 3:02 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

EXTERNAL

Thanks Feng.

However, this does not include a sample for me to practice the resuspension of the drug prior to treatment. Can you provide at least one additional sample, and maybe an extra in the event something happens during resuspension?

Also, please provide exact instructions for resuspension with the vehicle that was sent previously.

Thanks,
Adam

From: Feng Wang (b)(6)
Sent: Thursday, September 01, 2016 2:55 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

Hi Adam/Boyd,

Just an update, the test compound (labeled as GSKXXX) in five replicates are shipped out today and should arrive at UNC tomorrow. Once received, please store them in 4-8°C. There should be ~1.2mg in each bottle.

Best wishes,
feng

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

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From: Cockrell, Adam (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 (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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From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825

Phone: (b)(6)
Email: (b)(6)

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From: Baric, Ralph
Sent: Wed, 31 Aug 2016 20:19:53 +0000
To: Umerah, Nina; Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Leyva-Grado, Victor
Cc: Adams, Miranda (NIH/NIAID) [E]; Sims, Amy C
Subject: RE: A57 NCE?

Please keep us in the loop of the status of this request. thanks, ralph

---

From: Umerah, Nina (b)(6)
Sent: Wednesday, August 31, 2016 1:57 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph S; Adams, Miranda (NIH/NIAID) [E]
Subject: RE: A57 NCE?

Hi Erik,

The NCE request was sent directly to our finance office last week. I will follow up today.

Thanks,
Nina

Nina Umerah
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, August 31, 2016 1:40 PM
To: Cockrell, Adam; Leyva-Grado, Victor
Cc: Baric, Ralph; Umerah, Nina; Adams, Miranda (NIH/NIAID) [E]
Subject: A57 NCE?
Importance: High

Hi Adam,
Any news on the NCE? Technically we need to process the request 30 days before the end of the performance period, which is the end of September. If we don't get it in soon, the contract will end next month.

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, August 22, 2016 11:14 AM
To: Leyva-Grado, Victor (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Umerah, Nina (b)(6)
Subject: RE: AMC call today?

Hi Victor,

I will speak with Ralph about putting together the NCE and get that over to you.

Best Regards,

Adam

From: Leyva-Grado, Victor (b)(6)
Sent: Monday, August 22, 2016 11:10 AM
To: Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Umerah, Nina (b)(6)
Subject: RE: AMC call today?

Hi Adam,

Is Amy still helping you out with the administrative part of the contract? I talked to Nina last week and we haven't received the request from UNC (is this still correct Nina?). The only one we have is the previous NCE for the 5 months.

Cheers,

V

From: Feng Wang
Sent: Tue, 30 Aug 2016 14:52:42 +0000
To: Cockrell, Adam; Jeff Pouliot; Stemmy, Erik (NIH/NIAID) [E]; 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; Deborah Butler; Neil Pearson
Cc: Yount, Boyd L Jr
Subject: RE: GSK A57 Study

Hi Adam,

Sorry for the inconvenience! I will update your shipping address for future delivery. In addition, we will do the best to have the test compound delivered by the end of this week or early next week.

Have a nice vacation,
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)

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From: Cockrell, Adam (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 (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)

From: Cockrell, Adam (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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)

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From: Stemmy, Erik (NIH/NIAID) [E] (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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email: (b)(6)

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From: Munster, Vincent (NIH/NIAID) [E]
Sent: Mon, 29 Aug 2016 17:41:54 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: Re: MERS Model Workshop Draft Manuscript

Sounds good Erik,

Will send you my comments this week,

Cheers,

Vincent Munster
Chief, Virus Ecology Unit
Laboratory of Virology
Rocky mountain Laboratories
NIAID/NIH
903S 4th street
Hamilton, MT 59840
(b)(6)

From: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6)
Date: Thursday, August 25, 2016 at 12:45 PM
To: "Baric, Ralph" (b)(6) "Dreier, Thomas (OS/ASPR/BARDA)" (b)(6) "Erlandson, Karl (OS/ASPR)" (b)(6) "Hensley, Lisa (NIH/NIAID) [E]" (b)(6) "Munster, Vincent (NIH/NIAID) [E]" (b)(6) "Subbarao, Kanta (NIH/NIAID) [E]" (b)(6)
Cc: David Spiro (b)(6)
Subject: MERS Model Workshop Draft Manuscript

Hi Everyone,
I know it's been a while since the MERS Model workshop, but David and I have put together a draft manuscript that we would like to submit to EID for publication. We've put this together based on the detailed summary provided by the science writer. Since you all were part of the organizing committee for the workshop, we thought it would be good to have you as co-authors writing on behalf of the entire group. We're asking for your comments and feedback first, and then we will circulate an updated draft to the larger presenter/panelist group. If possible, we would appreciate it if you could please send any comments back to us by September 12th. Please also let me know if you'd prefer not to be listed as an author, or are otherwise unable to participate in preparing the paper.

In addition to the draft, I've also attached two recent, related, EID papers. Our thought is that this paper would be a follow on to these two. Please let me 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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 22 Aug 2016 15:04:37 +0000
To: Cockrell, Adam
Cc: Baric, Ralph; 'Umerah, Nina'; 'Leyva-Grado, Victor'
Subject: RE: AMC call today?

Ok, great. We can go ahead and cancel the call then. The current performance period ends Sept 30th, so in order to process the NCE we should ideally have the request in before Sept 6th.

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, August 22, 2016 11:01 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) 'Umerah, Nina' (b)(6) 'Leyva-Grado, Victor' (b)(6)
Subject: RE: AMC call today?

Hi Erik,
I have not received the compound yet to test. I think they are waiting on a patent to be filed.

I will speak with Ralph regarding the NCE, and how to go forward with this through Mt. Sinai.

Thanks,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, August 22, 2016 10:34 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) 'Umerah, Nina' (b)(6) 'Leyva-Grado, Victor' (b)(6)
Subject: RE: AMC call today?

Hi Adam,
I was just planning on a brief call, but if it's easier we can do it by email. Just wanted to check in and see if things are on track for the GSK study. I know you're waiting to receive the test compound to try out the sonication process. Any updates there? The only other issue is the No-Cost extension. We'll need to get that in ASAP, and OA has said that the NCE can extend past the contract end date. Can you let me know when you'll be able to send the request through Mt Sinai?

Thanks!
Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, August 22, 2016 10:29 AM

To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: AMC call today?

Hi Erik,

Just wanted to check in to see if there is a call today. Anything to discuss? We will not be receiving drug from GSK until mid-September, which means we probably will not have results to discuss until the October call.

Thanks,
Adam

Adam Cockrell
Post-Doctoral Fellow
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Phone: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 16 Aug 2016 11:32:43 +0000
To: 'Leyva-Grado, Victor'; 'Umerah, Nina'; Baric, Ralph; 'Cockrell, Adam'
Subject: A57 NCE

Hi Everyone,
I've checked in with our contracts office, and the NCE can extend past March 21, 2017. Please submit the NCE request for the additional time ASAP so we can process it before the end of the current performance period.

Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 2 Aug 2016 19:04:41 +0000
To: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; 'Cockrell, Adam'
Subject: NIAID A57 Call with GSK
Attachments: NIAID RDB Product Development Information Sheet from Requestors_Aug 1 20....docx

Hi Everyone,
Please see the attached information sheet for the call with GSK tomorrow. Please keep this confidential for internal A57 use only.

Thanks!
Erik

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

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.

NIAID Respiratory Disease Branch
Product Development
Information Sheet from Requestors

PLEASE PROVIDE THE FOLLOWING INFORMATION:

NAME: Deb Butler
INSTITUTION: GlaxoSmithKline
ADDRESS: 1250 S. Collegeville Rd Collegeville, PA 19426
TEL#: (b)(6)
FAX#:
E-MAIL: (b)(6)

If applicable, provide:
NIH GRANT OR CONTRACT:
GRANT OR CONTRACT NUMBER:
GRANT OR CONTRACT START DATE:
GRANT OR CONTRACT END DATE:

NIH GRANT OR CONTRACT FUNDING IS NOT A REQUIREMENT FOR ACCESS TO THESE RESOURCES

1. SERVICE REQUESTED:

- Testing of a GSK analog from a discovery program in the mouse in vivo MERS efficacy model

2. GENERAL PRODUCT INFORMATION (this information will be kept confidential)
Please be as complete and succinct as possible; indicate if the information is not available or not applicable to your request. References may be cited

a. Candidate name: to be determined

b. Manufacturer/developer: GSK

c. Product type (vaccine, adjuvant, therapeutic) and description (e.g. whole cell derived, subunit, vector based, etc.): Small molecule therapeutic

d. Target: confidential

e. Candidate composition or active ingredient (e.g. DNA vaccine, recombinant vaccine, enzyme/neuraminidase inhibitor, etc.): direct-acting antiviral inhibitor

f. Formulation (storage buffer, pH, salt conditions, etc.): Both IP and intranasal dosing formulations are available and will be discussed in conference.

g. Is the manufacturing process fully developed? (describe the current process) No. Our compound is synthesized at lab scale by GSK discovery chemists.

h. Is GMP material available? No

i. Amount of candidate available for the requested studies: Amounts on hand should be sufficient but will be discussed in conference.

j. Stability of candidate; storage and handling conditions: To be determined.

k. Current other support for product development including grants, contracts and private sources of funding: None. GSK investment only.

3. PROVIDE A CONCISE SCIENTIFIC JUSTIFICATION FOR USE OF THIS CANDIDATE (Include a discussion of the mode of action, if applicable):

The enzyme inhibited by these compounds is an established drug target required for viral growth, including that of the MERS pathogen. These compounds have been biochemically tested against the target enzyme with inhibition constants (IC_{50}) commonly in the nM range. Compounds have been tested in cell based efficacy assays with resulting inhibition constants (EC_{50}) ranging down to nM concentration.

Added value from this experiment comes from the fact that these inhibitors have in vitro activity against several viruses that do not have available in vivo efficacy models. The MERS in vivo efficacy model could therefore allow us not only to evaluate the compounds potential to treat MERS infections, but also to extrapolate the PK/PD relationship and allow better human dose predictions for these other viral infections.

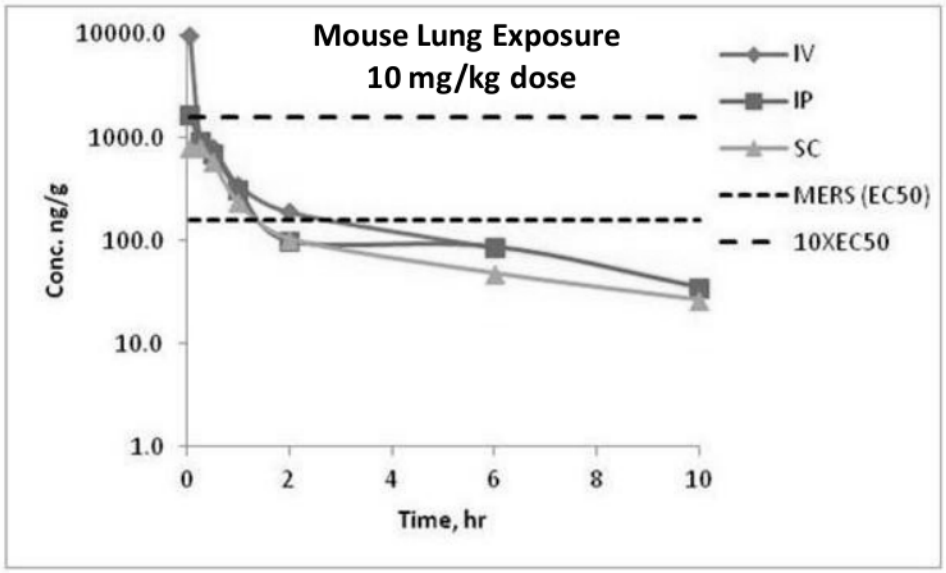
4. PROVIDE A SUMMARY OF EXISTING DATA:

Preclinical data

Provide a brief summary of *in vitro* and *in vivo* experimental results relevant to the candidate including but not limited to safety, immunogenicity, efficacy, pharmacokinetic and pharmacodynamic studies. Indicate if data are not available.

These compounds have been biochemically tested against the target viral enzyme with inhibition constants (IC_{50}) commonly in the nM range. Our compound has been tested against MERS in the MRC5 cell line with a resulting EC50 of 225 nM.

PK is being checked for multiple routes of administration, with data shown below.



Efficacy data

Provide a summary of efficacy data to date. Indicate if data are not available.

In vitro cellular activity detailed above.

Toxicity data

Limited data is available given the preclinical phase of compound development. The test compound was used in a cytotoxicity assay against a standard HeLa-Ohio cell line with a resulting CC50 of >32 μM. Analogs are negative in the Ames genetic toxicity assay.

5. DEVELOPMENT PLAN

Please indicate how data obtained via DMID/NIAD contract resources fit into the overall development plan of your product.

The data would be used 1) to define a PK/PD relationship for in vivo efficacy against MERS that can be extrapolated to make predictions for human dose efficacy 2) to similarly extrapolate dose predictions for efficacy against other viral infections/indications for which there are no good in vivo models

In addition please address:

- Have you filed a patent request? Filing is imminent
- Do you have IP rights? If so, please provide the U.S. patent# Filing is imminent
- If results warrant, do you plan to pursue licensure of the candidate? Yes, if supported by the scientific data and medical need.

6. REFERENCES

Please list references providing relevant background information on your product. References from peer reviewed publications are preferred.

From: Baric, Ralph
Sent: Fri, 22 Jul 2016 17:15:51 +0000
To: Cockrell, Adam; Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Heise, Mark T; Leyva-Grado, Victor
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Ok with me

From: Cockrell, Adam
Sent: Friday, July 22, 2016 7:00 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Baric, Ralph S; Heise, Mark T; Leyva-Grado, Victor
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Thanks Erik,

That sounds great.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, July 21, 2016 3:18 PM
To: Umerah, Nina (b)(6) Baric, Ralph S (b)(6) Heise, Mark T (b)(6) Leyva-Grado, Victor (b)(6) Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Everyone,
We're scheduled to have our A57 monthly call on Monday 7/25, but I don't think there's too much to discuss. Since we have scheduled a call with GSK on Aug 3rd I propose that we cancel the 7/25 call, and if necessary cover any issues after we finish speaking with GSK on 8/3. Let me know if that sounds reasonable.

Also, unless I missed it I think we're still waiting on your NCE request to extend the option period by 9 months. Let me know if I've missed it; I'd like to get that processed so we can focus on the studies.

Thanks!
Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 09, 2015 1:48 PM
To: 'Umerah, Nina'; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, July 25, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).

Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Leyva-Grado, Victor
Sent: Thu, 21 Jul 2016 21:34:58 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Baric, Ralph; (b)(6) 'Cockrell, Adam'
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Here at Mount Sinai are ok with cancelling the meeting for next month since we are connecting on 08/03.
Tomorrow I will check with Nina regarding the NCE request.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, July 21, 2016 3:18 PM
To: Umerah, Nina; Baric, Ralph; (b)(6) Leyva-Grado, Victor; 'Cockrell, Adam'
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Everyone,
We're scheduled to have our A57 monthly call on Monday 7/25, but I don't think there's too much to discuss. Since we have scheduled a call with GSK on Aug 3rd I propose that we cancel the 7/25 call, and if necessary cover any issues after we finish speaking with GSK on 8/3. Let me know if that sounds reasonable.

Also, unless I missed it I think we're still waiting on your NCE request to extend the option period by 9 months. Let me know if I've missed it; I'd like to get that processed so we can focus on the studies.

Thanks!
Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 09, 2015 1:48 PM
To: 'Umerah, Nina'; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, July 25, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Baric, Toni C
Sent: Tue, 19 Jul 2016 12:57:55 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Cockrell, Adam
Subject: RE: Call to discuss A57 Study

Dear Erik
The times below work for Ralph.

Monday 8/1 from 1-1:30
Wed 8/3 10-11 and 1-2

Best regards,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, July 19, 2016 8:56 AM
To: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Cockrell, Adam
Cc: Baric, Toni C
Subject: Call to discuss A57 Study

Hi Everyone,
I've been speaking with a group at GSK about testing a small molecule under A57. They've provided the potential times below for a call. Can you please let me know if any of them work for you?

Thanks!
Erik

Mon Aug 1st: 11-12:00pm; 1-1:30pm
Wed Aug 3rd; 9-11am; 1-2pm

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

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 30 Jun 2016 14:21:33 +0000
To: Baric, Toni C
Cc: Baric, Ralph; Jennifer Gillissen
Subject: Reimbursement for MERS Workshop
Importance: High

Hi Toni,
Hope things are going well! Our contractor for the MERS workshop from March noted that we never received Ralph's reimbursement request. We need to close out that contract so if you would like to be reimbursed can you please work with Jennifer (copied here) so submit the paperwork? Otherwise just let us know if you won't submit it.

Thanks!
Erik

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

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: Leyva-Grado, Victor
Sent: Tue, 21 Jun 2016 13:52:53 +0000
To: Baric, Ralph; Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

That's ok with Mount Sinai too.
Dear Dr Baric and Adam, if you haven't so could you please write a justification for option 2 as suggested by Erik and send it to Nina please.
Please cc me when you do.
Thanks a lot,
V

From: Baric, Ralph S (b)(6)
Sent: Tuesday, June 21, 2016 7:29 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Leyva-Grado, Victor
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Canceling is okay and best for unc. I'm going to be (b)(6) that day anyway. ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, June 21, 2016 7:23 AM
To: Umerah, Nina; Leyva-Grado, Victor
Cc: Baric, Ralph S; Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Nina and Victor,
I will be out of the office on Monday so won't be able to make the scheduled call. I think that we can go ahead and cancel unless you/UNC have something to discuss. The only thing I wanted to bring up was the Option that we just exercised. I'm ready to begin the paperwork to extend the period of performance for 9 more months, but will need an official request to come in from you. Could you please send a short justification and request 9 more months? Part of the justification can be the past performance from Option 1 showed that additional time is required to complete the studies and data analysis. Let me know if you have any questions.

Thanks!
Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 09, 2015 1:48 PM
To: 'Umerah, Nina'; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, June 27, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 2 Jun 2016 17:19:54 +0000
To: Stu Greenberg; 'Cockrell, Adam'
Cc: Baric, Ralph
Subject: RE: Progress

Hi Stu,
At this time we do not have the capacity to perform additional testing for your IgY under our contract with UNC. As such I can't approve them to perform an additional study. It is possible that we may be able to in the future. If that's the case I will get in touch with you to complete the necessary paperwork.

Best,
Erik

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

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: Stu Greenberg (b)(6)
Sent: Thursday, June 02, 2016 1:13 PM
To: 'Cockrell, Adam' (b)(6)
Cc: Baric, Ralph (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: Progress

Hi Adam,

My colleague Koichi Kimura is bringing over fresh anti-MERS IgY this evening. I would like to ship them to you on Monday for Tuesday delivery in Chapel Hill. What delivery address would you prefer?

Professor Tsukamoto had some thoughts to share on dosage based on an H5N1 study he has conducted with chicks in a BSL3 lab in Indonesia. The chicks were injected intra-muscularly with the ostrich IgY (1, 10 and 100mg/bird) at 1 hr post inoculation with A/H5N1. Then all chicks were boarded in individual cages. At 5-days post viral-challenge, the number of dead chicks was counted in each experimental group (over five individuals in each group). In the case of 10 and 100mg IgY, all birds were alive and no histopathologic lesions were found in the lungs. The body weight of the chicks was about 100g~150g. Professor Tsukamoto recommends that the dosage of IgY to mice be at least 2 mg per animal, because the mice in your study were about 20~30g in body weight.

Rather than taking time and effort to perform a neutralization assay, let me suggest an alternative approach. Before initiating another formal study, why not do a preliminary test with a 2mg dosage for just a few mice. If they survive, as we believe they will, then you could re-launch the study at the 2mg dosage. If they don't survive, then the study would not make much sense. What do you think?

Regards,
Stu Greenberg

From: Cockrell, Adam (b)(6)
Sent: Friday, April 15, 2016 9:51 PM
To: Stu Greenberg (b)(6)
Cc: Baric, Ralph S (b)(6) 'Stemmy, Erik (NIH/NIAID) [E]' (b)(6) (b)(6)
Subject: RE: Progress

Hi Stu,

I agree. Definitely disappointing. Testing the antibodies in a neutralization assay would provide the necessary information regarding degradation of the antibodies. However, due to time constraints I have over the next 1.5 months, with ongoing projects, it will be difficult for me to get to this right away. I will do my best to put it in the queue, but cannot make an immediate time commitment.

Best Regards,
Adam

From: Stu Greenberg (b)(6)
Sent: Thursday, April 14, 2016 11:24 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) 'Stemmy, Erik (NIH/NIAID) [E]' (b)(6) (b)(6)
Subject: RE: Progress

Hi Adam,

We are obviously disappointed that the sample we provided does not confer protection. I have discussed this with Dr. Tsukamoto, and he believes that the sample antibodies have degraded.
.
I think there might be a straightforward way to test Dr. Tsukamoto's hypothesis. The table below was produced by USAMRIID.

Compound ID	Plate ID	cell line	Pathogen	EC50, ug/ml	SD	Fit Model	CC50, ug/ml
MERS IgY 1	150616MervVeroAB001	Vero	MERV	(b)(4)		4pHill (AC50,n,S0,Sinf)	(b)(4)
MERS IgY 2	150616MervVeroAB002	Vero	MERV			3pHill (AC50, n, S0)	
MERS anti-serum 6W	150616MervVeroAB002	Vero	MERV			3pHill (AC50, n, S0)	
Pre-im IgY NC	150616MervVeroAB001	Vero	MERV			4pHill (AC50,n,S0,Sinf)	

The MERS antibody sample and the negative control we provided you correspond to Compound IDs "MERS IgY 2" and "Pre-im IgY NC," respectively. The relative neutralization power of the MERS antibodies to the control is shown to be about 13 to 1. If the MERS antibodies have indeed degraded, an in vitro neutralization test of the MERS antibodies and the control should show relative neutralization power nearer 1 to 1.

Does this make sense to you?

Regards,
Stu

From: Cockrell, Adam (b)(6)
Sent: Tuesday, April 12, 2016 9:53 AM
To: Stu Greenberg (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Progress

Hi Stu,

So far the accumulated data indicates that the anti-MERS IgY antibody does not confer protection from severe respiratory disease induced by MERS-CoV in our model, when delivered prophylactically at 12 hours prior to infection. See attachment.

Titer data will be ready in the next 1.5 weeks.

Processing of tissues for IHC and H&E will take another 2-3 weeks once the samples have been submitted for processing. However, based on our experience, we anticipate that the pathology will substantiate the observed disease assessed by the parameters in the summary.

Best Regards,

Adam

From: Stu Greenberg (b)(6)
Sent: Monday, April 11, 2016 11:22 AM
To: Cockrell, Adam (b)(6)
Subject: Progress

Hi Adam,

Can you give me a quick summary on how the mouse study is going? I would like to update my Japanese colleagues.

Regards,
Stu Greenberg
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 20 May 2016 16:26:12 +0000
To: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Cockrell, Adam; Heise, Mark T
Subject: RE: A57 Option 2

Hi Victor,
I think we're all set. The CO decided the best way to proceed is to execute Option 2 as written for 4 months, and then we'll do a modification to extend that to 9. You should hopefully get the official notice next week sometime.

Thanks,
Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Friday, May 20, 2016 11:59 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6)
Baric, Ralph (b)(6) Cockrell, Adam (b)(6) Heise, Mark T
(b)(6)
Subject: RE: A57 Option 2

Hi Erik,

Please let us know if you need anything from our end.

Cheers,

V

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, May 18, 2016 12:04 PM
To: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Cockrell, Adam; Heise, Mark T

Subject: A57 Option 2
Importance: High

Hi Everyone,
I'm in the process of exercising option 2 for A57. The performance period stated for it in the SOW is 4 months. I know in the past we decided that wasn't a reasonable amount of time for 4 studies so I was thinking of setting the performance period 9 months instead. Can you let me know ASAP if that would be reasonable? Our contracts office would also need you to confirm that no additional funds would be required for the longer performance period.

Let me 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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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
Sent: Wed, 18 May 2016 17:15:48 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Cockrell, Adam; Heise, Mark T
Subject: RE: A57 Option 2

9 months is fine. No additional funds are required. ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, May 18, 2016 12:04 PM
To: Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph S; Cockrell, Adam; Heise, Mark T
Subject: A57 Option 2
Importance: High

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Let me 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, Room 8E18
Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

From: Cockrell, Adam
Sent: Wed, 18 May 2016 16:13:28 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Baric, Ralph; Heise, Mark T
Subject: RE: A57 Option 2

Hi Erik,

My thoughts,
From an experimental standpoint, I think 9 months is feasible. Vaccination studies would require the most time (1.5-3 months for prime-boost-challenge, acquiring data, data analysis, and reporting). For planning purposes may want to, at least, initiate vaccination studies within the first 5 months of the performance period.

Ralph and Mark may have additional thoughts in this regard.

Thanks,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, May 18, 2016 12:04 PM
To: Leyva-Grado, Victor (b)(6) Umerah, Nina (b)(6)
Baric, Ralph S (b)(6) Cockrell, Adam (b)(6) Heise, Mark T
(b)(6)
Subject: A57 Option 2
Importance: High

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Erik

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

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****

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 29 Mar 2016 20:50:03 +0000
To: 'Cockrell, Adam'
Cc: Baric, Ralph
Subject: RE: (b)(4) data to share with AbViro

Great. If you don't mind please go ahead and prepare your summary to get the ball rolling. Copy me on the email though.

Thanks!
Erik

Sent with Good (www.good.com)

-----Original Message-----
From: Cockrell, Adam (b)(6)
Sent: Tuesday, March 29, 2016 04:21 PM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: (b)(4) data to share with AbViro

Hi Erik,

Wayne has given approval for use to share the (b)(4) data with AbViro, in the hopes that we can use this to fulfill their contract request, and not duplicate the therapeutic experiment with (b)(4)

Regards,

Adam Cockrell
Post-Doctoral Fellow
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Phone: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 29 Mar 2016 20:45:55 +0000
To: 'Perlman, Stanley'
Cc: Spiro, David (NIH/NIAID) [E]; Baric, Ralph; 'Frieman, Matthew'
Subject: RE: Multi-PI grant

Hi Stanley,
We would be happy to consider an application from you. It will still need to go through our division approval process before submission. For now go ahead and use the form from the PPG. I'll let you know if there is a different one for a large R01.

Erik

Sent with Good (www.good.com)

-----Original Message-----
From: Perlman, Stanley (b)(6)
Sent: Thursday, March 24, 2016 03:56 PM Eastern Standard Time
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]; Baric, Ralph; Frieman, Matthew
Subject: Re: Multi-PI grant

Dear Erik and David,

At the recent MERS Animal Workshop meeting, Ralph Baric, Matt Friemanand I proposed submitting a multi-PI grant comparing our different models of MERS, with the goal of elucidating factors important in pathogenesis. As you remember, we had three different hDPP4 "Knock-In" mice and several strains of mouse-adapted virus that resulted in lethal disease. In Matt's experiments, the Regeneron mice infected with wild type MERS-CoV caused disease, without any requirement for additional murine adaptation. We think that comparing these different models will provide several approaches to understanding both virus and host factors that are important in severe MERS-CoV-mediated respiratory disease.

The three of us recently discussed details of a potential project and we would like to submit a grant for the June 5 deadline, although we may submit it a little later since I am eligible for continuous submission (I believe that this type of grant is eligible for continuous submission). When we discussed budgets, we decided that a budget of between $600,000-$750,000 was required to complete the work. At this budget level, we need to obtain permission prior to submitting the application.

Does this sound reasonable to you and are you willing to look at a more complete pre-proposal application? If so, we plan to send you a document in the next 2 weeks. Should we use the same

form that I recently used when we obtained approval for our PPG proposal or does require a different form?

I hope that all is well.

Stanley

Stanley Perlman, MD, PhD
Professor
Departments of Microbiology and Pediatrics
BSB 3-712
University of Iowa
(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 29 Mar 2016 14:37:55 +0000
To: Umerah, Nina; Leyva-Grado, Victor
Cc: 'Amy Sims'
Subject: RE: NCE for A57?

Thanks Nina! It should also go directly to OA (Miranda and Stan), but please copy me as well.

Erik

From: Umerah, Nina (b)(6)
Sent: Tuesday, March 29, 2016 10:36 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6)
Cc: 'Amy Sims' (b)(6)
Subject: RE: NCE for A57?

Hi Erik,

For some reason the request was sent to our finance office. It was forwarded it to me last week so I will push my grants office to send it to you ASAP.

Thanks,
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: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, March 29, 2016 9:26 AM
To: Leyva-Grado, Victor; Umerah, Nina
Subject: NCE for A57?

Hi Victor and Nina,
Just checking in on the NCE. Have you had a chance to submit it? Ralph mentioned they submitted it to you guys about two weeks ago.

Erik

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

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
Sent: Mon, 28 Mar 2016 19:24:41 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
Attachments: CRISPR-Cas9 MERS Mouse Model manuscript 032516-rsb.docx, Manuscript Figures 03-19-16.pdf

Hi Erik, Here is a draft of the MERS animal model paper, which we are preparing to submit to nature medicine shortly. Thought you would want a draft of the paper before we submit, especially given the GOF exemptions associated with the contract. Likely be a week or so before we submit. Take care. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 28, 2016 10:31 AM
To: Leyva-Grado, Victor; Baric, Ralph S; Umerah, Nina; Heise, Mark T; Sims, Amy C
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Thanks Everyone. We'll cancel today but still plan to check in next month.

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Monday, March 28, 2016 10:25 AM
To: Baric, Ralph (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6) Heise, Mark T (b)(6) Sims, Amy C (b)(6)
Cc: Cockrell, Adam (b)(6)
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

That's Ok with us too.

V

From: Baric, Ralph S (b)(6)
Sent: Monday, March 28, 2016 10:22 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Heise, Mark T; Sims, Amy C; Leyva-Grado, Victor
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Eric, I'm okay with canceling. So lets cancel. ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 28, 2016 10:21 AM
To: Umerah, Nina; Baric, Ralph S; Heise, Mark T; Sims, Amy C; Leyva-Grado, Victor
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Everyone,
We've had a couple of calls over the last few weeks so I wanted to check in to see if there's a need for today's call. I received the monthly report and I think we're good to go for the remaining studies under this options period. I think we're just waiting to receive the NCE request from MSSM. If there aren't any other issues to discuss today, then I'm happy to cancel. Please let me know.

Thanks!
Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 9, 2015 1:48 PM
To: Umerah, Nina; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, March 28, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

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Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

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From: Baric, Ralph
Sent: Mon, 28 Mar 2016 14:51:59 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Leyva-Grado, Victor; Umerah, Nina; Heise, Mark T; Sims, Amy C
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

OK

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 28, 2016 10:31 AM
To: Leyva-Grado, Victor; Baric, Ralph S; Umerah, Nina; Heise, Mark T; Sims, Amy C
Cc: Cockrell, Adam
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Thanks Everyone. We'll cancel today but still plan to check in next month.

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Monday, March 28, 2016 10:25 AM
To: Baric, Ralph (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6) Heise, Mark T (b)(6) Sims, Amy C (b)(6)
Cc: Cockrell, Adam (b)(6)
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

That's Ok with us too.

V

From: Baric, Ralph S (b)(6)
Sent: Monday, March 28, 2016 10:22 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Heise, Mark T; Sims, Amy C; Leyva-Grado, Victor
Cc: Cockrell, Adam
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Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

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this options period. I think we're just waiting to receive the NCE request from MSSM. If there aren't any other issues to discuss today, then I'm happy to cancel. Please let me know.

Thanks!
Erik

-----Original Appointment-----
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Sent: Thursday, July 9, 2015 1:48 PM
To: Umerah, Nina; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, March 28, 2016 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Cockrell, Adam
Sent: Tue, 22 Mar 2016 12:59:12 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph
Subject: RE: Work with AbViro

I do not have an answer for that one.

Ralph, are we putting in the NCE request?

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, March 22, 2016 8:47 AM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Work with AbViro

Ok, thanks. I'll let Brennan know they'll be next in the queue.

Any word yet on the NCE request? I don't think I've seen anything come in from MSSM yet.

Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, March 21, 2016 5:37 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: RE: Work with AbViro

Hi Erik,

That sounds good. Once I get things to Wayne, and hear back from him, I will contact Brennan/AbViro.

Thanks,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 21, 2016 4:31 PM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Work with AbViro

Great. Email addresses are below. Please copy me when you email them.

For Ostrigen, we're finalizing the service request form now. I don't mind if they ship the compound before that's finished, but we like to have the SRF signed before the study starts so there's documentation of the submitter signing off on the study design. Avoids any confusion later on!

Thanks!
Erik

Brennan Klose (b)(6)
Urban Ramstedt (b)(6)

From: Cockrell, Adam (b)(6)
Sent: Monday, March 21, 2016 3:38 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: RE: Work with AbViro

Hi Erik,

I do not emails from any of the folks from AbViro. Could you provide?

Definitely would have to wait on discussing the therapeutic study with AbViro. I think it would be best for me to forward things to Wayne first, and ask him if it is alright to discuss things with AbViro. Do you think AbViro can wait until we get everything to Wayne, and hear back from him? May take a week, but the Ostrigen study will be in the works anyway. I am in agreement about the frustrating part!

Yeah, I received a call today from (b)(6) (Stu's connection at USAMRIID) to let me know that the antibodies should be shipped for arrival by Thursday. They are sending a boat load of antibody. I will be going forward with this one first.

Thanks,
Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 21, 2016 2:19 PM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6)
Subject: RE: Work with AbViro

Hi Adam,
We may need to check with AbViro on that. If it will be useful for them then I am ok with it as long as it wouldn't cost more than the A57 studies. Though if they have different development plans for (b)(4) (b)(4) they may still want to complete the (b)(4) study. Is there a follow on study that might be useful as well? Do you mind emailing Brennan back to ask? I'm not sure if you'll have to check with Wayne or not before discussing the (b)(4) study. It's a little frustrating they don't seem to be communicating!

Regardless, it looks like things are in place for the other Ostrigen study. We got their agreement signed at the end of last week so while we work out what to do with AbViro you guys should be good to proceed with that study if you're ready. Let me know if you have questions.

Thanks!
Erik

From: Cockrell, Adam (b)(6)
Sent: Monday, March 21, 2016 2:07 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6)
Subject: Work with AbViro

Hi Erik,

Wanted to check with you on something before I send the protocol.

As a collaboration with Wayne Marasco, I just completed a therapeutic dose (250ug/mouse) study of (b)(4) today. This is very similar to (b)(4) except a single modification of a glycosylation site. I will be able to put together the initial data on this within the next week or so. I will be forwarding the data to Wayne.

We have also done a prophylactic study with (b)(4) (250ug/mouse). This data has been provided to Wayne.

Would the therapeutic data with (b)(4) at this dose, suffice for AbViro, and the contract obligation?

Adam Cockrell
Post-Doctoral Fellow
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Phone: (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 21 Mar 2016 16:49:18 +0000
To: Cockrell, Adam; Baric, Ralph
Cc: 'Leyva-Grado, Victor'; Umerah, Nina
Subject: A57 AbViro Study

Hi Adam,
Just wanted to check in on the AbViro study design. Have you had a chance to draft it? Brennan will need to make arrangements for the isotype control and needs to know how much to order.

Erik

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

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 11 Mar 2016 18:18:34 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; 'Cockrell, Adam'; 'Baric, Toni C'; 'Leyva-Grado, Victor'; 'Umerah, Nina'; 'Brennan Klose'; 'Urban Ramstedt'
Subject: GoToMeeting Invitation - A57 Call with AbViro

updated start time to 9:00am

Hi Everyone,
Please see below for the dial in details for the next A57 study. Click the link to join the meeting, and then use either VoIP or the telephone number below to connect. A brief agenda also follows.

Erik

1. Overview of the therapeutic (AbViro)
2. Discuss details/requirements of the study (all)
3. Discuss scheduling (UNC)

1. Please join my meeting.
https://global.gotomeeting.com/join (b)(6)

2. Use your microphone and speakers (VoIP) - a headset is recommended. Or, call in using your telephone.

Dial 1 877 309 2073
Access Code: (b)(6)
Audio PIN: Shown after joining the meeting

Meeting ID: (b)(6)

GoToMeeting®
Online Meetings Made Easy®

Not at your computer? Click the link to join this meeting from your iPhone®, iPad®, Android® or Windows Phone® device via the GoToMeeting app.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 10 Mar 2016 19:14:27 +0000
To: Baric, Ralph
Subject: PNAS Paper?

Hi Ralph,
Question for you: do you and Vineet have a paper coming out next week in PNAS on your WIV1 work? We heard about it through a media request and I wondered if you'd mind sharing the draft with me so I can get a heads up on the details for myself and the DMID leadership. Please let me know.

Thanks!
Erik

Sent with Good (www.good.com)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 23 Feb 2016 21:06:35 +0000
To: Leyva-Grado, Victor; Umerah, Nina
Cc: (b)(6) Baric, Ralph
Subject: RE: A57 call

Hi Everyone,
Let's reschedule for late next week. I'll be in touch to reschedule.

Thanks,
Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Monday, February 22, 2016 4:48 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6)
Cc: (b)(6) Baric, Ralph (b)(6)
Subject: RE: A57 call

Hi Erik,

That will work for us at Mount Sinai. When confirmed, please send us the call in information.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, February 22, 2016 3:16 PM
To: Leyva-Grado, Victor; Umerah, Nina
Cc: (b)(6) Baric, Ralph
Subject: RE: A57 call

Hi Everyone,
Will noon on 2/24 work for the group? Please let me know and I'll send the dial in details.

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Tuesday, February 16, 2016 11:20 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Umerah, Nina (b)(6)
Subject: RE: A57 call

Dear Erik,

These are some options:

2/17 10-2
2/18 1-2
Following week:
2/23 before 1
2/24 before 11 or 12-2:30
2/25 between 11-3

Please let me know.

Cheers,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, February 11, 2016 10:24 AM
To: Umerah, Nina; Leyva-Grado, Victor
Subject: A57 call

Hi Nina and Victor,
I need to arrange a call with UNC and the next external submitter. Could you suggest two times that would work for UNC and MSSM? Should probably only need about 30-40 minutes.

Thanks!
Erik

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

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 11 Feb 2016 19:27:45 +0000
To: Hensley, Lisa (NIH/NIAID) [E]; Erlandson, Karl (OS/ASPR); Munster, Vincent (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Dreier, Thomas (OS/ASPR/BARDA); Spiro, David (NIH/NIAID) [E]
Subject: MERS-CoV Workshop Draft Agenda
Attachments: MERS Workshop Draft Agenda 2-11-2016.docx

Hi Everyone,
I think the agenda is just about in its final form, so I wanted to circulate it to the group to see if you have any comments. Things are shaping up, and we're looking forward to a productive discussion! I will paste the link to the registration site again below; please feel free to circulate it to anyone you think would be interested in attending.

Erik

https://respond.niaid.nih.gov/conferences/mers-cov_workshop2016/Pages/default.aspx

Standardizing MERS-CoV Animal Models

Current Status and the Path to Clinical Trials

Monday, February 29th, 2016		
8:30 – 9:00 am	Registration	
9:00 – 9:10 am	Welcome	

Session I: Virology, Epidemiology, and Clinical Experience		
9:10 – 9:30 am	Viral Update and Global Status	Dr Susan Gerber *Division of Viral Diseases, CDC*
9:30 – 9:50 am	Clinical Experience with MERS-CoV in the Kingdom of Saudi Arabia	Dr Hail Mater Alabdely *Ministry of Health, Kingdom of Saudi Arabia*
9:50 – 10:10 am	Clinical Experience with MERS-CoV in the Republic of Korea	Dr Sang Won Park *Seoul National University College of Medicine*
10:10 – 10:20 am	Break	

Session II: Animal Models of MERS-CoV Session Chairs: Dr Lisa Hensley and Dr Ralph Baric		
10:20 am – 12:25 pm	Mouse Models of MERS-CoV (25 minutes each presentation) Dr Stanley Perlman *University of Iowa* Dr Kent Tseng *University of Texas, Medical Branch* Dr Matthew Frieman *University of Maryland* Dr Vincent Munster *NIAID Rocky Mountain Laboratories* Dr Ralph Baric *University of North Carolina, Chapel Hill*	
12:30 – 2:00 pm	Lunch Break	***No USG funds provided for food or beverages***
2:00 – 2:20pm	Rabbit Model of MERS-CoV	Dr Katherine Houser *NIAID Laboratory of Infectious Diseases*
2:20 – 3:10 pm	Non-Human Primate Models of MERS-CoV	Dr Lisa Hensley *NIAID Integrated Research Facility* Dr Vincent Munster *NIAID Rocky Mountain Laboratories*
3:10 – 3:30 pm	Camelid Models of MERS-CoV	Danielle Adney *Colorado State University*
3:30 – 3:40 pm	Break	

Session III: Panel Discussion of MERS-CoV Models Session Chair: Dr Kanta Subbarao		
3:40 – 5:00 pm	Panel Discussion of Models Dr Stanley Perlman *University of Iowa* Dr Kent Tseng *University of Texas, Medical Branch* Dr Matthew Frieman *University of Maryland* Dr Vincent Munster *NIAID Rocky Mountain Laboratories* Dr Ralph Baric *University of North Carolina, Chapel Hill* Dr Katherine Houser *NIAID Laboratory of Infectious Diseases* Dr Lisa Hensley *NIAID Integrated Research Facility* Danielle Adney *Colorado State University*	
5:00 pm	Adjourn Day 1	

Tuesday March 1st, 2016		
8:30 – 9:00 am	Registration	
9:00 – 9:15 am	Recap of Day 1	

Session IV: Lessons Learned Session Chair: Dr Vincent Munster		
9:15 – 9:45 am	Public Health Preparedness and the Need for Human/Animal Medical Countermeasures	Dr Frederick Hayden *University of Virginia School of Medicine*
9:45 – 10:15 am	Lessons Learned from SARS-CoV	Dr Luis Enjuanes *Universidad Autonoma de Madrid*
10:15 – 10:45 am	Lessons Learned from the Kingdom of Saudi Arabia	Dr Hail Mater Alabdely *Ministry of Health, Kingdom of Saudi Arabia*
10:45 – 11:00 am	Break	

Session V: MERS MCM Development Session Chair: Dr Jean Hu-Primmer		
11:00 – 11:40 am	MERS-CoV Regulatory Questions	Dr Robert Fisher *FDA Office of Counterterrorism and Emerging Threats*
11:40 am – 12:10 pm	Animal Model Endpoints to Inform Clinical Trials	Dr Jim King *Biomedical Advanced Research and Development Authority (BARDA)*
12:10 – 12:30	Advanced MERS-CoV MCM Development	Dr Karl Erlandson *Biomedical Advanced Research and Development Authority (BARDA)*

Session VI: Summary and Next Steps		
12:30 – 1:00 pm	Meeting Summary	Dr Ralph Baric *University of North Carolina, Chapel Hill*
1:00 pm	Meeting Adjourns	

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 9 Feb 2016 13:49:19 +0000
To: Baric, Ralph
Subject: RE: MERS Model Workshop Summary?

Thanks Ralph!

I'll get Nina/MSSM to set up a time for a call with the next group for A57.

Erik

From: Baric, Ralph
Sent: Wednesday, February 03, 2016 6:11 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: MERS Model Workshop Summary?

I would be delighted. Also, we have finished the 2nd animal model experiment with the therapeutic antibody……so any more drugs? Ralph

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From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, February 03, 2016 10:07 AM
To: Baric, Ralph S
Subject: MERS Model Workshop Summary?

Hi Ralph,
As we're finalizing the workshop agenda, we thought it would be good to have a short summary talk at the end of day two to recap some highlights from the science and discussion. David and I were wondering if you might be willing to fill that role. At the moment it's scheduled for 12:30-1pm on Tues March 1st, with the meeting adjourning afterwards. Please let me know if you think that would be able to do, or if you think someone else might be a better fit.

Thanks!
Erik

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

****

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 14 Jan 2016 20:41:57 +0000
To: Subbarao, Kanta (NIH/NIAID) [E]; Hensley, Lisa (NIH/NIAID) [E]; Erlandson, Karl (OS/ASPR); Munster, Vincent (NIH/NIAID) [E]; Baric, Ralph; Dreier, Thomas (OS/ASPR/BARDA); Spiro, David (NIH/NIAID) [E]
Subject: MERS Animal Model Workshop Registration Website

Hi Everyone,
We've been working recently on contacting speakers and finalizing the agenda draft. I am still waiting on a few responses back and hope to send an updated version of the agenda by next week. In the meantime the registration website has been created, and I wanted to send it along and ask you to please forward it to anyone you think might be interested in attending.

Many thanks!
Erik

https://respond.niaid.nih.gov/conferences/mers-cov_workshop2016/Pages/default.aspx

From: (b)(6)
Sent: Sat, 19 Dec 2015 14:28:49 +0100
To: Cockrell, Adam
Cc: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Subject: Re: Summary of LCA60 data for prophylaxis study

Dear Adam,
Thanks!!! I am very happy of the outcome and also impressed by your mouse model.
I can't wait to see the virological data and to see if the Ab will be effective therapeutically.

Happy Christmas to you and Ralph!

Best regards,

(b)(6)

Inviato da iPhone

Il giorno 19-dic-2015, alle ore 13:49, Cockrell, Adam (b)(6) ha scritto:

Hi everyone.

I have attached a summary of the LCA60 antibody data that includes survival, weight loss, hemorrhage score, and respiratory function for the prophylactic study. The remaining data will be collected in the new year.

Hope everyone has happy holidays.

Adam Cockrell
Post-Doctoral Fellow
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, NC, 27599
Phone: (b)(6)

<Summary of Data LCA60.pdf>

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 15 Dec 2015 12:30:54 +0000
To: Baric, Ralph
Subject: RE: MERS Animal Model SAG

Thanks Ralph! The meeting is scheduled for Feb 29th and March 1st here in Fishers Lane.

From: Baric, Ralph
Sent: Monday, December 14, 2015 3:20 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: MERS Animal Model SAG

HI Erik, Sounds like a decent plan and luis is an outstanding speaker. Can you remind me the dates of this meeting again? I seem to have misplaced it. Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, December 14, 2015 2:47 PM
To: Hensley, Lisa (NIH/NIAID) [E]; Erlandson, Karl (OS/ASPR); Munster, Vincent (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph S; Dreier, Thomas (OS/ASPR/BARDA); Spiro, David (NIH/NIAID) [E]
Subject: RE: MERS Animal Model SAG

Hi Everyone,
David and I have been considering the speakers list with the funds we have to work with for the workshop. Unfortunately due to the cost it appears we will be limited to supporting three international speakers. Based on our earlier discussions with the group we feel it is important to invite someone from both the Kingdom of Saudi Arabia and South Korea for their perspectives and potential case descriptions. Our last version of the agenda included several other foreign speakers on topics of epidemiology, lessons learned from SARS, as well as NHP and mice model work from China.

In looking at the agenda David and I propose the final international speak we support cover the lessons learned from SARS model and MCM development, and we were thinking of inviting Luis Enjuanes for that role. We will attempt to have the other topics covered by others already attending the workshop.

We'd appreciate it if you could let us know if you agree with this plan. If not, please let us know who you think would be a better choice for the final speaker slot we can support.

Many thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Monday, November 9, 2015 10:33 AM
To: Hensley, Lisa (NIH/NIAID) [E] (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Dreier,

Thomas (OS/ASPR/BARDA) (b)(6) Spiro, David (NIH/NIAID) [E]
(b)(6)
Subject: RE: MERS Animal Model SAG

Hi Everyone,
Thank you again for your time last week. I have attached an updated version of the agenda that I think incorporates the discussion and speaker suggestions. I would appreciate it if you could please review and send me any updates by Monday Nov 16th. In particular there are a few highlighted areas that we still need to identify a potential speaker.

Please let me know if you have any questions.
Erik

From: Hensley, Lisa (NIH/NIAID) [E]
Sent: Monday, November 2, 2015 9:30 AM
To: Erlandson, Karl (OS/ASPR) (b)(6) Munster, Vincent (NIH/NIAID) [E]
(b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Subbarao, Kanta
(NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Dreier, Thomas
(OS/ASPR/BARDA) (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: (b)(6)
Subject: Re: MERS Animal Model SAG

Waiting for the leader to admit
Lisa Hensley

Sent from b berry

From: Erlandson, Karl (OS/ASPR)
Sent: Monday, November 02, 2015 09:21 AM
To: Munster, Vincent (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C' (b)(6)
Subject: RE: MERS Animal Model SAG

(301) 761-5000 (NIAID)
Code: (b)(6)

From: Munster, Vincent (NIH/NIAID) [E] (b)(6)
Sent: Monday, November 02, 2015 9:11 AM
To: Stemmy, Erik (NIH/NIAID) [E]; Erlandson, Karl (OS/ASPR); Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C'
Subject: Re: MERS Animal Model SAG

Trying to get onto the call?

Any ideas?

From: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6)
Date: Wednesday, October 28, 2015 at 12:01 PM
To: "Erlandson, Karl (OS/ASPR)" (b)(6) "Subbarao, Kanta (NIH/NIAID) [E]" (b)(6) "Baric, Ralph" (b)(6) "Munster, Vincent (NIH/NIAID) [E]" (b)(6) "Dreier, Thomas (OS/ASPR/BARDA)" (b)(6) "Hensley, Lisa (NIH/NIAID) [E]" (b)(6) David Spiro (b)(6)
Cc: "'Baric, Toni C'" (b)(6)
Subject: RE: MERS Animal Model SAG

Hi Everyone,
I've chosen some times over the next week for our next call. Please see the Doodle poll link below.

Thanks!
Erik

http://doodle.com/poll/(b)(6)

From: Erlandson, Karl (OS/ASPR)
Sent: Tuesday, October 27, 2015 11:18 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: 'Baric, Toni C' (b)(6)
Subject: RE: MERS Animal Model SAG

Hi Erik,

I also think it would be good to talk this over. I've made a few comments that could be used in the discussion.

Karl

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, October 23, 2015 8:15 AM
To: Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C'
Subject: RE: MERS Animal Model SAG

Hi Everyone,
I haven't received any comments back on the updated agenda. If it is easier for the group I can have a shot at suggesting organizers for the sessions and we can discuss the agenda by phone. I would

appreciate it if you could either send me your feedback, or let me know if scheduling a phone call would be easier, by Tuesday 10/27.

Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, October 13, 2015 8:58 AM
To: Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: 'Baric, Toni C' (b)(6)
Subject: RE: MERS Animal Model SAG

Hi Everyone,
Just a friendly reminder soliciting your feedback on the updated agenda draft attached again here. Also, I have looked into availability of the large conference room in our Fishers Lane building and come up with some potentials dates (listed below.) Could you please let me know if there are any that should be off the table due to conflicts, any that might be good to use to piggy back on other meetings, or any other preferences you have? I would ideally like to reserve the room in the next week.

Thanks!
Erik

Current Room Availability:
January: 18-19, 20-21
February: 10-11, 15-18, 22-23, 22-25, 29-March 1
March: 9-10, 28-31

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, October 02, 2015 12:55 PM
To: Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: 'Baric, Toni C' (b)(6)
Subject: MERS Animal Model SAG

Hi Everyone,

Thank you for your insightful discussion during our call on the 21st. David and I have incorporated your comments in the attached document. In particular we have expanded the agenda to a rough outline of a two day workshop, and would appreciate any feedback you have on the proposed session organization and topics. One other thing we'd like to ask is for volunteers to choose a session to chair. We anticipate

the session chairs will take the lead in setting the format for the session, suggesting speakers, and leading the session during the workshop.

If possible we'd like to ask for your feedback on this draft agenda and deliverables on or before Oct 14th. Please let me know If you have any questions.

Many thanks!
Erik

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

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

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From: Cockrell, Adam
Sent: Mon, 14 Dec 2015 19:50:51 +0000
To: (b)(6)
Cc: (b)(6) Baric, Ralph; Maria Zambon; Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Subject: RE: UPDATE MERS MABS

Thanks (b)(6)

I will keep an eye out for them.

Regards,
Adam

From: (b)(6)
Sent: Monday, December 14, 2015 5:45 AM
To: Cockrell, Adam (b)(6)
Cc: (b)(6) Baric, Ralph S (b)(6) Maria Zambon (b)(6) Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Adam,

The antibodies were shipped today with Fedex, we expect them to arrive on December 16.

Here is the tracking nr. 775167325653

Please find attached the description of the materials sent

Best Regards

(b)(6)

On 04.12.2015 21:18, Cockrell, Adam wrote:
Dear (b)(6)

Just to be on the safe side it might be best to wait to ship the following Monday (12-14-15). That will give a week in case of unforeseen events.

Regards,

Adam

From: (b)(6)
Sent: Friday, December 04, 2015 3:14 PM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Adam,
Here Tuesday will be public Holiday and it will be therefore better ship on Wednesday, or alternatively organize the shipment for the following week on Monday.
What do you prefer?

Best regards,

(b)(6)

(b)(6)
Humabs Biomed SA
Via Mirasole 1
CH-6500 Bellinzona
Switzerland
Tel: (b)(6)
E-mail: (b)(6)
http://www.humabs.com

Il giorno 03 dic 2015, alle ore 23:00, Cockrell, Adam (b)(6) ha scritto:

Dear (b)(6)

That sounds good. So the shipping goes smoothly, like the last shipment, could you ship on a Monday/Tuesday, and give me a notification of shipment so I can anticipate the date of receipt?

Once I have the data compiled I will definitely share it. I am leaving for the holidays on the 23rd and will not return until January 3rd. Provided all goes well I anticipate the initial experiment to be completed the 15th. I should be able to put together the weight loss and survival data.

Yes. I plan to use a mix of females/males that are 288-330 +/+ homozygous mice. We do not currently have the numbers to include the 288-330 +/- hets.

Cheers,

Adam

From: (b)(6)
Sent: Thursday, December 03, 2015 9:23 AM

To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Adam,
thanks for the clarifications.
We will aim to ship more material next week.
Would it be possible to have interim updates about the body weight loss and survival as soon as data will be available?

Another question, will you use 288-330 +/+ homozygous mice only?

Best regards,

(b)(6)

Il giorno 02 dic 2015, alle ore 12:41, Cockrell, Adam (b)(6) ha scritto:

Dear (b)(6)

Thanks. It would be helpful to have all of the antibody on hand. The previous shipping arrangement worked well.

Regarding the timeline. I would anticipate the first results early-mid January (experiment 1). Provided our University EHS approvals have been received, and taking into account the holidays, I should initiate the second experiment by mid-January, and accumulate the necessary data to move forward on the third experiment by the end of January-beginning of February. Provided all goes well this would put us in mid-late February, possibly beginning of March to complete assays and assemble all the data.

Cheers,

Adam

From: (b)(6)
Sent: Tuesday, December 01, 2015 5:17 PM
To: Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Adam,
Thanks for the slides! the description of the advantages of your model is indeed very helpful.

Could you clarify what could be the overall timeline for the completion of the three experiments if performed stepwise?
Since you are using 12 mice/group (6 used for the day 3 analysis and 6 for the day 6 readouts) you should need a little bit more than 20 mg. We can plan a shipment of more LCA60 and a matched IgG1 Ab (MPE8) in a week or two.

Best regards,

(b)(6)

(b)(6)
Humabs Biomed SA
Via Mirasole 1
CH-6500 Bellinzona
Switzerland
Tel: (b)(6)
E-mail: (b)(6)
http://www.humabs.com

Il giorno 01 dic 2015, alle ore 22:29, Cockrell, Adam (b)(6) ha scritto:

Hi everyone.

Here are the slides that we discussed on yesterday's phone call. The first couple describe the advantages of our model over existing mouse models and why it is the first model to recapitulate the severe respiratory disease that believe is occurring in humans.

The last 3 slides demonstrate the timeline for the study.

Please let me know if there are any comments/questions regarding the studies.

Regards,

Adam

From: Baric, Ralph S
Sent: Monday, November 30, 2015 9:06 AM
To: Maria Zambon (b)(6) Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Subject: RE: UPDATE MERS MABS

From: Maria Zambon (b)(6)
Sent: Sunday, November 29, 2015 7:31 AM
To: (b)(6) Baric, Toni C

Cc: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Colleagues,

Is there material in regards the mouse model set up by ralph Baric to be shared before this meeting tomorrow (as suggested in some of the earlier correspondance). I will be doing the phone call externally, so would appreciate an early view of any data, as I am not sure whether I will have good email access during the day tomorrow

thanks

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
National Infection Service
Public Health England
(b)(6)
Tel: (b)(6)
www.gov.uk/phe Follow us on Twitter@PHE.uk
Protecting and improving the nation's health

From: (b)(6)
Sent: 10 November 2015 17:32
To: Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Maria Zambon; Cockrell, Adam; Ralph Baric; Robin Gopal
Subject: Re: UPDATE MERS MABS

Dear Toni,

This is fine. I can provide the call-in number.

Here it is:

UK: 0808 234 88 76
Switzerland: 0800 329 329
USA: +1 866 591 43 61 (or +1 888 50 333 35)

Participant access code: (b)(6)

Best regards,

(b)(6)

Il giorno 10 nov 2015, alle ore 17:52, Baric, Toni C (b)(6) ha scritto:

Hi Everyone,
Let's set this call for Nov 30 at 9 am EST/ 2pm UK time. Does this work? Also, does someone have a call-in number or should I set this up?
Thank you,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, November 05, 2015 9:30 AM
To: Baric, Toni C; Maria Zambon; Cockrell, Adam; (b)(6)
Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

My preference would be for 11/30. I can do any time before 1pm EST.

Erik

From: Baric, Toni C (b)(6)
Sent: Thursday, November 05, 2015 9:26 AM
To: Maria Zambon (b)(6) Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Group,

Let's we revisit the following dates:
11/30 9-10 am EST or after 10 am EST
12/2 before 2 pm EST.

Please let me know the day and time range that works for all of you, keeping in mind that Maria will be calling in from UK.
Thanks
Toni

From: Maria Zambon (b)(6)
Sent: Wednesday, November 04, 2015 5:49 PM
To: Cockrell, Adam; Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

Hello,

Sorry if late to the party. I have already sent back a note saying the Monday of this week would work for me. Unfortunately I will be in Hng Kong the 17th to 20th, so would suggest we try earlier if we can

maria

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
National Infection Service
Public Health England
(b)(6)
Tel: (b)(6)
www.gov.uk/phe Follow us on Twitter@PHE.uk
Protecting and improving the nation's health

From: Cockrell, Adam (b)(6)
Sent: 04 November 2015 20:21
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Cc: Baric, Ralph S; Maria Zambon; Robin Gopal
Subject: RE: UPDATE MERS MABS

That sounds good for me.
Thanks,
Adam

From: Baric, Toni C
Sent: Wednesday, November 04, 2015 3:11 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

11/20 sounds good. How about 10 am? If this works for everyone, please let me know. Otherwise, please suggest a time before 1 pm that suits or a different day.
Thank you,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, November 04, 2015 3:07 PM
To: (b)(6) Baric, Toni C
Cc: Baric, Ralph S; Maria Zambon; Cockrell, Adam; Robin Gopal
Subject: RE: UPDATE MERS MABS

On 11/20 I can do any time before 1pm EST. Can we aim for that date?

Erik

From: (b)(6)
Sent: Wednesday, November 4, 2015 3:02 PM
To: Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Toni,

I am available on all dates with the exception of 12/4.

Best regards,

(b)(6)

Il giorno 04 nov 2015, alle ore 20:25, Baric, Toni C (b)(6) ha scritto:

How about the following:

Friday 11/20 Ralph is open all day. Then the next day is 11/30 –after 11, Wednesday 12/2 before 2 and all day on 12/4.

Best regards,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, November 04, 2015 2:13 PM
To: Baric, Toni C; Baric, Ralph S; Maria Zambon; Cockrell, Adam
Cc: (b)(6) Robin Gopal
Subject: RE: UPDATE MERS MABS

I am leaving for a meeting in Riyadh on 11/12, so we'll have to schedule a call after I return on 11/16.

Erik

From: Baric, Toni C (b)(6)
Sent: Wednesday, November 4, 2015 12:06 PM
To: Baric, Ralph (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6)
Cc: (b)(6) Robin Gopal (b)(6) Stemmy, Erik

(NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Maria,
Ralph is available on 11/12 after 3:30 and between 11:30-3 on Friday 11/13
Best regards,
Toni

From: Baric, Ralph S
Sent: Tuesday, November 03, 2015 4:11 PM
To: Maria Zambon; Cockrell, Adam; Baric, Toni C
Cc: (b)(6) Robin Gopal; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: UPDATE MERS MABS

Hi Maria, We have recently received 20mg of pure antibody from (b)(6) and have support by Erik Stemmy to perform your studies in the mouse model. Initially, we will evaluate protection prior to infection. We currently don't have approval to use sharps for therapeutic intervention postinfection, but are in the process of putting in the paperwork to administer drug postinfection. I recommend a two phase study, first prior to infection to demonstrate efficacy and then drug dose at day 1 or 2 postinfection (single dose?). We likely need to set up a time to discuss the experiments. We will also share the model details at that time. Toni can assist. We also are planning on doing the protection study in early December, post infection study would likely be jan at best. Adam is a key contact person for discussion. Hope you are doing well. It's a pleasure to work with you again. Thoughts? ralph

---

From: Maria Zambon (b)(6)
Sent: Friday, October 23, 2015 3:52 PM
To: Baric, Ralph S
Cc: (b)(6) Robin Gopal
Subject: UPDATE MERS MABS

Dear Ralph,

Greetings , we have not corresponded for a while…I think another pesky virus (Ebola) has caused a bit of a diversion for all of us. (b)(6) has mentioned that you have developed a new animal model for MERS which is transgenic, and is very sensitive. This is just a brief note to explore the possibility of extending mouse model work for LCA60. We have submitted a proposal to the Medical Research Council (MRC) in the UK to take LCA60 into a Phase 1 clinical study. This proposal included the costs for Phase 1 scale up to GMP and also a Phase 1 Pk study in healthy volunteers, and is a large proposal.

The response from the MRC has been favourable, but they are requesting strengthening of the pre-clinical package in the proposal to try and give more indication of how the Mab could be used. We would appreciate your advice/collaboration in this

(1) Could we propose more work in your mouse model to extend understanding of prophylaxis duration and the window for treatment. I am thinking about extending the time points post infection at which Mab is given and also refining knowledge of the duration of protection if given before challenge. One of the questions we are asked to address is to what are the parameters under which this might be used clinically. Currently the data we hold is more of a

YES/NO format, rather than a considered model approach to window of treatment opportunity.

(2) If you thought some more work was feasible, would this be possible without provision of funding from us under existing NIH contracts, or would you require additional funding, and if so, what would that be . (NB could we also slip in some work on LCA57, the non neutralising Mab that we have got ?). We would be pleased to include you as a co-applicant for MRC funding, subject to MRC rules for overseas applicants, but the full proposal application cannot be submitted before March, meaning that you might well have already done the work before we could provide any funding

(3) What is your advice about whether the animal model you have developed is suitable for use…Suggestions welcome

Grateful for a rapid response

Maria Zambon
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Deputy Director, NIS
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****
<Slides for LCA60 Human mAb study.pdf>

--

(b)(6)

Humabs BioMed SA
Via Murate 5a
6500 Bellinzona

Ph (b)(6)
Cell (b)(6)
Fax (b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 4 Dec 2015 16:28:57 +0000
To: 'Baric, Toni C'; Baric, Ralph
Subject: RE: UPDATE MERS MABS

Will do!

Erik

From: Baric, Toni C (b)(6)
Sent: Friday, December 04, 2015 11:27 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6)
Subject: RE: UPDATE MERS MABS

Perfect. Can you call Ralph's office? (b)(6)

Best regards
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, December 04, 2015 11:04 AM
To: Baric, Toni C; Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Thanks Toni! Let's say 11:30am.

Erik

From: Baric, Toni C (b)(6)
Sent: Friday, December 04, 2015 11:02 AM
To: Baric, Ralph (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik,
Ralph is available on Monday morning between 11 am and 5 pm.
Best regards,
Toni

From: Baric, Ralph S
Sent: Friday, December 04, 2015 10:59 AM
To: Baric, Toni C
Subject: FW: UPDATE MERS MABS

Can you find a time? Assume I get in around 10PM

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, December 04, 2015 10:55 AM
To: Baric, Ralph S
Subject: RE: UPDATE MERS MABS

No problem! Monday morning is actually pretty open for me. Let me know what time works for you.

Erik

From: Baric, Ralph
Sent: Friday, December 04, 2015 9:00 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik, I'm in a call from 11:30 to 1 or so, followed by someone from my group presenting in virology in progress series at unc. How about Monday?sorry again for spacing out while writing! ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, December 04, 2015 7:31 AM
To: Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Hi Ralph,
Sorry, I had something else at 3:30. I'm afraid I'm a bit swamped today, but should have some time around noon if you want to call then. Let me know.

Erik

From: Baric, Ralph
Sent: Thursday, December 03, 2015 3:43 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik, sorry for the delay in calling, got involved in writing and lost tract of time. Let me know when your available. Sorry--ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, December 03, 2015 10:05 AM
To: Baric, Ralph S
Subject: RE: UPDATE MERS MABS

That's fine. 3pm should work for me. I should be at my desk so you can reach me at (b)(6)

Erik

From: Baric, Ralph
Sent: Thursday, December 03, 2015 9:16 AM

To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik, any chance we can do sometime between 3-4PM today? ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, December 02, 2015 5:25 PM
To: Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Hi Ralph,
Sure. How about tomorrow afternoon at 2pm?

Erik

From: Baric, Ralph
Sent: Wednesday, December 2, 2015 4:51 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik, Can I talk with you tomorrow. Jarhling/Hensley/Johnson and Julie Dyall have completed MTA paperwork to obtain some of our MERS viruses for testing in primates and to replicate the mouse model in their facility. I want to make sure we don't inadvertently trip a GOF regulation inadvertently by sending the viruses. So I want to make sure this is good to go before I send anything. Do you have to have some time tomorrow or the next day-and if so suggest some times? Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, December 02, 2015 7:50 AM
To: Cockrell, Adam; Baric, Ralph S
Cc: Leyva-Grado, Victor (b)(6)
Subject: RE: UPDATE MERS MABS

Thanks Adam and Ralph. In terms of this A57 contract for now I'm only going to approve the first prophylactic study. We may be able to also do some or all of the other ones under the contract, but I need to also consider the other requests for this model. I should have a better idea in the next couple weeks, and will keep you posted.

Erik

From: Cockrell, Adam (b)(6)
Sent: Tuesday, December 1, 2015 4:29 PM
To: Baric, Ralph (b)(6) Maria Zambon (b)(6)
(b)(6) Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi everyone.

Here are the slides that we discussed on yesterday's phone call. The first couple describe the advantages of our model over existing mouse models and why it is the first model to recapitulate the severe respiratory disease that believe is occurring in humans.

The last 3 slides demonstrate the timeline for the study.

Please let me know if there are any comments/questions regarding the studies.

Regards,

Adam

From: Baric, Ralph S
Sent: Monday, November 30, 2015 9:06 AM
To: Maria Zambon (b)(6) Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Cockrell, Adam (b)(6)
Subject: RE: UPDATE MERS MABS

From: Maria Zambon (b)(6)
Sent: Sunday, November 29, 2015 7:31 AM
To: (b)(6) Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Colleagues,

Is there material in regards the mouse model set up by ralph Baric to be shared before this meeting tomorrow (as suggested in some of the earlier correspondance). I will be doing the phone call externally, so would appreciate an early view of any data, as I am not sure whether I will have good email access during the day tomorrow

thanks

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
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Public Health England
(b)(6)
Tel: (b)(6)
www.gov.uk/phe Follow us on Twitter@PHE.uk
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From: (b)(6)
Sent: 10 November 2015 17:32
To: Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Maria Zambon; Cockrell, Adam; Ralph Baric; Robin Gopal
Subject: Re: UPDATE MERS MABS

Dear Toni,

This is fine. I can provide the call-in number.

Here it is:

UK: 0808 234 88 76
Switzerland: 0800 329 329
USA: +1 866 591 43 61 (or +1 888 50 333 35)

Participant access code: (b)(6)

Best regards,

(b)(6)

Il giorno 10 nov 2015, alle ore 17:52, Baric, Toni C (b)(6) ha scritto:

Hi Everyone,
Let's set this call for Nov 30 at 9 am EST/ 2pm UK time. Does this work? Also, does someone have a call-in number or should I set this up?
Thank you,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, November 05, 2015 9:30 AM
To: Baric, Toni C; Maria Zambon; Cockrell, Adam; (b)(6)
Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

My preference would be for 11/30. I can do any time before 1pm EST.

Erik

From: Baric, Toni C (b)(6)
Sent: Thursday, November 05, 2015 9:26 AM
To: Maria Zambon (b)(6) Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Group,

Let's we revisit the following dates:
11/30 9-10 am EST or after 10 am EST
12/2 before 2 pm EST.

Please let me know the day and time range that works for all of you, keeping in mind that Maria will be calling in from UK.
Thanks
Toni

From: Maria Zambon (b)(6)
Sent: Wednesday, November 04, 2015 5:49 PM
To: Cockrell, Adam; Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

Hello,

Sorry if late to the party. I have already sent back a note saying the Monday of this week would work for me. Unfortunately I will be in Hng Kong the 17th to 20th, so would suggest we try earlier if we can

maria

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
National Infection Service
Public Health England
(b)(6)
Tel: (b)(6)
www.gov.uk/phe Follow us on Twitter@PHE.uk
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From: Cockrell, Adam (b)(6)
Sent: 04 November 2015 20:21
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)

Cc: Baric, Ralph S; Maria Zambon; Robin Gopal
Subject: RE: UPDATE MERS MABS

That sounds good for me.
Thanks,
Adam

From: Baric, Toni C
Sent: Wednesday, November 04, 2015 3:11 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

11/20 sounds good. How about 10 am? If this works for everyone, please let me know. Otherwise, please suggest a time before 1 pm that suits or a different day.
Thank you,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, November 04, 2015 3:07 PM
To: (b)(6) Baric, Toni C
Cc: Baric, Ralph S; Maria Zambon; Cockrell, Adam; Robin Gopal
Subject: RE: UPDATE MERS MABS

On 11/20 I can do any time before 1pm EST. Can we aim for that date?

Erik

From: (b)(6)
Sent: Wednesday, November 4, 2015 3:02 PM
To: Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Toni,

I am available on all dates with the exception of 12/4.

Best regards,

(b)(6)

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How about the following:

Friday 11/20 Ralph is open all day. Then the next day is 11/30 –after 11, Wednesday 12/2 before 2 and all day on 12/4.

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in early December, post infection study would likely be jan at best. Adam is a key contact person for discussion. Hope you are doing well. It's a pleasure to work with you again. Thoughts? ralph

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From: Maria Zambon (b)(6)
Sent: Friday, October 23, 2015 3:52 PM
To: Baric, Ralph S
Cc: (b)(6) Robin Gopal
Subject: UPDATE MERS MABS

Dear Ralph,

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The response from the MRC has been favourable, but they are requesting strengthening of the pre-clinical package in the proposal to try and give more indication of how the Mab could be used. We would appreciate your advice/collaboration in this

(1) Could we propose more work in your mouse model to extend understanding of prophylaxis duration and the window for treatment. I am thinking about extending the time points post infection at which Mab is given and also refining knowledge of the duration of protection if given before challenge. One of the questions we are asked to address is to what are the parameters under which this might be used clinically. Currently the data we hold is more of a YES/NO format, rather than a considered model approach to window of treatment opportunity.
(2) If you thought some more work was feasible, would this be possible without provision of funding from us under existing NIH contracts, or would you require additional funding, and if so, what would that be . (NB could we also slip in some work on LCA57, the non neutralising Mab that we have got ?). We would be pleased to include you as a co-applicant for MRC funding, subject to MRC rules for overseas applicants, but the full proposal application cannot be submitted before March, meaning that you might well have already done the work before we could provide any funding
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Grateful for a rapid response

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From: Cockrell, Adam
Sent: Fri, 4 Dec 2015 16:15:01 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Cc: Leyva-Grado, Victor (b)(6)
Subject: RE: UPDATE MERS MABS

Thanks Erik. That will be enough time for me. I will shift things around accordingly. Since we may not know until the end of the month, should we keep (b)(6) group in the loop on the potential for timeline changes?

Regards,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, December 04, 2015 10:57 AM
To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6)
Cc: Leyva-Grado, Victor (b)(6)
Subject: RE: UPDATE MERS MABS

Thanks Adam. My plan is to have a priority set for by the end of the month. Will that be enough time to work out the timing for the other LCA60 work?

Erik

From: Cockrell, Adam (b)(6)
Sent: Wednesday, December 02, 2015 8:23 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6)
Cc: Leyva-Grado, Victor (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Erik.

That sounds good. This will be important for this LCA60 project since it could alter the timeline of the second two therapeutic studies. It would be difficult to test additional drugs in concurrent studies due to animal availability, and the amount of time to execute those studies. Therefore, the two LCA60 therapeutic studies may have to be shifted to a later time in lieu of additional therapeutics. We would probably need to make (b)(6) group aware of any timeline changes as soon as possible if they are needing this information for IND submission.

Regards,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, December 02, 2015 7:50 AM

To: Cockrell, Adam (b)(6) Baric, Ralph S (b)(6)
Cc: Leyva-Grado, Victor (b)(6)
Subject: RE: UPDATE MERS MABS

Thanks Adam and Ralph. In terms of this A57 contract for now I'm only going to approve the first prophylactic study. We may be able to also do some or all of the other ones under the contract, but I need to also consider the other requests for this model. I should have a better idea in the next couple weeks, and will keep you posted.

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Subject: Re: UPDATE MERS MABS

Dear Toni,

This is fine. I can provide the call-in number.

Here it is:

UK: 0808 234 88 76
Switzerland: 0800 329 329
USA: +1 866 591 43 61 (or +1 888 50 333 35)

Participant access code: (b)(6)

Best regards,

(b)(6)

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Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

Hello,

Sorry if late to the party. I have already sent back a note saying the Monday of this week would work for me. Unfortunately I will be in Hng Kong the 17th to 20th, so would suggest we try earlier if we can

maria

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
National Infection Service
Public Health England
(b)(6)
Tel: (b)(6)
www.gov.uk/phe Follow us on Twitter@PHE.uk
Protecting and improving the nation's health

From: Cockrell, Adam (b)(6)
Sent: 04 November 2015 20:21
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Cc: Baric, Ralph S; Maria Zambon; Robin Gopal
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Cc: (b)(6) Robin Gopal
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****

****

****

From: Baric, Toni C
Sent: Tue, 1 Dec 2015 16:45:55 +0000
To: Baric, Toni C; Baric, Ralph; Beisel, Christopher (NIH/NIAID) [E]; Damania, Blossom A; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Sims, Amy C; Dugan, Vivien (NIH/NIAID) [E]
Subject: UNC-NIAID Monthly Conference call

Hi Everyone,
I am setting up another Outlook invitation for our monthly conference calls. The calling instructions will be the same every month.

Phone: 1-800-747-5150
Passcode: (b)(6)

Best regards,
Toni

From: Baric, Ralph
Sent: Mon, 30 Nov 2015 05:36:18 +0000
To: Maria Zambon; (b)(6) Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam
Subject: RE: UPDATE MERS MABS
Attachments: Baric-MERS-CoV-Model Description-Confidential.pptx

Hi Everyone, Figures describing MERS model, please keep confidential. Will discuss tomorrow. ralph

---

From: Maria Zambon (b)(6)
Sent: Sunday, November 29, 2015 7:31 AM
To: (b)(6) Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Cockrell, Adam; Baric, Ralph S
Subject: RE: UPDATE MERS MABS

Colleagues,

Is there material in regards the mouse model set up by ralph Baric to be shared before this meeting tomorrow (as suggested in some of the earlier correspondance). I will be doing the phone call externally, so would appreciate an early view of any data, as I am not sure whether I will have good email access during the day tomorrow

thanks

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From: (b)(6)
Sent: 10 November 2015 17:32
To: Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Maria Zambon; Cockrell, Adam; Ralph Baric; Robin Gopal
Subject: Re: UPDATE MERS MABS

Dear Toni,

This is fine. I can provide the call-in number.

Here it is:

UK: 0808 234 88 76
Switzerland: 0800 329 329
USA: +1 866 591 43 61 (or +1 888 50 333 35)

Participant access code: (b)(6)

Best regards,

(b)(6)

Il giorno 10 nov 2015, alle ore 17:52, Baric, Toni C (b)(6) ha scritto:

Hi Everyone,
Let's set this call for Nov 30 at 9 am EST/ 2pm UK time. Does this work? Also, does someone have a call-in number or should I set this up?
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Cc: Baric, Ralph S; Robin Gopal
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(b)(4)

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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 24 Nov 2015 15:35:56 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Maria Zambon; Cockrell, Adam; Baric, Ralph; Robin Gopal; (b)(6) Leyva-Grado, Victor (b)(6) (b)(6) 'Baric, Toni C'
Subject: Call to Discuss Humabs Study in TOA57

Hello Everyone,
Please see below for dial in information.

Best,
Erik

UK: 0808 234 88 76
Switzerland: 0800 329 329
USA: +1 866 591 4361 (or +1 888 503 3335)

Participant access code: (b)(6)

From: Cockrell, Adam
Sent: Tue, 10 Nov 2015 16:53:27 +0000
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; Maria Zambon; (b)(6)
Cc: Baric, Ralph; Robin Gopal
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The response from the MRC has been favourable, but they are requesting strengthening of the pre-clinical package in the proposal to try and give more indication of how the Mab could be used. We would appreciate your advice/collaboration in this

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(2) If you thought some more work was feasible, would this be possible without provision of funding from us under existing NIH contracts, or would you require additional funding, and if so, what would that be . (NB could we also slip in some work on LCA57, the non neutralising Mab that we have got ?). We would be pleased to include you as a co-applicant for MRC funding, subject to MRC rules for overseas applicants, but the full proposal application cannot be submitted before March, meaning that you might well have already done the work before we could provide any funding
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Grateful for a rapid response

Maria Zambon
Director, Reference Microbiology
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From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 9 Nov 2015 13:21:35 +0000
To: 'Leyva-Grado, Victor'
Cc: 'Umerah, Nina'; 'Amy Sims' (b)(6) Baric, Ralph
Subject: RE: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57

Hi Victor,
Just following up on this again. Without having the revised pdf of the extension request I can't begin routing it for approval. If it is not submitted before this afternoon, I can't guarantee that it will be approved. That means that that contract will end as scheduled on Nov 15th.

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, November 06, 2015 5:53 PM
To: Leyva-Grado, Victor (b)(6)
Cc: Umerah, Nina (b)(6)
Subject: RE: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57

Hi Victor,
Tell them to plan as if all 4 compounds are in hand. They will start the first in December, and continue on until all four are completed. We would ship the compounds to them as soon as the previous study finishes.

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Friday, November 6, 2015 5:40 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Umerah, Nina (b)(6)
Subject: FW: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57
Importance: High

Hi Erik,

Please see the e-mail below from Amy Sims describing UNC's plan for the NCE option 1 and let me know what do you think. I sent them a copy of your previous e-mail where it mentions 4 tests and that you have the compounds.

Cheers,

V

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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: Sims, Amy C (b)(6)
Sent: Friday, November 06, 2015 4:34 PM
To: Leyva-Grado, Victor
Cc: Baric, Ralph S; Umerah, Nina
Subject: Re: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57
Importance: High

Victor,

As you and I discussed earlier, If you can confirm how many compounds UNC will receive for Option Period 1 and when the last one will make it to UNC then I can use that information to modify our current request and to get the necessary signatures so I can return the revised paperwork to Mt. Sinai.

I have communicated this with Ralph and he agrees with this plan.

Please let me know what Dr. Stemmy says. Thank you, Amy

On Nov 6, 2015, at 3:10 PM, Leyva-Grado, Victor (b)(6) wrote:

Dear Dr Baric,

Sorry to bother you again but Amy told me she will be on the road and probably not available through e-mail.

As per the e-mail below from Erik, we will need to modify the request of the NEC considering that the first experiment of option 1 will start next month (the current NEC is for 2 months ending in January 14th!) .

If you do the 4 studies one after the other (NIH already have the other 2 compounds), how much time will you need to complete them? As Erik said, considering the experiments, analysis, breeding of the colony and Christmas holidays?

I need to convey this info to Erik as soon as possible because he wants to start the paper work today. Also I will need a very simple time frame of the experiments to attach it to the request of extension letter.

Thanks a lot,

V

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, November 06, 2015 2:52 PM
To: Leyva-Grado, Victor
Subject: RE: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57
Importance: High

Hi Victor,
I think even the two studies planned will likely go over the two months you've requested. The last email I had from Ralph said the first study would likely start in December, and the second would be January at best. The 2 months would only take you to January 15th. I think we have the compounds available, so ask them how much more time they'd need to comfortable do 4 studies back to back, with the first starting in December. Be sure they are taking in to account breeding time, analysis, and holidays as well.

Also, regarding the budget, they're not asking for any additional money, right? On the last monthly call we discussed a no-cost extension. Since none of the option studies started you shouldn't have invoiced us for any of the option funds yet.

For the paperwork, I would say revise the request letter and be sure to state no additional funds are necessary. Then as a second page, just give a brief timeframe for the 4 back-to-back studies starting in December. Does that make sense? I will need to get this into our computer system today, so please let me know right away the length of the extension request. The letter can follow a little bit later today.

Thanks!
Erik

Amy C. Sims, Ph.D.
2107 McGavran-Greenberg Hall
CB 7435
Chapel Hill, NC 27599-7435

Office: (b)(6)

(b)(6)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 6 Nov 2015 15:12:18 +0000
To: Umerah, Nina
Cc: Ralph Baric; 'Amy Sims' (b)(6)
Subject: RE: Formal request for an extension to Option 1 of contract HHSN272201000019I HHSN27200003 Task A57

Hi Nina,
Just reviewed this request. Is it correct you're only asking for a 2 month extension? Will that be enough time for Ralph to complete all 4 studies by January 15th? I thought on the last call he indicated that he would be starting the first study in December.

Please let me know.
Thanks!
Erik

From: Umerah, Nina (b)(6)
Sent: Friday, November 6, 2015 9:56 AM
To: Knight, Stanley (NIH/NIAID) [E] (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) PETERPALESE (b)(6)
Subject: Formal request for an extension to Option 1 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 1 for Task A57. Please feel to contact me with any questions or concerns.

Have a good weekend,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Cockrell, Adam
Sent: Thu, 5 Nov 2015 14:32:03 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Toni C; Maria Zambon;(b)(6)
Cc: Baric, Ralph; Robin Gopal
Subject: RE: UPDATE MERS MABS

11/30 sounds great for me.

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, November 05, 2015 9:30 AM
To: Baric, Toni C (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6)
Cc: Baric, Ralph S (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

My preference would be for 11/30. I can do any time before 1pm EST.

Erik

From: Baric, Toni C (b)(6)
Sent: Thursday, November 05, 2015 9:26 AM
To: Maria Zambon (b)(6) Cockrell, Adam (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Group,

Let's we revisit the following dates:
11/30 9-10 am EST or after 10 am EST
12/2 before 2 pm EST.

Please let me know the day and time range that works for all of you, keeping in mind that Maria will be calling in from UK.
Thanks
Toni

From: Maria Zambon (b)(6)
Sent: Wednesday, November 04, 2015 5:49 PM
To: Cockrell, Adam; Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E];(b)(6)
Cc: Baric, Ralph S; Robin Gopal
Subject: RE: UPDATE MERS MABS

Hello,

Sorry if late to the party. I have already sent back a note saying the Monday of this week would work for me. Unfortunately I will be in Hng Kong the 17th to 20th, so would suggest we try earlier if we can

maria

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
National Infection Service
Public Health England
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From: Cockrell, Adam (b)(6)
Sent: 04 November 2015 20:21
To: Baric, Toni C; Stemmy, Erik (NIH/NIAID) [E]; (b)(6)
Cc: Baric, Ralph S; Maria Zambon; Robin Gopal
Subject: RE: UPDATE MERS MABS

That sounds good for me.
Thanks,
Adam

From: Baric, Toni C
Sent: Wednesday, November 04, 2015 3:11 PM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Baric, Ralph S (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: RE: UPDATE MERS MABS

11/20 sounds good. How about 10 am? If this works for everyone, please let me know. Otherwise, please suggest a time before 1 pm that suits or a different day.
Thank you,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, November 04, 2015 3:07 PM
To: (b)(6) Baric, Toni C
Cc: Baric, Ralph S; Maria Zambon; Cockrell, Adam; Robin Gopal
Subject: RE: UPDATE MERS MABS

On 11/20 I can do any time before 1pm EST. Can we aim for that date?

Erik

From: (b)(6)
Sent: Wednesday, November 4, 2015 3:02 PM
To: Baric, Toni C (b)(6)
Cc: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6) Robin Gopal (b)(6)
Subject: Re: UPDATE MERS MABS

Dear Toni,

I am available on all dates with the exception of 12/4.

Best regards,

(b)(6)

Il giorno 04 nov 2015, alle ore 20:25, Baric, Toni C (b)(6) ha scritto:

How about the following:

Friday 11/20 Ralph is open all day. Then the next day is 11/30 –after 11, Wednesday 12/2 before 2 and all day on 12/4.

Best regards,
Toni

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, November 04, 2015 2:13 PM
To: Baric, Toni C; Baric, Ralph S; Maria Zambon; Cockrell, Adam
Cc: (b)(6) Robin Gopal
Subject: RE: UPDATE MERS MABS

I am leaving for a meeting in Riyadh on 11/12, so we'll have to schedule a call after I return on 11/16.

Erik

From: Baric, Toni C (b)(6)
Sent: Wednesday, November 4, 2015 12:06 PM
To: Baric, Ralph (b)(6) Maria Zambon (b)(6) Cockrell, Adam (b)(6)

Cc: (b)(6) Robin Gopal (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

Hi Maria,
Ralph is available on 11/12 after 3:30 and between 11:30-3 on Friday 11/13
Best regards,
Toni

From: Baric, Ralph S
Sent: Tuesday, November 03, 2015 4:11 PM
To: Maria Zambon; Cockrell, Adam; Baric, Toni C
Cc: (b)(6) Robin Gopal; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: UPDATE MERS MABS

Hi Maria, We have recently received 20mg of pure antibody from (b)(6) and have support by Erik Stemmy to perform your studies in the mouse model. Initially, we will evaluate protection prior to infection. We currently don't have approval to use sharps for therapeutic intervention postinfection, but are in the process of putting in the paperwork to administer drug postinfection. I recommend a two phase study, first prior to infection to demonstrate efficacy and then drug dose at day 1 or 2 postinfection (single dose?). We likely need to set up a time to discuss the experiments. We will also share the model details at that time. Toni can assist. We also are planning on doing the protection study in early December, post infection study would likely be jan at best. Adam is a key contact person for discussion. Hope you are doing well. It's a pleasure to work with you again. Thoughts? ralph

---

From: Maria Zambon (b)(6)
Sent: Friday, October 23, 2015 3:52 PM
To: Baric, Ralph S
Cc: (b)(6) Robin Gopal
Subject: UPDATE MERS MABS

Dear Ralph,

Greetings , we have not corresponded for a while…I think another pesky virus (Ebola) has caused a bit of a diversion for all of us. (b)(6) has mentioned that you have developed a new animal model for MERS which is transgenic, and is very sensitive. This is just a brief note to explore the possibility of extending mouse model work for LCA60. We have submitted a proposal to the Medical Research Council (MRC) in the UK to take LCA60 into a Phase 1 clinical study. This proposal included the costs for Phase 1 scale up to GMP and also a Phase 1 Pk study in healthy volunteers, and is a large proposal.

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parameters under which this might be used clinically. Currently the data we hold is more of a YES/NO format, rather than a considered model approach to window of treatment opportunity.

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(3) What is your advice about whether the animal model you have developed is suitable for use…Suggestions welcome

Grateful for a rapid response

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From: Maria Zambon
Sent: Wed, 4 Nov 2015 22:44:27 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Toni C; Baric, Ralph; Cockrell, Adam
Cc: (b)(6) Robin Gopal
Subject: RE: UPDATE MERS MABS

Dear colleagues,

Monday afternoon the 16th of November will work fine for me, assuming around 5pm in the UK. We are currently 5 hours ahead of Washington. Would be delighted to work with you again and discuss details of the model. Is there anything published yet, or in press to look at before then ? Agree prophylaxis might be best to demonstrate best effect, but hope it can move swiftly to treatment

(Afraid I get very confused about date formats US vs European, so hope I have got the month correct)

Best wishes

Maria Zambon
Director, Reference Microbiology
Deputy Director, NIS
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From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: 04 November 2015 19:13
To: Baric, Toni C; Baric, Ralph; Maria Zambon; Cockrell, Adam
Cc: (b)(6) Robin Gopal
Subject: RE: UPDATE MERS MABS

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Cc: (b)(6) Robin Gopal (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Subject: RE: UPDATE MERS MABS

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Sent: Tuesday, November 03, 2015 4:11 PM
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Subject: RE: UPDATE MERS MABS

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From: Maria Zambon (b)(6)
Sent: Friday, October 23, 2015 3:52 PM
To: Baric, Ralph S
Cc: (b)(6) Robin Gopal
Subject: UPDATE MERS MABS

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From: Subbarao, Kanta (NIH/NIAID) [E]
Sent: Mon, 2 Nov 2015 09:58:01 -0500
To: Erlandson, Karl (OS/ASPR); Munster, Vincent (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Dreier, Thomas (OS/ASPR/BARDA); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: mbio papers
Attachments: Lipkin commentary MERS recomb mBio 2015.pdf, Wang MERS recombination mBio 2015.pdf

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Chief, Emerging Respiratory Viruses Section
Laboratory of Infectious Diseases,
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33 North Drive, MSC 3203
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Middle East Respiratory Syndrome Coronavirus Recombination and the Evolution of Science and Public Health in China

W. Ian Lipkin

Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, New York, USA

Since the discovery of Middle East respiratory syndrome coronavirus (MERS-CoV) in late 2012, more than 1,400 people have received a laboratory diagnosis of MERS and over 450 people have died. Most of the cases have been documented on the Arabian Peninsula; however, sporadic cases have also been reported in Europe and Asia in travelers returning from the Middle East. Except in South Korea, the imported MERS-CoV has not established a substantive chain of infection beyond the index traveler case. The spread within South Korea to 186 people, resulting in 36 deaths, has been attributed to a delay in diagnosis and isolation of the index case, lapses in infection control, and care of patients by family members rather than trained medical staff. This interpretation was supported by a preliminary report from a World Health Organization panel wherein no mutations linked to transmissibility or pathogenesis were found in sequences obtained in South Korea and China. However, in a recent *mBio* article, Wang and colleagues report detailed genomic analysis of the virus implicated in the first known case of MERS in China (1). They describe 11 amino acid substitutions, 8 of them shared with the South Korean strain and MERS-CoV strains recently circulating in Saudi Arabia, and define a recombination event that they speculate may have contributed to enhanced human-to-human transmission of MERS-CoV and the rapid spread of the virus in South Korea.

Recombination is common in coronaviruses and has been implicated in the emergence of pathogenic coronaviruses in poultry, cats, and pigs (2, 3). It would not be surprising, therefore, if recombination were to occur in MERS-CoV and to result in enhanced transmission or virulence. Wang et al. clearly demonstrate through bootstrap scanning and single-nucleotide polymorphism analyses that the viruses found in South Korea and China represent a recombinant virus that contains a clade B group 3 coronavirus sequence in the 5′ portion of the genome and a clade B group 5 coronavirus sequence in the 3′ end of the genome, with a site of recombination between nucleotide positions 17206 and 17311, a region that spans the junction between the ORF1a and S genes. They note that the recombination is evident in recent strains identified in human cases of MERS in Saudi Arabia and estimate that the recombination occurred in Saudi Arabia in the later months of 2014.

The paper is important in two respects. First, the recombination event may have resulted in the evolution of a new lineage of MERS-CoV with different transmission properties. Additional field work in epidemiology and studies of recombinant viruses in culture and in animal models will be required to determine whether this proves true. However, the paper itself is evidence of an evolutionary advance in scientific expertise and transparency that is at least as important for microbiology and public health. China has come a long way since the emergence of SARS-CoV in 2002/2003.

REFERENCES

1. **Wang B, Liu D, Shi W, Lu R, Wang W, Zhao Y, Deng Y, Zhou W, Ren H, Wu J, Wang Y, Wu G, Gao GF, Tan W.** 2015. Origin and possible genetic recombination of the Middle East respiratory syndrome coronavirus from the first imported case in China: phylogenetics and coalescence analysis. mBio **6**(4):e01280-15. http://dx.doi.org/10.1128/mBio.00237-15.
2. **Tian PF, Jin YL, Xing G, Qv LL, Huang YW, Zhou JY.** 2014. Evidence of recombinant strains of porcine epidemic diarrhea virus, United States, 2013. Emerg Infect Dis **20**:1735–1738. http://dx.doi.org/10.3201/eid2010.140338.
3. **Terada Y, Matsui N, Noguchi K, Kuwata R, Shimoda H, Soma T, Mochizuki M, Maeda K.** 2014. Emergence of pathogenic coronaviruses in cats by homologous recombination between feline and canine coronaviruses. PLoS One **9**:e106534. http://dx.doi.org/10.1371/journal.pone.0106534.

Published 8 September 2015

Citation Lipkin WI. 2015. Middle East respiratory syndrome coronavirus recombination and the evolution of science and public health in China. mBio 6(5):e01381-15. doi: 10.1128/mBio.01381-15.

Address correspondence to wil2001@columbia.edu.

The views expressed in this Commentary do not necessarily reflect the views of this journal or of ASM.

Origin and Possible Genetic Recombination of the Middle East Respiratory Syndrome Coronavirus from the First Imported Case in China: Phylogenetics and Coalescence Analysis

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ABSTRACT **The Middle East respiratory syndrome coronavirus (MERS-CoV) causes a severe acute respiratory tract infection with a high fatality rate in humans. Coronaviruses are capable of infecting multiple species and can evolve rapidly through recombination events. Here, we report the complete genomic sequence analysis of a MERS-CoV strain imported to China from South Korea. The imported virus, provisionally named ChinaGD01, belongs to group 3 in clade B in the whole-genome phylogenetic tree and also has a similar tree topology structure in the open reading frame 1a and -b (ORF1ab) gene segment but clusters with group 5 of clade B in the tree constructed using the S gene. Genetic recombination analysis and lineage-specific single-nucleotide polymorphism (SNP) comparison suggest that the imported virus is a recombinant comprising group 3 and group 5 elements. The time-resolved phylogenetic estimation indicates that the recombination event likely occurred in the second half of 2014. Genetic recombination events between group 3 and group 5 of clade B may have implications for the transmissibility of the virus.**

IMPORTANCE **The recent outbreak of MERS-CoV in South Korea has attracted global media attention due to the speed of spread and onward transmission. Here, we present the complete genome of the first imported MERS-CoV case in China and demonstrate genetic recombination events between group 3 and group 5 of clade B that may have implications for the transmissibility of MERS-CoV.**

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Middle East respiratory syndrome coronavirus (MERS-CoV), first detected in the Kingdom of Saudi Arabia (KSA) in 2012, causes severe acute respiratory tract infection in humans, with a high case fatality rate (CFR) (1–4). Dromedary camels are believed to be important reservoir hosts or vectors for human infection; bats may also be implicated (5–8). As of 17 July 2015, 1,368 laboratory-confirmed cases of human infection with MERS-CoV had been reported to the World Health Organization (WHO), including at least 490 deaths, corresponding to a CFR as high as 35.45% (9). Recent MERS clusters in South Korea are thought to be the largest outbreak outside the Middle East countries (10). As of 25 July 2015, 186 laboratory-confirmed cases of MERS-CoV infection have been confirmed (including 36 deaths) in South Korea (9). A South Korean man who was a relative of some of the laboratory-confirmed cases traveled to Guangdong Province (10) and was diagnosed as the first imported MERS-CoV case in China by molecular detection of MERS-CoV (11, 12). The rapid spread of disease in South Korea raised concerns that the imported virus had evolved to become more transmissible. Here, we report a comprehensive phylogenetic analysis of the complete MERS-CoV genome sequence of the first Chinese imported case of MERS (ChinaGD01), and the results indicate its probable origin and show evidence of genetic recombination.

RESULTS

Patient and sample history. The current outbreak in South Korea and China was initiated when a 68-year-old Korean man flew back to Seoul on 4 May 2015 after a visit to four Middle East countries (Bahrain, United Arab Emirates, Saudi Arabia, and Qatar). On 26 May 2015, a 44-year-old South Korean man presented with fever to a hospital in Guangdong. He was in close contact with the

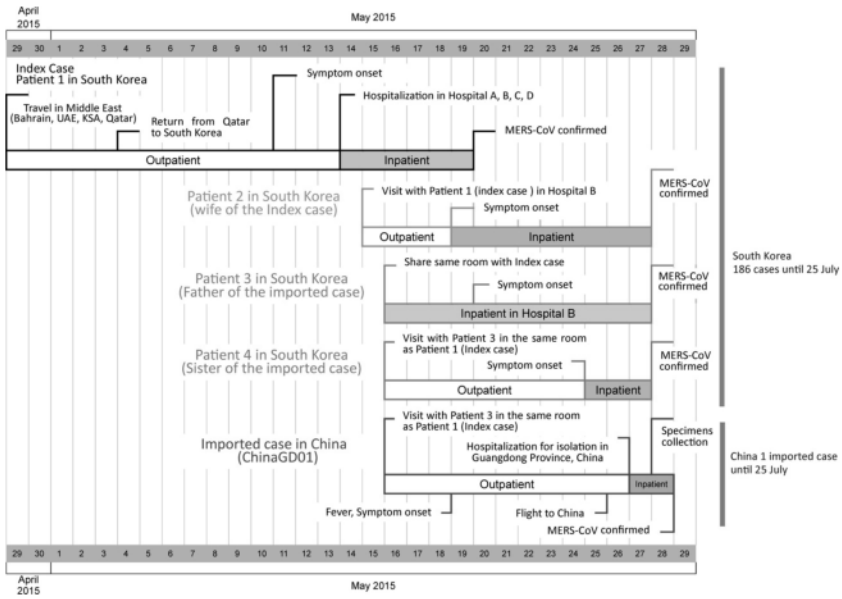

FIG 1 Timeline of the travel history, potential virus exposure, onset of disease, and diagnosis of the first imported MERS-CoV case in China. UAE, United Arab Emirates; KSA, Kingdom of Saudi Arabia.

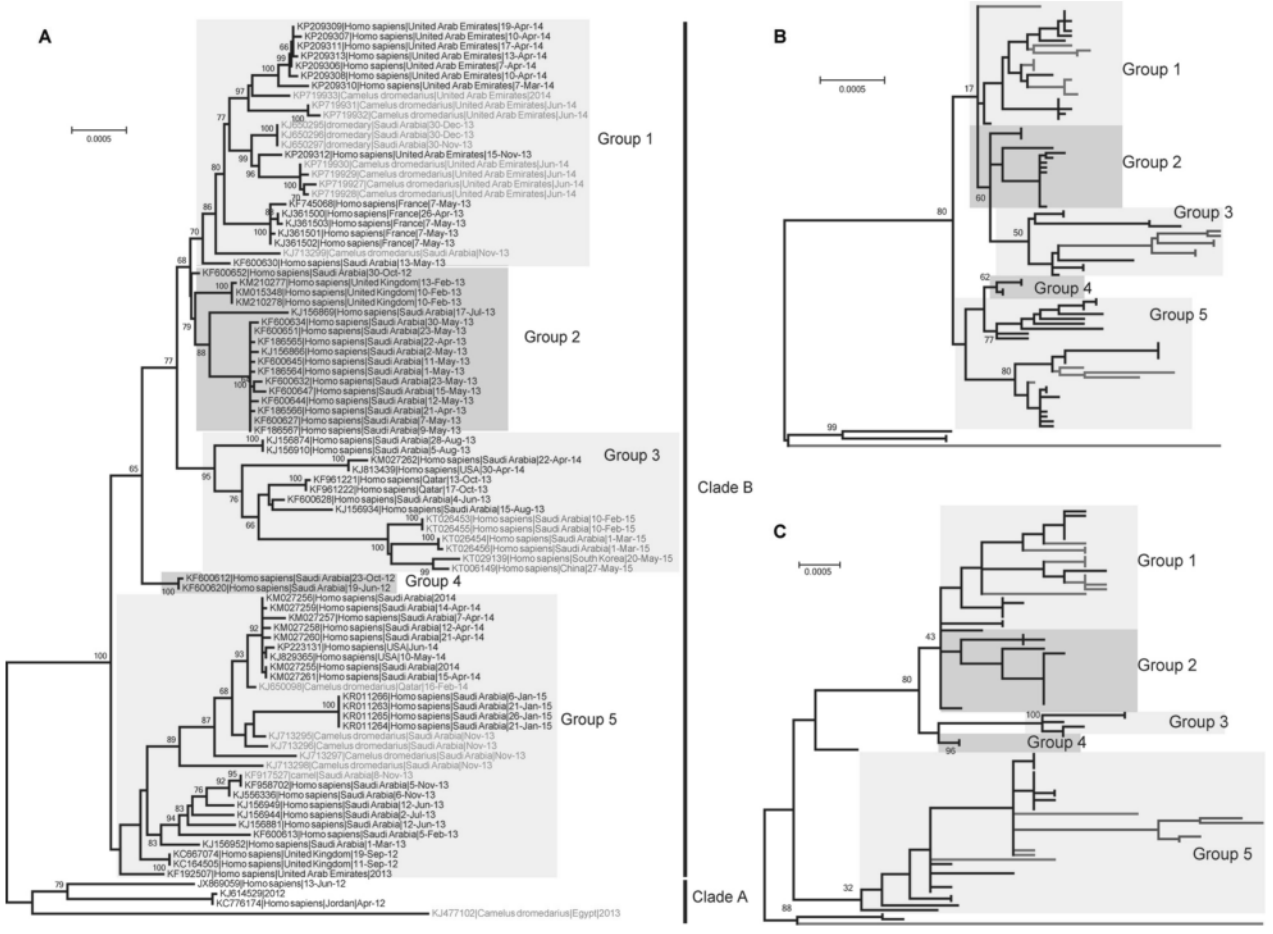

FIG 2 Phylogenetic relationships based on complete genomes (A), ORF1ab genes (B), and S genes (C) of MERS-CoV strains. China's first imported MERS-CoV strain (GenBank accession no. KT006149.2), South Korea's first MERS-CoV strain (GenBank accession no. KT029139), and the latest MERS-CoV strains prevalent in the Middle East (GenBank accession no. KT026453 to KT026456) are indicated in red. The MERS-CoV strains derived from camels are indicated in blue. All of the complete genomes were analyzed by nucleotide sequence alignment using the maximum-likelihood method implemented in the RAxML. Numbers at the nodes indicate bootstrap support for each node (percentage of 1,000 bootstrap replicates). Scale bars indicate the expected number of nucleotide substitutions per site.

index patient in South Korea on 16 May 2015 (Fig. 1), as well as a suspected second-generation patient. The timeline of the travel history, potential virus exposure, onset of disease, and diagnosis of the first imported MERS-CoV case in China are presented in Fig. 1.

Characterization of genome. With informed consent and the approval of the ethical committee of the National Institute of Viral Disease Control and Prevention, China Center for Disease Control and Prevention (CDC), nasopharyngeal swabs were collected and used for RNA extraction, followed by reverse transcription PCR and genome sequencing. Through both Sanger and Ion Torrent sequencing, the full-length virus genome (30,144 bp) of ChinaGD01 was obtained and deposited in GenBank (accession no. KT006149). Over 2,000,000 paired-end reads were quality trimmed and processed to remove human genome sequences. Nonhuman reads were assembled into contigs by CLC Genomic Workbench and aligned against representative sequences of MERS-CoV. No nucleotide insertions or deletions were observed in the genome.

The genome sequence of this virus, referred to as ChinaGD01, had high levels of nucleotide identity (99.33% to 99.79%) to previously published MERS-CoV genomes (Fig. 2), with 99.31% to 99.78% sequence identity in the open reading frame 1a and -b (ORF1ab) gene segment and 98.91% to 99.60% identity in the S gene. The E, M, and N genes had 98.93% to 100% identity with previously described MERS-CoV strains. In total, ChinaGD01 possessed 11 nonsynonymous nucleotide substitutions (Table 1), which occurred in the ORF1ab ($n = 8$), ORF3 ($n = 1$), ORF4b ($n = 1$), and M ($n = 1$) genes, respectively (Table 1). Although there were five nucleotide substitutions in the S gene, no amino acid change was discovered. Of note, in comparison with previously published MERS-CoV genomes, the ChinaGD01 genome shows 11 unique amino acid substitutions, and 8 of them were shared with the newly released South Korean strains and the latest strains prevalent in Saudi Arabia (Table 1).

TABLE 1 Comparison of sites of variation between gene sequences of ChinaGD01, the first South Korean strain, the latest Saudi Arabia strains, and other MERS-CoV strains[a]

Gene	Position (bp)	China		South Korea		Saudi Arabia		Others	
		Nt	Aa	Nt	Aa	Nt	Aa	Nt	Aa
ORF1ab	**472**	**G**	**Val**	**G**	**Val**	**G**	**Val**	**T**	**Phe**
	2496	C	Phe	C	Phe	C	Phe	T	Phe
	2930	**G**	**Gly**	**G**	**Gly**	**A**	**Asp**	**A**	**Asp**
	3706	**A**	**Thr**	**A**	**Thr**	**A**	**Thr**	**G**	**Ala**
	5895	C	Ser	C	Ser	C	Ser	T	Ser
	6357	**T**	**Ile**	**T**	**Ile**	**T**	**Ile**	**G**	**Met**
	6876	C	Phe	C	Phe	T	Phe	T	Phe
	7277	**T**	**Ile**	**T**	**Ile**	**T**	**Ile**	**C**	**Thr**
	9678	T	Ser	T	Ser	C	Ser	C	Ser
	10716	T	Val	T	Val	C	Val	C	Val
	11649	C	Asp	C	Asp	T	Asp	T	Asp
	17868	**A**	**Ile**	**A**	**Ile**	**A**	**Ile**	**G**	**Val**
	19739	**T**	**Ile**	**T**	**Ile**	**T**	**Ile**	**G**	**Met**
	20685	**A**	**Ser**	**A**	**Ser**	**G**	**Gly**	**G**	**Gly**
S	258	C	Val	C	Val	C	Val	T	Val
	1848	C	Val	T	Val	T	Val	T	Val
	2841	C	Tyr	C	Tyr	C	Tyr	T	Tyr
	3177	C	Asp	C	Asp	T	Asp	T	Asp
	3267	T	Ala	T	Ala	C	Ala	T	Ala
ORF3	**49**	**T**	**Phe**	**T**	**Phe**	**T**	**Phe**	**C**	**Leu**
	183	T	Asp	T	Asp	C	Asp	C	Asp
	237	T	Ser	T	Ser	T	Ser	A	Ser
ORF4a	258	C	Asp	T	Asp	C	Asp	T	Asp
ORF4b	**17**	**C**	**Thr**	**T**	**Met**	**C**	**Thr**	**T**	**Met**
ORF5	228	T	Leu	T	Leu	T	Leu	G	Leu
M	**367**	**A**	**Ile**	**A**	**Ile**	**A**	**Ile**	**T**	**Phe**
	438	T	Gly	T	Gly	T	Gly	C	Gly

[a] The positions of amino acid substitutions are indicated by boldface. China, imported MERS-CoV strain ChinaGD01 (GenBank accession no. KT006149); South Korea, South Korea's first MERS-CoV strain (GenBank accession no. KT029139); Saudi Arabia, MERS-CoV strains recently identified in Saudi Arabia (GenBank accession no. KT026453 to KT026456); Others, other MERS-CoV strains detected worldwide; Nt, nucleotide; Aa, amino acid.

Phylogenetic analysis. To further investigate the genetic relationship between ChinaGD01 and other MERS-CoV strains whose genomes are available, we performed phylogenetic analyses using the complete genome, the ORF1ab gene, and the S gene. From the whole-genome phylogeny, all available MERS-CoV strains can be clustered into two clades, the earlier clade A and the more recent clade B (Fig. 2A). ChinaGD01 fell into group 3 of clade B (Fig. 2A). Within group 3, ChinaGD01 and the South Korean and Saudi Arabian strains from 2015 were closely clustered and formed a long branch, separate from others of group 3. The nearest strain to this branch was Hafr-Al-Batin-1-2013 (GenBank accession no. KF600628), isolated in August 2013. Phylogenetic analysis of the ORF1ab gene indicated a similar topology in which ChinaGD01 and the recent MERS-CoV strains identified in South Korea were closely adjacent to Hafr-Al-Batin-1-2013 in group 3 (Fig. 2B). However, the phylogeny of the S gene differed in that the new viruses fell into group 5 and were closely related to viruses from both humans and dromedaries (Fig. 2C). These findings are consistent with recombination, a phenomenon not uncommon in coronaviruses.

Genetic recombination analysis. To examine whether genetic recombination has occurred in ChinaGD01, we performed bootscanning analyses. We compared ChinaGD01 with representative viruses from group 3 (Hafr-Al-Batin-1-2013; GenBank accession no. KF600628), group 5 (KSA-CAMEL-378; GenBank accession no. KJ713296), and group 1 (Abu Dhabi_UAE_9_2013; GenBank accession no. KP209312) as controls. As shown in Fig. 3A, ChinaGD01 was more similar to the group 3 strain from position 1 to 15,000 and more similar to the group 5 strain from approximately position 18,000 to 24,000. We then compared the single-nucleotide polymorphisms (SNPs) of ChinaGD01 with consensus sequences of group 3 and group 5 (Fig. 3B; see also Fig. S1 and S2 in the supplemental material). There were 78 SNPs discovered along the ChinaGD01 genome (Fig. 3B). Whereas before position 17,206, ChinaGD01's SNP pattern is nearly identical to that of the group 3 viruses, its SNP pattern is more similar to that of group 5 viruses between positions 17,311 and 23,804. The consistency in the results of bootscanning and SNP analyses supports the hypothesis that the gene segment from approximately position 17,300 to 24,000, representing portions of the ORF1ab and S genes, reflects a recombination event (Fig. 3B).

Phylogenetic analysis was further performed using BEAST with the complete genome, the nonrecombinant region (positions 1 to 17,300), and the potential recombinant region (positions 17,301 to 24,000), respectively (Fig. 4). The phylogenies revealed by the BEAST trees were consistent with those from the maximum-likelihood trees. In the trees constructed using the

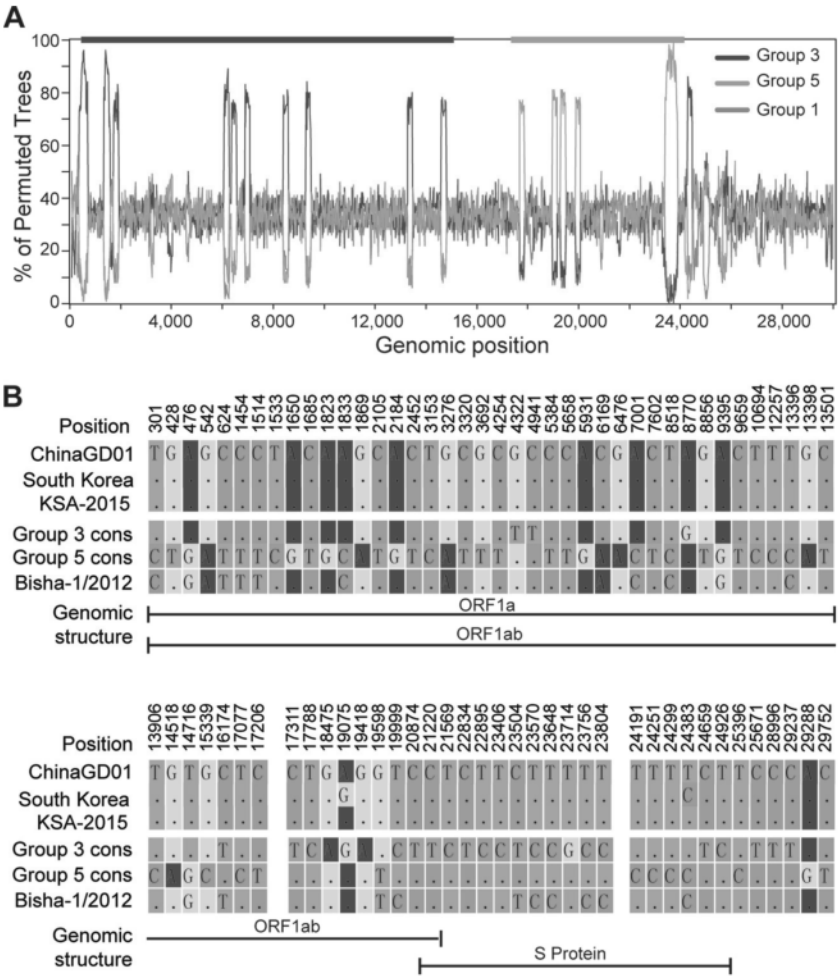

FIG 3 Recombination analyses of complete MERS-CoV genomes. (A) Bootscanning analysis of MERS-CoV genome. The ChinaGD01 strain was used as a query sequence and compared with one strain from group 3 (GenBank accession no. KF600628.1), one from group 5 (GenBank accession no. KJ713296.1), and one from group 1 (GenBank accession no. KP209312.1). (B) Single-nucleotide differences between the ChinaGD01 sequence and consensus sequences of group 3 and group 5. Group 3 cons, consensus sequences of group 3 strains; group 5 cons, consensus sequences of group 5 strains; South Korea, first MERS-CoV strain (GenBank accession no. KT029139) in South Korea; KSA-2015, latest strains prevalent in Saudi Arabia (GenBank accession no. KT026453 to KT026456), Bisha-1/2012, an earlier strain used as a control.

complete genome and the nonrecombinant region, ChinaGD01 fell within group 3; however, trees constructed using the recombinant region clustered with the group 5 sequences.

To date the recombination event, we estimated the time to most recent common ancestor for the novel MERS-CoV from 2015. Although there was a slight difference among results from different models, the time to most recent common ancestor of the 2015 cluster was estimated to be between 0.5 and 0.7 years before the identification of the imported case in the latter months of 2014 (Table 2). Given the observation of similar recombination events in the newly released South Korean strains and the latest strains prevalent in Saudi Arabia, the travel histories of patients, and potential opportunities for virus exposure, we surmise that the recombination likely occurred in the Arabian Peninsula.

DISCUSSION

Over the past 3 years, MERS-CoV infections have continued to increase, posing a serious threat to global public health. Previous studies have revealed that MERS-CoV infections are likely due to repeated introductions of MERS-CoV from dromedary camels to humans (13–15), resulting in only limited human-to-human transmission (16). However, the large number of second- and third-generation cases in South Korea raised concerns that MERS-CoV may have evolved to become more adapted to human-to-human transmission.

Our results indicate that at the whole-genome level, ChinaGD01 is >99% similar to the previously identified MERS-CoV strains. Phylogenetic analysis based on the whole-genome sequence revealed that it belongs to group 3 of clade B MERS-CoV strains and forms a separate small branch with viruses from South Korea and Saudi Arabia from 2015. Different phylogenies were observed in the trees constructed using the full-length genome and the S gene, indicating the possibility of a recombination event. Further evidence of a recombination event was obtained through bootscanning and SNP analyses. BEAST analysis revealed that it might have occurred recently, in the second half of 2014, in the Middle East.

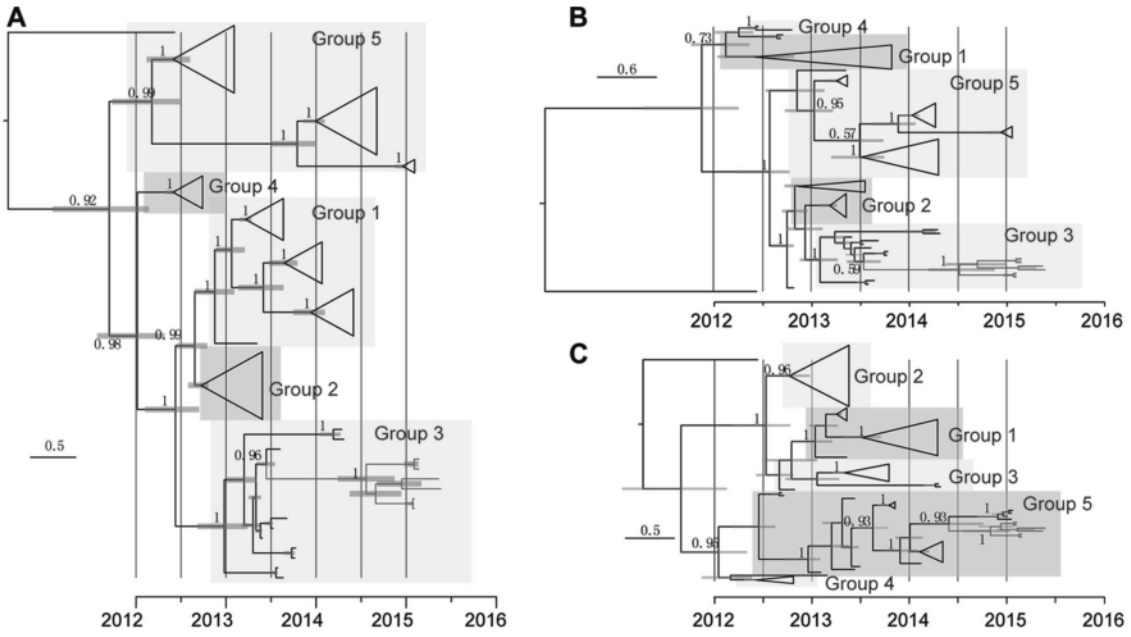

FIG 4 Time-resolved phylogenetic analyses of complete genomes (A), nonrecombination regions (B), and recombination regions (C) of MERS-CoV strains using BEAST. The nonrecombination region is approximately bp 1 to 17,300, and the recombination region is approximately bp 17,301 to 24,000. ChinaGD01 (GenBank accession no. KT006149), South Korea's first MERS-CoV strain (GenBank accession no. KT029139), and the latest strains prevalent in Saudi Arabia (GenBank accession no. KT026453 to KT026456) are indicated in red.

Genetic recombination has been well established in severe acute respiratory syndrome coronavirus (SARS-CoV) (17, 18); however, there is only one report of genetic recombination in MERS-CoV (19). Dudas and Rambaut point to frequent recombination in MERS-CoV and partition the genome into two parts in which nucleotides 1 to 23,722 and nucleotides 23,723 to 30,126 have independent molecular clock rates. Based on the latest genome sequences from South Korea and the Kingdom of Saudi Arabia, our research indicated that a novel type of genetic recombination has occurred in the MERS-CoV strains prevalent in South Korea. We note that six MERS-CoV isolates from 2015 (ChinaGD01, the first MERS-CoV strain from South Korea, and the four latest strains from Saudi Arabia) had high levels of nucleotide identity (99.90% to 99.96%) and showed the same recombination signal in our analyses. We speculate that they arose from a common recombination event. However, more studies are needed to understand the relationship between genetic recombination of MERS-CoV, the biological properties it conveys, and its relevance to the recent high rate of transmission.

MATERIALS AND METHODS

Full-length genomic sequencing. Nasopharyngeal swabs from the South Korean patient diagnosed with MERS-CoV infection were collected and used for viral RNA extraction with the QIAamp viral RNA minikit. Forty-four sets of specific primer pairs were designed and used to amplify the complete genome, followed by Sanger sequencing; meanwhile, the extracted viral RNA was also used for next-generation sequencing with the Ion Torrent PGM after random amplification.

Phylogenetic analysis. We downloaded all (n = 92) available full-length genome sequences of MERS-CoV from GenBank and used RAxML (20) for phylogenetic analyses of the complete genome, the ORF1ab gene, and the S gene, respectively. One thousand bootstrap replicates were run. Furthermore, the Bayesian Markov chain Monte Carlo method, implemented in BEAST (21), was used to estimate the time to the most recent common ancestor. Twelve different model combinations were applied. For all the analyses, we used the general time-reversible nucleotide substitution model with gamma-distributed rate heterogeneity. Bayesian Markov chain Monte Carlo analysis was run for 50 million steps. Trees and parameters were sampled every 5,000 steps, with the first 10% removed as burn-in.

Genetic recombinant analysis. Similarity plots and bootscanning analysis were generated by SimPlot (22); a sliding window of 200 nucleotides was used, moving in 20-nucleotide steps. Single-nucleotide-difference analysis was used to confirm the recombination event.

Nucleotide sequence accession number. The full-length virus genome (30,144 bp) of ChinaGD01 was deposited in GenBank under accession no. KT006149.

TABLE 2 Estimated times in years to most recent common ancestor of the 2015 cluster

Molecular clock model	Value for indicated coalescent model [mean (95% CI)]			
	Constant size	Exponential growth	Logistic growth	GMRF Bayesian skyride[a]
Strict clock	0.6594 (0.4259, 0.9137)	0.6046 (0.371, 0.8562)	0.6621 (0.4167, 0.9201)	0.6007 (0.3611, 0.8396)
Exponential relaxed clock	0.6008 (0.3586, 0.8944)	0.5208 (0.3339, 0.7868)	0.6037 (0.3578, 0.9059)	0.5199 (0.3141, 0.8026)
Lognormal relaxed clock	0.6394 (0.4049, 0.9247)	0.582 (0.3684, 0.8437)	0.641 (0.4085, 0.9167)	0.5711 (0.3351, 0.8264)

[a] GMRF, Gauss Markov random fields.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at http://mbio.asm.org/lookup/suppl/doi:10.1128/mBio.01280-15/-/DCSupplemental.

Figure S1, PDF file, 0.5 MB.

Figure S2, PDF file, 0.4 MB.

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22. **Lole KS, Bollinger RC, Paranjape RS, Gadkari D, Kulkarni SS, Novak NG, Ingersoll R, Sheppard HW, Ray SC**. 1999. Full-length human immunodeficiency virus type 1 genomes from subtype C-infected seroconverters in India, with evidence of intersubtype recombination. J Virol **73:**152–160.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 2 Nov 2015 13:18:27 +0000
To: Baric, Ralph; Leyva-Grado, Victor (b)(6)
(b)(6) (b)(6)
Cc: Sims, Amy C
Subject: RE: A57 Option 1

Nope, unfortunately when we wrote the statement of work back in 2013 the options were only for 4 months. I think we'd discussed over the summer about a NCE, but it fell off my radar with our EOY work.

From: Baric, Ralph
Sent: Sunday, November 01, 2015 10:04 AM
To: Stemmy, Erik (NIH/NIAID) [E] (b)(6) Leyva-Grado, Victor (b)(6)
(b)(6) (b)(6) (b)(6)
(b)(6) (b)(6)
Cc: Sims, Amy C (b)(6)
Subject: RE: A57 Option 1

Hi Erik, My understanding is that option 1 was for six months, not four. Amy is this correct? Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, October 30, 2015 12:37 PM
To: Baric, Ralph S; Leyva-Grado, Victor (b)(6) (b)(6)
(b)(6)
Subject: A57 Option 1
Importance: High

Hi Ralph, Victor, and Nina,
After our call yesterday I pulled up the option we exercised and noticed that the period of performance for the option ends in November (11/14/15). Did we discuss in the past requesting a no cost extension? We'll need to figure out what to do pretty quickly. Similar to what we did after the GoF pause we'll need a written request with the justification for why more time is needed (delays breeding and passaging to achieve the lethal model?). We'll also need a summary of the funds spent/remaining. The last thing to include should be an updated timeline for the extension setting out the timeframe for the four studies, starting with the LCA60 one in November.

Let me know if that makes sense. Thanks!
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18

Bethesda, MD 20892-9825
Phone: (b)(6)
Email:

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
Sent: Thu, 29 Oct 2015 18:03:59 +0000
To: Leyva-Grado, Victor; NIAID DMID IDIQ; Stemmy, Erik (NIH/NIAID) [E]
Cc: Umerah, Nina; Heise, Mark T; Baric, Toni C
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - November progress report

Can someone send me the passcode. I can't seem to connect?

From: Leyva-Grado, Victor (b)(6)
Sent: Thursday, October 29, 2015 1:21 PM
To: 'idiq@mail.nih.gov'; 'Stemmy, Erik (NIH/NIAID) [E]'
Cc: Umerah, Nina; Baric, Ralph S; Heise, Mark T
Subject: HHSN272201000019I-HHSN27200003-Task A57 - November progress report

Dear Erik,

Attached you will find the October 2015 progress report for Task A57.

Please let us know if further information is required.

Thanks a lot,

Victor

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 29 Oct 2015 17:58:53 +0000
To: Leyva-Grado, Victor; NIAID DMID IDIQ
Cc: Umerah, Nina; Baric, Ralph; 'Heise, Mark T'
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - November progress report

Hi Victor,
This appears to be an old report from 2014. Can you check to see if it is the correct one?

Erik

From: Leyva-Grado, Victor (b)(6)
Sent: Thursday, October 29, 2015 1:21 PM
To: NIAID DMID IDIQ <idiq@mail.nih.gov>; Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Cc: Umerah, Nina (b)(6) Baric, Ralph (b)(6) 'Heise, Mark T' (b)(6)
Subject: HHSN272201000019I-HHSN27200003-Task A57 - November progress report

Dear Erik,

Attached you will find the October 2015 progress report for Task A57.

Please let us know if further information is required.

Thanks a lot,

Victor

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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: Mathur, Punam (NIH/NIAID) [E]
Sent: Mon, 26 Oct 2015 14:22:22 +0000
To: Mathur, Punam (NIH/NIAID) [E]; Baric, Ralph; Dugan, Vivien (NIH/NIAID) [E]; Yao, Alison (NIH/NIAID) [E]; Graham, Rachel; Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: ORFEOME-NIAID Call

Dear All,

Our monthly teleconference for next month has been rescheduled to Thursday, November 5th from 3 – 4 pm EST.

Standing Agenda:

* Project Updates
* Core Updates
* Data Submission
* BEI submission
* Manuscript updates
* Website updates
* Scientific call/webinar once per quarter with Co-PIs from each project.

Call in information
Toll free number: 866-795-4107
Passcode: (b)(6)

Best,
Punam

From: Subbarao, Kanta (NIH/NIAID) [E]
Sent: Mon, 26 Oct 2015 09:44:40 -0400
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Cc: 'Baric, Toni C'
Subject: Re: MERS Animal Model SAG

It might be better to discuss over the phone.

About the dates:
January 18 and Feb 15 are federal holidays
Feb 21-26: Gordon Conference of Biology of Acute Respiratory Infections in Galveston
March 10 and 11: NAS GOF meeting
March 31 is the first day of the International Respiratory Viruses meeting in Lisbon

I won't be available from Feb 11-27 (vacation)

Kanta

--
Kanta Subbarao, MD, MPH
Chief, Emerging Respiratory Viruses Section
Laboratory of Infectious Diseases,
NIAID, NIH
Bldg 33, Room 3E13C.1,
33 North Drive, MSC 3203
Bethesda, MD 20892-3203

Phone: (b)(6)
Fax: 301-480-4749
Email: (b)(6)

From: "Stemmy, Erik (NIH/NIAID) [E]" (b)(6)
Date: Friday, October 23, 2015 at 8:14 AM
To: kanta s (b)(6) Ralph Baric (b)(6) "Munster, Vincent (NIH/NIAID) [E]" (b)(6) "Dreier, Thomas (OS/ASPR/BARDA)"

(b)(6) "Erlandson, Karl (OS/ASPR)" (b)(6) "Hensley, Lisa (NIH/NIAID) [E]" (b)(6) "Spiro, David (NIH/NIAID) [E]" (b)(6)
Cc: "'Baric, Toni C'" (b)(6)
Subject: RE: MERS Animal Model SAG

Hi Everyone,
I haven't received any comments back on the updated agenda. If it is easier for the group I can have a shot at suggesting organizers for the sessions and we can discuss the agenda by phone. I would appreciate it if you could either send me your feedback, or let me know if scheduling a phone call would be easier, by Tuesday 10/27.

Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, October 13, 2015 8:58 AM
To: Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)
Cc: 'Baric, Toni C' (b)(6)
Subject: RE: MERS Animal Model SAG

Hi Everyone,
Just a friendly reminder soliciting your feedback on the updated agenda draft attached again here. Also, I have looked into availability of the large conference room in our Fishers Lane building and come up with some potentials dates (listed below.) Could you please let me know if there are any that should be off the table due to conflicts, any that might be good to use to piggy back on other meetings, or any other preferences you have? I would ideally like to reserve the room in the next week.

Thanks!
Erik

Current Room Availability:
January: 18-19, 20-21
February: 10-11, 15-18, 22-23, 22-25, 29-March 1
March: 9-10, 28-31

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, October 02, 2015 12:55 PM
To: Subbarao, Kanta (NIH/NIAID) [E] (b)(6) Baric, Ralph (b)(6) Munster, Vincent (NIH/NIAID) [E] (b)(6) Dreier, Thomas (OS/ASPR/BARDA) (b)(6) Erlandson, Karl (OS/ASPR) (b)(6) Hensley, Lisa (NIH/NIAID) [E] (b)(6) Spiro, David (NIH/NIAID) [E] (b)(6)

Cc: 'Baric, Toni C' (b)(6)
Subject: MERS Animal Model SAG

Hi Everyone,

Thank you for your insightful discussion during our call on the 21st. David and I have incorporated your comments in the attached document. In particular we have expanded the agenda to a rough outline of a two day workshop, and would appreciate any feedback you have on the proposed session organization and topics. One other thing we'd like to ask is for volunteers to choose a session to chair. We anticipate the session chairs will take the lead in setting the format for the session, suggesting speakers, and leading the session during the workshop.

If possible we'd like to ask for your feedback on this draft agenda and deliverables on or before Oct 14th. Please let me know If you have any questions.

Many thanks!
Erik

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

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: Fri, 2 Oct 2015 16:30:50 +0000
To: Baric, Toni C; Baric, Ralph; Beisel, Christopher (NIH/NIAID) [E]; Damania, Blossom A; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Sims, Amy C; Dugan, Vivien (NIH/NIAID) [E]
Subject: UNC-NIH U19 AI107810 monthly call

Monthly NIH-UNC call needed to be changed due to scheduling conflicts. Please note the new day and time. The calling instructions are:

Phone: 1-800-747-5150
Passcode: (b)(6)

Thank you,
Toni Baric

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 24 Sep 2015 15:09:23 +0000
To: Umerah, Nina
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi Nina,
So sorry, but I just found out that I have to attend an all-day meeting on Monday. So I'll need to reschedule our A57 call. I could do Tuesday 9/29 between 1 and 3pm, Wednesday 9/30 any time before 2:30, Thursday 10/1 any time before 3pm, or Friday 10/2 before 1pm. Please let me know if any of those times would work.

Thanks!
Erik

-----Original Appointment-----
From: Umerah, Nina (b)(6)
Sent: Thursday, July 9, 2015 1:48 PM
To: Umerah, Nina; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6) PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Monday, September 28, 2015 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tue, 15 Sep 2015 18:42:31 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Dreier, Thomas (OS/ASPR/BARDA); Erlandson, Karl (OS/ASPR); Hensley, Lisa (NIH/NIAID) [E]; 'Baric, Toni C'; Spiro, David (NIH/NIAID) [E]
Subject: MERS Animal Model SAG Call
Attachments: MERS Model Standardization Workshop Draft Sessions 9-15-2015.docx

Greetings!
Thanks again for your willingness to help organize the MERS Animal Model Standardization workshop. This time seems to work for the group, so I wanted to send along the dial in details. You may either join by VoIP using the Lync Meeting link below, or use the dial in number to connect by phone. I have attached a document with some overarching goals we identified for the workshop, as well as a series of draft sessions. Please consider these a tool for brainstorming and a place to get our discussion started. We very much value your input and welcome suggestions for changes! The agenda for the call will be as follows:

1. Brief background and introductions
2. Identify goals and deliverables from the workshop
3. Format for the workshop and sessions
4. Division of responsibilities
5. Timeframe and milestones for moving forward
6. Future call frequency?

Let me know if you have any questions before the call. Otherwise, we look forward to speaking with you next week!
Erik

.....
→
Join Lync Meeting

Join by phone
(301) 761-5000 (NIAID) English (United States)
Find a local number

Conference ID: (b)(6)

Forgot your dial-in PIN? | Help

[!OC([1033])!]

Overarching themes and questions to be addressed by the workshop include:

1. What is the current status of the various models in development (e.g. mouse, rabbit, mink, NHP, camel), and what are the similarities/differences between the models?
2. Is there a need for standardization of viral challenge, such as: viral strain; route of inoculation, etc?
3. Is there a better, or more appropriate, model for MCM development? Are different models needed for vaccine vs therapeutic development? What endpoints are currently possible/desirable?
4. What are current gaps/hurdles in advancing model development?
5. What are potential regulatory pathways for promising MCM candidates?

DRAFT Workshop Sessions

Session 1: Viral and Epidemiology

A. Global status, including case study of Korean outbreak
B. Viral update, including differences between KSA vs ROK cases

Session 2: Model Summary

A. Large animal models (NHP, camel)
B. Small animal models (mice, rabbit, mink?)

Session 3: Discussion of Models

A. Differences/Similarities
B. Pros/Cons
C. Characteristics (challenge strain, route of inoculation, etc)
D. Need for cross-model comparison?

Session 4: Regulatory Issues

A. Possibility of animal rule
B. Desired vs available clinical endpoints/outcomes
    a. Viral load reduction?
    b. Weight loss?
    c. Standard lung pathology score?
    d. Mortality?

Session 5: Path Forward

A. Gaps/hurdles
B. Need for standardization?
C. Goals/milestones necessary in models to advance MCM development

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Thu, 10 Sep 2015 12:47:04 +0000
To: Subbarao, Kanta (NIH/NIAID) [E]; Baric, Ralph; Munster, Vincent (NIH/NIAID) [E]; Erlandson, Karl (OS/ASPR); Dreier, Thomas (OS/ASPR/BARDA)
Cc: Spiro, David (NIH/NIAID) [E]; 'Baric, Toni C'
Subject: Planning Call for the MERS Animal Model Workshop

Dear Colleagues,
I am writing to organize the first planning call for the MERS Animal Model Standardization Workshop. We anticipate convening the workshop in our building in Fishers Lane in Bethesda this winter, ideally somewhere in the January-March 2016 timeframe. We would like to begin planning as soon as possible, so I have set up a Doodle Poll (link below) to gauge your availability for the first call. I will circulate an agenda once we finalize a time, but broad goals for the call will be: to discuss the goals/deliverables from the workshop, discuss the format for the workshop and individual sessions, begin dividing up responsibilities, and set a timeframe and milestones for the rest of the planning process.

Thank you again for assistance!
Erik

Doodle Poll: http://doodle.com/poll/(b)(6)

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

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: Mathur, Punam (NIH/NIAID) [E]
Sent: Fri, 4 Sep 2015 15:04:57 +0000
To: Mathur, Punam (NIH/NIAID) [E]; Baric, Ralph; Peter Myler; Wayne F Anderson (b)(6) 'Robin Stacy'; 'Elisabetta Sabini' (b)(6) Graham, Rachel; Yao, Alison (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]; Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E]
Subject: ORFEOME-CSGID-SSGCID-NIAID Call

Dear All,

We have set up a GoToMeeting link for our virtual meeting on **Tuesday, September 8th from 12 – 1 pm EST**. Please use the link or dial in information below to join the webinar:

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): 1 877 309 2070

Access Code: (b)(6)

Here is the agenda:

12:00 – 12:05: Introductions
12:05 – 12:15: Ralph Baric – ORFEOME
12:15 – 12:25: Wayne Anderson – CSGID
12:25 – 12:35: Peter Myler – SSGCID
13:35 – 1:00: Discussion

Feel free to forward the meeting link and dial in information to others in your groups that will be joining the call.

Have a good weekend!

Punam

From: Mathur, Punam (NIH/NIAID) [E]
Sent: Tue, 1 Sep 2015 14:42:43 +0000
To: Mathur, Punam (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Peter Myler; Wayne F Anderson (b)(6) 'Robin Stacy'; 'Elisabetta Sabini' (b)(6) (b)(6) Graham, Rachel; Yao, Alison (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]; Baric, Toni C (b)(6)
Subject: FW: ORFEOME-CSGID-SSGCID-NIAID Call

Hi Erik,

Please forward to David if you think he might be interested in joining the call.

Thank you,
Punam

-----Original Appointment-----
From: Mathur, Punam (NIH/NIAID) [E]
Sent: Thursday, August 13, 2015 11:40 AM
To: Mathur, Punam (NIH/NIAID) [E]; Baric, Ralph; Peter Myler; Wayne F Anderson (b)(6) (b)(6) 'Robin Stacy'; 'Elisabetta Sabini' (b)(6) Graham, Rachel; Yao, Alison (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]; Baric, Toni C (b)(6)
Subject: ORFEOME-CSGID-SSGCID-NIAID Call
When: Tuesday, September 08, 2015 12:00 PM-1:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where: 7A21

Dear All,

We look forward to this call between the 2 Structural Genomics Centers and the ORFEOME Functional Genomics Program on **Tuesday, September 8th, 2015 from 12 – 1 pm EST**. Please feel free to include others in your groups that might like to join this call. Let us know if you are planning on presenting slides in which case we will setup a Lync Meeting.

Call-in information:

Number: 866 795 4107
Passcode: (b)(6)

Best,
Punam

From: Umerah, Nina
Sent: Wed, 26 Aug 2015 13:29:46 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; (b)(6)
PETERPALESE; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
Importance: High

Dear all,

Just a reminder that Monday's conference call has been rescheduled for tomorrow at 11am EST. The call in details are below.

Best,
Nina

Nina Umerah
(b)(6)

-----Original Appointment-----
From: Umerah, Nina
Sent: Wednesday, June 24, 2015 2:09 PM
To: Umerah, Nina; 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; (b)(6) Palese, Peter; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Thursday, August 27, 2015 11:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
Where:
Importance: High

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Leyva-Grado, Victor
Sent: Mon, 24 Aug 2015 14:20:12 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Lim, Jean; Baric, Ralph; Umerah, Nina; Heise, Mark T; Sims, Amy C; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Since most of us are ok with either day, let's do it on Thursday that seems to be best for Dr. Baric.

So let's call in Thursday at 11:00 AM.

V

-----Original Message-----
From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, August 24, 2015 7:04 AM
To: Lim, Jean; Baric, Ralph; Umerah, Nina; Heise, Mark T; Sims, Amy C; Leyva-Grado, Victor; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Either day is fine with me, also. Thanks!

-----Original Message-----
From: Lim, Jean (b)(6)
Sent: Sunday, August 23, 2015 10:45 AM
To: Baric, Ralph (b)(6) Umerah, Nina (b)(6) Stemmy, Erik (NIH/NIAID) [E] (b)(6) Heise, Mark T (b)(6) Sims, Amy C (b)(6) Leyva-Grado, Victor (b)(6) Moore, Victoria L (b)(6)
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Either day is good for me.

From: Baric, Ralph S (b)(6)
Sent: Saturday, August 22, 2015 11:20 AM
To: Umerah, Nina; 'Stemmy, Erik (NIH/NIAID) [E]'; Heise, Mark T; Sims, Amy C; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Wed is a maybe, Thursday is good. ralph

-----Original Message-----
From: Umerah, Nina (b)(6)
Sent: Friday, August 21, 2015 5:24 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; Heise, Mark T; Sims, Amy C; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Dear all,

This Monday's call needs to be rescheduled. Is everyone available at 11am EST on Wednesday or Thursday?

Thank you,
Nina

Nina Umerah
(b)(6)

Sent from my iPad

From: Umerah, Nina
Sent: Thursday, July 09, 2015 1:47 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; (b)(6) Palese, Peter; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Occurs every month on the fourth Monday of the month from 11:00 AM to 12:00 PM effective 7/27/2015 until 11/28/2016.
Where:

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Heise, Mark T
Sent: Sat, 22 Aug 2015 10:56:50 +0000
To: Leyva-Grado, Victor; Umerah, Nina; Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph; Sims, Amy C; Lim, Jean; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Both days work for me as well.
Thanks
Mark

-----Original Message-----
From: Leyva-Grado, Victor (b)(6)
Sent: Friday, August 21, 2015 9:27 PM
To: Umerah, Nina; 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; Heise, Mark T; Sims, Amy C; Lim, Jean; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Hi everybody,

Either day is Ok with me.

V

-----Original Message-----
From: Umerah, Nina
Sent: Friday, August 21, 2015 5:24 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; (b)(6) 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: RE: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call

Dear all,

This Monday's call needs to be rescheduled. Is everyone available at 11am EST on Wednesday or Thursday?

Thank you,
Nina

Nina Umerah
(b)(6)

Sent from my iPad

From: Umerah, Nina
Sent: Thursday, July 09, 2015 1:47 PM
To: 'Stemmy, Erik (NIH/NIAID) [E]'; Baric, Ralph S; (b)(6) Palese, Peter; 'Amy Sims'; Lim, Jean; Leyva-Grado, Victor; Moore, Victoria L
Subject: HHSN272201000019I-HHSN27200003-Task A57 - Conference Call
When: Occurs every month on the fourth Monday of the month from 11:00 AM to 12:00 PM effective 7/27/2015 until 11/28/2016.
Where:

Dear all,

The number for the conference call scheduled for the 4th Monday of the month at 11am EST is 1-877-701-7113. The participant passcode is (b)(6)

Thanks,
Nina

Nina Umerah
Grants and Contracts Manager
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

From: Baric, Toni C
Sent: Fri, 17 Jul 2015 20:13:50 +0000
To: Baric, Ralph; Beisel, Christopher (NIH/NIAID) [E]; Damania, Blossom A; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Sims, Amy C; Dugan, Vivien (NIH/NIAID) [E]
Subject: NIAID Orfeome call

Hello group,
We have rescheduled the time for Tuesday's NIAID/UNC Orfeome monthly call. The call is now on 7/21 at 3:30 pm. The calling information is below:

Phone: 1-800-747-5150
Passcode: (b)(6)

Thank you,

Toni Baric

Department of Microbiology and Immunology
9025 Burnett Womack
CB# 7292
Chapel Hill, NC 27599-7292
Office: (b)(6)
(b)(6)

From: Mathur, Punam (NIH/NIAID) [E]
Sent: Fri, 17 Jul 2015 20:10:51 +0000
To: Mathur, Punam (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]; Baric, Ralph; 'Graham, Rachel'; 'Baric, Toni C (b)(6) Stemmy, Erik (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: ORFEOME -NIAID Call

Call-in information to follow…

From: Baric, Toni C
Sent: Tue, 7 Jul 2015 12:36:26 +0000
To: Baric, Ralph; Beisel, Christopher (NIH/NIAID) [E]; Damania, Blossom A; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Sims, Amy C; Dugan, Vivien (NIH/NIAID) [E]
Subject: UNC-NIH U19-AI107810 conference call-rescheduled

Hello everyone,
Due to the CDC visit to UNC the conference call normally scheduled for today has been rescheduled to July 21 at 2 pm. The conferencing information is below:

Phone: 1-800-747-5150
Passcode: (b)(6)

Toni Baric

Department of Microbiology and Immunology
9025 Burnett Womack
CB# 7292
Chapel Hill, NC 27599-7292
Office: (b)(6)
(b)(6)

From: Dugan, Vivien (NIH/NIAID) [E]
Sent: Thu, 2 Jul 2015 16:43:18 -0400
To: Baric, Ralph
Cc: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: advice

Hi Ralph,

After speaking with several colleagues and searching our resources, we're not aware of NIAID grant mechanisms that transition industry researchers to academic settings. You might consider looking at the eligibility criteria for a Career Development Award (K), the NIH Common Fund programs, and non-NIH funding sources – see links below.

Thanks for the update on Gryphon's visit and hope you have a nice July 4th weekend.
Vivien

Career Development Awards (K)
http://www.niaid.nih.gov/researchfunding/traincareer/pages/career.aspx

NIH Common Fund Programs
https://commonfund.nih.gov/initiativeslist

Finding Foundations and Other Funding Sources
http://www.niaid.nih.gov/researchfunding/ann/pages/found.aspx

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

From: Baric, Ralph
Sent: Wednesday, July 01, 2015 10:53 AM
To: Dugan, Vivien (NIH/NIAID) [E]
Cc: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: advice

Hi Vivien and Erik, I was wondering if you could provide some assistance and advice. I have a new research assistant professor who was at (b)(6) and has joined the laboratory with the goal of returning to academic research. I have a recollection that there is (or was) an NIH grants program that was designed to help transition industry researchers back into academic settings. Do you know of this program and if it still exists? So far, we have failed to find evidence of such a program. Appreciate any help or thoughts and advice that you could provide. Hope life is treating you both well. Just had Gryphon visit and interview the lab about GOF, SARS-CoV and MERS-CoV risk/benefit/biosecurity. Interesting day.
Ralph

From: Baric, Ralph
Sent: Fri, 19 Jun 2015 17:54:46 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Sims, Amy C
Subject: RE: Animal models contract options

Hi Eric, Yes, also, there is no other way to interpret the GOF exemption letter. If it is not specified exactly what is allowed, I'm afraid it doesn't exist and I won't get permission to proceed locally. I place this generally under the heading of the law of unintended consequences. Amy is on the committee, so I've cc'd her in on this correspondence in case she'd like to comment. I greatly appreciate you looking into this. ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, June 19, 2015 1:22 PM
To: Baric, Ralph S
Subject: RE: Animal models contract options

Hi Ralph,
I'll discuss with our internal group and will clarify things for you. Are you saying that your IBC only approved mutations in the S protein based on their interpretation of the stop work cancellation letter?

Erik

From: Baric, Ralph
Sent: Friday, June 19, 2015 12:02 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Animal models contract options

Hi Erik, the exemption granted making targeted mutations in the MERS S glycoprotein RBD to enhance receptor binding and b) serial passage of MERS-CoV in vitro and in vivo. Part C of our request was to reintroduce the mutations derived by serial passage in vivo/in vitro back into the MERS-CoV molecular clone. Some of these mutations reside outside of the S glycoprotein---hence the local IBC only granted these exact experiments. If we cannot introduce all of the mouse adapted mutations back into the molecular clone to reproduce the mouse strain exactly, it won't produce the lethal disease phenotype and ARDS pathology. Consequently, we can't ask about the role of genes in pathogenesis, test live attenuated vaccine outcomes, evaluate the impact of escape mutants in a virulent backbone. It is possible that this exempt because it is an exact replicate of the mouse adapted virus produced during passage-but its not 100% clear. I think I'm going to need to have this on paper.
Sorry to bring this up
Ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, June 19, 2015 11:33 AM
To: Baric, Ralph S
Subject: RE: Animal models contract options

Hi Ralph,
Looking at the letter cancelling the stop work order, I'm not sure I see where the limits to the S protein come in. Is that the letter you're referring to? If so can you point out the restrictive language?

Thanks,
Erik

From: Baric, Ralph
Sent: Wednesday, June 17, 2015 2:09 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Animal models contract options

Erik, The exemption clause was for the Animal Models Contract. The mouse model was developed and the virus was passaged under the animal models contract. We're moving toward the point where we want to introduce those mouse adapted mutations into the recombinant clone to recapitulate the phenotype. Unless I'm reading it wrong, the stipulation is that S changes only are allowed…..which quite frankly will not reproduce the mouse adapted strain. The RO1 is not involved at all. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, June 17, 2015 12:33 PM
To: Baric, Ralph S
Cc: Sims, Amy C
Subject: RE: Animal models contract options

Hi Ralph,
Always happy to chat. For the animal models contract options we'll need to loop in Mt Sinai since they're the prime. We're coming up on our next monthly call so we can always bump it up a bit. Let me know what you prefer.

For your second question, which project are you referring to? The Exemption for adapting MERS, or the R01? The R01 shouldn't have included any passaging work, but if that's the project you mean let me know which aim you're referring to and I'll have a look.

Erik

From: Baric, Ralph
Sent: Wednesday, June 17, 2015 12:02 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Sims, Amy C
Subject: RE: Animal models contract options

Hi Erik, Hope you are doing well. If possible, I'd like to talk with you asap about the Animal Models Contract option period. I'd also like to discuss the GOF permission document…..which if I have re-read it correctly, only allows me to recover spike mutations associated with MERS mouse passage back into the molecular clone. Given work with sars and other mouse adapted viruses, were pretty sure mutations in the replicase as well as some other ORFs are critical for in vivo disease outcomes/lethality. To reconstitute a pathogenic phenotype, recombinant mouse adapted virus is going to need all of the

mouse adapted mutations, not just S. If we cannot reconstitute recombinant viruses with the entire mouse adapted mutation panel, then the utility of the model is compromised. Examples, can't evaluate live attenuated virus vaccine strategies for MERS, can't evaluate the role of individual genes in viral pathogenesis, can't evaluate the pathogenesis of antibody escape mutants---as escape mutations oftentimes selected for attenuated variants, and this goes on and on. I need to petition for permission to recover the entire mouse adapted genome in recombinant viruses, not just S. I initially requested to reconstitute the entire mouse adapted genome. Don't know how I missed this when I received the waiver or how it got included in the letter, but in my opinion, this has disastrous public health implications in vaccine and therapeutic design.
Desperately in need of help.
Ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, April 27, 2015 2:28 PM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Ralph,

The previous determination letter we sent on March 19th confirmed that the alternate experiments you proposed removed almost all the potential GoF experiments from the award. At that time the only potential GoF work remaining was the serial passaging studies you proposed under Aim 3. The alternative experiments you proposed in your response dated April 2nd replaced these experiments. At this time the award does not contain any proposed experiments that would be subject to the GoF research funding pause provided you perform the experiments as outlined in the terms placed on the Notice of Award.

However if you unexpectedly observe a phenotype of enhanced pathogenicity or transmissibility via the respiratory route, or if you observe growth enhancement greater than 1 log on any MERS or CoV variant, you must stop the work immediately and notify NIAID.

I hope this answers your questions.

Best Regards,
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-7630
Phone: (b)(6)
Email:

****

From: Baric, Ralph
Sent: Monday, April 20, 2015 9:00 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

HI Erik, a letter stating final disposition regarding all of the proposed experiments. Without this letter, my IBC will likely declare everything I'm trying to do as DURC research (and yes it is an arbitrary extension to the current DURC regulations) and require tons of additional, local paperwork. Several higher up administrators have also requested copies of the final disposition regarding all proposed experiments triggering GOF review. I believe it falls under the general heading as GOF "unintended consequences", "drift" and "cover my butt". Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, April 20, 2015 8:31 AM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Ralph,
I'm glad to see the award was released! I think the original plan was to use the specific terms of award to acknowledge the replaced experiments. Are you asking for a final letter summarizing everything in the award? Or just the last bit that wasn't covered by the previous letter?

I'll bring this up at our meeting this week and let you know.

Erik

From: Baric, Ralph
Sent: Sunday, April 19, 2015 12:45 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Erik, hope you are doing well and nice seeing you a couple of days ago. We received the notice of award on this grant which is great news. Will you still be sending a final NIH letter in response to GOF-related experiments of concern that were associated with this grant? (I realize the limitations are spelled out in the notice of award). However, this final official letter on GOF determination is actually very important as my IBC likely won't approve any MERS/HKU4, etc. experiments unless accompanied by the

final NIH letter taking a position as to whether experiments are exempt, not GOF, GOF and waived, GOF and not permissible, etc. Thanks for all your help. Ralph

From: Leyva-Grado, Victor
Sent: Tue, 16 Jun 2015 19:50:15 +0000
To: NIAID DMID IDIQ; Stemmy, Erik (NIH/NIAID) [E]
Cc: PETERPALESE; Baric, Ralph; Heise, Mark T; Lim, Jean; Umerah, Nina; 'Sims, Amy C'
Subject: HHSN272201000019I-HHSN27200003-Task A57 - May 2015 progress report
Attachments: Task order A57 Monthly report June 2015-B.pdf

Dear Erik,

Please find attached the latest monthly report for Task order TOA-57.

Please let us know if you have any comments.

Thank you,

Victor

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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

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:
May 1, 2015-May 31, 2015

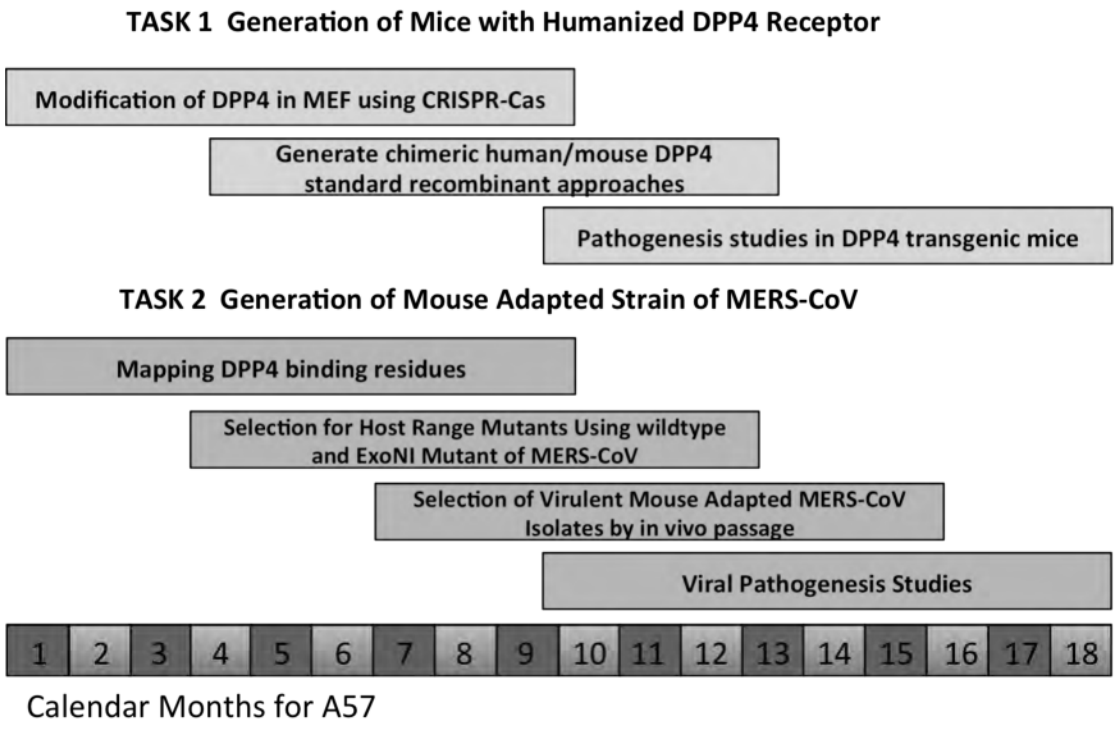
Contractor's Name and Address:
Dr. Peter Palese
Horace W. Goldsmith Professor and Chair Department of Microbiology
Professor, Department of Medicine Mount Sinai School of Medicine
1 Gustave Levy Pl.
New York, New York 10029-6574
Tel (b)(6)
Fax 212-722-3634
e-mail:(b)(6)

Date of Submission:
June 15, 2015

A. Scope

The objective of this task is to make a lethal mouse model (80% lethal by 10 days post infection) for the recently identified human coronavirus Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Our group will develop transgenic mice that express humanized dipeptidyl-peptidase receptors and select for mouse-adapted strains of the MERS-CoV.

B. Timeline



C. Progress on Model and Supporting Data

A Disease Model of MERS-CoV infection through adaptation in 288-330 heterozygous mice. Central to our understanding of MERS-CoV viral pathogenesis are the underlying host responses to lung infection. Viral replication was robust in our current 288L/330R genetic model, but there was no clear evidence of disease in the lungs of these mice. Through viral adaptation in these mice we have been able to obtain a disease model within the CRISPR-Cas mice. The *in vivo* studies were initiated with a MERS-CoV that harbors a mutation in the S gene as a result of 10 *in vitro* passages on NIH3T3 cells overexpressing the 288L/330R mutant mDPP4. The first mouse was inoculated intranasally with 50ul of viral stock (~$5x10^6$ Pfu). Heterozygous mice were used for adaptation for at least two reason: i) current availability of these mice and ii) these mice express both the wild-type mDPP4 receptor and the mutant mDPP4 receptor, allowing for the virus to potentially adapt around our mutations and utilize the wild-type mDPP4 receptor. A MERS-CoV adapted to the wild-type mDPP4 would expand the use of this virus to all available mouse lines.

Virus was passaged every 3 days. At 3 days post-infection lungs were harvested for titering, RNA, and histology. Subsequently, 50ul of lung lysate was intranasally inoculated into the next mouse until getting to passage 20. (b)(4); (b)(6)

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

Page 638 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 639 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 640 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 641 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 642 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 643 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

From: Sisak, Stephanie (NIH/NIAID) [C]
Sent: Wed, 3 Jun 2015 13:15:50 -0400
To: Baric, Ralph; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]
Subject: Follow-up to NIAID-Orfeome June 2nd teleconference

Hello everyone,

Below are the action items from Tuesday's call. The next call is scheduled for Tuesday, July 7th – if you would like to reschedule, please let me know. Otherwise, feel free to contact me if you have any questions or comments.

Best,
Stephanie

Action Items:

1. NIAID: Vivien will email Yoshi in regards to publishing bat ebola work
2. NIAID will send a reminder email to PIs for names of WG participants
3. Orfeome: Blossom to draft/ send paragraph to NIAID detailing plan for synthesizing 18kb ncRNA for review
4. Orfeome: Ralph will send NIAID list of Orfeome participants for the call with the Structural Genomics Centers
5. NIAID will set up call with Structural Genomics centers in the next few months (July/August)
6. Orfeome: Rachel will follow-up with Carly in regards to accession #s and Batch IDs and will update NIAID.
7. Orfeome: Send NIAID list of participants for ncRNA and Data Analysis and Dissemination Working Groups.
8. Orfeome: provide NIAID with alternative date for July 7th 12PM call
9. Orfeome: Next call - present previous mouse adapted SARS strains (work done years ago)

Points of Information:

- UNC will host 2017 Functional Genomics Annual meeting

Stephanie Sisak [C]
Scientific Program Analyst
Office of Genomics and Advanced Technologies (OGAT)
Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
5601 Fishers Lane Room 7A23 Bethesda, MD 20892-9826
Email: (b)(6)

From: Baric, Toni C
Sent: Mon, 1 Jun 2015 18:12:24 +0000
To: Baric, Ralph; Beisel, Christopher (NIH/NIAID) [E]; Damania, Blossom A; Spiro, David (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Graham, Rachel; Mathur, Punam (NIH/NIAID) [E]; Sims, Amy C; Dugan, Vivien (NIH/NIAID) [E]
Cc: Gabi Neumann; Pete Halfman; YOSHIHIROKAWAOKA
Subject: UNC-NIH U19-AI107810 conference call reminder

Hello everyone,

This is note to confirm that we will be having our monthly conference call on Tuesday June2 from 12-1pm EST. The call-in information is below.

Phone: 1-800-747-5150
Passcode: (b)(6)

Thank you,

Toni Baric

Department of Microbiology and Immunology
9025 Burnett Womack
CB# 7292
Chapel Hill, NC 27599-7292
Office: (b)(6)
(b)(6)

From: Baric, Ralph
Sent: Mon, 27 Apr 2015 18:29:29 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Erik, Okay. Thanks, ralph

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, April 27, 2015 2:28 PM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Ralph,

The previous determination letter we sent on March 19th confirmed that the alternate experiments you proposed removed almost all the potential GoF experiments from the award. At that time the only potential GoF work remaining was the serial passaging studies you proposed under Aim 3. The alternative experiments you proposed in your response dated April 2nd replaced these experiments. At this time the award does not contain any proposed experiments that would be subject to the GoF research funding pause provided you perform the experiments as outlined in the terms placed on the Notice of Award.

However if you unexpectedly observe a phenotype of enhanced pathogenicity or transmissibility via the respiratory route, or if you observe growth enhancement greater than 1 log on any MERS or CoV variant, you must stop the work immediately and notify NIAID.

I hope this answers your questions.

Best Regards,
Erik

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-7630
Phone: (b)(6)
Email:

****

or any other action based on the contents of this material. If you have received this communication in error, please permanently delete this from your system immediately. Thank you.

From: Baric, Ralph
Sent: Monday, April 20, 2015 9:00 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

HI Erik, a letter stating final disposition regarding all of the proposed experiments. Without this letter, my IBC will likely declare everything I'm trying to do as DURC research (and yes it is an arbitrary extension to the current DURC regulations) and require tons of additional, local paperwork. Several higher up administrators have also requested copies of the final disposition regarding all proposed experiments triggering GOF review. I believe it falls under the general heading as GOF "unintended consequences", "drift" and "cover my butt". Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, April 20, 2015 8:31 AM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Ralph,
I'm glad to see the award was released! I think the original plan was to use the specific terms of award to acknowledge the replaced experiments. Are you asking for a final letter summarizing everything in the award? Or just the last bit that wasn't covered by the previous letter?

I'll bring this up at our meeting this week and let you know.

Erik

From: Baric, Ralph
Sent: Sunday, April 19, 2015 12:45 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Erik, hope you are doing well and nice seeing you a couple of days ago. We received the notice of award on this grant which is great news. Will you still be sending a final NIH letter in response to GOF-related experiments of concern that were associated with this grant? (I realize the limitations are spelled out in the notice of award). However, this final official letter on GOF determination is actually very important as my IBC likely won't approve any MERS/HKU4, etc. experiments unless accompanied by the final NIH letter taking a position as to whether experiments are exempt, not GOF, GOF and waived, GOF and not permissible, etc. Thanks for all your help. Ralph

From: Sims, Amy C
Sent: Mon, 27 Apr 2015 15:06:14 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Umerah, Nina; Jean Lim; Leyva-Grado, Victor
Cc: PETERPALESE; Baric, Ralph; Heise, Mark T
Subject: Fwd: A57 Animal Models Report April 2015
Attachments: AMC report update for April 2015 FINAL.docx

Begin forwarded message:

From: "Sims, Amy C" (b)(6)
Subject: A57 Animal Models Report April 2015
Date: April 17, 2015 at 9:51:15 AM EDT
To: Nina Umerah (b)(6) "Leyva-Grado, Victor" (b)(6)
(b)(6) Jean Lim (b)(6) "Palese, Peter"
(b)(6)
Cc: "Baric, Ralph S" (b)(6) "Heise, Mark T"
(b)(6)

All,

Attached is this month□s A57 animal model□s report.

My apologies for the delay.

Please let me know if you have any questions.

Thank you! Amy

Amy C. Sims, Ph.D.
2107 McGavran-Greenberg Hall
CB 7435
Chapel Hill, NC 27599-7435

Office: (b)(6)
(b)(6)

Amy C. Sims, Ph.D.

2107 McGavran-Greenberg Hall
CB 7435
Chapel Hill, NC 27599-7435

Office: (b)(6)
(b)(6)

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:
March 1, 2015-March 31, 2015

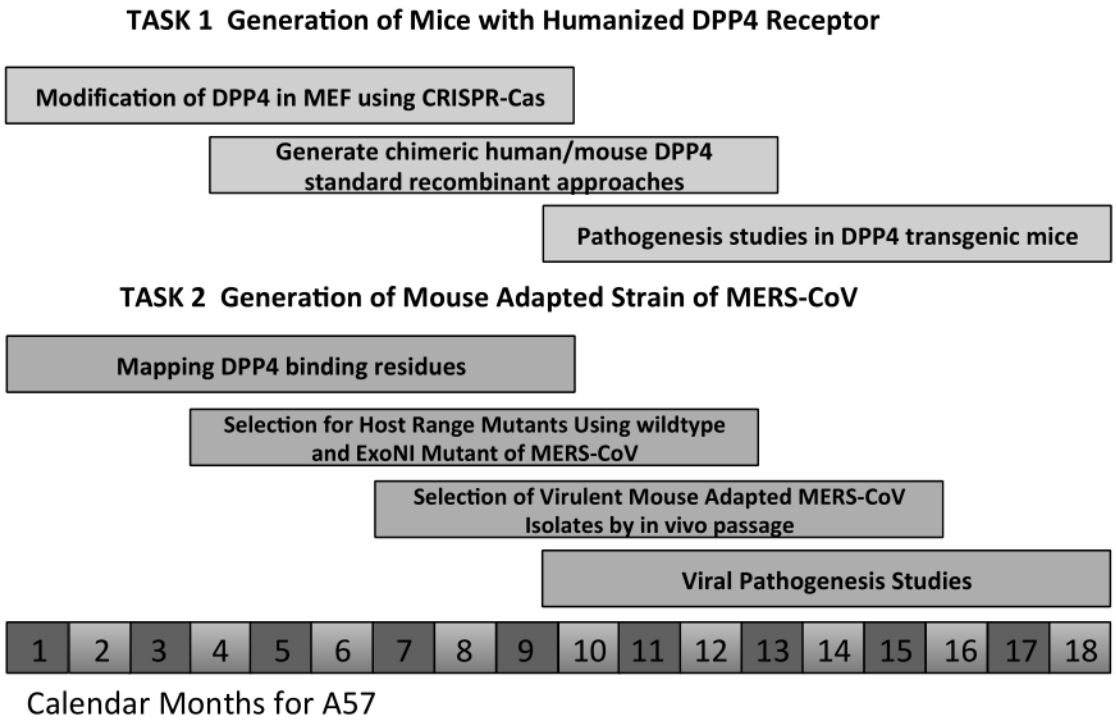
Contractor's Name and Address:
Dr. Peter Palese
Horace W. Goldsmith Professor and ChairDepartment of Microbiology
Professor, Department of MedicineMount Sinai School of Medicine
1 Gustave Levy Pl.
New York, New York 10029-6574
Tel (b)(6)
Fax 212-722-3634
e-mail: (b)(6)

Date of Submission:
April 15, 2015

A. Scope

The objective of this task is to make a lethal mouse model (80% lethal by 10 days post infection) for the recently identified human coronavirus Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Our group will develop transgenic mice that express humanized dipeptidyl-peptidase receptors and select for mouse-adapted strains of the MERS-CoV.

B. Timeline



Page 652 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

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From: Baric, Ralph
Sent: Mon, 20 Apr 2015 12:59:32 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

HI Erik, a letter stating final disposition regarding all of the proposed experiments. Without this letter, my IBC will likely declare everything I'm trying to do as DURC research (and yes it is an arbitrary extension to the current DURC regulations) and require tons of additional, local paperwork. Several higher up administrators have also requested copies of the final disposition regarding all proposed experiments triggering GOF review. I believe it falls under the general heading as GOF "unintended consequences", "drift" and "cover my butt". Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, April 20, 2015 8:31 AM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Ralph,
I'm glad to see the award was released! I think the original plan was to use the specific terms of award to acknowledge the replaced experiments. Are you asking for a final letter summarizing everything in the award? Or just the last bit that wasn't covered by the previous letter?

I'll bring this up at our meeting this week and let you know.

Erik

From: Baric, Ralph
Sent: Sunday, April 19, 2015 12:45 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01 Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis

Hi Erik, hope you are doing well and nice seeing you a couple of days ago. We received the notice of award on this grant which is great news. Will you still be sending a final NIH letter in response to GOF-related experiments of concern that were associated with this grant? (I realize the limitations are spelled out in the notice of award). However, this final official letter on GOF determination is actually very important as my IBC likely won't approve any MERS/HKU4, etc. experiments unless accompanied by the final NIH letter taking a position as to whether experiments are exempt, not GOF, GOF and waived, GOF and not permissible, etc. Thanks for all your help. Ralph

From: Sisak, Stephanie (NIH/NIAID) [C]
Sent: Tue, 7 Apr 2015 14:42:21 -0400
To: Baric, Ralph; 'Graham, Rachel'; Stemmy, Erik (NIH/NIAID) [E]; Mathur, Punam (NIH/NIAID) [E]; Dugan, Vivien (NIH/NIAID) [E]
Subject: UNC-NIH Call Notes & Action Items
Attachments: UNC-NIH Orfeome 4-7-15 Notes.docx

Hello everyone,

Below are the action items from the call today, and I have also included the notes in an attached document. Our next call is scheduled for Tuesday, May 5th.

Action Items:

1. NIAID to send out Steering Committee feedback to all FG PIs
2. Ralph to send Vivien the official, signed administrative supplement – deadline is April 10th
3. Orfeome to send accession #s and batch #s to NIAID when available
4. Orfeome to discuss internally possibility of call with Structural Genomics Centers
5. Ralph to get more information from PI requesting mutations in clones (rabbit), will send to Vivien and Erik, who will discuss with NIAID GOF group
6. Orfeome feedback for defining the term 'characterized' – for discussion on next call
7. Ralph to relay NIAID's guidance for publishing Lloviu virus experiments to Yoshi

Best,
Stephanie

Stephanie Sisak [C]
Scientific Program Analyst
Office of Genomics and Advanced Technologies (OGAT)
Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
5601 Fishers Lane Room 7A23 Bethesda, MD 20892-9826
Email: (b)(6)

UNC-NIH Orfeome 4-7-15
Participants = Ralph, Rachel, Punam, Vivien, Erik, Stephanie

Action Items

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7. Ralph to relay NIAID's guidance for publishing Lloviu virus experiments to Yoshi

Call Summary

- Orfeome administrative supplement to be completed by Friday, should be sent directly to Vivien
    - Unknown how much end-of-year money is available
    - Moving the supplement from Yoshi's group forward, the other supplement should not focus on creating new unknowns, may be able to recycle the idea or resubmit next year
- Vivien will send out feedback and a few bullet points detailing the steering committee recommendations (general ideas, etc.)
- Discussion about when a gene is considered characterized; what are the requirements? May not be easily definable within the program, something to keep in mind for the next annual meeting
    - Ralph and Rachel to discuss defining uncharacterized genes internally, perhaps talk about the issue again on the next call
- Another comment from the steering committee: how is negative data communicated to the research community?
    - Ralph detailed two different methods, one being to include other ORFs as control, focusing on particular hits in more detail (but may still have gaps of unpublished data)
    - Could write reviews (3-4) and compile all the screening data
    - PLOS ONE and BMC journals are more data-driven
- Reagent data submission: some in BEI, RNA-Seq datasets submitted to SRA but not yet accepted, will send accession #s and NCBI batch #s to NIAID when available
- Progress report: metagenomics approaches, RNA SHAPE supplement, Ralph would like to test this with MERS, include polyribosome profiling (5'/3' structure reproduced in SHAPE data)
    - Template in RNA viruses genome, 20 stretches in U' segments that are universal switches, will have a good idea if it works or not
    - Prioritizing hypotheticals or moving to an unknown, already having some preliminary data, Ralph wants to start with MERS because it is not a select agent, 200-300k to do the polysome analysis
    - If it has an impact could discuss with the group about moving forward to next year (may put in as a supplement with even more data)
- Punam could set up a call with the structural genomics centers to discuss structures, Ralph will first look internally to see if someone will write a white paper, put on hold for next month
- Ralph was asked to create mutations in public clones that may increase transmissibility or pathogenicity in rabbits, he was wondering how these requests should be handled. He would be making a reagent and sending it to them, and to his knowledge the person requesting has an

exception – Ralph to get more information from PI to Vivien this week, Vivien and Erik will discuss with NIAID GOF group on Friday

- Vivien let Ralph know that Yoshi's Lloviu virus work can be published if he wants to publish it, but it must reference the NIAID grant (Pete Halfmann's work) and a draft should be sent before publication to NIAID as well
    - Ralph will pass the information along to Yoshi and his group
- Ralph also submitted a pre-submission inquiry about bat spike work to Science

From: Sims, Amy C
Sent: Fri, 3 Apr 2015 18:07:13 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph; Cockrell, Adam
Subject: Re: CATG Presentation

Dear Erik,

It was very nice to see you again. It was a very interesting meeting and very helpful to see what others with similar funding sources are doing.

Thank you very much for including us in such a welcoming and productive group!

Best wishes, Amy

On Apr 3, 2015, at 7:55 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:

Hi Adam and Amy,
Sorry I had to duck out before the end of the session at CATG yesterday; something had come up that I had to take care of before 3pm. I hope you two found the CATG meeting useful, and that it gave you some sense of how NIAID's antiviral screening program works. I'm optimistic that you guys will have the model up and running and will be able to present some screening results next year!

Adam, I thought your presentation was excellent and I know the other folks in the room had been eager to see it as well.

Hope you both had a safe trip back to NC. Looking forward to the next update call in a few weeks!

Erik

Amy C. Sims, Ph.D.
2107 McGavran-Greenberg Hall
CB 7435
Chapel Hill, NC 27599-7435

Office: (b)(6)
(b)(6)

From: Perkins, Miriam (NIH/NIAID) [E]
Sent: Fri, 3 Apr 2015 14:03:11 -0400
To: O'Rear, Julian (FDA/CDER); Adam Cockrell; Adams, Miranda (NIH/NIAID) [E]; Agneta Von Gegerfelt; Alexander Freiberg; Krafft, Amy (NIH/NIAID) [E]; Amy Sims; Eakin, Ann (NIH/NIAID) [E]; Aurigemma, Rosemarie (NIH/NIAID) [E]; Baek Kim; Styrt, Barbara (FDA/CDER); Barrett, Alan; Bart Tarbet; Bill Wold; Korba, Brent; Brett Hurst; Brian E. Gilbert; Brian Gowen; Buck, Alexandra (NIH/NIAID) [E]; Laughlin, Catherine (NIH/NIAID) [E]; Chadwick, Tiffany (NIH/NIAID) [E]; Craig Day; Cassetti, Cristina (NIH/NIAID) [E]; Dale Barnard; Darci Smith; Bernstein, David; Spiro, David (NIH/NIAID) [E]; Quenelle, Debra; Smee, Donald; Ellen Faaleolea; Gupta, Emily (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]; Park, Eun-Chung (NIH/NIAID) [E]; Cassels, Fred (NIH/NIAID) [E]; Garry Lund; Kennedy, George (NIH/NIAID) [E]; Gregg N. Milligan; Hartmann, Richard (NIH/NIAID) [E]; Greenstone, Heather (NIH/NIAID) [E]; Heilman, Carole (NIH/NIAID) [E]; Schiltz, Helen (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Jackson, Charles (NIH/NIAID) [E]; Moffat, Jennifer; Bogdan, John (NIH/NIAID) [E]; Morrey, John; Campbell, Joseph (NIH/NIAID) [E]; Justin Julander; Karoly Toth; Kasparian, Sevag (NIH/NIAID) [E]; Kathy Keith; Knight, Stanley (NIH/NIAID) [E]; Lorne Tyrrell; Mark Buller; Challberg, Mark (NIH/NIAID) [E]; Lewis, Mark; Prichard, Mark; Holbrook, Michael (NIH/NIAID) [C]; Murray, Michael; Bray, Mike (NIH/NIAID) [E]; Perkins, Miriam (NIH/NIAID) [E]; Christensen, Neil; Nguyen, Tam (NIH/NIAID) [E]; Nigel Bourne; Norm Kneteman; Bryant, Paula (NIH/NIAID) [E]; Jahrling, Peter (NIH/NIAID) [E]; Koshy, Rajen (NIH/NIAID) [E]; Ramaswamy, Aishwarya (NIH/NIAID) [C]; Natarajan, Ramya (NIH/NIAID) [E]; Kincaid, Randall (NIH/NIAID) [E]; Repik, Patricia (NIH/NIAID) [E]; Rhonda Cardin; Roger Ptak; Alarcon, Rodolfo (NIH/NIAID) [E]; Scott Parker; Smith, Cristina (NIH/NIAID) [E]; Kim, Sonnie (NIH/NIAID) [E]; Spinelli, Beth (NIH/NIAID) [E]; Stephen Menne; Teo, Swee (NIH/NIAID) [E]; Guina, Tina (NIH/NIAID) [E]; Tony Piedra; Laporte, Tracy (NIH/NIAID) [E]; Tseng, Christopher (NIH/NIAID) [E]; Viebrock, Courtney (NIH/NIAID) [E]; Dowling, William (NIH/NIAID) [E]; Wong, Anna (NIH/NIAID) [E]
Subject: Recipes from CATG Dinner
Attachments: Filet Mignon with Truffled Mushroom Ragout.doc, Brown Sugar Glazed Brussels Sprouts.docx, Salmon with a Lemon, Caper and Dill Yogurt Sauce.docx

Hi All,

I have attached the recipes for the Filet Mignon with Mushroom Ragout and the Salmon with Lemon, Caper and Dill Yogurt Sauce from the CATG Dinner. Bon Appetit!

Once we have had a chance to review and add narrative to the pictures from the meeting, I will email each of you a copy.

Special Thanks to Justin Julander for being our photographer.

Miriam
Miriam Perkins, M.A.T.
Health Specialist, Virology Branch
DMID/NIAID/NIH
5601 Fishers Lane, Room 8E60
Rockville, MD 20852
Phone: (b)(6)
Email: (b)(6)

Filet Mignon with Truffled Mushroom Ragout

This dish — rosy steaks smothered in mushrooms fragrant with a drizzle of truffle oil — is positively swoon-worthy.

What to drink: A good Merlot, such as the 1999 Wente Crane Ridge Reserve.

Servings: Makes 2 servings.

Ingredients

3 tablespoons butter
1 garlic clove, chopped
1/2 teaspoon dried marjoram
12 ounces crimini or button mushrooms, quartered
1/3 cup canned low-salt chicken broth
1/3 cup dry red wine
3 tablespoons whipping cream

1 1/2 teaspoons peanut oil
2 1-inch-thick filet mignons (about 6 ounces each)
1/2 teaspoon truffle oil*

Preparation

Melt butter in large nonstick skillet over medium heat. Add chopped garlic and marjoram; sauté 30 seconds. Add mushrooms; toss to coat with butter. Sprinkle with salt. Cover and cook until mushrooms have released their juices, about 13 minutes. Add chicken broth, wine, and whipping cream and bring to boil. Cook uncovered until mushrooms are tender and sauce coats mushrooms, about 5 minutes. Season mushroom ragout to taste with salt and pepper. (Ragout can be made 3 hours ahead. Cover skillet and refrigerate.)

Heat heavy medium skillet over high heat until hot. Add peanut oil and tilt skillet to coat evenly. Sprinkle steaks with salt and pepper. Add to skillet and cook to desired doneness, about 4 minutes per side for medium-rare. Transfer steaks to plates. Rewarm mushroom ragout in skillet over medium heat, stirring frequently. Spoon ragout partially over steaks and onto plates. Drizzle mushrooms on each plate with 1/4 teaspoon truffle oil.

* Available at Italian markets, specialty foods stores, and some supermarkets.

Brown Sugar Glazed Brussels Sprouts

Ingredients:

2 bags of TJ's Brussels Sprouts

3/4 stick of butter (more if you are feeling frisky)

1 large yellow onion chopped (more or less depending on your love for onion)

3-5 tablespoons of brown sugar (this usually changes depending on how bitter the sprouts are)

2 cloves of garlic

Ingredients:

Take sprouts out of their packaging. Soak in water & rinse. Cut the ends off all the sprouts & quarter the sprouts. Set aside.

Place 1/2 stick of butter in a pan on medium heat. Stir in onions & garlic. Cook on medium until onions are translucent. Add sprouts & toss them in the butter/onion mixture. Let sit- stir occasionally. At this point, you are working on steaming them.

When the sprouts are softened (about 10 minutes), add brown sugar & remaining butter. Turn the heat to high and brown the sprouts. The brown sugar & butter help caramelize them. Put the little beauties in a dish & serve.

This dish has the power to change someone into a Brussel Sprout Lover. You'll see……

Salmon with a Lemon, Caper and Dill Yogurt Sauce

This sauce will be great on any fish or chicken. Add as little or as much of these ingredients as you want — you can't mess this up.

Try serving with garlic and butter fingerling potatos.

Ingredients

Salmon, ½ lb per person

1 C Greek yogurt

1-2 T Capers, rinsed and chopped

1 Lemon, zest and juice

1 handful of Fresh Dill, chopped

Salt and Pepper, to taste

Instructions

1. Combine the yogurt, capers, lemon zest, lemon juice, fresh dill, salt and pepper.
2. Taste the sauce. Does it need more lemon juice? more dill? more salt? more yogurt? Play with it until you want to eat it by the spoonful.
3. Season the salmon with salt and pepper.
4. Cook over medium heat in a little olive oil and butter, about ½ T of each.
5. Cook for about 5 minutes with the skin side down and then about 3 minutes on the other side.
6. Transfer the salmon to a plate and top with the lemon, caper, and dill yogurt sauce.

From: Cockrell, Adam
Sent: Fri, 3 Apr 2015 13:00:20 +0000
To: Stemmy, Erik (NIH/NIAID) [E]; Sims, Amy C
Cc: Baric, Ralph
Subject: RE: CATG Presentation

Hi Erik.

It was nice meeting you. Thank you for the opportunity to present at the CATG meeting. NIAID has assembled a wonderful group of scientists. All of my interactions were very positive. It was good to hear that the in vitro studies have yielded a few strong antiviral candidates against coronaviruses.

I think the model is progressing in the right direction. I look forward to our future interactions.

Sincerely,

Adam

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Friday, April 03, 2015 7:56 AM
To: Cockrell, Adam; Sims, Amy C
Cc: Baric, Ralph S
Subject: CATG Presentation

Hi Adam and Amy,
Sorry I had to duck out before the end of the session at CATG yesterday; something had come up that I had to take care of before 3pm. I hope you two found the CATG meeting useful, and that it gave you some sense of how NIAID's antiviral screening program works. I'm optimistic that you guys will have the model up and running and will be able to present some screening results next year!

Adam, I thought your presentation was excellent and I know the other folks in the room had been eager to see it as well.

Hope you both had a safe trip back to NC. Looking forward to the next update call in a few weeks!

Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Fri, 3 Apr 2015 11:18:40 +0000
To: Baric, Ralph
Subject: RE: MERS Stakeholder Workshop

Thanks Ralph, looks great! See you later this morning.

Erik

From: Baric, Ralph
Sent: Friday, April 3, 2015 7:05 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop

Hi Erik, Revised talk, thanks for your thoughts. Look forward to seeing you today. I will also bring a copy of this on a disk. ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, April 02, 2015 5:29 PM
To: Baric, Ralph S
Subject: RE: MERS Stakeholder Workshop

Thanks Ralph. You'll only have 10 minutes, so you may need to cut a bit down to stay within time. I'd suggest maybe picking a few broad themes to focus on. Does that help?

From: Baric, Ralph
Sent: Thursday, April 2, 2015 5:15 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop

Hi Erik, heres the slides. I might bring a slightly modified version for the morning. Truth is I haven't had any chance to think about the flow and time to polish. Is this what you were hoping for? Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Thursday, April 02, 2015 5:06 PM
To: Baric, Ralph S
Subject: RE: MERS Stakeholder Workshop

Hi Ralph,
Sorry I missed you in our building yesterday and today! Just wanted to check in about your slides. Do you have a set ready to send? I don't know if they can include them in the meeting materials, but if possible I think they'd like all of them before tomorrow morning. Please let me know.

Thanks!
Erik

From: Baric, Ralph
Sent: Wednesday, April 1, 2015 12:57 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

Hi Erik, I am presenting at a U19 meeting tomorrow (2 talks), I'll put together the slides for Friday on Wednesday night. Is Thursday morning okay? ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, March 31, 2015 4:09 PM
To: Baric, Ralph S
Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

Hi Ralph,
Just sending you a quick reminder to please send any slides you'll be using on Friday to myself and George Korch (copied here). Let us know if you have any questions.

Best,
Erik

From: Baric, Ralph
Sent: Friday, March 27, 2015 3:39 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop

Sure, be glad to help

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, March 25, 2015 3:08 PM
To: Baric, Ralph S
Cc: Spiro, David (NIH/NIAID) [E]
Subject: MERS Stakeholder Workshop

Hi Ralph,

I am part of the group organizing the MERS Stakeholder Workshop scheduled for Friday April 3rd. We would like to invite you to give a short 10 minute talk on coronavirus virology. Specifically the main emphasis of the meeting will be medical countermeasure development, and if you're willing we would ask that you cover areas of unique virology, pathogenesis, and natural history that would be relevant for advancing MCM work. There will be other sessions on MERS epidemiology, animal models, diagnostics, therapeutics, and vaccines and we're envisioning the CoV virology talk would be early in the Workshop to give context for the subsequent focused sessions.

If you're willing to present we would appreciate hearing from you as soon as possible, but no later than this Friday March 27th. We would also need a copy of any slides you'll be presenting by Wednesday April 1st. Please let us know if you have any questions, and if you're able to present. We are looking forward to a productive workshop next week!

Best,
Erik

From: Baric, Ralph
Sent: Fri, 3 Apr 2015 11:05:14 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop
Attachments: Baric MERS-CoV Symposium 2015.pptx

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From: Baric, Ralph
Sent: Thu, 2 Apr 2015 21:15:13 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop
Attachments: Baric MERS-CoV Symposium 2015.pptx

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Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

Hi Erik, I am presenting at a U19 meeting tomorrow (2 talks), I'll put together the slides for Friday on Wednesday night. Is Thursday morning okay? ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, March 31, 2015 4:09 PM
To: Baric, Ralph S
Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

Hi Ralph,
Just sending you a quick reminder to please send any slides you'll be using on Friday to myself and George Korch (copied here). Let us know if you have any questions.

Best,
Erik

From: Baric, Ralph
Sent: Friday, March 27, 2015 3:39 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]
Subject: RE: MERS Stakeholder Workshop

Sure, be glad to help

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, March 25, 2015 3:08 PM
To: Baric, Ralph S
Cc: Spiro, David (NIH/NIAID) [E]
Subject: MERS Stakeholder Workshop

Hi Ralph,

I am part of the group organizing the MERS Stakeholder Workshop scheduled for Friday April 3rd. We would like to invite you to give a short 10 minute talk on coronavirus virology. Specifically the main emphasis of the meeting will be medical countermeasure development, and if you're willing we would ask that you cover areas of unique virology, pathogenesis, and natural history that would be relevant for advancing MCM work. There will be other sessions on MERS epidemiology, animal models, diagnostics, therapeutics, and vaccines and we're envisioning the CoV virology talk would be early in the Workshop to give context for the subsequent focused sessions.

If you're willing to present we would appreciate hearing from you as soon as possible, but no later than this Friday March 27th. We would also need a copy of any slides you'll be presenting by Wednesday April 1st. Please let us know if you have any questions, and if you're able to present. We are looking forward to a productive workshop next week!

Best,
Erik

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Withheld pursuant to exemption

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of the Freedom of Information and Privacy Act

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Page 691 of 775

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Page 710 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

From: Cyr, Robin L
Sent: Thu, 2 Apr 2015 16:35:25 +0000
To: Eisenman, Laura (NIH/NIAID) [E]
Cc: Baric, Ralph; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Response to GoF letter needed
Attachments: Baric-Li Grant-GOF Alternative Experiments 4-1-15.pdf

Good afternoon, all.

Attached is Dr. Baric's revision to the scope of work for R01AI110700-01A1.

Please don't hesitate to contact us in the event that you have additional questions or need clarification of the changes made. We appreciate the opportunity to submit this revision and hope that it is met with a favorable review.

Thank you,

Robin L. Cyr
Associate Vice Chancellor for Research
Director, Office of Sponsored Research
University of North Carolina at Chapel Hill
104 Airport Drive, Suite 2200
Chapel Hill, NC 27599-1350
Ph: (b)(6)
Fax: (919) 962-5011
Executive Assistant, Jackie Treschl (b)(6)
Email: (b)(6)

"Alone we can do so little; together we can do so much." – Helen Keller

http://research.unc.edu/Offices/sponsored-research/index.htm

From: Eisenman, Laura (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, March 31, 2015 12:37 PM
To: Cyr, Robin L
Cc: Baric, Ralph S; OSR Research Admin; Stemmy, Erik (NIH/NIAID) [E]
Subject: Response to GoF letter needed

Dear Ms. Cyr,

Please see attached GoF letter which was sent out on March 19th. As of today, we have not received your response.

Please respond no later than: April 3, 2015.

Many thanks,

Laura C. Eisenman
Lead Grants Management Specialist
National Institute of Allergy &
Infectious Diseases (NIAID)
5601 Fishers Lane, Room 4E41, MSC 9824
Bethesda, Maryland 20892-2962
Use Rockville, MD 20852 for overnight and courier deliveries)
Telephone: (b)(6)
Facsimile: 301-493-0597
E-Mail: (b)(6)
****

****
IMPORTANT NOTICES:
NEW! ***"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."***
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http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-097.html
NEW Guide Notice!
****

NIH Request for Final Clarification-R01AI110700-01A1.

We thank the NIH for considering our exemption requests regarding RO1AI110700-01A1. We acknowledge that NIAID has determined that one section of our grant application is subject to the GoF research funding pause and cannot be pursued at this time. Specifically, in vivo passage experiments to improve animal model development for MERS-CoV and HKU4 were paused. In addition, we acknowledge that should certain group 2c bat coronavirus chimeras, full length viruses or MERS-CoV mutants that replicate >1 log more efficiently than the MERS-CoV parental virus in vitro and/or prove more pathogenic in vivo are of concern. To emphasize our original position regarding this issue, we will halt experiments, inform the local IBC and our NIH program officer and participate in downstream discussions regarding future studies. This restriction also applies to the alternative experiments listed below. Importantly, we were directed to either propose alternative experiments that would not be subject to the GoF research funding pause or remove the experiments from the research plan and request to have our award budget renegotiated.

In response to this request, we have decided to propose alternative experiments that are not subject to the GoF research funding pause. These alternative experiments are listed below. These experiments will include: a) in vivo testing of more MERS-CoV and HKU4 derivative viruses (specifically encoding receptor binding domain or proteolytic site loss of function mutations only, and b) the in vivo evaluation of select other group 2c bat coronavirus spikes, which use bat and/or human DPP4 receptors. These viruses include: (i) betacoronavirus BtCoV/KW2E-F93/Nyc_spec/GHA/2010 (GenBank accession code of the spike protein: AGC51116.1), (ii) betacoronavirus BtCoV/133/2005 (GenBank accession code of the spike protein: ABG47052.1), and (iii) betacoronavirus Neoromicia/PML-PHE1/RSA/2011 (GenBank accession code of the spike protein: AGY29650.2). In aims 1 and 2, we had already requested and granted approval to use pseudotypes from these strains to evaluate various human and animal DPP4 receptor usages and then use these data to direct the synthesis of select chimeric or full length clones and isolate recombinant virus. Recombinant virus growth will be evaluated on nonpermissive cell lines expressing human, bat and camel DPP4 receptors and then in primary cell lines. A select subset of these mutants and/or recombinant viruses (it is anticipated that some bat strains won't use any DPP4 receptor for entry and hence cannot be studied further) will be evaluated for replication efficiency and pathogenesis using the CRISPR/cas DPP4 transgenic mouse model (see below). At this time, we will not introduce receptor or protease enhancing mutations into these new backgrounds. Rather, a subset of the already approved loss of function mutants will be evaluated that attenuate human DPP4 receptor or human protease use. Thus, it is reasonably anticipated that these viruses will demonstrate less efficient growth in vivo and in vivo and hence are not subject to the pause.

Virus Model. Aim 3. MERS-CoV, HKU4 and Derivative Virus Pathogenesis in Mice. Background. Under NIH Contract HHSN272201000019I Task Order No. HHSN27200003 (A57) "Mouse Model for Evaluation of Medical Countermeasures against Middle East Respiratory Syndrome (MERS-CoV), a waiver has been granted to allow for passage of MERS-CoV in mutagenized mDPP4 transgenic mice encoding human codons at positions 288 and 330. We were also approved to passage MERS-CoV in straight hDPP4 transgenic mice. In CRISPR humanized DPP4 mice, wildtype MERS-CoV replicates to titers of ~5.0 x 10^6 PFU/g through day 4, although little if any clinical weight loss is evident. After 15 passages, wildtype virus titers now approach 10^8 PFU/g and some weight loss is evident, without mortality. Twenty to twenty five passages will likely produce a mouse adapted virulent strain. In hDPP4 transgenic mice, wildtype MERS-CoV replicates to ~5.0 x 10^5 PFU/g, a less robust animal model. Thus, the existing CRISPR/cas DPP4 mice is the most robust mouse model for in vivo studies. The contract is slated to end sometime around July, 2015. We note that the stated goal of this NIH sponsored contract research is to generate and provide to the research community a more virulent "mouse-adapted" strain for pathogenesis studies, vaccine and therapeutic testing. Therefore, we assume that NIH intends for the research community to take advantage of these reagents. HKU4 growth has not been evaluated in either transgenic model, and will be tested during the course of this grant application. No passage experiments will be performed as part of this RO1 and all passage experiments will stop in July.

Therefore, wildtype HKU4, HKU5 and MERS-CoV viruses and their approved derivatives will be evaluated in the CRISPR/CAS DPP4 mice. We will also take advantage of the final mouse-adapted MERS-CoV generated under the HHSN272201000019I contract. Thus, in addition to making and evaluating the impact of the approved mutation sets in wildtype MERS-CoV, a subset of these approved mutation sets will also be introduced into the "mouse adapted" MERS-CoV strain for in vivo testing, as loss of function mutants should

attenuate pathogenesis. Our program officer (and the local UNC IBC) will be informed of the nucleotide sequence, including in vitro and in vivo phenotypes associated with the selected mouse adapted MERS-CoV strain, as this information becomes available at the end of this contract. As discussed earlier, any significant gain in mouse adapted virus virulence (change in mean day of death, mortality, etc.) will result in stoppage, informing local IBC and NIH, and participation in discussions to move forward. The slight delay in the finalization of the mouse adapted MERS-CoV will not impact the progress of the program, as we will first evaluate approved mutation sets in the wildtype MERS-CoV and HKU4 backbone.

We hope that NIH finds these alternative experiments as acceptable alternatives to the MERS-CoV and HKU4 passage experiments originally proposed in one of the subaims of Aim 3. We believe that the newly proposed experiments will enrich the program, provide critical information regarding the potential existence of other pre-pandemic group 2c threat viruses, and simultaneously protect the public health by providing critical reagents for the testing of broadly protective therapeutics and vaccines.

Please contact us immediately should you require additional clarifications, as we are hoping for an April 2015 start date for this grant application. Thank you for considering this information

Ralph S. Baric
Fang Li

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 1 Apr 2015 21:42:44 +0000
To: 'Eddie Sullivan'; 'Christos Kyratsous'; 'Sheridan, Bill'; 'Keith Wycoff'; (b)(6) Baric, Ralph
Cc: Spiro, David (NIH/NIAID) [E]
Subject: RE: Therapeutics Session at MERS Stakeholder Meeting
Attachments: Final Agenda for MERS Stakeholder Workshop.docx

Hi Everyone,
I have attached the current version of the agenda so you can see how the day will be structured. One thing to note is that due to the time constraints there will not be a lunch break. Light refreshments will be available, but you should feel free to pack a lunch if you like. If you plan to present slides and haven't sent them yet, please send them to me as soon as possible. They will be printing meeting materials for the attendees, and any slides sent in after 8:00am tomorrow morning will not be included.

Thanks!
Erik

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Tuesday, March 31, 2015 4:07 PM
To: 'Eddie Sullivan'; 'Christos Kyratsous'; 'Sheridan, Bill'; 'Keith Wycoff'; (b)(6)
Cc: Spiro, David (NIH/NIAID) [E]
Subject: RE: Therapeutics Session at MERS Stakeholder Meeting

Greetings!
Just a friendly reminder to please be sure to send me any slides you'll be using for your presentations by tomorrow (4/1/2015) afternoon. Let me know if you have any questions.

Best,
Erik

Please note my updated contact information below:

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

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: Stemmy, Erik (NIH/NIAID) [E]
Sent: Friday, March 27, 2015 3:05 PM
To: 'Eddie Sullivan'; 'Christos Kyratsous'; 'Sheridan, Bill'; 'Keith Wycoff'; (b)(6)
Cc: Spiro, David (NIH/NIAID) [E]
Subject: Therapeutics Session at MERS Stakeholder Meeting

Hi Everyone,
Thank you all very much for agreeing to present and participate in the panel discussion at next week's MERS Stakeholder Workshop. To help you prepare for the session I wanted to share the questions that we'll use to guide the discussion. They will be:

1. What scientific gaps need to be filled to facilitate the development of MERS therapeutics?
2. What are the major obstacles to MERS therapeutics development and what role can governmental and multi-governmental bodies play?
3. Are there any lessons learned from MERS (or SARS) therapeutics development so far?

We will be very limited in time (20 minutes), so we will cover as much as possible. These questions may also guide you as you frame your talk for the session. We're looking forward to an engaging discussion next week!

Erik

Please note my updated contact information below:

Erik J. Stemmy, Ph.D.
Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
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Agenda for MERS CoV Stakeholder Workshop
3 April 2015
Willow Conference Room (LL Level)
O'Neill Congressional Building
200 C Street SW, Washington D.C.

Toll free number: 1-888-395-7964
General Participant/Audience passcode: 4725913
PRESENTERS ONLY passcode: 59662

1. *Join the webinar meeting at: https://www.mymeetings.com/nc/join/*
2. *Enter the required fields (Conference number: PW3217113; Audience passcode: 4725913)*
3. *Indicate that you have read the Privacy Policy*
4. *Click on Proceed*

10:00 – 10:05 Welcome Dr. Nicole Lurie, Assistant Secretary for Preparedness and Response

10:05 - 10:10 Introduction and Purpose (George Korch)

10:10 – 10:20 Introduction to Coronaviruses Virology (Ralph Baric)

10:20 – 10:55 Epidemiology and Clinical Management

a.) **Peter Ben Embarek (20 minutes) – Current International Epidemiological Findings and Case Management**
b.) **David Swerdlow (15 minutes) – U.S. Preparedness and Response to Domestic Cases**

10:55 – 11:40 Animal Models (Lisa Hensley)

Format: Facilitated panel discussion with 6-7 researchers developing models.

a.) **Introductions - (Lisa Hensley)**
b.) **Short Overview on Models (Matt Frieman)**
c.) **Sharing of Unpublished data (Frieman, Tseng, and others)**
d.) **Panel Discussion with audience participation (25 minutes) guided by Facilitator using questions to prompt panelists/audience**

11:40 – 11:50 Break (10 minutes)

11:50 – 12:20 Diagnostics (Sally Hojvat)

a.) **Introduction (2 min). FDA's Emergency Use Authorization Regulatory Path- Sally Hojvat , FDA/CDRH/OIR**
b.) **(8-10 minutes) CDC Laboratory Response to MERS.- Dean Erdman, CDC**
c.) **(15-20 minutes) Open Discussion: What are the main challenges to developing a MERS Co-V diagnostic?**
    i. **David Ecker, (Abbott)**
    ii. **Elizabeth Holmes (Theranos)**
    iii. **Karen Li (ThermoFisher)**
    iv. **Others including DoD … work in progress**

12:20 – 1:05 Therapeutics (David Spiro)

a) **Format: Five short examples of therapeutics in development followed by group discussion with audience/additional panel members with other perspectives.**
b) **Introduction David Spiro, NIAID/DMID**
c) **Immunotherapeutics**
    i) **(5 minutes) Eddie Sullivan, SAB (Transchromosomic Bovine IgG)**
    ii) **(5 minutes) Christos Kyratsous, Regeneron (REGN3048/3051)**
d) **Small Molecule/Drug (5 mins). Bill Sheridan, BioCryst (BCX4430)**
e) **Other Strategies**
    i) **(5 minutes) Keith Wycoff, Planet Biotech (Receptor Decoy)**
    ii) **(5 minutes) Matt Frieman, University of Maryland (Repurposing FDA-approved Drugs)**
f) **Group Discussion (15 minutes) Guided by facilitator to answer/pose questions from community.**
    i) **What scientific gaps need to be filled to facilitate the development of MERS Therapeutics?**
    ii) **What are major obstacles to MERS therapeutics development, and what role can governmental and multi-governmental bodies play?**
    iii) **Are there any lessons learned from MERS (or SARS) therapeutics development?**
g) **Audience Comments (5-10 minutes)**

1:05 - 1:15 Break (10 minutes)

1:15 – 2:00 Vaccines (Rick Bright)

Format short presentation of lessons from SARS vaccine experience, followed by discussion

a) **Overview from the Internal Portfolio Review - R. Bright (5 minutes)**
b) **Lessons Learned from SARS Vaccine Development – F. Cassels (10 minutes)**
c) **Industry State of the Art Presentations (20 minutes)**
    i) **Novavax - G. Smith**
    ii) **Greffex – U. Staerz**
    iii) **Inovio - N. Sardesai**
d) **Audience Comments (10 minutes)**

2:00 – 2:05 International Issues (Maria Julia Marinissen)

2:05 – 2:30 Final Perspectives and Action Items (George Korch)

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 1 Apr 2015 19:36:51 +0000
To: Baric, Ralph
Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

Hi Ralph,
Thursday morning should be fine. The earlier the better, though, as I believe they'll be preparing meeting materials for the attendees and will need plenty of time to put them together.

Thanks!
Erik

From: Baric, Ralph
Sent: Wednesday, April 01, 2015 12:57 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
Subject: RE: MERS Stakeholder Workshop

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Cc: Spiro, David (NIH/NIAID) [E]; Korch, George (HHS/ASPR/IO)
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Erik

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Sure, be glad to help

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If you're willing to present we would appreciate hearing from you as soon as possible, but no later than this Friday March 27th. We would also need a copy of any slides you'll be presenting by Wednesday April 1st. Please let us know if you have any questions, and if you're able to present. We are looking forward to a productive workshop next week!

Best,
Erik

From: Eisenman, Laura (NIH/NIAID) [E]
Sent: Tue, 31 Mar 2015 14:02:49 -0400
To: Cyr, Robin L
Cc: Baric, Ralph; OSR Research Admin; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Response to GoF letter needed

Many thanks Robin.

From: Cyr, Robin L (b)(6)
Sent: Tuesday, March 31, 2015 1:43 PM
To: Eisenman, Laura (NIH/NIAID) [E]
Cc: Baric, Ralph; OSR Research Admin; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Response to GoF letter needed

Good afternoon, Laura.

Dr. Baric is currently out of the office/lab however I do know that he is working on the revisions as required in the letter dated March 19, 2015. It is his hope to have this ready to send by close of business tomorrow and if not then it will be sent by the April 3rd deadline.

Have a nice afternoon,

Robin L. Cyr
Associate Vice Chancellor for Research
Director, Office of Sponsored Research
University of North Carolina at Chapel Hill
104 Airport Drive, Suite 2200
Chapel Hill, NC 27599-1350
Ph: (b)(6)
Fax: (919) 962-5011
Executive Assistant, Jackie Treschl (b)(6)
Email: (b)(6)

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Sent: Tuesday, March 31, 2015 12:37 PM
To: Cyr, Robin L
Cc: Baric, Ralph S; OSR Research Admin; Stemmy, Erik (NIH/NIAID) [E]
Subject: Response to GoF letter needed

Dear Ms. Cyr,

Please see attached GoF letter which was sent out on March 19th. As of today, we have not received your response.

Please respond no later than: April 3, 2015.

Many thanks,

Laura C. Eisenman

Lead Grants Management Specialist
National Institute of Allergy &
Infectious Diseases (NIAID)
5601 Fishers Lane, Room 4E41, MSC 9824
Bethesda, Maryland 20892-2962
Use Rockville, MD 20852 for overnight and courier deliveries)
Telephone: (b)(6)
Facsimile: 301-493-0597
E-Mail: (b)(6)

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http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-097.html
NEW Guide Notice!
****

From: Eisenman, Laura (NIH/NIAID) [E]
Sent: Tue, 31 Mar 2015 12:36:43 -0400
To: (b)(6)
Cc: Baric, Ralph; resadminosr@unc.edu; Stemmy, Erik (NIH/NIAID) [E]
Subject: Response to GoF letter needed
Attachments: GoF Letter_FINAL version.pdf

Dear Ms. Cyr,

Please see attached GoF letter which was sent out on March 19th. As of today, we have not received your response.

Please respond no later than: April 3, 2015.

Many thanks,

Laura C. Eisenman
Lead Grants Management Specialist
National Institute of Allergy &
Infectious Diseases (NIAID)
5601 Fishers Lane, Room 4E41, MSC 9824
Bethesda, Maryland 20892-2962
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

March 19, 2015

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

RE: R01AI110700-01A1 PI: Baric

Dear Ms. Cyr:

Thank you for your correspondence of January 21, 2015, regarding the October 17, 2014 White House announcement of a U.S. Government-wide pause on certain gain-of-function (GoF) experiments and its potential impact on your research (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). The pause pertains to GoF research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the resulting virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID reviewed the original grant application, and the additional information provided by you, and made the following assessments:

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

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

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

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

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

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

Please remember that the institution must comply in full with all terms and conditions placed on this grant. If your research evolves to include experiments that may be subject to the pause or you observe enhanced pathogenicity and/or transmissibility of MERS-CoV in mammals via the respiratory route at any time during the course of conducting these experiments, you must immediately stop these research activities and provide the NIAID Program Officer and Grants Management Specialist with the relevant data and information related to these unanticipated outcomes.

As indicated above, NIAID determinations are based on information from multiple sources, but primarily on our communication with you about the details of your proposed experiments and your research results. Should NIAID's determination change based on information obtained through the U.S. Government gain-of-function deliberative process, described here http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf, you will be notified; however, until such time, or until the pause is lifted, NIAID's determination, indicated above, is final.

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

Sincerely,

(b)(6)

Laura Eisenman
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

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

From: Perkins, Miriam (NIH/NIAID) [E]
Sent: Sun, 29 Mar 2015 20:49:17 -0400
To: Earl Kern; O'Rear, Julian (FDA/CDER); Adam Cockrell; Adams, Miranda (NIH/NIAID) [E]; Agneta Von Gegerfelt; Alexander Freiberg; Krafft, Amy (NIH/NIAID) [E]; Amy Sims; Eakin, Ann (NIH/NIAID) [E]; Aurigemma, Rose (NIH/NCI) [E]; Baek Kim; Styrt, Barbara (FDA/CDER); Barrett, Alan; Bart Tarbet; Bill Wold; Korba, Brent; Brett Hurst; Brian E. Gilbert; Brian Gowen; Buck, Alexandra (NIH/NIAID) [E]; Laughlin, Catherine (NIH/NIAID) [E]; Chadwick, Tiffany (NIH/NCI) [E]; Craig Day; Cassetti, Cristina (NIH/NIAID) [E]; Dale Barnard; Darci Smith; Bernstein, David; Spiro, David (NIH/FIC) [E]; Quenelle, Debra; Smee, Donald; Ellen Faaleolea; Gupta, Emily (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]; Park, Eun-Chung (NIH/NIAID) [E]; Cassels, Fred (NIH/NIAID) [E]; Garry Lund; Kennedy, George (NIH/NIAID) [E]; Gregg N. Milligan; Hartmann, Richard (NIH/NIAID) [E]; Greenstone, Heather (NIH/NIAID) [E]; Heilman, Carole (NIH/NIAID) [E]; Schiltz, Helen (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Jackson, Charles (NIH/NIAID) [E]; Moffat, Jennifer; Bogdan, John (NIH/NIAID) [E]; Morrey, John; Campbell, Joseph (NIH/NIAID) [E]; Justin Julander; Karoly Toth; Kasparian, Sevag (NIH/NIAID) [E]; Kathy Keith; Knight, Stanley (NIH/NIAID) [E]; Lorne Tyrrell; Mark Buller; Challberg, Mark (NIH/NIAID) [E]; Lewis, Mark; Prichard, Mark; Holbrook, Michael (NIH/NIAID) [C]; Murray, Michael; Bray, Mike (NIH/NIAID) [E]; Perkins, Miriam (NIH/NIAID) [E]; Christensen, Neil; Nguyen, Tam (NIH/NIAID) [E]; Nichols, Courtney (NIH/NIAID) [E]; Nigel Bourne; Norm Kneteman; Bryant, Paula (NIH/NIAID) [E]; Jahrling, Peter (NIH/NIAID) [V]; Koshy, Rajen (NIH/NIAID) [E]; Ramaswamy, Aishwarya (NIH/NIAID) [E]; Natarajan, Ramya (NIH/NIAID) [E]; Kincaid, Randall (NIH/NIAID) [E]; Repik, Patricia (NIH/NIAID) [E]; Rhonda Cardin; Roger Ptak; Alarcon, Rodolfo (NIH/NIAID) [E]; Scott Parker; Smith, Cristina (NIH/NIAID) [E]; Kim, Sonnie (NIH/NIAID) [E]; Spinelli, Beth (NIH/NIAID) [E]; Stephen Menne; Teo, Swee (NIH/NIAID) [E]; Guina, Tina (NIH/NIAID) [E]; Tony Piedra; Laporte, Tracy (NIH/NIAID) [E]; Tseng, Christopher (NIH/NIAID) [E]; Dowling, William (NIH/NIAID) [E]; Wong, Anna (NIH/NIAID) [E]
Subject: Final Announcement for 2015 Annual CATG Meeting
Attachments: 2015 CATG Agenda.docx, 2015 Menu Choices.docx
Importance: High

Hi All,

This is the final announcement for the **25th Annual CATG Meeting**.

I have attached a copy of the Agenda and the Menu Choices. Please let me know if there are any errors in the Menu Choices as soon as possible so I can let the restaurant know. This year the meeting will be held in the new **NIAID building** at **5601 Fishers Lane** in the **Grand Hall, Room 1D13** at **5601 Fishers Lane** *(two buildings down Fishers Lane from last year)*. There is an on-site **cafeteria** and a **coffee bar** just inside the lobby. **WiFi** is available throughout the building and there are several **business kiosks** with PowerPoint, Excel and Word as well as internet access *(for printing boarding passes)*.

Non-NIAID employees must enter the building at the main entrance on Fishers Lane. There will be a table set-up with Security Badges with a bar code on the back. These badges will allow you to leave and reenter the building and should be returned to the guard at the conclusion of the meeting. Be sure not to return the badge when you leave on Wednesday as you will need it for entry on Thursday.

A greeter will escort you to the reception desk where the **2015 CATG Agenda** and **Name Tags** will be available. Be sure to have your Name Tag clearly displayed as the meeting is **BY INVITATION ONLY** *(due to the unpublished data that will be discussed)*. Non-NIAID employees will have both a Security Badge and a CATG Name Tag. NIAID employees will have their ID Card and a CATG Name Tag.

IT staff will be available to assist you in uploading your slides *(from your thumb drives)* onto the computer. Please remember not to remove them after your presentation. I need to copy them at the end of both days for NIAID's records.

As I had mentioned in an earlier email, Irene Glowinski, Deputy Director DMID, will open the meeting with a presentation on *DMID's Scientific Priorities*. Earl Kern (UAB), Brian Gilbert (BCM) and Bob Sidwell (USU), the initial CATG Investigators, will be attending. Both Carole Heilman, Director DMID, and Irene Glowinski, Deputy Director DMID, will be joining us at our **Annual Dinner** to help us celebrate 25 years of antiviral drug research and development.

The cost of the dinner is $47 per person. Non-alcoholic beverages *(soft drinks and tea)* as well as tax and tip are *included* in the $47. Payment for BEER and WINE will be expected when you are served.

I will be collecting payment for dinner during the Wednesday morning break to take to the restaurant at noon. If you are not going to be at the meeting at that time, please send your payment with a colleague or contact me and I will make arrangements to meet you. Please try to have exact change *(there is an ATM in the lobby)*. You will receive a **Dinner Place Card** when you pay. It serves as your *dinner ticket* and your *dinner order*. Please remember to bring it with you Wednesday evening. Everything is prepaid – no waiting to process credit cards after dinner. Individual receipts will be provided *(same as in the past)*.

If you have any questions you can reach me by email until 6:00 pm Tuesday and again on Wednesday morning from 7:00 am on.

If you are driving, there is a public parking lot located behind 5635 Fishers Lane.

For those of you traveling, I wish you a safe and pleasant trip to D.C. The temperature is predicted to be in the low 60s on Wednesday and Thursday with a possible shower on Thursday evening.

See you bright and early Wednesday morning.

Miriam
Miriam Perkins, M.A.T.
Health Specialist, Virology Branch
DMID/NIAID/NIH
5601 Fishers Lane, Room 8E60
Rockville, MD 20852
Phone: (b)(6)
Email:

2015 CATG Annual Meeting

April 1-2

Room 1D13

NIAID Fishers Lane Building

5601 Fishers Lane

Rockville, MD

AGENDA
Wednesday, April 1, 2015

8:00 – 8:30		SIGN-IN / MORNING COFFEE

8:30 – 8:35	Cathy Laughlin	Welcome
8:35 – 8:50	Irene Glowinski	DMID's Scientific Priorities

Biodefense RNA & Orthopox & Non-Biodefense Viruses Session

8:50 – 9:20	Justin Julander	(30) *in vitro* - BioD RNA Viruses
9:20 – 9:50	Brian Gowen	(30) *in vivo* - BioD RNA Viruses
9:50 – 10:20	Justin Julander	(30) *in vivo* - BioD RNA Viruses
10:20 – 10:40	John Morrey	(20) *in vivo* - WNV
10:40 – 11:00		BREAK
11 :00 – 11:20	Nigel Bourne	(20) *in vivo* - Dengue
11:20 – 11:35	Don Smee	(15) *in vivo* - Pox
11:35 – 11:50	Scott Parker	(15) *in vivo - Pox*
11:50 – 12:05	Mark Prichard	(15) *in vitro - Pox*
12:05 – 12:20	Don Smee	(15) *in vitro - Non-BioD Viruses, ENTV68*
12:20 – 1:35		LUNCH

Ebola Session

1:35 – 1:50	Darci Smith	(15) *in vitro - EBOV*
1:50 – 2:05	Alex Freiberg.....	(15) *in vitro - EBOV*
2:05 – 2:20	Baek Kim	(15) *in vitro - replicon EBOV*
2:20 – 2:40	Alex Freiberg	(20) *in vivo - EBOV*
2:40 – 3:00		BREAK

Hepatitis Session

3:00 – 3:15	Brent Korba	(15) *in vitro - HBV*
3:15 – 3:35	Michael Murray.....	(20) *in vitro - HBV, HCV*
3:35 – 3:55	John Morrey	(20) *in vivo - HBV*
3:55 – 4:15	Stephan Menne	(20) *in vivo - HBV*
4:15 – 4:35	Norman Kneteman	(20) *in vivo - HCV*
6:00 – ???		HAPPY HOUR *followed by* DINNER *at* Mosaic (186 Halpine Road, Rockville MD 20852)

AGENDA
Thursday, April 2, 2015

8:00 – 8:30		MORNING COFFEE

Herpesvirus Session

8:30 – 8:50	Mark Prichard	(20)	*in vitro* - Herpes
8:50 – 9:10	Debra Quenelle	(20)	*in vivo* - Herpes
9:10 – 9:40	Rhonda Cardin	(30)	*in vivo* - Herpes
9:40 – 10:00	Jennifer Moffat	(20)	*in vivo* - VZV

10:00 – 10:20		BREAK

Adenovirus, BK virus and Papillomavirus Session

10:20 – 10:40	Karoly Toth.....	(20)	*in vivo - Adenovirus*
10:40 – 11:00	Neil Christensen	(20)	*in vivo - HPV*
11:00 – 11:30	Mark Prichard	(30)	*in vitro - HPV, BK, JC*

Norovirus Session

11:30 – 11:45	Brent Korba	(15)	*in vitro* - NoV

11:45 – 1:00		LUNCH

Respiratory Viruses Session

1:00 – 1:15	Craig Day	(15)	*in vitro - Respiratory viruses (B17)*
1:15 – 1:30	Don Smee	(15)	*in vitro - Respiratory viruses (B16)*
1:30 – 1:50	Brian Gilbert	(20)	*in vivo - RSV, PIV*
1:50 – 2:10	Adam Cockrell	(20)	*in vivo - MERS*

2:10 – 2:30		BREAK

2:30 – 3:00	Don Smee	(30)	*in vivo - Respiratory viruses (A66)*
3:00 – 3:30	Bart Tarbet	(30)	*in vivo - Respiratory viruses (A66)*
3:30 – 3:45	Heather Greenstone/Chris Tseng		CLOSING

3:45		ADJOURN *Safe Journey, until we meet again . . .*

2015 CATG Dinner Choices

	Name	First Course	Main Course	Dessert
1	Stephan Menne	Wild Mushroom Soup	Filet Mignon **M**	Lemon Crème Brulée
2	Alan Barrett	Caesar Salad	Filet Mignon **MW**	Chocolate Waffle
3	David Bernstein	Wild Mushroom Soup	Stuffed Chicken Breast	Lemon Crème Brulée
4	Neil Christensen	Wild Mushroon Soup	Filet Mignon **MR**	Crepes Suzette
5	Adam Cockrell	Mosaic Salad	Salmon	Lemon Crème Brulée
6	Pedro Piedra	Caesar Salad	Filet Mignon **MR**	Lemon Crème Brulée
7	Amy Sims	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulée
8	Deb Quenelle	Wild Mushroom Soup	Vegetable Tian	Crepes Suzette
9	Rhonda Cardin	Wild Mushroom Soup	Stuffed Chicken Breast	Chocolate Waffle
10	Mark Prichard	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
11	Miriam Perkins	Mosaic Salad	Salmon	Chocolate Waffle
12	Scott Parker	Mosaic Salad	Stuffed Chicken Breast	Chocolate Waffle
13	Lorne Tyrrell	Wild Mushroom Soup	Filet Mignon **MR**	Crepes Suzette
14	John Morrey	Mosaic Salad	Salmon	Lemon Crème Brulée
15	Don Smee	Caesar Salad	Filet Mignon **M**	Crepes Suzette
16	Justin Julander	Caesar Salad	Filet Mignon **MR**	Chocolate Waffle
17	Bart Tarbet	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulée
18	Brain Gowen	Caesar Salad	Filet Mignon **MR**	Chocolate Waffle
19	Craig Day	Caesar Salad	Salmon	Lemon Crème Brulée
20	Brett Hurst	Caesar Salad	Filet Mignon **MR**	Lemon Crème Brulée
21	Kathy Keith	Caesar Salad	Filet Mignon **W**	Chocolate Waffle
22	Earl Kern	Mosaic Salad	Stuffed Chicken Breast	Lemon Crème Brulée
23	Alex Freiberg	Wild Mushroom Soup	Filet Mignon **W**	Crepes Suzette

24	Bob Sidwell	Wild Mushroom Soup	Filet Mignon **R**	Crepes Suzette
25	Ramya Natarajan	Mosaic Salad	Vegetable Tian	Chocolate Waffle
26	Erik Stemmy	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
27	Amy Krafft	Mosaic Salad	Salmon	Lemon Crème Brulée
28	Jennifer Moffat	Mosaic Salad	Salmon	Lemon Crème Brulée
29	Cathy Laughlin	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
30	Heather Greenstone	Mosaic Salad	Filet Mignon **M**	Crepes Suzette
31	Dave Matthews	Caesar Salad	Filet Mignon **MR**	Chocolate Waffle
32	Chris Tseng	Caesar Salad	Filet Mignon **M**	Chocolate Waffle
33	Lucy Tseng	Caesar Salad	Salmon	Lemon Crème Brulée
34	Mike Murray	Caesar Salad	Salmon	Lemon Crème Brulée
35	Roger Ptak	Caesar Salad	Filet Mignon **MR**	Lemon Crème Brulée
36	Mark Challberg	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulee
37	Brent Korba	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulee
38	Bill Wold	Wild Mushroom Soup	Salmon	Crepes Suzette
39	Baek Kim	Mosaic Salad	Filet Mignon **M**	Lemon Crème Brulee
40	Karoly Toth	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulee
41	Brian Gilbert	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulee
42	Carol Gilbert	Caesar Salad	Salmon	Lemon Crème Brulee
43	Norm Kneteman	Mosaic Salad	Salmon	Lemon Crème Brulee
44	Nigel Bourne	Caesar Salad	Stuffed Chicken Breast	Chocolate Waffle
45	Pat Repik	Caesar Salad	Stuffed Chicken Breast	Lemon Crème Brulee
46	Garry Lund	Caesar Salad	Filet Mignon **MR**	Crepes Suzette
47	Irene Glowinski	Wild Mushroom Soup	Filet Mignon **MR**	Crepes Suzette
48	Carole Heilman	Mosaic Salad	Salmon	Lemon Crème Brulee

From: Perkins, Miriam (NIH/NIAID) [E]
Sent: Wed, 25 Mar 2015 14:43:54 -0400
To: Earl Kern; O'Rear, Julian (FDA/CDER); Adam Cockrell; Adams, Miranda (NIH/NIAID) [E]; Agneta Von Gegerfelt; Alexander Freiberg; Krafft, Amy (NIH/NIAID) [E]; Amy Sims; Eakin, Ann (NIH/NIAID) [E]; Aurigemma, Rosemarie (NIH/NIAID) [E]; Baek Kim; Styrt, Barbara (FDA/CDER); Barrett, Alan; Bart Tarbet; Bill Wold; Korba, Brent; Brett Hurst; Brian E. Gilbert; Brian Gowen; Buck, Alexandra (NIH/NIAID) [E]; Laughlin, Catherine (NIH/NIAID) [E]; Chadwick, Tiffany (NIH/NIAID) [E]; Craig Day; Cassetti, Cristina (NIH/NIAID) [E]; Dale Barnard; Darci Smith; Bernstein, David; Spiro, David (NIH/NIAID) [E]; Quenelle, Debra; Smee, Donald; Ellen Faaleolea; Gupta, Emily (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]; Park, Eun-Chung (NIH/NIAID) [E]; Cassels, Fred (NIH/NIAID) [E]; Garry Lund; Kennedy, George (NIH/NIAID) [E]; Gregg N. Milligan; Hartmann, Richard (NIH/NIAID) [E]; Greenstone, Heather (NIH/NIAID) [E]; Heilman, Carole (NIH/NIAID) [E]; Schiltz, Helen (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Jackson, Charles (NIH/NIAID) [E]; Moffat, Jennifer; Bogdan, John (NIH/NIAID) [E]; Morrey, John; Campbell, Joseph (NIH/NIAID) [E]; Justin Julander; Karoly Toth; Kasparian, Sevag (NIH/NIAID) [E]; Kathy Keith; Knight, Stanley (NIH/NIAID) [E]; Lorne Tyrrell; Mark Buller; Challberg, Mark (NIH/NIAID) [E]; Lewis, Mark; Prichard, Mark; Holbrook, Michael (NIH/NIAID) [C]; Murray, Michael; Bray, Mike (NIH/NIAID) [E]; Perkins, Miriam (NIH/NIAID) [E]; Christensen, Neil; Nguyen, Tam (NIH/NIAID) [E]; Nichols, Courtney (NIH/NIAID) [E]; Nigel Bourne; Norm Kneteman; Bryant, Paula (NIH/NIAID) [E]; Jahrling, Peter (NIH/NIAID) [E]; Koshy, Rajen (NIH/NIAID) [E]; Ramaswamy, Aishwarya (NIH/NIAID) [C]; Natarajan, Ramya (NIH/NIAID) [E]; Kincaid, Randall (NIH/NIAID) [E]; Repik, Patricia (NIH/NIAID) [E]; Rhonda Cardin; Roger Ptak; Alarcon, Rodolfo (NIH/NIAID) [E]; Scott Parker; Smith, Cristina (NIH/NIAID) [E]; Kim, Sonnie (NIH/NIAID) [E]; Spinelli, Beth (NIH/NIAID) [E]; Stephen Menne; Teo, Swee (NIH/NIAID) [E]; Guina, Tina (NIH/NIAID) [E]; Tony Piedra; Laporte, Tracy (NIH/NIAID) [E]; Tseng, Christopher (NIH/NIAID) [E]; Dowling, William (NIH/NIAID) [E]; Wong, Anna (NIH/NIAID) [E]
Subject: 2015 CATG Dinner
Attachments: 2015 Menu Choices.docx, 2015 CATG Dinner Menu.docx, Menu Template.docx

Hi All,

I have attached a list of the menu choices for those of you have indicated you will be attending our annual dinner. Please let me know if there are any corrections.

If anyone else would like to join us, please send me your menu selections on the attached menu template. I have attached a copy of the menu for your reference.

Thanks.

Miriam
Miriam Perkins, M.A.T.
Health Specialist, Virology Branch
DMID/NIAID/NIH
5601 Fishers Lane, Room 8E60
Rockville, MD 20852
Phone: (b)(6)
Email: (b)(6)

2015 CATG Dinner Choices

	Name	First Course	Main Course	Dessert
1	Stephan Menne	Wild Mushroom Soup	Filet Mignon **M**	Lemon Crème Brulée
2	Alan Barrett	Caesar Salad	Filet Mignon **MW**	Chocolate Waffle
3	David Bernstein	Wild Mushroom Soup	Stuffed Chicken Breast	Lemon Crème Brulée
4	Neil Christensen	Wild Mushroon Soup	Filet Mignon **MR**	Crepes Suzette
5	Adam Cockrell	Mosaic Salad	Salmon	Lemon Crème Brulée
6	Pedro Piedra	Caesar Salad	Filet Mignon **MR**	Lemon Crème Brulée
7	Amy Sims	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulée
8	Deb Quenelle	Wild Mushroom Soup	Vegetable Tian	Crepes Suzette
9	Rhonda Cardin	Wild Mushroom Soup	Stuffed Chicken Breast	Chocolate Waffle
10	Mark Prichard	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
11	Miriam Perkins	Mosaic Salad	Salmon	Chocolate Waffle
12	Scott Parker	Mosaic Salad	Stuffed Chicken Breast	Chocolate Waffle
13	Lorne Tyrrell	Wild Mushroom Soup	Filet Mignon **MR**	Crepes Suzette
14	John Morrey	Mosaic Salad	Salmon	Lemon Crème Brulée
15	Don Smee	Caesar Salad	Filet Mignon **M**	Crepes Suzette
16	Justin Julander	Caesar Salad	Filet Mignon **MR**	Chocolate Waffle
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24	Bob Sidwell	Wild Mushroom Soup	Filet Mignon **R**	Crepes Suzette
25	Ramya Natarajan	Mosaic Salad	Vegetable Tian	Chocolate waffle
26	Erik Stemmy	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
27	Amy Krafft	Mosaic Salad	Salmon	Lemon Crème Brulée
28	Jennifer Moffat	Mosaic Salad	Salmon	Lemon Crème Brulée
29	Cathy Laughlin	Mosaic Salad	Filet Mignon **MR**	Lemon Crème Brulée
30	Heather Greenstone	Mosaic Salad	Filet Mignon **M**	Crepes suzette
31	Dave Matthews	Caesar Salad	Filet Mignon **MR**	Chocolate waffle
32	Chris Tseng	Caesar Salad	Filet Mignon **M**	Chocolate waffle
33	Lucy Tseng	Caesar Salad	Salmon	Lemon Crème Brulée
34	Mike Murray	Caesar Salad	Salmon	Lemon Crème Brulée
35	Roger Ptak	Caesar Salad	Filet Mignon **MR**	Lemon Crème Brulée
36	Mark Challberg	Wild Mushroom Soup	Filet Mignon **MR**	Lemon Crème Brulee
37	Brent Korba	Mosaic salad	Filet Mignon **MR**	Lemon Crème Brulee
38	Bill Wold	Wild Mushroom Soup	Salmon	Crepes suzette
39	Baek Kim	Mosaic salad	Filet Mignon **M**	Lemon Crème Brulee

MOSAIC CUISINE AND CAFÉ

APPETIZER

Spinach Artichoke Dip ***(vegetarian)***

FIRST COURSE *(choose one)*

Caesar Salad

Wild Mushroom Soup ***(vegetarian)***

Mosaic Salad ***(vegetarian)***

MAIN COURSE *(choose one)*

Roasted Chicken Breast Stuffed with Fontina and Sage Pinot Grigio Sauce
Garlic mashed potatoes and green beans with lemon and toasted almonds

Grilled Filet Mignon with Mushroom Ragout
Garlic and butter fingerling potatoes and green beans with lemon and toasted almonds

Portobello and Vegetable Tian ***(vegetarian)***
Asparagus with hollandaise sauce, brown sugar glazed brussel sprouts and scalloped potatoes with gruyere

Salmon Fillet with a Lemon, Caper and Dill Yogurt Sauce
Garlic and butter fingerling potatoes and brown sugar glazed brussel sprouts

DESSERTS *(choose one)*

Chocolate Waffle

Crêpes Suzette with Orange Sauce

Lemon Crème Brulée

Dinner ***(tax and tip included)*** . . . . . **$47 per guest**

Coffee, tea & soft drinks ***(included)*** . . . . . **no charge**

Beer & Wine ***(by the bottle/glass)*** . . . . . CASH *when served*

Mosaic Cuisine and Café + Event Planning | 186 Halpine Road, Rockville Maryland 20852
T 301.468.0682 | **F** 301.468.0684 | tjugnet@mosaiccuisine.com | W.mosaiccuisine.com

Menu Template

Name	First Course	Main Course	Dessert

Please put your last name in the first column under **Name**.

No need to specify the appetizer, it is the same for all, **Spinach Artichoke Dip**.

Please enter one of the following: **Caesar Salad**, **Wild Mushroom Soup**, or **Mosaic Salad** in the second column under the **First Course**.

Please enter one of the following: **Stuffed Chicken Breast**, **Filet Mignon**, **Vegetable Tian**, or **Roasted Salmon** in the third column under **Main Course**. If you select **Filet Mignon**, please specify how you would like it cooked (**R, MR, M, MW, W**).

Please enter one of the following: **Chocolate waffle**, **Crepes Suzette**, or **Lemon crème brulee** in the fourth column under **Dessert**.

Please ***return to me*** by **4:00 pm Wednesday, March 25**.

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Mon, 23 Mar 2015 11:05:55 +0000
To: Baric, Ralph
Subject: RE: 1R01AI110700-01A1

Hi Ralph,
Sure, I'm happy to chat with you. I think in essence it was just the passaging work in Aim 3 that we determined would be GoF because you said you'd be selecting for more pathogenic variants. Since we can't fund that portion you can either cut it and reduce the budget or propose alternative work to take its place. Once we get that last detail worked out we should be able to award the grant pretty quickly.

Let me know if you still want to speak by phone, or if you have any other questions.

Erik

From: Baric, Ralph
Sent: Saturday, March 21, 2015 7:13 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01A1

Hi Erik, Hope your doing well. I was wondering if we could have a short chat next week. Was wondering if I need to respond to gof letter by suggesting some alternative experiments for aim 3….i was unsure of next step in process. Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Monday, March 16, 2015 10:44 AM
To: Baric, Ralph S
Subject: RE: 1R01AI110700-01A1

Hi Ralph,
So sorry that things are taking so long. We should have everything thing we need from you at this point. I hope to have news for you very soon. Thanks again for your patience and willingness to help!

Erik

From: Baric, Ralph
Sent: Monday, March 16, 2015 10:40 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: 1R01AI110700-01A1

Hi Erik, I was just wondering how the GOF process is moving forward. Any roadblocks? Anything that we can do to help? Provide additional clarification? Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, October 29, 2014 9:42 AM
To: Baric, Toni C; Fang Li

Cc: Baric, Ralph S
Subject: RE: 1R01AI110700-01A1

No worries. Thanks!

From: Baric, Toni C (b)(6)
Sent: Wednesday, October 29, 2014 9:41 AM
To: Fang Li
Cc: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph
Subject: RE: 1R01AI110700-01A1

Yes, Ralph was detained. He will dial in now.

From: Fang Li (b)(6)
Sent: Wednesday, October 29, 2014 9:38 AM
To: Baric, Toni C
Cc: Stemmy, Erik (NIH/NIAID) [E]; Baric, Ralph S
Subject: Re: 1R01AI110700-01A1

Are we having the teleconference now?

On Thu, Oct 23, 2014 at 10:56 AM, Baric, Toni C (b)(6) wrote:
Dear Erik, Ralph and Fang,
It looks like Wednesday Oct 29 works best for all. I would like to schedule the call for 9:30 ET. The calling numbers are:

Phone: 1-800-747-5150
Passcode: (b)(6)

If this time is in conflict with your schedule, please let me know.
Best regards,
Toni

From: Fang Li (b)(6)
Sent: Wednesday, October 22, 2014 9:06 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Baric, Ralph S; Baric, Toni C
Subject: Re: 1R01AI110700-01A1

Hi all,

I will be available Wednesday 10/29 from 8 am ET to 4 pm ET..

Thursday 10/30 from 10:30 am to noon should also work for me.

Thanks,
Fang

On Wed, Oct 22, 2014 at 5:40 AM, Stemmy, Erik (NIH/NIAID) [E] (b)(6) wrote:
Hi Ralph,
Sure, I'd be happy to discuss. Wednesday 10/29 I'm pretty flexible, and I can do Thursday 10/30 any time between about 10:30 and noon.

Toni, please let me know what works best. Thanks!

Erik

From: Baric, Ralph
Sent: Tuesday, October 21, 2014 10:52 PM
To: Stemmy, Erik (NIH/NIAID) [E]; Baric, Toni C
Cc: (b)(6)
Subject: 1R01AI110700-01A1

Hi Erik, hope your doing well. Fang and I would like to discuss the implications of the presidential directive on the mers research in this grant application next week. We would also like to discuss its potential for funding, considering the (b)(6) impact score. Could we set up a conference call for next week, toni can help arrange. Ralph

--
****
Fang Li, Ph.D.
Associate Professor
Department of Pharmacology
University of Minnesota Twin Cities
(b)(6)
http://www.msi.umn.edu/~lifang
****

--
****
Fang Li, Ph.D.
Associate Professor
Department of Pharmacology
University of Minnesota Twin Cities
(b)(6)
http://www.msi.umn.edu/~lifang
****

From: Perkins, Miriam (NIH/NIAID) [E]
Sent: Fri, 20 Mar 2015 17:27:09 -0400
To: O'Rear, Julian (FDA/CDER); Adam Cockrell; Adams, Miranda (NIH/NIAID) [E]; Agneta Von Gegerfelt; Alexander Freiberg; Krafft, Amy (NIH/NIAID) [E]; Amy Sims; Eakin, Ann (NIH/NIAID) [E]; Aurigemma, Rose (NIH/NCI) [E]; Baek Kim; Styrt, Barbara (FDA/CDER); Barrett, Alan; Bart Tarbet; Bill Wold; Korba, Brent; Brett Hurst; Brian E. Gilbert; Brian Gowen; Buck, Alexandra (NIH/NIAID) [E]; Laughlin, Catherine (NIH/NIAID) [E]; Chadwick, Tiffany (NIH/NCI) [E]; Craig Day; Cassetti, Cristina (NIH/NIAID) [E]; Dale Barnard; Darci Smith; Bernstein, David; Spiro, David (NIH/FIC) [E]; Quenelle, Debra; Smee, Donald; Ellen Faaleolea; Gupta, Emily (NIH/NIAID) [C]; Stemmy, Erik (NIH/NIAID) [E]; Park, Eun-Chung (NIH/NIAID) [E]; Cassels, Fred (NIH/NIAID) [E]; Garry Lund; Kennedy, George (NIH/NIAID) [E]; Gregg N. Milligan; Hartmann, Richard (NIH/NIAID) [E]; Greenstone, Heather (NIH/NIAID) [E]; Heilman, Carole (NIH/NIAID) [E]; Schiltz, Helen (NIH/NIAID) [E]; Glowinski, Irene (NIH/NIAID) [E]; Jackson, Charles (NIH/NIAID) [E]; Moffat, Jennifer; Bogdan, John (NIH/NIAID) [E]; Morrey, John; Campbell, Joseph (NIH/NIAID) [E]; Justin Julander; Karoly Toth; Kasparian, Sevag (NIH/NIAID) [E]; Kathy Keith; Knight, Stanley (NIH/NIAID) [E]; Lorne Tyrrell; Mark Buller; Challberg, Mark (NIH/NIAID) [E]; Lewis, Mark; Prichard, Mark; Holbrook, Michael (NIH/NIAID) [C]; Murray, Michael; Bray, Mike (NIH/NIAID) [E]; Perkins, Miriam (NIH/NIAID) [E]; Christensen, Neil; Nguyen, Tam (NIH/NIAID) [E]; Nichols, Courtney (NIH/NIAID) [E]; Nigel Bourne; Norm Kneteman; Bryant, Paula (NIH/NIAID) [E]; Jahrling, Peter (NIH/NIAID) [V]; Koshy, Rajen (NIH/NIAID) [E]; Ramaswamy, Aishwarya (NIH/NIAID) [E]; Natarajan, Ramya (NIH/NIAID) [E]; Kincaid, Randall (NIH/NIAID) [E]; Repik, Patricia (NIH/NIAID) [E]; Rhonda Cardin; Roger Ptak; Alarcon, Rodolfo (NIH/NIAID) [E]; Scott Parker; Smith, Cristina (NIH/NIAID) [E]; Kim, Sonnie (NIH/NIAID) [E]; Spinelli, Beth (NIH/NIAID) [E]; Stephen Menne; Teo, Swee (NIH/NIAID) [E]; Guina, Tina (NIH/NIAID) [E]; Tony Piedra; Laporte, Tracy (NIH/NIAID) [E]; Tseng, Christopher (NIH/NIAID) [E]; Dowling, William (NIH/NIAID) [E]; Wong, Anna (NIH/NIAID) [E]; Earl Kern
Cc: 'Mosaic Restaurant (b)(6) '
Subject: 2015 CATG Annual Dinner
Attachments: 2015 CATG Dinner Menu.docx, Menu Template.docx

Hi All,

As you are aware, this is the 25th Annual CATG Meeting. This year's dinner will celebrate 25 years of antiviral drug research and development. As part of that celebration, special thanks go out to investigators, Earl Kern and Brian Gilbert, and NIAID program staff, Chris Tseng and Catherine Laughlin, who have been part of Collaborative Antiviral Testing Group since its inception in 1989. We hope you can join us.

The annual dinner will be held on Wednesday, April 1, from 6:00 to 8:30 at the Mosaic Cafe. Happy Hour will be from 5:30pm to 6:00pm. Mosaic Café is the restaurant where we held the dinner last year. It is in easy walking distance from the Hilton Hotel.

I have attached the Dinner Menu and the usual WORD template for your dinner choices. ***Please enter your choices in the template and return to me no later than 4:00 pm on Wednesday, March 25****. If you are having filet mignon, be sure to include how you would like it cooked (**RARE**, **MED RARE**, **MED**, **MED WELL**, **WELL**)*. I need to let the restaurant know the number of attendees and their selections by Thursday noon, March 26.

The cost of the dinner is $47 per person. Non-alcoholic beverages *(soft drinks and tea)* as well as tax and tip are included in the $47. Payment for BEER and WINE will be expected when you are served.

I will collect payment for dinner during the Tuesday morning break and take it to the restaurant at noon. That way everything is prepaid and we can leave when we are done – no waiting to process credit cards. Individual receipts will be provided *(same as in the past)*.

Please let me know if you have any questions. It should be a very enjoyable evening.

Miriam
Miriam Perkins, M.A.T.
Health Specialist, Virology Branch
DMID/NIAID/NIH
5601 Fishers Lane, Room 8E60
Rockville, MD 20852
Phone: (b)(6)
Email: (b)(6)

MOSAIC CUISINE AND CAFÉ

APPETIZER

Spinach Artichoke Dip ***(vegetarian)***

FIRST COURSE *(choose one)*

Caesar Salad

Wild Mushroom Soup ***(vegetarian)***

Mosaic Salad ***(vegetarian)***

MAIN COURSE *(choose one)*

Roasted Chicken Breast Stuffed with Fontina and Sage Pinot Grigio Sauce
Garlic mashed potatoes and green beans with lemon and toasted almonds

Grilled Filet Mignon with Mushroom Ragout
Garlic and butter fingerling potatoes and green beans with lemon and toasted almonds

Portobello and Vegetable Tian ***(vegetarian)***
Asparagus with hollandaise sauce, brown sugar glazed brussel sprouts and scalloped potatoes with gruyere

Salmon Fillet with a Lemon, Caper and Dill Yogurt Sauce
Garlic and butter fingerling potatoes and brown sugar glazed brussel sprouts

DESSERTS *(choose one)*

Chocolate Waffle

Crêpes Suzette with Orange Sauce

Lemon Crème Brulée

Dinner ***(tax and tip included)*** . . . . . **$47 per guest**

Coffee, tea & soft drinks ***(included)*** . . . . . **no charge**

Beer & Wine ***(by the bottle/glass)*** . . . . . CASH *when served*

Mosaic Cuisine and Café + Event Planning | 186 Halpine Road, Rockville Maryland 20852
T 301.468.0682 | **F** 301.468.0684 | tjugnet@mosaiccuisine.com | W.mosaiccuisine.com

Menu Template

Name	First Course	Main Course	Dessert

Please put your last name in the first column under **Name**.

No need to specify the appetizer, it is the same for all, **Spinach Artichoke Dip**.

Please enter one of the following: **Caesar Salad**, **Wild Mushroom Soup**, or **Mosaic Salad** in the second column under the **First Course**.

Please enter one of the following: **Stuffed Chicken Breast**, **Filet Mignon**, **Vegetable Tian**, or **Roasted Salmon** in the third column under **Main Course**. If you select **Filet Mignon**, please specify how you would like it cooked (**R, MR, M, MW, W**).

Please enter one of the following: **Chocolate waffle**, **Crepes Suzette**, or **Lemon crème brulee** in the fourth column under **Dessert**.

Please ***return to me*** by **4:00 pm Wednesday, March 25**.

From: Cyr, Robin L
Sent: Thu, 19 Mar 2015 17:05:46 +0000
To: Eisenman, Laura (NIH/NIAID) [E]
Cc: Baric, Ralph; Glowinski, Irene (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Signed GoF Letter for - Grant Number: 1R01AI110700 - 01A1 PI Name: Baric, Ralph S

Good afternoon.

I write to acknowledge receipt your email and the attached GoF letter.

Thank you for the thorough analysis of our January 21, 2015 submission and the detailed guidance sent in response to your review. We appreciate your time and support of this important research and will make the required changes, as well as notations regarding when we need to make further modifications or send NAID notifications. I have circulated this to all internal parties that support Dr. Baric's research and I know that he is presently reviewing the document to ensure his understanding of the provisions delineated in the letter.

Many thanks,

Robin L. Cyr
Associate Vice Chancellor for Research
Director, Office of Sponsored Research
University of North Carolina at Chapel Hill
104 Airport Drive, Suite 2200
Chapel Hill, NC 27599-1350
Ph: (b)(6)
Fax: (919) 962-5011
Executive Assistant, Jackie Treschl (b)(6)
Email: (b)(6)

"Alone we can do so little; together we can do so much." – Helen Keller

http://research.unc.edu/Offices/sponsored-research/index.htm

From: Eisenman, Laura (NIH/NIAID) [E] (b)(6)
Sent: Thursday, March 19, 2015 10:02 AM
To: Cyr, Robin L
Cc: Baric, Ralph S; Glowinski, Irene (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Stemmy, Erik

(NIH/NIAID) [E]
Subject: Re: Signed GoF Letter for - Grant Number: 1R01AI110700 - 01A1 PI Name: Baric, Ralph S

Dear Ms. Cyr,

Please see attached final signed version of the Gain of Function (GoF) letter for your records.

Thank you,

Laura C. Eisenman
Lead Grants Management Specialist
National Institute of Allergy &
Infectious Diseases (NIAID)
5601 Fishers Lane, Room 4E41, MSC 9824
Bethesda, Maryland 20892-2962
Use Rockville, MD 20852 for overnight and courier deliveries)
Telephone: (b)(6)
Facsimile: 301-493-0597
E-Mail: (b)(6)
****

****
IMPORTANT NOTICES:
NEW! ***"Effective October 1, 2014, NIH closeout policy has changed (see NOT-OD-14-084). In order to avoid unilateral closeout, final reports must be submitted in a timely manner. Failure to submit accurate final reports could result in enforcement actions such as revisions to NOA funding levels, or delay in future funding."***
****
Extension of eRA Commons User IDs to Individuals in Graduate and Undergraduate Student Project Roles with Measurable Effort on an NIH Annual Progress Report (PHS2590 & RPPR)
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-097.html
NEW Guide Notice!
****

From: Eisenman, Laura (NIH/NIAID) [E]
Sent: Thu, 19 Mar 2015 10:02:04 -0400
To: (b)(6)
Cc: Baric, Ralph; Glowinski, Irene (NIH/NIAID) [E]; Kirker, Mary (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]
Subject: Re: Signed GoF Letter for - Grant Number: 1R01AI110700 - 01A1 PI Name: Baric, Ralph S
Attachments: GoF Letter_FINAL version.pdf

Dear Ms. Cyr,

Please see attached final signed version of the Gain of Function (GoF) letter for your records.

Thank you,

Laura C. Eisenman
Lead Grants Management Specialist
National Institute of Allergy &
Infectious Diseases (NIAID)
5601 Fishers Lane, Room 4E41, MSC 9824
Bethesda, Maryland 20892-2962
Use Rockville, MD 20852 for overnight and courier deliveries)
Telephone: (b)(6)
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****

****
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NEW Guide Notice!
****

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

March 19, 2015

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

RE: R01AI110700-01A1 PI: Baric

Dear Ms. Cyr:

Thank you for your correspondence of January 21, 2015, regarding the October 17, 2014 White House announcement of a U.S. Government-wide pause on certain gain-of-function (GoF) experiments and its potential impact on your research (http://www.whitehouse.gov/blog/2014/10/17/doing-diligence-assess-risks-and-benefits-life-sciences-gain-function-research). The pause pertains to GoF research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the resulting virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route.

NIAID reviewed the original grant application, and the additional information provided by you, and made the following assessments:

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

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

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

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

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

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

Please remember that the institution must comply in full with all terms and conditions placed on this grant. If your research evolves to include experiments that may be subject to the pause or you observe enhanced pathogenicity and/or transmissibility of MERS-CoV in mammals via the respiratory route at any time during the course of conducting these experiments, you must immediately stop these research activities and provide the NIAID Program Officer and Grants Management Specialist with the relevant data and information related to these unanticipated outcomes.

As indicated above, NIAID determinations are based on information from multiple sources, but primarily on our communication with you about the details of your proposed experiments and your research results. Should NIAID's determination change based on information obtained through the U.S. Government gain-of-function deliberative process, described here http://www.phe.gov/s3/dualuse/Documents/gain-of-function.pdf, you will be notified; however, until such time, or until the pause is lifted, NIAID's determination, indicated above, is final.

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

Sincerely,

(b)(6)

Laura Eisenman
Grants Management Specialist
NIAID/NIH/DHHS

(b)(6)

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

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

From: Stemmy, Erik (NIH/NIAID) [E]
Sent: Wed, 4 Mar 2015 00:19:04 +0000
To: Baric, Ralph
Subject: RE: Pending R01AI110700-01A1

Hi Ralph,
Thanks very much for the thorough reply. We'll be reviewing this week and hope to have everything ready for an award to be made very soon.

Best,
Erik

From: Baric, Ralph
Sent: Sunday, March 01, 2015 10:35 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Pending R01AI110700-01A1

HI Eric, Please find our responses to your thoughtful questions. Let me know if you need any additional information. Hope you are doing well. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, February 25, 2015 10:52 AM
To: Baric, Ralph S
Subject: Pending R01AI110700-01A1

Dear Ralph,
Apologies for the delayed response. We have been reviewing your response to the gain-of-function potential for your pending R01 (AI110700-01A1) and wanted to ask you to clarify one area. In parts of the application and your response you propose to create fully replicating recombinant CoV variants containing RBD binding residues and/or protease cleavage sites from MERS-CoV. We feel that these experiments will create novel MERS-Like viruses that may be reasonably anticipated to have increased pathogenicity compared to wild type strains since they will confer attributes of MERS to non-MERS CoVs. Thus we feel that these experiments would meet the intent of the GoF funding pause, which is not to produce novel CoVs with increased pathogenicity and/or transmissibility in mammals.

We would like to ask you to justify whether in your view the novel MERS-like CoV variants you propose to create would be reasonably anticipated to have increased pathogenicity and/or mammalian transmissibility compared to the wild type strains. Alternatively, you could limit your experiments to those that do not involve the creation of fully replicating recombinant viruses; we feel comfortable funding your proposed research with pseudoviruses.

Thanks very much for your help, and let me know if you have any questions.
Erik

Please note my updated contact information below:
Erik J. Stemmy, Ph.D.

Program Officer
Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/NIH/HHS
5601 Fishers Lane, Room 8E18
Bethesda, MD 20892-7630
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
Sent: Mon, 2 Mar 2015 03:34:43 +0000
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: Pending R01AI110700-01A1
Attachments: Baric-Li Grant-Final GOF Response 2015.pdf

HI Eric, Please find our responses to your thoughtful questions. Let me know if you need any additional information. Hope you are doing well. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Wednesday, February 25, 2015 10:52 AM
To: Baric, Ralph S
Subject: Pending R01AI110700-01A1

Dear Ralph,
Apologies for the delayed response. We have been reviewing your response to the gain-of-function potential for your pending R01 (AI110700-01A1) and wanted to ask you to clarify one area. In parts of the application and your response you propose to create fully replicating recombinant CoV variants containing RBD binding residues and/or protease cleavage sites from MERS-CoV. We feel that these experiments will create novel MERS-Like viruses that may be reasonably anticipated to have increased pathogenicity compared to wild type strains since they will confer attributes of MERS to non-MERS CoVs. Thus we feel that these experiments would meet the intent of the GoF funding pause, which is not to produce novel CoVs with increased pathogenicity and/or transmissibility in mammals.

We would like to ask you to justify whether in your view the novel MERS-like CoV variants you propose to create would be reasonably anticipated to have increased pathogenicity and/or mammalian transmissibility compared to the wild type strains. Alternatively, you could limit your experiments to those that do not involve the creation of fully replicating recombinant viruses; we feel comfortable funding your proposed research with pseudoviruses.

Thanks very much for your help, and let me know if you have any questions.
Erik

Please note my updated contact information below:
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Program Officer
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Phone: (b)(6)
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Getting ready to publish? Share the good news with your program officer asap! NIAID may be able to help publicize your article. And, remember to list your NIAID grant or contract number in the publication.

NIH Request for Clarification-R01AI110700-01A1.

In parts of the application and your response you propose to create fully replicating recombinant CoV variants (HKU4) containing RBD binding residues and/or protease cleavage sites from MERS-CoV. We feel that these experiments will create novel MERS-Like viruses that may be reasonably anticipated to have increased pathogenicity compared to wild type strains since they will confer attributes of MERS to non-MERS CoVs. Thus we feel that these experiments would meet the intent of the GoF funding pause, which is not to produce novel CoVs with increased pathogenicity and/or transmissibility in mammals.

1) We would like to ask you to justify whether in your view the novel MERS-like CoV variants (HKU4) you propose to create would be reasonably anticipated to have increased pathogenicity and/or mammalian transmissibility compared to the wild type strains. Alternatively, you could limit your experiments to those that do not involve the creation of fully replicating recombinant viruses; we feel comfortable funding your proposed research with pseudoviruses.

Summary of the Response: We do not believe that the proposed RBD or protease cleavage site HKU4 variants would be reasonably anticipated to have increased pathogenesis or mammalian transmissibility like that seen with the MERS-CoV. Rather, we would anticipate that such mutants will still be attenuated in terms of in vitro replication (HAE) and pathogenesis. Justification for this position is summarized below.

Background: The current pause specifically targets SARS and MERS coronaviruses, hence we had believed and had been informed by program that studies involving HKU4 and other bat coronaviruses were exempt from the GOF pause. The above new interpretation would appear to expand the pause definition, to in essence, include all coronaviruses, which would be tragic in terms of public health pandemic preparedness and animal health (PEDV has killed 12million+ pigs in the US since its emergence). We also understand and appreciate the concerns expressed above.

HKU4 is a group 2c bat coronavirus and is a distant relative to MERS-CoV (also the closest at the moment). The HKU4 and MERS-CoV S glycoprotein is ~30% different (70% identical) in amino acid sequence. Nevertheless and despite significant variation in the receptor binding domains of these two viruses, HKU4 is able to use the human and bat dipepidyl peptidase 4 (hDPP4/bDPP4) receptors for docking and entry into cells (PMID:25211075; PMC4151778). We and others have shown that 1-2 mutations can enhance hDPP4 receptor binding and pseudotype entry into cells, but not as efficiently as MERS-CoV (PMID:25211075; PMC4151778). Thus, the mutant HKU4 RBD is still inferior to the MERS-CoV RBD. Dr. Li has shown that certain human proteases poorly cleave the HKU4, but not the MERS-CoV, S glycoprotein, contributing to reduced fusion domain activation and pseudotype entry into human cells (under review). Using pseudotypes, one to two mutations at either site can enhance HKU4 infection, approaching but not exceeding levels of MERS-CoV. Thus, a total of 2-4 mutations restrict the ability of HKU4 to enter efficiently into human cells. Given RNA virus error rates, we note that the existing quasispecies variation in HKU4 in the wild likely encodes either, multiple combinations of, or both sets of these mutations, thus “prepandemic” human strains already exist in nature. Thus, we will not be creating anything that doesn’t already exist in nature. We also note that the mutation sets which theoretically correct the HKU4 species restriction are also readily available in the published literature.

It is important to note that coronavirus cross species transmission and pathogenesis is likely regulated by: **i**) S-receptor interactions, **ii**) S-mediated host proteolytic cleavage, **iii**) tissue distributions of receptors and appropriate proteases (at least 5 or more different proteases can process CoV S glycoproteins), **iv**) other sites of virus-host interaction critical for efficient replication, and importantly, **v**) sensitivity to and ability to antagonize human antiviral defense pathways (innate immune restriction). Viral genes which interface with host genes to increase replicative capacity or antagonize host antiviral defense programs are all encoded outside of the S glycoprotein gene; throughout the genome backbone sequence (PMID:22572391). Thus, while we believe that the incorporation of hDPP4 and human protease enhancing mutations will certainly increase HKU4 replication in human cells, data from several sources support the hypotheses that these changes, in isolation, are reasonably anticipated to fail to increase HKU4 transmissibility and pathogenesis in vivo. Importantly, it is also reasonable to anticipate that its transmissibility and pathogenic potential would be significantly attenuated as compared to MERS-CoV, and not subject to the pause.

1) **HKU4 Genome Variation**. HKU4 is a distant relative of MERS-CoV. It has never been cultured and to our knowledge, never circulated in human populations. The percent amino acid identity between HKU4 and

MERS-CoV is 69.3% in ORF1, 70.9% in the S glycoprotein, 67.1% in ORF3, 47% in ORF4a, 55.7% in ORF4b, 42.8% in ORF5, 74.7% in the E structural protein, 73.7% in the M structural glycoprotein, and 69.7% in the nucleocapsid protein. Given the significant genome wide variation, there is no reason to suspect that the HKU4 backbone is intrinsically-primed to increased transmissibility or pathogenesis after virus entry, especially compared to MERS-CoV which has already circulated in human populations for some time. We provide evidence that documents the importance of the backbone genome sequence in regulating pathogenic outcomes in vivo and replication efficiency in primary human airway epithelial cells (HAE).

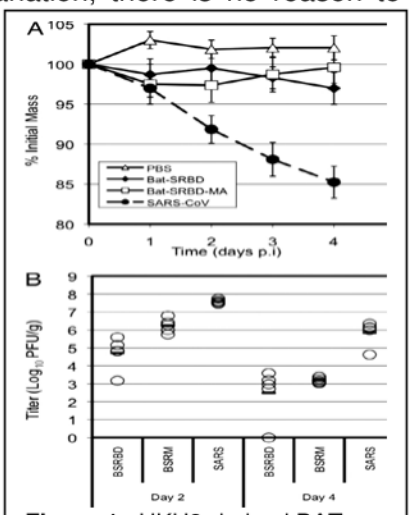


Figure 1. HKU3-derived BAT-SRBD MA virus replication in vitro and in vivo is attenuated as compared to wt SARS-CoV MA.

a) BAT-SRBD MA. BAT-SRBD was generating by incorporating the SARS-CoV mouse adapted receptor binding domain (RBD; about 230 residues) into the HKU3 genetic backbone (PMC2588415). Despite encoding the SARS-CoV RBD and being capable of using the human and mouse ACE2 as receptors for entry, BAT-SRBD MA replication in HAE (see Figure 4a in PMC2588415) and in mice was attenuated as compared to wildtype SARS-CoV (Figure 1). In fact, to generate fully virulent strains for mice, the BAT-SRBD MA variant required an additional 15 serial passages in mice (unpublished). The data underscore the critical observation that genome backbone sequences significantly contribute to the pathogenic potential of emerging coronaviruses.

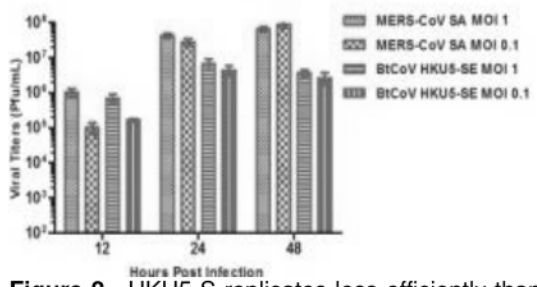


Figure 2. HKU5-S replicates less efficiently than MERS-CoV in Vero cells. It is also significantly attenuated in 10 and 1 yr aged mice as compared to SARS-CoV.

b) HKU5-S MA Variants. HKU5 cannot use ACE2 or DPP4 for entry and is more distantly related to MERS-CoV, than HKU4. HKU5 cannot replicate in human cells, unless you insert the SARS-CoV S ectodomain (N-terminal 2/3 of the S glycoprotein including the RBD)(PMC3977350). The SARS S glcyoprotein promoted HKU5 replication in cell culture (Vero), but at levels about 1 log less efficiently than MERS-CoV (Figure 2). HKU5-S can use the human and mouse ACE2 receptor. However, it does not produce clinical disease in young mice; even with the mouse adapted SARS S mutations. One year aged mice lose ~10% body weight and recover. Under identical conditions in both models, SARS-CoV MA results in lethal disease. For HKU5-S MA, in vivo passage selected for mutations outside of S (nsp13, nsp14, ORF5) that enhanced replication/pathogenesis in vivo. A logical interpretation is that genome backbone sequences matter in virulence, pathogenesis and transmissibility. Thus, entry mutations in isolation are necessary but not sufficient. We have not evaluated HKU5-S growth in HAE cultures, as compared to MERS and SARS-CoV.

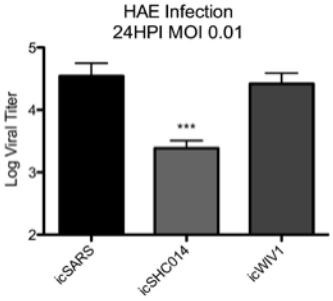


Figure 3. Although the S glycoproteins of WIV1 and SHC014 promote normal levels of SARS-CoV replication in HAE, full length icSHC014, but not the more closely related WIV1 growth is attenuated as compared to SARS-CoV.

c) Group 2b bat coronaviruses, icWIV1 and icSHC014. *Using funds from* U19 AI109761(PI: Lipkin), we have synthesized full length molecular clones of the group 2b bat coronaviruses, WIV1 and SHC014. These two bat coronaviruses have never been detected in human populations, but encode S glycoproteins that can use the human, bat and civet ACE2 receptors for docking and entry; just like the SARS-CoV epidemic strains (see other GOF reports). SARS-CoV recombinants encoding the WIV1 and SHC014 S glycoproteins replicate to equivalent titers as wildtype SARS-CoV in primary human HAE cultures, fully documenting the ability of these S glycoproteins to replicate efficient SARS-CoV infection and growth in human airway cells. However, a different picture emerges if these S glycoproteins are evaluated in the context of the original bat genome backbone sequences from which they were originally derived. Importantly, the full length icSHC014 recombinant (but not the full length WIV1 recombinant virus strain) replicates about 1 log less efficiently than wildtype SARS-CoV in primary HAE cultures (Figure 3). The backbone genome sequences of WIV1 and SHC014 differ by 1 and ~5% respectively, as compared to SARS-CoV. These data indicated that the

increased amount of backbone sequence (non S gene) variation in icSHC014 influences virus growth efficiency in primary HAE cultures. WIV1, which is much more closely related to SARS-CoV throughout the entire genome, replicated to equivalent titers. Importantly, both bat coronaviruses are completely attenuated in mice and required serial passage in vivo to select for mouse adapted strains (data not shown). Thus, entry mutations are necessary but not sufficient to promote pathogenesis and virulence. No transmissibility models exist for any emerging coronavirus.

Conclusions: These examples repeatedly demonstrate that other bottlenecks exist within some (more genetically distant) bat coronavirus genomes that limit host range replication efficiency and pathogenesis. This is also reflected during mouse adaptation. SARS-CoV mouse adapted mutations have been identified in nsp4, nsp5, nsp9, nsp12, nsp13, S and the M glycoprotein genes (PMC3255850). Although the functions of most of these mutations are unclear, mutations in the M glycoprotein enhance virus yields/cell up to about 10 fold/cell. Such findings are consistent with the extensive levels of mutation and positive selection identified throughout the SARS genome that occurred after serial human transmission and passage during the 2003-2004 expanding epidemic (Figure 4). Thus, evolving a highly pathogenic and transmissible human pandemic strain requires mutations in the S glycoprotein, but also in other key replicase, structural and accessory ORF genes. There does appear to be a general correlation between bat coronavirus genome wide identity and the ability to replicate wildtype epidemic strain (SARS-CoV) pathogenesis, potentially explaining efficient WIV1, but not

Figure 4. Evolution of Zoonotic to Epidemic SARS-CoV during the 2003-2004 Pandemic. Note extensive numbers of mutations in ORF1a, ORF1b, the M glycoprotein, ORF3a and ORF8. SZ16 (early civet), HC/SZ/61/03 (late civet), early human epidemic, middle human epidemic and late phase epidemic strain variation is recorded.

		ORF 1A												1B		Spike																		M	Orf 3a				Orf 8
	AA change	A-S	V-A	I-T	P-L	L-I	L-F	C-Y	L-S	C-W	V-A	V-A	V-A	D-E	R-K	G-D	N-K	S-L	I-T	T-K	R-K	F-S	N-K	T-S	S-P	L-S	S-L	T-A	V-A	Y-D	T-A	E-K	G-S	F-I	C-S	H-Y	C-G	
Phase	AA position	549	1021	1121	1136	1663	2116	2222	2269	2746	2971	3047	3072	1389	2532	77	227	239	244	261	344	360	479	487	607	665	701	743	754	778	894	1163	5	7	81	93	121	Δ or +
Animal	SZ16	S	A	T	L	I	F	Y	S	W	A	A	A	E	K	D	K	L	T	K	R	S	K	S	P	S	L	A	A	D	A	E	S	I	S	Y	G	+29
	HC/SZ/61/03	A	V	T	P	I	L	C	L	C	A	A	A	E	R	D	K	S	T	T	R	S	R	S	S	S	S	T	V	D	T	E	S	I	S	H	G	+29
Early	GZ02	A	V	T	P	I	F	Y	L	W	A	A	A	E	K	D	N	L	T	T	R	F	N	T	S	L	S	T	V	D	T	E	G	F	C	H	C	+29
Middle	CUHK-W1	A	V	I	P	L	L	C	L	C	V	A	A	E	R	D	N	S	T	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C	Δ29
Late	Urbani	A	V	I	P	L	L	C	L	C	V	V	V	D	R	G	N	S	I	T	K	F	N	T	S	L	S	T	V	Y	T	K	G	F	C	H	C	Δ29

SHC014 replication in HAE. Importantly, HKU4 is >30% different across the genome as compared to MERS-CoV. Given the variation in amino acid sequence and function across the genome, it is reasonable to anticipate that such variants will be attenuated in vitro and in vivo as compared to wildtype MERS-CoV. We also note that there is no evidence to indicate that genes encoded in HKU4 will be more pathogenic than those encoded in MERS-CoV. Rather, MERS-CoV, but not HKU4, has infected humans for some time. Thus, it is reasonable to anticipate that MERS-CoV, but not HKU4, has evolved mutations that enhance growth and pathogenic outcomes in humans. Hence, these variants are likely attenuated and not subject to the pause.

We hope that these responses ally concerns regarding the pathogenic and transmission potential of the HKU4 mutant recombinant viruses proposed in this application. The current data support the hypothesis that receptor and protease enhancing mutations are essential but not sufficient to produce pandemic viruses with pathogenic and transmission potentials. Rather, all of the available data support the idea that the increasing genetic distance in backbone genome sequence identity correlates with reduced replication efficacy and pathogenesis in alternative hosts; requiring successive rounds of adaptation in the new host to select for mutations in the genome which promote new virus-host interaction networks for efficient virus growth, antagonize recipient species antiviral defense programs to promote growth and pathogenesis, and other mutations that increase virus yields/cell. Should we identify HKU4 mutants that enhance virus growth to equivalent levels as MERS-CoV in primary human cells (e.g., primary human airway epithelial cells (HAE) and/or increase pathogenesis and virulence in our newly developed CRISPR/CAS ‘humanized” mouse models of MERS-CoV, we will immediately: i) stop all experiments with the mutant, ii) inform program and the UNC IBC of these results and iii) participate in decision making trees to decide appropriate paths forward.

Please contact us immediately should you require additional clarifications, as we are hoping for an April 1, 2015 start date for this grant application. Thank you for considering this information.

Sincerely,
Ralph S. Baric
Fang Li

From: Knight, Stanley (NIH/NIAID) [E]
Sent: Wed, 18 Feb 2015 15:17:18 -0500
To: Baric, Ralph; Stemmy, Erik (NIH/NIAID) [E]
Cc: Sims, Amy C; Cockrell, Adam; Adams, Miranda (NIH/NIAID) [E]
Subject: RE: A57: CATG 2015 Annual Meeting

Hi Ralph,

You'll need to provide a request for Contracting Officer's Authorization (COA) on regular business letterhead. The letter should be signed by your
business point of contact. Please include in your letter the duration/purpose of the travel, as well as the estimated costs, i.e., airfare, hotel, ground transportation,
per diem, and/or other estimated expenses. Please address the letter to Stanley A. Knight, Sr. Team Leader/Contracting Officer. An electronic pdf copy
is fine.

Hope this helps.

Regards,

Stanley A. Knight, Sr.
Team Leader/Contracting Officer
Microbiology and Infectious Diseases
Research Contracts Branch-A (MIDRCB-A)
Office of Acquisitions, DEA, NIAID, NIH-DHHS
5601 Fishers Lane, Room 3D50, MSC 9821
Rockville, MD 20892-9821
Phone: (b)(6)
Email:

From: Baric, Ralph
Sent: Wednesday, February 18, 2015 1:53 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Sims, Amy C; Cockrell, Adam; Adams, Miranda (NIH/NIAID) [E]; Knight, Stanley (NIH/NIAID) [E]
Subject: RE: A57: CATG 2015 Annual Meeting

How do we do that?

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, February 17, 2015 10:45 AM
To: Baric, Ralph S
Cc: Sims, Amy C; Cockrell, Adam; Adams, Miranda (NIH/NIAID) [E]; Knight, Stanley (NIH/NIAID) [E]
Subject: RE: A57: CATG 2015 Annual Meeting

One other item: the travel will need to be authorized by the CO, so please be sure to submit a COA request ASAP. Thanks!

From: Baric, Ralph
Sent: Friday, February 13, 2015 11:11 AM
To: Stemmy, Erik (NIH/NIAID) [E]
Cc: Sims, Amy C; Cockrell, Adam
Subject: RE: A57: CATG 2015 Annual Meeting

Hi Erik, Amy and Adam are planning on attending the meeting from our group. We will be set up to present for 30 mins (Adam). Is there a registration platform? Thanks, we are looking forward to showing our data. Ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, February 10, 2015 2:28 PM
To: Baric, Ralph S
Subject: RE: A57: CATG 2015 Annual Meeting

Hi Ralph,
Sure. It's a fairly informal meeting with the contractor PIs and program staff. Anyone from your group would be welcome to present, around 20-30 minutes would be ideal.

Erik

From: Baric, Ralph
Sent: Tuesday, February 10, 2015 2:22 PM
To: Stemmy, Erik (NIH/NIAID) [E]
Subject: RE: A57: CATG 2015 Annual Meeting

Hi Erik, Thanks for the invitation. Mark and I have already been scheduled to attend a U19 meeting at NIH on systems immunogenetics on the 1st and 2nd of April-I will need to look at meeting details to see if it's a one day or 1.5 day meeting and get back to you. We have very interesting data on the mers model. Could a postdoc present our data at this meeting in our absence? Thanks, ralph

---

From: Stemmy, Erik (NIH/NIAID) [E] (b)(6)
Sent: Tuesday, February 10, 2015 12:15 PM
To: (b)(6) PETERPALESE; Baric, Ralph S; Leyva-Grado, Victor (b)(6)
Cc: Adams, Miranda (NIH/NIAID) [E]; Knight, Stanley (NIH/NIAID) [E]
Subject: A57: CATG 2015 Annual Meeting

Hi Everyone,
You may be familiar with the annual Collaborative Antiviral Testing Group (CATG) Meeting that NIAID holds each year in Bethesda. This meeting brings together various PIs from our antiviral screening task orders to present updates on the contract work they're performing. This year the meeting will be held April 1-2 in our Fishers Lane building in Bethesda, and I'd like to invite Ralph (or someone else from your group at UNC) to attend and give a short talk on the development of the transgenic mice under

A57. Looking at the current spending submitted on your invoices there appears to be sufficient funds available to cover travel and two nights in Bethesda. Ralph, please let me know if this is the case and if you or someone from your group will be available to attend and I can send along the accommodation and location information. Note that this will still need to have a COA approved by the Contracting Officer so if someone from UNC will be available to attend, and the travel cost can be absorbed by the contract, I'd ask that you submit an official request for the COA to Miranda.

I also wanted to check to see about the status of the no-cost extension request we discussed on our last monthly call. I don't think I've seen anything come in, so please let me know if you have any questions.

Many thanks!
Erik

Please note my updated contact information below:

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

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: Leyva-Grado, Victor
Sent: Tue, 17 Feb 2015 21:57:15 +0000
To: NIAID DMID IDIQ; Stemmy, Erik (NIH/NIAID) [E]
Cc: PETERPALESE; Baric, Ralph; 'Heise, Mark T'; Lim, Jean; Umerah, Nina; 'Sims, Amy C'
Subject: HHSN272201000019I-HHSN27200003-Task A57 - January progress report
Attachments: A57 Task Order-Research Program Feb 2015 FINAL.docx

Dear Erik,

Attached you will find the January 2015 progress report for Task A57.

Please let us know if you have any questions.

Thanks a lot,

Victor

Victor H Leyva-Grado DVM, PhD
Postdoctoral Fellow
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

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:
January 1, 2015-January 31, 2015

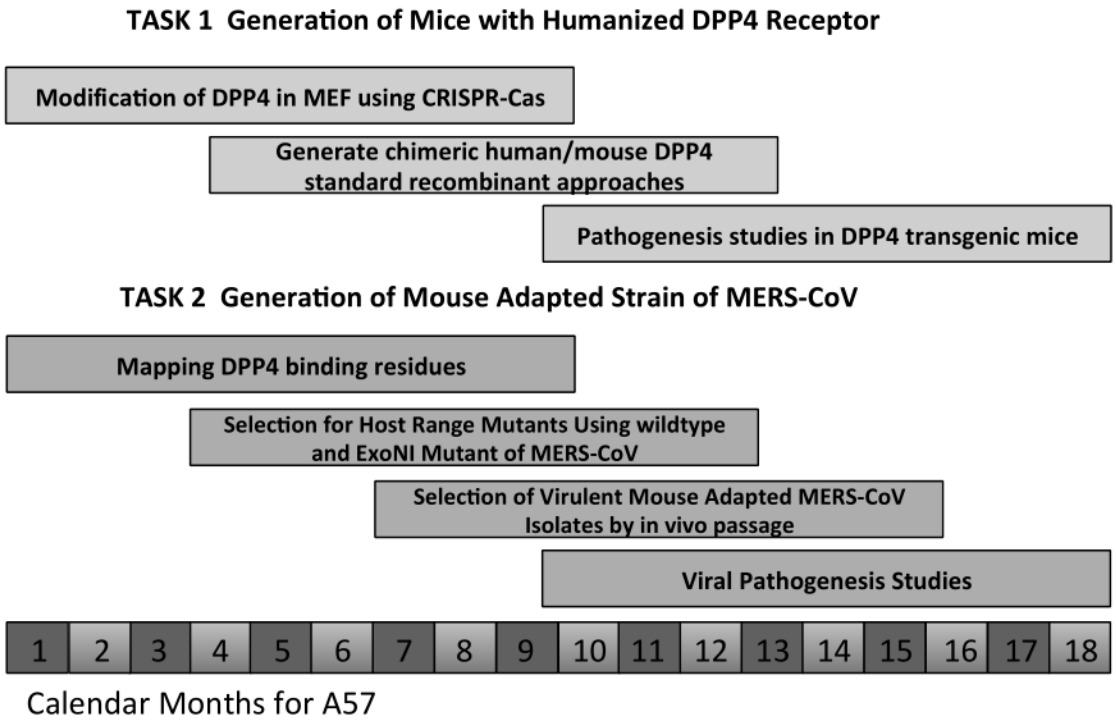
Contractor's Name and Address:
Dr. Peter Palese
Horace W. Goldsmith Professor and ChairDepartment of Microbiology
Professor, Department of MedicineMount Sinai School of Medicine
1 Gustave Levy Pl.
New York, New York 10029-6574
Tel (b)(6)
Fax 212-722-3634
e-mail: (b)(6)

Date of Submission:
February 16, 2015

A. Scope

The objective of this task is to make a lethal mouse model (80% lethal by 10 days post infection) for the recently identified human coronavirus Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Our group will develop transgenic mice that express humanized dipeptidyl-peptidase receptors and select for mouse-adapted strains of the MERS-CoV.

B. Timeline



Page 767 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 768 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 769 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 770 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 771 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 772 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 773 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 774 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act

Page 775 of 775

Withheld pursuant to exemption

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

of the Freedom of Information and Privacy Act