From: Schaefer, Alexandra[aschaefe@email.unc.edu]
Sent: Sat 2/15/2020 1:26:18 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Baric lab order question

Hi Amy,

I sent a separate email from my gmail account---
it looked like there were problems with the prism attachment (??) in the UNC account

Hope it all went through now---
let me know if there were problems
Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Saturday, February 15, 2020 4:24 AM
To: Sims, Amy C <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

Hi Amy,

attached is a first analysis (excel) for
MVEs for H3K4me3 and H3K27me3
for all three donors for following ISGs:
IFI16 (down - regulated)
IFI6 (up-regulated)
SMADL9 (down-regualted)

- it shows the fold enrichment for each histone modification for the individual donor triplicates
- then the average for all three triplicates per donor with standard deviation

also, attached is the MVE ISG consensus list from which the ISG targets for the PCR were chosen (based on 24hpi expression)

I have results for an additional 3 ISGs: EPSTI1, MyD88, and TNF213-
that I am still in the process of analyzing

So far, it looks like ISG expression is regulated via histone modification
(e.g. IFI16 and SMADL9 expression is down-regulated with an larger H3K27me3 enrichment over mock compared to H3K4me3, respectively)
AND
e.g. IFI6 expression is up-regulated with an larger H3K4me3 enrichment over mock compared to H3K27me3, respectively)

However, there are differences among donors, so there are most likely host-dependent differences occuring

based on a first impression it looks like that this trend will hold true with further analysis of the 3 additional genes, which I am working on

Please let me know if you have any questions,
Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5′UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>

Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....

- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>

Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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Fax +1-800-718-2056

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Sat 2/15/2020 4:06:08 AM (UTC-08:00)
To: Caldwell, Chandra[ccaldwel@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]
Subject: Fwd: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

Hi Amy. I just got this email. How are we going to move forward on this? T

Begin forwarded message:

From: "era-notify@mail.nih.gov" <era-notify@mail.nih.gov>
Date: February 15, 2020 at 6:04:11 AM EST
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020
Reply-To: eraNotifications@mail.nih.gov

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

The progress report for NIH Grant Number is due by 04/15/2020.

The next budget period start date for the above-referenced award is 06/01/ 2020. The due date for Progress Reports for grants excluded from the Streamlined Non-Competing Award Process (SNAP) authorities grants is the 1st of the month preceding the month in which the current budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). If the 1st falls on a weekend or Federal holiday, the due date is automatically extended to the next business day. If you are unsure whether the award is excluded from SNAP authorities, check the Notice of Award (NoA) under Section III Terms and Conditions.

NOTE: NIH POLICY REQUIRES ELECTRONIC SUBMISSION OF ALL ANNUAL PROGRESS REPORTS USING THE RPPR MODULE IN eRA COMMONS (see NOT-OD-15-014). RPPR instructions and resoures can be found at http://grants.nih.gov/grants/rppr/index.htm.

Questions regarding the eRA Commons should be addressed to:

eRA Commons Help Desk

Web: http://era.nih.gov/help/ (Preferred method of contact)

Toll-free: 1-866-504-9552

Phone:301-402-7469

Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time

Please submit the progress report by the due date noted above. If you have already submitted the progress report, disregard this notice.

Thank you.

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Sat 2/15/2020 8:24:06 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

Cool. I guess your email slipped through the cracks!

On Feb 15, 2020, at 8:48 AM, Sims, Amy C <amy.sims@pnnl.gov> wrote:

I am writing up the science and trying to work with Chandra on budget stuff.

I emailed both of you last week about this but no one answered. I will call the fiscal office next week.

Thanks. Amy

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From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Saturday, February 15, 2020 4:06 AM
To: Caldwell, Chandra; Sims, Amy C
Subject: Fwd: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

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Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time

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Thank you.

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Sat 2/15/2020 9:58:44 AM (UTC-08:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: Re: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

No worries. The "No response" comment was about fiscal office not you. This isn't your problem and I really appreciate you being the UNC stand in PI.

Hope you get a break this weekend. Thank you. Amy

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From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Saturday, February 15, 2020 8:24 AM
To: Sims, Amy C
Subject: Re: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

Cool. I guess your email slipped through the cracks!

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>
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>
> Thanks. Amy
>
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> > **Date:** February 15, 2020 at 6:04:11 AM EST
> > **To:** "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>

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Reply-To: eraNotifications@mail.nih.gov

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

The progress report for NIH Grant Number is due by 04/15/2020.

The next budget period start date for the above-referenced award is 06/01/ 2020. The due date for Progress Reports for grants excluded from the Streamlined Non-Competing Award Process (SNAP) authorities grants is the 1st of the month preceding the month in which the current budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). If the 1st falls on a weekend or Federal holiday, the due date is automatically extended to the next business day. If you are unsure whether the award is excluded from SNAP authorities, check the Notice of Award (NoA) under Section III Terms and Conditions.

NOTE: NIH POLICY REQUIRES ELECTRONIC SUBMISSION OF ALL ANNUAL PROGRESS REPORTS USING THE RPPR MODULE IN eRA COMMONS (see NOT-OD-15-014). RPPR instructions and resoures can be found at http://grants.nih.gov/grants/rppr/index.htm.

Questions regarding the eRA Commons should be addressed to:

eRA Commons Help Desk

Web: http://era.nih.gov/help/ (Preferred method of contact)

Toll-free: 1-866-504-9552

Phone:301-402-7469

Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time

Please submit the progress report by the due date noted above. If you have already submitted the progress report, disregard this notice.

Thank you.

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 2/17/2020 6:07:42 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
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Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

Get Outlook for iOS

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage

at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.

We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Phone +1- 800-426-8157 | Fax +1-800-718-2056
www.qiagen.com

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM

To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not.

But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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www.qiagen.com

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,

So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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Fax +1-800-718-2056

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist

UNC Gillings School of Public Health
caitedw@unc.edu

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 2/17/2020 1:17:07 PM (UTC-08:00)
To: Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: Baric lab order question

Thank you. I would not have thought of it. Please let me know what I need to do. I hope you are hanging in there and haven't gotten the nasty crud that is going around. Sounds like you have been a very busy man. Hope to catch up in person soon.

Thank you again, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 17, 2020 at 6:08 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

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Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

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Hi Amy,

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currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

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Thank you again. Good luck! Amy

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Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

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Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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Sent: Tuesday, January 21, 2020 6:48 AM
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When is the report due?
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Thought they were annually

Alex

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>

Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM

To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina
Email: jeremy.sanders@qiagen.com
Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM

To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health

caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 2/17/2020 2:19:09 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Cc: Young, Ellen F[ellen_young@med.unc.edu]
Subject: RE: Baric lab order question

Hi Ellen, can you direct amy to the UNC web site for invention reports?
Hi Amy, Its been hectic, overwhelming really. Compounded by an unfortunate decision to do study section in feb.
Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 4:17 PM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you. I would not have thought of it. Please let me know what I need to do. I hope you are hanging in there and haven't gotten the nasty crud that is going around. Sounds like you have been a very busy man. Hope to catch up in person soon.

Thank you again, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 17, 2020 at 6:08 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B

BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>

Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

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I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

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Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>

Cc: Edwards, Caitlin E <caitedw@unc.edu>
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Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

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Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
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To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

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To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

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Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

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Thank you!!!
Cait

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Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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www.qiagen.com

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

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Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

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Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

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I'm hoping for a response by the end of the day.

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Hi Jeremy!

Just wanted to check in about this order.

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To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

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Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
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Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Young, Ellen F[ellen_young@med.unc.edu]
Sent: Mon 2/17/2020 4:35:32 PM (UTC-08:00)
To: Baric, Ralph S[rbaric@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Baric lab order question

Hi Amy,
You want to go to
https://apps.research.unc.edu/blue/
and use your onyen
I am hoping you still have an onyen
Let me know if this works if not, I will try again.
Hope you are loving the west coast!!
Ellen

From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Monday, February 17, 2020 5:19 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Young, Ellen F <ellen_young@med.unc.edu>
Subject: RE: Baric lab order question

Hi Ellen, can you direct amy to the UNC web site for invention reports?
Hi Amy, Its been hectic, overwhelming really. Compounded by an unfortunate decision to do study section in feb.
Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 4:17 PM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you. I would not have thought of it. Please let me know what I need to do. I hope you are hanging in there and haven't gotten the nasty crud that is going around. Sounds like you have been a very busy man. Hope to catch up in person soon.

Thank you again, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 17, 2020 at 6:08 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>

Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).

As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>

Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!

Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

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Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

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Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

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Subject: Re: Baric lab order question

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caitedw@unc.edu

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Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

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For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

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Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Young, Ellen F[ellen_young@med.unc.edu]
Sent: Mon 2/17/2020 5:26:48 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]
Subject: RE: Baric lab order question
Attachment: Welcome to the Office of Technology Commercialization innovation reporting website.docx

Hi Amy,
This should get you started.
After these questions, they want a Title and a Description.
Let me know how you wish to proceed.
I couldn't get past the Title and Description page without filling it in.
Best Wishes,
Ellen

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 8:07 PM
To: Young, Ellen F <ellen_young@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thanks Ellen. I can't do that. It turns out that if you opted for only getting access to your W2 electronically that you have to lose access to your onyen to do your taxes after leaving UNC.

If you want to log on and send me a list of the questions I can answer them and then work with someone on that end to get the answers uploaded.

Thank you, Amy

From: "Young, Ellen F" <ellen_young@med.unc.edu>
Date: Monday, February 17, 2020 at 4:35 PM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy,
You want to go to
https://apps.research.unc.edu/blue/
and use your onyen
I am hoping you still have an onyen
Let me know if this works if not, I will try again.
Hope you are loving the west coast!!
Ellen

From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Monday, February 17, 2020 5:19 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Young, Ellen F <ellen_young@med.unc.edu>
Subject: RE: Baric lab order question

Hi Ellen, can you direct amy to the UNC web site for invention reports?
Hi Amy, Its been hectic, overwhelming really. Compounded by an unfortunate decision to do study section in feb.
Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 4:17 PM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you. I would not have thought of it. Please let me know what I need to do. I hope you are hanging in there and haven't gotten the nasty crud that is going around. Sounds like you have been a very busy man. Hope to catch up in person soon.

Thank you again, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 17, 2020 at 6:08 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM

To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

Hl Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>

Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that

she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

Welcome to the Office of Technology Commercialization innovation reporting website. In the following screens, you'll be asked to provide information about your new innovation and asked to provide details about who was involved in the creation of the work and all sources of funding used to support the research leading to this innovation. Please try to be as complete as possible as this will help us evaluate your innovation as quickly as possible.

Once you have completed your report, OTC will follow up with a confirmation letter telling you who at OTC will be working with you on this innovation. We will be in touch with you to schedule a meeting with you as soon as possible and at that time we can discuss any questions you may have. OTC requires up to 60 days to fully evaluate an invention report and assess its readiness for commercialization and we may need to talk with you or get additional information from you during this time.

We look forward to working with you. Please contact OTC at otc@unc.edu or 966-3929 if you have any questions while completing this report.

>> ROI Screening Information

Please complete and submit this disclosure within 90 days from starting it. The Office of Technology Commercialization will monitor this disclosure and will contact you if it remains unsubmitted for 90 days.

1. Type of innovation being reported *
   - (•) Inventions (such as materials, compounds, methods, devices, etc.)
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2. Is this innovation related to a previous report of an innovation to OTC? *
   - ( ) Yes (•) No
3. Were any materials or supplies from other institutions or companies used in the research or testing of the innovation? *
   - ( ) Yes (•) No
4. Please indicate all funding sources used in the research leading to this innovation. *
   - [ ] Contract or Grant (Federal, State, Industry, Non-Profit)
   - [ ] Gift funds
   - [x] UNC/Dept funds
   - [ ] No Funding Sources

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Tue 2/18/2020 2:45:23 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Baric lab order question

I'll give you a call todaysometime after 11this okay. Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 8:33 PM
To: Young, Ellen F <ellen_young@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Ellen. I really appreciate it.

Ralph, not trying to be dense but I might require a 15 minute conversation on this. Sorry, I know you are swamped. Thank you! Amy

---

From: "Young, Ellen F" <ellen_young@med.unc.edu>
Date: Monday, February 17, 2020 at 5:28 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: RE: Baric lab order question

Hi Amy,
This should get you started.
After these questions, they want a Title and a Description.
Let me know how you wish to proceed.
I couldn't get past the Title and Description page without filling it in.
Best Wishes,
Ellen

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 8:07 PM
To: Young, Ellen F <ellen_young@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thanks Ellen. I can't do that. It turns out that if you opted for only getting access to your W2 electronically that you have to lose access to your onyen to do your taxes after leaving UNC.

If you want to log on and send me a list of the questions I can answer them and then work with someone on that end to get the answers uploaded.

Thank you, Amy

From: "Young, Ellen F" <ellen_young@med.unc.edu>
Date: Monday, February 17, 2020 at 4:35 PM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy,
You want to go to

https://apps.research.unc.edu/blue/
and use your onyen
I am hoping you still have an onyen
Let me know if this works if not, I will try again.
Hope you are loving the west coast!!
Ellen

From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Monday, February 17, 2020 5:19 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Young, Ellen F <ellen_young@med.unc.edu>
Subject: RE: Baric lab order question

Hi Ellen, can you direct amy to the UNC web site for invention reports?
Hi Amy, Its been hectic, overwhelming really. Compounded by an unfortunate decision to do study section in feb.
Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, February 17, 2020 4:17 PM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you. I would not have thought of it. Please let me know what I need to do. I hope you are hanging in there and haven't gotten the nasty crud that is going around. Sounds like you have been a very busy man. Hope to catch up in person soon.

Thank you again, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 17, 2020 at 6:08 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Baric lab order question

Hi Amy, it occurred to me with the new data in your paper, you need to submit an invention report at UNC (that inludes PNNL collaborators) as an invention that 1) MERS-CoV, 2) all coronaviruses, and then 3) viruses in general. I'll get your paperwork reviewed in the epid faculty meetin gthis year. Talk wit hyou soon. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--

currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):

SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

Get Outlook for iOS

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

Get Outlook for iOS

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS

Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,

From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Burkhart, Carol J.[carol_burkhart@unc.edu]
Sent: Tue 2/18/2020 7:09:49 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Cc: Moore, Victoria L[victoria_moore@unc.edu]; Caldwell, Chandra[ccaldwel@email.unc.edu]
Subject: FW: NIH request letter for Amy Sims
Attachment: Prior_Approval_LetterPI_Sims_5R211AL14687201.pdf

Hi Amy,

Attached is the letter sent to NIH. The revised NOA was received on 2/3 and is in process at OSR. Once we receive the new project ID we can start processing your subcontract.

Please let me know if you need other information.

Thanks,

Carol

From: Caldwell, Chandra <ccaldwel@email.unc.edu>
Sent: Monday, February 17, 2020 8:05 PM
To: Burkhart, Carol J. <carol_burkhart@unc.edu>
Cc: Moore, Victoria L <victoria_moore@unc.edu>
Subject: NIH request letter for Amy Sims

Hi Carol,

Do you by chance have the letter that was sent to NIH (via OSR) requesting that Tim Sheahan be the contact PI for Amy Sims' R21 grant (IPF: 19-1455)? As of this weekend, Amy is officially locked out of her UNC email account and she cannot access any of her files. She has tried to work with the IT staff since she hadn't retrieved her W2 forms yet, but to no avail. If by chance you have a copy of the letter, can you please send it to Amy's PNNL email - amy.sims@pnnl.gov

Thanks,
Chandra

UNC
GILLINGS SCHOOL OF
GLOBAL PUBLIC HEALTH

THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL

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

December 23, 2019

Tseday G. Girma
Grants Management Specialist
Financial Management Branch
NIDCR
National Institutes of Health
BG 31 RM2C39
31 Center Drive
Bethesda, MD 20814

Re: 5R21AI146872-01, *How MERS-CoV Regulates Innate Immunity in Primary Human Lung Cells*

Dear Ms. Girma:

We respectfully request permission to subcontract with Battelle-PNWD (Battelle) on the referenced grant beginning January 1, 2020. Dr. Amy Sims, the principal investigator for the grant is beginning a new position at the Pacific Northwest National Laboratory (PNNL) which is operated by Battelle-PNWD. By allowing us to subcontract with Battelle for the remainder of Year 1, Dr. Sims will be able to continue work on the project without interruption. Dr. Sims will continue to supervise the overall direction of the project. No additional funds are needed for the proposed work. If approved, we will rebudget existing Year 1 funds to cover the cost of the subcontract. Attached are a budget and justification for Battelle's participation.

To ensure there is no conflict with Dr. Sims remaining as a principal investigator under a subagreement, we also are requesting that Dr. Timothy Sheahan be named as lead principal investigator for UNC for the remainder of the year. Dr. Sheana will provide oversight of the work at UNC. He and Dr. Alex Schaefer (currently a co-investigator on the project) will work closely with Dr. Sims to ensure steady progress on the project. Dr. Sheahan's biosketch and other support are attached.

We anticipate transferring the project from UNC to Battelle with the beginning of Year 2. To that end, UNC will provide a relinquishing statement and will work with Battelle to prepare a submission package including a progress report for the current year.

We appreciate your consideration of this request. If you need any additional information, please contact Victoria Moore at victoria_moore@unc.edu or 919-966-7470.

Sincerely,

Amy Sims
Principal Investigator

Timothy Sheahan
Research Assistant Professor

Terry Magnuson
Vice Chancellor for Research

cc: Erik Stemmy, Program Official NIDCR

From: Poole, Jessica[jmmarsha@email.unc.edu]
Sent: Wed 2/19/2020 3:31:16 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: References for Amy's suitability review

Amy,

I think I can do a suitability interview for you  Hope you are doing well. How do you like it so far?

Jessica

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, February 18, 2020 7:59 PM
To: Coulson, Garry Brian <garry.coulson@ehs.unc.edu>; Poole, Jessica <jmmarsha@email.unc.edu>
Subject: References for Amy's suitability review

Hi,

I have added you guys as references for my suitability review. I hope you don't mind. Both of you have worked with me for a good amount of time and have a good idea of who I am and how I work.

If you are not comfortable with this please let me know.
The email will come from Jonda Franklin at PNNL.

Thank you and I hope all is well! Amy

From: Coulson, Garry Brian[garry.coulson@ehs.unc.edu]
Sent: Wed 2/19/2020 5:43:10 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Poole, Jessica[jmmarsha@email.unc.edu]
Subject: RE: References for Amy's suitability review

HI Amy,

Absolutely happy to help provide a reference!

Kind regards,
Garry

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, February 18, 2020 7:59 PM
To: Coulson, Garry Brian <garry.coulson@ehs.unc.edu>; Poole, Jessica <jmmarsha@email.unc.edu>
Subject: References for Amy's suitability review

Hi,

I have added you guys as references for my suitability review. I hope you don't mind. Both of you have worked with me for a good amount of time and have a good idea of who I am and how I work.

If you are not comfortable with this please let me know.
The email will come from Jonda Franklin at PNNL.

Thank you and I hope all is well! Amy

From: Caldwell, Chandra[ccaldwel@email.unc.edu]
Sent: Wed 2/19/2020 8:56:29 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Second email Re: NIH request letter for Amy Sims

FYI: May one of them (C or V) get back to you soon! I reminded them of your emails and they bot acknowledged they saw it since your questions involve asking their friends at OSR, who are holding up progress!

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, February 18, 2020 12:31 PM
To: Burkhart, Carol J. <carol_burkhart@unc.edu>
Cc: Moore, Victoria L <victoria_moore@unc.edu>; Caldwell, Chandra <ccaldwel@email.unc.edu>
Subject: Second email Re: NIH request letter for Amy Sims

Carol,

I should have added this to the previous email but how far is UNC from getting a project ID generated? I really need these funds to support my salary and I have been here for almost two months without it.

Thank you, Amy

From: "Burkhart, Carol J." <carol_burkhart@unc.edu>
Date: Tuesday, February 18, 2020 at 7:12 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Cc: "Moore, Victoria L" <victoria_moore@unc.edu>, "Caldwell, Chandra" <ccaldwel@email.unc.edu>
Subject: FW: NIH request letter for Amy Sims

Hi Amy,

Attached is the letter sent to NIH. The revised NOA was received on 2/3 and is in process at OSR. Once we receive the new project ID we can start processing your subcontract.

Please let me know if you need other information.

Thanks,

Carol

From: Caldwell, Chandra <ccaldwel@email.unc.edu>
Sent: Monday, February 17, 2020 8:05 PM
To: Burkhart, Carol J. <carol_burkhart@unc.edu>
Cc: Moore, Victoria L <victoria_moore@unc.edu>
Subject: NIH request letter for Amy Sims

Hi Carol,

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Thanks,
Chandra

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Wed 2/19/2020 10:56:23 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Fast chat Wed/Thurs?

How is your day looking today? This afternoon? My afternoon that is…

From: Amy Sims <amy.sims@pnnl.gov>
Date: Tuesday, February 18, 2020 at 8:13 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Fast chat Wed/Thurs?

Hi,

I would love to chat briefly on where you think the apoptosis paper should go with the new data.

You have worked with the editors of several of the journals Ralph is tossing about and I would like your input.

Let me know if you have any time the rest of this week. Thank you, Amy

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Wed 2/19/2020 11:01:48 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Fast chat Wed/Thurs?

Any time between 2pm (11am PST) and 4pm EST (1pm PST).

From: Amy Sims <amy.sims@pnnl.gov>
Date: Wednesday, February 19, 2020 at 2:00 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Re: Fast chat Wed/Thurs?

Might be able to fit it in. Lots of meetings for me today.

Send me some times that you can do and I will do my best. Thank you. Amy

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, February 19, 2020 10:57 AM
To: Sims, Amy C
Subject: Re: Fast chat Wed/Thurs?

How is your day looking today? This afternoon? My afternoon that is…

From: Amy Sims <amy.sims@pnnl.gov>
Date: Tuesday, February 18, 2020 at 8:13 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Fast chat Wed/Thurs?

Hi,

I would love to chat briefly on where you think the apoptosis paper should go with the new data.

You have worked with the editors of several of the journals Ralph is tossing about and I would like your input.

Let me know if you have any time the rest of this week. Thank you, Amy

From: Sheahan, Timothy Patrick [sheahan@email.unc.edu]
Sent: 2/19/2020 11:07:24 AM
To: Sims, Amy C [amy.sims@pnnl.gov]
Subject: Re: Fast chat Wed/Thurs?

Personal Cell Phone

Sweet 5 U.S.C. § 552(b)(6) ase you forgot

From: Amy Sims <amy.sims@pnnl.gov>
Date: Wednesday, February 19, 2020 at 2:06 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Re: Fast chat Wed/Thurs?

Awesome. Will call when I get back to my office.

Thank you. Amy

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, February 19, 2020 11:03 AM
To: Sims, Amy C
Subject: Re: Fast chat Wed/Thurs?

Any time between 2pm (11am PST) and 4pm EST (1pm PST).

From: Amy Sims <amy.sims@pnnl.gov>
Date: Wednesday, February 19, 2020 at 2:00 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Re: Fast chat Wed/Thurs?

Might be able to fit it in. Lots of meetings for me today.

Send me some times that you can do and I will do my best. Thank you. Amy

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, February 19, 2020 10:57 AM
To: Sims, Amy C
Subject: Re: Fast chat Wed/Thurs?

How is your day looking today? This afternoon? My afternoon that is…

From: Amy Sims <amy.sims@pnnl.gov>
Date: Tuesday, February 18, 2020 at 8:13 PM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Fast chat Wed/Thurs?

Hi,

I would love to chat briefly on where you think the apoptosis paper should go with the new data.

You have worked with the editors of several of the journals Ralph is tossing about and I would like your input.

Let me know if you have any time the rest of this week. Thank you, Amy

From: Waters, Katrina M[Katrina.Waters@pnnl.gov]
Sent: Wed 2/19/2020 5:39:33 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]; Gralinski, Lisa E[lgralins@email.unc.edu]
Subject: RE: MERS/Perk histo data!

I have Nature editor contacts from a colleague that I could use to pitch the paper, if you can provide a short summary. I would ask for quick turn-around peer review if they want to publish it.

Katrina Waters
Tel: 509-375-3907
Biological Sciences Division

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 5:24 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Hi Ralph and Lisa (and Katrina),

I had a chat with Katrina and Hugh today about the new data for the paper and they were very excited.

Katrina suggested that PNAS may be a good place to send the paper. I am concerned that the dataset is not comprehensive enough for Science/Nature journals.

Let me know what you think so I can revise the paper to meet all of the formatting requirements.

Thank you! Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Wednesday, February 12, 2020 at 10:07 AM
To: "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: MERS/Perk histo data!

Awesome! Freaking Awesome! Aim high Amy, Aim High! Nat Micro, Nat Med, Sci transl medicine, nature communication…..Lisa thoughts? Amy thoughts? Ralph

From: Gralinski, Lisa E <lgralins@email.unc.edu>
Sent: Wednesday, February 12, 2020 12:46 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Baric, Ralph S <rbaric@email.unc.edu>
Subject: MERS/Perk histo data!

Hey Amy,
I sat with Stephanie Montgomery this morning and she scored all of the males from SM126, the second drug experiment, using the system she and Tim developed for MERS. These were all D7 mice with half having gotten drug and half being sham treated. I haven't had time to make graphs yet but to summarize - we have differences!
Drug treatment led to improvement in neutrophils in the alveolar space, protein in the airspace, the overall

Matute-Bello Score and DAD. We saw no changes in neutrophils in the interstitial membranes, hyaline membrane formation or septal thickening.
I will work on putting this together in a figure. Do you think you will want lung images or just quantification?
Lisa

From: Gralinski, Lisa E[lgralins@email.unc.edu]
Sent: Wed 2/19/2020 5:42:17 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]; Waters, Katrina M[Katrina.Waters@pnnl.gov]
Subject: Re: MERS/Perk histo data!

Hey Amy,
PNAS could be a great choice. Although based on review requests I'm getting right now I would not worry about the usual standards for high tier journals. If the formatting isn't onerous, I would consider even higher than PNAS.

For a histo update - I'm meeting with Stephanie again next Wednesday to finish up the SM126 histo scoring (all of the females). I'll get a preliminary figure to you before then though.

good luck!
Lisa

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:23 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

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Sent: Wed 2/19/2020 5:44:27 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: MERS/Perk histo data!

Just as an example, the Muc4 paper led by Jess Plante is getting expedited review at mBio right now - whereas before the new virus hit we were going to submit the revised version to Virology.
Obviously not at the same level, but you know how different those journals are!

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:23 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
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From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Wed 2/19/2020 7:03:08 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Gralinski, Lisa E[lgralins@email.unc.edu]; Waters, Katrina M[Katrina.Waters@pnnl.gov]
Subject: RE: MERS/Perk histo data!

Nat Micro
Sci Translation
Nature Communications
Cell host and Micro
PNAS

Data is good enough

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To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
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Lisa

From: Poole, Jessica [jmmarsha@email.unc.edu]
Sent: 2/20/2020 3:43:36 AM
To: Sims, Amy C [amy.sims@pnnl.gov]; Coulson, Garry Brian [garry.coulson@ehs.unc.edu]; England, Erika [ee42@email.unc.edu]
Subject: RE: Sims UIN

b(6) - Personal Identification Number

Redacted

Jessica

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:15 PM
To: Coulson, Garry Brian <garry.coulson@ehs.unc.edu>; Poole, Jessica <jmmarsha@email.unc.edu>; England, Erika <ee42@email.unc.edu>
Subject: Sims UIN

All,

Can you please send me my UIN? I am working my way through the select agent clearance process in Washington.

I hope you all are doing well. Thank you, Amy

From: Coulson, Garry Brian[garry.coulson@ehs.unc.edu]
Sent: Thur 2/20/2020 4:54:52 AM (UTC-08:00)
To: Poole, Jessica[jmmarsha@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; England, Erika[ee42@email.unc.edu]
Subject: Re: Sims UIN

Thanks Jessica!

Get Outlook for iOS

From: Poole, Jessica <jmmarsha@email.unc.edu>
Sent: Thursday, February 20, 2020 6:43:36 AM
To: Sims, Amy C <amy.sims@pnnl.gov>; Coulson, Garry Brian <garry.coulson@ehs.unc.edu>; England, Erika <ee42@email.unc.edu>
Subject: RE: Sims UIN

5 U.S.C. § 552(b)(6) Personal Identification Number

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From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Sat 2/22/2020 8:34:29 PM (UTC-08:00)

To: Sims, Amy C[amy.sims@pnnl.gov]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; 'Greg Bluemling'[gblueml@emory.edu]; Lockwood, Mark[mlockwo@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Tomas Cihlar[Tomas.Cihlar@gilead.com]; Danielle Porter[Danielle.Porter@gilead.com]; Joy Feng[Joy.Feng@gilead.com]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@email.unc.edu]

Subject: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Attachment: 20200222 NHC CoV Nat Med Figs.pdf

Attachment: 20200222 EIDD1931 Draft Nat Med 2.docx

Dear Co-Authors,

Please see the attached paper chronicling our in vitro and in vivo efficacy of EIDD-1931 (NHC) against multiple CoV including 2019-nCoV (SARS-CoV-2) data.

1. Due to the current pandemic threat of SARS-CoV-2, we feel this paper is very timely and will be of great interest to the research community. Thus, we are aiming high and will initially submit to Nature Medicine. Because of the urgency of this situation, we will aim to submit this paper by Tuesday February 25th. Sorry for the short timeline but we feel like we need to try and ride the wave of CoV publications here. **Thus, if you would like to make comments, please do so by Monday afternoon.**
2. I've attached a Word File and a PDF of the Figures. We are over by a few hundred words in the paper. So, adding in extra verbiage is not an option unless words are taken out.
3. Please make sure that I've not missed authors and that your affiliations are correct.

Thanks!

I look forward to hearing from you.

Tim

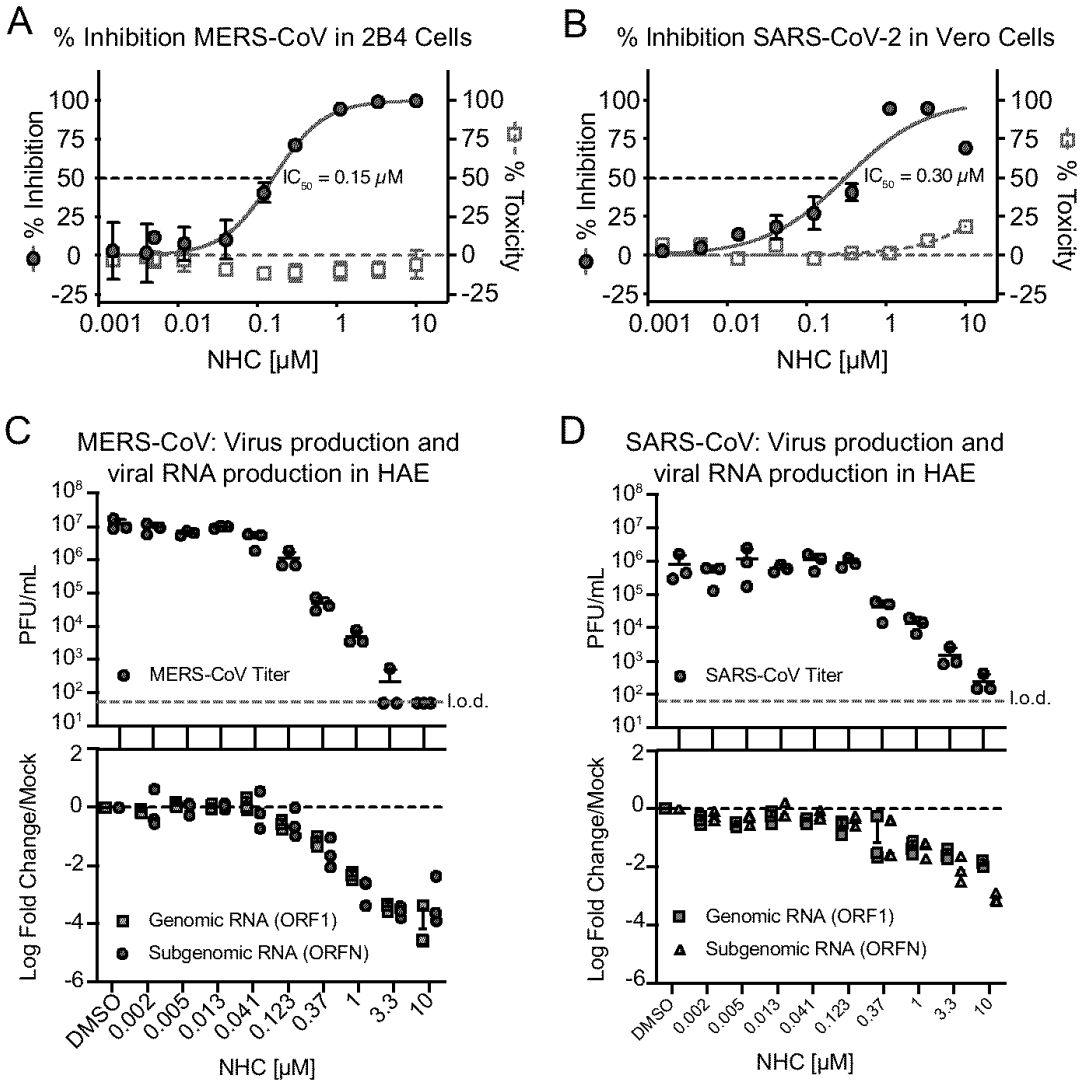
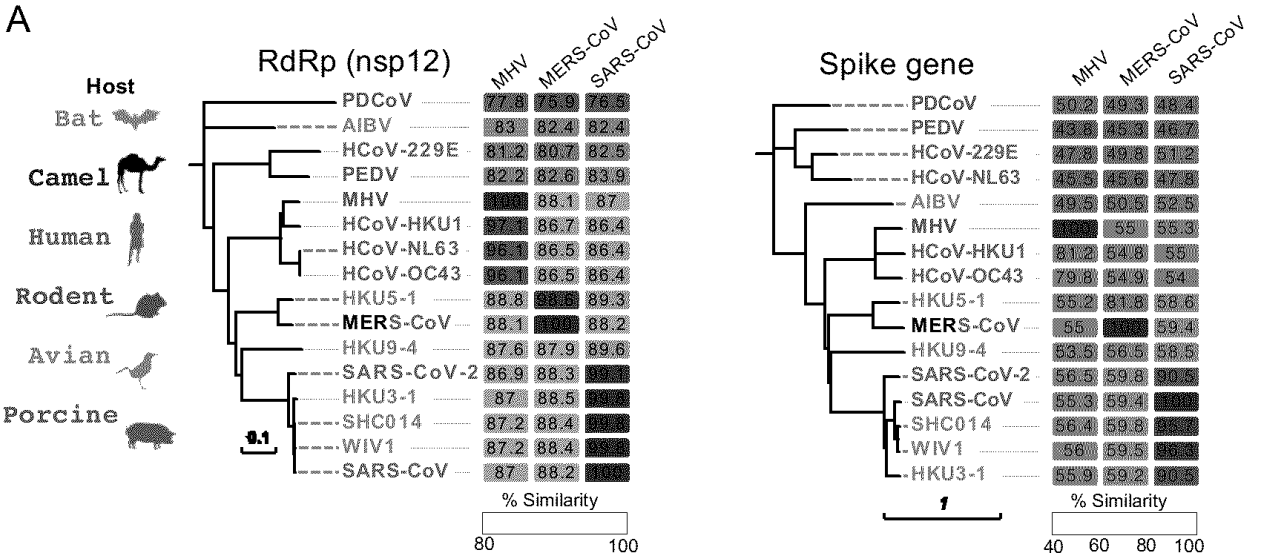

A
% Inhibition MERS-CoV in 2B4 Cells
% Inhibition
% Toxicity
IC50 = 0.15 μM
NHC [μM]
B
% Inhibition SARS-CoV-2 in Vero Cells
IC50 = 0.30 μM
C
MERS-CoV: Virus production and viral RNA production in HAE
PFU/mL
MERS-CoV Titer
l.o.d.
Log Fold Change/Mock
Genomic RNA (ORF1)
Subgenomic RNA (ORFN)
DMSO
D
SARS-CoV: Virus production and viral RNA production in HAE
SARS-CoV Titer

Figure 1



B

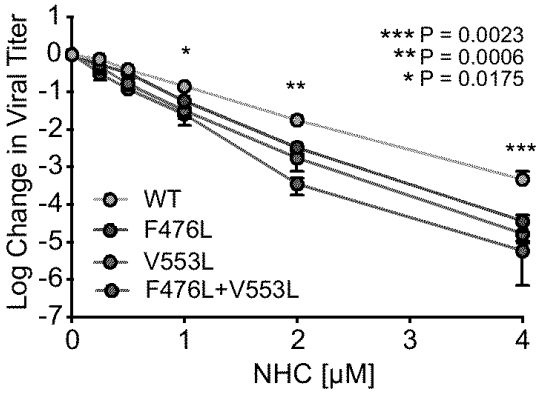
Conserved resistance motifs

	F476L	V553L
PDCoV	DKYFXCY	ARTVAGV
229E	DKYLEPY	ARTVGGV
NL63	ARYFDCY	ARTVAGV
OC43	YKYFEIY	ARTVAGV
MHV	YKYFEIY	ARTVAGV
HKU1	NKYFEIY	ARTVAGV
MERS	YKYFEIY	ARTVAGV
HKU9-4	NKYFEIY	ARTVAGV
SARS-CoV-2	DKYFDCY	ARTVAGV
HKU3	DKYFDCY	ARTVAGV
SARS-CoV	DKYFDCY	ARTVAGV
SHC014	DKYFDCY	ARTVAGV

F480L SARS-CoV V557L in SARS-CoV

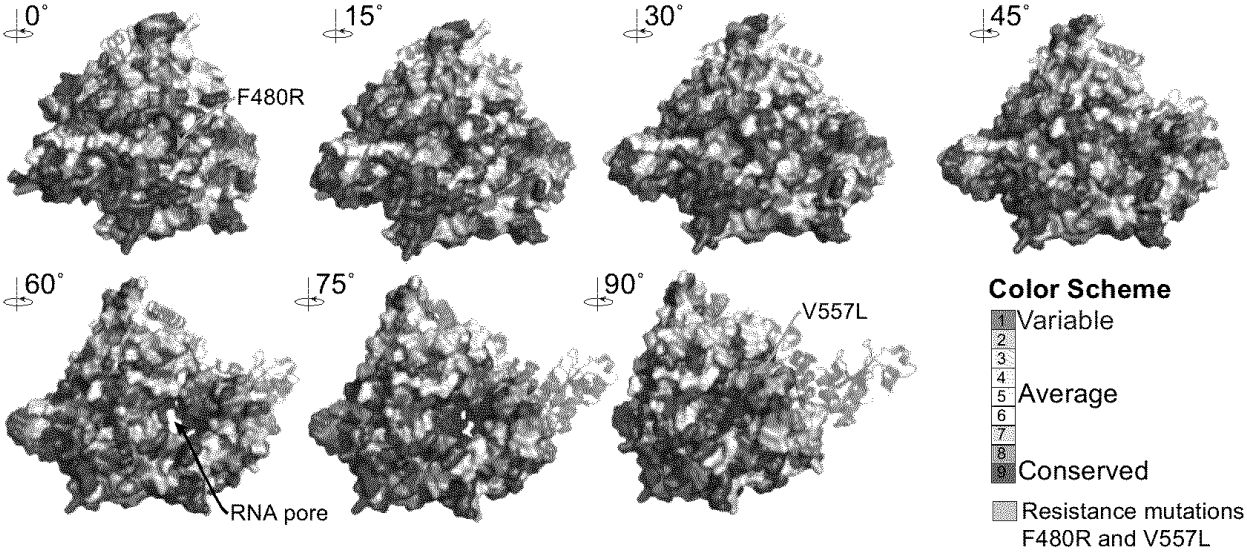
C

Cross-susceptibility of RDV-resistant virus



D

Family-wide conservation of RNA interaction sites



Stats in done by Mann-Whitney test

Figure 2

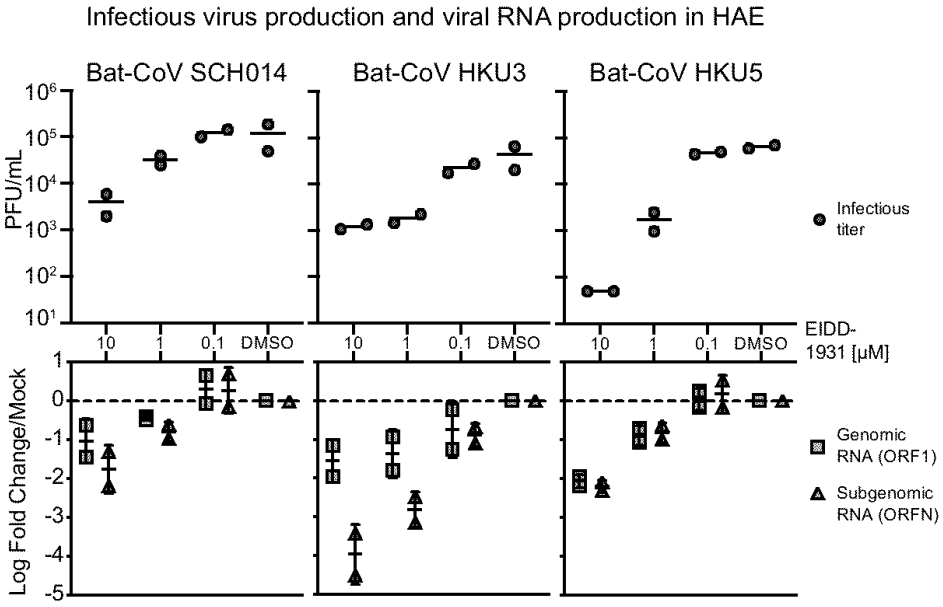

Infectious virus production and viral RNA production in HAE
Bat-CoV SCH014
Bat-CoV HKU3
Bat-CoV HKU5
PFU/mL
Infectious titer
EIDD-1931 [μM]
Log Fold Change/Mock
Genomic RNA (ORF1)
Subgenomic RNA (ORFN)

Figure 3

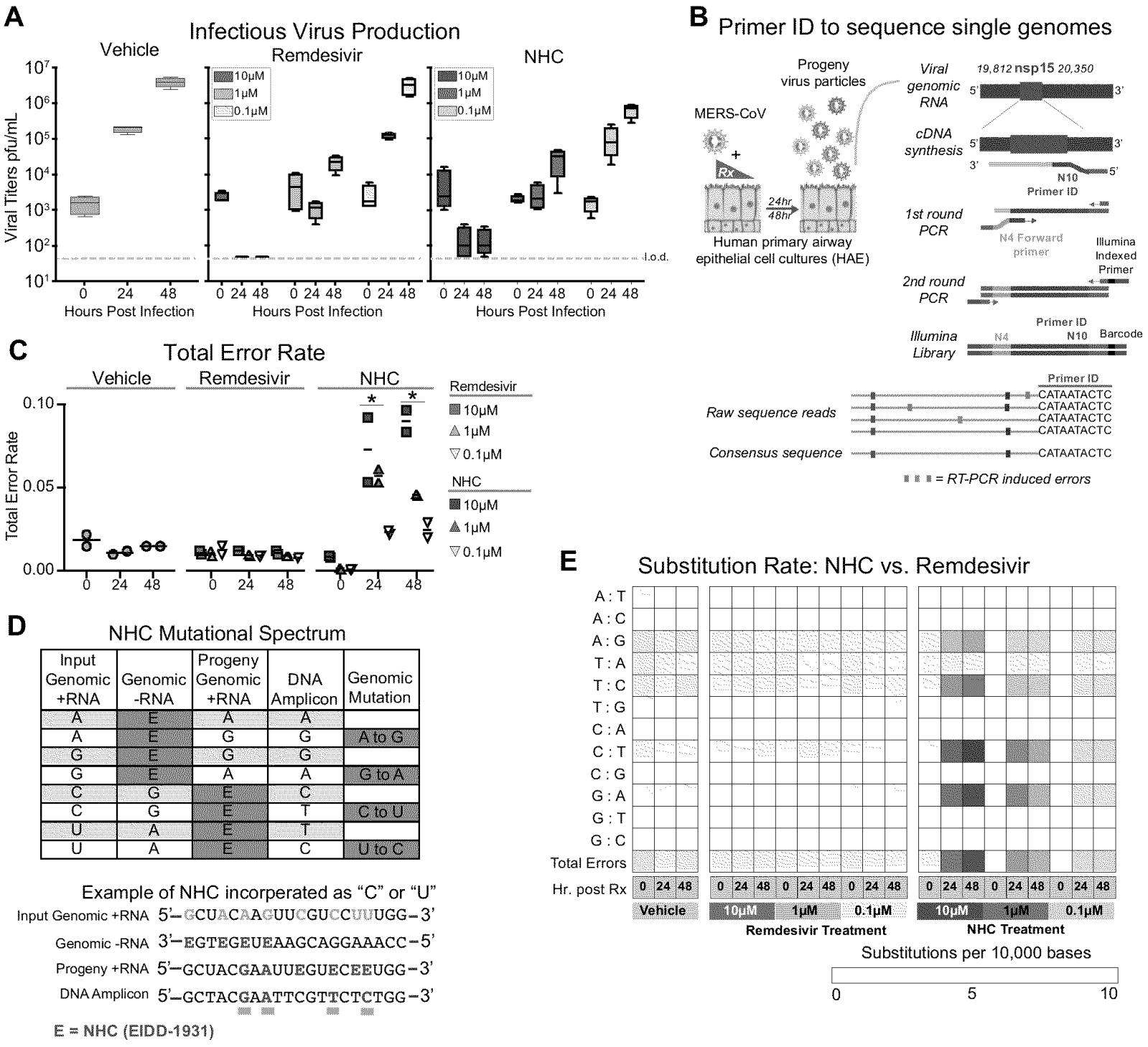

A
Infectious Virus Production
Vehicle
Remdesivir
NHC
10μM
1μM
0.1μM
Viral Titers pfu/mL
Hours Post Infection
l.o.d.
B
Primer ID to sequence single genomes
Progeny virus particles
MERS-CoV
Human primary airway epithelial cell cultures (HAE)
24hr
48hr
Viral genomic RNA
19,812 nsp15 20,350
cDNA synthesis
N10
Primer ID
1st round PCR
N4 Forward primer
Illumina Indexed Primer
2nd round PCR
Illumina Library
N4
Barcode
Raw sequence reads
CATAATACTC
Consensus sequence
= RT-PCR induced errors
C
Total Error Rate
Total Error Rate
D
NHC Mutational Spectrum
Input Genomic +RNA
Genomic -RNA
Progeny Genomic +RNA
DNA Amplicon
Genomic Mutation
A to G
G to A
C to U
U to C
Example of NHC incorperated as "C" or "U"
Input Genomic +RNA 5'–GCUACAAGUUCGUCCUUUGG–3'
Genomic -RNA 3'–EGTEGEUEAAGCAGGAAACC–5'
Progeny +RNA 5'–GCUACGAAUUEGUECEEUGG–3'
DNA Amplicon 5'–GCTACGAATTCGTTCTCTGG–3'
E = NHC (EIDD-1931)
E
Substitution Rate: NHC vs. Remdesivir
A : T
A : C
A : G
T : A
T : C
T : G
C : A
C : T
C : G
G : A
G : T
G : C
Total Errors
Hr. post Rx
Vehicle
Remdesivir Treatment
NHC Treatment
Substitutions per 10,000 bases

Figure 4

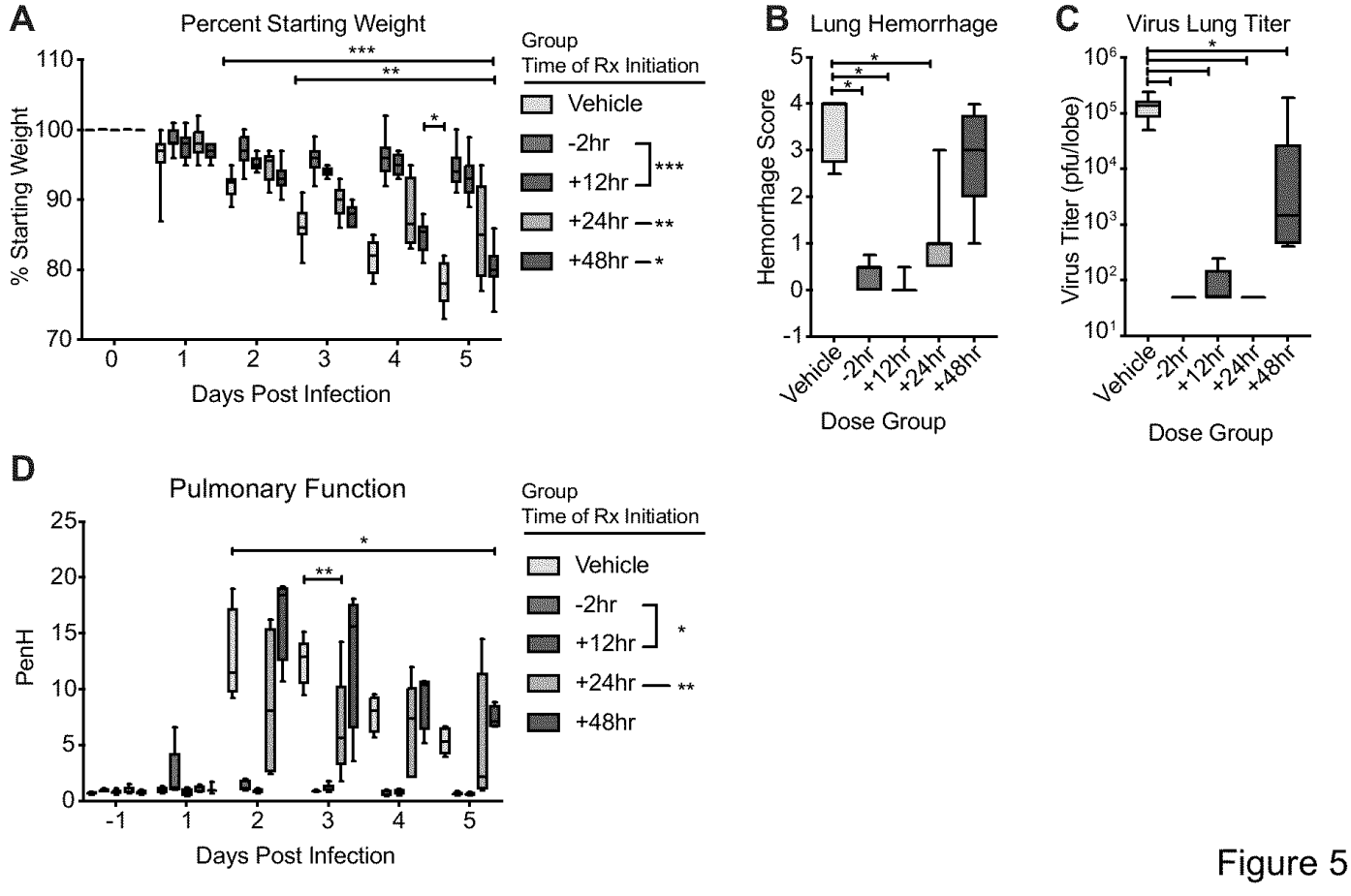

A
Percent Starting Weight
% Starting Weight
Days Post Infection
Group
Time of Rx Initiation
Vehicle
-2hr
+12hr
+24hr
+48hr
B
Lung Hemorrhage
Hemorrhage Score
Dose Group
C
Virus Lung Titer
Virus Titer (pfu/lobe)
Dose Group
D
Pulmonary Function
PenH
Days Post Infection

Figure 5

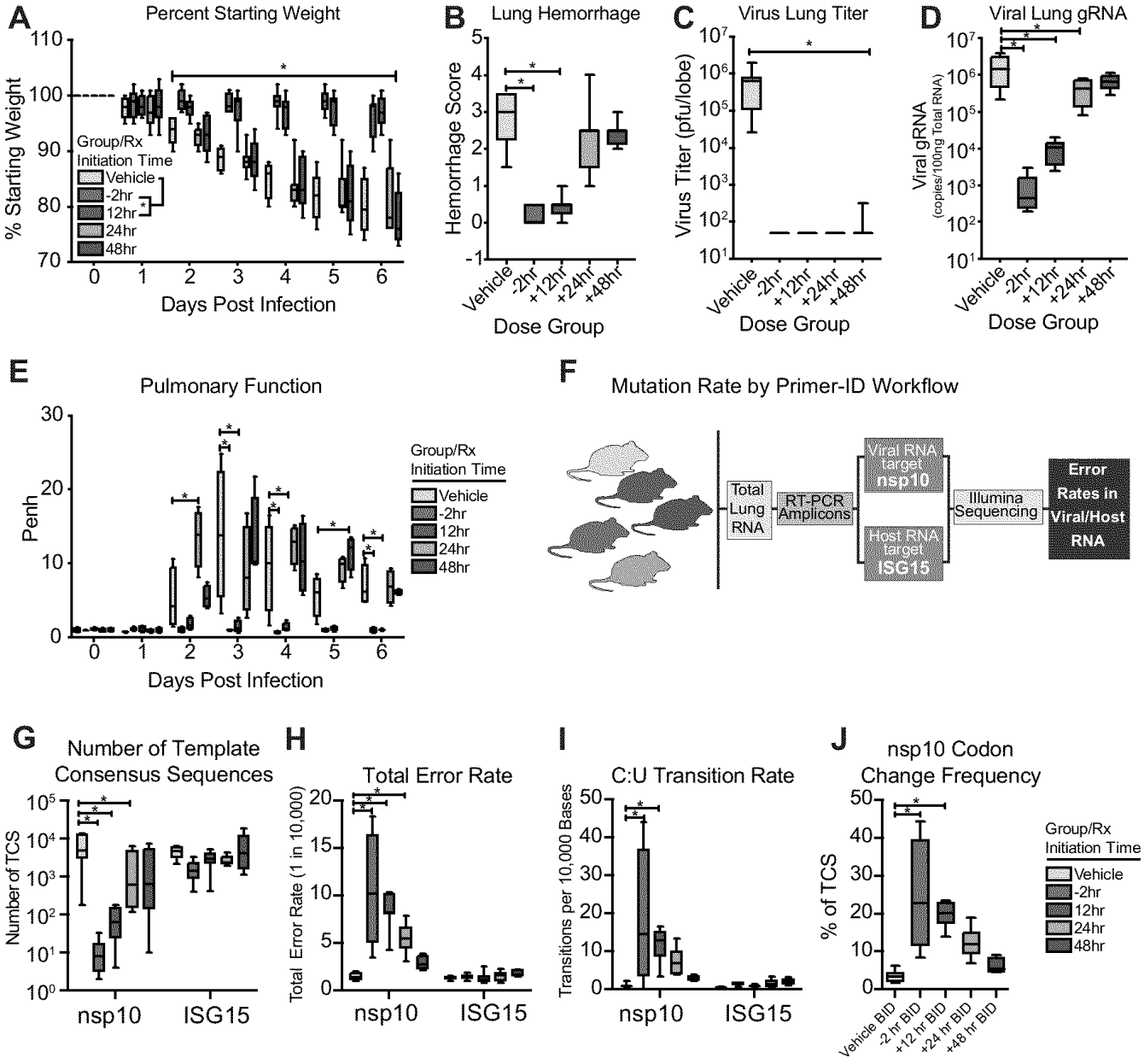
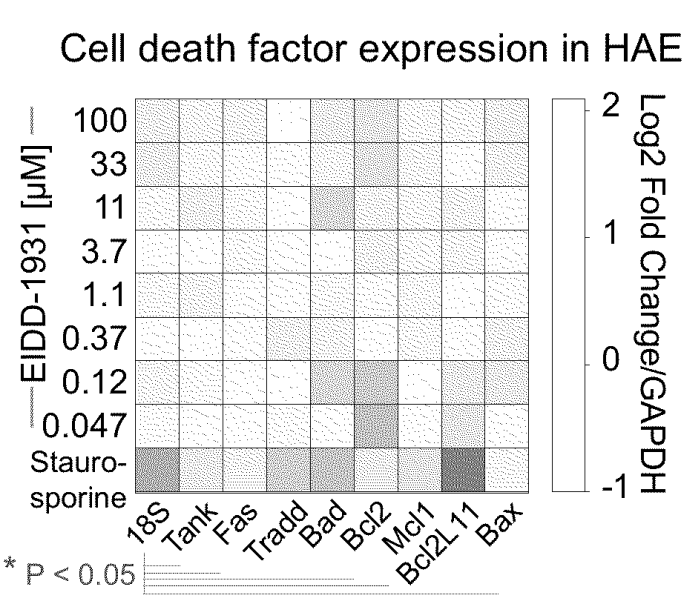
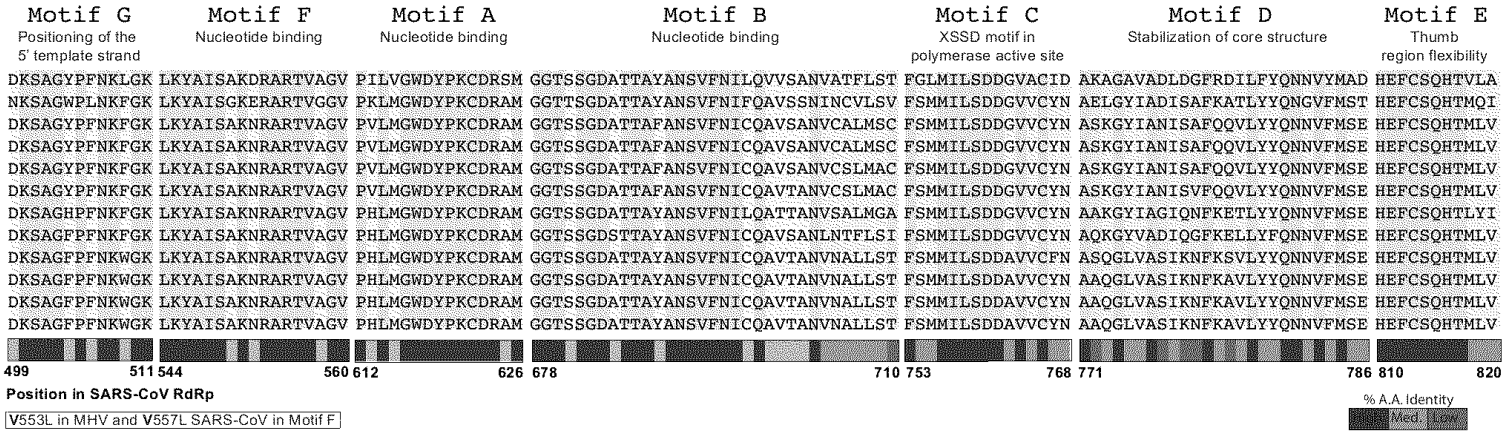

A
Percent Starting Weight
% Starting Weight
Days Post Infection
Group/Rx Initiation Time
Vehicle
-2hr
12hr
24hr
48hr
B
Lung Hemorrhage
Hemorrhage Score
Dose Group
C
Virus Lung Titer
Virus Titer (pfu/lobe)
D
Viral Lung gRNA
Viral gRNA (copies/100ng Total RNA)
E
Pulmonary Function
Penh
F
Mutation Rate by Primer-ID Workflow
Total Lung RNA
RT-PCR Amplicons
Viral RNA target nsp10
Host RNA target ISG15
Illumina Sequencing
Error Rates in Viral/Host RNA
G
Number of Template Consensus Sequences
Number of TCS
nsp10
ISG15
H
Total Error Rate
Total Error Rate (1 in 10,000)
I
C:U Transition Rate
Transitions per 10,000 Bases
J
nsp10 Codon Change Frequency
% of TCS
Vehicle BID
-2 hr BID
+12 hr BID
+24 hr BID
+48 hr BID

Figure 6

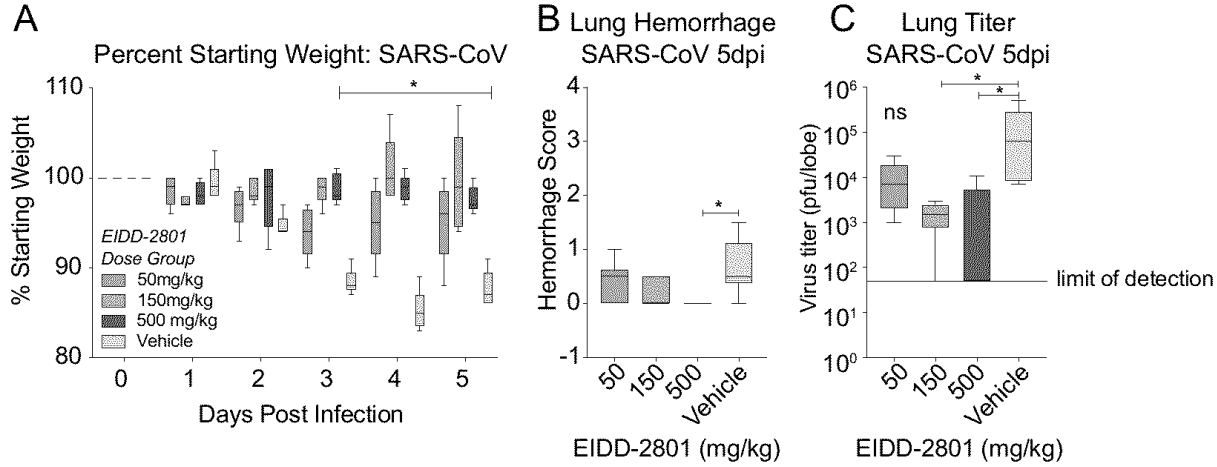


Supplementary Figure 1

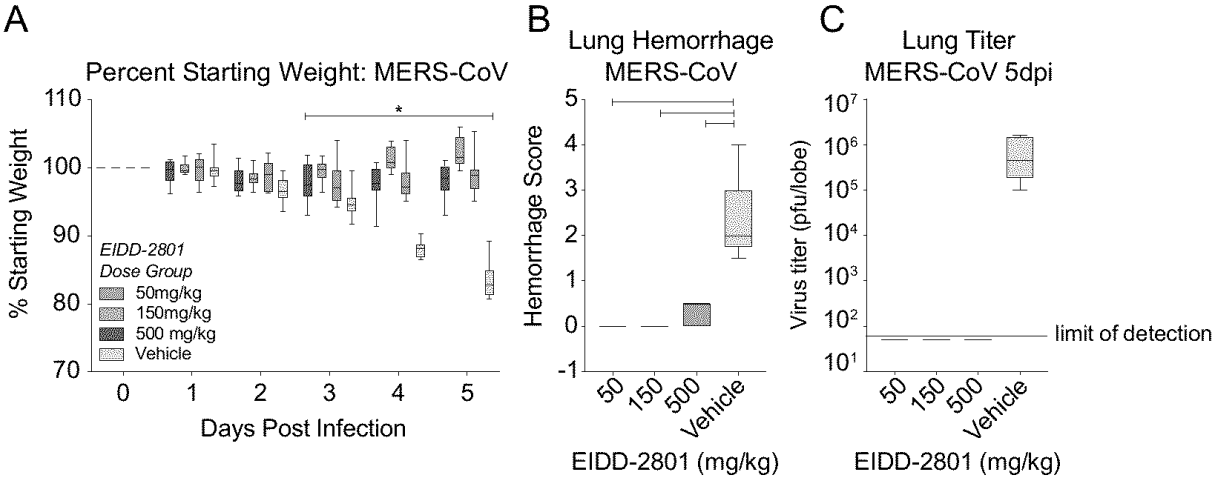
Conservation of key RdRp motif residues



Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4

Supplementary Table 1. Real-time PCR primer/probe sets for indicators of cellular apoptosis/toxicity

Primer/Probe Target	Assay Reference Number*
Bax	Hs00180269_m1
Bad	Hs00188930_m1
Bcl2L11	Hs00708019_s1
Bcl2	Hs00608023_m1
Mcl1	Hs01050896_m1
Tradd	Hs00601065_g1
Fas	Hs00236330_m1
Tank	Hs00370305_m1
18S	4352930E
GAPD**	4352934E

* Validated assays available from Life Technologies

** The housekeeping gene hGAPDH was used for normalization of real-time results.

Supplementary Table 2. Primer used for MiSeq library prep and sequencing.

Primer	5'-3'	Comment
41R_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATGACCTTCCTGTTGCTTCT	cDNA primer. Targeting 20331-20350 on the reference genome.
nsp10_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTCCTAAAGACGACATCAGTGG	cDNA primer. Targeting 13488-13507 on the reference genome.
nsp12_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATAGCCAAAGACACAAACCG	cDNA primer. Targeting 15983-16002 on the reference genome.
nsp14_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGAACATCGACAAAGAAAGGG	cDNA primer. Targeting 18715-18734 on the reference genome.
ifit3_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTTTCAGCCACTCCTTTATCCC	cDNA primer. Targeting mice IFIT3 mRNA.
isg15_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGGGGCTTTAGGCCATACTC	cDNA primer. Targeting mice ISG15 mRNA.
41F_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNGCTACAAGTTCGTCCTTTGG	1st round PCR forward primer. Targeting 19812-19831 on the reference genome
nsp10_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGCTCAGGTGCTAAGCGAAT	1st round PCR forward primer. Targeting 12983-13002 on the reference genome
nsp12_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATAGGCTTCGATGTTGAGGG	1st round PCR forward primer. Targeting 15388-15407 on the reference genome
nsp14_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATTGCAAGCTGGTTCTAACA	1st round PCR forward primer. Targeting 18260-18279 on the reference genome
ifit3_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNCGATCCACAGTGAACAACAG	1st round PCR forward primer. Targeting mice IFIT3 mRNA.
isg15_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGGGACCTAAAGGTGAAGATG	1st round PCR forward primer. Targeting mice ISG15 mRNA.
Adapter R	GTGACTGGAGTTCAGACGTGTGCTC	1st round PCR reverse primer
Universal Adapter	AATGATACGGCGACCACCGAGATCTACACGCCTCCCTCGCGCCATCAGAGATGTG	2nd round PCR forward primer with Illumina adapter sequence
Indexed Adapter	CAAGCAGAAGACGGCATACGAGATNNNNNNGTGACTGGAGTTCAGACGTGTGCTC	2nd round PCR reverse primer with Illumina adapter sequence and indices (NNNNNNN)
Old Nextera	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAG	Customized sequencing primer

Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Note: potential for additional authors from Gilead.

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Abstract (158)

Coronaviruses (CoV) can move into new host species resulting in novel disease outbreaks, most recently exemplified by the newly emerged SARS-like coronavirus in Wuhan China in 2019 (SARS-CoV-2). There are no approved therapies for any human coronavirus. Here we show the orally bioavailable ribonucleoside analog, β-D-N^4-hydroxycytidine (NHC, EIDD-1931), has broad spectrum antiviral activity against MERS-

CoV, SARS-CoV, SARS-CoV-2 and related Bat-CoVs as well as coronavirus bearing resistance mutations to another nucleoside inhibitor. In SARS- or MERS-CoV infected mice, both prophylactic and therapeutic administration of oral NHC-prodrug (i.e. EIDD-2801, β-D-N^4-hydroxycytidine-5'-isopropyl ester) improved pulmonary function and reduced virus titer, and body weight loss. Using Primer ID, we show increased mutation rates coincident with a decrease in MERS-CoV yields *in vitro* and protective efficacy *in vivo* suggesting the mechanism of action (MOA) of lethal mutagenesis. The broad activity and therapeutic efficacy of EIDD-1931 highlight its potential as a stand-alone or combinatorial cocktail to diminish emerging coronavirus disease severity in an outbreak setting.

Word Limit: Intro to Discussion = 4000 words. Now at 4362.

Introduction

The genetically diverse Orthocoronavirinae (coronavirus, CoV) family circulates in many avian and mammalian species. CoV encode the largest positive sense RNA genome in nature and escape error-prone catastrophe by encoding proteins that improve replication fidelity as compared to other RNA viruses [1]. Increased replication fidelity of CoV is mediated by a viral protein called, ExoN (nsp14), in concert with the RNA dependent RNA polymerase (RdRp, nsp12) and other members of the replication complex to produce viral genomic and subgenomic RNA[1]. Despite a fidelity repair system, CoV can rapidly adapt to changing environments and species, resulting in novel disease outbreaks. Three new human CoV have emerged in the past 20 years with severe acute respiratory syndrome CoV (SARS-CoV) in 2002 in Guangdong, China, Middle East respiratory syndrome CoV (MERS-CoV) in 2012 in the Kingdom of Saudi Arabia, and now SARS-CoV-2 in 2019 in Wuhan, China[2-4]. The ongoing SARS-CoV-2 epidemic has thus far caused over 70,000 infections and over 1,700 deaths in 29 countries and like SARS- and MERS-CoV, the respiratory disease caused by SARS-CoV-2 can progress to acute lung injury (ALI), an end stage lung disease with limited treatment options and very poor prognoses[4-6]. This emergence paradigm is not limited to humans. A novel CoV called swine acute diarrhea syndrome CoV (SADS-CoV) recently emerged from bats causing the deaths of over 20,000 pigs in Guangdong Province, China[7]. More alarmingly, SARS-like and MERS-like coronaviruses are

circulating in bat reservoir species that can use human receptors and replicate efficiently in primary human lung cells without adaptation[7-10]. The presence of these "pre-epidemic" zoonotic strains foreshadow the emergence and epidemic potential of SARS- and MERS-like viruses in the future as we are now realizing with the emergence of SARS-CoV-2. Given the diversity of strains in zoonotic reservoirs and a penchant for virus cross species transmission, broadly active antivirals are clearly needed for rapid response to new CoV outbreaks in humans and domesticated animals.

Currently, there are no approved therapies specific for any human CoV. β-D-N4-hydroxycytidine (NHC, EIDD-1931) is orally bioavailable ribonucleoside analog with broad-spectrum antiviral activity against various unrelated RNA viruses including influenza, Ebola, CoV and Venezuelan equine encephalitis virus (VEEV)[11-14]. For VEEV, the mechanism of action (MOA) for NHC has been shown to be through lethal mutagenesis where deleterious transition mutations accumulate in viral RNA[12,15]. Here, we demonstrate that NHC exerts potent, broad-spectrum activity against SARS-CoV, MERS-CoV and their related bat-CoV in primary human airway epithelial cell cultures (HAE), a biologically relevant model of the human conducting airway. In addition, we show that NHC is potently antiviral against the newly emerging SARS-CoV-2 as well as against coronavirus bearing resistance mutations to another nucleoside inhibitor. In SARS- or MERS-CoV infected mice, both prophylactic and therapeutic administration of oral NHC-prodrug (i.e. EIDD-2801, β-D-N^4-hydroxycytidine-5'-isopropyl ester) improved pulmonary function and reduced virus titer and body weight loss. Using Primer ID, we show increased mutation rates coincident with a decrease in MERS-CoV yields *in vitro* and protective efficacy *in vivo* suggesting the mechanism of action (MOA) of lethal mutagenesis. The broad activity and therapeutic efficacy of NHC highlight its potential to diminish epidemic disease today and limit future outbreaks emerging CoV outbreaks.

Results

NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2 Replication.

To determine whether NHC blocks the replication of highly pathogenic human CoV, we performed antiviral assays in continuous and primary human lung cell

cultures. We first assessed the antiviral activity of NHC against MERS-CoV in the human lung epithelial cell line Calu-3 2B4 ("2B4" cells). Using a recombinant MERS-CoV expressing nanoluciferase (MERS-nLUC)[16], we measured virus replication in cultures exposed to a dose response of drug for 48hr. NHC was potently antiviral with an average half-maximum effective concentration (IC_{50}) of 0.15μM and no observed cytoxicity in similarly treated uninfected cultures across the dose range (50% cytotoxic concentration, CC_{50}, >10μM) (Fig. 1A). The therapeutic index for NHC was >100. Similarly, NHC exerted robust antiviral activity against SARS-CoV-2 (2019-nCoV) in Vero cells with an IC_{50} of 0.3μM and CC_{50} of >10μM (Fig. 1B). Human primary airway epithelial (HAE) cell cultures model the architecture and cellular complexity of the conducting airway and are readily infected by multiple human and zoonotic CoV, including SARS- and MERS-CoV[17]. We first assessed cytotoxicity of NHC in HAE treated with an extended dose range for 48hr using quantitative PCR of cell death related gene transcripts as our metric. Unlike the positive control (1μM staurosporine), which significantly ($P < 0.05$) induced death related gene expression in HAE, NHC treatment did not appreciably alter gene expression even at doses up to 100μM (Supplementary Figure 1). In MERS-CoV infected HAE, NHC dramatically reduced virus production with maximal titer reduction of > 5 logs at 10μM (average IC_{50} = 0.024 μM), which correlated with reduced genomic (ORF1) and subgenomic (ORFN) RNA in paired samples (Fig. 1C). We observed similar trends in titer reduction (> 3 log at 10μM, average IC_{50} = 0.14 μM) as well as in the levels of genomic and subgenomic RNA in SARS-CoV infected HAE (Fig. 1D). Thus, NHC exerted potent antiviral activity against emerging CoV including SARS-CoV-2 in both cell lines and in human primary HAE cell cultures without cytotoxicity.

NHC is effective against drug resistant virus and multiple distinct zoonotic CoV.

All human CoV are thought to have emerged as zoonoses most recently exemplified by SARS-CoV, MERS-CoV and SARS-CoV-2[18-20]. Although taxonomically divided into multiple genogroups (alpha 1, beta 2, gamma 3, delta 4), human CoV are found in only the alpha and beta subgroups thus far (Fig. 2A). There is high sequence conservation in the RdRp, the protein target of NHC, across CoV (Fig. 2A). For

example, the RdRp of SARS-CoV-2 is incredibly similar (99.9% similarity and 96% amino acid identity) to that of SARS-CoV (Fig. 2A). We previously reported the antiviral resistance to another nucleoside analog, remdesivir (RDV), which is mediated by RdRp residues F480L and V557L in SARS-CoV facilitating a 5-fold shift in IC_{50} (Fig. 2B)[21]. Resistance is transferable to a model CoV, mouse hepatitis virus (MHV), by inserting equivalent mutations in the RdRp[21]. As drug resistance is possible through drug treatment, we aimed to determine if resistance to one nucleoside analog, RDV, would transfer resistance to another, NHC. In Figure 2C, we show that RDV resistant CoV is actually more susceptible to the antiviral activity of NHC as evidenced by an increased reduction in virus production over a dose range of NHC. These data indicate that NHC will likely require a novel set of resistance mutations as compared to remdesivir, suggesting that the two drugs may select for antagonistic mutations. To gain insight into structural conservation of RdRp across the CoV family, we modeled the variation encapsulated in the RdRp dendrogram in Fig. 2A onto the structure of the SARS-CoV RdRp[22] (Fig. 2D). The core of the RdRp molecule and main structural motifs that all RdRp harbor (Supplementary Figure 2) are highly conserved among CoV including SARS-CoV-2. Thus, it is likely that existing effective nucleoside antivirals will be similarly effective against current and future emerging CoV.

To explore the breadth of antiviral efficacy against zoonotic CoV, we performed antiviral assays in HAE with three Bat-CoV, SCH014, HKU3 and HKU5. Closely related to the beta 2b SARS-CoV, Bat-CoV SHC014 is poised for emergence and is capable is replicating in human cells without adaptation[9]. Bat-CoV HKU3 is a more distantly related SARS-like beta 2b CoV that harbors the receptor binding domain of SARS-CoV to drive infection in human/primate cells[23]. Lastly, Bat-CoV HKU5 is a MERS-like beta 2c CoV and like HKU3 was modified to facilitate infection in human cells. Importantly, each of these Bat-CoV encode their native zoonotic RdRp. NHC diminished infectious virus production and the levels of genomic/subgenomic viral RNA in HAE in a dose dependent manner for all three Bat-CoV (Fig. 3). Therefore, the antiviral activity of NHC was not limited by natural amino acid variation in the RdRp, which among the group 2b and group 2c CoV can vary by almost 20% (Fig. 2A). Moreover, these data suggest that

if a SARS- or MERS-like virus were to emerge in the future that was similar to those noted above, they would likely be susceptible to the antiviral activity of NHC.

NHC antiviral activity is associated with increased viral mutation rates.

We aimed to determine if NHC would increase the mutation rate of MERS-CoV in human primary cells as it was recently shown that NHC treatment increases the mutation rate in viral genomic RNA of RSV, influenza and MHV[14,24]. In MERS-CoV infected HAE treated with either vehicle or a dose response of NHC or RDV, we show both drugs reduced virus titers dose dependently (Fig. 4A). We then employed a highly sensitive high throughput deep sequencing based approach designated "Primer ID" to determine the effects of antiviral treatment on viral RNA production[25]. Primer ID is designed to specifically remove spurious RT-PCR mutations, while facilitating highly accurate sequence determination of single RNA molecules, because each cDNA is created with a barcoded degenerate primer (N10, 4^{10} combinations) from which Illumina indexed libraries are made (Fig. 4B). We created an accurate template consensus sequence (TCS) for each viral template RNA is created from all reads for a given primer ID after identifying and removing reverse transcriptase and PCR induced errors (Fig. 4B). Using this approach, we analyzed a 538bp region of viral genomic RNA in nonstructural protein 15 (nsp15). Unlike the consistently low error rates (i.e. # mutations/10,000 bases) in vehicle (0.01) or remdesivir (0.01) treated cultures, the error rate was significantly increased in MERS-CoV RNA dose dependently (10-fold at 10μM, 5-fold at 1μM) at both 24 and 48hpi (Fig. 4C). As RDV is reported to act via chain termination of nascent viral RNA rather than lethal metagenesis, the low error rates in RDV treated cultures are in line with the reported MOA[26]. In addition, the magnitude of the error rate in NHC treated cultures correlated with virus titer reduction. For example, at 48hpi the respective error rate and virus titer for vehicle treated cultures was 0.015 and 3.96E+06 pfu/mL but were 0.090 and 1.5E+02 pfu/mL cultures treated with 10μM NHC and 0.045 and 2.86E+04 pfu/mL for cultures treated with 1μM NHC. Thus, a 6-fold increase in error rate resulted in a 26,000 fold decrease in virus titer with 10μM NHC while a 3-fold increase in error rate resulted in a 138-fold decrease in virus titer with 1μM NHC.

We then examined the mutational spectra induced by NHC, which is known to be incorporated into viral RNA as a cytosine (C) or Uridine (U). CoV are positive sense RNA viruses that replicate their genomes through a negative sense intermediate. Therefore, mutagenic antivirals like NHC have the opportunity to get incorporated into both nascent negative and positive sense RNA (Fig. 4D). Interestingly, adenine (A) to guanine (G) and uridine (U) to cytosine (C) transitions were enriched in MERS-CoV genomic RNA in an NHC dose dependent manner (Fig. 4E). Collectively, these data demonstrate a specific enrichment for A:G and C:U transitions in MERS-CoV RNA after NHC treatment of primary HAE cell cultures, consistent with the MOA of lethal mutagenesis.

Therapeutic NHC prodrug reduces SARS-CoV replication and pathogenesis.

Given the promising antiviral activity of NHC in vitro, we next evaluated its in vivo efficacy using an orally bioavailable prodrug of NHC designated EIDD-2801 (β-D-N^4-hydroxycytidine-5'-isopropyl ester) designed for improved in vivo pharmacokinetics and oral bioavailability in humans and non-human primates[13]. Importantly, the plasma profiles of NHC and EIDD-2801 were similar in mice following oral delivery[13]. We first performed a prophylactic dose escalation study in C57BL/6 mice where we orally administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500 mg/kg EIDD-2801 2hr prior to intranasal infection with 5E+04 PFU mouse adapted SARS-CoV (SARS-MA15), and then every 12hr thereafter. Beginning on 3dpi and through the end of the study, body weight loss observed with vehicle treatment was significantly diminished (50mg/kg) or prevented (150, 500mg/kg) with EIDD-2801 prophylaxis ($P < 0.0001$) (Supplemental Figure 2A). Lung hemorrhage was also significantly reduced 5dpi with 500mg/kg EIDD-2801 treatment (Supplemental Figure 2B). Interestingly, there was a dose dependent reduction in SARS-CoV lung titer (median titers: 50mg/kg = 7E+03 pfu/mL, 150mg/kg = 2.5E+03 pfu/mL, 500mg/kg = 50 pfu/mL, vehicle = 6.5E+04 pfu/mL) with significant differences among the vehicle, 150 mg/kg ($P = 0.03$) and 500mg/kg ($P = 0.006$) groups. Thus, prophylactic EIDD-2801 was robustly antiviral and able to prevent SARS-CoV replication and disease.

Given that only the 500mg/kg group significantly diminished weight loss, hemorrhage and reduced lung titer to near undetectable levels, we tested this dose under therapeutic treatment conditions to determine if EIDD-2801 could improve the outcomes of an ongoing CoV infection. As a control, we initiated oral vehicle or EIDD-2801 2hr prior to infection with 1E+04 pfu SARS-MA15. For therapeutic conditions, we initiated EIDD-2801 treatment 12, 24, or 48hr after infection. After initiating treatment, dosing for all groups was performed every 12hr for the duration of the study. Both prophylactic treatment initiated 2hr prior to infection and therapeutic treatment initiated 12hr after infection significantly prevented body weight loss following SARS-CoV infection on 2dpi and thereafter (-2hr: $P = 0.0002$ to <0.0001; +12hr: $P = 0.0289$ to <0.0001) (Fig. 5A). Treatment initiated 24hpi also significantly reduced body weight loss (3-5dpi, $P = 0.01$ to <0.0001) although not to the same degree as the earlier treatment groups. When initiated 48hpi, body weight loss was only different from vehicle on 4dpi ($P = 0.037$, Fig. 5A). Therapeutic EIDD-2801 significantly reduced lung hemorrhage when initiated up to 24hr after infection mirroring the body weight loss phenotypes (Fig. 5B). Interestingly, all EIDD-2801 treated mice had significantly reduced viral loads in the lungs even in the +48hr group (Fig. 5C), which experienced the least protection from body weight loss and lung hemorrhage. We then measured pulmonary function via whole body plethysmography (WPB). In Figure 5D, we show the WBP PenH metric, which is a surrogate marker for bronchoconstriction or pulmonary obstruction, was significantly improved throughout the course of the study if treatment was initiated up to 12hr after infection, although the +24hr group showed sporadic improvement as well (Fig. 5D). Altogether, therapeutic EIDD-2801 was potently antiviral against SARS-CoV in vivo but the degree of clinical benefit was dependent on the time of initiation post infection.

Prophylactic and therapeutic NHC prodrug reduces MERS-CoV replication and pathogenesis.

After obtaining promising in vivo efficacy data with SARS-CoV, we determined if EIDD-2801 was effective against MERS-CoV. As the murine ortholog of the MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), does not support viral binding and entry, all in

vivo studies were performed in genetically modified mice encoding a murine DPP4 receptor encoding two human residues at positions 288 and 330 (hDPP4 mice)[16,27]. Similar to our SARS-CoV data (Supplementary Figure 3), all doses of prophylactic EIDD-2801 (50, 150 and 500mg/kg) protected hDPP4 288/330 mice from significant body weight loss ($P = 0.03$ to < 0.0001), lung hemorrhage ($P = 0.01$ to <0.0001), and virus replication which was undetectable ($P < 0.0001$) regardless of drug dose following intranasal infection with 5E+04 PFU mouse adapted MERS-CoV (Supplementary Figure 4).

We then evaluated the therapeutic efficacy EIDD-2801 following the promising results of our prophylactic studies. Similar to our SARS-CoV , EIDD-2801 treatment administered before or 12hr after intranasal mouse adapted MERS-CoV infection (5E+04 PFU) prevented body weight loss from 2 through 6dpi (Fig. 6A, $P = 0.02$ to <0.0001) and lung hemorrhage on 6dpi (Fig. 6B, $P = 0.0004$ to < 0.0001), but treatment initiated 24 or 48hr did not afford similar protection. Unlike body weight loss and lung hemorrhage data which varied by treatment initiation time, virus lung titer on 6dpi was significantly reduced to the limit of detection in all treatment groups (Fig. 6C, $P < 0.0001$). Interestingly, when viral genomic RNA was quantitated in parallel samples of lung tissue, EIDD-2801 significantly reduced levels of viral RNA ($P <0.0001$ to 0.017) in an initiation time dependent manner for all groups except for +48hr (Fig. 6D). The discrepancy among infectious titers and viral RNA suggests that accumulated mutations render the particles non-infectious and undetectable by plaque assay consistent with the MOA. To gauge the effect of EIDD-2801 treatment on lung function, we assessed pulmonary function by WBP. Mirroring the body weight loss data, normal pulmonary function was only observed in groups where treatment was initiated prior to or 12hr after infection (Fig. 6E). Collectively, these data demonstrate that NHC prodrug, EIDD-2801, robustly reduces MERS-CoV infectious titers, viral RNA, and pathogenesis under both prophylactic and therapeutic conditions.

Therapeutic efficacy correlates with MERS-CoV mutation rate in vivo.

To study the molecular mechanisms associated with in vivo drug performance, we investigated the correlation between infectious virus production and NHC-prodrug

(EIDD-2801) mediated mutagenesis of MERS-CoV RNA by under therapeutic treatment conditions. Using Primer ID, we measured the mutation rates of both viral genomic RNA (i.e. non-structural protein 10, nsp10) and host interferon stimulated gene 15 (ISG15) mRNA, a highly upregulated innate immune related gene after MERS-CoV infection (Fig. 6F). Primer ID measures the mutational frequency in single RNA molecules each of which are represented by a single template consensus sequence (TCS, See Fig. 4B)[25]. Viral TCS were significantly reduced in a treatment initiation time dependent manner (Fig. 6G) similar to viral genomic RNA measured by qRT-PCR (Fig. 6D). In contrast, the numbers of ISG15 TCS were similar ($P = 0.2$ to 0.8) for all groups indicating that neither vehicle nor drug treatment significantly affected the levels of ISG15 gene expression (Fig. 6G). Similar to our TCS data, the total error rate in viral nsp10 was significantly increased in groups where treatment was initiated prior to (-2hr, median error rate = 10.5 errors/10,000 bases, $P < 0.0001$) and up to 24hr post infection (12hr, median error rate = 8.2 errors/10,000 bases, $P < 0.0001$; +24hr, median error rate = 5.4 errors/10,000 bases, $P = 0.0003$) but the error rates in ISG15 remained at baseline for all groups (Fig. 6G). In addition, nucleotide transitions observed in MERS-CoV genomes in vitro (i.e. C to U transitions, Fig. 3), were also observed in vivo in groups where treatment was initiated prior to and up to 12hr post infection ($P = 0.0003$ to < 0.0001) (Fig. 5I). Importantly, these transitions were not observed in host ISG15 mRNA (Fig. 5I). Lastly, the EIDD-2801-dose dependent mutagenesis of viral RNA correlated with an increase in codon change frequency, including stop codons, in mice where treatment was initiated 12hr or before (vehicle median = 3.4; -2hr median = 22.8, $P = 0.0035$; +12hr median = 20.0, $P = 0.0004$, Fig. 5I). Thus, approximately 20% of the mutations observed in the -2hr and +12hr groups resulted in a codon change and alteration of the nsp10 protein sequence. When extrapolating our results from nsp10 to the entirety of the 30kb MERS-CoV genome, EIDD-2801 likely causes between 15 (+24hr treatment) and 30 (-2hr treatment) mutations per genome 10-20% of which result in amino acid coding changes. Altogether, our data demonstrates that EIDD-2801-driven mutagenesis correlates well with the reductions in viral load, strongly suggestive of an error catastrophe driven mechanism of action under therapeutic conditions.

Discussion

In the past 20 years, humanity has experienced the two largest ever Ebola virus outbreaks, pandemic Zika virus spread across the Americas, a resurgence of yellow fever virus, a novel H1N1 influenza virus pandemic and the emergence of three human coronaviruses[28,29]. The ease of global travel, coupled with population density, development, land use, agricultural and human behavioral changes, have increased the risk of zoonotic viral emergence events, potentially leading to rapid global dissemination in the 21st century[28]. Zoonotic viruses exist as large pools of heterologous strains, making it difficult to develop therapies that are effective against unknowns as exemplified by group 2b SARS-like CoV encompass zoonotic strains that can use human ACE2 receptors, grow well in primary human airway cells, yet vary by as much as 25% in key therapeutic and vaccine gene targets[9,30]. For these reasons, therapies with broad activity against multiple virus families prone to emergence are especially critical as they provide an immediate potential intervention strategy to treat patients infected by newly emerging virus and slow spread among the community. As drug resistance or natural genetic variation in the zoonotic pool may diminish monotherapy performance, multiple broad-spectrum antivirals are needed to optimize response strategies or provide opportunities for sequential or combination use to optimize intervention tactics for improved global health. We have recently reported the broad-spectrum potency of the nucleoside prodrug, remdesivir (RDV), against an array of epidemic, contemporary and zoonotic CoV both in vitro and in vivo[16,17,21,30]. Herein, we report the broad-spectrum antiviral activity of a second nucleoside prodrug, NHC, against SARS-CoV, MERS-CoV and related bat-CoV as well as against the newly emerging SARS-CoV-2. Like RDV, which also has broad antiviral activity against many virus families, NHC has reported activity against multiple genetically distinct viruses including Venezuelan equine encephalitis (VEE), influenza A and B, Ebola, and Chikungunya viruses[11-13,17,21,24,31-33]. Thus, both compounds contain broad spectrum antiviral activity that targets multiple emerging viruses, including CoV, for which there are no approved therapies. Compound synergy is also high, as NHC not only encodes a unique mutagenic mechanism of action as compared to the chain terminator RDV, but importantly, potently blocks the replication of RDV resistant CoV.

Small molecule antivirals can exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoding enzyme, blocking virus particle formation, targeting a host factor required for replication[34]. For VEE, NHC exerts its antiviral activity on the RNA dependent RNA polymerase by inducing error catastrophe, an occurrence where the error rate of replication surpasses the error threshold required to sustain a virus population[12,13]. This process occurs when NHC is misincorporated during RNA synthesis driving increased mutation rates. However, the NHC mechanism of action is less clear after CoV infection, because these viruses encode an RNA proofreading activity, encoded by the nsp14 exonuclease function that could prevent error catastrophe[1]. Here, we present data using Primer ID, a state of the art deep sequencing-based approach, to quantitate the frequency and identity of the mutational spectra in the MERS-CoV genome in both drug treated cells and in mice at single genome resolution[25]. As CoV are positive sense RNA viruses that replicate through a negative sense RNA intermediate, NHC incorporation as a “C” or a “U” can occur in both polarities of RNA. With Primer ID, we found increased nucleotide transitions (A to G, G to A, C to U, U to C) consistent with those reported after influenza and VEE infections[12,13]. Under identical conditions, remdesivir did not alter the mutation rate in MERS-CoV genomic RNA, supporting its reported mechanism of action as a chain terminator of viral RNA synthesis[26]. In primary human lung cell cultures and mice infected with MERS-CoV, the NHC mutation rates inversely correlated with a reduction in infectious virus. In addition, we found a positive correlation between increased mutation rates and the frequency of nonsynonymous mutations and the degree of therapeutic efficacy in mice. To explore the potential off-target effect in host mRNA which may contribute to drug toxicity, we also examined the impact of NHC treatment on transcripts from the highly MERS-CoV induced interferon stimulated gene 15 (ISG15). While present in great abundance, an accumulation of mutations was not observed in ISG15 transcripts. Thus, mutagenesis of host RNA does not appear to be widespread in this model even at 500mg/kg dosing. These data also support previous studies using RNAseq to demonstrate that the model coronavirus, MHV displayed increased mutation frequencies following NHC treatment in vitro[14]. All together, these data strongly support the notion that NHC and its prodrug, EIDD-2801, exert its antiviral

effect through the induction of error catastrophe in the targeted virus. While our data suggest that the MERS-CoV nsp14 proof reading activity appeared ineffective against NHC treatment in vitro and in vivo, future studies will need to investigate the NHC mutagenic potential in the presence or absence of the nsp14 proof-reading activity, as loss of this activity increased the sensitivity of MHV and SARS-CoV replication to remdesivir treatment[1].

Collectively, our studies have shown that a number of highly genetically divergent group 1, group 2 and group 3 coronaviruses (>50% divergence) are highly vulnerable to RDV and/or NHC treatment[16,17,30]. In the absence of preexisting immunity, diseases caused by a newly emerging coronavirus are very severe as evidenced by mortality rates of 10%, 35% and ~2.5% after SARS-CoV, MERS-CoV or SARS-CoV-2 infections, respectively[3,4]. Our group and others have previously demonstrated that several group 2b SARS-like bat coronaviruses like WIV1, SHC014 and WIV16 are genetically diverse (~8-10% different), poised for emergence, because they can use the human ACE2 receptor for entry, replicate efficiently in primary human airway epithelial cells and evade current immunotherapeutics and vaccines developed against SARS-CoV[9,10]. In contrast, SARS-CoV-2, which emerged in Wuhan China in Dec 2019, is ~25% different in the S glycoprotein, as compared with the SARS-CoV, cause mortality rates of ~2-5%, and may escape currently available immune therapeutics and vaccines[4,35]. Importantly, the 2019-nCoV RNA dependent RNA polymerase is 98% identical to the other group 2b SARS-like bat coronaviruses. Although speculative, these data suggest that 2019-nCoV will prove highly vulnerable to RDV and NHC treatment modalities in vivo an outcome for RDV currently under evaluation in human clinical trial in China[36]. The data provided in this manuscript suggest that NHC should be quickly evaluated in primate models of human disease, using immediate models for MERS-CoV and SARS-CoV pathogenesis[37,38]. As SARS-CoV-2 small and large animal models become available, these drugs should be tested to protect against the 2019-nCoV. Unfortunately, number of SARS-CoV-2 cases continue to increase each day with over 70,000 cases and almost 2000 deaths in 29 countries including the United States. Given the data reported here and elsewhere, it is imperative that broadly acting therapies such as NHC and remdesivir be considered for compassionate human use.

Finally, as SARS-CoV-2 marks the third human coronavirus outbreak in the 21st century, this argues for systematic basic and applied studies designed to produce broadly active drugs, immunotherapeutic and vaccines against SARS-like and MERS-like bat coronaviruses. Our data support the continued development of NHC as a one of these broad spectrum antivirals that could be developed to treat emerging coronavirus infections of the future.

Materials and Methods

Compounds. The parental compound β–D–N4-hydroxycytidine (NHC, all in vitro studies) and its prodrug EIDD-2801 (all in vivo studies) was supplied by Emory University Institute for Drug Discovery (EIDD). NHC was supplied as a 10mM stock in DMSO and EIDD-2801 as a solid to be mixed immediately prior to use. The solubilized compound needed each day was prepared in vehicle containing 10% PEG400, 2.5% Cremophor RH40 in water (10/2.5/87.5%, all v/v). Remdesivir (RDV) was solubilized in 100% DMSO and provided by Gilead Sciences, Inc.

Virus strains. All viruses used for these studies were derived from infectious clones and isolated as previously described[39]. Virus strains for in vitro experiments include SARS-CoV expressing the green fluorescent protein (GFP) in place of open reading frames 7a/b (ORF7a/b, SARS-GFP)[39], bat-spike receptor binding domain (Bat-SRBD)[23] is a chimeric CoV strain derived from the HKU3 SARS-like bat coronavirus genomic sequence that has the wild type (Urbani SARS-CoV strain) RBD in the HKU3 spike gene to allow for virus replication in non-human primate cell lines and HAE cultures, SHC014 SARS-like bat coronavirus[9], MERS-CoV expression nanoluciferase (MERS-nLUC)[17] and MERS-CoV expressing the red fluorescent protein gene (RFP, MERS-RFP)[40] in place of open reading frame 5 (ORF 5). The virus stock utilized for MERS-CoV *in vivo* studies was derived from a plaque purified isolate of the mouse adapted MERS-CoV p35C4 strain[41]. The virus stock utilized for SARS-CoV *in vivo* studies was derived from the infectious clone of the mouse adapted SARS-CoV MA15 (MA15) strain[42].

***In vitro* experiments** Calu**:** At 48hrs prior to infection, Calu3 2B4 cells were plated in a 96-well black walled clear bottom plate at $5x10^4$ cells/well. A 10mM stock of NHC was serially diluted in 100% DMSO in 3-fold increments to obtain a ten-point dilution series. MERS-nLUC was diluted in DMEM 10% FBS, and 1% Antibiotic-Antimycotic to achieve a multiplicity of infection (MOI) of 0.08. Cells were infected and treated with NHC in triplicate per drug dilution for 1hr after which, viral inoculum was aspirated, cultures were rinsed once and fresh medium containing drug or vehicle was added. At 48hrs post infection, nanoluciferase expression as a surrogate for virus replication was quantitated on a Spectramax (Molecular Devices) plate reader according to the manufacturer's instructions (Promega, NanoGlo). For our 100% inhibition control, diluted MERS-nLUC was exposed to short-wave UV light (UVP, LLC) for 6 minutes to inhibit the ability of the virus to replicate. For our 0% inhibition control, cells were infected in the presence of vehicle only. DMSO was kept constant in all conditions at 0.05%. Values from triplicate wells per condition were averaged and compared to controls to generate a percent inhibition value for each drug dilution. The IC_{50} value was defined as the concentration at which there was a 50% decrease in luciferase expression. Data was analyzed using GraphPad Prism 8.0 (La Jolla, CA). The IC_{50} values were calculated by non-linear regression analysis using the dose-response (variable slope) equation (four parameter logistic equation): Y = Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)). To measure cell viability to determine if there was any NHC induced cytotoxicity, Calu3 2B4 cells were plated and treated with NHC only as described above. Cells were exposed to the same ten-point dilution series created for the in vitro efficacy studies. As above, 0.05% DMSO-treated cells served as our 0% cytotoxicity control. Wells without cells served as our 100% cytotoxic positive control. After 48hr, cell viability was measured on a Spectramax (Molecular Devices) via Cell-Titer Glo Assay (Promega) according to the manufacturer's protocol. Similar data was obtained in three independent experiments.

HAE: Human tracheobronchial epithelial cells were obtained from airway specimens resected from patients undergoing surgery under University of North Carolina Institutional Review Board-approved protocols by the Cystic Fibrosis Center Tissue Culture Core. Primary cells were expanded to generate passage 1 cells and passage 2

cells were plated at a density of 250,000 cells per well on Transwell-COL (12mm diameter) supports. Human airway epithelium cultures (HAE) were generated by provision of an air-liquid interface for 6 to 8 weeks to form well-differentiated, polarized cultures that resembled in vivo pseudostratified mucociliary epithelium[43]. At 48 hours prior to infection the apical surface of the culture was washed with 500 µL PBS for 1.5 hours at 37˚C and the cultures moved into fresh air liquid interface (ALI) media. Immediately prior to infection, apical surfaces were washed twice with 500 µL of PBS with each wash lasting 30 minutes at 37˚C and HAE cultures were moved into ALI media containing various concentrations of NHC ranging from 10 µM to 0.0016 µM as indicated for each experiment (final % DMSO < 0.05%). Upon removing the second PBS wash, 200 µL of viral inoculum (multiplicity of infection of (MOI) 0.5) was added to the apical surface and HAE cultures were incubated for 3 hours at 37 ˚C. Viral inoculum was then removed, and the apical surface of the cultures were washed three times with 500µL PBS and then incubated at 37°C until 48 hours post infection (hpi). For all HAE cultures, infectious virus produced was collected by washing the apical surface of the culture with 100 µL PBS. Apical washes were stored at -80 ˚C until analysis and titered by plaque assay as previously described[17].

Real-time PCR Analyses*:* Total RNA was isolated using the Zymo Direct-zol RNA MiniPrep Kit (Zymo Research Corp., Irvine, CA, USA) according to the manufacturer's directions. First-strand cDNA was generated using Superscript III reverse transcriptase (Life Technologies, Carlsbad, CA, USA). For quantification of cellular markers of toxicity/apoptosis, real-time PCR was performed using commercially validated TaqMan-based primer-probe sets (**Supplementary Table 1**) and TaqMan Universal PCR Mix (Life Technologies). Results were then normalized as described above.

Primer ID and Deep Sequencing

We used multiplexed Primer ID library prep approach and MiSeq sequencing to investigate the mutations in the viral genomes and mice mRNA. We designed cDNA primers targeting multiple regions on the viral genome and mice mRNA, each with a block of random nucleotides (11-bp long) as the Primer ID[25,44] (**Supplementary Table**

2). Viral RNA was extracted using QIAamp viral RNA kit. A pre-amplification of titrations of templates was performed to estimate the amount of template to use. We used SuperScript III to make cDNA with multiplexed cDNA primers based on the specific aims of sequencing. We used 41R_PID11 for the pilot sequencing and titration determination. For the MERS-CoV sequencing, we multiplexed nsp10_PID11, nsp12_PID11 and nsp14_PID11 for the cDNA reaction; for the mice mRNA sequencing, we used mixed primers of nsp10_PID11, ifit3_PID11, isg15_PID11. After beads purification, we amplified the cDNA with a mixture of forward primers (based on the described schemes) and a universal reverse primer, followed by another round of PCR to incorporated Illumina sequencing adaptors and barcodes in the amplicons. After gel-purification and quantification, we pooled 24 libraries for MiSeq 300 bp paired-end sequencing. The TCS pipeline version 1.38 (https://github.com/SwanstromLab/PID) was used to process the Primer ID sequencing data and construct the template consensus sequences (TCSs) to represent each individual input templates, and the sequences of each region in the pool was de-multiplexed. The RUBY package viral_seq version 1.0.6 (https://rubygems.org/gems/viral_seq) was used to calculate the mutation rate at each position.

***In vivo* experiments.** We performed 4 mouse studies to evaluate the in vivo efficacy of the NHC prodrug (EIDD-2018). First, we performed prophylactic dose escalation studies for both SARS- and MERS-CoV to determine the most efficacious dose of EIDD-2801 per virus. For SARS-CoV, in cohorts of equivalent numbers of male and female 20-29 week old SPF C57BL/6J (Stock 000664 Jackson Labs) mice (n = 10/dose group), we administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500mg/kg EIDD-2801 by oral gavage 2hr prior to infection with 1E+04 PFU mouse adapted SARS-CoV strain MA15. Mice were anaesthetized with a mixture of ketamine/xylazine prior to intranasal infection. Vehicle or drug was administered every 12hr for the remainder of the study. Body weight and pulmonary function by whole body plethysmography was measured daily. On 5dpi, animals were sacrificed by isoflurane overdose, lungs were scored for lung hemorrhage, and the inferior right lobe was frozen at −80°C for viral titration via plaque assay. Briefly, 500,000 Vero E6 cells/well

were seeded in 6-well plates. The following day, medium was removed and serial dilutions of sample was added per plate (10^{-1} to 10^{-6} dilutions) and incubated at 37˚C for 1hr after which wells were overlayed with 1X DMEM, 5% Fetal Clone 2 serum, 1X antibiotic/antimycotic, 0.8% agarose. Two days after, plaque were enumerated to generate a plaque/ml value. Lung hemorrhage is a gross pathological phenotype readily observed by the naked eye driven by the degree of virus replication where the coloration of the lung changes from pink to dark red[45,46]. The large left lobe was placed in 10% buffered formalin and stored at 4°C for 1-3 weeks until histological sectioning and analysis. For MERS-CoV, the prophylactic dose escalation studies we performed exactly as done for SARS-CoV with the following exceptions. First, MERS-CoV binds the human receptor dipeptidyl peptidase 4 (DPP4) to gain entry into cells and two residues (288 and 330) in the binding interface of mouse DPP4 prevent infection of mice. We recently developed a mouse model for MERS-CoV through the mutation of mouse DPP4 at 288 and 330 thus humanizing the receptor (*hDPP4*) and rendering mice susceptible to MERS-CoV infection[27]. We performed all in vivo studies with EIDD-2801 in equivalent numbers of 10-14 week old female and male C57BL/6J hDPP4 mice. Second, we infected mice with 5E+04 PFU/ml mouse adapted MERS-CoV strain M35C4. Third, to titer lungs by plaque assay, Vero CCL81 cells were used and plaques were enumerated 3 days post infection.

To determine the time at which therapeutic administration of EIDD-2801 would fail to improve outcomes with SARS-CoV or MERS-CoV infection, we performed therapeutic efficacy studies in mice where we initiated treatment 2hr prior to infection or 12, 24 or 48hr after infection. As 500mg/kg provided the most complete protection from disease in prophylactic SARS-CoV studies, this dose was used for both therapeutic efficacy studies. Vehicle or EIDD-2801 was given via oral gavage twice daily following initiation of treatment. For both SARS-CoV and MERS-CoV, the infectious dose for the therapeutic studies and the mouse strains were the same as that used in the prophylactic studies. The numbers of mice per group for the SARS-CoV studies were as follows: Vehicle (n = 10), -2hr (n = 10), +12hr (n = 10), +24hr (n = 10), +48hr (n = 10). The numbers of mice per group for the MERS-CoV therapeutic studies were as follows: Vehicle (n = 9), -2hr (n = 9), +12hr (n = 9), +24hr (n = 7), +48hr (n = 10). As

described above, each day mouse body weight and pulmonary function was quantitated. On 5dpi for SARS-CoV and 6dpi for MERS-CoV, animals were humanely sacrificed and tissues were harvested and analyzed as described above. In addition, for the MERS-CoV study, lung tissue was harvested and stored in RNAlater (Thermo Fisher) at -80˚C and then thawed, homogenized in Trizol reagent (Invitrogen) and total RNA was isolated using a Direct-zol RNA MiniPrep kit (Zymo Research). This total RNA was then used for Primer ID and qRT-PCR.

Whole body plethysmography. Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.). Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes.

MERS-CoV genomic RNA qRT-PCR. Mouse lungs were stored in RNAlater (ThermoFisher) at -80°C until processed via homogenization in TRIzol (Invitrogen). Total RNA was isolated using Direct-zol RNA MiniPrep kit (Zymo Research). Previously published TaqMan primers were synthesized by Integrated DNA Technologies (IDT) to quantify MERS genomic RNA (targeting orf1a. Forward: 5'-GCACATCTGTGGTTCTCCTCTCT-3', Probe (6-FAM/ZEN/IBFQ): 5'-TGCTCCAACAGTTACAC-3', Reverse: 5'-AAGCCCAGGCCCTACTATTAGC) [PMID 24023385]. qRT-PCR was performed using 100ng total RNA compared to an RNA standard curve using TaqMan Fast Virus 1-Step Master Mix (ThermoFisher) on a Quant Studio 3 (Applied Biosystems).

nsp12 phylogenetic analysis and conservation modeling. Coronavirus RdRp (nsp12) protein sequence alignments and phylogenetic trees of were generated using Geneious Tree Builder in Geneious Prime (version 2020.0.5) and visualized using Evolview (https://www.evolgenius.info/evolview/). Protein similarity scores were calculated using Blosom62 matrix. The accession numbers used were : PDCoV (KR265858), AIBV (NC_001451), HCoV-229E (JX503060), PEDV (NC_003436), MHV (AY700211), HCoV-HKU1 (DQ415904), HCoV-NL63 (JX504050), HCOV-OC43 (AY903460), HKU5-1 (NC_009020), MERS-CoV (JX869059), HKU9-4 (EF065516),

2019-nCoV (MN996528), HKU3-1 (DQ022305), SHC014 (KC881005), WIV1 (KF367457), SARS-CoV (AY278741). Amino acid conservation scores of coronavirus RdRp were generated using ConSurf Server (https://consurf.tau.ac.il/) using the protein alignment described above and visualized on the SARS-CoV RdRp structure (PDB: 6NUR) in PyMol (version 1.8.6.0)[22,47].

Statistical analysis. All statistical data analysis was performed in Graphpad Prism 8. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. Specific tests are noted in each figure legend.

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

Figure Legends

Figure 1: NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2 Replication. a, NHC antiviral activity and cytotoxicity in Calu-3 cells infected with MERS-CoV. Calu3 cells were infected in triplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of MERS-CoV–expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via Cell-Titer-Glo assay. Data is combined from 3 independent experiments. **b**, NHC antiviral activity and cytotoxicity in Vero cells infected with SARS-CoV-2. Vero cells were infected in duplicate with SARS-CoV-2 clinical isolate virus at an MOI of 0.05 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of cell viability by Cell-Titer-Glo assay. Cytotoxicity was measured as in **a**. Data is combined from 2 independent experiments. **c**, NHC inhibits MERS-CoV virus production and RNA synthesis in primary human lung epithelial cell cultures (HAE). HAE cells were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of NHC for 48 hours, after which apical washes were collected for virus titration. qRT-PCR for MERS-CoV ORF1 and ORFN mRNA. Total RNA was isolated from cultures in **c** for qRT-PCR analysis. Representative data from three separate experiments with three different cell donors are displayed. PFU, plaque-forming units. **d**, NHC inhibits SARS-CoV virus production

and RNA synthesis in primary human lung epithelial cell cultures (HAE). Studies performed as in **c** but with SARS-CoV green fluorescent protein (GFP). Representative data from two separate experiments with two different cell donors are displayed.

Figure 2. NHC is effective against drug resistant virus and multiple distinct zoonotic CoV. a, Neighbor-joining trees created with representatives from all four CoV genogroups showing the genetic similarity of CoV nsp12 (RdRp) and CoV spike glycoprotein, which mediates host tropism and entry into cells. Text color of the virus strain label corresponds to virus host species on the left. The heatmap adjacent to each neighbor-joining tree depicts percent amino acid identity (% A.A. similarity) against mouse hepatitis virus (MHV), SARS-CoV or MERS-CoV. **b**, Amino acid sequence of CoV in panel **a** at known resistance alleles to antiviral drug remdesivir (RDV). **c**, RDV resistant viruses are more susceptible to NHC antiviral activity. Virus titer reduction assay across a dose response of NHC with recombinant MHV bearing resistance mutations to RDV. Asterisks indicate statistically significant differences by Mann-Whitney test. **d**, Core residues of the CoV RdRp are highly conserved among CoV. The variation encompassed in panel **a** was modeled onto the RdRp structure of the SARS-CoV RdRp.

Figure 3: NHC is effective against multiple genetically distinct zoonotic CoV. Top: Antiviral efficacy of NHC in HAE cells against SARS-like (HKU3, SHC014, group 2b) and MERS-like (HKU5, group 2c) bat-CoV. HAE cells were infected at an MOI of 0.5 in the presence of NHC in duplicate. After 48 hours, virus produced was titrated via plaque assay. Each data point represents the titer per culture. Bottom: qRT-PCR for CoV ORF1 and ORFN mRNA in total RNA from cultures in the top panel. Representative data from two separate experiments with two different cell donors are displayed.

Figure 4: NHC antiviral activity is associated with increased viral mutation rates. **a**, Both remdesivir (RDV) and NHC reduce MERS-CoV infectious virus production in primary human HAE. Cultures were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of vehicle, RDV or NHC for 48 hours, after which apical washes were collected for virus titration. Data is combined from two independent studies. **b,** A deep sequencing approach called Primer ID to gain accurate sequence data for single RNA genomes of MERS-CoV. **c**, The total error rate for MERS-CoV RNA isolated from cultures in panel **a** as determined by Primer ID. Error rate values are # mutations per 10,000 bases. Asterisks indicate significant differences as compared to untreated by 2-way ANOVA with a Dunnett's multiple comparison test. **d**, description of potential NHC mutational spectra on both positive and negative sense viral RNA. **e**, Nucleotide transitions adenine (A) to guanine (G) and uridine (U) to cytosine (C) transitions are enriched in MERS-CoV genomic RNA in an NHC dose dependent manner.

Figure 5: Prophylactic and Therapeutic NHC prodrug reduces SARS-CoV replication and pathogenesis. Equivalent numbers of 25-29 week old male and

female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **d,** Pulmonary function by whole body plethysmography was performed daily on five animals per group. Asterisks indicate differences by two-way ANOVA with a Dunnett's multiple comparison test.

Figure 6: Prophylactic and therapeutic NHC prodrug reduces MERS-CoV replication and pathogenesis coincident with increased viral mutation rates. Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 5E+04 PFU mouse adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test. **d**, MERS-CoV genomic RNA in lung tissue by qRT-PCR. Asterisks indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **e**, Pulmonary function by whole body plethysmography was performed daily on four animals per group. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **f**, Workflow to measure mutation rate in MERS-CoV RNA and host transcript ISG15 by Primer ID in mouse lung tissue. **g**, Number of template consensus sequences for MERS-CoV nsp10 and ISG15. **h**, Total error rate in MERS-CoV nsp10 and ISG15. **i**, The cytosine to uridine transition rate in MERS-CoV nsp10 and ISG15. In panels **g-i,** asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **j**, Codon change frequency in MERS-CoV nsp10. Asterisks indicate differences on Kruskal-Wallis with Dunn's multiple comparison test.

Supplementary Figure 1: Assessment of cytotoxicity of NHC in primary human epithelial cell cultures by qRT-PCR. Companion figure to **Figure 1c** and **d**. Primary human epithelial cell cultures were exposed to positive control 1μM staurosporine or a dose response of NHC for 48hr. Cytotoxicity was assessed by qRT-PCR for cell death factor gene expression.

Supplementary Figure 2: High conservation of RdRp functional domains for SARS-CoV -2. Companion figure to **Figure 2a.** Multiple sequence alignment of the

RNA dependent RNA polymerase (RdRp) from viruses in the dendrogram in Figure 2a showing high conservation in the RdRp structural motifs A-G.

Supplementary Figure 3: Prophylactic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Companion figure to **Figure 5**. Equivalent numbers of 20 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at 2hr prior to infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with a Dunn's multiple comparison test.

Supplementary Figure 4: Prophylactic EIDD-2801 reduces MERS-CoV replication and pathogenesis. Companion figure to **Figure 6.** Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning 2hr prior to infection every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 5E+04 PFU mouse adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test.

1. Smith, E.C., Blanc, H., Surdel, M.C., Vignuzzi, M. & Denison, M.R. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. *PLoS Pathog* **9**, e1003565 (2013).
2. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). (2018).
3. de Wit, E., van Doremalen, N., Falzarano, D. & Munster, V.J. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* **14**, 523-534 (2016).
4. Wang, D., *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
5. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D. & Fouchier, R.A. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* **367**, 1814-1820 (2012).
6. Hsu, L.Y., *et al.* Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* **9**, 713-717 (2003).
7. Zhou, P., *et al.* Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* **556**, 255-258 (2018).

8. Woo, P.C., *et al.* Molecular diversity of coronaviruses in bats. *Virology* **351**, 180-187 (2006).
9. Menachery, V.D., *et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
10. Menachery, V.D., *et al.* SARS-like WIV1-CoV poised for human emergence. *Proc Natl Acad Sci U S A* **113**, 3048-3053 (2016).
11. Reynard, O., *et al.* Identification of a New Ribonucleoside Inhibitor of Ebola Virus Replication. *Viruses* **7**, 6233-6240 (2015).
12. Urakova, N., *et al.* beta-d-N (4)-Hydroxycytidine Is a Potent Anti-alphavirus Compound That Induces a High Level of Mutations in the Viral Genome. *J Virol* **92**(2018).
13. Toots, M., *et al.* Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. *Sci Transl Med* **11**(2019).
14. Agostini, M.L., *et al.* Small-Molecule Antiviral beta-d-N (4)-Hydroxycytidine Inhibits a Proofreading-Intact Coronavirus with a High Genetic Barrier to Resistance. *J Virol* **93**(2019).
15. Jordan, P.C., *et al.* Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase. *PLoS Pathog* **14**, e1006889 (2018).
16. Sheahan, T.P., *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222 (2020).
17. Sheahan, T.P., *et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* **9**(2017).
18. Anthony, S.J., *et al.* Further Evidence for Bats as the Evolutionary Source of Middle East Respiratory Syndrome Coronavirus. *mBio* **8**(2017).
19. Hu, B., Ge, X., Wang, L.F. & Shi, Z. Bat origin of human coronaviruses. *Virol J* **12**, 221 (2015).
20. Huynh, J., *et al.* Evidence supporting a zoonotic origin of human coronavirus strain NL63. *J Virol* **86**, 12816-12825 (2012).
21. Agostini, M.L., *et al.* Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *MBio* **9**(2018).
22. Kirchdoerfer, R.N. & Ward, A.B. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun* **10**, 2342 (2019).
23. Becker, M.M., *et al.* Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. *Proc Natl Acad Sci U S A* **105**, 19944-19949 (2008).
24. Yoon, J.J., *et al.* Orally Efficacious Broad-Spectrum Ribonucleoside Analog Inhibitor of Influenza and Respiratory Syncytial Viruses. *Antimicrob Agents Chemother* **62**(2018).
25. Zhou, S., Jones, C., Mieczkowski, P. & Swanstrom, R. Primer ID Validates Template Sampling Depth and Greatly Reduces the Error Rate of Next-Generation Sequencing of HIV-1 Genomic RNA Populations. *J Virol* **89**, 8540-8555 (2015).

26. Tchesnokov, E.P., Feng, J.Y., Porter, D.P. & Gotte, M. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses* **11**(2019).
27. Cockrell, A.S.*, et al.* A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. *Nat Microbiol* **2**, 16226 (2016).
28. Marston, H.D., Folkers, G.K., Morens, D.M. & Fauci, A.S. Emerging viral diseases: confronting threats with new technologies. *Sci Transl Med* **6**, 253ps210 (2014).
29. Paules, C.I., Marston, H.D. & Fauci, A.S. Coronavirus Infections-More Than Just the Common Cold. *JAMA* (2020).
30. Brown, A.J.*, et al.* Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* **169**, 104541 (2019).
31. Ehteshami, M.*, et al.* Characterization of beta-d-N(4)-Hydroxycytidine as a Novel Inhibitor of Chikungunya Virus. *Antimicrob Agents Chemother* **61**(2017).
32. Warren, T.K.*, et al.* Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* **531**, 381-385 (2016).
33. Lo, M.K.*, et al.* GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep* **7**, 43395 (2017).
34. Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S. & Yuen, K.Y. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov* **15**, 327-347 (2016).
35. Zhou, P.*, et al.* Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. *bioRxiv*, 2020.2001.2022.914952 (2020).
36. Cai, B. Severe 2019-nCoV Remdesivir RCT (NCT04257656). (2020).
37. de Wit, E.*, et al.* Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proc Natl Acad Sci U S A* **110**, 16598-16603 (2013).
38. McAuliffe, J.*, et al.* Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. *Virology* **330**, 8-15 (2004).
39. Sims, A.C.*, et al.* Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: role of ciliated cells in viral spread in the conducting airways of the lungs. *J Virol* **79**, 15511-15524 (2005).
40. Scobey, T.*, et al.* Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. *Proc Natl Acad Sci U S A* **110**, 16157-16162 (2013).
41. Douglas, M.G., Kocher, J.F., Scobey, T., Baric, R.S. & Cockrell, A.S. Adaptive evolution influences the infectious dose of MERS-CoV necessary to achieve severe respiratory disease. *Virology* **517**, 98-107 (2018).
42. Roberts, A.*, et al.* A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. *PLoS Pathog* **3**, e5 (2007).
43. Fulcher, M.L., Gabriel, S., Burns, K.A., Yankaskas, J.R. & Randell, S.H. Well-differentiated human airway epithelial cell cultures. *Methods Mol Med* **107**, 183-206 (2005).

44. Jabara, C.B., Jones, C.D., Roach, J., Anderson, J.A. & Swanstrom, R. Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID. *Proc Natl Acad Sci U S A* **108**, 20166-20171 (2011).
45. Fukushi, M.*, et al.* Serial histopathological examination of the lungs of mice infected with influenza A virus PR8 strain. *PLoS One* **6**, e21207 (2011).
46. Matute-Bello, G.*, et al.* An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* **44**, 725-738 (2011).
47. Ashkenazy, H.*, et al.* ConSurf 2016: an improved methodology to estimate and visualize evolutionary conservation in macromolecules. *Nucleic Acids Res* **44**, W344-350 (2016).

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 2/24/2020 7:09:50 AM (UTC-08:00)
To: Sims, Amy C[sims0018@email.unc.edu]
Cc: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE:

Hi Amy, thanks for the reminder on the drug license. Do you happen to have a copy of the business plan/back end pages (facilities, cvs, etc.) for Kizzie's animal model contract? I have the grant but not the back end pages in my files. As you might imagine, they have asked for an animal model contract proposal for the novel cov. Sorry to be a bother. ralph

From: Schaefer, Alexandra[aschaefe@email.unc.edu]
Sent: Mon 2/24/2020 8:07:15 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Baric lab order question
Attachment: MVE_FB_ISG_consensus.pzfx
Attachment: chipqpcranalysis_MVE_graphData.xlsx

Hi Amy,

please find attached the updated analysis
MVEs for H3K4me3 and H3K27me3
for all three donors for following ISGs:
IFI16 (down - regulated)
IFI6 (up-regulated)
SMADL9 (down-regualted)
and in addition for:
RNF213 (up-regulated)
EPSTI1 (up-regulated)
MyD88 (down-regulated)

we seem to see a similar trend in regulation with the additional ISG
however, there are definitely donor differences.

Attached is also the prism file with the ISG heatmaps for MVE and FB

hope all that will go through now

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, February 18, 2020 8:03 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Baric lab order question

Hi Alex,

I finally have access to Prism but when I download your files and try to open them I can't. If you can send them to me as pdf for now that would be great.

Maybe once you are back in the US we can figure out a way for you to send me the Prism files.

Thank you and I hope you are having a nice break. Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Saturday, February 15, 2020 at 1:26 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

Hi Amy,

attached is a first analysis (excel) for
MVEs for H3K4me3 and H3K27me3
for all three donors for following ISGs:
IFI16 (down - regulated)
IFI6 (up-regulated)
SMADL9 (down-regualted)

- it shows the fold enrichment for each histone modification for the individual donor triplicates
- then the average for all three triplicates per donor with standard deviation

also, attached is the MVE ISG consensus list from which the ISG targets for the PCR were chosen (based on 24hpi expression)

I have results for an additional 3 ISGs: EPSTI1, MyD88, and TNF213-
that I am still in the process of analyzing

So far, it looks like ISG expression is regulated via histone modification
(e.g. IFI16 and SMADL9 expression is down-regulated with an larger H3K27me3 enrichment over mock compared to H3K4me3, respectively)
AND
e.g. IFI6 expression is up-regulated with an larger H3K4me3 enrichment over mock compared to H3K27me3, respectively)

However, there are differences among donors, so there are most likely host-dependent differences occuring

based on a first impression it looks like that this trend will hold true with further analysis of the 3 additional genes, which I am working on

Please let me know if you have any questions,
Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE
--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L

IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM
To: Sims, Amy C
Subject: Fwd: Baric lab order question

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

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From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

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From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health

caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially

delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina
Email: jeremy.sanders@qiagen.com

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN

Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>

Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM

To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

Project info 1

Experiment Date
2018-09-19

Experiment ID

Notebook ID

Project

Experimenter

Protocol

MVE_ISG_treat_consensus

Learn about heat maps in Prism

Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

APOBEC3G

APOL1

APOL2

APOL6

BATF2

BST2

C1R

C1S

CASP1

CMPK2

CNP

CXCL10

CXCL11

DDX58

DDX60

DDX60L

DHX58

DTX3L

EIF2AK2

EPSTI1

ETV7

FAM46A

FAM83H-AS1

GBP1

GBP2

GBP4

GBP5

GCH1

GJD3

GMPR

HELZ2

HERC5

HERC6

HERC6

HES4

HLA-F

IFI16

IFI27

IFI30

IFI35

IFI44

IFI44L

IFI6

IFIH1

IFIT1

IFIT2

IFIT3

IFIT5

IFITM1

IL15

IRF7

IRF9

ISG15

ISG20

JADE2

JAK2

LAP3

MLKL

MX1

MX2

MYD88

NLRC5

NMI

NTNG2

OAS1

OAS2

OAS3

OASL

ODF3B

PARP10

PARP12

PARP14

PARP9

PI4K2B

PLEKHA4

PLSCR1

PNPT1

PPM1K

PSMB9

PTK2B

RNF213

RSAD2

RTP4

SAMD9

SAMD9L

SAMHD1

SECTM1

SLC15A3

SLC25A28

SOCS1

SP100

SP110

STAT1

STAT2

SYNE1

TAP1

TAP2

TDRD7

THEMIS2

TLR3

TMEM229B

TNFSF10

TREX1

TRIM14

TRIM21

TRIM22

TRIM25

UBE2L6

USP18

USP30-AS1

USP41

XAF1

ZC3HAV1

ZNFX1

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0

0

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0.19035964

-0.1457996

0.2653675

0.20656135

-0.218984

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0.16870659

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-0.5604172

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-0.1704264

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-0.8389157

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-0.245626

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-0.0037463

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-0.0807746

-0.0799065

-0.4167463

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-0.4931604

-0.1325839

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0

-0.1422824

0.04944623

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0

0

-0.2151828

0

0

0

0.20761585

0

3hr

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3.31676252

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2.30023736

2.19662704

3.29283956

4.36211971

4.92575623

1.84163515

0.97974975

1.6067655

1.44333512

0.95227571

2.03693315

1.61123653

3.44736227

6.18629631

1.16998383

2.17341913

3.4559565

0.63966856

2.54366728

1.27471083

4.02759268

4.96130911

0.87598478

1.69930066

1.68062368

0.86621354

2.72412625

1.5315455

1.77053327

3.87663292

1.91845663

2.97664509

1.40075888

1.19721349

2.85662659

1.19478268

2.11874712

2.92227596

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7.91562019

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1.00057901

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1.20125816

0.69174965

0.69409125

4.23851556

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1.15119875

2.00321639

0.54367006

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3.33459473

3.8107496

1.743532

1.86824128

0.55268143

2.06546826

0.72886171

6hr

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4.58242787

1.73981646

2.0174913

3.01559872

2.34011531

4.48035967

4.11109023

5.45900565

2.33964722

1.932197

2.25635937

1.99582566

1.96817945

2.17257074

1.80780013

3.82345649

7.21452221

1.74316314

1.8429819

3.58165475

1.70669275

2.92908849

1.87219292

4.81822977

4.85078883

1.71688693

2.35960431

2.52017707

1.96785352

3.30871369

2.85099586

1.65907611

3.35686315

3.01370124

4.79029567

2.34431603

1.54387827

1.65187136

1.70007028

2.63817518

4.34119299

1.57910381

7.98529769

2.95987274

1.60697514

3.14427486

3.78568221

1.54661221

2.46391296

2.77897022

4.51767997

2.02353984

2.10691701

1.60926748

2.6799035

4.78285316

1.53635477

2.6668176

2.39112002

1.59962595

1.78171024

3.01527191

2.00263883

2.14770294

2.70968995

2.14887434

3.30849864

6.20989008

4.39205336

2.25171634

3.5963645

1.57707787

2.2705849

3.01804233

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2.33652958

5.47921223

2.0267238

1.93398075

3.66984324

2.37516625

2.42348706

3.14433611

5.17380335

1.96633237

1.55252703

2.81902544

1.70430662

1.63882483

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4.35934585

1.72518598

1.55966123

3.37718923

1.87578295

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1.71076363

2.27774059

3.67547463

6.30398789

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2.48553458

1.61633361

3.68377311

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24hr

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1.66502844

1.43504829

2.26389445

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2.02059268

3.59534481

3.56384067

2.16183116

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1.97653538

2.45391558

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1.11892928

1.15499828

3.51493191

7.38079105

0.65948761

1.01711765

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1.4397452

2.66354399

1.20676918

4.80091716

2.43876713

2.23385871

2.41844174

1.4878587

0.68365066

2.46046324

2.30880918

0.94581018

2.49374016

3.02667348

6.39076499

2.35297328

0.87628852

0.28080741

0.64710064

1.17993811

5.25626899

1.17383399

6.59834679

2.0680727

0.85089004

1.70892504

3.25498813

1.47264516

1.81379595

2.76181302

5.17616342

0.59122977

1.40876656

1.77594016

2.93912235

5.18677349

0.93021579

2.17541373

0.86556836

1.56161577

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1.17770403

1.27066405

2.63763374

1.28022628

2.87137218

1.71286711

1.98536382

2.65349572

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1.17950941

1.2389788

1.34928863

3.58353373

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1.77565765

1.02327797

0.54450277

1.53331303

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1.89714854

1.88651122

7.01151664

1.84005102

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2.75652094

0.8575103

2.0296782

2.27657051

4.12646825

1.20963786

0.41711182

2.53415511

1.21119024

0.28955084

1.5758665

0.81896046

0.72836151

1.08064944

2.75873332

2.38842647

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2.72320748

2.08299074

3.21908388

6.12780936

2.23269997

1.45409295

2.41503858

4.30445738

0.2243767

MVE_ISG_MERSinf_consensus

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APOBEC3G

APOL1

APOL2

APOL6

BATF2

BST2

C1R

C1S

CASP1

CMPK2

CNP

CXCL10

CXCL11

DDX58

DDX60

DDX60L

DHX58

DTX3L

EIF2AK2

EPSTI1

ETV7

FAM46A

FAM83H-AS1

GBP1

GBP2

GBP4

GBP5

GCH1

GJD3

GMPR

HELZ2

HERC5

HERC6

HES4

HLA-F

IFI16

IFI27

IFI30

IFI35

IFI44

IFI44L

IFI6

IFIH1

IFIT1

IFIT2

IFIT3

IFIT5

IFITM1

IL15

IRF7

IRF9

ISG15

ISG20

JADE2

JAK2

LAP3

MLKL

MX1

MX2

MYD88

NLRC5

NMI

NTNG2

OAS1

OAS2

OAS3

OASL

ODF3B

PARP10

PARP12

PARP14

PARP9

PI4K2B

PLEKHA4

PLSCR1

PNPT1

PPM1K

PSMB9

PTK2B

RNF213

RSAD2

RTP4

SAMD9

SAMD9L

SAMHD1

SECTM1

SLC15A3

SLC25A28

SOCS1

SP100

SP110

STAT1

STAT2

SYNE1

TAP1

TAP2

TDRD7

THEMIS2

TLR3

TMEM229B

TNFSF10

TREX1

TRIM14

TRIM21

TRIM22

TRIM25

UBE2L6

USP18

USP30-AS1

USP41

XAF1

ZC3HAV1

ZNFX1

0hpi

-0.091696

0

0

0.114669

0.19036

-0.1458

0.265368

0.206561

-0.218984

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0.004507

0

0.168707

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-0.179424

0.092507

-0.560417

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-0.001237

-0.656849

0.011465

-0.213611

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0

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0

0

0.1115

0

0.149788

-0.016266

-0.170426

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0.00715

0.056834

-0.078299

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-0.124684

0.358391

0.007191

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-0.071388

0

-0.193138

0

-0.026819

-0.144267

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-0.039156

-0.202866

0.089027

0.292041

-0.163214

0.044496

-0.257511

-0.838916

-0.060184

-0.245626

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-0.102588

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-0.027407

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-0.22923

-0.003309

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-0.177055

-0.128196

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-0.416055

-0.003746

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-0.080775

-0.079907

-0.416746

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36hpi

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0.21168381

-1.4039902

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-0.925258

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-0.8115776

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0.1592551

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48hpi

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0.03371735

0.03455576

-0.4612733

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-0.879707

-0.4291481

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-0.1809319

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0.47296248

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0.23125032

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0

-1.8369852

0.24204108

-0.0174061

-0.1102756

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0.69992479

0.23024278

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0.06404909

1.99409719

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0

-1.4002472

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FB_ISG_treat_consensus

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ANGPTL1

APOBEC3G

APOL1

APOL2

APOL3

APOL6

ARHGAP27

BATF2

BST2

C17orf67

CASP7

CCL8

CLDN23

CMPK2

CXCL10

CXCL11

DDX58

DDX60

DDX60L

DHX58

DTX3L

EIF2AK2

EPSTI1

ETV7

FAM83H-AS1

GBP1

GBP4

GBP5

GCH1

GIMAP2

GMPR

HELZ2

HERC5

HERC6

HES4

HLA-F

IDO1

IFI16

IFI27

IFI30

IFI44

IFI44L

IFI6

IFIH1

IFIT1

IFIT2

IFIT2

IFIT3

IFIT5

IFITM1

IL15RA

IL22RA1

IL4I1

IL7

IRF7

IRF9

ISG15

ISG20

JAK2

LAP3

LGALS9C

LMO2

LOC200830

MASTL

MLKL

MX1

MX2

MYD88

NLRC5

NMI

OAS1

OAS2

OAS3

OASL

OGFR

PARP12

PARP14

PARP9

PDZD2

PLEKHA4

PLSCR1

PML

PNPT1

PPM1K

RASGRP3

RNF122

RNF213

RSAD2

RTP4

SAMD9

SAMD9L

SAMHD1

SECTM1

SLC15A3

SLC25A28

SP110

STAT1

STAT2

TAP1

TAP2

TDRD7

THEMIS2

TLR3

TNFSF10

TNFSF13B

TRANK1

TREX1

TRIM14

TRIM21

TRIM22

TRIM25

TRIM38

TRIM5

USP18

USP30-AS1

USP41

USP49

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ZC3HAV1

ZNF107

ZNFX1

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FB_ISG_MERSinf_consensus

Learn about heat maps in Prism

Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

ANGPTL1

APOBEC3G

APOL1

APOL2

APOL3

APOL6

ARHGAP27

BATF2

BST2

C17orf67

CASP7

CCL8

CLDN23

CMPK2

CXCL10

CXCL11

DDX58

DDX60

DDX60L

DHX58

DTX3L

EIF2AK2

EPSTI1

ETV7

FAM83H-AS1

GBP1

GBP4

GBP5

GCH1

GIMAP2

GMPR

HELZ2

HERC5

HERC6

HES4

HLA-F

IDO1

IFI16

IFI27

IFI30

IFI44

IFI44L

IFI6

IFIH1

IFIT1

IFIT2

IFIT3

IFIT5

IFITM1

IL15RA

IL22RA1

IL4I1

IL7

IRF7

IRF9

ISG15

ISG20

JAK2

LAP3

LGALS9C

LMO2

LOC200830

MASTL

MLKL

MX1

MX2

MYD88

NLRC5

NMI

OAS1

OAS2

OAS3

OASL

OGFR

PARP12

PARP14

PARP9

PDZD2

PLEKHA4

PLSCR1

PML

PNPT1

PPM1K

RASGRP3

RNF122

RNF213

RSAD2

RTP4

SAMD9

SAMD9L

SAMHD1

SECTM1

SLC15A3

SLC25A28

SP110

STAT1

STAT2

TAP1

TAP2

TDRD7

THEMIS2

TLR3

TNFSF10

TNFSF13B

TRANK1

TREX1

TRIM14

TRIM21

TRIM22

TRIM25

TRIM38

TRIM5

USP18

USP30-AS1

USP41

USP49

XAF1

ZBTB42

ZC3HAV1

ZNF107

ZNFX1

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1.378650726

MVE_ISG_treat_consensus_sorted

Learn about heat maps in Prism

Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

SAMD9L

IFI16

TNFSF10

MYD88

ETV7

C1S

HERC5

PLSCR1

OAS1

CASP1

PSMB9

IFIH1

TRIM21

BST2

IFI35

USP18

PTK2B

IL15

NLRC5

DDX60L

MX2

APOBEC3G

SP100

BATF2

NTNG2

CXCL11

TRIM14

GBP1

HERC6

HES4

IFI44L

SYNE1

OASL

APOL1

APOL2

CMPK2

CXCL10

DDX58

DTX3L

GBP2

GBP4

GBP5

GCH1

GJD3

HELZ2

HLA-F

IFIT3

IFIT5

IFITM1

IRF7

ISG15

JAK2

OAS3

ODF3B

PARP10

PARP14

PARP9

PLEKHA4

PPM1K

SAMD9

SAMHD1

SECTM1

SLC15A3

SLC25A28

STAT1

STAT2

THEMIS2

TREX1

TRIM22

TRIM25

UBE2L6

USP30-AS1

USP41

XAF1

ZNFX1

MX1

FAM83H-AS1

DHX58

PARP12

RTP4

ZC3HAV1

NMI

SP110

EIF2AK2

TMEM229B

DDX60

IFI44

CNP

IRF9

RSAD2

GMPR

OAS2

IFI27

IFI6

MLKL

SOCS1

TAP2

FAM46A

JADE2

ISG20

IFIT1

C1R

APOL6

PNPT1

IFI30

RNF213

PI4K2B

TLR3

TAP1

TDRD7

IFIT2

LAP3

EPSTI1

0hr

0.102158

0.00715

0.105813

-0.163214

0.011465

0.206561

0.149788

-0.22923

-0.060184

-0.218984

0.143559

0.320066

0.049446

-0.1458

0.171542

-0.215183

0

-0.071388

0.044496

0.092507

0.292041

-0.091696

-0.416055

0.19036

-0.838916

0.168707

-0.142282

0.035122

-0.016266

-0.170426

0.006043

0.271759

0.019443

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0.089027

0.287165

-0.560417

-0.102588

-0.128196

0.207616

-0.257511

-0.003746

-0.001237

-0.132584

-0.179424

0.137062

0.004507

-0.193138

-0.177055

0.1115

-0.245626

0.056834

0.097214

-0.202866

0.025464

-0.079907

-0.213611

-0.144267

-0.026819

-0.124684

0.265368

0.114669

-0.003309

-0.078299

0.164105

-0.027407

-0.49316

-0.080775

-0.416746

0.358391

-0.039156

-0.656849

3hr

1.312424

1.400759

0.431504

1.089735

3.455957

4.36212

1.531546

1.816601

2.526876

4.925756

1.945109

7.91562

2.003216

2.196627

1.194783

3.81075

1.285311

1.458761

1.031378

1.611237

1.803219

3.893426

1.022552

2.300237

1.222757

1.443335

1.151199

1.274711

1.770533

1.918457

2.922276

1.000579

3.094942

3.316763

0.846608

1.841635

1.606766

0.952276

6.186296

4.027593

4.961309

0.875985

1.699301

1.680624

2.724126

2.976645

2.47515

3.29478

2.401559

2.228507

1.309711

1.773043

1.336832

5.75857

4.793569

3.026118

1.104092

2.311903

0.881321

1.671789

3.601396

1.426078

1.783291

2.855858

5.2066

2.14017

0.694091

2.985456

0.54367

1.134978

3.334595

1.743532

1.868241

0.552681

0.728862

1.880622

2.543667

3.447362

1.74128

1.098848

2.065468

1.979278

2.570433

1.169984

0.91418

2.036933

2.118747

0.97975

2.840196

2.552156

0.866214

1.803467

1.197213

1.925491

1.281603

2.134516

1.201258

0.639669

1.259929

2.493889

2.255106

3.29284

1.545551

1.574728

2.856627

1.757318

1.407019

4.238516

2.38715

0.69175

1.37105

3.937903

2.173419

6hr

2.33653

2.344316

1.559661

1.599626

3.581655

4.11109

2.850996

4.498728

2.147703

5.459006

1.802596

7.985298

1.985401

2.340115

1.70007

6.303988

1.56826

2.463913

1.78171

1.8078

2.39112

4.949744

2.423487

3.015599

2.002639

1.995826

1.875783

1.872193

1.659076

3.013701

4.341193

1.552527

3.308499

4.582428

1.739816

2.339647

2.256359

1.968179

7.214522

4.81823

4.850789

1.716887

2.359604

2.520177

3.308714

4.790296

3.144275

3.785682

1.546612

2.77897

2.02354

2.679904

2.148874

6.20989

4.392053

3.596365

1.577078

3.018042

2.114797

2.718466

5.479212

2.026724

1.933981

3.669843

5.173803

1.966332

1.841431

3.377189

1.710764

2.277741

3.675475

1.862189

2.485535

1.616334

1.624494

2.666818

2.929088

3.823456

2.251716

2.362806

3.683773

3.015272

3.144336

1.743163

1.725186

2.172571

2.638175

1.932197

4.51768

2.800763

1.967854

2.70969

1.543878

1.579104

1.536355

2.375166

1.704307

1.706693

1.609267

2.106917

2.959873

4.48036

2.017491

1.819987

1.651871

1.81312

2.270585

4.359346

2.819025

1.638825

1.606975

4.782853

1.842982

24hr

1.886511

2.352973

1.080649

1.561616

5.383203

3.595345

2.308809

3.583534

1.270664

3.563841

1.023278

6.598347

1.20658

1.002825

0.647101

6.127809

0.544503

1.813796

1.165219

1.154998

0.865568

4.583246

2.029678

2.263894

1.177704

2.453916

2.388426

1.206769

0.94581

3.026673

5.256269

0.417112

2.871372

3.31934

1.665028

2.161831

1.976535

1.455114

7.380791

4.800917

2.438767

2.233859

2.418442

1.487859

2.460463

6.390765

1.708925

3.254988

1.472645

2.761813

0.59123

2.939122

1.280226

1.712867

1.985364

3.522476

1.179509

1.349289

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7.011517

1.840051

2.377525

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2.758733

2.723207

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2.2327

1.454093

2.415039

0.224377

2.175414

2.663544

3.514932

2.653496

0.849764

4.304457

2.757969

2.276571

0.659488

0.728362

1.118929

1.179938

1.098159

5.176163

2.150977

0.683651

2.637634

0.876289

1.173834

0.930216

0.85751

1.21119

1.439745

1.77594

1.408767

2.068073

2.020593

1.435048

0.775097

0.280807

1.533313

1.238979

0.81896

2.534155

0.289551

0.85089

5.186773

1.017118

MVE_ISG_MERSinf_consensus_sorted36

Learn about heat maps in Prism

Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

SAMD9L

IFI16

TNFSF10

MYD88

ETV7

C1S

HERC5

PLSCR1

OAS1

CASP1

PSMB9

IFIH1

TRIM21

BST2

IFI35

USP18

PTK2B

IL15

NLRC5

DDX60L

MX2

APOBEC3G

SP100

BATF2

NTNG2

CXCL11

TRIM14

GBP1

HERC6

HES4

IFI44L

SYNE1

OASL

APOL1

APOL2

CMPK2

CXCL10

DDX58

DTX3L

GBP2

GBP4

GBP5

GCH1

GJD3

HELZ2

HLA-F

IFIT3

IFIT5

IFITM1

IRF7

ISG15

JAK2

OAS3

ODF3B

PARP10

PARP14

PARP9

PLEKHA4

PPM1K

SAMD9

SAMHD1

SECTM1

SLC15A3

SLC25A28

STAT1

STAT2

THEMIS2

TREX1

TRIM22

TRIM25

UBE2L6

USP30-AS1

USP41

XAF1

ZNFX1

MX1

FAM83H-AS1

DHX58

PARP12

RTP4

ZC3HAV1

NMI

SP110

EIF2AK2

TMEM229B

DDX60

IFI44

CNP

IRF9

RSAD2

GMPR

OAS2

IFI27

IFI6

MLKL

SOCS1

TAP2

FAM46A

JADE2

ISG20

IFIT1

C1R

APOL6

PNPT1

IFI30

RNF213

PI4K2B

TLR3

TAP1	
TDRD7	
IFIT2	
LAP3	
EPSTI1	
	0hpi
	0.102158
	0.00715
	0.105813
	-0.163214
	0.011465
	0.206561
	0.149788
	-0.22923
	-0.060184
	-0.218984
	0.143559
	0.320066
	0.049446
	-0.1458
	0.171542
	-0.215183
	0
	-0.071388
	0.044496

0.092507

0.292041

-0.091696

-0.416055

0.19036

-0.838916

0.168707

-0.142282

0.035122

-0.016266

-0.170426

0.006043

0.271759

0.019443

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0

0.007191

0.089027

0.287165

-0.560417

-0.102588

-0.128196

0.207616

-0.257511

-0.003746

-0.001237

-0.132584

-0.179424

0.137062

0.004507

-0.193138

-0.177055

0.1115

-0.245626

0.056834

0.097214

-0.202866

0.025464

-0.079907

-0.213611

-0.144267

-0.026819

-0.124684

0.265368

0.114669

-0.003309

-0.078299

0.164105

-0.027407

-0.49316

-0.080775

-0.416746

0.358391

-0.039156

-0.656849

12hpi

-0.654861

-0.931904

-0.580642

-0.645743

-0.59863

-0.347229

-0.581873

-0.149843

-0.351229

-0.343329

0.265836

-0.677265

-1.013006

-0.197058

-0.711171

0.812114

-0.690953

-0.967796

-0.486708

0.660195

-0.675412

0.249091

-0.272232

-0.498139

-0.116273

-0.425227

-0.40915

-0.284556

-0.808314

-0.126688

-1.228026

-0.212986

1.052867

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-0.603317

-0.736731

1.537998

1.137568

0.307289

-0.209156

0.082744

-0.060058

-0.477074

-0.205268

-0.081357

-0.020426

0.885218

0.298166

0.300643

0.726188

0.749039

0.676173

0.402301

0.478378

-0.033768

-0.490128

-0.091751

-0.221989

-0.326405

0.155723

-0.246851

-0.312312

1.205381

0.365217

0.008561

0.590231

-0.629583

1.046864

-0.020784

0.011893

1.251677

0.524686

24hpi

-1.809555

-1.443733

-1.317382

-1.775704

-1.173561

-1.209378

-0.908438

-0.769337

-0.769278

-0.633201

-0.412215

-0.980432

-1.390098

-1.142718

-1.219185

-0.116779

-1.336484

-0.760398

-0.483729

-0.807681

-1.542319

-0.669324

-0.509459

-0.909044

-0.136287

-0.969201

-0.796149

-1.162061

-0.774392

-0.991845

-0.390794

-0.363151

1.001579

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-0.943395

-0.052476

0.952172

0.804458

-0.520275

-0.334048

-0.088168

-0.065862

0.423124

-0.090538

0.233041

-0.001716

0.693188

0.963116

0.358995

0.534145

0.519087

0.516485

1.512707

0.931104

0.250236

0.37246

0.501907

1.086227

0.794227

1.190238

0.083959

1.065904

0.787636

1.471869

1.690432

0.539462

1.480743

1.919365

1.130104

0.773675

1.266954

2.216659

36hpi

-1.844205

-1.808886

-1.40399

-1.308638

-1.179151

-1.166714

-1.065503

-1.032105

-0.992009

-0.981945

-0.963893

-0.940035

-0.925258

-0.87577

-0.856029

-0.811578

-0.747895

-0.700666

-0.656609

-0.591395

-0.535985

-0.467647

-0.434017

-0.424134

-0.40758

-0.36671

-0.365683

-0.311856

-0.30209

-0.275804

-0.238961

-0.225605

-0.192661

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0.066211

0.082631

0.090231

0.098218

0.155741

0.159255

0.16965

0.180825

0.203531

0.211684

0.212201

0.281732

0.373641

0.390749

0.392952

0.455376

0.466553

0.579076

0.579915

0.591142

0.608563

0.650489

0.67936

0.710581

0.710581

0.759827

1.008192

1.025923

1.076985

1.092305

1.092765

1.217362

1.377152

1.407651

1.473802

1.503225

1.562726

2.269828

48hpi

-1.751325

-1.836985

-1.000827

-0.323645

0.18963

-0.879707

0.095364

-1.195738

-0.480388

-0.429148

-0.632296

0.360006

0.57507

-0.461273

-0.110276

-1.400247

-0.462295

0.193268

0.190542

0.153562

0.228934

-0.063886

-0.932439

0.034556

0.07754

0.641645

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0.472962

0.23125

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0.666344

-2.108241

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-0.512927

1.055964

0.706223

0.683824

0.730289

1.175643

0.68227

0.626482

0.628562

-0.180932

0.103397

0.626104

-0.237968

0.33731

0.242041

0.230243

0.444493

0.25165

1.502727

0.615958

0.555051

1.27681

0.064049

1.681263

0.033717

0.00286

-0.017406

0.325959

1.087531

0.98946

0.319684

0.864709

1.994097

1.139178

0.184842

FB_ISG_treat_consensus_sorted

Learn about heat maps in Prism

Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

APOBEC3G

SECTM1

HLA-F

GMPR

APOL3

IFI30

CASP7

CLDN23

USP49

STAT1

ANGPTL1

APOL1

APOL2

APOL6

BST2

CCL8

CXCL10

CXCL11

DHX58

ETV7

FAM83H-AS1

GBP1

GBP4

GBP5

GCH1

GIMAP2

IDO1

IFI16

IL22RA1

IL4I1

IL7

LAP3

LGALS9C

LMO2

MLKL

NLRC5

NMI

OGFR

PARP14

PDZD2

PML

PPM1K

RTP4

SAMD9

SAMHD1

SLC15A3

STAT2

TAP2

THEMIS2

TLR3

TNFSF13B

TRANK1

TREX1

TRIM22

TRIM38

TRIM5

USP30-AS1

ZNF107

PARP9

DTX3L

SAMD9L

OAS2

ISG15

DDX60L

OAS3

IFITM1

IFI6

RNF122

XAF1

PLSCR1

EPSTI1

SLC25A28

IRF7

TAP1

IFIT5

IFIH1

PARP12

MASTL

HERC6

TRIM21

USP41

TDRD7

MYD88

EIF2AK2

RNF213

ZNFX1

USP18

HERC5

TRIM14

RASGRP3

IFI27

LOC200830

SP110

C17orf67

IFIT2

DDX58

IRF9

OASL

IFI44L

MX2

OAS1

CMPK2

DDX60

ISG20

PLEKHA4

PNPT1

TRIM25

IL15RA

JAK2

RSAD2

IFI44

TNFSF10

HELZ2

BATF2

IFIT1

ZC3HAV1

HES4

MX1

IFIT3

ZBTB42

ARHGAP27

0hr

0.088452

0.280967

0.029013

0.121728

0.032825

0.143999

0.121997

0.249735

0.107732

-0.125031

0

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-0.050123

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0.064514

0.029914

0.135032

0.119019

-0.302283

-0.009502

-0.074296

0.378574

0.225046

1.01004

0.019671

0.144713

-0.167152

-0.05837

0.234706

0.192915

0.103082

0.067982

0

-0.067126

0.132891

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1.96049

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1.874081

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FB_ISG_MERSinf_consensus_sorted36

Learn about heat maps in Prism

0Each value represents normalized gene expression. Go to the linked graph, and choose a Heat map. Double click on that graph to fine tune its appearance.

APOBEC3G

SECTM1

HLA-F

GMPR

APOL3

IFI30

CASP7

CLDN23

USP49

STAT1

ANGPTL1

APOL1

APOL2

APOL6

BST2

CCL8

CXCL10

CXCL11

DHX58

ETV7

FAM83H-AS1

GBP1

GBP4

GBP5

GCH1

GIMAP2

IDO1

IFI16

IL22RA1

IL4I1

IL7

LAP3

LGALS9C

LMO2

MLKL

NLRC5

NMI

OGFR

PARP14

PDZD2

PML

PPM1K

RTP4

SAMD9

SAMHD1

SLC15A3

STAT2

TAP2

THEMIS2

TLR3

TNFSF13B

TRANK1

TREX1

TRIM22

TRIM38

TRIM5

USP30-AS1

ZNF107

PARP9

DTX3L

SAMD9L

OAS2

ISG15

DDX60L

OAS3

IFITM1

IFI6

RNF122

XAF1

PLSCR1

EPSTI1

SLC25A28

IRF7

TAP1

IFIT5

IFIH1

PARP12

MASTL

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TRIM21

USP41

TDRD7

MYD88

EIF2AK2

RNF213

ZNFX1

USP18

HERC5

TRIM14

RASGRP3

IFI27

LOC200830

SP110

C17orf67

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DDX58

IRF9

OASL

IFI44L

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OAS1

CMPK2

DDX60

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TRIM25

IL15RA

JAK2

RSAD2

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HELZ2

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Fold enrichment over mock

	IFI16	
	K4	K27
26M	2.4	15.3
	0.4	1.5
	0.2	9.3
4P	0.2	0.1
	3.3	1.8
	5.1	6.3
7P	6.4	1.4
	2.5	2
	2.5	0.5

	IFI6	
	K4	K27
26M	4.1	0
	1.9	1.3
	1.6	0.1
4P	1.5	0.1
	1.2	1.2
	1.9	0
7P	xxx	0.1
	2.3	0
	4.4	0.6

	ave	**stdv**	**ave**	**stdv**
26M	**1**	**1.21655**	**8.7**	**6.91954**
4P	**2.86667**	**2.47857**	**2.73333**	**2.72091**
7P	**3.8**	**2.25167**	**1.3**	**0.75498**

	ave	**stdv**	**ave**
26M	**2.53333**	**1.36504**	**0.46667**
4P	**1.53333**	**0.35119**	**0.43333**
7P	**3.35**	**1.48492**	**0.23333**

		SMADL9			MyD88
K27		K4	K27		K4
	26M	0	xxx	26M	0.5
		0.4	2.9		0.8
		0.1	0		0.8
	4P	0.1	0.1	4P	1.1
		1.1	1.2		1.9
		1	xxx		1
	7P	0.9	10.9	7P	1.1
		1.6	4.3		1.2
		3	6.5		2.1

stdv		**ave**	**stdv**				**ave**
0.72342	**26M**	**0.16667**	**0.20817**	**1.45**	**2.05061**	**26M**	**0.7**
0.66583	**4P**	**0.73333**	**0.55076**	**0.65**	**0.77782**	**4P**	**1.33333**
0.32146	**7P**	**1.83333**	**1.06927**	**7.23333**	**3.36056**	**7P**	**1.46667**

MyD88				EPSTI1			
K4		K27			K4		K27
		2.3		26M	2.4		1.6
		1.9			4.2		0.1
		2.1			2.9		0.4
		10.6		4P	0.1		0.3
		4.1			2		2.3
		12.2			0.1		0
		17		7P	1.8		0
		16.2			2		0.1
		16.1			1.2		0.1

stdv				**ave**		**stdv**	
0.17321	**2.1**	**0.14142**		**26M**	**3.16667**	**0.92916**	**0.7**	**0.21213**
0.49329	**7.35**	**4.59619**		**4P**	**0.73333**	**1.09697**	**1.3**	**1.41421**
0.55076	**16.43333**	**0.49329**		**7P**	**1.66667**	**0.41633**	**0.06667**	**0.05774**

	RNF213	
	K4	K27
26M	1.6	0.2
	1.8	0
	1.7	0
4P	1.9	0
	1.1	1
	2.9	0
7P	14.6	0
	5.6	0.3
	6.6	1.3

	ave		**stdv**	
26M	**1.7**	**0.1**	**0.06667**	**0**
4P	**1.96667**	**0.90185**	**0.5**	**0.70711**
7P	**8.93333**	**4.93288**	**0.53333**	**0.68069**

From: Fritch, Ethan James[ejfritch@email.unc.edu]
Sent: Wed 2/26/2020 9:25:11 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: A549-ACE2 Cells

Amy,

Do you happen to know if we have A549 cells overexpressing the human ACE2 receptor frozen somewhere. I asked Boyd and Tim, but they were both unsure. If you have an inkling of a freezer box or two in the -140 where they may be I can go ahead and go diving to search for them.

Best,

Ethan J. Fritch
(570) 294-4249
PhD Candidate | Baric Laboratory
Department of Microbiology and Immunology
University of North Carolina at Chapel Hill

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Wed 2/26/2020 12:51:09 PM (UTC-08:00)

To: Sims, Amy C[amy.sims@pnnl.gov]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; 'Greg Bluemling'[gblueml@emory.edu]; Lockwood, Mark[mlockwo@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@email.unc.edu]

Subject: Nidovirus 2020 Meeting Abstract

Attachment: 20200224 NHC Nido Abstract.docx

Dear All,

See the attached abstract for the international nidovirus meeting that is happening this Summer. Sorry this is last minute, but abstracts are due this Friday. This is just the abstract for our paper that I hope to submit soon. Since we've all seen this before, comments may not be necessary unless you think they would be helpful.

Thank you for all of your help in making this story a reality.

Tim

An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and zoonotic coronavirus

Timothy P. Sheahan[1*], Amy C. Sims[1*], Shuntai Zhou[2], Rachel L. Graham[1], Collin S. Hill[2], Sarah R. Leist[1], Alexandra Schäfer[1], Kenneth H. Dinnon III[1], Stephanie A. Montgomery[3], Maria L. Agostini[4], Andrea J. Pruijssers[4], James D. Chapell[4], Ariane J. Brown[1], Gregory R. Bluemling[5,6], Mark A. Lockwood[5] , Michael G. Natchus[5] , Manohar Saindane[5] , Alexander A. Kolykhalov[5,6], George Painter[5,6,7], Ron Swanstrom[2,8] , Mark R. Denison[4], Ralph S. Baric[1,9]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC
[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC
[3]Department of Pathology & Laboratory Medicine, University of North Carolina, Chapel Hill, NC
[4]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN
[5]Emory Institute of Drug Development (EIDD), Emory University, Atlanta, GA
[6]Drug Innovation Ventures at Emory (DRIVE), Atlanta, GA
[7]Department of Pharmacology and Chemical Biology, Emory University, Atlanta, GA
[8]Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill, Chapel Hill, NC
[9]Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, Chapel Hill, NC
*Authors contributed equally.

Abstract

Coronaviruses (CoV) traffic frequently between species resulting in novel disease outbreaks, most recently exemplified by the newly emerged SARS-CoV-2. Herein, we show that the ribonucleoside analog β-D-N^4-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against SARS-CoV 2, MERS-CoV, SARS-CoV, and

related zoonotic group 2b or 2c Bat-CoVs, as well as increased potency against a coronavirus bearing resistance mutations to another nucleoside analog inhibitor. In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of the oral NHC prodrug (EIDD-2801, β-D-N^4-hydroxycytidine-5'-isopropyl ester) improved pulmonary function, and reduced virus titer and body weight loss. Decreased MERS-CoV yields *in vitro* and *in vivo* were associated with increased transition mutation frequency in viral but not host cell RNA, supporting a mechanism of lethal mutagenesis. The potency of NHC against multiple coronaviruses, its therapeutic efficacy, and oral bioavailability *in vivo*, all highlight its potential utility as an effective antiviral against SARS-CoV-2 and other future zoonotic coronaviruses.

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Wed 2/26/2020 1:51:07 PM (UTC-08:00)

To: Natchus, Michael[mnatchu@emory.edu]

Cc: Painter, George R.[george.r.painter@emory.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]

Subject: Contract that funded some of the EIDD-1931 work?

Hi Mike,

Can I have some brief details about the contract that was awarded for 1yr that covered some of the EIDD0-1931 data we aim to publish very soon. Who awarded it? Who was it awarded to? EIDD and the subcontract to UNC/Dr. Sims?

If you can send this ASAP that would be great.

Tim

From: Natchus, Michael[mnatchu@emory.edu]
Sent: Thur 2/27/2020 8:02:11 AM (UTC-08:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Cc: Painter, George R.[george.r.painter@emory.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: [External] Contract that funded some of the EIDD-1931 work?

Hi Tim,

Sorry for the sluggish response. Let me kno0w if you have any further questions and I will respond quickly. See below:

Mike

The contract was a NIAID contract, HHSN272201500008C, and it was awarded to The Emory institute for Drug Development. There were 2 subcontracts awarded to look at efficacy against Coronavirus, one to Ralph Baric at UNC, the other to Mark Denison at Vanderbilt.

From: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Date: Wednesday, February 26, 2020 at 4:51 PM
To: Z Z <mnatchu@emory.edu>
Cc: "Painter, George R." <george.r.painter@emory.edu>, Amy Sims <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: [External] Contract that funded some of the EIDD-1931 work?

Hi Mike,

Can I have some brief details about the contract that was awarded for 1yr that covered some of the EIDD0-1931 data we aim to publish very soon. Who awarded it? Who was it awarded to? EIDD and the subcontract to UNC/Dr. Sims?

If you can send this ASAP that would be great.

Tim

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If you have received this message in error, please contact the sender by reply e-mail message and destroy all copies of the original message (including attachments).

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Sun 3/1/2020 6:19:55 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Gralinski, Lisa E[lgralins@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: RE: MERS/Perk histo data!

Hi Amy, hope your doing well. Hopefully no SARS-CoV2 cases in your general area. I was wondering if you could send us the latest draft of the paper for final comments. Also, if we haven't already done so, we can begin to incorporate the pathology data ..interacting with Stephanie. Take care out there. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 10:10 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Got it. Thank you. Amy

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From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Wednesday, February 19, 2020 7:03 PM
To: Sims, Amy C; Gralinski, Lisa E; Waters, Katrina M
Subject: RE: MERS/Perk histo data!

Nat Micro
Sci Translation
Nature Communications
Cell host and Micro
PNAS

Data is good enough

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:24 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Hi Ralph and Lisa (and Katrina),

I had a chat with Katrina and Hugh today about the new data for the paper and they were very excited.

Katrina suggested that PNAS may be a good place to send the paper. I am concerned that the dataset is not comprehensive enough for Science/Nature journals.

Let me know what you think so I can revise the paper to meet all of the formatting requirements.

Thank you! Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Wednesday, February 12, 2020 at 10:07 AM

To: "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: MERS/Perk histo data!

Awesome! Freaking Awesome! Aim high Amy, Aim High! Nat Micro, Nat Med, Sci transl medicine, nature communication…..Lisa thoughts? Amy thoughts? Ralph

---

From: Gralinski, Lisa E <lgralins@email.unc.edu>
Sent: Wednesday, February 12, 2020 12:46 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Baric, Ralph S <rbaric@email.unc.edu>
Subject: MERS/Perk histo data!

Hey Amy,
I sat with Stephanie Montgomery this morning and she scored all of the males from SM126, the second drug experiment, using the system she and Tim developed for MERS. These were all D7 mice with half having gotten drug and half being sham treated. I haven't had time to make graphs yet but to summarize - we have differences!
Drug treatment led to improvement in neutrophils in the alveolar space, protein in the airspace, the overall Matute-Bello Score and DAD. We saw no changes in neutrophils in the interstitial membranes, hyaline membrane formation or septal thickening.
I will work on putting this together in a figure. Do you think you will want lung images or just quantification?
Lisa

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/2/2020 8:49:41 AM (UTC-08:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Re: Baric lab order question

Thank you. I turned my email off for my trip to Bangkok and am just now sorting through them. I will get back to you this week. Thank you for sending this. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Monday, February 24, 2020 at 8:09 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

Hi Amy,

please find attached the updated analysis
MVEs for H3K4me3 and H3K27me3
for all three donors for following ISGs:
IFI16 (down - regulated)
IFI6 (up-regulated)
SMADL9 (down-regualted)
and in addition for:
RNF213 (up-regulated)
EPSTI1 (up-regulated)
MyD88 (down-regulated)

we seem to see a similar trend in regulation with the additional ISG
however, there are definitely donor differences.

Attached is also the prism file with the ISG heatmaps for MVE and FB

hope all that will go through now

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, February 18, 2020 8:03 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Baric lab order question

Hi Alex,

I finally have access to Prism but when I download your files and try to open them I can't. If you can send them to me as pdf for now that would be great.

Maybe once you are back in the US we can figure out a way for you to send me the Prism files.

Thank you and I hope you are having a nice break. Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>

Date: Saturday, February 15, 2020 at 1:26 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

Hi Amy,

attached is a first analysis (excel) for
MVEs for H3K4me3 and H3K27me3
for all three donors for following ISGs:
IFI16 (down - regulated)
IFI6 (up-regulated)
SMADL9 (down-regualted)

- it shows the fold enrichment for each histone modification for the individual donor triplicates
- then the average for all three triplicates per donor with standard deviation

also, attached is the MVE ISG consensus list from which the ISG targets for the PCR were chosen (based on 24hpi expression)

I have results for an additional 3 ISGs: EPSTI1, MyD88, and TNF213-
that I am still in the process of analyzing

So far, it looks like ISG expression is regulated via histone modification
(e.g. IFI16 and SMADL9 expression is down-regulated with an larger H3K27me3 enrichment over mock compared to H3K4me3, respectively)
AND
e.g. IFI6 expression is up-regulated with an larger H3K4me3 enrichment over mock compared to H3K27me3, respectively)

However, there are differences among donors, so there are most likely host-dependent differences occuring

based on a first impression it looks like that this trend will hold true with further analysis of the 3 additional genes, which I am working on

Please let me know if you have any questions,
Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Thursday, February 13, 2020 6:23 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Okay. Thank you for letting me know. I appreciate it. Have a safe trip. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Thursday, February 13, 2020 at 10:37 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy,

I have been running PCR plates until late yesterday--
currently working on the analysis while I am waiting at the airport.

Will send you something after I arrive in Germany tomoorrow

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 5:37 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Thank you, Alex. This looks great. I just wanted to make sure you got the reagents you needed to do the experiments.

If you have any figures I could add to the progress report (from previous studies) that would be great. I am not entirely sure when I will need to get the science to UNC but I didn't want to bother you while you were in Germany.

Thank you again. Good luck! Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Wednesday, February 5, 2020 at 2:25 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Baric, Ralph S" <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Amy,

attached are the sequences for the PCR primers

Alex

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, February 5, 2020 5:21 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Baric lab order question

Hi Amy, Hi Ralph!

Amy,
as I emailed you a couple of weeks ago (Jan.21)- I have been very busy in the BSL3.
Today was my first day of my 10-day flight restriction; therefore I have started the MVE set, as I emailed you that I would.
I will be done with the IP part most likely by Friday (36 IP o/n samples today/36 IP o/n samples tomorrow).
As it looks I will start running PCRs on Monday and send you data and analysis for what I will have finished before I leave for Germany.

following ISGs for MVE

--- chosen by expression level at 24hpi from the transcriptomics data
downregulated (top6 most downreg.):
SAMD9L
IFI16
MyD88
TNFSF10
PTK2B
BST2
upregulated (top6 most upreg.):
EPSTI
TAP1
IFI6
IFI30
RNF213
TLR3
for the Histone ChIP-PCR

Please see below regarding the PCR primers (from the mBIO, 2014 paper):
To determine the histone modification distribution, quantitative real-time PCR was performed targeting the 5'UTR (−750 bp—TSS [region 750 base pairs upstream of the transcriptional start site]) of select genes; target and primer information is included in the supplemental material. ChIP results were reported as fold difference (or differential occupancy), allowing comparison across multiple samples. For this, each sample was normalized to the input and then the fold enrichment was calculated using the $\Delta\Delta C_T$ method. The fold difference for each gene was determined by dividing the appropriate time-matched mock by the experimental group. Finally, the fold difference values were converted to $\log_2$ and plotted. Data presented are the means ± standard errors for triplicate samples.

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 10:19 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Fwd: Baric lab order question

Alex,

Can you please update me on how things are going with the R21 experiments ? I know this week and next are it before you leave the country. Thank you.

Also can you send me the data for the endothelial cell and fibroblast ISGs for the progress report? It would be great if that data could include how you chose the targets for the ChIP studies.

Thank you. Amy

PS I hope you are doing well. I know everyone is super busy with the crazy 2019-nCoV.

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 5, 2020 7:14 AM

To: Sims, Amy C
Subject: Fwd: Baric lab order question

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:59 AM
To: Schaefer, Alexandra; Sims, Amy C
Subject: Re: Baric lab order question

Good to know we are on the same page.

Reports are do 90 days before the roll date which is June 1. The grant started a month earlier than anticipated. UNC has to submit it so I need time to get everything straight at two places.

We will be cutting it close for the report as there's also analysis after you're done.

When you have time can you send me (PNNL email address) the ISG analysis you did to arrive at your target genes? Anything else you think we can include would be great. I want to start working on the report sooner rather than later as I still am not sure what next week will be like for me here. Thank you. Amy

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From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 6:48 AM
To: Sims, Amy C; amy.sims@pnnl.gov
Subject: Re: Baric lab order question

Okay, this was my thought too!
I will go ahead and order the kits.

I will be very busy in the BSL3 for the next 10-14 days..... FACS Experiments....
- not sure I will be able to do the CHips at the same time
I will try but can't promise
I will be flying to germany on 02/13th.... so there's time to def. Do them

When is the report due?
Is it already for the R21?
Thought they were annually

Alex

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From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Tuesday, January 21, 2020 9:15:10 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>; amy.sims@pnnl.gov <amy.sims@pnnl.gov>
Subject: Re: Baric lab order question

The samples are too expensive to potentially waste on experiments that are small and might have batch effects.

Wait until you have the appropriate number of kits.

Get the kits ordered today, we can't wait any longer.

Make sure you know when the kits are coming in. I had no idea the kits would come as so many shipments that required different storage conditions so please stay on top of it. This is too complex and costly to rely just on the undergrads.

We have a report to do next month and I would really like to have some new data to put in it.

Thank you for the update. Amy

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From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Tuesday, January 21, 2020 4:46 AM
To: amy.sims@pnnl.gov
Cc: Sims, Amy C
Subject: Re: Baric lab order question

HI Amy,

We were able to finally locate the boxes with the enzyme in a 4C fridge.....

I contacted Qiagen Tech Service about the issue-
unfortunately, they can/will not guarantee that the enzymes are still fully functional after 'improper' storage at 4C for 4wks+

I could talk the lady into replacing one of the kits, which will give me 12 rxs..... she suggested to work with Jeremy for the replacement/reordering of the other 6 kits

alright, i have done the sonifications so far, but not started the actual ChIP--

just for an overview
with 12 rxs i can do

1 sample of each donor in triplicates for the 2 histone modification OR
1 sample of each donor for all 4 antibodies

I also could do
2 sample next to each other with the new enzymes AND the 4C enzymes to see if they still work
(not sure if that is the best use of the samples since I am already testing antibodies)

Or wait until we have word from Jeremy and see what he can offer

Let me know what your thoughts are,
Alex

From: Sims, Amy C <sims0018@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:17 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Okay. That is really bad news. Please keep me posted on your progress. We should be able to argue that we paid for an incomplete shipment unless they can produce shipping documents that state that we signed for the reagents.

Its possible the shipment went to the wrong place. Thank you, Amy

---

From: Schaefer, Alexandra <aschaefe@email.unc.edu>
Sent: Wednesday, January 15, 2020 11:08 AM
To: Sims, Amy C <sims0018@email.unc.edu>
Cc: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Fw: Baric lab order question

Hi Amy,

just a quick update on the ChIP-Seq kits:

We were not able to locate those little 2nd boxes of that kit, after extensively searching all freezers in all the labs.
We are currently not sure if those boxes actually arrived.

That's why Cait has contacted Jeremy and she is currently communicating with him.

I went ahead and called Tech Service to find out if I could order the reagents/contents of the missing boxes (it's mostly enzymes) separately --- they don't sell those separately--
which means we might have to order the whole kits again

So, let's hope Jeremy will come up with a better plan!!

Alex

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Wednesday, January 15, 2020 9:23 AM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: FW: Baric lab order question

Keep you posted!

Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 4:50 PM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

I'll look into this and will let you know what we can do.

Sorry I couldn't provide an easier solution for this.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Phone +1- 800-426-8157 | Fax +1-800-718-2056
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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 11:55 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hmm okay, thank you! We'll do another hunt and see if we can locate them. If not, is there a way to just order the boxes we're missing without ordering whole kits again since we have 4* box?

Thanks!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 11:22 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
From what I can see everything shipped and was delivered 12/4/2019. I attached a screenshot from our system showing the items as fully shipped. If there was an item still in limbo this area would show partially delivered.
Do I need to dig for more information for you?

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:58 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi again!

Can you actually check something for me? We are trying to determine whether half of a kit arrived or not. I have attached the shipping confirmation. We definitely have box 1 of 2 (the 4* part), but the second boxes (the 20*) with the proteinase K in them are nowhere to be found. Nobody can confirm that they arrived, so I wanted to double check that it all did ship.

Thank you!!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:19 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Thanks for letting me know!

If I can hunt anything down on my side just let me know a confirmation number and I'll get to work for you right away.

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, January 14, 2020 10:16 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy,

No worries. It wasn't the antibody kit we were looking for – she also ordered a EpiTect ChIP OneDay Kit. We had one of the two boxes that was to come in the kit and were trying to determine whether the second boxes arrived or not. But I think we have it figured out.

Thank you!!
Cait

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, January 14, 2020 at 10:13 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I just got a call from Alex in the lab about the Cat. No. 334481 EpiTect ChIP Antibody Kit and I wanted to follow-up with you about the message I sent on Dec 18, 2019 (included below). We discontinued this product in early Dec 2019 without much notice and don't have a replacement product. My side cancelled your order and refunded any invoice.

I am glad to call Alex back but I'm currently in a demo and won't be available until after 3PM so I wanted to get this to her ASAP.

I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.
Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Sent: Wednesday, December 18, 2019 9:34 AM
To: Edwards, Caitlin E <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
So I don't have the best news to relay to you this morning. I was just told the 334481 has been discontinued effective immediately and we don't have a replacement product. My side is going to cancel your order and wanted me to pass the information along.
I sincerely apologize for the fact our systems allowed for us to quote the product initially and if I can offer a freebie kit please let me know and I'll send some your way.

Please let me know if I can address anything else.

Sincerely,
Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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Germantown, MD

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:46
To: Jeremy Sanders - QIAGEN
Subject: Re: Baric lab order question

Awesome, thank you! That actually kind of is true, especially if it needs to be at a specific temperature. The university is closed Dec 24-Jan 2.

Thanks so much!!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Tuesday, December 17, 2019 at 11:44 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm pushing to get this delivered by the end of the week. I told my side the lab may not be able to accept delivery after this due to the upcoming holiday (I don't know if this is true but I'm trying to light a fire under them).

I'm hoping for a response by the end of the day.

Jeremy

Jeremy Vann Sanders

Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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19300 Germantown Road
Germantown, MD

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Get Outlook for iOS

From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Tuesday, December 17, 2019 11:33:21 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Re: Baric lab order question

Hi Jeremy!

Just wanted to check in about this order.

Thanks!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Date: Friday, December 13, 2019 at 10:09 AM
To: "Edwards, Caitlin E" <caitedw@unc.edu>
Subject: Re: Baric lab order question

Hi Cait,
I'm working on this now and will let you know as soon as I find anything about the order.
For your reference I believe this is the UNC PO:
Purchase Order Number
UNCCH.2000459643

Jeremy

Jeremy Vann Sanders
Customer Solutions Manager-North Carolina

Email: jeremy.sanders@qiagen.com

Phone: 919-412-6833

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From: Edwards, Caitlin E <caitedw@unc.edu>
Sent: Friday, December 13, 2019 10:00 AM
To: Jeremy Sanders - QIAGEN <Jeremy.Sanders@qiagen.com>
Subject: Baric lab order question

Hey Jeremy!

We are trying to determine whether all of the items from the order Amy placed while you were here at UNC helping us arrived. She has since left for her new adventure, so unfortunately I don't have the order number but was hoping you could possibly still help us. I know two of the kits came in, but the lab member who they are for mentioned that she wasn't sure if everything else arrived.

Thank you so much for your help!
Cait

Caitlin E. Edwards, MS
Research Specialist
UNC Gillings School of Public Health
caitedw@unc.edu

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Mon 3/2/2020 8:54:46 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Hi Amy,

Don't bother. That's an old draft. Old news. The paper is much different now for the better and we are about to send it in maybe tonight.

T

From: Amy Sims <amy.sims@pnnl.gov>
Date: Monday, March 2, 2020 at 11:45 AM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Re: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Hi,

I turned off my email for the Bangkok trip and I just saw this. I will get it to you by later today but I am not sure I can make the deadline with the time difference. Thank you, Amy

---

From: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Date: Saturday, February 22, 2020 at 8:36 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Zhou, Shuntai" <shuntaiz@email.unc.edu>, "Hill, Collin Siva" <collinh@live.unc.edu>, "Leist, Sarah Rebecca" <leist@email.unc.edu>, "Schaefer, Alexandra" <aschaefe@email.unc.edu>, "Agostini, Maria L K" <maria.l.agostini.1@vumc.org>, "Pruijssers, Ardina" <ardina.pruijssers@vumc.org>, "Brown, Ariane" <ajbrown7@email.unc.edu>, 'Greg Bluemling' <gblueml@emory.edu>, "Lockwood, Mark" <mlockwo@emory.edu>, "Natchus, Michael" <mnatchu@emory.edu>, "msainda@emory.edu" <msainda@emory.edu>, "a.kolykhalov@emory.edu" <a.kolykhalov@emory.edu>, "Painter, George R." <george.r.painter@emory.edu>, "Denison, Mark" <mark.denison@vumc.org>, "Swanstrom, Ronald I" <ron_swanstrom@med.unc.edu>, "Baric, Ralph S" <rbaric@email.unc.edu>, Tomas Cihlar <Tomas.Cihlar@gilead.com>, Danielle Porter <Danielle.Porter@gilead.com>, Joy Feng <Joy.Feng@gilead.com>, "Dinnon, Kenneth Harold III" <kdinnon@email.unc.edu>, "Graham, Rachel" <rlgraham@email.unc.edu>
Subject: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Dear Co-Authors,

Please see the attached paper chronicling our in vitro and in vivo efficacy of EIDD-1931 (NHC) against multiple CoV including 2019-nCoV (SARS-CoV-2) data.

1. Due to the current pandemic threat of SARS-CoV-2, we feel this paper is very timely and will be of great interest to the research community. Thus, we are aiming high and will initially submit to Nature Medicine. Because of the urgency of this situation, we will aim to submit this paper by Tuesday February 25th. Sorry for the short timeline but we feel like we need to try and ride the wave of CoV publications here. **Thus, if you would like to make comments, please do so by Monday afternoon.**

2. I've attached a Word File and a PDF of the Figures. We are over by a few hundred words in the paper. So, adding in extra verbiage is not an option unless words are taken out.
3. Please make sure that I've not missed authors and that your affiliations are correct.

Thanks!

I look forward to hearing from you.

Tim

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Mon 3/2/2020 8:54:58 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

How was the trip?

From: Amy Sims <amy.sims@pnnl.gov>
Date: Monday, March 2, 2020 at 11:45 AM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: Re: Paper Draft: Broad spectrum antiviral EIDD-1931 inhibits multiple endemic, epidemic and zoonotic coronavirus including SARS-CoV-2

Hi,

I turned off my email for the Bangkok trip and I just saw this. I will get it to you by later today but I am not sure I can make the deadline with the time difference. Thank you, Amy

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Date: Saturday, February 22, 2020 at 8:36 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Zhou, Shuntai" <shuntaiz@email.unc.edu>, "Hill, Collin Siva" <collinh@live.unc.edu>, "Leist, Sarah Rebecca" <leist@email.unc.edu>, "Schaefer, Alexandra" <aschaefe@email.unc.edu>, "Agostini, Maria L K" <maria.l.agostini.1@vumc.org>, "Pruijssers, Ardina" <ardina.pruijssers@vumc.org>, "Brown, Ariane" <ajbrown7@email.unc.edu>, 'Greg Bluemling' <gblueml@emory.edu>, "Lockwood, Mark" <mlockwo@emory.edu>, "Natchus, Michael" <mnatchu@emory.edu>, "msainda@emory.edu" <msainda@emory.edu>, "a.kolykhalov@emory.edu" <a.kolykhalov@emory.edu>, "Painter, George R." <george.r.painter@emory.edu>, "Denison, Mark" <mark.denison@vumc.org>, "Swanstrom, Ronald I" <ron_swanstrom@med.unc.edu>, "Baric, Ralph S" <rbaric@email.unc.edu>, Tomas Cihlar <Tomas.Cihlar@gilead.com>, Danielle Porter <Danielle.Porter@gilead.com>, Joy Feng <Joy.Feng@gilead.com>, "Dinnon, Kenneth Harold III" <kdinnon@email.unc.edu>, "Graham, Rachel" <rlgraham@email.unc.edu>
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1. Due to the current pandemic threat of SARS-CoV-2, we feel this paper is very timely and will be of great interest to the research community. Thus, we are aiming high and will initially submit to Nature Medicine. Because of the urgency of this situation, we will aim to submit this paper by Tuesday February 25th. Sorry for the short timeline but we feel like we need to try and ride the wave of CoV publications here. **Thus, if you would like to make comments, please do so by Monday afternoon.**
2. I've attached a Word File and a PDF of the Figures. We are over by a few hundred words in the paper. So, adding in extra verbiage is not an option unless words are taken out.
3. Please make sure that I've not missed authors and that your affiliations are correct.

Thanks!

I look forward to hearing from you.

Tim

From: Gralinski, Lisa E[lgralins@email.unc.edu]
Sent: Mon 3/2/2020 9:28:50 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: RE: MERS/Perk histo data!

Hi all,
I have the full slide scoring from Stephanie with me (I really do not think the females will show significant differences though). I am in MA now with my family and am not sure when I'll be back to NC. No photos have been taken yet but the slide box is on my desk with a printout of the infection spreadsheet. If someone else has time to take the histo photos I can recommend some slides to focus on.
Thanks,
Lisa

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 12:26 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Subject: Re: MERS/Perk histo data!

Hi Ralph,

I was in Bangkok last week for the US Japan Emerging Infectious Diseases meeting. I will get you a draft this week but I do not have the most up to date data from Lisa G or I missed her email. Lisa if you could resend it that would be great.

Thank you very much, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Sunday, March 1, 2020 at 6:20 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: RE: MERS/Perk histo data!

Hi Amy, hope your doing well. Hopefully no SARS-CoV2 cases in your general area. I was wondering if you could send us the latest draft of the paper for final comments. Also, if we haven't already done so, we can begin to incorporate the pathology data ..interacting with Stephanie. Take care out there. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 10:10 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Got it. Thank you. Amy

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From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Wednesday, February 19, 2020 7:03 PM
To: Sims, Amy C; Gralinski, Lisa E; Waters, Katrina M
Subject: RE: MERS/Perk histo data!

Nat Micro
Sci Translation
Nature Communications
Cell host and Micro
PNAS

Data is good enough

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:24 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Hi Ralph and Lisa (and Katrina),

I had a chat with Katrina and Hugh today about the new data for the paper and they were very excited.

Katrina suggested that PNAS may be a good place to send the paper. I am concerned that the dataset is not comprehensive enough for Science/Nature journals.

Let me know what you think so I can revise the paper to meet all of the formatting requirements.

Thank you! Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Wednesday, February 12, 2020 at 10:07 AM
To: "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: MERS/Perk histo data!

Awesome! Freaking Awesome! Aim high Amy, Aim High! Nat Micro, Nat Med, Sci transl medicine, nature communication.....Lisa thoughts? Amy thoughts? Ralph

---

From: Gralinski, Lisa E <lgralins@email.unc.edu>
Sent: Wednesday, February 12, 2020 12:46 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Baric, Ralph S <rbaric@email.unc.edu>
Subject: MERS/Perk histo data!

Hey Amy,
I sat with Stephanie Montgomery this morning and she scored all of the males from SM126, the second drug experiment, using the system she and Tim developed for MERS. These were all D7 mice with half having gotten drug and half being sham treated. I haven't had time to make graphs yet but to summarize - we have differences!
Drug treatment led to improvement in neutrophils in the alveolar space, protein in the airspace, the overall Matute-Bello Score and DAD. We saw no changes in neutrophils in the interstitial membranes, hyaline membrane formation or septal thickening.
I will work on putting this together in a figure. Do you think you will want lung images or just quantification?
Lisa

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 3/2/2020 9:31:34 AM (UTC-08:00)
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Subject: RE: MERS/Perk histo data!

Hi Amy, good lord I had forgotten. Hope you stayed away from anyone coughing on the plane. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 12:26 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
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Subject: RE: MERS/Perk histo data!

Nat Micro
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Cell host and Micro
PNAS

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Cc: Baric, Ralph S <rbaric@email.unc.edu>
Subject: MERS/Perk histo data!

Hey Amy,
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I will work on putting this together in a figure. Do you think you will want lung images or just quantification?
Lisa

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/2/2020 10:02:04 AM (UTC-08:00)
To: Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re:

Hi,

Just found this in my junk folder.

I can look when I get home. Do you still need this? Thank you, Amy

PS. Did you get the license for storage?

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 24, 2020 at 7:11 AM
To: "Sims, Amy C" <sims0018@email.unc.edu>
Cc: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE:

Hi Amy, thanks for the reminder on the drug license. Do you happen to have a copy of the business plan/back end pages (facilities, cvs, etc.) for Kizzie's animal model contract? I have the grant but not the back end pages in my files. As you might imagine, they have asked for an animal model contract proposal for the novel cov. Sorry to be a bother. ralph

From: Fritch, Ethan James[ejfritch@email.unc.edu]
Sent: Mon 3/2/2020 10:13:55 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: A549-ACE2 Cells

All good, thank you very much for getting back to me!

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 12:02 PM
To: Fritch, Ethan James <ejfritch@email.unc.edu>
Subject: Re: A549-ACE2 Cells

Hi,

Sorry for the delayed response. I was in Bangkok last week and turned off my email. Long story. I have never used those cells. I have no idea where they might be.

Thank you, Amy

From: "Fritch, Ethan James" <ejfritch@email.unc.edu>
Date: Wednesday, February 26, 2020 at 9:25 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: A549-ACE2 Cells

Amy,

Do you happen to know if we have A549 cells overexpressing the human ACE2 receptor frozen somewhere. I asked Boyd and Tim, but they were both unsure. If you have an inkling of a freezer box or two in the -140 where they may be I can go ahead and go diving to search for them.

Best,

Ethan J. Fritch

(570) 294-4249

PhD Candidate | Baric Laboratory

Department of Microbiology and Immunology

University of North Carolina at Chapel Hill

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 3/2/2020 10:55:02 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE:

Hi amy, don't worry about it. I solved it and found all the documents. We got it submitted …I think in the right format. Hope you had a nice meeting in Asia. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 1:02 PM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re:
Importance: High

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PS. Did you get the license for storage?

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, February 24, 2020 at 7:11 AM
To: "Sims, Amy C" <sims0018@email.unc.edu>
Cc: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE:

Hi Amy, thanks for the reminder on the drug license. Do you happen to have a copy of the business plan/back end pages (facilities, cvs, etc.) for Kizzie's animal model contract? I have the grant but not the back end pages in my files. As you might imagine, they have asked for an animal model contract proposal for the novel cov. Sorry to be a bother. ralph

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 3/2/2020 10:56:13 AM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Gralinski, Lisa E[lgralins@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: RE: MERS/Perk histo data!

Yes, its here

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 12:36 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Subject: Re: MERS/Perk histo data!

Well, there wasn't anywhere to go. Everyone but the Americans (and many of them) had on masks. No one wears them properly and everyone took them off to eat. Decided explaining why this was a bad plan wouldn't be well received.

It would appear I am more likely to get SARS-CoV2 stateside. Just keep washing those hands! Thanks, Amy

---

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, March 2, 2020 at 9:32 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: RE: MERS/Perk histo data!

Hi Amy, good lord I had forgotten. Hope you stayed away from anyone coughing on the plane. Ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 2, 2020 12:26 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Subject: Re: MERS/Perk histo data!

Hi Ralph,

I was in Bangkok last week for the US Japan Emerging Infectious Diseases meeting. I will get you a draft this week but I do not have the most up to date data from Lisa G or I missed her email. Lisa if you could resend it that would be great.

Thank you very much, Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Sunday, March 1, 2020 at 6:20 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>, "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: RE: MERS/Perk histo data!

Hi Amy, hope your doing well. Hopefully no SARS-CoV2 cases in your general area. I was wondering if you could send us the latest draft of the paper for final comments. Also, if we haven't already done so, we can begin to incorporate the pathology data ..interacting with Stephanie. Take care out there. Ralph

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 10:10 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Got it. Thank you. Amy

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From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Wednesday, February 19, 2020 7:03 PM
To: Sims, Amy C; Gralinski, Lisa E; Waters, Katrina M
Subject: RE: MERS/Perk histo data!

Nat Micro
Sci Translation
Nature Communications
Cell host and Micro
PNAS

Data is good enough

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Wednesday, February 19, 2020 8:24 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Gralinski, Lisa E <lgralins@email.unc.edu>; Waters, Katrina M <Katrina.Waters@pnnl.gov>
Subject: Re: MERS/Perk histo data!

Hi Ralph and Lisa (and Katrina),

I had a chat with Katrina and Hugh today about the new data for the paper and they were very excited.

Katrina suggested that PNAS may be a good place to send the paper. I am concerned that the dataset is not comprehensive enough for Science/Nature journals.

Let me know what you think so I can revise the paper to meet all of the formatting requirements.

Thank you! Amy

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Wednesday, February 12, 2020 at 10:07 AM
To: "Gralinski, Lisa E" <lgralins@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: MERS/Perk histo data!

Awesome! Freaking Awesome! Aim high Amy, Aim High! Nat Micro, Nat Med, Sci transl medicine, nature communication.....Lisa thoughts? Amy thoughts? Ralph

---

From: Gralinski, Lisa E <lgralins@email.unc.edu>
Sent: Wednesday, February 12, 2020 12:46 PM
To: Sims, Amy C <amy.sims@pnnl.gov>
Cc: Baric, Ralph S <rbaric@email.unc.edu>

Subject: MERS/Perk histo data!

Hey Amy,
I sat with Stephanie Montgomery this morning and she scored all of the males from SM126, the second drug experiment, using the system she and Tim developed for MERS. These were all D7 mice with half having gotten drug and half being sham treated. I haven't had time to make graphs yet but to summarize - we have differences!
Drug treatment led to improvement in neutrophils in the alveolar space, protein in the airspace, the overall Matute-Bello Score and DAD. We saw no changes in neutrophils in the interstitial membranes, hyaline membrane formation or septal thickening.
I will work on putting this together in a figure. Do you think you will want lung images or just quantification?
Lisa

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

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For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

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From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Fri 3/6/2020 1:57:20 PM (UTC-08:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Meeting next week?

Alex,

Do you have time to talk for an hour or so next week? I would like to talk about the data and figure out next steps. Thank you! Amy

From: Schaefer, Alexandra[aschaefe@email.unc.edu]
Sent: Fri 3/6/2020 2:44:43 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Meeting next week?

Hi Amy,

In general yes, but next is totally full for me....
2 Facs days in Bsl3 and then U19 face-to-face Meeting, etc.

How about early the week after?
Monday or Tuesday... i can be flexible on time so far...

Let me know what works for you,
Alex

Get Outlook for iOS

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 4:57:20 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Meeting next week?

Alex,

Do you have time to talk for an hour or so next week? I would like to talk about the data and figure out next steps.
Thank you! Amy

From: Schaefer, Alexandra[aschaefe@email.unc.edu]
Sent: Fri 3/6/2020 2:54:23 PM (UTC-08:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Meeting next week?

Okay, sounds good to me-
Talk to you then!

Have a good weekend,
Alex

Get Outlook for iOS

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 5:49:13 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

Can you do 4 to 6pm eastern on Monday, March 16th? We might not need that long but better to plan for two hours.

Thank you, Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Friday, March 6, 2020 at 2:45 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

Hi Amy,

In general yes, but next is totally full for me....
2 Facs days in Bsl3 and then U19 face-to-face Meeting, etc.

How about early the week after?
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Alex

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 4:57:20 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Meeting next week?

Alex,

Do you have time to talk for an hour or so next week? I would like to talk about the data and figure out next steps.
Thank you! Amy

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Fri 3/6/2020 2:57:19 PM (UTC-08:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Re: Meeting next week?

Great. Thank you! I just sent you a calendar invite so I have it on mine! Have a great weekend. Hope you and the family are doing well. Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Friday, March 6, 2020 at 2:54 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

Okay, sounds good to me-
Talk to you then!

Have a good weekend,
Alex

Get Outlook for iOS

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 5:49:13 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

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Thank you, Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Friday, March 6, 2020 at 2:45 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

Hi Amy,

In general yes, but next is totally full for me....
2 Facs days in Bsl3 and then U19 face-to-face Meeting, etc.

How about early the week after?
Monday or Tuesday... i can be flexible on time so far...

Let me know what works for you,
Alex

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 4:57:20 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>

Subject: Meeting next week?

Alex,

Do you have time to talk for an hour or so next week? I would like to talk about the data and figure out next steps. Thank you! Amy

From:	Schaefer, Alexandra[aschaefe@email.unc.edu]
Location:	Conference call
Subject:	Accepted: Talk to Alex Schaefer R21
Importance:	Normal
Start Time:	Mon 3/16/2020 12:00:00 PM (UTC-08:00)
End Time:	Mon 3/16/2020 2:00:00 PM (UTC-08:00)
Required Attendees:	Sims, Amy C

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Tue 3/10/2020 9:56:43 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Cc: Gully, Kendra[klgully@email.unc.edu]
Subject: ACE2 genotyping primers?

Hi Amy,

Do you know what the primer sequences are for the ACE2 genotyping?

They are called something like SEACE2TG and ANACE2TG

Tim

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Tue 3/10/2020 10:14:22 AM (UTC-07:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Cc: Gully, Kendra[klgully@email.unc.edu]
Subject: Re: ACE2 genotyping primers?

Will take me a little while to find them but I should. May also be able to direct you to where they are in my notebooks.

Older dog is sick and need time. Big me if I don't answer by tomorrow. Thank you for your patience. Amy

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Tuesday, March 10, 2020 9:57 AM
To: Sims, Amy C
Cc: Gully, Kendra
Subject: ACE2 genotyping primers?

Hi Amy,

Do you know what the primer sequences are for the ACE2 genotyping?

They are called something like SEACE2TG and ANACE2TG

Tim

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Sat 3/14/2020 10:34:48 AM (UTC-07:00)

To: Sims, Amy C[amy.sims@pnnl.gov]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; 'Greg Bluemling'[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: FW: Your Science Translational Medicine Manuscript abb5883 for Revision

Attachment: abb5883_Blinded_Review_Report_seq1_v1.pdf

Dear Co-Authors,

The reviews came back from Science Translations Med on our EIDD-1931/NHC paper. They are pretty positive. We are going to come up with a path forward in the next 24-48hr. What the reviewers and editors need to understand is the urgency of this work.

Tim

On 3/13/20, 6:43 PM, "Lindsey Pujanandez" <scitranslmededitors@aaas.org> wrote:

13-Mar-2020

Dear Dr. Sheahan:

Manuscript number: abb5883

Thank you for sending us your manuscript "An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus."

Our review of your paper is now complete. We are potentially interested in publishing it as a Research Article, but we cannot accept it in its present form. We would like to invite you to revise the manuscript and then return it to us. To view your reviews and other documents related to your revision, log in to your account at the Science Journals Manuscript Submission and Information Portal at https://cts.sciencemag.org. You can access your files by clicking on the Action button to the right of the paper's listing in your task list. Navigate to the Manuscript Document tab in the manuscript record where the files can be downloaded.

The following aspects of the paper need to be addressed in the revision.

1. ADDRESS REVIEWERS' COMMENTS (see Review Report file). Please revise your manuscript in accord with the referees' comments. When you return the manuscript to us, include a point-by-point response explaining how you have addressed each of the reviewers' comments.

2. ADDRESS EDITOR'S COMMENTS (see combined PDF). Please address follow all of the instructions from me on the marked version of the paper and on the Revision Checklist.

3. FORMAT (see instructions in the Revision Checklist file). Carefully follow the formatting instructions for your revised manuscript and figures. The format for revised papers is different than that for initial submission.

4. FIGURES. It is very important that you provide high resolution, correctly sized figures with type and symbols that are correctly styled and that will be visible in the final published version of the paper. Red and green should not be used

together.

Returning your revised manuscript. Prepare your revised manuscript documents and a cover letter with your point-by-point response to the referees' comments. Return your revised manuscript documents by uploading them through your account at our Manuscript Submission and Information Portal at https://cts.sciencemag.org.

Authorship, Conflict of Interest, and License forms. Science Translational Medicine requires information verifying authorship, conflicts of interest, and several other conditions of acceptance from every author on a manuscript. We must have this information from all authors before we can accept your paper. We also require first and corresponding authors to provide their ORCID numbers. You and each co-author will receive an email with instructions about how to go to our Manuscript Submission and Information Portal to enter this information and agree to our publication license.

If your paper is accepted and published, note that there will be a processing fee of $300 for each figure. We will, however, provide a free electronic reprint URL that can be posted on your website to give unrestricted access to your paper. Information about this service will be sent to you by email a few days after publication.

In order for your paper to be considered an active submission, we must receive your revision within one month of your receipt of this letter. If you cannot complete your revisions within that time, please contact me to discuss.

If your paper involves a method that would benefit from the publication of a step-by-step protocol (e.g., https://protect2.fireeye.com/v1/url?k=70ccaa42-2c7995fb-70cc8057-0cc47adc5fce-1b86bfa41923787c&q=1&e=b8114f06-d19c-41e0-8a64-c8fc027fa70e&u=https%3A%2F%2Fbio-protocol.org%2Fe2339) and you would be interested in submitting one to Bio-protocol, which curates high-quality life science protocols, please contact Bio-protocol (https://protect2.fireeye.com/v1/url?k=2825a772-749098cb-28258d67-0cc47adc5fce-99a6395747028a55&q=1&e=b8114f06-d19c-41e0-8a64-c8fc027fa70e&u=https%3A%2F%2Fbio-protocol.org%2Flogin.aspx%3Fin%3D1) who can advise further. This will not delay the processing of your paper at Science Translational Medicine.

I look forward to reading your revised manuscript. Please let me know if you cannot access the files uploaded to our website or if I can otherwise be of assistance.

Sincerely,

Lindsey Pujanandez, Ph.D.
Associate Editor
Science Translational Medicine
lpujanandez@aaas.org

Reviewer: 1

Review: An orally broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus (Sheahan et al., 2020)

In this present global crisis of SARS-CoV-2, there is a great need for therapeutics to lower transmission events and diminish global morbidity and mortality. In this manuscript, Sheahan and Sims et al. demonstrate that the ribonucleoside analog beta-D-N4-hydroxycytidine (NHC), administered using its orally bioavailable prodrug EIDD-2801, has a broad-spectrum antiviral effect against SARS-CoV, MERS-CoV, SARS-CoV-2 as well as several bat coronaviruses. Based on both past studies and work shown here, the authors demonstrate that EIDD-2801 induces hypermutation of the genome in a concentration dependent manner. This mode of action is distinct from remdesivir, another proposed antiviral for SARS-CoV-2, which is reported to act as a chain terminator for viral RNA synthesis. The authors show hat in human lung cultures and mice infected with a related coronavirus, that mutation rates in the virus correlated with a decrease in infectious virus titers as well as an increase in the frequency of nonsynonymous mutations. Off target effects were not found by investigating the mutation frequency of ISG15 mRNA, an interferon induced gene that is significantly upregulated upon infection. This mechanism of action is likely to be accurate as this same compound has also been found to be effective against a broad spectrum of unrelated viruses suggesting that RNA dependent RNA polymerases readily recognize and incorporate this nucleotide during the process of replication.

Given the need for an antiviral against SARS-CoV-2, this paper is certainly important. However, it is important to note that the in vivo studies presented in this manuscript are limited to mice and really only show effectiveness when EIDD-2801 is given prior to challenge or shortly thereafter. While the authors mention that the virus life cycle in mice is compressed, this reviewer finds it misleading to describe it as a therapeutic in the abstract.

A more minor comment that this reviewer feels is lacking in this manuscript concerns Ribavirin. Similar to EIDD-2801, Ribavirin is a nucleoside analog and can be used as a broad spectrum antiviral that functions by the induction of hypermutation. This reviewer finds it interesting that past work (see Ferron et al, PNAS 2018) has demonstrated that the proof reading capacity of coronaviruses prevents its effectiveness. Can the authors comment on how EIDD-2801 may differ from Ribaviran in this way? Moreover, administration of Ribavirin commonly induced vomiting, stomach pain, nausea, and headache amongst other things which is why it is rarely clinically used. If EIDD-2801 were to be used prophylactically, can the authors comment on whether any of these symptoms are also likely to be evident?

Minor additional comments

This reviewer is somewhat dubious about the stats in Figure 5 and 6: the star just indicates differences. I appreciate that it is difficult to show stars for so many multiple comparisons,

but that gives the reader a whole confused reading of the figure in my opinion, especially since not all of them are different to each other.

Line 216: the authors claim that body weight loss with treatment 48hpi was different at 4dpi in Fig 5A, but that doesn't look right from the figure.

Reviewer: 2

Sheahan and colleagues have presented a study on the broad spectrum anti-coronavirus activity of β-D-N4-hydroxycytidine (NHC, EIDD-1931) both in vitro and in vivo. The authors have provided a thorough characterization of NHC against multiple coronaviruses. This is obviously a timely study given the current pandemic of SARS-CoV-2 and continued circulation of MERS-CoV.

Overall, the study is quite well presented for the activities of NHC both in vitro and in vivo. While the data is quite strong for both MERS- and SARS-CoV, it did feel as if the SARS-CoV-2 data had been added to the manuscript fairly randomly. While the importance of data for SARS-CoV-2 data is important, the addition of the antiviral activity data in Vero cells felt somewhat misplaced in the results given that there was little to no justification for why Vero cells were used in contrast to either the Calu cells or HAEs. Unless the authors can provide a clear justification for not testing the effectiveness of NHC against SARS-CoV-2 in at least the Calu cells, it would be questionable as to what value this data has in the current manuscript. Further, given the timeliness of this paper with the current pandemic, it would be beneficial to perform these experiments.

Additional comments:

1. Line 196: Was the decrease in lung hemorrhage only signficant at this high dose? If so, what does that suggest in terms of limitations for the lower doses? In addition, it appeared that lung hemorrhage was significantly reduced at all tested EIDD-2801 concentrations against MERS-CoV in contrast to SARS-CoV where only the highest concentration resulted in this. It would be good for the authors to comment on this potential discrepancy.

2. Line 331: please use SARS-CoV-2 as per prior usage in the paper.

3. Lines 384-397: There is no information provided for SARS-CoV-2 in this section (where was it obtained from?).

4. In the HAE model, the cells are tracheobronchial cells. Would the authors postulate any differences had they used alveolar epithelial cells?

5.Prior analysis by Davis and Chertow (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4409941/) suggested removal of mucous as a requirement for long-term culturing and differentiation of NHBECs on transwells. Did the authors mimic this and if not, would they postulate any implications for not doing this?

From: Denison, Mark[mark.denison@vumc.org]

Sent: Sat 3/14/2020 10:39:22 AM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; 'Greg Bluemling'[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: Re: Your Science Translational Medicine Manuscript abb5883 for Revision

Thanks, Tim

I echo this 100%. The work is important, the need great.
Personally I think there were trivial concerns in the review that were "business as usual" and that did not recognize the urgency.
All of us in clinical ID are feeling the increasing urgency of this.

I would love to see this turned around in a very short time.
I encourage all to take time today to respond Tim with your comments. I think we can all get comments thoughts back to you in 24 hours.

Mark

On 3/14/20, 12:35 PM, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu> wrote:

Dear Co-Authors,

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13-Mar-2020

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Manuscript number: abb5883

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Our review of your paper is now complete. We are potentially interested in publishing it as a Research Article, but we cannot accept it in its present form. We would like to invite you to revise the manuscript and then return it to us. To view your reviews and other documents related to your revision, log in to your account at the Science Journals Manuscript Submission and Information Portal at https://protect2.fireeye.com/v1/url?k=fa5e1a57-a6eb2498-fa5e3042-0cc47adc5e60-fccf2014341611a3&q=1&e=65d71337-ed08-4bba-99cb-2e1b7a9627fb&u=https%3A%2F%2Fnam05.safelinks.protection.outlook.com%2F%3Furl%3Dhttps%253A%252F%252Fcts.sciencemag.org%26amp%3Bdata%3D02%257C01%257Cmark.denison%2540vumc.org%257Ce8fd59040bbd461e312b08d7c83e0072%257Cef57503014244ed8b83c12c533d879ab%257C0%257C0%257C637198041059658288%26amp%3

Bsdata%3DpyihinqhlNrnI%252BpS167XNxlBTrwBgqMe8S3SnoO0rBg%253D%26amp%3Breserved%3D0. You can access your files by clicking on the Action button to the right of the paper's listing in your task list. Navigate to the Manuscript Document tab in the manuscript record where the files can be downloaded.

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Sincerely,

Lindsey Pujanandez, Ph.D.
Associate Editor
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Sent: Sat 3/14/2020 10:56:43 AM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Cc: Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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Sent: Sat 3/14/2020 11:10:14 AM (UTC-07:00)

To: Zhou, Shuntai[shuntaiz@email.unc.edu]

Cc: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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George

George Painter, M.S., Ph.D

Professor of Pharmacology, Emory University, School of Medicine
Director, Emory Institute for Drug Development |EIDD
Section Head, Yerkes National Primate Center
CEO, Drug Innovation Ventures at Emory |DRIVE

954 Gatewood Rd. NE |Atlanta, GA,USA 30329

Voice: +1-404-712-6886
email: grpaint@emory.edu

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From: Hill, Collin Siva[collinh@live.unc.edu]

Sent: Sat 3/14/2020 12:59:02 PM (UTC-07:00)

To: Painter, George R.[george.r.painter@emory.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]

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Subject: Re: [External] Re: Your Science Translational Medicine Manuscript abb5883 for Revision

Attachment: MERS-CoV In Vitro - NHC, RBV, and FAV.pzfx

Attachment: La Crosse Virus.pzfx

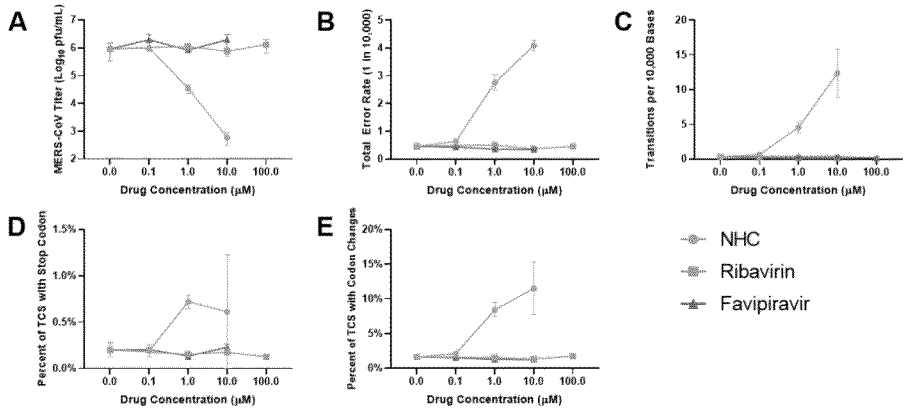
Hi Tim,

Thank you for sharing the feedback.

I'm in agreement with what Shuntai said. We did not see any significant antiviral or mutagenic effects of ribavirin on MERS-CoV or Zika virus. We did observe some mutagenic effects caused by ribavirin on La Crosse virus, however it was only at the highest dosage concentration of 100 uM and it only increased the mutation rate modestly, on par with NHC at a dosage concentration of 1.0 uM (See attached Prism files and photos)

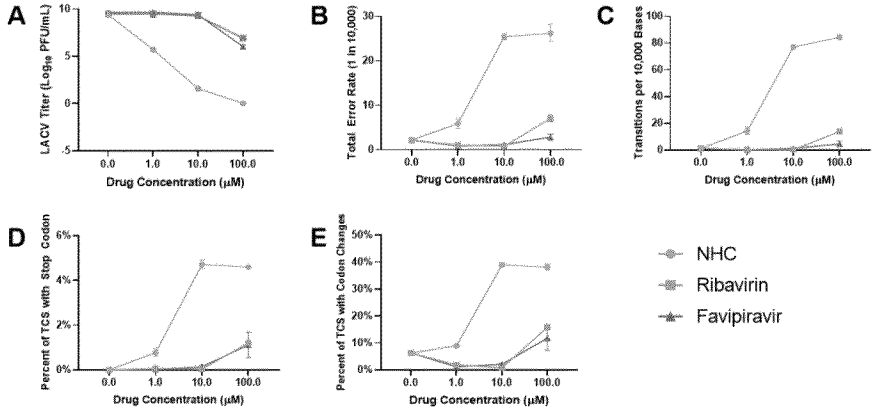
Hope this helps,
Collin

Figure 1. MERS-CoV Drug Panel Antiviral Activity and Mutagenic Effects



Panel A: MERS-CoV titer as determined from nanoluciferase assay. Panel B: Total error rate (error per 10,000) of NSP12 primer region of MERS-CoV under different compound and concentration conditions. Panel C: Cytidine to uracil (C to U) transition error rate (per 10,000) of NSP12 primer region of MERS-CoV in the drug panel. Panel D: Percent of template consensus sequences (TCS) with a change in codon to UAG, UAA, an UGA (stop codons) within the NSP12 primer region of MERS-CoV. Panel E: Percent of TCS with a change in codon (other than stop codons) within the NSP12 primer region of MERS-CoV. For all panels, the error bars indicate the range of each data set.

Figure 4. La Crosse Virus Drug Panel Antiviral and Mutagenic Effects



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>> Thank you for sending us your manuscript "An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus."
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>>
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>>

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>>
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>> <abb5883_Blinded_Review_Report_seq1_v1.pdf>

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Project info 1

Experiment Date
2020-01-18

Experiment ID

Notebook ID

Project

Experimenter

Protocol

Project info 1

Experiment Date
2020-01-18

Experiment ID

Notebook ID

Project

Experimenter

Protocol

NSP10 Total Error

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (mM)	NHC	Favipiravir
0	0.70518733	0.70518733
0.1	1.118265215	0.520434358
1	4.501517252	
10	3.700766587	
100	0.706114956	
	0.961475125	
	3.143350447	
	4.668352461	

0.897505554

0.657441989

0.706114956

0.628432062

0.609618128

0.707410579

Ribavirin

0.70518733

0.854345052

0.608461767

0.819768392

0.706114956

0.725877264

0.643746793

0.686712963

NSP12 Total Error

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.472102727

0.656446877

3.030759047

3.893813418

0.461084205

0.610702316

2.482511486

4.281432853

Favipiravir

0.472102727

0.376167717

0.413616472

0.329226395

0.461084205

0.494909708

0.296586228

0.367300395

Ribavirin

0.472102727

0.489732139

0.423184332

0.454154252

0.461084205

0.524976013

0.31494896

0.457047079

NSP14 Total Error

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.893200592

1.248758337

3.523309301

3.998001

0.931966449

1.089147298

4.24183209

6.085192698

Favipiravir

0.893200592

0.712581715

0.709322758

0.716906247

0.931966449

0.60845756

0.644406621

0.664994943

Ribavirin

0.893200592

0.621310966

0.722471025

0.752152181

0.931966449

0.677528703

0.62115259

0.737401949

NSP10 C->T

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (μM)	NHC	Favipiravir
0	0.291535382	0.180840002
0.1	0.770100134	0.843487555
1	4.632042152	3.850141974
10	7.61614623	4.670278349
100		

0.291535382

0.112319797

0.511892417

0.269501999

0.180840002

0.233513917

0.23347156

0.186646791

Ribavirin

0.291535382

0.705533736

0.132810062

0.331728505

0.180840002

0.312334073

0.224004301

0.37097798

NSP12 C->T

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.401962423

0.641909998

5.379770892

8.909252896

0.288237046

0.688009444

3.731865466

15.86042823

Favipiravir

0.401962423

0.118316125

0.141126329

0.150657512

0.288237046

0.323537092

0.13232446

0.20253985

Ribavirin

0.401962423

0.348072627

0.373604204

0.074958398

0.288237046

0.341366833

0.264717561

0.314649873

NSP14 C->T

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.524057313

1.456943486

5.758710049

8.270321361

1.196849023

1.408724013

6.610378294

3.196930946

Favipiravir

0.524057313

0.622582913

0.60979328

0.387979972

1.196849023

0.529093531

0.750691077

0.582272142

Ribavirin

0.524057313

0.290863399

0.535041075

0.484959781

1.196849023

0.489711968

0.554145563

0.522994317

NSP10 G->A

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.436377238

1.022153736

3.934402776

3.136516898

0.377026518

0.69930861

3.567562747

3.462004501

Favipiravir

0.436377238

0.182133249

0.260112246

0.416203393

0.377026518

0.291274417

0.266259733

0.415075065

Ribavirin

0.436377238

0.33898223

0.276890702

0.430334042

0.377026518

0.39359824

0.394370875

0.534722594

NSP12 G->A

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.216891149

0.538362767

2.167406813

1.505570611

0.176795803

0.448747525

2.41747731

0

Favipiravir

0.216891149

0.248816566

0.222589495

0.220649388

0.176795803

0.236922342

0.151786815

0.233446493

Ribavirin

0.216891149

0.162202359

0.155981095

0.315272178

0.176795803

0.220261083

0.127576169

0.283586878

NSP14 G->A

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

0.24079881

1.098133174

3.480837543

0

0.472170283

0.890683932

4.498572192

5.549389567

Favipiravir

0.24079881

0.381427046

0.396940909

0.283568281

0.472170283

0.34440994

0.229956423

0.467465654

Ribavirin

0.24079881

0.176713235

0.357211748

0.252545093

0.472170283

0.247935933

0.336669568

0.491746229

NSP10 TCS

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

4415

4757

1026

117

2190

8921

2263

106

Favipiravir

4415

3526

5996

7715

2190

11024

5513

7957

Ribavirin

4415

3789

2982

4477

2190

7925

4420

2402

NSP12 TCS

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

4873

10118

1763

162

3219

19929

1547

13

Favipiravir

4873

5228

10227

4790

3219

4461

8570

13234

Ribavirin

4873

6516

4691

4126

3219

3322

7010

4587

NSP14 TCS

Drug Concentration (
m

M)

0

0.1

1

10

100

Drug Concentration (
m

M)

0

0.1

1

10

100

NHC

3526

5670

1057

92

1998

11651

1447

34

Favipiravir

3526

2968

5704

5323

1998

6574

4923

7467

Ribavirin

3526

3737

2641

3362

1998

5327

3923

2494

Luciferase Assay

0

0.1

1

10

100

0

0.1

1

10

100

Ribavirin

1500000

800000

500000

1980000

335000

1450000

1000000

630000

Favipirivir

1500000

867000

900000

925000

335000

3080000

775000

3030000

NHC

1500000

750000

47500

300

335000

1230000

22500

875

Data 16

0.0

0.1

1.0

10.0

100.0

NSP10 - NHC

0.70518733

1.118265215

4.501517252

3.700766587

0.706114956

0.961475125

3.143350447

4.668352461

NSP10 - Favipiravir

0.70518733

0.520434358

0.897505554

0.657441989

0.706114956

0.628432062

0.609618128

0.707410579

NSP10 - Ribavirin

0.70518733

0.854345052

0.608461767

0.819768392

0.706114956

0.725877264

0.643746793

0.686712963

NSP12 - NHC

0.472102727

0.656446877

3.030759047

3.893813418

0.461084205

0.610702316

2.482511486

4.281432853

NSP12 - Favipiravir

0.472102727

0.376167717

0.413616472

0.329226395

0.461084205

0.494909708

0.296586228

0.367300395

NSP12 - Ribavirin

0.472102727

0.489732139

0.423184332

0.454154252

0.461084205

0.524976013

0.31494896

0.457047079

NSP14 - NHC

0.893200592

1.248758337

3.523309301

3.998001

0.931966449

1.089147298

4.24183209

6.085192698

NSP14 - Favipiravir

0.893200592

0.712581715

0.709322758

0.716906247

0.931966449

0.60845756

0.644406621

0.664994943

NSP14 - Ribavirin

0.893200592

0.621310966

0.722471025

0.752152181

0.931966449

0.677528703

0.62115259

0.737401949

NSP10 Stop Codon Change

0.0

0.1

1.0

10.0

100.0

NHC

0.04530011

0.10510826

0.58479532

0

0

0.03362852

0.30932391

0

Ribavirin

0.04530011

0.05278438

0.03353454

0.08934554

0

0.0126183

0.04524887

0

Favipiravir

0.04530011

0

0.05003336

0.02592353

0

0.02721335

0.01813894

0.03770265

NSP10 Non-stop Codon Change

0.0

0.1

1.0

10.0

100.0

NHC

1.0419026

2.22829514

9.06432749

9.4017094

1.23287671

1.73747338

7.24701723

12.2641509

Ribavirin

1.0419026

1.92662972

0.67069081

1.47420147

1.23287671

1.13564669

0.70135747

1.45711907

Favipiravir

1.0419026

0.70901872

1.38425617

0.99805574

1.23287671

0.78011611

0.81625249

1.1687822

NSP14 Stop Codon Change

0.0

0.1

1.0

10.0

100.0

NHC

0.0567215

0.15873016

0.75685904

0

0.05005005

0.15449318

1.10573601

2.94117647

Ribavirin

0.0567215

0.0802783

0

0.1784652

0.05005005

0.05631688

0.10196278

0.16038492

Favipiravir

0.0567215

0

0.03506311

0.09393199

0.05005005

0.04563432

0.04062563

0.05356904

NSP14 Non-Stop Codon Change

0.0

0.1

1.0

10.0

100.0

NHC

2.1554169

2.91005291

8.89309366

6.52173913

1.3013013

2.80662604

9.46786455

11.7647059

Ribavirin

2.1554169

1.76612256

1.70390004

1.51695419

1.3013013

1.55810024

1.35100688

1.88452285

Favipiravir

2.1554169

1.44878706

2.0687237

1.70956228

1.3013013

1.23212656

1.09689214

1.82134726

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FPXdhsuTJxsbatP32fi9OwusZcr9z3GKfM0h23GK7z1GUc5lovECye4Njk6konyQE80qt1nt
dnkL3ck9simmw9sNO253s0aMGQV9jyxfYYp2w8HLmbU+stWQ6/2KUJRzBdL36rJii1U+3rhE
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Project info 1

Experiment Date
2020-01-21

Experiment ID

Notebook ID

Project

Experimenter

Protocol

Total Error Rates L7

0.0

1.0

10.0

100.0

NHC

2.2

7

26.1

26

4.8

24.7

28.2

24.3

Ribavirin

2.2

1.7

0.8

7.9

0.4

0.8

6.2

Favipiravir

2.2

0.9

1.2

2.2

0.8

1.2

3.5

C to T L7

0.0

1.0

10.0

100.0

NHC

1.3

17

78.2

82.4

11.4

75.9

86.1

Ribavirin

1.3

0.8

0.2

15.9

0

0.3

11.8

Favipiravir

1.3

0.1

1.3

2.6

0.1

1.2

6.7

TCS with Stop codon

0.0

1.0

10.0

100.0

NHC

0

0.95565749

4.52457088

4.55116133

0.600699

4.9157128

4.64874961

Ribavirin

0

0.0969368

0.04378284

1.19646757

0.0410509

0.02926544

1.22149381

Favipiravir

0

0

0.07194245

0.54139125

0.03557453

0.21744383

1.69068736

TCS with other codon changes

0.0

1.0

10.0

100.0

NHC

6.34146341

9.72859327

38.2511854

36.9821092

8.27872433

39.7960458

39.2964616

Ribavirin

6.34146341

2.88483908

0.74430823

16.1997911

1.02627258

0.87796313

15.6076652

Favipiravir

6.34146341

1.32450331

1.72661871

7.28045326

1.13838492

2.5851655

16.4045177

NHC Mutagenic Profile

A -> U

0

0.1

0.1

A -> C

0

0.1

0

A -> G

10.4

6.6

7.2

U -> A

0

0.1

0.1

U -> C

3.7

5.8

6.4

U -> G

0

0.3

0.2

C -> A

0

0.1

0.2

C -> U

74

71.4

68.3

C -> G

0

0.1

0.1

G -> A

48.9

30.9

33.4

G -> U

1.2

0.1

0.1

G -> C

0

0.1

0.1

Total

26

20.2

20.9

Ribavirin Mutagenic Profile

A -> U

0.1

0.1

A -> C

0

0

A -> G

0.9

1.3

U -> A

0.1

0

U -> C

0.4

0.5

U -> G

0.7

0.2

C -> A

0.3

0.2

C -> U

15.4

13.5

C -> G

0

0.1

G -> A

18.6

17.7

G -> U

0.2

0.1

G -> C

0

0.1

Total

7.3

6.8

Favipiravir Mutagenic Profile

A -> U

0.1

0.2

A -> C

0

0

A -> G

1.6

2.6

U -> A

0.1

0.1

U -> C

0.7

1

U -> G

0.2

0.2

C -> A

0.3

0.1

C -> U

6.7

18.4

C -> G

0

0

G -> A

6.9

17.5

G -> U

0.1

1

G -> C

0

0.1

Total

3.5

8.2

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AAAA//8DAJz0qGk=

From: Baric, Ralph S[rbaric@email.unc.edu]

Sent: Sat 3/14/2020 1:43:13 PM (UTC-07:00)

To: Zhou, Shuntai[shuntaiz@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Cc: Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: RE: Your Science Translational Medicine Manuscript abb5883 for Revision

Shuntai, that's a great idea. Can you pass it on to Tim! Thanks, ralph

-----Original Message-----
From: Zhou, Shuntai <shuntaiz@email.unc.edu>
Sent: Saturday, March 14, 2020 1:57 PM
To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Cc: Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Greg Bluemling <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; msainda@emory.edu; a.kolykhalov@emory.edu; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
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Dear Tim

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Shuntai

> On Mar 14, 2020, at 1:34 PM, Sheahan, Timothy Patrick <sheahan@email.unc.edu> wrote:
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>
> 13-Mar-2020
>

> Dear Dr. Sheahan:
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> Manuscript number: abb5883
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> Thank you for sending us your manuscript "An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus."
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> Our review of your paper is now complete. We are potentially interested in publishing it as a Research Article, but we cannot accept it in its present form. We would like to invite you to revise the manuscript and then return it to us. To view your reviews and other documents related to your revision, log in to your account at the Science Journals Manuscript Submission and Information Portal at https://cts.sciencemag.org. You can access your files by clicking on the Action button to the right of the paper's listing in your task list. Navigate to the Manuscript Document tab in the manuscript record where the files can be downloaded.
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> The following aspects of the paper need to be addressed in the revision.
>
> 1. ADDRESS REVIEWERS' COMMENTS (see Review Report file). Please revise your manuscript in accord with the referees' comments. When you return the manuscript to us, include a point-by-point response explaining how you have addressed each of the reviewers' comments.
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> 2. ADDRESS EDITOR'S COMMENTS (see combined PDF). Please address follow all of the instructions from me on the marked version of the paper and on the Revision Checklist.
>
> 3. FORMAT (see instructions in the Revision Checklist file). Carefully follow the formatting instructions for your revised manuscript and figures. The format for revised papers is different than that for initial submission.
>
> 4. FIGURES. It is very important that you provide high resolution, correctly sized figures with type and symbols that are correctly styled and that will be visible in the final published version of the paper. Red and green should not be used together.
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> In order for your paper to be considered an active submission, we must receive your revision within one month of your receipt of this letter. If you cannot complete your revisions within that time, please contact me to discuss.
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> If your paper involves a method that would benefit from the publication of a step-by-step
> protocol (e.g., https://protect2.fireeye.com/v1/url?k=47d0c46c-1b65fbd5-47d0ee79-0cc47adc5fce-e8728d9b4678990c&q=1&e=3caeb769-937f-4b09-a8c8-eb1f495ab2b4&u=https%3A%2F%2Fbio-protocol.org%2Fe2339) and you would be interested in submitting
> one to Bio-protocol, which curates high-quality life science protocols, please contact Bio-protocol (https://protect2.fireeye.com/v1/url?k=35c21660-697729d9-35c23c75-0cc47adc5fce-ddd753049e8d0695&q=1&e=3caeb769-937f-4b09-a8c8-eb1f495ab2b4&u=https%3A%2F%2Fbio-protocol.org%2Flogin.aspx%3Fin%3D1) who can advise further. This will not delay the processing of your paper at Science Translational Medicine.
>
> I look forward to reading your revised manuscript. Please let me know if you cannot access the files uploaded to our website or if I can otherwise be of assistance.
>
> Sincerely,
>

> Lindsey Pujanandez, Ph.D.
> Associate Editor
> Science Translational Medicine
> lpujanandez@aaas.org
>
> <abb5883_Blinded_Review_Report_seq1_v1.pdf>

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Sat 3/14/2020 2:18:29 PM (UTC-07:00)

To: Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]

Cc: Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: Re: Your Science Translational Medicine Manuscript abb5883 for Revision

Attachment: 20200302 NHC Draft 5 Final Figs Embeded.pdf

Attachment: 20200302 NHC Draft 5 Final Figs Embeded.docx

Just so everyone is on the same page. I've attached the final version of the paper. The figures are embedded in the back.

T

On 3/14/20, 4:43 PM, "Baric, Ralph S" <rbaric@email.unc.edu> wrote:

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>
> Returning your revised manuscript. Prepare your revised manuscript documents and a cover letter with your point-by-point response to the referees' comments. Return your revised manuscript documents by uploading them through your account at our Manuscript Submission and Information Portal at https://cts.sciencemag.org.
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> If your paper is accepted and published, note that there will be a processing fee of $300 for each figure. We will, however, provide a free electronic reprint URL that can be posted on your website to give unrestricted access to your paper. Information about this service will be sent to you by email a few days after publication.
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> In order for your paper to be considered an active submission, we must receive your revision within one month of your receipt of this letter. If you cannot complete your revisions within that time, please contact me to discuss.
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> If your paper involves a method that would benefit from the publication of a step-by-step
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> one to Bio-protocol, which curates high-quality life science protocols, please contact Bio-protocol

(https://protect2.fireeye.com/v1/url?k=ecc48422-b071bb9b-ecc4ae37-0cc47adc5fce-385e61ec03a8563e&q=1&e=4323948b-2128-448a-8a34-4e05b50c4894&u=https%3A%2F%2Fbio-protocol.org%2Flogin.aspx%3Fin%3D1) who can advise further. This will not delay the processing of your paper at Science Translational Medicine.

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> I look forward to reading your revised manuscript. Please let me know if you cannot access the files uploaded to our website or if I can otherwise be of assistance.

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> Sincerely,

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> Lindsey Pujanandez, Ph.D.
> Associate Editor
> Science Translational Medicine
> lpujanandez@aaas.org

>

> <abb5883_Blinded_Review_Report_seq1_v1.pdf>

An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus

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Abstract (153)

Coronaviruses (CoVs) traffic frequently between species resulting in novel disease outbreaks, most recently exemplified by the newly emerged SARS-CoV-2. Herein, we show that the ribonucleoside analog β-D-N[4]-hydroxycytidine (NHC, EIDD-1931) has broad spectrum antiviral activity against SARS-CoV 2, MERS-CoV, SARS-CoV, and

related zoonotic group 2b or 2c Bat-CoVs, as well as increased potency against a coronavirus bearing resistance mutations to another nucleoside analog inhibitor. In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801, an orally bioavailable NHC-prodrug (□-D-N^4-hydroxycytidine-5'-isopropyl ester), improved pulmonary function, and reduced virus titer and body weight loss. Decreased MERS-CoV yields *in vitro* and *in vivo* were associated with increased transition mutation frequency in viral but not host cell RNA, supporting a mechanism of lethal mutagenesis. The potency of NHC/EIDD-2801 against multiple coronaviruses, its therapeutic efficacy, and oral bioavailability *in vivo*, all highlight its potential utility as an effective antiviral against SARS-CoV-2 and other future zoonotic coronaviruses.

Introduction

The genetically diverse *Orthocoronavirinae* (coronavirus, CoV) family circulates in many avian and mammalian species. Phylogenetically, CoVs are divided into 4 genera: alpha (group 1), beta (group 2), gamma (group 3) and delta (group 4). Three new human CoV have emerged in the past 20 years with severe acute respiratory syndrome CoV (SARS-CoV) in 2002, Middle East respiratory syndrome CoV (MERS-CoV) in 2012, and now SARS-CoV-2 in 2019[1-3]. The ongoing SARS-CoV-2 epidemic (referred to as COVID-19, Coronavirus disease 2019) has caused over 89,000 infections and over 3,000 deaths in 71 countries. Like SARS- and MERS-CoV, the respiratory disease caused by SARS-CoV-2 can progress to acute lung injury (ALI), an end stage lung disease with limited treatment options and very poor prognoses[3-5]. This emergence paradigm is not limited to humans. A novel group 1 CoV called swine acute diarrhea syndrome CoV (SADS-CoV) recently emerged from bats causing the loss of over 20,000 pigs in Guangdong Province, China[6]. More alarmingly, many group 2 SARS-like and MERS-like coronaviruses are circulating in bat reservoir species that can use human receptors and replicate efficiently in primary human lung cells without adaptation[6-9]. The presence of these "pre-epidemic" zoonotic strains foreshadow the emergence and epidemic potential of additional SARS-like and MERS-like viruses in the future. Given the diversity of CoV strains in zoonotic reservoirs and a penchant for

63 emergence, broadly active antivirals are clearly needed for rapid response to new CoV
64 outbreaks in humans and domesticated animals.
65 Currently, there are no approved therapies specific for any human CoV. β-D-N4-
66 hydroxycytidine (NHC, EIDD-1931) is orally bioavailable ribonucleoside analog with
67 broad-spectrum antiviral activity against various unrelated RNA viruses including
68 influenza, Ebola, CoV and Venezuelan equine encephalitis virus (VEEV)[10-13]. For VEEV,
69 the mechanism of action (MOA) for NHC has been shown to be through lethal
70 mutagenesis where deleterious transition mutations accumulate in viral RNA[11,14]. Here,
71 we demonstrate that NHC exerts potent, broad-spectrum activity against SARS-CoV,
72 MERS-CoV and their related bat-CoV in primary human airway epithelial cell cultures
73 (HAE), a biologically relevant model of the human conducting airway. In addition, we
74 show that NHC is potently antiviral against the newly emerging SARS-CoV-2 as well as
75 against coronavirus bearing resistance mutations to the potent nucleoside analog
76 inhibitor, remdesivir (RDV). In SARS- or MERS-CoV infected mice, both prophylactic
77 and therapeutic administration EIDD-2801, an oral NHC-prodrug (□-D-N^4-
78 hydroxycytidine-5'-isopropyl ester) improved pulmonary function and reduced virus titer
79 and ameliorated disease severity. In addition, therapeutic EIDD-2801 reduced the
80 pathological features of ALI in SARS-CoV infected mice. Using a high-fidelity deep
81 sequencing approach (Primer ID), we found that increased mutation rates coincide with
82 decreased MERS-CoV yields *in vitro* and protective efficacy *in vivo* supporting the MOA
83 of lethal mutagenesis against emerging CoV[13]. The broad activity and therapeutic
84 efficacy of NHC/EIDD-2801 highlight its potential to diminish epidemic disease today
85 and limit future emerging CoV outbreaks.
86
87 **Results**
88 **NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2**
89 **Replication.**
90 To determine whether NHC blocks the replication of highly pathogenic human
91 CoV, we performed antiviral assays in continuous and primary human lung cell cultures.
92 We first assessed the antiviral activity of NHC against MERS-CoV in the human lung
93 epithelial cell line Calu-3 2B4 ("Calu3" cells). Using a recombinant MERS-CoV

expressing nanoluciferase (MERS-nLUC)[15], we measured virus replication in cultures exposed to a dose range of drug for 48hr. NHC was potently antiviral with an average half-maximum effective concentration (IC_{50}) of 0.15μM and no observed cytoxicity in similarly treated uninfected cultures across the dose range (50% cytotoxic concentration, CC_{50}, >10μM) (Fig. 1A). The therapeutic index for NHC was >100. Similarly, NHC strongly inhibited SARS-CoV-2 replication in Vero cells with an IC_{50} of 0.3μM and CC_{50} of >10μM (Fig. 1B). Human primary airway epithelial (HAE) cell cultures model the architecture and cellular complexity of the conducting airway and are readily infected by multiple human and zoonotic CoV, including SARS- and MERS-CoV[16]. We first assessed cytotoxicity of NHC in HAE treated with an extended dose range for 48hr using quantitative PCR of cell death-related gene transcripts as our metric. NHC treatment did not appreciably alter gene expression even at doses up to 100μM (Supplementary Figure 1). In MERS-CoV infected HAE, NHC dramatically reduced virus production with maximal titer reduction of > 5 logs at 10μM (average IC_{50} = 0.024 μM), which correlated with reduced genomic (ORF1) and subgenomic (ORFN) RNA in paired samples (Fig. 1C). We observed similar trends in titer reduction (> 3 log at 10μM, average IC_{50} = 0.14 μM) and levels of genomic and subgenomic RNA in SARS-CoV infected HAE (Fig. 1D). Thus, NHC was potently antiviral against MERS-CoV and SARS-CoV-2 in cell lines and MERS-CoV and SARS-CoV in human primary HAE cell cultures without cytotoxicity.

NHC is effective against remdesivir resistant virus and multiple distinct zoonotic CoV.

All human CoV are thought to have emerged as zoonoses most recently exemplified by SARS-CoV, MERS-CoV and SARS-CoV-2[17-19]. Although taxonomically divided into multiple genogroups (alpha , beta , gamma , delta), human CoV are found in only the alpha and beta subgroups thus far (Fig. 2A). There is high sequence conservation in the RdRp across CoV (Fig. 2A). For example, the RdRp of SARS-CoV-2 has 99.1% similarity and 96% amino acid identity to that of SARS-CoV (Fig. 2A). To gain insight into structural conservation of RdRp across the CoV family, we modeled the variation reflected in the RdRp dendrogram in Fig. 2A onto the structure of the SARS-

CoV RdRp[20] (Fig. 2B). The core of the RdRp molecule and main structural motifs that all RdRp harbor (Fig. 2B and Supplementary Figure 2) are highly conserved among CoV including SARS-CoV-2. We previously reported that CoV resistance to another broad spectrum nucleoside analog, remdesivir (RDV) was mediated by RdRp residues F480L and V557L in a model coronavirus mouse hepatitis virus (MHV) and in SARS-CoV, resulting in a 5-fold shift in IC_{50} (Fig. 2C)[21]. Consequently, we tested whether RDV resistance mutations in MHV conferred cross resistance to NHC (Figure 2D). In fact, the two RDV resistance mutations, alone or together conferred increased sensitivity to inhibition by NHC. As our previous studies have demonstrated a high genetic barrier to NHC for VEEV, influenza and coronavirus[11-13], the lack of cross resistance further suggests that NHC and RDV may select for exclusive and mutually sensitizing resistance pathways.

To explore the breadth of antiviral efficacy against zoonotic CoV, we performed antiviral assays in HAE with three zoonotic Bat-CoV, SHC014, HKU3 and HKU5. Closely related to the beta 2b SARS-CoV, Bat-CoV SHC014 is capable of replicating in human cells without adaptation[8] suggesting its potential for zoonotic emergence. More distantly related SARS-like beta 2b CoV, recombinant Bat-CoV HKU3 has a modified receptor binding domain to facilitate growth in cell culture[22]. Lastly, Bat-CoV HKU5 is a MERS-like beta 2c CoV[23]. NHC diminished infectious virus production and the levels of genomic/subgenomic viral RNA in HAE in a dose-dependent manner for all three Bat-CoVs (Fig. 3). Therefore, the antiviral activity of NHC was not limited by natural amino acid variation in the RdRp, which among the group 2b and group 2c CoV can vary by almost 20% (Fig. 2A). Moreover, these data suggest that if another SARS- or MERS-like virus were to spillover into humans in the future, they would likely be susceptible to the antiviral activity of NHC.

NHC antiviral activity is associated with increased viral mutation rates.

It has recently been shown that NHC treatment increases the mutation rate in viral genomic RNA of RSV[24], VEEV[11], influenza[24], and our previous study used RNA seq to show that overall transition mutation frequency is increased during NHC treatment of MHV and MERS-CoV during infection in continuous cell lines[13]. We sought

to determine if NHC would increase the mutation frequency during MERS-CoV infection in human primary human airway epithelial cells (HAE). Using MERS-CoV infected HAE treated with either vehicle or a dose range of NHC or RDV, we show that both drugs reduced virus titers in a dose-dependent manner (Fig. 4A). We then employed a highly-sensitive high-fidelity deep sequencing approach (Primer ID NGS), which uses barcoded degenerate primers and Illumina indexed libraries to determine accurate mutation rates after antiviral treatment on viral RNA production[25]. Using this approach, we analyzed a 538bp region of viral genomic RNA in nonstructural protein 15 (nsp15). The error rates (#mutations/10,000 bases) in vehicle (0.01) or RDV (0.01) treated cultures were very low. RDV is reported to act via chain termination of nascent viral RNA, and thus the low error rates in RDV-treated cultures are in line with the proposed MOA[26]. In contrast, the error rate was significantly increased in NHC-treated MERS-CoV RNA in a dose-dependent manner (10-fold at 10μM and 5-fold at 1μM) at both 24 and 48hpi (Fig. 4C). The magnitude of the error rate in NHC-treated cultures correlated with virus titer reduction. At 48hpi the respective error rate and virus titer was 0.015 and 3.96E+06 pfu/mL for vehicle treatment, 0.045 and 2.86E+04 pfu/mL with 1μM NHC; and 0.090 and 1.5E+02 pfu/mL 10μM NHC. Thus, with 1μM NHC a 3-fold increase in error rate resulted in a 138-fold decrease in virus titer, while with 10μM NHC a 6-fold increase in error rate resulted in a 26,000-fold decrease in virus titer.

We then examined the mutational spectra induced by NHC, which can be incorporated into viral RNA as a substitution for either cytosine (C) or Uridine (U). RNA-mutagenic antivirals may incorporate in both nascent negative and positive sense RNA during genome replication (Fig. 4D). Adenine-to-guanine (A-to-G) and uracil-to-cytosine (U-to-C) transitions were enriched in MERS-CoV genomic RNA in an NHC dose-dependent manner (Fig. 4E). Collectively, these data used high-fidelity sequence analysis to demonstrate a specific enrichment for A:G and C:U transitions in MERS-CoV RNA after NHC treatment of primary HAE cell cultures.

Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis.

Given the promising antiviral activity of NHC in vitro, we next evaluated its *in vivo* efficacy using EIDD-2801, an orally bioavailable prodrug of NHC (□-D-N^4-

hydroxycytidine-5'-isopropyl ester), designed for improved *in vivo* pharmacokinetics and oral bioavailability in humans and non-human primates[12]. Importantly, the plasma profiles of NHC and EIDD-2801 were similar in mice following oral delivery[12]. We first performed a prophylactic dose escalation study in C57BL/6 mice where we orally administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500 mg/kg EIDD-2801 2hr prior to intranasal infection with 5E+04 PFU of mouse-adapted SARS-CoV (SARS-MA15), and then every 12hr thereafter. Beginning on 3dpi and through the end of the study, body weight loss compared to vehicle treatment was significantly diminished (50mg/kg) or prevented (150, 500mg/kg) with EIDD-2801 prophylaxis ($P < 0.0001$) (Supplemental Figure 2A). Lung hemorrhage was also significantly reduced 5dpi with 500mg/kg EIDD-2801 treatment (Supplemental Figure 2B). Interestingly, there was a dose-dependent reduction in SARS-CoV lung titer (median titers: 50mg/kg = 7E+03 pfu/mL, 150mg/kg = 2.5E+03 pfu/mL, 500mg/kg = 50 pfu/mL, vehicle = 6.5E+04 pfu/mL) with significant differences among the vehicle, 150 mg/kg ($P = 0.03$) and 500mg/kg ($P = 0.006$) groups. Thus, prophylactic orally administered EIDD-2801 was robustly antiviral and able to prevent SARS-CoV replication and disease.

Since only the 500mg/kg group significantly diminished weight loss, hemorrhage and reduced lung titer to near undetectable levels, we tested this dose under therapeutic treatment conditions to determine if EIDD-2801 could improve the outcomes of an ongoing CoV infection. As a control, we initiated oral vehicle or EIDD-2801 2hr prior to infection with 1E+04 pfu SARS-MA15. For therapeutic conditions, we initiated EIDD-2801 treatment 12, 24, or 48hr after infection. After initiating treatment, dosing for all groups was performed every 12hr for the duration of the study. Both prophylactic treatment initiated 2hr prior to infection and therapeutic treatment initiated 12hr after infection significantly prevented body weight loss following SARS-CoV infection on 2dpi and thereafter (-2hr: $P = 0.0002$ to <0.0001; +12hr: $P = 0.0289$ to <0.0001) (Fig. 5A). Treatment initiated 24hpi also significantly reduced body weight loss (3-5dpi, $P = 0.01$ to <0.0001) although not to the same degree as the earlier treatment initiation groups. When initiated 48hpi, body weight loss was only different from vehicle on 4dpi ($P = 0.037$, Fig. 5A). Therapeutic EIDD-2801 significantly reduced lung hemorrhage when

initiated up to 24hr after infection mirroring the body weight loss phenotypes (Fig. 5B). Interestingly, all EIDD-2801 treated mice had significantly reduced viral loads in the lungs even in the +48hr group (Fig. 5C), which experienced the least protection from body weight loss and lung hemorrhage. We also measured pulmonary function via whole body plethysmography (WPB). In Figure 5D, we show the WBP PenH metric, which is a surrogate marker for bronchoconstriction or pulmonary obstruction[27], was significantly improved throughout the course of the study if treatment was initiated up to 12hr after infection, although the +24hr group showed sporadic improvement as well (Fig. 5D). Lastly, we blindly evaluated hematoxylin and eosin stained lung tissue sections for histological features of ALI using two different and complementary scoring tools[15], which show that treatment initiated up to +12hr significantly reduced ALI (Fig. 5E). Altogether, therapeutic EIDD-2801 was potently antiviral against SARS-CoV *in vivo* but the degree of clinical benefit was dependent on the time of initiation post infection.

Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis.

After obtaining promising *in vivo* efficacy data with SARS-CoV, we investigated whether EIDD-2801 would be effective against MERS-CoV. As the murine ortholog of the MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), does not support viral binding and entry, all *in vivo* studies were performed in genetically modified mice encoding a murine DPP4 receptor encoding two human residues at positions 288 and 330 (hDPP4 288/330 mice)[15,28]. Similar to our SARS-CoV data (Supplementary Figure 3), all doses of prophylactic EIDD-2801 (50, 150 and 500mg/kg) protected hDPP4 288/330 mice from significant body weight loss ($P = 0.03$ to < 0.0001), lung hemorrhage ($P = 0.01$ to <0.0001), and virus replication which was undetectable ($P < 0.0001$) regardless of drug dose following intranasal infection with 5E+04 PFU mouse-adapted MERS-CoV (Supplementary Figure 4).

We then evaluated the therapeutic efficacy EIDD-2801 following the promising results of our prophylactic studies. Similar to our SARS-CoV study, EIDD-2801 treatment administered before or 12hr after intranasal mouse-adapted MERS-CoV infection (5E+04 PFU) prevented body weight loss from 2 through 6dpi (Fig. 6A, P =

0.02 to <0.0001) and lung hemorrhage on 6dpi (Fig. 6B, P = 0.0004 to < 0.0001), but treatment initiated 24 or 48hr did not offer similar protection. Unlike body weight loss and lung hemorrhage data which varied by treatment initiation time, virus lung titer on 6dpi was significantly reduced to the limit of detection in all treatment groups (Fig. 6C, P < 0.0001). Interestingly, when viral genomic RNA was quantified in paired samples of lung tissue, EIDD-2801 significantly reduced levels of viral RNA (P <0.0001 to 0.017) in an initiation time-dependent manner for all groups except for +48hr (Fig. 6D). The discrepancy among infectious titers and viral RNA suggests that accumulated mutations render the particles non-infectious and undetectable by plaque assay consistent with the MOA. To gauge the effect of EIDD-2801 treatment on lung function, we assessed pulmonary function by WBP. Mirroring the body weight loss data, normal pulmonary function was only observed in groups where treatment was initiated prior to or 12hr after infection (Fig. 6E). Collectively, these data demonstrate that NHC prodrug, EIDD-2801, robustly reduces MERS-CoV infectious titers, viral RNA, and pathogenesis under both prophylactic and therapeutic conditions.

Therapeutic efficacy correlates with an increased MERS-CoV mutation rate i*n vivo*, without increased mutations in cellular RNA.

To study the molecular mechanisms associated with drug performance *in vivo*, we investigated the correlation between infectious virus production and EIDD-2801-mediated mutagenesis of MERS-CoV RNA under therapeutic treatment conditions. Using Primer ID NGS, we measured the mutation rates of both viral genomic RNA (i.e. non-structural protein 10, nsp10) and host interferon stimulated gene 15 (ISG15) mRNA, a highly upregulated innate immune related gene after MERS-CoV infection (Fig. 6F). Primer ID NGS measures the mutational frequency in single RNA molecules each of which are represented by a single template consensus sequence (TCS, See Fig. 4B)[25]. Viral TCS were significantly reduced in a treatment initiation time-dependent manner (Fig. 6G) similar to viral genomic RNA measured by qRT-PCR (Fig. 6D). In contrast, the numbers of ISG15 TCS were similar (P = 0.2 to 0.8) for all groups indicating that neither vehicle nor drug treatment significantly affected the levels of or mutated ISG15 mRNA transcripts (Fig. 6G). Similar to our TCS data in Figure 6G, the

total error rate in viral nsp10 was significantly increased in groups where treatment was initiated prior to (-2hr, median error rate = 10.5 errors/10,000 bases, $P < 0.0001$) and up to 24hr post infection (12hr, median error rate = 8.2 errors/10,000 bases, $P < 0.0001$; +24hr, median error rate = 5.4 errors/10,000 bases, $P = 0.0003$) but the error rates in ISG15 remained at baseline for all groups (Fig. 6H). In addition, nucleotide transitions observed in MERS-CoV genomes in vitro (i.e. C to U transitions, Fig. 3), were also observed *in vivo* in groups where treatment was initiated prior to and up to 12hr post infection ($P = 0.0003$ to < 0.0001) (Fig. 5I). Importantly, these transitions were not observed in host ISG15 mRNA (Fig. 5I). Lastly, the EIDD-2801 dose-dependent mutagenesis of viral RNA correlated with an increase in codon change frequency, including stop codons, in mice where treatment was initiated 12hr or before (vehicle median = 3.4; -2hr median = 22.8, $P = 0.0035$; +12hr median = 20.0, $P = 0.0004$, Fig. 5I). Thus, approximately 20% of the mutations observed in the -2hr and +12hr groups resulted in a codon change and alteration of the nsp10 protein sequence. When extrapolating our results from nsp10 to the entirety of the 30kb MERS-CoV genome, EIDD-2801 likely causes between 15 (+24hr treatment) and 30 (-2hr treatment) mutations per genome 10-20% of which result in amino acid coding changes. Altogether, our data demonstrates that EIDD-2801-driven mutagenesis correlates well with the reductions in viral load, strongly suggestive of an error catastrophe-driven mechanism of action under therapeutic conditions.

Discussion

In the past 20 years, three novel human coronaviruses have emerged[29,30]. The group 2b SARS-like CoV represent an existential and future threat to global health as evidenced by the emergence of SARS-CoV and SARS-CoV2 and zoonotic SARS-like bat CoV strains that can use human ACE2 receptors, grow well in primary human airway cells and vary by as much as 25% in key therapeutic and vaccine gene targets[8,31]. Thus, to address the current public health emergency of COVID-19 and to maximize pandemic preparedness in the future, broad-based vaccines and therapeutics, which are active against the higher risk RNA virus families prone to emergence are desperately needed.

We recently reported the broad-spectrum potency of the nucleoside prodrug, remdesivir (RDV), against an array of epidemic, contemporary and zoonotic CoV both in vitro and *in vivo*[15,16,21,31]. Currently RDV therapeutic efficacy is under investigation in several human clinical trials in China, the United States and elsewhere[32]. Here, we report the broad-spectrum antiviral activity of NHC and its orally bioavailable prodrug EIDD-2801, against SARS-CoV, MERS-CoV and related bat-CoV in primary human airway epithelial cells, as well as against the current pandemic strain SARS-CoV-2. In addition, NHC is broadly active against multiple genetically distinct viruses including coronaviruses, Venezuelan equine encephalitis (VEE), influenza A and B, Ebola, and Chikungunya viruses[10-13,16,21,24,33-35]. Here, we show that prophylactic and therapeutic EIDD-2801 significantly reduced lung viral loads and improved pulmonary function in mouse models of both SARS- and MERS-CoV pathogenesis. Although the improvement in both SARS- and MERS-CoV outcomes diminished with the increase of treatment initiation time, it is important to note that the kinetics of disease in mice are compressed as compared to that in humans. While SARS- and MERS-CoV lung titers peak on 2dpi in mice concurrent with the onset of clinical signs and notable damage to the lung epithelium, in humans this occurs 7-10 days after the onset of symptoms[16,28,36,37]. Thus, in mice, the window within which to treat emerging CoV infection prior to peak replication is compressed (e.g., 24-48hr) but should be much longer in humans. Although speculative, the SARS- and MERS-CoV *in vivo* data provided herein suggest that 2019-nCoV will prove highly vulnerable to NHC treatment modalities *in vivo*, critical experiments that must be performed as animal models become available. The data provided in this manuscript suggest that NHC should be quickly evaluated in primate models of human disease, using immediate models for MERS-CoV and SARS-CoV pathogenesis[38,39].

Small molecule antivirals can exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoded enzyme, blocking virus particle formation, or targeting a host factor required for replication[40]. For VEE, EIDD-2801 exerts its antiviral activity on the RNA-dependent RNA polymerase leading to error catastrophe by inducing an error rate of replication that surpasses the error threshold allowed to sustain a virus population[11,12]. This process occurs when NHC is

incorporated during RNA synthesis then subsequently misread thus increasing mutation rates. Therefore, the NHC MOA would appear less likely to be affected by the RNA proofreading activity encoded by the nsp14 exonuclease function that otherwise limits misincorperation[41]. Here, we present data using Primer ID NGS, a state of the art deep sequencing-based approach, to quantitate the frequency and identity of the mutational spectra in the MERS-CoV genome in both drug treated primary human airway cells and in mice at single genome resolution[25]. As CoV are positive sense RNA viruses that replicate through a negative sense RNA intermediate, NHC incorporation as a “C” or a “U” can occur in both polarities of RNA. Using Primer ID NGS, we found increased nucleotide transitions (A to G, G to A, C to U, U to C) consistent with those reported after influenza and VEE infections[11,12]. Under identical conditions, remdesivir did not alter the mutation rate in MERS-CoV genomic RNA, supporting its reported mechanism of action as a chain terminator of viral RNA synthesis[26]. In primary human lung cell cultures and mice infected with MERS-CoV, the NHC mutation rates inversely correlated with a reduction in infectious virus. In addition, we found a positive correlation between increased mutation rates and the frequency of nonsynonymous mutations and the degree of therapeutic efficacy in mice. To explore the potential off-target effect in host mRNA which may contribute to drug toxicity, we also examined the impact of NHC treatment on transcripts from the highly MERS-CoV induced interferon stimulated gene 15 (ISG15). While ISG15 is present in great abundance, an accumulation of mutations was not observed in ISG15 in this model even at 500mg/kg dosing. These data also support previous studies using RNAseq to demonstrate that the model coronavirus MHV displayed increased mutation frequencies following NHC treatment in vitro[13]. All together, these data strongly support the notion that EIDD-2801 and its active nucleoside analog NHC, exert their antiviral effect through the induction of error catastrophe in the targeted virus. While our data suggest that the MERS-CoV nsp14 proofreading activity appeared ineffective against NHC in vitro and EIDD-2801 *in vivo*, future studies should investigate the antiviral activity of NHC in the presence or absence of the nsp14 proofreading activity, as loss of this activity increased the sensitivity of MHV and SARS-CoV replication to remdesivir treatment[41].

Together, our data support the continued development of EIDD-2801 as a potent broad spectrum antiviral that could be useful in treating contemporary, newly emerged and emerging coronavirus infections of the future.

Materials and Methods

Compounds. The parental compound □□D□N^4-hydroxycytidine (NHC, all in vitro studies) and its prodrug EIDD-2801 (all *in vivo* studies) was supplied by Emory University Institute for Drug Discovery (EIDD). NHC was supplied as a 10mM stock in DMSO and EIDD-2801 as a solid and solubilized in vehicle containing 10% PEG400, 2.5% Cremophor RH40 in water (10/2.5/87.5%, all v/v) prior to use. Remdesivir (RDV) was solubilized in 100% DMSO and provided by Gilead Sciences, Inc as previously described[15,16].

Virus strains. All viruses used for these studies were derived from infectious clones and isolated as previously described[42]. Virus strains for in vitro experiments include SARS-CoV expressing the green fluorescent protein (GFP) in place of open reading frames 7a/b (ORF7a/b, SARS-GFP)[42], bat-spike receptor binding domain (Bat-SRBD)[22] is a chimeric CoV strain derived from the HKU3 SARS-like bat coronavirus genomic sequence that has the wild type (Urbani SARS-CoV strain) RBD in the HKU3 spike gene to allow for virus replication in non-human primate cell lines and HAE cultures, SHC014 SARS-like bat coronavirus[8], MERS-CoV expressing nanoluciferase in the place of ORF3 (MERS-nLUC)[16] and MERS-CoV expressing the red fluorescent protein gene in the place of ORF 5 (RFP, MERS-RFP)[43]. The virus stock utilized for MERS-CoV *in vivo* studies was derived from a plaque purified isolate of the mouse-adapted MERS-CoV p35C4 strain[44]. The virus stock utilized for SARS-CoV *in vivo* studies was derived from the infectious clone of the mouse-adapted SARS-CoV MA15 (MA15) strain[45].

***In vitro* experiments** Calu3**:** At 48hrs prior to infection, Calu3 2B4 cells were plated in a 96-well black walled clear bottom plate at 5x10^4 cells/well. A 10mM stock of NHC was serially diluted in 100% DMSO in 3-fold increments to obtain a ten-point dilution series. MERS-nLUC was diluted in DMEM supplemented with 10% FBS, and 1% Antibiotic-

Antimycotic to achieve a multiplicity of infection (MOI) of 0.08. Cells were infected and treated with NHC in triplicate per drug dilution for 1hr, after which viral inoculum was aspirated, cultures were rinsed once and fresh medium containing drug or vehicle was added. At 48hrs post infection, nanoluciferase expression as a surrogate for virus replication was quantitated on a Spectramax (Molecular Devices) plate reader according to the manufacturer's instructions (Promega, NanoGlo). For our 100% inhibition control, diluted MERS-nLUC was exposed to short-wave UV light (UVP, LLC) for 6 minutes to inhibit the ability of the virus to replicate. For our 0% inhibition control, cells were infected in the presence of vehicle only. DMSO was kept constant in all conditions at 0.05%. Values from triplicate wells per condition were averaged and compared to controls to generate a percent inhibition value for each drug dilution. The IC_{50} value was defined as the concentration at which there was a 50% decrease in luciferase expression. Data was analyzed using GraphPad Prism 8.0 (La Jolla, CA). The IC_{50} values were calculated by non-linear regression analysis using the dose-response (variable slope) equation (four parameter logistic equation): Y = Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)). To measure cell viability to determine if there was any NHC induced cytotoxicity, Calu3 2B4 cells were plated and treated with NHC only as described above. Cells were exposed to the same ten-point dilution series created for the in vitro efficacy studies. As above, 0.05% DMSO-treated cells served as our 0% cytotoxicity control. Wells without cells served as our 100% cytotoxic positive control. After 48hr, cell viability was measured on a Spectramax (Molecular Devices) via Cell-Titer Glo Assay (Promega) according to the manufacturer's protocol. Similar data was obtained in three independent experiments.

HAE: Human tracheobronchial epithelial cells were obtained from airway specimens resected from patients undergoing surgery under University of North Carolina Institutional Review Board-approved protocols by the Cystic Fibrosis Center Tissue Culture Core. Primary cells were expanded to generate passage 1 cells and passage 2 cells were plated at a density of 250,000 cells per well on Transwell-COL (12mm diameter) supports. Human airway epithelium cultures (HAE) were generated by provision of an air-liquid interface for 6 to 8 weeks to form well-differentiated, polarized cultures that resembled *in vivo* pseudostratified mucociliary epithelium[46]. At 48 hours

prior to infection the apical surface of the culture was washed with 500 µL PBS for 1.5 hours at 37˚C and the cultures moved into fresh air liquid interface (ALI) media. Immediately prior to infection, apical surfaces were washed twice with 500 µL of PBS with each wash lasting 30 minutes at 37˚C and HAE cultures were moved into ALI media containing various concentrations of NHC ranging from 10 µM to 0.0016 µM as indicated for each experiment (final % DMSO < 0.05%). Upon removing the second PBS wash, 200 µL of viral inoculum (multiplicity of infection of (MOI) 0.5) was added to the apical surface and HAE cultures were incubated for 3 hours at 37˚C. Viral inoculum was then removed, and the apical surface of the cultures were washed three times with 500µL PBS and then incubated at 37˚C until 48 hours post infection (hpi). For all HAE cultures, infectious virus produced was collected by washing the apical surface of the culture with 100 µL PBS. Apical washes were stored at -80 ˚C until analysis and titered by plaque assay as previously described[16].

qRT-PCR approach to assess cytotoxicity: Total RNA was isolated using the Zymo Direct-zol RNA MiniPrep Kit (Zymo Research Corp., Irvine, CA, USA) according to the manufacturer's directions. First-strand cDNA was generated using Superscript III reverse transcriptase (Life Technologies, Carlsbad, CA, USA). For quantification of cellular markers of toxicity/apoptosis, real-time PCR was performed using commercially validated TaqMan-based primer-probe sets (**Supplementary Table 1**) and TaqMan Universal PCR Mix (Life Technologies). Results were then normalized as described above.

Primer ID and Deep Sequencing

Primer ID NGS is designed to specifically identify and remove RT-PCR mutations, while facilitating highly accurate sequence determination of single RNA molecules, because each cDNA is created with a barcoded degenerate primer (N10, 4^{10} combinations) from which Illumina indexed libraries are made. We used a multiplexed Primer ID library prep approach and MiSeq sequencing to investigate the presence of mutations in the viral genomes and murine mRNA. We designed cDNA primers targeting multiple regions on the viral genome and murine mRNA, each with a block of random nucleotides (11 bp

long) as the Primer ID[25,47] (**Supplementary Table 2**). Viral RNA was extracted using QIAamp viral RNA kit. A pre-amplification titration of templates was performed to estimate the amount of template to use. We used SuperScript III to make cDNA with multiplexed cDNA primers based on the regions to be sequenced. We used 41R_PID11 for the pilot sequencing and titration determination. For the MERS-CoV sequencing, we multiplexed nsp10_PID11, nsp12_PID11 and nsp14_PID11 for the cDNA reaction; for the murine mRNA sequencing, we used mixed primers of nsp10_PID11, ifit3_PID11, isg15_PID11. After bead purification, we amplified the cDNA with a mixture of forward primers (based on the described schemes) and a universal reverse primer, followed by another round of PCR to incorporate Illumina sequencing adaptors and barcodes in the amplicons. After gel-purification and quantification, we pooled 24 libraries for MiSeq 300 base paired-end sequencing. The TCS pipeline version 1.38 (https://github.com/SwanstromLab/PID) was used to process the Primer ID sequencing data and construct template consensus sequences (TCSs) to represent each individual input templates, and the sequences of each region in the pool was de-multiplexed. The RUBY package viral_seq version 1.0.6 (https://rubygems.org/gems/viral_seq) was used to calculate the mutation rate at each position.

***In vivo* experiments.** We performed 4 mouse studies to evaluate the *in vivo* efficacy of the NHC prodrug (EIDD-2801). First, we performed prophylactic dose escalation studies for both SARS- and MERS-CoV to determine the most efficacious dose of EIDD-2801 per virus. For SARS-CoV, in cohorts of equivalent numbers of male and female 20-29 week old SPF C57BL/6J (Stock 000664 Jackson Labs) mice (n = 10/dose group), we administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500mg/kg EIDD-2801 by oral gavage 2hr prior to intranasal infection with 1E+04 PFU mouse-adapted SARS-CoV strain MA15 in 50µl. Mice were anaesthetized with a mixture of ketamine/xylazine prior to intranasal infection. Vehicle or drug was administered every 12hr for the remainder of the study. Body weight and pulmonary function by whole body plethysmography was measured daily. On 5dpi, animals were sacrificed by isoflurane overdose, lungs were scored for lung hemorrhage, and the inferior right lobe was frozen at −80°C for viral titration via plaque assay. Briefly,

500,000 Vero E6 cells/well were seeded in 6-well plates. The following day, medium was removed and serial dilutions of clarified lung homogenate were added per plate (10^{-1} to 10^{-6} dilutions) and incubated at 37˚C for 1hr after which wells were overlayed with 1X DMEM, 5% Fetal Clone 2 serum, 1X antibiotic/antimycotic, 0.8% agarose. Two days after, plaques were enumerated to generate a plaque/ml value. Lung hemorrhage is a gross pathological phenotype readily observed by the naked eye driven by the degree of virus replication where the coloration of the lung changes from pink to dark red[48,49]. The large left lobe was placed in 10 % buffered formalin and stored at 4°C for 1-3 weeks until histological sectioning and analysis. For MERS-CoV, the prophylactic dose escalation studies we performed exactly as done for SARS-CoV with the following exceptions. First, MERS-CoV binds the human receptor dipeptidyl peptidase 4 (DPP4) to gain entry into cells and two residues (288 and 330) in the binding interface of mouse DPP4 prevent infection of mice. We recently developed a mouse model for MERS-CoV through the mutation of mouse DPP4 at 288 and 330 thus humanizing the receptor (*hDPP4*) and rendering mice susceptible to MERS-CoV infection[28]. We performed all *in vivo* studies with EIDD-2801 in equivalent numbers of 10-14 week old female and male C57BL/6J hDPP4 mice. Second, we intranasally infected mice with 5E+04 PFU mouse-adapted MERS-CoV strain M35C4 in 50µl. Third, to titer lungs by plaque assay, Vero CCL81 cells were used and plaques were enumerated 3 days post infection.

To determine the time at which therapeutic administration of EIDD-2801 would fail to improve outcomes with SARS-CoV or MERS-CoV infection, we performed therapeutic efficacy studies in mice where we initiated treatment 2hr prior to infection or 12, 24 or 48hr after infection. As 500mg/kg provided the most complete protection from disease in prophylactic SARS-CoV studies, this dose was used for both therapeutic efficacy studies. Vehicle or EIDD-2801 was given via oral gavage twice daily following initiation of treatment. For both SARS-CoV and MERS-CoV, the infectious dose for the therapeutic studies and the mouse strains were the same as that used in the prophylactic studies. The numbers of mice per group for the SARS-CoV studies were as follows: Vehicle (n = 10), -2hr (n = 10), +12hr (n = 10), +24hr (n = 10), +48hr (n = 10). The numbers of mice per group for the MERS-CoV therapeutic studies were as follows: Vehicle (n = 9), -2hr (n = 9), +12hr (n = 9), +24hr (n = 7), +48hr (n = 10). As described

above, each day mouse body weight and pulmonary function was quantitated. On 5dpi for SARS-CoV and 6dpi for MERS-CoV, animals were humanely sacrificed and tissues were harvested and analyzed as described above. In addition, for the MERS-CoV study, lung tissue was harvested and stored in RNAlater (Thermo Fisher) at -80˚C and then thawed, homogenized in Trizol reagent (Invitrogen) and total RNA was isolated using a Direct-zol RNA MiniPrep kit (Zymo Research). This total RNA was then used for Primer ID and qRT-PCR.

Whole body plethysmography. Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.). Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes.

Acute lung injury histological assessment tools. Two different and complementary quantitative histologic tools were used to determine if antiviral treatments diminished the histopathologic features associated with lung injury. Both analyses and scoring were performed by a Board Certified Veterinary Pathologist who was blinded to the treatment groups.

American Thoracic Society Lung Injury Scoring Tool. In order to help quantitate histological features of ALI observed in mouse models and increase their translation to the human condition, we used the ATS scoring tool[49]. In a blinded manner, we chose three random diseased fields of lung tissue at high power (60 ×), which were scored for the following: (A) neutrophils in the alveolar space (none = 0, 1–5 cells = 1, > 5 cells = 2), (B) neutrophils in the interstitial space/ septae (none = 0, 1–5 cells = 1, > 5 cells = 2), (C) hyaline membranes (none = 0, one membrane = 1, > 1 membrane = 2), (D) Proteinaceous debris in air spaces (none = 0, one instance = 1, > 1 instance = 2), (E) alveolar septal thickening (< 2× mock thickness = 0, 2–4× mock thickness = 1, > 4× mock thickness = 2). To obtain a lung injury score per field, the scores for A–E were then put into the following formula, which contains multipliers that assign varying levels of importance for each phenotype of the disease state.: score = [(20x A) + (14 x B) + (7

x C) + (7 x D) + (2 x E)]/100. The scores for the three fields per mouse were averaged to obtain a final score ranging from 0 to and including 1.

Diffuse Alveolar Damage (DAD) Tool. The second histological tool to quantitate lung injury was reported by Schmidt et al.[50]. DAD is the pathological hallmark of ALI[49,50]. Three random diseased fields of lung tissue were score at high power (60 ×) for the following in a blinded manner: 1 = absence of cellular sloughing and necrosis, 2 = Uncommon solitary cell sloughing and necrosis (1–2 foci/field), 3 = multifocal (3 + foci) cellular sloughing and necrosis with uncommon septal wall hyalinization, or 4 = multifocal (>75% of field) cellular sloughing and necrosis with common and/or prominent hyaline membranes. The scores for the three fields per mouse were averaged to get a final DAD score per mouse.

MERS-CoV genomic RNA qRT-PCR. Mouse lungs were stored in RNAlater (ThermoFisher) at -80°C until processed via homogenization in TRIzol (Invitrogen). Total RNA was isolated using Direct-zol RNA MiniPrep kit (Zymo Research). Previously published TaqMan primers were synthesized by Integrated DNA Technologies (IDT) to quantify MERS genomic RNA (targeting orf1a. Forward: 5'-GCACATCTGTGGTTCTCCTCTCT-3', Probe (6-FAM/ZEN/IBFQ): 5'-TGCTCCAACAGTTACAC-3', Reverse: 5'-AAGCCCAGGCCCTACTATTAGC)[51]. qRT-PCR was performed using 100ng total RNA compared to an RNA standard curve using TaqMan Fast Virus 1-Step Master Mix (ThermoFisher) on a Quant Studio 3 (Applied Biosystems).

nsp12 phylogenetic analysis and conservation modeling. Coronavirus RdRp (nsp12) protein sequence alignments and phylogenetic trees were generated using Geneious Tree Builder in Geneious Prime (version 2020.0.5) and visualized using Evolview (https://www.evolgenius.info/evolview/). Protein similarity scores were calculated using Blosom62 matrix. The accession numbers used were : PDCoV (KR265858), AIBV (NC_001451), HCoV-229E (JX503060), PEDV (NC_003436), MHV (AY700211), HCoV-HKU1 (DQ415904), HCoV-NL63 (JX504050), HCOV-OC43 (AY903460), HKU5-1 (NC_009020), MERS-CoV (JX869059), HKU9-4 (EF065516), 2019-nCoV (MN996528), HKU3-1 (DQ022305), SHC014 (KC881005), WIV1

(KF367457), SARS-CoV (AY278741). Amino acid conservation scores of coronavirus RdRp were generated using ConSurf Server (https://consurf.tau.ac.il/) using the protein alignment described above and visualized on the SARS-CoV RdRp structure (PDB: 6NUR) in PyMol (version 1.8.6.0)[20,52].

Statistical analysis. All statistical data analyses were performed in Graphpad Prism 8. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. Specific tests are noted in each figure legend.

Ethics regulation of laboratory animals. Efficacy studies were performed in animal biosafety level 3 facilities at UNC Chapel Hill. All work was conducted under protocols approved by the Institutional Animal Care and Use Committee at UNC Chapel Hill (IACUC protocol #16-284) according to guidelines set by the Association for the Assessment and Accreditation of Laboratory Animal Care and the U.S. Department of Agriculture.

Funding: We would like to acknowledge the following funding sources, Antiviral Drug Discovery and Development Center (5U19AI109680), a partnership grant from the National Institutes of Health (5R01AI132178) and an NIAID R01 grant (AI108197). NIAID contract, HHSN272201500008C, was awarded to G.P. and The Emory institute for Drug Development and a subcontract from this was awarded to R.S.B. and M.R.D.

Author contributions: A.C.S., T.P.S, designed *in vitro* efficacy studies. A.C.S., A.J.B., T.P.S. and R.L.G. executed and/or analyzed *in vitro* efficacy studies. J.H., A.T. and N.J.T. providing the clinical isolate of SARS-CoV-2. T.P.S., A.A.K., M.G.N., G.P. and R.S.B. designed *in vivo* efficacy studies. T.P.S., A.C.S., S.Z., C.S.H, and R.S. designed, executed and/or analyzed the Primer ID NGS data. K.H.D 3rd performed structural

611 modeling and phylogenetics and sequence alignments. M.L.A., A.J.P., J.D.C. and
612 M.R.D. designed, performed and/or executed the construction of RDV resistant MHV
613 and performed cross-resistance studies. T.P.S., A.S. and S.R.L. executed and analyzed
614 *in vivo* efficacy studies. A.S. and S.R.L. performed whole body plethysmography for *in*
615 *vivo* studies. S.A.M. assessed all lung pathology. G.R.B., and M.S., were responsible
616 for synthesis, and scale-up of small molecules. T.P.S., A.C.S., S.Z., S.R.L, A.S., K.H.D.
617 3rd, M.L.A., A.J.P., J.D.C, G.R.B., A.A.K., G.P., R.S. M.R.D., and R.S.B., wrote the
618 manuscript.

619 **Disclaimers**

620 The findings and conclusions in this report are those of the author(s) and do not
621 necessarily represent the official position of the Centers for Disease Control and
622 Prevention. Names of specific vendors, manufacturers, or products are included for
623 public health and informational purposes; inclusion does not imply endorsement of the
624 vendors, manufacturers, or products by the Centers for Disease Control and Prevention
625 or the US Department of Health and Human Services.

626 **Competing financial interests:** A.C.S. received a contract from NIAID to support the *in*
627 *vitro* and *in vivo* efficacy studies reported herein. UNC is pursuing IP protection for
628 Primer ID and R.S. has received nominal royalties.

629

Figures

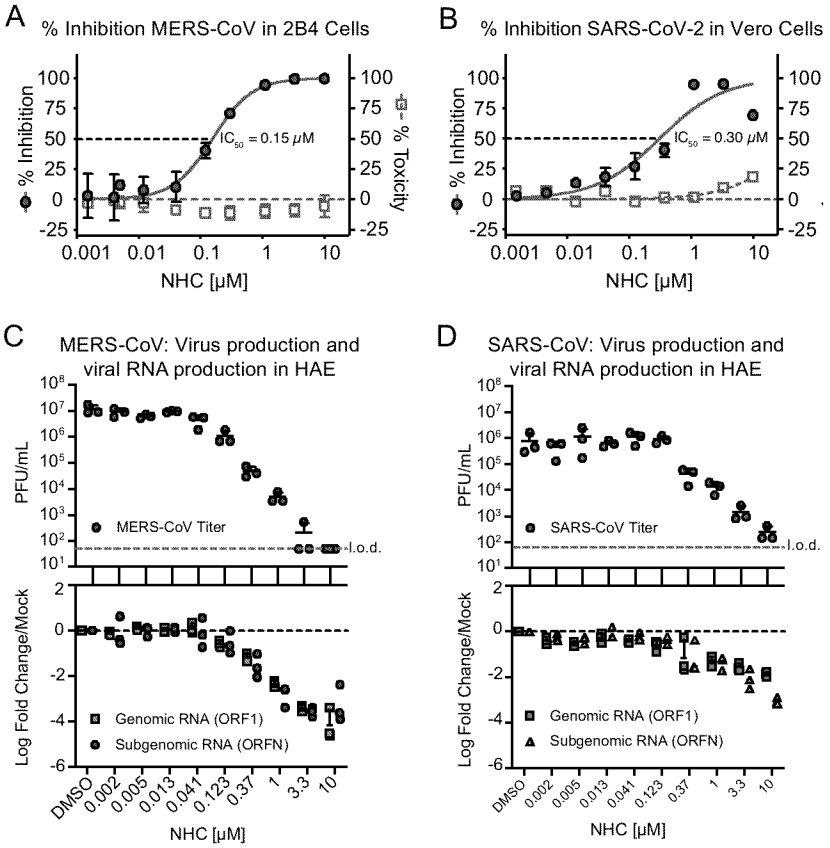


Figure 1: NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2 Replication. a, NHC antiviral activity and cytotoxicity in Calu3 cells infected with MERS-CoV. Calu3 cells were infected in triplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of MERS-CoV–expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via CellTiter-Glo assay. Data is combined from 3 independent experiments. **b**, NHC antiviral activity and cytotoxicity in Vero cells infected with SARS-CoV-2. Vero cells were infected in duplicate with SARS-CoV-2 clinical isolate virus at an MOI of 0.05 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of cell viability by CellTiter-Glo assay. Cytotoxicity was measured as in **a**. Data is combined from 2 independent experiments. **c**, NHC inhibits MERS-CoV virus production and RNA synthesis in primary human lung epithelial cell cultures (HAE). HAE cells were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of NHC for 48 hours, after which apical washes were collected for virus titration. qRT-PCR for MERS-CoV ORF1 and ORFN mRNA. Total RNA was isolated from cultures in **c** for qRT-PCR analysis. Representative data from three separate experiments with three different cell donors are displayed. PFU, plaque-forming units. **d**, NHC inhibits SARS-CoV virus production and RNA synthesis in primary human lung epithelial cell cultures (HAE). Studies performed as in **c** but with SARS-CoV green fluorescent protein (GFP). Representative data from two separate experiments with two different cell donors are displayed.

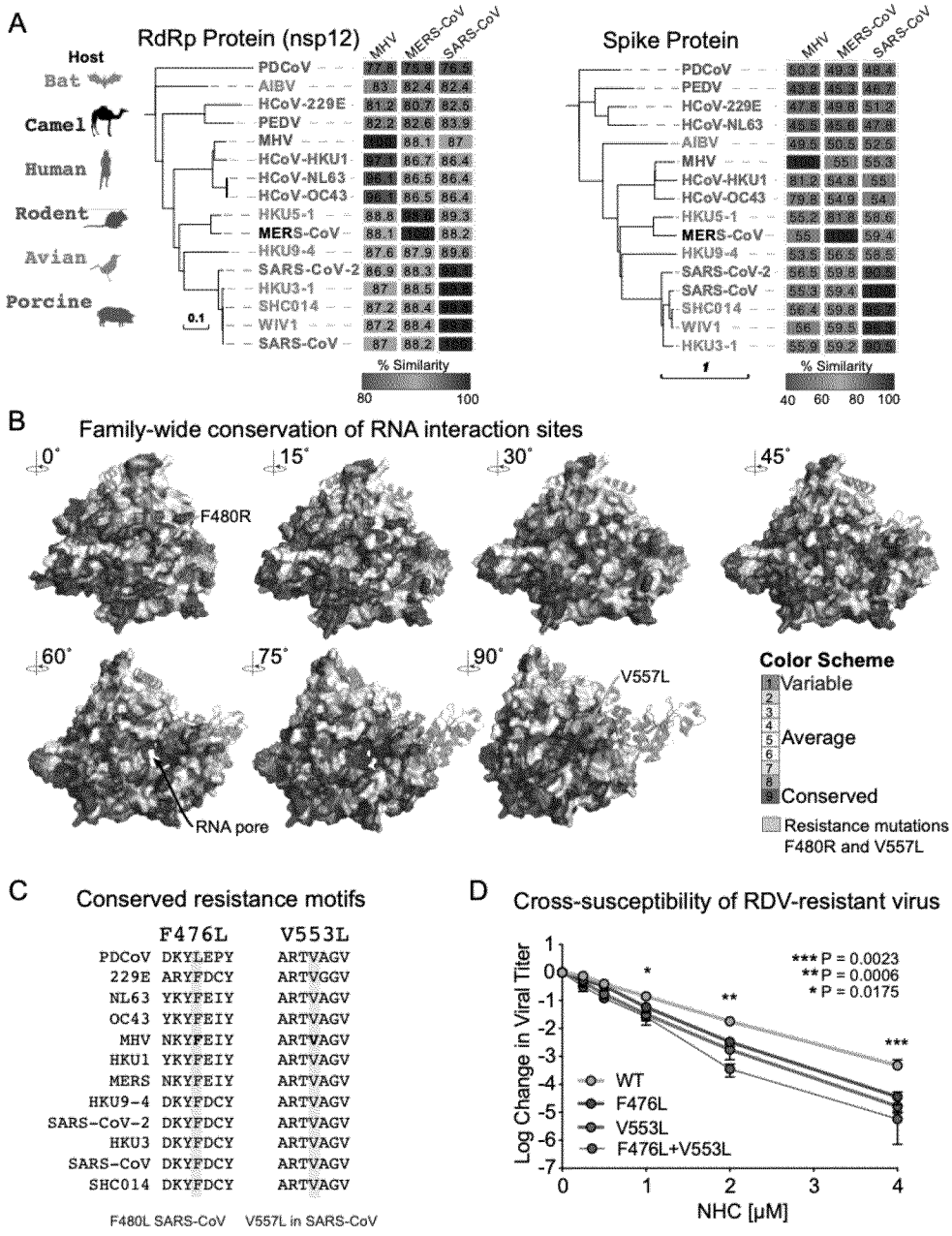


Figure 2

Figure 2. Remdesivir resistance mutations in the highly conserved RNA -dependent RNA polymerase increase susceptibility to NHC. a, Neighbor-joining trees created with representatives from all four CoV genogroups showing the genetic similarity of CoV nsp12 (RdRp) and CoV spike glycoprotein, which mediates host tropism and entry into cells. Text color of the virus strain label correspon ds to virus host species on the left. The heatmap adjacent to each neighbor-joining tree depicts percent amino acid identity (% A.A. similarity) against mouse hepatitis virus (MHV), SARS-CoV or MERS-CoV. **b**, Core residues of the CoV RdRp are highly conserved among CoV. The variation encompassed in panel **a** was modeled onto the RdRp structure of the SARS -CoV RdRp. **c**, Amino acid sequence of CoV in panel **a** at known resistance alleles to antiviral drug remdesivir (RDV). **d**, RDV resistant viruses are more susceptib le to NHC antiviral activity. Virus titer reduction assay across a dose response of NHC with recombinant MHV bearing resistance mutations to RDV. Asterisks indicate statistically significant differences by Mann - Whitney test.

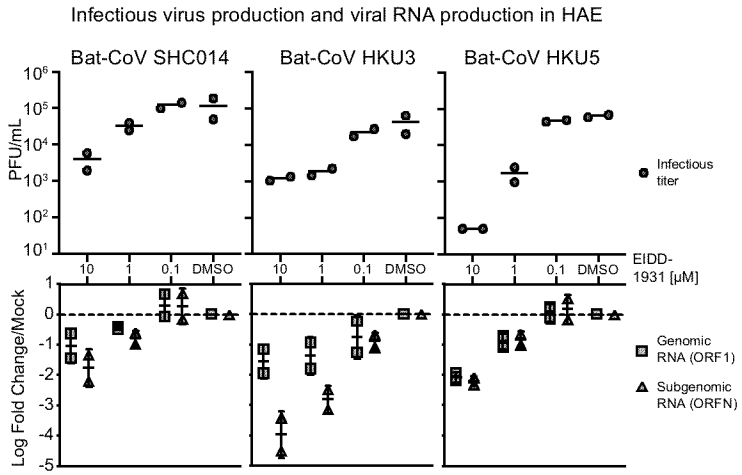


Figure 3: NHC is effective against multiple genetically distinct Bat-CoV. Top: Antiviral efficacy of NHC in HAE cells against SARS-like (HKU3, SHC014, group 2b) and MERS-like (HKU5, group 2c) bat-CoV. HAE cells were infected at an MOI of 0.5 in the presence of NHC in duplicate. After 48 hours, virus produced was titrated via plaque assay. Each data point represents the titer per culture. Bottom: qRT-PCR for CoV ORF1 and ORFN mRNA in total RNA from cultures in the top panel. Representative data from two separate experiments with two different cell donors are displayed.

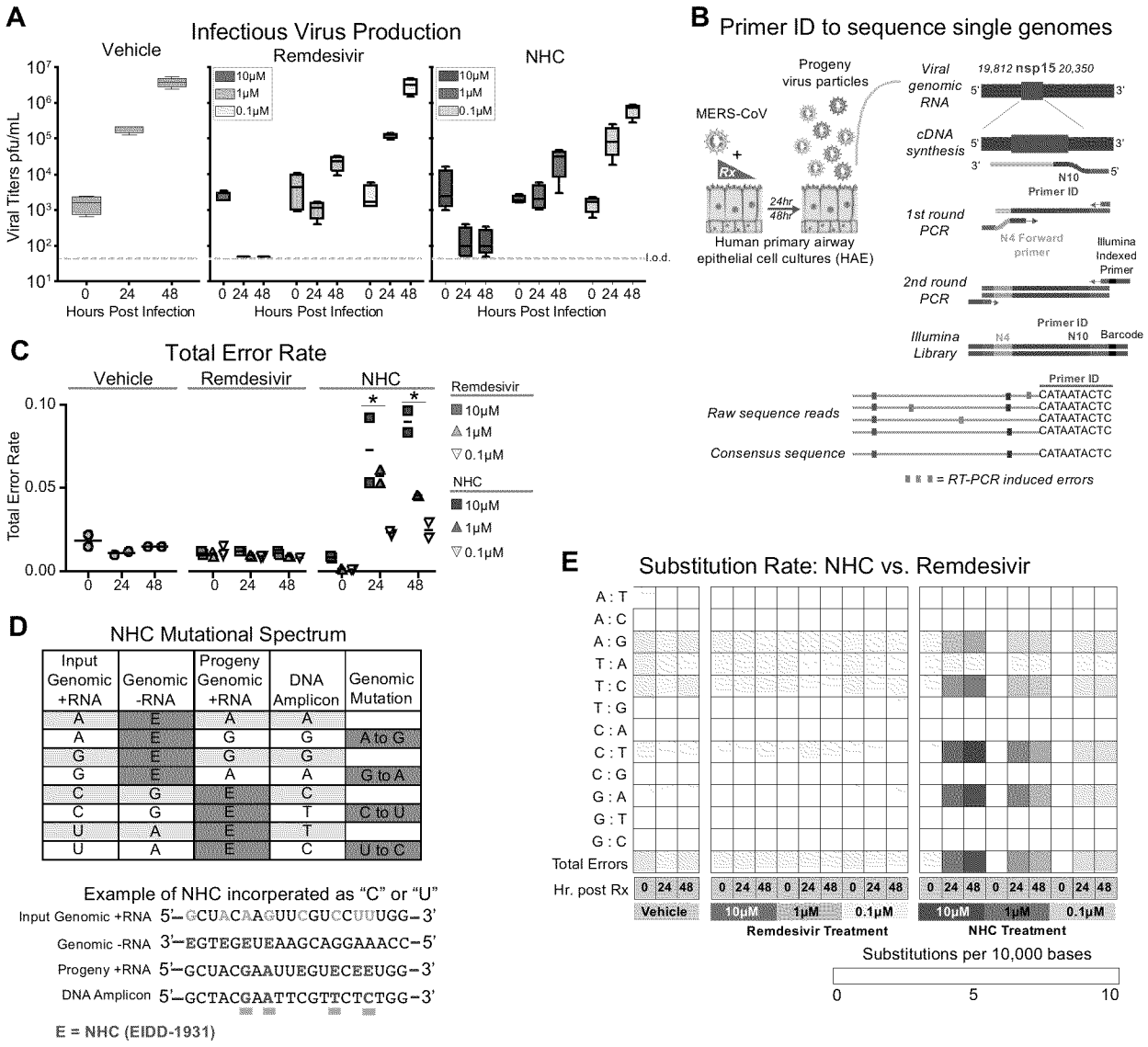


Figure 4: NHC antiviral activity is associated with increased viral mutation rates a, Both remdesivir (RDV) and NHC reduce MERS-CoV infectious virus production in primary human HAE. Cultures were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of vehicle, RDV or NHC for 48 hours, after which apical washes were collected for virus titration. Data is combined from two independent studies. **b,** A deep sequencing approach called Primer ID to gain accurate sequence data for single RNA genomes of MERS-CoV. **c**, The total error rate for MERS-CoV RNA isolated from cultures in panel **a** as determined by Primer ID. Error rate values are # mutations per 10,000 bases. Asterisks indicate significant differences as compared to untreated by 2 -way ANOVA with a Dunnett's multiple comparison test. **d**, description of potential NHC mutational spectra on both positive and negative sense viral RNA. **e**, Nucleotide transitions adenine (A) to guanine (G) and uridine (U) to cytosine (C) transitions are enriched in MERS-CoV genomic RNA in an NHC dose dependent manner.

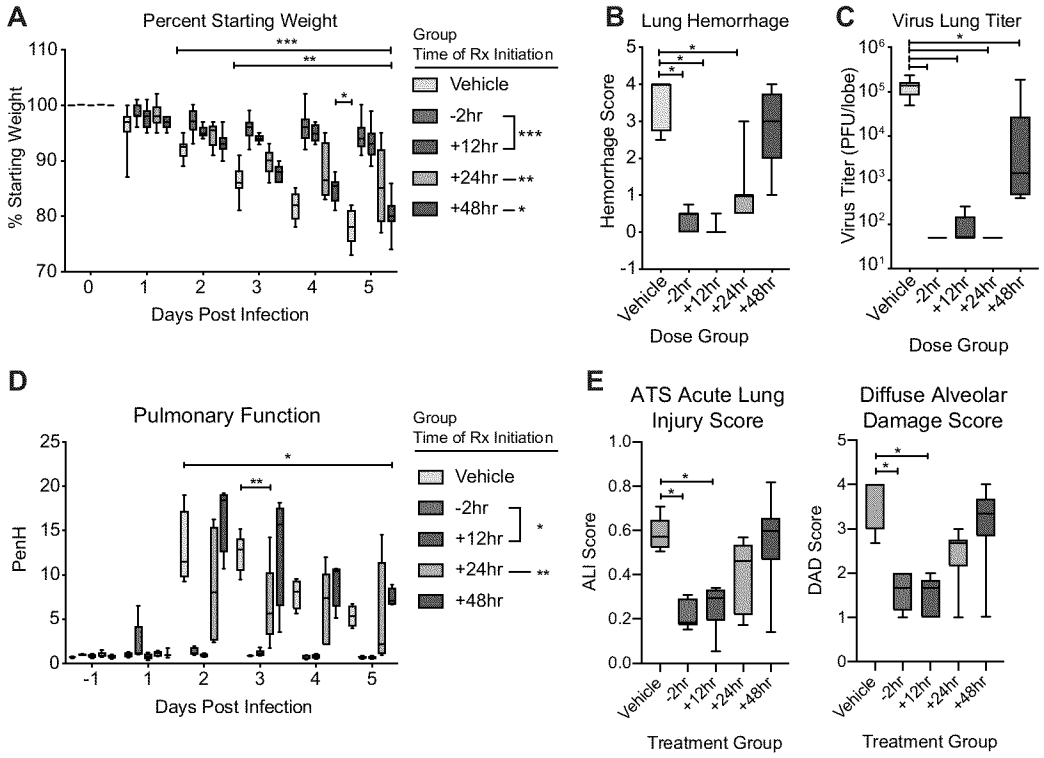


Figure 5: Prophylactic and Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Equivalent numbers of 25-29 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse-adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **d,** Pulmonary function by whole body plethysmography was performed daily on five animals per group. Asterisks indicate differences by two-way ANOVA with a Dunnett's multiple comparison test. **e,** Therapeutic EIDD-2801 reduces acute lung injury (ALI). The histological features of ALI were blindly scored using the American Thoracic Society Lung Injury Scoring system and a Diffuse Alveolar Damage Scoring System. Three randomly chosen high power (60X) fields of diseased lung were assessed per mouse. The numbers of mice scored per group: Vehicle N = 7,-2hr N = 9, +12hr N = 9, +24hr N = 10, +48hr N = 9. Asterisks indicate statistical significance by Kruskal-Wallis with a Dunn's multiple comparison test. For all panels, the boxes encompass the 25th to 75th percentile, the line is at the median, while the whiskers represent the range.

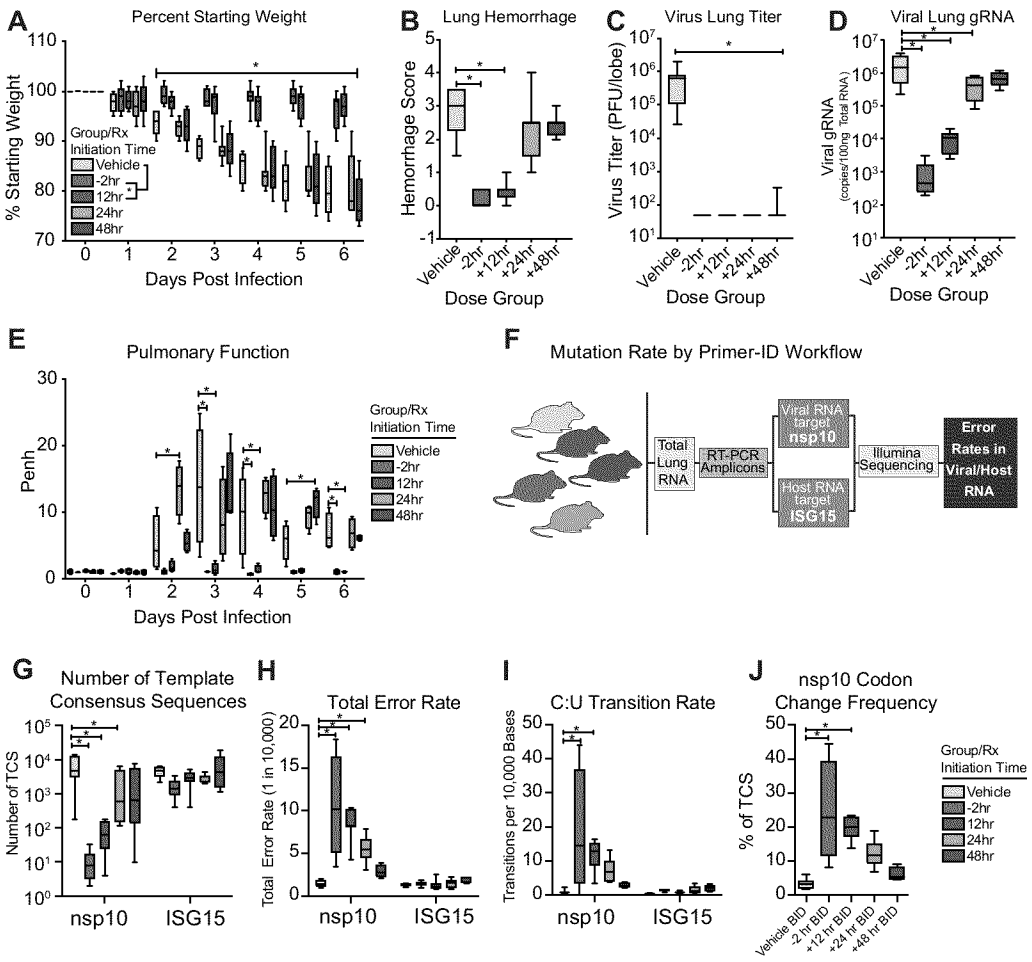
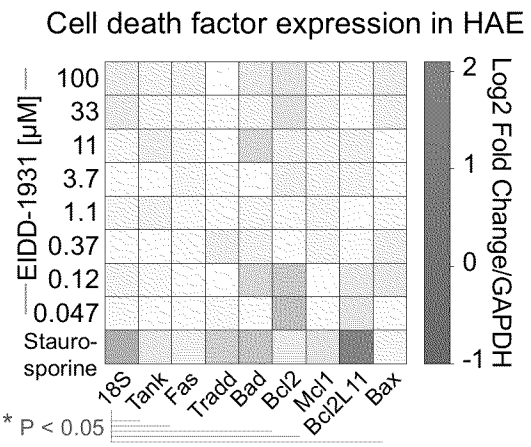
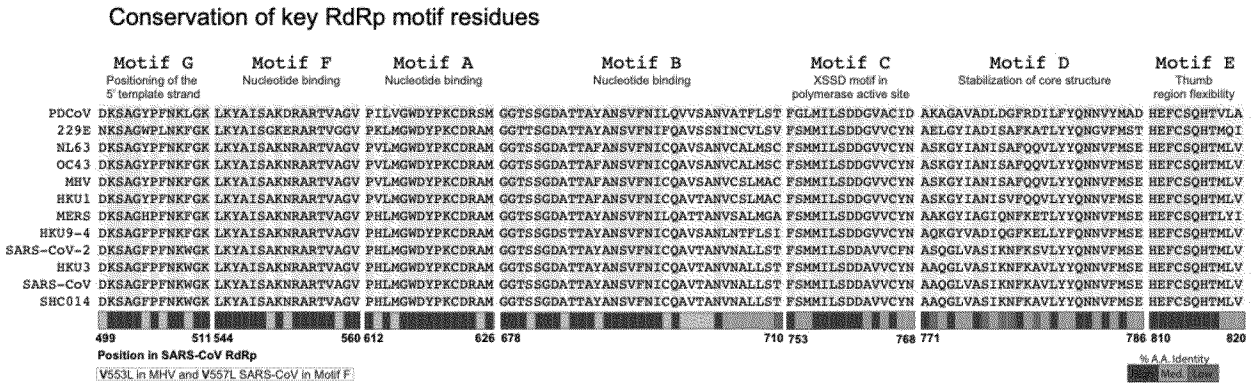


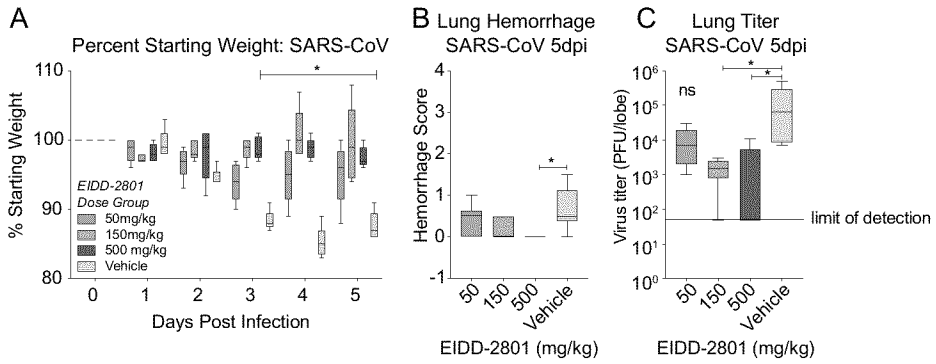
Figure 6: Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis coincident with increased viral mutation rates . Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with5E+04 PFU mouse-adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test. **d**, MERS-CoV genomic RNA in lung tissue by qRT-PCR. Asterisks indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **e**, Pulmonary function by whole body plethysmography was performed daily on four animals per group. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **f**, Workflow to measure mutation rate in MERS-CoV RNA and host transcript ISG15 by Primer ID in mouse lung tissue. **g**, Number of template consensus sequences for MERS-CoV nsp10 and ISG15. **h**, Total error rate in MERS-CoV nsp10 and ISG15. **i**, The cytosine to uridine transition rate in MERS-CoV nsp10 and ISG15. In panels **g-i,** asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **j**, Codon change frequency in MERS-CoV nsp10. Asterisks indicate differences on Kruskal-Wallis with Dunn's multiple comparison test.



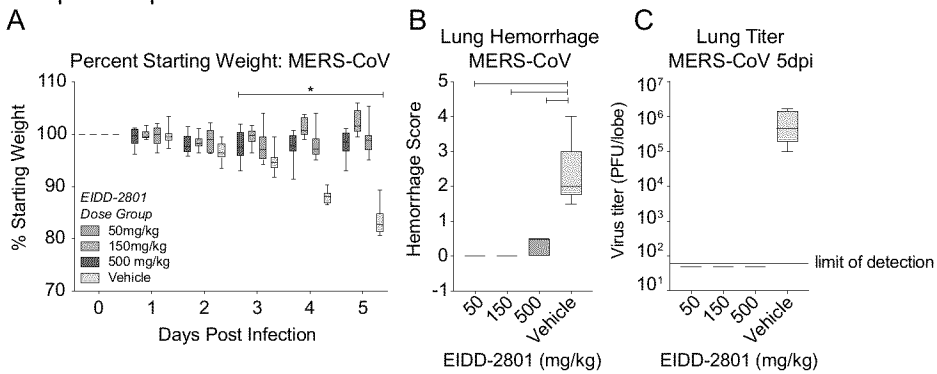
Supplementary Figure 1: Assessment of cytotoxicity of NHC in primary human epitheli al cell cultures by qRT-PCR. Companion figure to **Figure 1c** and **d**. Primary human epithelial cell cultures were exposed to positive control 1µM staurosporine or a dose response of NHCfor 48hr. Cytotoxicity was assessed by qRT-PCR for cell death factor gene expression.



Supplementary Figure 2: High conservation of RdRp functional domains for SARS-CoV-2. Companion figure to **Figure 2a.** Multiple sequence alignment of the RNA dependen t RNA polymerase (RdRp) from viruses in the dendrogram in Figure 2a showing high conservation in the RdRp structural motifs A-G.



Supplementary Figure 3: Prophylactic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Companion figure to **Figure 5**. Equivalent numbers of 20 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at 2hr prior to infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse -adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with a Dunn's multiple comparison test.



Supplementary Figure 4: Prophylactic EIDD-2801 reduces MERS-CoV replication and pathogenesis. Companion figure to **Figure 6.** Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning 2hr prior to infection every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 5E+04 PFU mouse -adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test.

Supplementary Table 1. Real-time PCR primer/probe sets for indicators of cellular apoptosis/toxicity

Primer/Probe Target	Assay Reference Number*
Bax	Hs00180269_m1
Bad	Hs00188930_m1
Bcl2L11	Hs00708019_s1
Bcl2	Hs00608023_m1
Mcl1	Hs01050896_m1
Tradd	Hs00601065_g1
Fas	Hs00236330_m1
Tank	Hs00370305_m1
18S	4352930E
GAPD**	4352934E

* Validated assays available from Life Technologies

** The housekeeping gene hGAPDH was used for normalization of real-time results.

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Supplementary Table 2. Primer used for MiSeq library prep and sequencing.

Primer	5'-3'	Comment
41R_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATGACCTTCCTGTTGCTTCT	cDNA primer. Targeting 20331-20350 on the reference genome.
nsp10_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTCCTAAAGACGACATCAGTGG	cDNA primer. Targeting 13488-13507 on the reference genome.
nsp12_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATAGCCAAAGACACAAACCG	cDNA primer. Targeting 15983-16002 on the reference genome.
nsp14_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGAACATCGACAAAGAAAGGG	cDNA primer. Targeting 18715-18734 on the reference genome.
ifit3_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTTTCAGCCACTCCTTTATCCC	cDNA primer. Targeting mice IFIT3 mRNA.
isg15_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGGGGCTTTAGGCCATACTC	cDNA primer. Targeting mice ISG15 mRNA.
41F_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNGCTACAAGTTCGTCCTTTGG	1st round PCR forward primer. Targeting 19812-19831 on the reference genome
nsp10_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGCTCAGGTGCTAAGCGAAT	1st round PCR forward primer. Targeting 12983-13002 on the reference genome
nsp12_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATAGGCTTCGATGTTGAGGG	1st round PCR forward primer. Targeting 15388-15407 on the reference genome
nsp14_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATTGCAAGCTGGTTCTAACA	1st round PCR forward primer. Targeting 18260-18279 on the reference genome
ifit3_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNCGATCCACAGTGAACAACAG	1st round PCR forward primer. Targeting mice IFIT3 mRNA.
isg15_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGGGACCTAAAGGTGAAGATG	1st round PCR forward primer. Targeting mice ISG15 mRNA.
Adapter R	GTGACTGGAGTTCAGACGTGTGCTC	1st round PCR reverse primer
Universal Adapter	AATGATACGGCGACCACCGAGATCTACACGCCTCCCTCGCGCCATCAGAGATGTG	2nd round PCR forward primer with Illumina adapter sequence
Indexed Adapter	CAAGCAGAAGACGGCATACGAGATNNNNNNGTGACTGGAGTTCAGACGTGTGCTC	2nd round PCR reverse primer with Illumina adapter sequence and indices (NNNNNNN)
Old Nextera	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAG	Customized sequencing primer

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1. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). (2018).
2. de Wit, E., van Doremalen, N., Falzarano, D. & Munster, V.J. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* **14**, 523-534 (2016).
3. Wang, D.*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
4. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D. & Fouchier, R.A. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* **367**, 1814-1820 (2012).
5. Hsu, L.Y.*, et al.* Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* **9**, 713-717 (2003).
6. Zhou, P.*, et al.* Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* **556**, 255-258 (2018).
7. Woo, P.C.*, et al.* Molecular diversity of coronaviruses in bats. *Virology* **351**, 180-187 (2006).
8. Menachery, V.D.*, et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
9. Menachery, V.D.*, et al.* SARS-like WIV1-CoV poised for human emergence. *Proc Natl Acad Sci U S A* **113**, 3048-3053 (2016).
10. Reynard, O.*, et al.* Identification of a New Ribonucleoside Inhibitor of Ebola Virus Replication. *Viruses* **7**, 6233-6240 (2015).
11. Urakova, N.*, et al.* beta-d-N (4)-Hydroxycytidine Is a Potent Anti-alphavirus Compound That Induces a High Level of Mutations in the Viral Genome. *J Virol* **92**(2018).
12. Toots, M.*, et al.* Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. *Sci Transl Med* **11**(2019).
13. Agostini, M.L.*, et al.* Small-Molecule Antiviral beta-d-N (4)-Hydroxycytidine Inhibits a Proofreading-Intact Coronavirus with a High Genetic Barrier to Resistance. *J Virol* **93**(2019).
14. Jordan, P.C.*, et al.* Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase. *PLoS Pathog* **14**, e1006889 (2018).
15. Sheahan, T.P.*, et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222 (2020).
16. Sheahan, T.P.*, et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* **9**(2017).
17. Anthony, S.J.*, et al.* Further Evidence for Bats as the Evolutionary Source of Middle East Respiratory Syndrome Coronavirus. *mBio* **8**(2017).
18. Hu, B., Ge, X., Wang, L.F. & Shi, Z. Bat origin of human coronaviruses. *Virol J* **12**, 221 (2015).
19. Huynh, J.*, et al.* Evidence supporting a zoonotic origin of human coronavirus strain NL63. *J Virol* **86**, 12816-12825 (2012).
20. Kirchdoerfer, R.N. & Ward, A.B. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun* **10**, 2342 (2019).

21. Agostini, M.L., *et al.* Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *MBio* **9**(2018).
22. Becker, M.M., *et al.* Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. *Proc Natl Acad Sci U S A* **105**, 19944-19949 (2008).
23. Agnihothram, S., *et al.* A mouse model for Betacoronavirus subgroup 2c using a bat coronavirus strain HKU5 variant. *MBio* **5**, e00047-00014 (2014).
24. Yoon, J.J., *et al.* Orally Efficacious Broad-Spectrum Ribonucleoside Analog Inhibitor of Influenza and Respiratory Syncytial Viruses. *Antimicrob Agents Chemother* **62**(2018).
25. Zhou, S., Jones, C., Mieczkowski, P. & Swanstrom, R. Primer ID Validates Template Sampling Depth and Greatly Reduces the Error Rate of Next-Generation Sequencing of HIV-1 Genomic RNA Populations. *J Virol* **89**, 8540-8555 (2015).
26. Tchesnokov, E.P., Feng, J.Y., Porter, D.P. & Gotte, M. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses* **11**(2019).
27. Menachery, V.D., Gralinski, L.E., Baric, R.S. & Ferris, M.T. New Metrics for Evaluating Viral Respiratory Pathogenesis. *PLoS One* **10**, e0131451 (2015).
28. Cockrell, A.S., *et al.* A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. *Nat Microbiol* **2**, 16226 (2016).
29. Marston, H.D., Folkers, G.K., Morens, D.M. & Fauci, A.S. Emerging viral diseases: confronting threats with new technologies. *Sci Transl Med* **6**, 253ps210 (2014).
30. Paules, C.I., Marston, H.D. & Fauci, A.S. Coronavirus Infections-More Than Just the Common Cold. *JAMA* (2020).
31. Brown, A.J., *et al.* Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* **169**, 104541 (2019).
32. Cai, B. Severe 2019-nCoV Remdesivir RCT (NCT04257656). (2020).
33. Ehteshami, M., *et al.* Characterization of beta-d-N(4)-Hydroxycytidine as a Novel Inhibitor of Chikungunya Virus. *Antimicrob Agents Chemother* **61**(2017).
34. Warren, T.K., *et al.* Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* **531**, 381-385 (2016).
35. Lo, M.K., *et al.* GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep* **7**, 43395 (2017).
36. Oh, M.D., *et al.* Viral Load Kinetics of MERS Coronavirus Infection. *N Engl J Med* **375**, 1303-1305 (2016).
37. Peiris, J.S., *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767-1772 (2003).
38. de Wit, E., *et al.* Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proc Natl Acad Sci U S A* **110**, 16598-16603 (2013).

39. McAuliffe, J., *et al.* Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. *Virology* **330**, 8-15 (2004).
40. Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S. & Yuen, K.Y. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov* **15**, 327-347 (2016).
41. Smith, E.C., Blanc, H., Surdel, M.C., Vignuzzi, M. & Denison, M.R. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. *PLoS Pathog* **9**, e1003565 (2013).
42. Sims, A.C., *et al.* Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: role of ciliated cells in viral spread in the conducting airways of the lungs. *J Virol* **79**, 15511-15524 (2005).
43. Scobey, T., *et al.* Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. *Proc Natl Acad Sci U S A* **110**, 16157-16162 (2013).
44. Douglas, M.G., Kocher, J.F., Scobey, T., Baric, R.S. & Cockrell, A.S. Adaptive evolution influences the infectious dose of MERS-CoV necessary to achieve severe respiratory disease. *Virology* **517**, 98-107 (2018).
45. Roberts, A., *et al.* A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. *PLoS Pathog* **3**, e5 (2007).
46. Fulcher, M.L., Gabriel, S., Burns, K.A., Yankaskas, J.R. & Randell, S.H. Well-differentiated human airway epithelial cell cultures. *Methods Mol Med* **107**, 183-206 (2005).
47. Jabara, C.B., Jones, C.D., Roach, J., Anderson, J.A. & Swanstrom, R. Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID. *Proc Natl Acad Sci U S A* **108**, 20166-20171 (2011).
48. Fukushi, M., *et al.* Serial histopathological examination of the lungs of mice infected with influenza A virus PR8 strain. *PLoS One* **6**, e21207 (2011).
49. Matute-Bello, G., *et al.* An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* **44**, 725-738 (2011).
50. Schmidt, M.E., *et al.* Memory CD8 T cells mediate severe immunopathology following respiratory syncytial virus infection. *PLoS Pathog* **14**, e1006810 (2018).
51. Almazan, F., *et al.* Engineering a replication-competent, propagation-defective Middle East respiratory syndrome coronavirus as a vaccine candidate. *mBio* **4**, e00650-00613 (2013).
52. Ashkenazy, H., *et al.* ConSurf 2016: an improved methodology to estimate and visualize evolutionary conservation in macromolecules. *Nucleic Acids Res* **44**, W344-350 (2016).

An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus

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Abstract (153)

Coronaviruses (CoVs) traffic frequently between species resulting in novel disease outbreaks, most recently exemplified by the newly emerged SARS-CoV-2. Herein, we show that the ribonucleoside analog β-D-N[4]-hydroxycytidine (NHC, EIDD-1931) has

broad spectrum antiviral activity against SARS-CoV 2, MERS-CoV, SARS-CoV, and related zoonotic group 2b or 2c Bat-CoVs, as well as increased potency against a coronavirus bearing resistance mutations to another nucleoside analog inhibitor. In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801, an orally bioavailable NHC-prodrug (β-D-N^4-hydroxycytidine-5'-isopropyl ester), improved pulmonary function, and reduced virus titer and body weight loss. Decreased MERS-CoV yields *in vitro* and *in vivo* were associated with increased transition mutation frequency in viral but not host cell RNA, supporting a mechanism of lethal mutagenesis. The potency of NHC/EIDD-2801 against multiple coronaviruses, its therapeutic efficacy, and oral bioavailability *in vivo*, all highlight its potential utility as an effective antiviral against SARS-CoV-2 and other future zoonotic coronaviruses.

Introduction

The genetically diverse *Orthocoronavirinae* (coronavirus, CoV) family circulates in many avian and mammalian species. Phylogenetically, CoVs are divided into 4 genera: alpha (group 1), beta (group 2), gamma (group 3) and delta (group 4). Three new human CoV have emerged in the past 20 years with severe acute respiratory syndrome CoV (SARS-CoV) in 2002, Middle East respiratory syndrome CoV (MERS-CoV) in 2012, and now SARS-CoV-2 in 2019[1-3]. The ongoing SARS-CoV-2 epidemic (referred to as COVID-19, Coronavirus disease 2019) has caused over 89,000 infections and over 3,000 deaths in 71 countries. Like SARS- and MERS-CoV, the respiratory disease caused by SARS-CoV-2 can progress to acute lung injury (ALI), an end stage lung disease with limited treatment options and very poor prognoses[3-5]. This emergence paradigm is not limited to humans. A novel group 1 CoV called swine acute diarrhea syndrome CoV (SADS-CoV) recently emerged from bats causing the loss of over 20,000 pigs in Guangdong Province, China[6]. More alarmingly, many group 2 SARS-like and MERS-like coronaviruses are circulating in bat reservoir species that can use human receptors and replicate efficiently in primary human lung cells without adaptation[6-9]. The presence of these "pre-epidemic" zoonotic strains foreshadow the emergence and epidemic potential of additional SARS-like and MERS-like viruses in

the future. Given the diversity of CoV strains in zoonotic reservoirs and a penchant for emergence, broadly active antivirals are clearly needed for rapid response to new CoV outbreaks in humans and domesticated animals.

Currently, there are no approved therapies specific for any human CoV. β-D-N4-hydroxycytidine (NHC, EIDD-1931) is orally bioavailable ribonucleoside analog with broad-spectrum antiviral activity against various unrelated RNA viruses including influenza, Ebola, CoV and Venezuelan equine encephalitis virus (VEEV)[10-13]. For VEEV, the mechanism of action (MOA) for NHC has been shown to be through lethal mutagenesis where deleterious transition mutations accumulate in viral RNA[11,14]. Here, we demonstrate that NHC exerts potent, broad-spectrum activity against SARS-CoV, MERS-CoV and their related bat-CoV in primary human airway epithelial cell cultures (HAE), a biologically relevant model of the human conducting airway. In addition, we show that NHC is potently antiviral against the newly emerging SARS-CoV-2 as well as against coronavirus bearing resistance mutations to the potent nucleoside analog inhibitor, remdesivir (RDV). In SARS- or MERS-CoV infected mice, both prophylactic and therapeutic administration EIDD-2801, an oral NHC-prodrug (β-D-N^4-hydroxycytidine-5'-isopropyl ester) improved pulmonary function and reduced virus titer and ameliorated disease severity. In addition, therapeutic EIDD-2801 reduced the pathological features of ALI in SARS-CoV infected mice. Using a high-fidelity deep sequencing approach (Primer ID), we found that increased mutation rates coincide with decreased MERS-CoV yields *in vitro* and protective efficacy *in vivo* supporting the MOA of lethal mutagenesis against emerging CoV[13]. The broad activity and therapeutic efficacy of NHC/EIDD-2801 highlight its potential to diminish epidemic disease today and limit future emerging CoV outbreaks.

Results

NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2 Replication.

To determine whether NHC blocks the replication of highly pathogenic human CoV, we performed antiviral assays in continuous and primary human lung cell cultures. We first assessed the antiviral activity of NHC against MERS-CoV in the

human lung epithelial cell line Calu-3 2B4 ("Calu3" cells). Using a recombinant MERS-CoV expressing nanoluciferase (MERS-nLUC)[15], we measured virus replication in cultures exposed to a dose range of drug for 48hr. NHC was potently antiviral with an average half-maximum effective concentration (IC_{50}) of 0.15μM and no observed cytoxicity in similarly treated uninfected cultures across the dose range (50% cytotoxic concentration, CC_{50}, >10μM) (Fig. 1A). The therapeutic index for NHC was >100. Similarly, NHC strongly inhibited SARS-CoV-2 replication in Vero cells with an IC_{50} of 0.3μM and CC_{50} of >10μM (Fig. 1B). Human primary airway epithelial (HAE) cell cultures model the architecture and cellular complexity of the conducting airway and are readily infected by multiple human and zoonotic CoV, including SARS- and MERS-CoV[16]. We first assessed cytotoxicity of NHC in HAE treated with an extended dose range for 48hr using quantitative PCR of cell death-related gene transcripts as our metric. NHC treatment did not appreciably alter gene expression even at doses up to 100μM (Supplementary Figure 1). In MERS-CoV infected HAE, NHC dramatically reduced virus production with maximal titer reduction of > 5 logs at 10μM (average IC_{50} = 0.024 μM), which correlated with reduced genomic (ORF1) and subgenomic (ORFN) RNA in paired samples (Fig. 1C). We observed similar trends in titer reduction (> 3 log at 10μM, average IC_{50} = 0.14 μM) and levels of genomic and subgenomic RNA in SARS-CoV infected HAE (Fig. 1D). Thus, NHC was potently antiviral against MERS-CoV and SARS-CoV-2 in cell lines and MERS-CoV and SARS-CoV in human primary HAE cell cultures without cytotoxicity.

NHC is effective against remdesivir resistant virus and multiple distinct zoonotic CoV.

All human CoV are thought to have emerged as zoonoses most recently exemplified by SARS-CoV, MERS-CoV and SARS-CoV-2[17-19]. Although taxonomically divided into multiple genogroups (alpha , beta , gamma , delta), human CoV are found in only the alpha and beta subgroups thus far (Fig. 2A). There is high sequence conservation in the RdRp across CoV (Fig. 2A). For example, the RdRp of SARS-CoV-2 has 99.1% similarity and 96% amino acid identity to that of SARS-CoV (Fig. 2A). To gain insight into structural conservation of RdRp across the CoV family, we modeled

the variation reflected in the RdRp dendrogram in Fig. 2A onto the structure of the SARS-CoV RdRp[20] (Fig. 2B). The core of the RdRp molecule and main structural motifs that all RdRp harbor (Fig. 2B and Supplementary Figure 2) are highly conserved among CoV including SARS-CoV-2. We previously reported that CoV resistance to another broad spectrum nucleoside analog, remdesivir (RDV) was mediated by RdRp residues F480L and V557L in a model coronavirus mouse hepatitis virus (MHV) and in SARS-CoV, resulting in a 5-fold shift in IC_{50} (Fig. 2C)[21]. Consequently, we tested whether RDV resistance mutations in MHV conferred cross resistance to NHC (Figure 2D). In fact, the two RDV resistance mutations, alone or together conferred increased sensitivity to inhibition by NHC. As our previous studies have demonstrated a high genetic barrier to NHC for VEEV, influenza and coronavirus[11-13], the lack of cross resistance further suggests that NHC and RDV may select for exclusive and mutually sensitizing resistance pathways.

To explore the breadth of antiviral efficacy against zoonotic CoV, we performed antiviral assays in HAE with three zoonotic Bat-CoV, SHC014, HKU3 and HKU5. Closely related to the beta 2b SARS-CoV, Bat-CoV SHC014 is capable of replicating in human cells without adaptation[8] suggesting its potential for zoonotic emergence. More distantly related SARS-like beta 2b CoV, recombinant Bat-CoV HKU3 has a modified receptor binding domain to facilitate growth in cell culture[22]. Lastly, Bat-CoV HKU5 is a MERS-like beta 2c CoV[23]. NHC diminished infectious virus production and the levels of genomic/subgenomic viral RNA in HAE in a dose-dependent manner for all three Bat-CoVs (Fig. 3). Therefore, the antiviral activity of NHC was not limited by natural amino acid variation in the RdRp, which among the group 2b and group 2c CoV can vary by almost 20% (Fig. 2A). Moreover, these data suggest that if another SARS- or MERS-like virus were to spillover into humans in the future, they would likely be susceptible to the antiviral activity of NHC.

NHC antiviral activity is associated with increased viral mutation rates.

It has recently been shown that NHC treatment increases the mutation rate in viral genomic RNA of RSV[24], VEEV[11], influenza[24], and our previous study used RNA seq to show that overall transition mutation frequency is increased during NHC

treatment of MHV and MERS-CoV during infection in continuous cell lines[13]. We sought to determine if NHC would increase the mutation frequency during MERS-CoV infection in human primary human airway epithelial cells (HAE). Using MERS-CoV infected HAE treated with either vehicle or a dose range of NHC or RDV, we show that both drugs reduced virus titers in a dose-dependent manner (Fig. 4A). We then employed a highly-sensitive high-fidelity deep sequencing approach (Primer ID NGS), which uses barcoded degenerate primers and Illumina indexed libraries to determine accurate mutation rates after antiviral treatment on viral RNA production[25]. Using this approach, we analyzed a 538bp region of viral genomic RNA in nonstructural protein 15 (nsp15). The error rates (#mutations/10,000 bases) in vehicle (0.01) or RDV (0.01) treated cultures were very low. RDV is reported to act via chain termination of nascent viral RNA, and thus the low error rates in RDV-treated cultures are in line with the proposed MOA[26]. In contrast, the error rate was significantly increased in NHC-treated MERS-CoV RNA in a dose-dependent manner (10-fold at 10μM and 5-fold at 1μM) at both 24 and 48hpi (Fig. 4C). The magnitude of the error rate in NHC-treated cultures correlated with virus titer reduction. At 48hpi the respective error rate and virus titer was 0.015 and 3.96E+06 pfu/mL for vehicle treatment, 0.045 and 2.86E+04 pfu/mL with 1μM NHC; and 0.090 and 1.5E+02 pfu/mL 10μM NHC. Thus, with 1μM NHC a 3-fold increase in error rate resulted in a 138-fold decrease in virus titer, while with 10μM NHC a 6-fold increase in error rate resulted in a 26,000-fold decrease in virus titer.

We then examined the mutational spectra induced by NHC, which can be incorporated into viral RNA as a substitution for either cytosine (C) or Uridine (U). RNA-mutagenic antivirals may incorporate in both nascent negative and positive sense RNA during genome replication (Fig. 4D). Adenine-to-guanine (A-to-G) and uracil-to-cytosine (U-to-C) transitions were enriched in MERS-CoV genomic RNA in an NHC dose-dependent manner (Fig. 4E). Collectively, these data used high-fidelity sequence analysis to demonstrate a specific enrichment for A:G and C:U transitions in MERS-CoV RNA after NHC treatment of primary HAE cell cultures.

Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis.

Given the promising antiviral activity of NHC in vitro, we next evaluated its *in vivo* efficacy using EIDD-2801, an orally bioavailable prodrug of NHC (β-D-N^4-hydroxycytidine-5'-isopropyl ester), designed for improved *in vivo* pharmacokinetics and oral bioavailability in humans and non-human primates[12]. Importantly, the plasma profiles of NHC and EIDD-2801 were similar in mice following oral delivery[12]. We first performed a prophylactic dose escalation study in C57BL/6 mice where we orally administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500 mg/kg EIDD-2801 2hr prior to intranasal infection with 5E+04 PFU of mouse-adapted SARS-CoV (SARS-MA15), and then every 12hr thereafter. Beginning on 3dpi and through the end of the study, body weight loss compared to vehicle treatment was significantly diminished (50mg/kg) or prevented (150, 500mg/kg) with EIDD-2801 prophylaxis ($P < 0.0001$) (Supplemental Figure 2A). Lung hemorrhage was also significantly reduced 5dpi with 500mg/kg EIDD-2801 treatment (Supplemental Figure 2B). Interestingly, there was a dose-dependent reduction in SARS-CoV lung titer (median titers: 50mg/kg = 7E+03 pfu/mL, 150mg/kg = 2.5E+03 pfu/mL, 500mg/kg = 50 pfu/mL, vehicle = 6.5E+04 pfu/mL) with significant differences among the vehicle, 150 mg/kg ($P = 0.03$) and 500mg/kg ($P = 0.006$) groups. Thus, prophylactic orally administered EIDD-2801 was robustly antiviral and able to prevent SARS-CoV replication and disease.

Since only the 500mg/kg group significantly diminished weight loss, hemorrhage and reduced lung titer to near undetectable levels, we tested this dose under therapeutic treatment conditions to determine if EIDD-2801 could improve the outcomes of an ongoing CoV infection. As a control, we initiated oral vehicle or EIDD-2801 2hr prior to infection with 1E+04 pfu SARS-MA15. For therapeutic conditions, we initiated EIDD-2801 treatment 12, 24, or 48hr after infection. After initiating treatment, dosing for all groups was performed every 12hr for the duration of the study. Both prophylactic treatment initiated 2hr prior to infection and therapeutic treatment initiated 12hr after infection significantly prevented body weight loss following SARS-CoV infection on 2dpi and thereafter (-2hr: $P = 0.0002$ to <0.0001; +12hr: $P = 0.0289$ to <0.0001) (Fig. 5A). Treatment initiated 24hpi also significantly reduced body weight loss (3-5dpi, $P = 0.01$ to <0.0001) although not to the same degree as the earlier treatment initiation groups.

When initiated 48hpi, body weight loss was only different from vehicle on 4dpi (P = 0.037, Fig. 5A). Therapeutic EIDD-2801 significantly reduced lung hemorrhage when initiated up to 24hr after infection mirroring the body weight loss phenotypes (Fig. 5B). Interestingly, all EIDD-2801 treated mice had significantly reduced viral loads in the lungs even in the +48hr group (Fig. 5C), which experienced the least protection from body weight loss and lung hemorrhage. We also measured pulmonary function via whole body plethysmography (WPB). In Figure 5D, we show the WBP PenH metric, which is a surrogate marker for bronchoconstriction or pulmonary obstruction[27], was significantly improved throughout the course of the study if treatment was initiated up to 12hr after infection, although the +24hr group showed sporadic improvement as well (Fig. 5D). Lastly, we blindly evaluated hematoxylin and eosin stained lung tissue sections for histological features of ALI using two different and complementary scoring tools[15], which show that treatment initiated up to +12hr significantly reduced ALI (Fig. 5E). Altogether, therapeutic EIDD-2801 was potently antiviral against SARS-CoV *in vivo* but the degree of clinical benefit was dependent on the time of initiation post infection.

Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis.

After obtaining promising *in vivo* efficacy data with SARS-CoV, we investigated whether EIDD-2801 would be effective against MERS-CoV. As the murine ortholog of the MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), does not support viral binding and entry, all *in vivo* studies were performed in genetically modified mice encoding a murine DPP4 receptor encoding two human residues at positions 288 and 330 (hDPP4 288/330 mice)[15,28]. Similar to our SARS-CoV data (Supplementary Figure 3), all doses of prophylactic EIDD-2801 (50, 150 and 500mg/kg) protected hDPP4 288/330 mice from significant body weight loss (P = 0.03 to < 0.0001), lung hemorrhage (P = 0.01 to <0.0001), and virus replication which was undetectable (P < 0.0001) regardless of drug dose following intranasal infection with 5E+04 PFU mouse-adapted MERS-CoV (Supplementary Figure 4).

We then evaluated the therapeutic efficacy EIDD-2801 following the promising results of our prophylactic studies. Similar to our SARS-CoV study, EIDD-2801 treatment administered before or 12hr after intranasal mouse-adapted MERS-CoV infection (5E+04 PFU) prevented body weight loss from 2 through 6dpi (Fig. 6A, P = 0.02 to <0.0001) and lung hemorrhage on 6dpi (Fig. 6B, P = 0.0004 to < 0.0001), but treatment initiated 24 or 48hr did not offer similar protection. Unlike body weight loss and lung hemorrhage data which varied by treatment initiation time, virus lung titer on 6dpi was significantly reduced to the limit of detection in all treatment groups (Fig. 6C, P < 0.0001). Interestingly, when viral genomic RNA was quantified in paired samples of lung tissue, EIDD-2801 significantly reduced levels of viral RNA (P <0.0001 to 0.017) in an initiation time-dependent manner for all groups except for +48hr (Fig. 6D). The discrepancy among infectious titers and viral RNA suggests that accumulated mutations render the particles non-infectious and undetectable by plaque assay consistent with the MOA. To gauge the effect of EIDD-2801 treatment on lung function, we assessed pulmonary function by WBP. Mirroring the body weight loss data, normal pulmonary function was only observed in groups where treatment was initiated prior to or 12hr after infection (Fig. 6E). Collectively, these data demonstrate that NHC prodrug, EIDD-2801, robustly reduces MERS-CoV infectious titers, viral RNA, and pathogenesis under both prophylactic and therapeutic conditions.

Therapeutic efficacy correlates with an increased MERS-CoV mutation rate i*n vivo*, without increased mutations in cellular RNA.

To study the molecular mechanisms associated with drug performance *in vivo*, we investigated the correlation between infectious virus production and EIDD-2801-mediated mutagenesis of MERS-CoV RNA under therapeutic treatment conditions. Using Primer ID NGS, we measured the mutation rates of both viral genomic RNA (i.e. non-structural protein 10, nsp10) and host interferon stimulated gene 15 (ISG15) mRNA, a highly upregulated innate immune related gene after MERS-CoV infection (Fig. 6F). Primer ID NGS measures the mutational frequency in single RNA molecules each of which are represented by a single template consensus sequence (TCS, See Fig. 4B)[25]. Viral TCS were significantly reduced in a treatment initiation time-dependent

manner (Fig. 6G) similar to viral genomic RNA measured by qRT-PCR (Fig. 6D). In contrast, the numbers of ISG15 TCS were similar (P = 0.2 to 0.8) for all groups indicating that neither vehicle nor drug treatment significantly affected the levels of or mutated ISG15 mRNA transcripts (Fig. 6G). Similar to our TCS data in Figure 6G, the total error rate in viral nsp10 was significantly increased in groups where treatment was initiated prior to (-2hr, median error rate = 10.5 errors/10,000 bases, P < 0.0001) and up to 24hr post infection (12hr, median error rate = 8.2 errors/10,000 bases, P < 0.0001 ; +24hr, median error rate = 5.4 errors/10,000 bases, P = 0.0003) but the error rates in ISG15 remained at baseline for all groups (Fig. 6H). In addition, nucleotide transitions observed in MERS-CoV genomes in vitro (i.e. C to U transitions, Fig. 3), were also observed *in vivo* in groups where treatment was initiated prior to and up to 12hr post infection (P = 0.0003 to < 0.0001) (Fig. 5I). Importantly, these transitions were not observed in host ISG15 mRNA (Fig. 5I). Lastly, the EIDD-2801 dose-dependent mutagenesis of viral RNA correlated with an increase in codon change frequency, including stop codons, in mice where treatment was initiated 12hr or before (vehicle median = 3.4; -2hr median = 22.8, P = 0.0035; +12hr median = 20.0, P = 0.0004, Fig. 5I). Thus, approximately 20% of the mutations observed in the -2hr and +12hr groups resulted in a codon change and alteration of the nsp10 protein sequence. When extrapolating our results from nsp10 to the entirety of the 30kb MERS-CoV genome, EIDD-2801 likely causes between 15 (+24hr treatment) and 30 (-2hr treatment) mutations per genome 10-20% of which result in amino acid coding changes. Altogether, our data demonstrates that EIDD-2801-driven mutagenesis correlates well with the reductions in viral load, strongly suggestive of an error catastrophe-driven mechanism of action under therapeutic conditions.

Discussion

In the past 20 years, three novel human coronaviruses have emerged[29,30]. The group 2b SARS-like CoV represent an existential and future threat to global health as evidenced by the emergence of SARS-CoV and SARS-CoV2 and zoonotic SARS-like bat CoV strains that can use human ACE2 receptors, grow well in primary human airway cells and vary by as much as 25% in key therapeutic and vaccine gene

targets[8,31]. Thus, to address the current public health emergency of COVID-19 and to maximize pandemic preparedness in the future, broad-based vaccines and therapeutics, which are active against the higher risk RNA virus families prone to emergence are desperately needed.

We recently reported the broad-spectrum potency of the nucleoside prodrug, remdesivir (RDV), against an array of epidemic, contemporary and zoonotic CoV both in vitro and *in vivo*[15,16,21,31]. Currently RDV therapeutic efficacy is under investigation in several human clinical trials in China, the United States and elsewhere[32]. Here, we report the broad-spectrum antiviral activity of NHC and its orally bioavailable prodrug EIDD-2801, against SARS-CoV, MERS-CoV and related bat-CoV in primary human airway epithelial cells, as well as against the current pandemic strain SARS-CoV-2. In addition, NHC is broadly active against multiple genetically distinct viruses including coronaviruses, Venezuelan equine encephalitis (VEE), influenza A and B, Ebola, and Chikungunya viruses[10-13,16,21,24,33-35]. Here, we show that prophylactic and therapeutic EIDD-2801 significantly reduced lung viral loads and improved pulmonary function in mouse models of both SARS- and MERS-CoV pathogenesis. Although the improvement in both SARS- and MERS-CoV outcomes diminished with the increase of treatment initiation time, it is important to note that the kinetics of disease in mice are compressed as compared to that in humans. While SARS- and MERS-CoV lung titers peak on 2dpi in mice concurrent with the onset of clinical signs and notable damage to the lung epithelium, in humans this occurs 7-10 days after the onset of symptoms[16,28,36,37]. Thus, in mice, the window within which to treat emerging CoV infection prior to peak replication is compressed (e.g., 24-48hr) but should be much longer in humans. Although speculative, the SARS- and MERS-CoV *in vivo* data provided herein suggest that 2019-nCoV will prove highly vulnerable to NHC treatment modalities *in vivo*, critical experiments that must be performed as animal models become available. The data provided in this manuscript suggest that NHC should be quickly evaluated in primate models of human disease, using immediate models for MERS-CoV and SARS-CoV pathogenesis[38,39].

Small molecule antivirals can exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoded enzyme,

blocking virus particle formation, or targeting a host factor required for replication[40]. For VEE, EIDD-2801 exerts its antiviral activity on the RNA-dependent RNA polymerase leading to error catastrophe by inducing an error rate of replication that surpasses the error threshold allowed to sustain a virus population[11,12]. This process occurs when NHC is incorporated during RNA synthesis then subsequently misread thus increasing mutation rates. Therefore, the NHC MOA would appear less likely to be affected by the RNA proofreading activity encoded by the nsp14 exonuclease function that otherwise limits misincorperation[41]. Here, we present data using Primer ID NGS, a state of the art deep sequencing-based approach, to quantitate the frequency and identity of the mutational spectra in the MERS-CoV genome in both drug treated primary human airway cells and in mice at single genome resolution[25]. As CoV are positive sense RNA viruses that replicate through a negative sense RNA intermediate, NHC incorporation as a “C” or a “U” can occur in both polarities of RNA. Using Primer ID NGS, we found increased nucleotide transitions (A to G, G to A, C to U, U to C) consistent with those reported after influenza and VEE infections[11,12]. Under identical conditions, remdesivir did not alter the mutation rate in MERS-CoV genomic RNA, supporting its reported mechanism of action as a chain terminator of viral RNA synthesis[26]. In primary human lung cell cultures and mice infected with MERS-CoV, the NHC mutation rates inversely correlated with a reduction in infectious virus. In addition, we found a positive correlation between increased mutation rates and the frequency of nonsynonymous mutations and the degree of therapeutic efficacy in mice. To explore the potential off-target effect in host mRNA which may contribute to drug toxicity, we also examined the impact of NHC treatment on transcripts from the highly MERS-CoV induced interferon stimulated gene 15 (ISG15). While ISG15 is present in great abundance, an accumulation of mutations was not observed in ISG15 in this model even at 500mg/kg dosing. These data also support previous studies using RNAseq to demonstrate that the model coronavirus MHV displayed increased mutation frequencies following NHC treatment in vitro[13]. All together, these data strongly support the notion that EIDD-2801 and its active nucleoside analog NHC, exert their antiviral effect through the induction of error catastrophe in the targeted virus. While our data suggest that the MERS-CoV nsp14 proofreading activity appeared ineffective against NHC in vitro and EIDD-2801 *in*

vivo, future studies should investigate the antiviral activity of NHC in the presence or absence of the nsp14 proofreading activity, as loss of this activity increased the sensitivity of MHV and SARS-CoV replication to remdesivir treatment[41].

Together, our data support the continued development of EIDD-2801 as a potent broad spectrum antiviral that could be useful in treating contemporary, newly emerged and emerging coronavirus infections of the future.

Materials and Methods

Compounds. The parental compound β–D–N^4-hydroxycytidine (NHC, all in vitro studies) and its prodrug EIDD-2801 (all *in vivo* studies) was supplied by Emory University Institute for Drug Discovery (EIDD). NHC was supplied as a 10mM stock in DMSO and EIDD-2801 as a solid and solubilized in vehicle containing 10% PEG400, 2.5% Cremophor RH40 in water (10/2.5/87.5%, all v/v) prior to use. Remdesivir (RDV) was solubilized in 100% DMSO and provided by Gilead Sciences, Inc as previously described[15,16].

Virus strains. All viruses used for these studies were derived from infectious clones and isolated as previously described[42]. Virus strains for in vitro experiments include SARS-CoV expressing the green fluorescent protein (GFP) in place of open reading frames 7a/b (ORF7a/b, SARS-GFP)[42], bat-spike receptor binding domain (Bat-SRBD)[22] is a chimeric CoV strain derived from the HKU3 SARS-like bat coronavirus genomic sequence that has the wild type (Urbani SARS-CoV strain) RBD in the HKU3 spike gene to allow for virus replication in non-human primate cell lines and HAE cultures, SHC014 SARS-like bat coronavirus[8], MERS-CoV expressing nanoluciferase in the place of ORF3 (MERS-nLUC)[16] and MERS-CoV expressing the red fluorescent protein gene in the place of ORF 5 (RFP, MERS-RFP)[43]. The virus stock utilized for MERS-CoV *in vivo* studies was derived from a plaque purified isolate of the mouse-adapted MERS-CoV p35C4 strain[44]. The virus stock utilized for SARS-CoV *in vivo* studies was derived from the infectious clone of the mouse-adapted SARS-CoV MA15 (MA15) strain[45].

***In vitro* experiments** Calu3**:** At 48hrs prior to infection, Calu3 2B4 cells were plated in a 96-well black walled clear bottom plate at $5x10^4$ cells/well. A 10mM stock of NHC was serially diluted in 100% DMSO in 3-fold increments to obtain a ten-point dilution series. MERS-nLUC was diluted in DMEM supplemented with 10% FBS, and 1% Antibiotic-Antimycotic to achieve a multiplicity of infection (MOI) of 0.08. Cells were infected and treated with NHC in triplicate per drug dilution for 1hr, after which viral inoculum was aspirated, cultures were rinsed once and fresh medium containing drug or vehicle was added. At 48hrs post infection, nanoluciferase expression as a surrogate for virus replication was quantitated on a Spectramax (Molecular Devices) plate reader according to the manufacturer's instructions (Promega, NanoGlo). For our 100% inhibition control, diluted MERS-nLUC was exposed to short-wave UV light (UVP, LLC) for 6 minutes to inhibit the ability of the virus to replicate. For our 0% inhibition control, cells were infected in the presence of vehicle only. DMSO was kept constant in all conditions at 0.05%. Values from triplicate wells per condition were averaged and compared to controls to generate a percent inhibition value for each drug dilution. The IC_{50} value was defined as the concentration at which there was a 50% decrease in luciferase expression. Data was analyzed using GraphPad Prism 8.0 (La Jolla, CA). The IC_{50} values were calculated by non-linear regression analysis using the dose-response (variable slope) equation (four parameter logistic equation): Y = Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)). To measure cell viability to determine if there was any NHC induced cytotoxicity, Calu3 2B4 cells were plated and treated with NHC only as described above. Cells were exposed to the same ten-point dilution series created for the in vitro efficacy studies. As above, 0.05% DMSO-treated cells served as our 0% cytotoxicity control. Wells without cells served as our 100% cytotoxic positive control. After 48hr, cell viability was measured on a Spectramax (Molecular Devices) via Cell-Titer Glo Assay (Promega) according to the manufacturer's protocol. Similar data was obtained in three independent experiments.

HAE: Human tracheobronchial epithelial cells were obtained from airway specimens resected from patients undergoing surgery under University of North Carolina Institutional Review Board-approved protocols by the Cystic Fibrosis Center Tissue Culture Core. Primary cells were expanded to generate passage 1 cells and passage 2

cells were plated at a density of 250,000 cells per well on Transwell-COL (12mm diameter) supports. Human airway epithelium cultures (HAE) were generated by provision of an air-liquid interface for 6 to 8 weeks to form well-differentiated, polarized cultures that resembled *in vivo* pseudostratified mucociliary epithelium[46]. At 48 hours prior to infection the apical surface of the culture was washed with 500 µL PBS for 1.5 hours at 37˚C and the cultures moved into fresh air liquid interface (ALI) media. Immediately prior to infection, apical surfaces were washed twice with 500 µL of PBS with each wash lasting 30 minutes at 37˚C and HAE cultures were moved into ALI media containing various concentrations of NHC ranging from 10 µM to 0.0016 µM as indicated for each experiment (final % DMSO < 0.05%). Upon removing the second PBS wash, 200 µL of viral inoculum (multiplicity of infection of (MOI) 0.5) was added to the apical surface and HAE cultures were incubated for 3 hours at 37˚C. Viral inoculum was then removed, and the apical surface of the cultures were washed three times with 500µL PBS and then incubated at 37˚C until 48 hours post infection (hpi). For all HAE cultures, infectious virus produced was collected by washing the apical surface of the culture with 100 µL PBS. Apical washes were stored at -80 ˚C until analysis and titered by plaque assay as previously described[16].

qRT-PCR approach to assess cytotoxicity: Total RNA was isolated using the Zymo Direct-zol RNA MiniPrep Kit (Zymo Research Corp., Irvine, CA, USA) according to the manufacturer's directions. First-strand cDNA was generated using Superscript III reverse transcriptase (Life Technologies, Carlsbad, CA, USA). For quantification of cellular markers of toxicity/apoptosis, real-time PCR was performed using commercially validated TaqMan-based primer-probe sets (**Supplementary Table 1**) and TaqMan Universal PCR Mix (Life Technologies). Results were then normalized as described above.

Primer ID and Deep Sequencing

Primer ID NGS is designed to specifically identify and remove RT-PCR mutations, while facilitating highly accurate sequence determination of single RNA molecules, because each cDNA is created with a barcoded degenerate primer (N10, 4^{10} combinations) from

which Illumina indexed libraries are made. We used a multiplexed Primer ID library prep approach and MiSeq sequencing to investigate the presence of mutations in the viral genomes and murine mRNA. We designed cDNA primers targeting multiple regions on the viral genome and murine mRNA, each with a block of random nucleotides (11 bp long) as the Primer ID[25,47] (**Supplementary Table 2**). Viral RNA was extracted using QIAamp viral RNA kit. A pre-amplification titration of templates was performed to estimate the amount of template to use. We used SuperScript III to make cDNA with multiplexed cDNA primers based on the regions to be sequenced. We used 41R_PID11 for the pilot sequencing and titration determination. For the MERS-CoV sequencing, we multiplexed nsp10_PID11, nsp12_PID11 and nsp14_PID11 for the cDNA reaction; for the murine mRNA sequencing, we used mixed primers of nsp10_PID11, ifit3_PID11, isg15_PID11. After bead purification, we amplified the cDNA with a mixture of forward primers (based on the described schemes) and a universal reverse primer, followed by another round of PCR to incorporate Illumina sequencing adaptors and barcodes in the amplicons. After gel-purification and quantification, we pooled 24 libraries for MiSeq 300 base paired-end sequencing. The TCS pipeline version 1.38 (https://github.com/SwanstromLab/PID) was used to process the Primer ID sequencing data and construct template consensus sequences (TCSs) to represent each individual input templates, and the sequences of each region in the pool was de-multiplexed. The RUBY package viral_seq version 1.0.6 (https://rubygems.org/gems/viral_seq) was used to calculate the mutation rate at each position.

***In vivo* experiments.** We performed 4 mouse studies to evaluate the *in vivo* efficacy of the NHC prodrug (EIDD-2801). First, we performed prophylactic dose escalation studies for both SARS- and MERS-CoV to determine the most efficacious dose of EIDD-2801 per virus. For SARS-CoV, in cohorts of equivalent numbers of male and female 20-29 week old SPF C57BL/6J (Stock 000664 Jackson Labs) mice (n = 10/dose group), we administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500mg/kg EIDD-2801 by oral gavage 2hr prior to intranasal infection with 1E+04 PFU mouse-adapted SARS-CoV strain MA15 in 50µl. Mice were anaesthetized with a

mixture of ketamine/xylazine prior to intranasal infection. Vehicle or drug was administered every 12hr for the remainder of the study. Body weight and pulmonary function by whole body plethysmography was measured daily. On 5dpi, animals were sacrificed by isoflurane overdose, lungs were scored for lung hemorrhage, and the inferior right lobe was frozen at −80°C for viral titration via plaque assay. Briefly, 500,000 Vero E6 cells/well were seeded in 6-well plates. The following day, medium was removed and serial dilutions of clarified lung homogenate were added per plate (10^{-1} to 10^{-6} dilutions) and incubated at 37˚C for 1hr after which wells were overlayed with 1X DMEM, 5% Fetal Clone 2 serum, 1X antibiotic/antimycotic, 0.8% agarose. Two days after, plaques were enumerated to generate a plaque/ml value. Lung hemorrhage is a gross pathological phenotype readily observed by the naked eye driven by the degree of virus replication where the coloration of the lung changes from pink to dark red[48,49]. The large left lobe was placed in 10 % buffered formalin and stored at 4°C for 1-3 weeks until histological sectioning and analysis. For MERS-CoV, the prophylactic dose escalation studies we performed exactly as done for SARS-CoV with the following exceptions. First, MERS-CoV binds the human receptor dipeptidyl peptidase 4 (DPP4) to gain entry into cells and two residues (288 and 330) in the binding interface of mouse DPP4 prevent infection of mice. We recently developed a mouse model for MERS-CoV through the mutation of mouse DPP4 at 288 and 330 thus humanizing the receptor (*hDPP4*) and rendering mice susceptible to MERS-CoV infection[28]. We performed all *in vivo* studies with EIDD-2801 in equivalent numbers of 10-14 week old female and male C57BL/6J hDPP4 mice. Second, we intranasally infected mice with 5E+04 PFU mouse-adapted MERS-CoV strain M35C4 in 50µl. Third, to titer lungs by plaque assay, Vero CCL81 cells were used and plaques were enumerated 3 days post infection.

To determine the time at which therapeutic administration of EIDD-2801 would fail to improve outcomes with SARS-CoV or MERS-CoV infection, we performed therapeutic efficacy studies in mice where we initiated treatment 2hr prior to infection or 12, 24 or 48hr after infection. As 500mg/kg provided the most complete protection from disease in prophylactic SARS-CoV studies, this dose was used for both therapeutic efficacy studies. Vehicle or EIDD-2801 was given via oral gavage twice daily following

initiation of treatment. For both SARS-CoV and MERS-CoV, the infectious dose for the therapeutic studies and the mouse strains were the same as that used in the prophylactic studies. The numbers of mice per group for the SARS-CoV studies were as follows: Vehicle (n = 10), -2hr (n = 10), +12hr (n = 10), +24hr (n = 10), +48hr (n = 10). The numbers of mice per group for the MERS-CoV therapeutic studies were as follows: Vehicle (n = 9), -2hr (n = 9), +12hr (n = 9), +24hr (n = 7), +48hr (n = 10). As described above, each day mouse body weight and pulmonary function was quantitated. On 5dpi for SARS-CoV and 6dpi for MERS-CoV, animals were humanely sacrificed and tissues were harvested and analyzed as described above. In addition, for the MERS-CoV study, lung tissue was harvested and stored in RNAlater (Thermo Fisher) at -80˚C and then thawed, homogenized in Trizol reagent (Invitrogen) and total RNA was isolated using a Direct-zol RNA MiniPrep kit (Zymo Research). This total RNA was then used for Primer ID and qRT-PCR.

Whole body plethysmography. Pulmonary function was monitored once daily via whole-body plethysmography (Buxco Respiratory Solutions, DSI Inc.). Mice destined for this analysis were chosen prior to infection. Briefly, after a 30-minute acclimation time in the plethysmograph, data for 11 parameters was recorded every 2 seconds for 5 minutes.

Acute lung injury histological assessment tools. Two different and complementary quantitative histologic tools were used to determine if antiviral treatments diminished the histopathologic features associated with lung injury. Both analyses and scoring were performed by a Board Certified Veterinary Pathologist who was blinded to the treatment groups.

American Thoracic Society Lung Injury Scoring Tool. In order to help quantitate histological features of ALI observed in mouse models and increase their translation to the human condition, we used the ATS scoring tool[49]. In a blinded manner, we chose three random diseased fields of lung tissue at high power (60 ×), which were scored for the following: (A) neutrophils in the alveolar space (none = 0, 1–5 cells = 1, > 5 cells = 2), (B) neutrophils in the interstitial space/ septae (none = 0, 1–5 cells = 1, > 5 cells = 2), (C) hyaline membranes (none = 0, one membrane = 1, > 1 membrane = 2), (D)

Proteinaceous debris in air spaces (none = 0, one instance = 1, > 1 instance = 2), (E) alveolar septal thickening (< 2× mock thickness = 0, 2–4× mock thickness = 1, > 4× mock thickness = 2). To obtain a lung injury score per field, the scores for A–E were then put into the following formula, which contains multipliers that assign varying levels of importance for each phenotype of the disease state.: score = [(20x A) + (14 x B) + (7 x C) + (7 x D) + (2 x E)]/100. The scores for the three fields per mouse were averaged to obtain a final score ranging from 0 to and including 1.

Diffuse Alveolar Damage (DAD) Tool. The second histological tool to quantitate lung injury was reported by Schmidt et al.[50]. DAD is the pathological hallmark of ALI[49,50]. Three random diseased fields of lung tissue were score at high power (60 ×) for the following in a blinded manner: 1 = absence of cellular sloughing and necrosis, 2 = Uncommon solitary cell sloughing and necrosis (1–2 foci/field), 3 = multifocal (3 + foci) cellular sloughing and necrosis with uncommon septal wall hyalinization, or 4 = multifocal (>75% of field) cellular sloughing and necrosis with common and/or prominent hyaline membranes. The scores for the three fields per mouse were averaged to get a final DAD score per mouse.

MERS-CoV genomic RNA qRT-PCR. Mouse lungs were stored in RNAlater (ThermoFisher) at -80°C until processed via homogenization in TRIzol (Invitrogen). Total RNA was isolated using Direct-zol RNA MiniPrep kit (Zymo Research). Previously published TaqMan primers were synthesized by Integrated DNA Technologies (IDT) to quantify MERS genomic RNA (targeting orf1a. Forward: 5'-GCACATCTGTGGTTCTCCTCTCT-3', Probe (6-FAM/ZEN/IBFQ): 5'-TGCTCCAACAGTTACAC-3', Reverse: 5'-AAGCCCAGGCCCTACTATTAGC)[51]. qRT-PCR was performed using 100ng total RNA compared to an RNA standard curve using TaqMan Fast Virus 1-Step Master Mix (ThermoFisher) on a Quant Studio 3 (Applied Biosystems).

nsp12 phylogenetic analysis and conservation modeling. Coronavirus RdRp (nsp12) protein sequence alignments and phylogenetic trees were generated using Geneious Tree Builder in Geneious Prime (version 2020.0.5) and visualized using Evolview (https://www.evolgenius.info/evolview/). Protein similarity scores were

calculated using Blosom62 matrix. The accession numbers used were : PDCoV (KR265858), AIBV (NC_001451), HCoV-229E (JX503060), PEDV (NC_003436), MHV (AY700211), HCoV-HKU1 (DQ415904), HCoV-NL63 (JX504050), HCOV-OC43 (AY903460), HKU5-1 (NC_009020), MERS-CoV (JX869059), HKU9-4 (EF065516), 2019-nCoV (MN996528), HKU3-1 (DQ022305), SHC014 (KC881005), WIV1 (KF367457), SARS-CoV (AY278741). Amino acid conservation scores of coronavirus RdRp were generated using ConSurf Server (https://consurf.tau.ac.il/) using the protein alignment described above and visualized on the SARS-CoV RdRp structure (PDB: 6NUR) in PyMol (version 1.8.6.0)[20,52].

Statistical analysis. All statistical data analyses were performed in Graphpad Prism 8. Statistical significance for each endpoint was determined with specific statistical tests. For each test, a p-value <0.05 was considered significant. Specific tests are noted in each figure legend.

Ethics regulation of laboratory animals. Efficacy studies were performed in animal biosafety level 3 facilities at UNC Chapel Hill. All work was conducted under protocols approved by the Institutional Animal Care and Use Committee at UNC Chapel Hill (IACUC protocol #16-284) according to guidelines set by the Association for the Assessment and Accreditation of Laboratory Animal Care and the U.S. Department of Agriculture.

Funding: We would like to acknowledge the following funding sources, Antiviral Drug Discovery and Development Center (5U19AI109680), a partnership grant from the National Institutes of Health (5R01AI132178) and an NIAID R01 grant (AI108197). NIAID contract, HHSN272201500008C, was awarded to G.P. and The Emory institute for Drug Development and a subcontract from this was awarded to R.S.B. and M.R.D.

Author contributions: A.C.S., T.P.S, designed *in vitro* efficacy studies. A.C.S., A.J.B., T.P.S. and R.L.G. executed and/or analyzed *in vitro* efficacy studies. J.H., A.T. and N.J.T. providing the clinical isolate of SARS-CoV-2. T.P.S., A.A.K., M.G.N., G.P. and R.S.B. designed *in vivo* efficacy studies. T.P.S., A.C.S., S.Z., C.S.H, and R.S. designed, executed and/or analyzed the Primer ID NGS data. K.H.D 3rd performed structural modeling and phylogenetics and sequence alignments. M.L.A., A.J.P., J.D.C. and M.R.D. designed, performed and/or executed the construction of RDV resistant MHV and performed cross-resistance studies. T.P.S., A.S. and S.R.L. executed and analyzed *in vivo* efficacy studies. A.S. and S.R.L. performed whole body plethysmography for *in vivo* studies. S.A.M. assessed all lung pathology. G.R.B., and M.S., were responsible for synthesis, and scale-up of small molecules. T.P.S., A.C.S., S.Z., S.R.L, A.S., K.H.D. 3rd, M.L.A., A.J.P., J.D.C, G.R.B., A.A.K., G.P., R.S. M.R.D., and R.S.B., wrote the manuscript.

Disclaimers

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Names of specific vendors, manufacturers, or products are included for public health and informational purposes; inclusion does not imply endorsement of the vendors, manufacturers, or products by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

Competing financial interests: A.C.S. received a contract from NIAID to support the *in vitro* and *in vivo* efficacy studies reported herein. UNC is pursuing IP protection for Primer ID and R.S. has received nominal royalties.

Figures

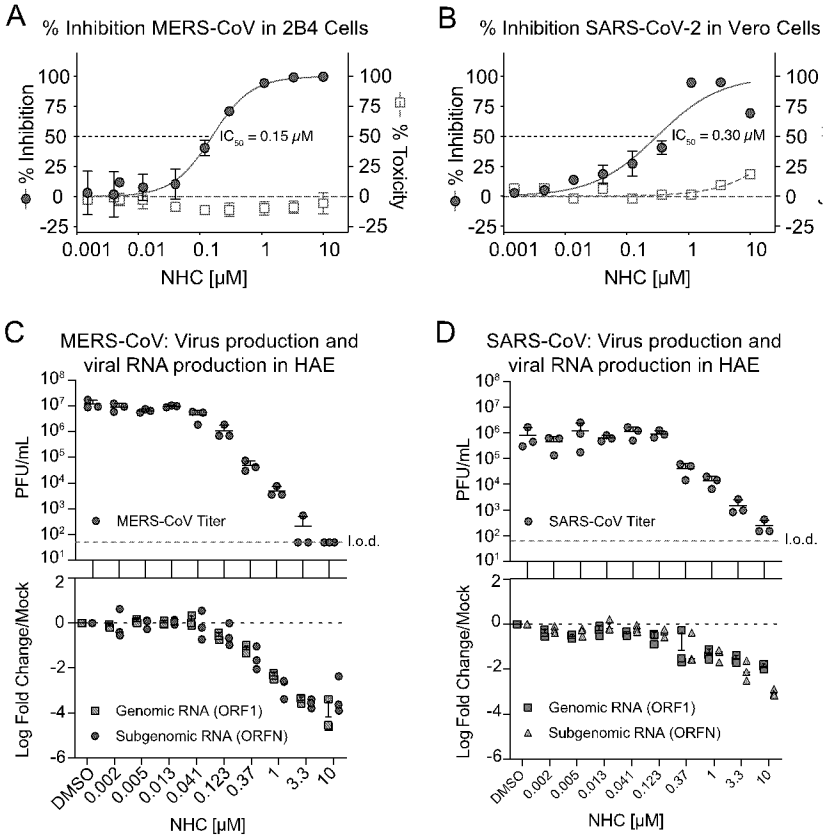


Figure 1: NHC potently Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2 Replication. a, NHC antiviral activity and cytotoxicity in Calu3 cells infected with MERS-CoV. Calu3 cells were infected in triplicate with MERS-CoV nanoluciferase (nLUC) at a multiplicity of infection (MOI) of 0.08 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of MERS-CoV–expressed nLUC. Cytotoxicity was measured in similarly treated but uninfected cultures via Cell-Titer-Glo assay. Data is combined from 3 independent experiments. **b**, NHC antiviral activity and cytotoxicity in Vero cells infected with SARS-CoV-2. Vero cells were infected in duplicate with SARS-CoV-2 clinical isolate virus at an MOI of 0.05 in the presence of a dose response of drug for 48 hours, after which replication was measured through quantitation of cell viability by Cell-Titer-Glo assay. Cytotoxicity was measured as in **a**. Data is combined from 2 independent experiments. **c**, NHC inhibits MERS-CoV virus production and RNA synthesis in primary human lung epithelial cell cultures (HAE). HAE cells were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of NHC for 48 hours, after which apical washes were collected for virus titration. qRT-PCR for MERS-CoV ORF1 and ORFN mRNA. Total RNA was isolated from cultures in **c** for qRT-PCR analysis. Representative data from three separate experiments with three different cell donors are displayed. PFU, plaque-forming units. **d**, NHC inhibits SARS-CoV virus production and RNA synthesis in primary human lung epithelial cell cultures (HAE). Studies performed as in **c** but with SARS-CoV green fluorescent protein (GFP). Representative data from two separate experiments with two different cell donors are displayed.

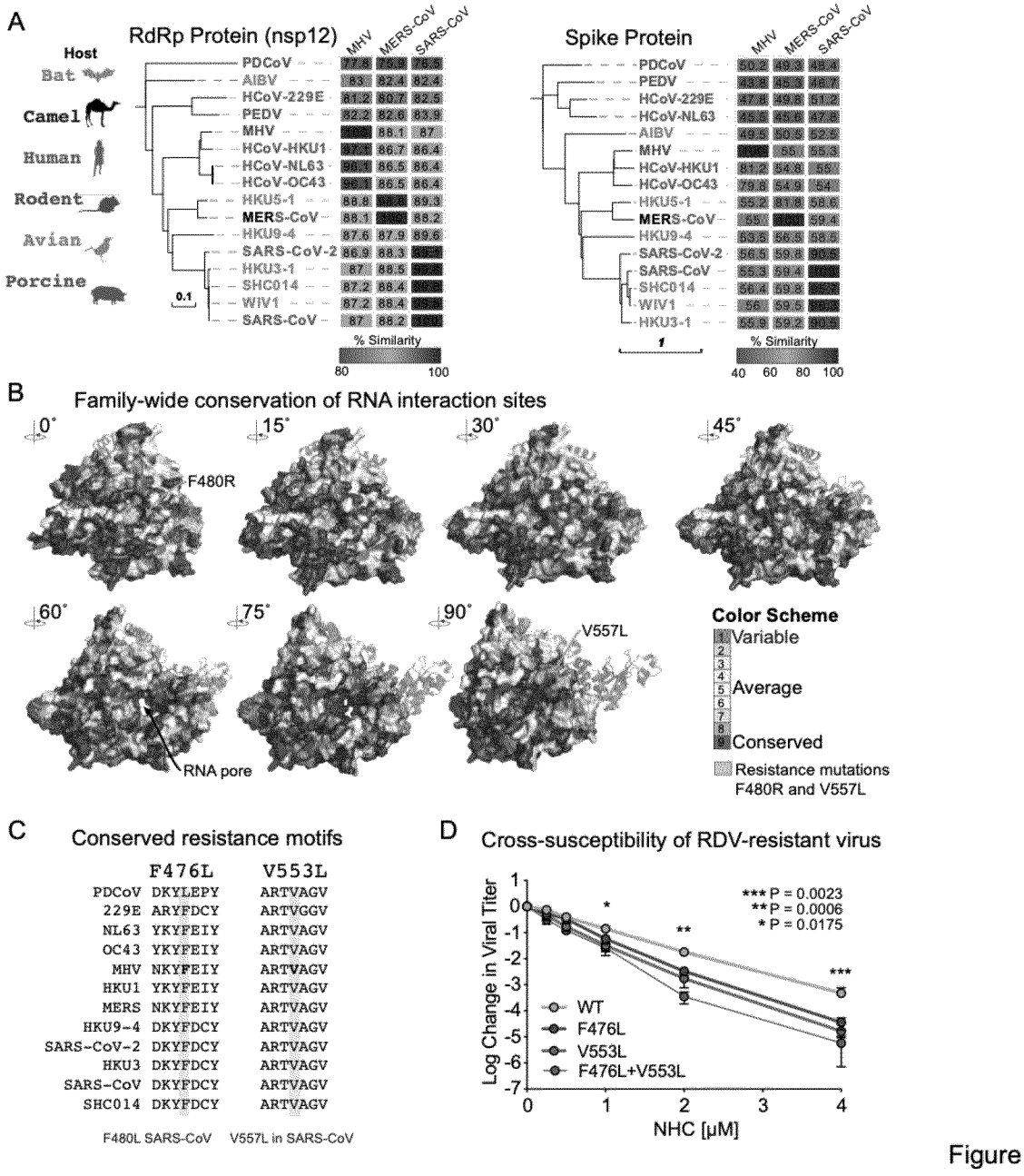


Figure 2

Figure 2. Remdesivir resistance mutations in the highly conserved RNA-dependent RNA polymerase increase susceptibility to NHC. a, Neighbor-joining trees created with representatives from all four CoV genogroups showing the genetic similarity of CoV nsp12 (RdRp) and CoV spike glycoprotein, which mediates host tropism and entry into cells. Text color of the virus strain label corresponds to virus host species on the left. The heatmap adjacent to each neighbor-joining tree depicts percent amino acid identity (% A.A. similarity) against mouse hepatitis virus (MHV), SARS-CoV or MERS-CoV. **b**, Core residues of the CoV RdRp are highly conserved among CoV. The variation encompassed in panel **a** was modeled onto the RdRp structure of the SARS-CoV RdRp. **c**, Amino acid sequence of CoV in panel **a** at known resistance alleles to antiviral drug remdesivir (RDV). **d**, RDV resistant viruses are more susceptible to NHC antiviral activity. Virus titer reduction assay across a dose response of NHC with recombinant MHV bearing resistance mutations to RDV. Asterisks indicate statistically significant differences by Mann-Whitney test.

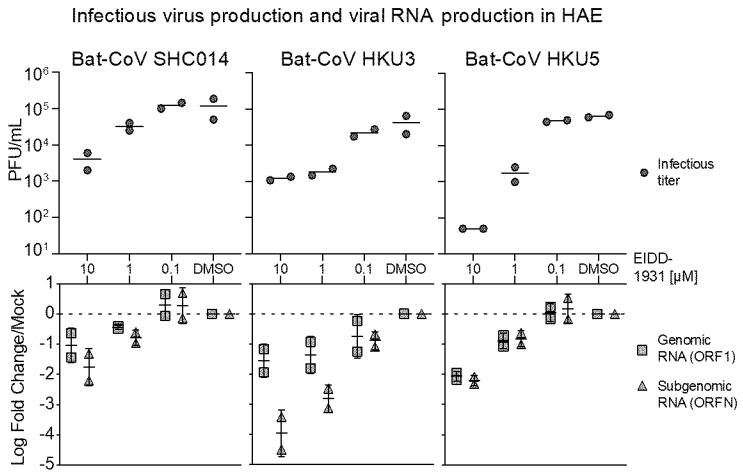


Figure 3: NHC is effective against multiple genetically distinct Bat-CoV. Top: Antiviral efficacy of NHC in HAE cells against SARS-like (HKU3, SHC014, group 2b) and MERS-like (HKU5, group 2c) bat-CoV. HAE cells were infected at an MOI of 0.5 in the presence of NHC in duplicate. After 48 hours, virus produced was titrated via plaque assay. Each data point represents the titer per culture. Bottom: qRT-PCR for CoV ORF1 and ORFN mRNA in total RNA from cultures in the top panel. Representative data from two separate experiments with two different cell donors are displayed.

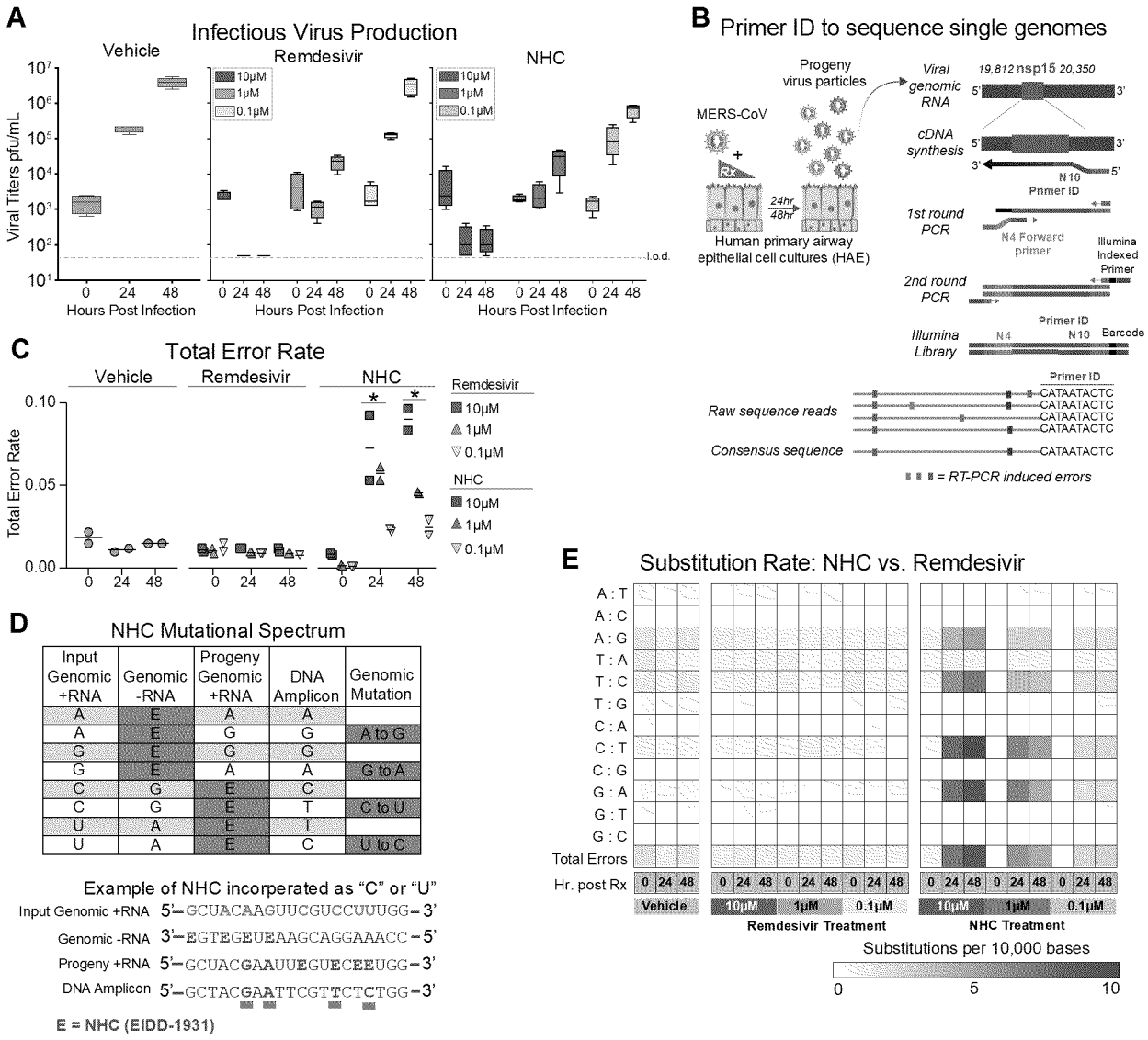


Figure 4: NHC antiviral activity is associated with increased viral mutation rates. **a**, Both remdesivir (RDV) and NHC reduce MERS-CoV infectious virus production in primary human HAE. Cultures were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of vehicle, RDV or NHC for 48 hours, after which apical washes were collected for virus titration. Data is combined from two independent studies. **b,** A deep sequencing approach called Primer ID to gain accurate sequence data for single RNA genomes of MERS-CoV. **c**, The total error rate for MERS-CoV RNA isolated from cultures in panel **a** as determined by Primer ID. Error rate values are # mutations per 10,000 bases. Asterisks indicate significant differences as compared to untreated by 2-way ANOVA with a Dunnett's multiple comparison test. **d**, description of potential NHC mutational spectra on both positive and negative sense viral RNA. **e**, Nucleotide transitions adenine (A) to guanine (G) and uridine (U) to cytosine (C) transitions are enriched in MERS-CoV genomic RNA in an NHC dose dependent manner.

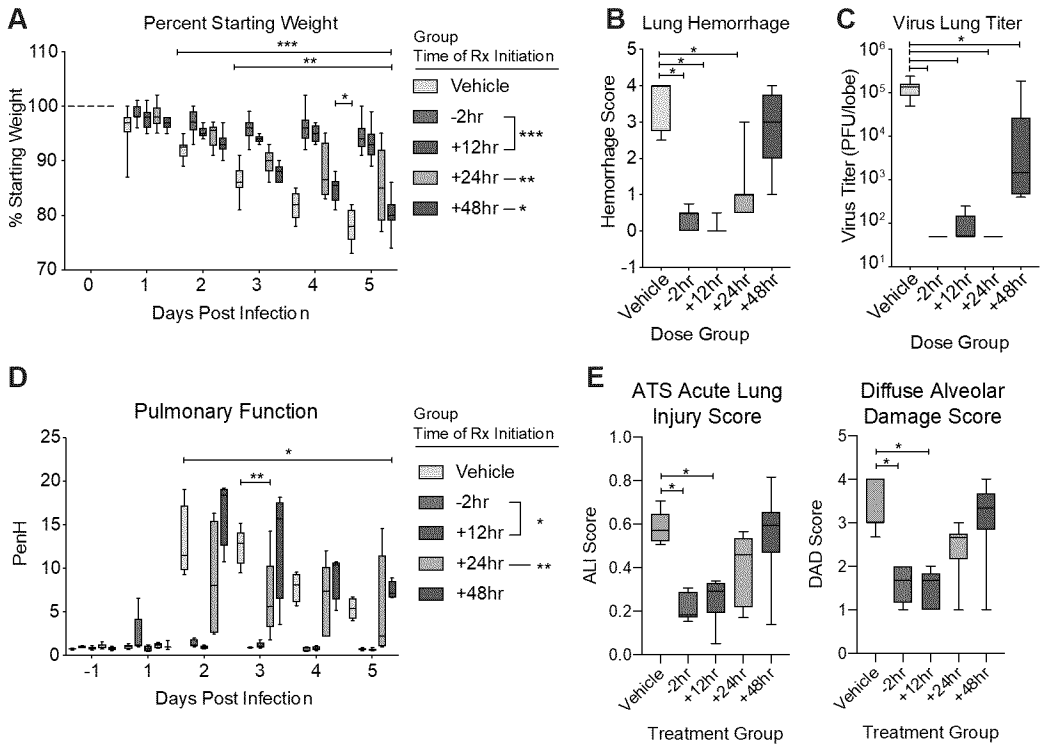


Figure 5: Prophylactic and Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Equivalent numbers of 25-29 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse-adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **d,** Pulmonary function by whole body plethysmography was performed daily on five animals per group. Asterisks indicate differences by two-way ANOVA with a Dunnett's multiple comparison test. **e,** Therapeutic EIDD-2801 reduces acute lung injury (ALI). The histological features of ALI were blindly scored using the American Thoracic Society Lung Injury Scoring system and a Diffuse Alveolar Damage Scoring System. Three randomly chosen high power (60X) fields of diseased lung were assessed per mouse. The numbers of mice scored per group: Vehicle N = 7, -2hr N = 9, +12hr N = 9, +24hr N = 10, +48hr N = 9. Asterisks indicate statistical significance by Kruskal-Wallis with a Dunn's multiple comparison test. For all panels, the boxes encompass the 25th to 75th percentile, the line is at the median, while the whiskers represent the range.

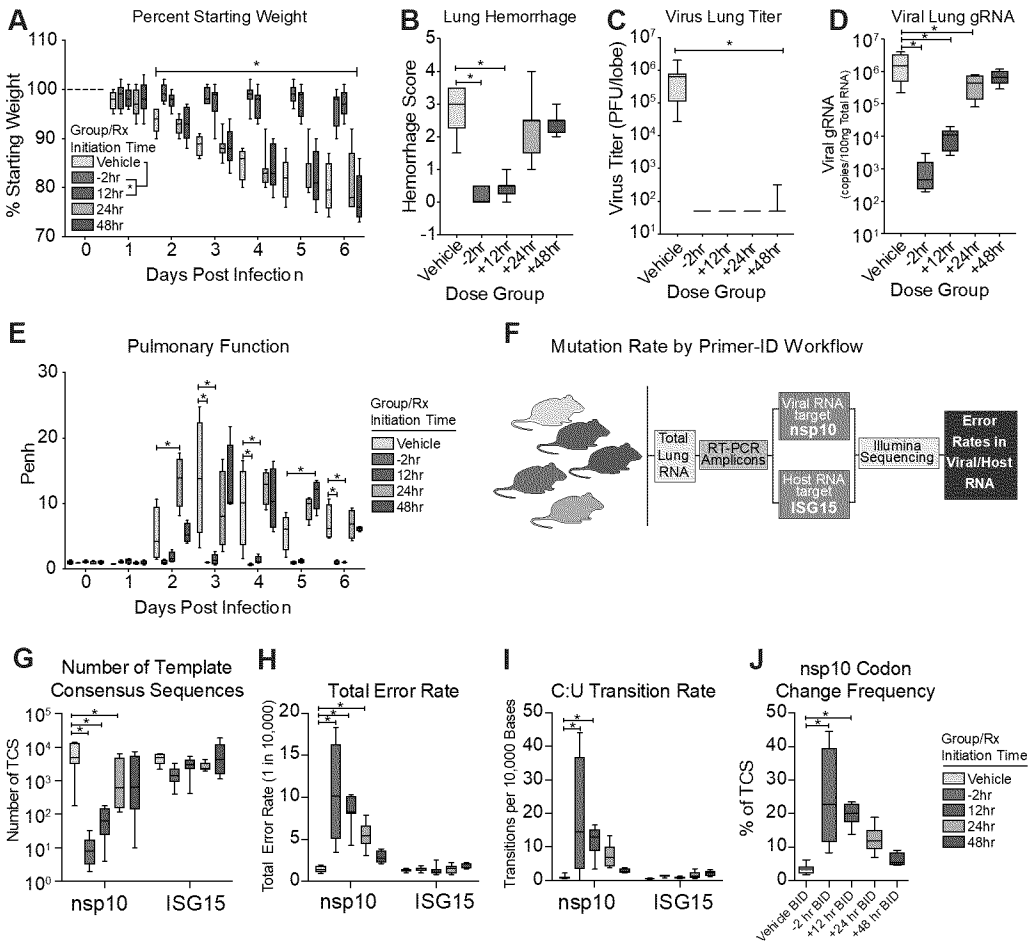
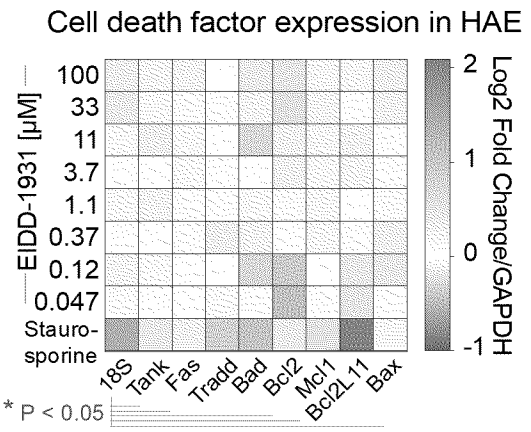
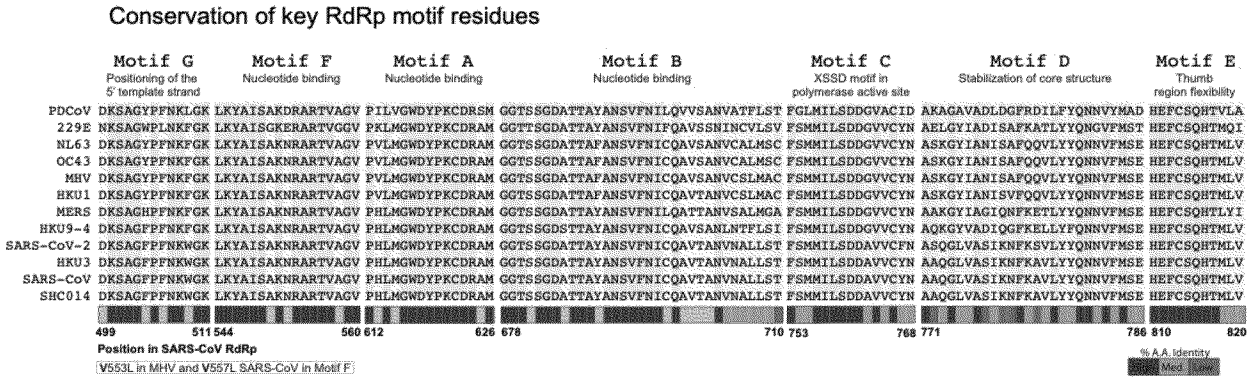


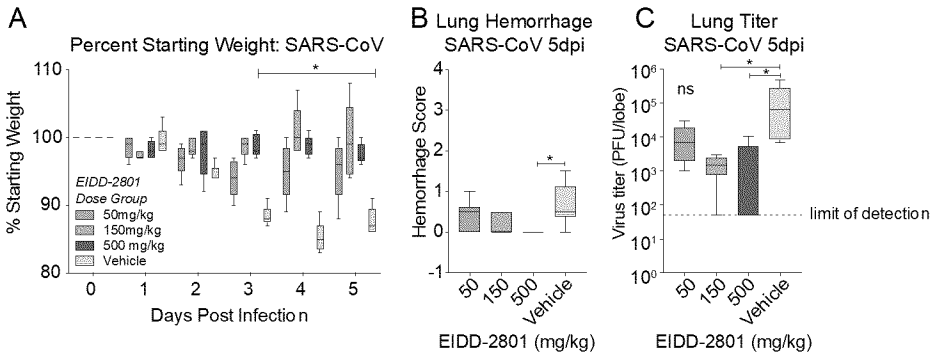
Figure 6: Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis coincident with increased viral mutation rates. Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 5E+04 PFU mouse-adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test. **d**, MERS-CoV genomic RNA in lung tissue by qRT-PCR. Asterisks indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **e**, Pulmonary function by whole body plethysmography was performed daily on four animals per group. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **f**, Workflow to measure mutation rate in MERS-CoV RNA and host transcript ISG15 by Primer ID in mouse lung tissue. **g**, Number of template consensus sequences for MERS-CoV nsp10 and ISG15. **h**, Total error rate in MERS-CoV nsp10 and ISG15. **i**, The cytosine to uridine transition rate in MERS-CoV nsp10 and ISG15. In panels **g-i,** asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **j**, Codon change frequency in MERS-CoV nsp10. Asterisks indicate differences on Kruskal-Wallis with Dunn's multiple comparison test.



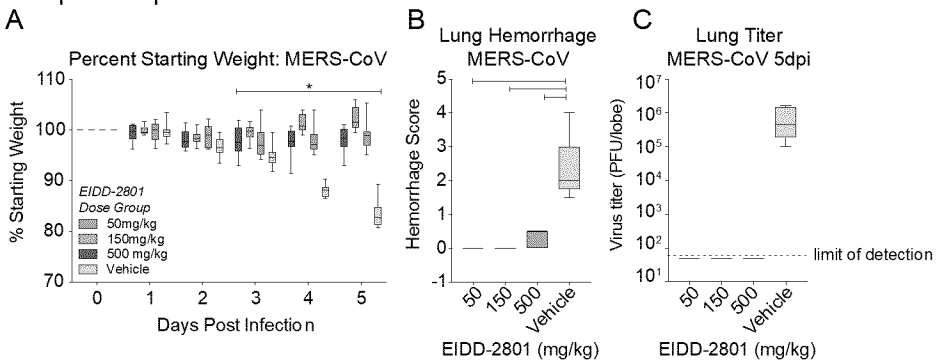
Supplementary Figure 1: Assessment of cytotoxicity of NHC in primary human epithelial cell cultures by qRT-PCR. Companion figure to **Figure 1c** and **d**. Primary human epithelial cell cultures were exposed to positive control 1μM staurosporine or a dose response of NHC for 48hr. Cytotoxicity was assessed by qRT-PCR for cell death factor gene expression.



Supplementary Figure 2: High conservation of RdRp functional domains for SARS-CoV-2. Companion figure to **Figure 2a.** Multiple sequence alignment of the RNA dependent RNA polymerase (RdRp) from viruses in the dendrogram in Figure 2a showing high conservation in the RdRp structural motifs A-G.



Supplementary Figure 3: Prophylactic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Companion figure to **Figure 5**. Equivalent numbers of 20 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at 2hr prior to infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse-adapted SARS-CoV MA15 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with a Dunn's multiple comparison test.



Supplementary Figure 4: Prophylactic EIDD-2801 reduces MERS-CoV replication and pathogenesis. Companion figure to **Figure 6.** Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning 2hr prior to infection every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 5E+04 PFU mouse-adapted MERS-CoV M35C4 strain. **a,** Percent starting weight. Asterisks indicate differences by two-way ANOVA with Dunnett's multiple comparison test. **b,** Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by Kruskal-Wallis with Dunn's multiple comparison test.

Supplementary Table 1. Real-time PCR primer/probe sets for indicators of cellular apoptosis/toxicity

Primer/Probe Target	Assay Reference Number*
Bax	Hs00180269_m1
Bad	Hs00188930_m1
Bcl2L11	Hs00708019_s1
Bcl2	Hs00608023_m1
Mcl1	Hs01050896_m1
Tradd	Hs00601065_g1
Fas	Hs00236330_m1
Tank	Hs00370305_m1
18S	4352930E
GAPD**	4352934E

* Validated assays available from Life Technologies

** The housekeeping gene hGAPDH was used for normalization of real-time results.

Supplementary Table 2. Primer used for MiSeq library prep and sequencing.

Primer	5'-3'	Comment
41R_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATGACCTTCCTGTTGCTTCT	cDNA primer. Targeting 20331-20350 on the reference genome.
nsp10_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTCCTAAAGACGACATCAGTGG	cDNA primer. Targeting 13488-13507 on the reference genome.
nsp12_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTATAGCCAAAGACACAAACCG	cDNA primer. Targeting 15983-16002 on the reference genome.
nsp14_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGAACATCGACAAAGAAAGGG	cDNA primer. Targeting 18715-18734 on the reference genome.
ifit3_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTTTCAGCCACTCCTTTATCCC	cDNA primer. Targeting mice IFIT3 mRNA.
isg15_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNNCAGTGGGGCTTTAGGCCATACTC	cDNA primer. Targeting mice ISG15 mRNA.
41F_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNGCTACAAGTTCGTCCTTTGG	1st round PCR forward primer. Targeting 19812-19831 on the reference genome
nsp10_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGCTCAGGTGCTAAGCGAAT	1st round PCR forward primer. Targeting 12983-13002 on the reference genome
nsp12_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATAGGCTTCGATGTTGAGGG	1st round PCR forward primer. Targeting 15388-15407 on the reference genome
nsp14_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATTGCAAGCTGGTTCTAACA	1st round PCR forward primer. Targeting 18260-18279 on the reference genome
ifit3_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNCGATCCACAGTGAACAACAG	1st round PCR forward primer. Targeting mice IFIT3 mRNA.
isg15_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNTGGGACCTAAAGGTGAAGATG	1st round PCR forward primer. Targeting mice ISG15 mRNA.
Adapter R	GTGACTGGAGTTCAGACGTGTGCTC	1st round PCR reverse primer
Universal Adapter	AATGATACGGCGACCACCGAGATCTACACGCCTCCCTCGCGCCATCAGAGATGTG	2nd round PCR forward primer with Illumina adapter sequence
Indexed Adapter	CAAGCAGAAGACGGCATACGAGATNNNNNNGTGACTGGAGTTCAGACGTGTGCTC	2nd round PCR reverse primer with Illumina adapter sequence and indices (NNNNNNN)
Old Nextera	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAG	Customized sequencing primer

References

1. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). (2018).
2. de Wit, E., van Doremalen, N., Falzarano, D. & Munster, V.J. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* **14**, 523-534 (2016).
3. Wang, D.*, et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* (2020).
4. Zaki, A.M., van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D. & Fouchier, R.A. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* **367**, 1814-1820 (2012).
5. Hsu, L.Y.*, et al.* Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. *Emerg Infect Dis* **9**, 713-717 (2003).
6. Zhou, P.*, et al.* Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature* **556**, 255-258 (2018).
7. Woo, P.C.*, et al.* Molecular diversity of coronaviruses in bats. *Virology* **351**, 180-187 (2006).
8. Menachery, V.D.*, et al.* A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* **21**, 1508-1513 (2015).
9. Menachery, V.D.*, et al.* SARS-like WIV1-CoV poised for human emergence. *Proc Natl Acad Sci U S A* **113**, 3048-3053 (2016).
10. Reynard, O.*, et al.* Identification of a New Ribonucleoside Inhibitor of Ebola Virus Replication. *Viruses* **7**, 6233-6240 (2015).
11. Urakova, N.*, et al.* beta-d-N (4)-Hydroxycytidine Is a Potent Anti-alphavirus Compound That Induces a High Level of Mutations in the Viral Genome. *J Virol* **92**(2018).
12. Toots, M.*, et al.* Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. *Sci Transl Med* **11**(2019).
13. Agostini, M.L.*, et al.* Small-Molecule Antiviral beta-d-N (4)-Hydroxycytidine Inhibits a Proofreading-Intact Coronavirus with a High Genetic Barrier to Resistance. *J Virol* **93**(2019).
14. Jordan, P.C.*, et al.* Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase. *PLoS Pathog* **14**, e1006889 (2018).
15. Sheahan, T.P.*, et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222 (2020).
16. Sheahan, T.P.*, et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* **9**(2017).
17. Anthony, S.J.*, et al.* Further Evidence for Bats as the Evolutionary Source of Middle East Respiratory Syndrome Coronavirus. *mBio* **8**(2017).
18. Hu, B., Ge, X., Wang, L.F. & Shi, Z. Bat origin of human coronaviruses. *Virol J* **12**, 221 (2015).
19. Huynh, J.*, et al.* Evidence supporting a zoonotic origin of human coronavirus strain NL63. *J Virol* **86**, 12816-12825 (2012).
20. Kirchdoerfer, R.N. & Ward, A.B. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun* **10**, 2342 (2019).

21. Agostini, M.L., *et al.* Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *MBio* **9**(2018).
22. Becker, M.M., *et al.* Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice. *Proc Natl Acad Sci U S A* **105**, 19944-19949 (2008).
23. Agnihothram, S., *et al.* A mouse model for Betacoronavirus subgroup 2c using a bat coronavirus strain HKU5 variant. *MBio* **5**, e00047-00014 (2014).
24. Yoon, J.J., *et al.* Orally Efficacious Broad-Spectrum Ribonucleoside Analog Inhibitor of Influenza and Respiratory Syncytial Viruses. *Antimicrob Agents Chemother* **62**(2018).
25. Zhou, S., Jones, C., Mieczkowski, P. & Swanstrom, R. Primer ID Validates Template Sampling Depth and Greatly Reduces the Error Rate of Next-Generation Sequencing of HIV-1 Genomic RNA Populations. *J Virol* **89**, 8540-8555 (2015).
26. Tchesnokov, E.P., Feng, J.Y., Porter, D.P. & Gotte, M. Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses* **11**(2019).
27. Menachery, V.D., Gralinski, L.E., Baric, R.S. & Ferris, M.T. New Metrics for Evaluating Viral Respiratory Pathogenesis. *PLoS One* **10**, e0131451 (2015).
28. Cockrell, A.S., *et al.* A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. *Nat Microbiol* **2**, 16226 (2016).
29. Marston, H.D., Folkers, G.K., Morens, D.M. & Fauci, A.S. Emerging viral diseases: confronting threats with new technologies. *Sci Transl Med* **6**, 253ps210 (2014).
30. Paules, C.I., Marston, H.D. & Fauci, A.S. Coronavirus Infections-More Than Just the Common Cold. *JAMA* (2020).
31. Brown, A.J., *et al.* Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* **169**, 104541 (2019).
32. Cai, B. Severe 2019-nCoV Remdesivir RCT (NCT04257656). (2020).
33. Ehteshami, M., *et al.* Characterization of beta-d-N(4)-Hydroxycytidine as a Novel Inhibitor of Chikungunya Virus. *Antimicrob Agents Chemother* **61**(2017).
34. Warren, T.K., *et al.* Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* **531**, 381-385 (2016).
35. Lo, M.K., *et al.* GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Sci Rep* **7**, 43395 (2017).
36. Oh, M.D., *et al.* Viral Load Kinetics of MERS Coronavirus Infection. *N Engl J Med* **375**, 1303-1305 (2016).
37. Peiris, J.S., *et al.* Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767-1772 (2003).
38. de Wit, E., *et al.* Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. *Proc Natl Acad Sci U S A* **110**, 16598-16603 (2013).

39. McAuliffe, J., *et al.* Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. *Virology* **330**, 8-15 (2004).
40. Zumla, A., Chan, J.F., Azhar, E.I., Hui, D.S. & Yuen, K.Y. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov* **15**, 327-347 (2016).
41. Smith, E.C., Blanc, H., Surdel, M.C., Vignuzzi, M. & Denison, M.R. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. *PLoS Pathog* **9**, e1003565 (2013).
42. Sims, A.C., *et al.* Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: role of ciliated cells in viral spread in the conducting airways of the lungs. *J Virol* **79**, 15511-15524 (2005).
43. Scobey, T., *et al.* Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. *Proc Natl Acad Sci U S A* **110**, 16157-16162 (2013).
44. Douglas, M.G., Kocher, J.F., Scobey, T., Baric, R.S. & Cockrell, A.S. Adaptive evolution influences the infectious dose of MERS-CoV necessary to achieve severe respiratory disease. *Virology* **517**, 98-107 (2018).
45. Roberts, A., *et al.* A mouse-adapted SARS-coronavirus causes disease and mortality in BALB/c mice. *PLoS Pathog* **3**, e5 (2007).
46. Fulcher, M.L., Gabriel, S., Burns, K.A., Yankaskas, J.R. & Randell, S.H. Well-differentiated human airway epithelial cell cultures. *Methods Mol Med* **107**, 183-206 (2005).
47. Jabara, C.B., Jones, C.D., Roach, J., Anderson, J.A. & Swanstrom, R. Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID. *Proc Natl Acad Sci U S A* **108**, 20166-20171 (2011).
48. Fukushi, M., *et al.* Serial histopathological examination of the lungs of mice infected with influenza A virus PR8 strain. *PLoS One* **6**, e21207 (2011).
49. Matute-Bello, G., *et al.* An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* **44**, 725-738 (2011).
50. Schmidt, M.E., *et al.* Memory CD8 T cells mediate severe immunopathology following respiratory syncytial virus infection. *PLoS Pathog* **14**, e1006810 (2018).
51. Almazan, F., *et al.* Engineering a replication-competent, propagation-defective Middle East respiratory syndrome coronavirus as a vaccine candidate. *mBio* **4**, e00650-00613 (2013).
52. Ashkenazy, H., *et al.* ConSurf 2016: an improved methodology to estimate and visualize evolutionary conservation in macromolecules. *Nucleic Acids Res* **44**, W344-350 (2016).

From: Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]

Sent: Sat 3/14/2020 5:33:12 PM (UTC-07:00)

To: Hill, Collin Siva[collinh@live.unc.edu]; Painter, George R.[george.r.painter@emory.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]

Cc: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: RE: [External] Re: Your Science Translational Medicine Manuscript abb5883 for Revision

Well, ladies and gentlemen,
the argument is not correct: Rbv did not have any mutagenicity for MERS because it was never incorporated (judging by complete absence of antiviral activity). Similarly, it had slight mutagenicity in LaCrose exactly because it was "slightly" incorporated (judging by slight inhibition at exactly slightly mutagenic concentration). So, I would say that, based on these data, there is no evidence that Rbv is not mutagenic in MERS.

Best
-Sasha

From: Hill, Collin Siva <collinh@live.unc.edu>
Sent: Saturday, March 14, 2020 3:59 PM
To: Painter, George R. <george.r.painter@emory.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>
Cc: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: Re: [External] Re: Your Science Translational Medicine Manuscript abb5883 for Revision

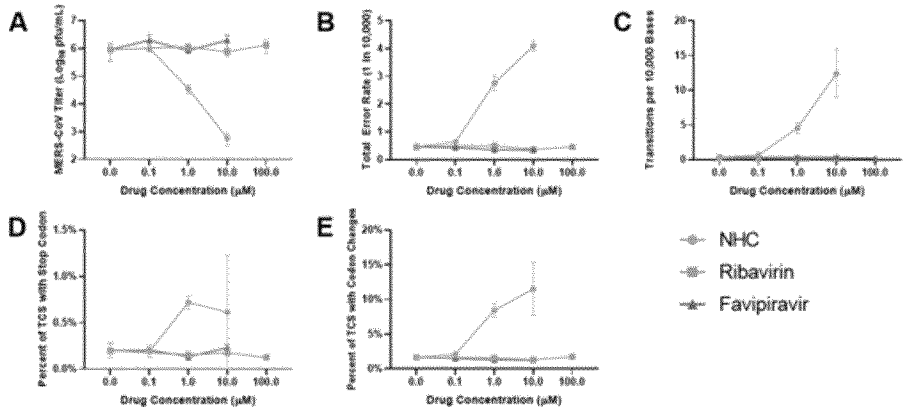
Hi Tim,

Thank you for sharing the feedback.

I'm in agreement with what Shuntai said. We did not see any significant antiviral or mutagenic effects of ribavirin on MERS-CoV or Zika virus. We did observe some mutagenic effects caused by ribavirin on La Crosse virus, however it was only at the highest dosage concentration of 100 uM and it only increased the mutation rate modestly, on par with NHC at a dosage concentration of 1.0 uM (See attached Prism files and photos)

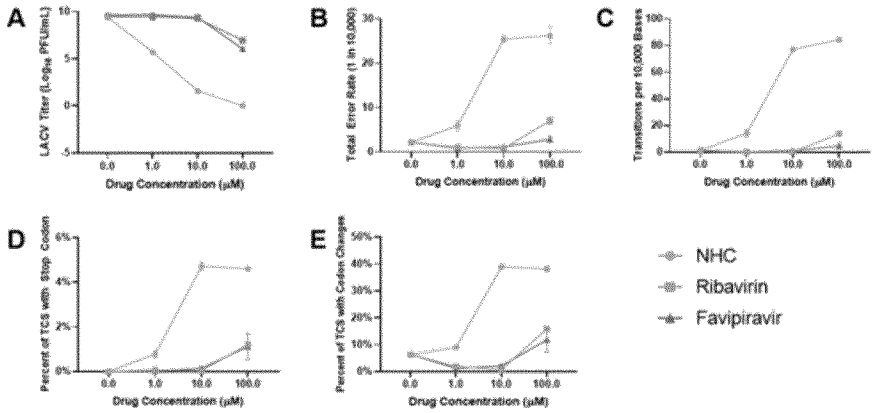
Hope this helps,
Collin

Figure 1. MERS-CoV Drug Panel Antiviral Activity and Mutagenic Effects



Panel A: MERS-CoV titer as determined from nanoluciferase assay. Panel B: Total error rate (error per 10,000) of NSP12 primer region of MERS-CoV under different compound and concentration conditions. Panel C: Cytidine to uracil (C to U) transition error rate (per 10,000) of NSP12 primer region of MERS-CoV in the drug panel. Panel D: Percent of template consensus sequences (TCS) with a change in codon to UAG, UAA, an UGA (stop codons) within the NSP12 primer region of MERS-CoV. Panel E: Percent of TCS with a change in codon (other than stop codons) within the NSP12 primer region of MERS-CoV. For all panels, the error bars indicate the range of each data set.

Figure 4. La Crosse Virus Drug Panel Antiviral and Mutagenic Effects



Panel A: La Crosse virus titer as determined from plaque-forming assay. Panel B: Total error rate (error per 10,000) of L fragment primer region of La Crosse virus under different compound and concentration conditions. Panel C: Cytidine to uracil (C to U) transition error rate (per 10,000) of L fragment primer region of La Crosse virus in the drug panel. Panel D: Percent of template consensus sequences (TCS) with a change in codon to UAG, UAA, an UGA (stop codons) within the L fragment primer region of La Crosse virus. Panel E: Percent of TCS with a change in codon (other than stop codons) within the L fragment primer region of La Crosse virus. For all panels, the error bars indicate the range of each data set.

From: Painter, George R. <george.r.painter@emory.edu>
Sent: Saturday, March 14, 2020 2:10 PM
To: Zhou, Shuntai <shuntaiz@email.unc.edu>
Cc: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD)

<nax3@cdc.gov>; zaq6@cdc.gov <zaq6@cdc.gov>; axt4@cdc.gov <axt4@cdc.gov>; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: Re: [External] Re: Your Science Translational Medicine Manuscript abb5883 for Revision

This just got more urgent as we are being asked to treat very sick COVID-19 patients under what I am anticipating will be compassionate use protocols. Having a peer reviewed paper demonstrating activity against SARS-CoV-2 goes a long way in increasing everyone's confidence.

George

George Painter, M.S., Ph.D

Professor of Pharmacology, Emory University, School of Medicine
Director, Emory Institute for Drug Development |EIDD
Section Head, Yerkes National Primate Center
CEO, Drug Innovation Ventures at Emory |DRIVE

954 Gatewood Rd. NE |Atlanta, GA,USA 30329

Voice: +1-404-712-6886
email: grpaint@emory.edu

> On Mar 14, 2020, at 1:56 PM, Zhou, Shuntai <shuntaiz@email.unc.edu> wrote:
>
> Dear Tim
>
> Thanks for sharing the review.
>
> I have one suggestion for reviewer 1's comment. Ron and I really don't believe rabavirin is a broad spectrum mutagen. The previous papers say that it is mutagenic at very high concentration. But we didn't see mutagenic effect in MERS-CoV or ZIKV at very high concentration (100 um). You may consider adding the MERS-CoV RBV data we did as supplement or use that to counter the reviewer's comment.
>
> Shuntai
>
>> On Mar 14, 2020, at 1:34 PM, Sheahan, Timothy Patrick <sheahan@email.unc.edu> wrote:
>>
>> Dear Co-Authors,
>>
>> The reviews came back from Science Translations Med on our EIDD-1931/NHC paper. They are pretty positive. We are going to come up with a path forward in the next 24-48hr. What the reviewers and editors need to understand is the urgency of this work.
>>
>> Tim
>>
>>
>>
>> On 3/13/20, 6:43 PM, "Lindsey Pujanandez" <scitranslmededitors@aaas.org> wrote:
>>
>> 13-Mar-2020
>>
>> Dear Dr. Sheahan:
>>
>> Manuscript number: abb5883
>>
>> Thank you for sending us your manuscript "An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2

and multiple endemic, epidemic and bat coronavirus."
>>
>> Our review of your paper is now complete. We are potentially interested in publishing it as a Research Article, but we cannot accept it in its present form. We would like to invite you to revise the manuscript and then return it to us. To view your reviews and other documents related to your revision, log in to your account at the Science Journals Manuscript Submission and Information Portal at https://cts.sciencemag.org. You can access your files by clicking on the Action button to the right of the paper's listing in your task list. Navigate to the Manuscript Document tab in the manuscript record where the files can be downloaded.
>>
>> The following aspects of the paper need to be addressed in the revision.
>>
>> 1. ADDRESS REVIEWERS' COMMENTS (see Review Report file). Please revise your manuscript in accord with the referees' comments. When you return the manuscript to us, include a point-by-point response explaining how you have addressed each of the reviewers' comments.
>>
>> 2. ADDRESS EDITOR'S COMMENTS (see combined PDF). Please address follow all of the instructions from me on the marked version of the paper and on the Revision Checklist.
>>
>> 3. FORMAT (see instructions in the Revision Checklist file). Carefully follow the formatting instructions for your revised manuscript and figures. The format for revised papers is different than that for initial submission.
>>
>> 4. FIGURES. It is very important that you provide high resolution, correctly sized figures with type and symbols that are correctly styled and that will be visible in the final published version of the paper. Red and green should not be used together.
>>
>> Returning your revised manuscript. Prepare your revised manuscript documents and a cover letter with your point-by-point response to the referees' comments. Return your revised manuscript documents by uploading them through your account at our Manuscript Submission and Information Portal at https://cts.sciencemag.org.
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>> Authorship, Conflict of Interest, and License forms. Science Translational Medicine requires information verifying authorship, conflicts of interest, and several other conditions of acceptance from every author on a manuscript. We must have this information from all authors before we can accept your paper. We also require first and corresponding authors to provide their ORCID numbers. You and each co-author will receive an email with instructions about how to go to our Manuscript Submission and Information Portal to enter this information and agree to our publication license.
>>
>> If your paper is accepted and published, note that there will be a processing fee of $300 for each figure. We will, however, provide a free electronic reprint URL that can be posted on your website to give unrestricted access to your paper. Information about this service will be sent to you by email a few days after publication.
>>
>> In order for your paper to be considered an active submission, we must receive your revision within one month of your receipt of this letter. If you cannot complete your revisions within that time, please contact me to discuss.
>>
>> If your paper involves a method that would benefit from the publication of a step-by-step
>> protocol (e.g., https://bio-protocol.org/e2339) and you would be interested in submitting
>> one to Bio-protocol, which curates high-quality life science protocols, please contact Bio-protocol (https://bio-protocol.org/login.aspx?in=1) who can advise further. This will not delay the processing of your paper at Science Translational Medicine.
>>
>> I look forward to reading your revised manuscript. Please let me know if you cannot access the files uploaded to our website or if I can otherwise be of assistance.
>>
>> Sincerely,
>>
>> Lindsey Pujanandez, Ph.D.
>> Associate Editor
>> Science Translational Medicine
>> lpujanandez@aaas.org

>>
>> <abb5883_Blinded_Review_Report_seq1_v1.pdf>

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From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Sun 3/15/2020 5:03:40 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: FW: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

FYI. I don't know if you got this too.

T

From: "era-notify@mail.nih.gov" <era-notify@mail.nih.gov>
Reply-To: "eraNotifications@mail.nih.gov" <eraNotifications@mail.nih.gov>
Date: Sunday, March 15, 2020 at 6:01 AM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

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

The progress report for NIH Grant Number is due by 04/15/2020.

The next budget period start date for the above-referenced award is 06/01/ 2020. The due date for Progress Reports for grants excluded from the Streamlined Non-Competing Award Process (SNAP) authorities grants is the 1st of the month preceding the month in which the current budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). If the 1st falls on a weekend or Federal holiday, the due date is automatically extended to the next business day. If you are unsure whether the award is excluded from SNAP authorities, check the Notice of Award (NoA) under Section III Terms and Conditions.

NOTE: NIH POLICY REQUIRES ELECTRONIC SUBMISSION OF ALL ANNUAL PROGRESS REPORTS USING THE RPPR MODULE IN eRA COMMONS (see NOT-OD-15-014). RPPR instructions and resoures can be found at http://grants.nih.gov/grants/rppr/index.htm.

Questions regarding the eRA Commons should be addressed to:

eRA Commons Help Desk

Web: http://era.nih.gov/help/ (Preferred method of contact)

Toll-free: 1-866-504-9552

Phone:301-402-7469

Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time

Please submit the progress report by the due date noted above. If you have already submitted the progress report, disregard this notice.

Thank you.

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Sun 3/15/2020 6:21:44 AM (UTC-07:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: Re: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

Sadly no. I am not sure what email address they are using. Thank you for sending this. Amy

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Sunday, March 15, 2020 5:03:40 AM
To: Sims, Amy C <amy.sims@pnnl.gov>
Subject: FW: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

FYI. I don't know if you got this too.

T

From: "era-notify@mail.nih.gov" <era-notify@mail.nih.gov>
Reply-To: "eraNotifications@mail.nih.gov" <eraNotifications@mail.nih.gov>
Date: Sunday, March 15, 2020 at 6:01 AM
To: "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: NIH Automated Email: Progress Report for Grant 5 R21 AI146872-02, Due by 04/15/2020

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

The progress report for NIH Grant Number is due by 04/15/2020.

The next budget period start date for the above-referenced award is 06/01/ 2020. The due date for Progress Reports for grants excluded from the Streamlined Non-Competing Award Process (SNAP) authorities grants is the 1st of the month preceding the month in which the current budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). If the 1st falls on a weekend or Federal holiday, the due date is automatically extended to the next business day. If you are unsure whether the award is excluded from SNAP authorities, check the Notice of Award (NoA) under Section III Terms and Conditions.

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Questions regarding the eRA Commons should be addressed to:

eRA Commons Help Desk

Web: http://era.nih.gov/help/ (Preferred method of contact)

Toll-free: 1-866-504-9552

Phone:301-402-7469

Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time

Please submit the progress report by the due date noted above. If you have already submitted the progress report, disregard this notice.

Thank you.

From: Gralinski, Lisa E[lgralins@email.unc.edu]
Sent: Sun 3/15/2020 6:44:39 PM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: MERS histo figure
Attachment: SM126 histo data.pzfx

Hey Amy,
Here is a draft of the figure for the MERS histology data. All of the lung pictures are from male mice since that's where the drug treatment made a difference in the pathology. Please let me know what you would like changed, I am not wedded to this presentation!
I hope you and Brian are safe and sound,
Lisa

Lisa Gralinski
Assistant Professor
Department of Epidemiology
University of North Carolina
919-966-3890

Project info 1

Experiment Date
2020-03-15

Experiment ID

Notebook ID

Project

Experimenter

Protocol

SM126 males - DAD

MERS + Sham

3

4

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4

MERS + Drug

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mock

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SM126 females - DAD

MERS + Sham

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4

4

MERS + Drug

4

4

4

3

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3

4

4

4

3

3

4

mock

1

1

1

2

2

1

2

2

2

1

1

1

SM126 males - Matute-Bello Score

MERS + Sham

0.64

0.71

0.84

0.64

0.84

0.64

0.71

0.64

0.64

0.64

0.84

0.71

0.84

0.84

0.84

MERS + Drug

0.57

0.64

0.64

0.64

0.51

0.64

0.16

0.37

0.5

0.37

0.37

0.45

0.57

0.57

0.37

mock

0.14

0.14

0

0.14

0.14

0.28

SM126 females- Matute-Bello Score

MERS + Sham

0.66

0.46

0.46

0.7

0.64

0.46

0.64

0.64

0.64

0.64

0.37

0.37

0.5

0.64

0.64

MERS + Drug

0.5

0.5

0.5

0.43

0.16

0.43

0.5

0.64

0.84

0.64

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mock

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iy7KTM9Mp7k5MbeNzZ2bg/NySpG8mlls/LqyzOueWVZ2fb0sGjGLUelcNlkrJscxt3FXsHl0
Yh6TVlS3rKDMw6brxXQxgsbfilIVDyT5bHzkv/fsuTRQCyrPueFOTZUThYceC0ec8/8BAAD/
/wMAmtgOVg==

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Sun 3/15/2020 6:48:15 PM (UTC-07:00)
To: Gralinski, Lisa E[lgralins@email.unc.edu]
Subject: Re: MERS histo figure

Thank you very much. I will let you know ASAP.

Brian is in NC still. I'm doing okay. Ready to have another human around!

Hope your family is as good as possible.

Thank you again. Amy

Get Outlook for iOS

From: Gralinski, Lisa E <lgralins@email.unc.edu>
Sent: Sunday, March 15, 2020 6:46 PM
To: Sims, Amy C
Subject: MERS histo figure

Hey Amy,
Here is a draft of the figure for the MERS histology data. All of the lung pictures are from male mice since that's where the drug treatment made a difference in the pathology. Please let me know what you would like changed, I am not wedded to this presentation!
I hope you and Brian are safe and sound,
Lisa

Lisa Gralinski
Assistant Professor
Department of Epidemiology
University of North Carolina
919-966-3890

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/16/2020 9:09:35 AM (UTC-07:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Re: Meeting next week?

Just making sure you can still chat today at 4pm eastern.

Please try to call my office number 509 372 6496 as I finally got an actual phone. Thank you, Amy

---

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Friday, March 6, 2020 at 2:54 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

Okay, sounds good to me-
Talk to you then!

Have a good weekend,
Alex

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 5:49:13 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

Can you do 4 to 6pm eastern on Monday, March 16th? We might not need that long but better to plan for two hours.

Thank you, Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Friday, March 6, 2020 at 2:45 PM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

Hi Amy,

In general yes, but next is totally full for me....
2 Facs days in Bsl3 and then U19 face-to-face Meeting, etc.

How about early the week after?
Monday or Tuesday... i can be flexible on time so far...

Let me know what works for you,

Alex

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 6, 2020 4:57:20 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Meeting next week?

Alex,

Do you have time to talk for an hour or so next week? I would like to talk about the data and figure out next steps. Thank you! Amy

From: Schaefer, Alexandra[aschaefe@email.unc.edu]
Sent: Mon 3/16/2020 10:14:49 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: Re: Meeting next week?

yes,
however, we are having a mandatory EHS meeting at 3:00pm, not sure if it will be done in an hour
I can text in case it takes longer?

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 16, 2020 12:09 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

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To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

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From: Sims, Amy C <amy.sims@pnnl.gov>
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To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

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To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Meeting next week?

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Thank you! Amy

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/16/2020 10:17:43 AM (UTC-07:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Re: Meeting next week?

Okay. Later is fine with me but I appreciate it can be harder for you. Let me know when you can talk and if we need more time we will find another time this week to finish up.

Thank you, Amy

From: "Schaefer, Alexandra" <aschaefe@email.unc.edu>
Date: Monday, March 16, 2020 at 10:15 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

yes,
however, we are having a mandatory EHS meeting at 3:00pm, not sure if it will be done in an hour
I can text in case it takes longer?

Alex

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Monday, March 16, 2020 12:09 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

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To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: Re: Meeting next week?

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Sent: Friday, March 6, 2020 5:49:13 PM
To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Re: Meeting next week?

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To: "Sims, Amy C" <amy.sims@pnnl.gov>
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To: Schaefer, Alexandra <aschaefe@email.unc.edu>
Subject: Meeting next week?

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From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/16/2020 1:01:34 PM (UTC-07:00)
To: Schaefer, Alexandra[aschaefe@email.unc.edu]
Subject: Need 5 minutes and attached agenda to start with
Attachment: notes for talking with Alex pre talk 3_16_2020.docx

Aims and proposed experiments for each

Specific Aim 1 Does histone modification status coordinate with ISG expression patterns in MERS-CoV infected MVE and FB?

Define interferon type I ISG for MVE and FB. Compare data to Calu3/HAE

Define interferon type III ISG from MVE and FB. Compare data to Calu3/HAE

Look at whether transcription factors STAT1, IRF3, ISGF3 (STAT1/IRF9) regulate ISG expression

Look at H3K4/H3K27 methylation states for MVE, FB and HAE using ChIP PCR followed by ChIP Seq (requires second set of samples different processing)

Specific Aim 2 Exploring modulation of host chromatin remodeling enzymes following MERS-Cov infectin of MVE, HAE, FB

Use PrimePCR Pathway arrays from BioRad to determine if genes that modify chromatin architecture are differentially expressed following MERS-CoV infection. Assuming doing this for both MVE and FB with two viruses wild type and delta 3-5

Determine if histone deacetylase and histone methyltransferase are activated or inhibited during MERS-CoV infection (Abcam HMT or HDAC activity assays) (harvest at 12 and 24 hours post infection and generate nuclear extracts for testing on fluorescent microplate reader)

DNA methyltransferase DNMT/HMT/HDAC determine if inhibitors of these enzymes alter ISG expression and or MERS-CoV replication use MERS-CoV expressing nanoluc for drug assays

Use BioID to define viral host protein protein interactions that modulate ISG expression Propsed putting BirA tag on HMT/DNMT/HDACs to determine MERS-CoV proteins that may interact with these enzymes and mediate the ISG regulation phenotype Calu3 cell only TURBO delivered by lentivirus 24 hours prior to infection

Next steps

Timeline for testing the FB samples

Does Ethan still think he can do the BioID studies?

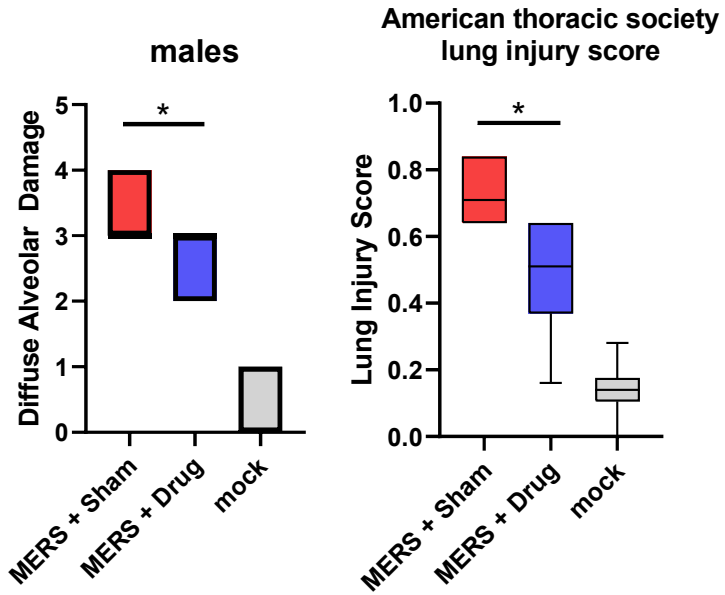
What experiments in Aim 2 can be done entirely at UNC?

Can the existing MVE and FB samples be used for any of the experiments in Aim 2?

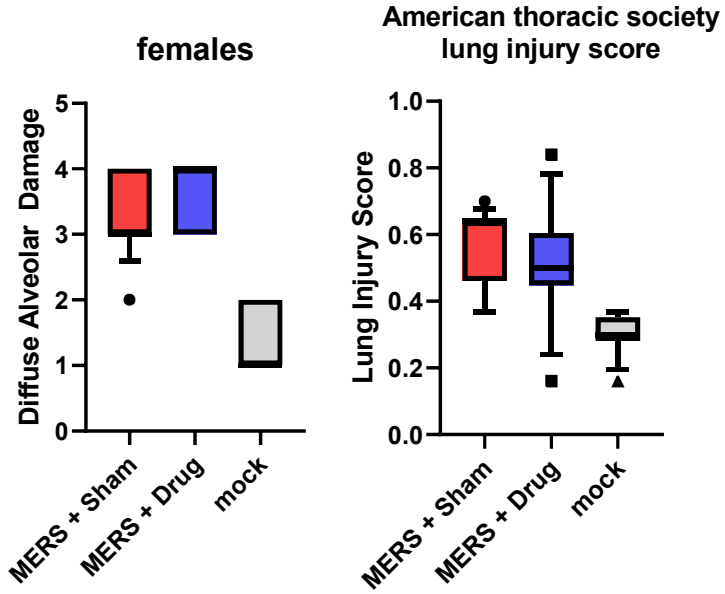
From: Gralinski, Lisa E[lgralins@email.unc.edu]
Sent: Mon 3/16/2020 2:38:00 PM (UTC-07:00)
To: Baric, Ralph S[rbaric@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]
Subject: mers histo scoring
Attachment: sm126 histo figure.pdf

I did the calculations with all of the mice today (instead of separated by sex) and to my surprise, the stats are still significant between groups. So that was a good question Ralph! I can add the combined data to the figure tomorrow but here is the current version so Ralph can see.
Lisa

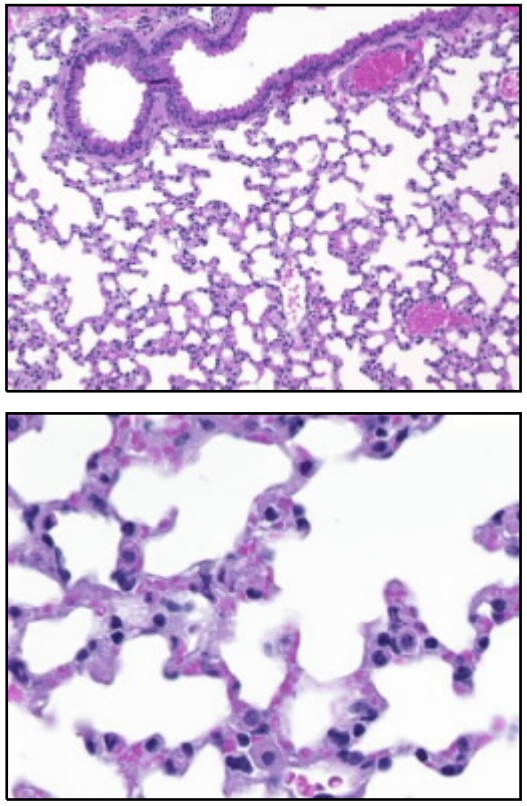
A



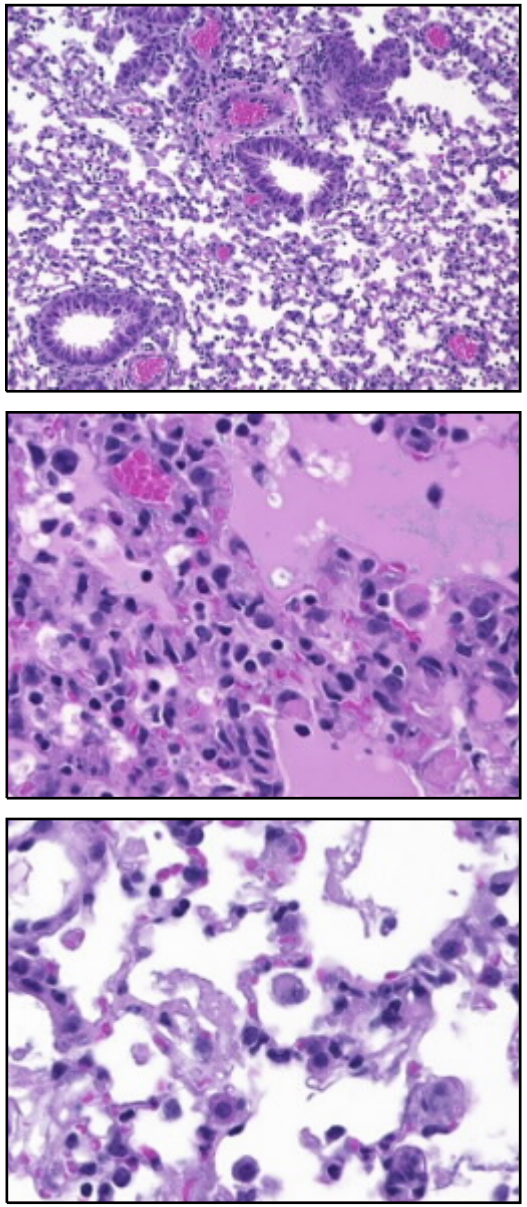
B



C Mock infected



D MERS + sham



E MERS + drug

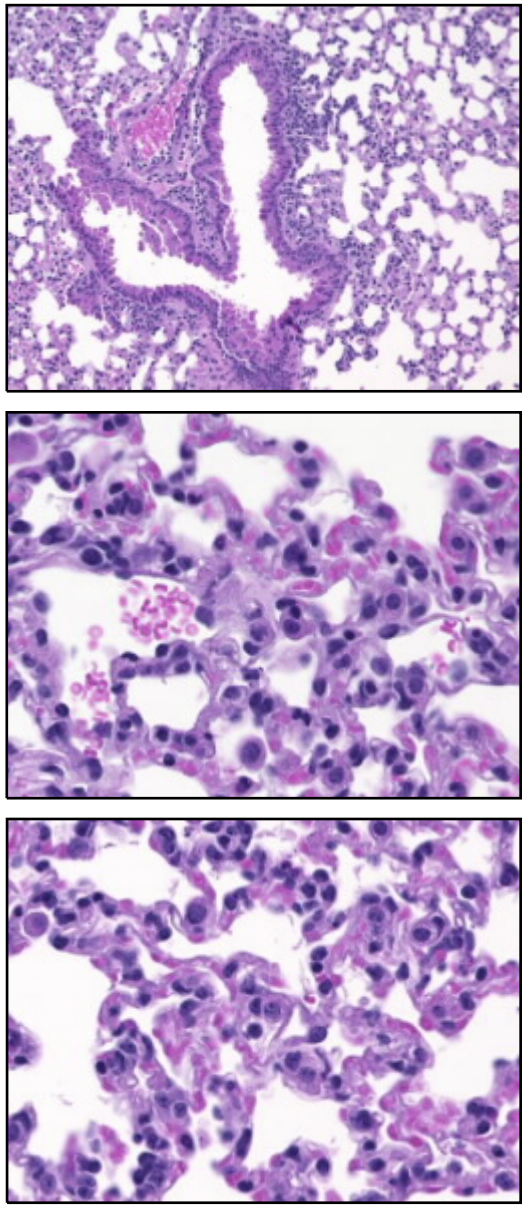


Figure Legend. The histological features of acute lung injury were blindly scored using the American Thoracic Society Lung Injury Scoring system by Batute-Bello, creating an aggregate score for: neutrophils in the alveolar and interstitial space, hyaline membranes, proteinaceous debris filling the air spaces, and alveolar septal thickening. A) and B) Scoring for acute lung injury and diffuse alveolar damage in male and female mice, respectively. Representative lung pathology for C) mock infected, D) MERS-CoV infected and sham treated and E) MERS-CoV infected and PERK'AMG treated male mice at 7 dpi. * indicates a p value of <0.001.

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/16/2020 2:55:37 PM (UTC-07:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: Funds remaining on R21

Hi Tim,

I had a call with Alex today and she is going to need some more reagents.

How much is left on the R21 for UNC? Just curious. Thank you, Amy

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Tue 3/17/2020 1:51:39 PM (UTC-07:00)
To: Gralinski, Lisa E[lgralins@email.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: mers histo scoring

Lisa,

Really great data. Thank you for sending it. Should we add in a panel that shows the data for both sexes together or are we better off to keep the figure separated by sex as that is how the histology images are shown?

I am trying to revise the paper for submitting to Science Translational Medicine. I think there is space to have two figures for the mouse data. Let me know what you think.

Thank you, Amy

From: "Gralinski, Lisa E" <lgralins@email.unc.edu>
Date: Monday, March 16, 2020 at 2:38 PM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: mers histo scoring

I did the calculations with all of the mice today (instead of separated by sex) and to my surprise, the stats are still significant between groups. So that was a good question Ralph! I can add the combined data to the figure tomorrow but here is the current version so Ralph can see.
Lisa

From: Purvine, Emilie[Emilie.Purvine@pnnl.gov]

Sent: Tue 3/17/2020 4:29:22 PM (UTC-07:00)

To: Amie Eisfeld[amie.eisfeld@wisc.edu]; shufang.fan@wisc.edu[shufang.fan@wisc.edu]; KEVIN B WALTERS[kevin.walters@wisc.edu]; Peter Halfmann[peter.halfmann@wisc.edu]; danielle.westhoffsmith@wisc.edu[danielle.westhoffsmith@wisc.edu]; YOSHIHIRO KAWAOKA[yoshihiro.kawaoka@wisc.edu]; Thackray, Larissa[lthackray@wustl.edu]; qtan@dom.wustl.edu[qtan@dom.wustl.edu]; Diamond, Michael[mdiamond@wustl.edu]; vmenach@UTMB.edu[vmenach@UTMB.edu]; Sims, Amy C[amy.sims@pnnl.gov]; sheahan@email.unc.edu[sheahan@email.unc.edu]; jacob.kocher@unc.edu[jacob.kocher@unc.edu]; Ralph Baric[rbaric@email.unc.edu]; Stratton, Kelly G[kelly.stratton@pnnl.gov]; Waters, Katrina M[Katrina.Waters@pnnl.gov]; Bramer, Lisa M[Lisa.Bramer@pnnl.gov]; adam_cockrell@unc.edu[adam_cockrell@unc.edu]; Heller, Natalie C[natalie.heller@pnnl.gov]

Cc: Feng, Song[song.feng@pnnl.gov]; Heath, Emily J[emily.heath@pnnl.gov]; Jefferson, Brett A[brett.jefferson@pnnl.gov]; Joslyn, Cliff A[Cliff.Joslyn@pnnl.gov]; Kvinge, Henry J[henry.kvinge@pnnl.gov]; Mcdermott, Jason E[Jason.McDermott@pnnl.gov]; Praggastis, Brenda[Brenda.Praggastis@pnnl.gov]; Mitchell, Hugh D[Hugh.Mitchell@pnnl.gov]

Subject: FW: ISMB 2020 notification for paper 230

Hello all,

Apologies for not sending this out on Friday when I received it. Unfortunately the paper we submitted to ISMB was not accepted. The reviewers note a few things below, many of which are with respect to the p-value interpretation of our results. The core team here at PNNL is planning on reviewing these comments and revising the paper. Of course we welcome your input on that as well if you like. I'd also like to take this time to open up discussion among all of us for ways to strengthen the work and/or consider follow-on activities. With so many authors one zoom call is probably difficult to manage. But perhaps I can talk with the group from each institution separately? Or we can have email dialogue? I welcome suggestions!

My team here is still interested in posting a version of this work on arXiv and/or bioRxiv but completely understand the reservations. If we address the reviewer comments and send out a new version, would people be comfortable at that point with posting it?

Thank you, and I look forward to a closer collaboration this time around!

_____

Emilie Purvine, Ph.D.
Senior Data Scientist and Mathematician
Pacific Northwest National Laboratory
Phone: 206-528-3461

-----Original Message-----
From: ismb2020@easychair.org <ismb2020@easychair.org>
Sent: Friday, March 13, 2020 3:45 PM
To: Purvine, Emilie <Emilie.Purvine@pnnl.gov>
Subject: ISMB 2020 notification for paper 230

Dear Emilie,

Thank you for your submission to the ISMB/ECCB 2020 Proceedings Track. We regret to inform you that we are unable to accept your paper for publication. There were many strong submissions this year and only a small fraction could be accepted.

A total of 329 papers were submitted. Of these, 64 manuscripts have been conditionally accepted, giving the final acceptance rate of 19.4%. Each paper was reviewed by several members of the Program Committee, overseen by the Senior Program Committee. Papers were individually reviewed and subsequently discussed by their reviewers to encourage a robust debate and possible resolution of discrepancies between reviewers. Based on the reviews and the outcomes of these discussions, papers were nominated for acceptance into the program. A discussion of the Area Chairs, moderated by the Proceedings Chairs, brought us to a final selection of papers for continued consideration.

We hope you will be able to participate at ISMB 2020 in Montreal, Canada, July 12-16. You may wish to consider submitting to the Abstract Track which includes talks and posters. Submission details are available at:

https://protect2.fireeye.com/v1/url?k=4fe4e0ee-1351df57-4fe4cafb-0cc47adc5fce-7b620eb8b16d56d2&q=1&e=80918fc6-a178-45ad-b2bf-7808767122fb&u=https%3A%2F%2Fwww.iscb.org%2Fismb2020-submit%2Fabstracts.

We understand that the current public health situation is leaving summer travel plans uncertain at this time, but we are considering virtual options for those who may not be able to attend in person.

Conference registration is open at:

https://protect2.fireeye.com/v1/url?k=4e209516-1295aaaf-4e20bf03-0cc47adc5fce-3cd212c767924f6f&q=1&e=80918fc6-a178-45ad-b2bf-7808767122fb&u=https%3A%2F%2Fwww.iscb.org%2Fismb2020-registration

Sincerely,

Nadia El-Mabrouk and Donna Slonim
ISMB 2020 Proceedings Chairs

SUBMISSION: 230
TITLE: Hypergraph Models of Biological Networks to Identify Genes Critical to Pathogenic Viral Response

---------- REVIEW 1 ----------
SUBMISSION: 230
TITLE: Hypergraph Models of Biological Networks to Identify Genes Critical to Pathogenic Viral Response
AUTHORS: Song Feng, Emily Heath, Brett Jefferson, Cliff Joslyn, Henry Kvinge, Jason McDermott, Hugh Mitchell, Brenda Praggastis, Amie Eisfeld, Amy Sims, Larissa Thackray, Shufang Fan, Kevin Walters, Peter Halfmann, Danielle Westhoff-Smith, Qing Tan, Vineet Menachery, Timothy Sheahan, Adam Cockrell, Jacob Kocher, Kelly Stratton, Natalie Heller, Lisa Bramer, Michael Diamond, Ralph Baric, Katrina Waters, Yoshihiro Kawaoka and Emilie Purvine

---------- Overall evaluation ----------
SCORE: -2 (reject)
----- TEXT:
The motivation for using hypergraphs to represent molecular networks and reactions is well-accepted, even if algorithms and applications are still uncommon. This manuscript uses a hypergraph to represent the sets of differentially-expressed genes in a moderately-sized compendium of gene expression datasets related to viral pathogenesis. The authors compute the centrality and closeness of every node (gene) in this hypergraph, estimate the enrichment of three specific gene sets in the lists of genes so ordered, and compare the enrichment scores and p-values to genes ordered based on other criteria, including those

based on graphs.

While this use of hypergraphs in systems biology is most welcome, the paper has some major weaknesses.

* The definitions of hypergraph centrality come from another paper (citation 2). Thus, there is very little computational innovation in this manuscript.

* Considering enrichment p-values is not strictly appropriate and is also an uninteresting way of comparing different approaches.

* The results do not support the authors' contention that hypergraph-based centrality "beats" other approaches. Considering Figure 7, the average s-betweenness does have a higher enrichment score than other approaches. But this score is not appropriate for comparing different methods. For each of the three gene sets, the s-betweenness has a p-value that is larger by several orders of magnitude than some of the graph-based methods such as 1-betwenness and CLR graph degree.

I have some other comments below.

The authors of this manuscript do not mention algorithms to compute the hypergraph-based centrality and closeness values. I presume some generalization of BFS or Dijkstra's algorithm will serve the purpose here for computing the s-distance. Providing information on the algorithms for this problem and for computing centrality values with their running times will be useful in this manuscript.

The example in Figure 1 could be replaced by a relevant instance from molecular biology, e.g., the example in Figure 2. In this case, there need be just one figure.

Section 2.3 on GSEA seems unnecessary. It merely explain the GSEA algorithm, which is not necessary to understand this manuscript.

I do not see the value of Figure 3, especially when there is no discussion on it. The authors should remove it.

I do not understand how the authors rank genes by edge size, especially after saying "Since edges in our hypergraph represent genes, ..." A gene can be present in many hyperedges. How do the authors choose among these options to decide where to rank the gene?

The dataset in Dyer et al is over 11 years old. There are several databases of virus-host interactions. The authors should use these updated datasets.

Reference 21 has a single author so the relevant sentence should say "The author of [21] ...".

The word "uniform" is mis-spelt in citation 22.

Several citations in the bibliography, e.g., 7, 10, 13, are missing page numbers and/or other details.

---------- REVIEW 2 ----------
SUBMISSION: 230
TITLE: Hypergraph Models of Biological Networks to Identify Genes Critical to Pathogenic Viral Response
AUTHORS: Song Feng, Emily Heath, Brett Jefferson, Cliff Joslyn, Henry Kvinge, Jason McDermott, Hugh Mitchell, Brenda Praggastis, Amie Eisfeld, Amy Sims, Larissa Thackray, Shufang Fan, Kevin Walters, Peter Halfmann, Danielle Westhoff-Smith, Qing Tan, Vineet Menachery, Timothy Sheahan, Adam Cockrell, Jacob Kocher, Kelly Stratton, Natalie Heller, Lisa Bramer, Michael Diamond, Ralph Baric, Katrina Waters, Yoshihiro Kawaoka and Emilie Purvine

---------- Overall evaluation ----------
SCORE: -2 (reject)
----- TEXT:
The manuscript considers a hyper-graph model where the vertices are samples and the hyper-edges represent genes that are significantly differentially expressed in the corresponding sample. This model seems equivalent to a heterogeneous bipartite graph where the edges between genes and samples represent differentially expressed genes. The manuscript proposes that using graph centrality metrics based on this hyper graph can improve the prediction of genes important for viral response. The utility of the hyper-graph centrality metrics in this context are evaluated based on their enrichment in related gene ontology terms using gene set enrichment analysis (GSEA).

The manuscript is well-organized and easy to follow. My main concern is regarding the evaluation and the derived conclusions:
- The manuscript concludes that hyper-graphs centrality metrics are better than their graph counterparts because they exhibit higher GSEA scores (Figure 5 and Figure 7). However, it is not meaningful to compare the GSEA scores directly since GSEA scores are inherently biased depending on the distribution of the rank measures. To overcome this bias, it is necessary to compare the metrics based on the statistical significance of the enrichment (p-values). The comparisons based on p-values is provided in Figure 6. However, these are in contrast with the conclusions of the manuscript and suggest that the graph centrality metrics (s=1) exhibit more significant enrichment (lower p-values) compared to the proposed hyper-graph centrality metrics (s>=2).
- In a similar manner, the manuscript concludes that betweenness centrality outperforms closeness centrality because of higher enrichment scores. But, there does not seem to be considerable difference between them based on the p-values in Figure 6.
- Another thing that confuse me is regarding Figure 6: Here, there are p-values as low as 10^-12. However, methods section states that the p-values are computed based on a permutation test of 10000 permutations, in which case the lowest possible p-value would be 10^-4. It is unclear why there is such a discrepancy.

---------- REVIEW 3 ----------
SUBMISSION: 230
TITLE: Hypergraph Models of Biological Networks to Identify Genes Critical to Pathogenic Viral Response
AUTHORS: Song Feng, Emily Heath, Brett Jefferson, Cliff Joslyn, Henry Kvinge, Jason McDermott, Hugh Mitchell, Brenda Praggastis, Amie Eisfeld, Amy Sims, Larissa Thackray, Shufang Fan, Kevin Walters, Peter Halfmann, Danielle Westhoff-Smith, Qing Tan, Vineet Menachery, Timothy Sheahan, Adam Cockrell, Jacob Kocher, Kelly Stratton, Natalie Heller, Lisa Bramer, Michael Diamond, Ralph Baric, Katrina Waters, Yoshihiro Kawaoka and Emilie Purvine

---------- Overall evaluation ----------
SCORE: -1 (weak reject)
----- TEXT:
This paper investigates the usefulness of undirected hypergraphs (a generalization of graphs) in prioritizing genes related to viral response across a broad set of gene expression datasets. The authors present a new way to represent this diverse gene expression data, by building a hypergraph where the nodes are conditions, the hyperedges are genes that are differentially expressed in the conditions. They then prioritize genes by hyperedge-based measures of closeness and centrality, which are borrowed from previous work, and evaluate these measures in terms of gene set enrichment for three "gold standard" sets of genes that are known to be involved in viral infection and response.

This paper presents some nice ideas, and I was excited to read it. However, the contributions are relatively understated in this paper, and there does not seem to be enough rigorous evaluation and comparison of hypergraph measures on their dataset.
- General statistics about the hypergraphs are not completely described. In Figure 4, many of the genes

appear in only one condition. What should the reader glean from the middle panel of Figure 4? Is the pairwise intersection size in Figure 4 substantially different from randomized data?
- The hypergraph is constructed by taking the absolute value of fold enrichment, rather than looking and over-expressed genes and under-expressed genes. What is the rationale for this approach, and would the authors find anything else if they separated these two conditions?
- The authors choose three very general gene sets for evaluation - while they are from different sources, is there any further benefit for more specific GO terms than "immune response", for example? Do any other pathways appear when considering the entire ontology?
- There seem to be some data limitations, in that an enormous amount of data is boiled down into a relatively small hypergraph with 179 nodes. I appreciate that this dual representation has benefits, but a discussion of the limitations and the necessarily general evaluation would help give more context for this application.

Finally, and perhaps most importantly, the comparison to other, previously-published enrichment methods (including those that use graphs and those that do not) are missing. The authors build a hypergraph, and then compare centralities and other statistics of that representation to the case when the hypergraph becomes a graph. A major limitation is that the authors thresholded all the gene expression data to build the hypergraph in the first place. While the authors have shown that the hypergraph measures are better than those applied to the graph version, they have not demonstrated that hypergraphs achieve better enrichment than other methods that, for example, consider the gene expression fold change. While I think that hypergraph-based methods still may hold some unique power in this comparison, it has not been adequately described in this paper.

Minor comments:
- The authors might want to discuss the difference between hypergraphs and bipartite graphs to help the reader understand the benefits of hypergraphs.
- There should be more details for the mutual information for enriching for important genes in the network, and the context likelihood of relatedness, since they are important for understanding the results.
- The authors should consider whether singletons should be considered part of the hypergraph (do they contribute in any way to centrality measures?). Further, the size of the hypergraph shrinks considerably when removing all genes that appear in only one condition.
- There is some recent work on directed hypergraphs (e.g. those that cite Klamt et al 2009), which might be useful to include in the discussion.

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Wed 3/18/2020 11:39:06 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: mers histo scoring

Hi Amy, Hope your doing well in all this madness. Can you send the revised manuscript to me with the new data? I filed a invention disclosure with you, me, Hugh and Katrina listed. They also will want to talk with PNNL at ome point. However, I need the revised draft with figures asap. Is this possible? Lab is a madhouse. ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, March 17, 2020 4:52 PM
To: Gralinski, Lisa E <lgralins@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: mers histo scoring

Lisa,

Really great data. Thank you for sending it. Should we add in a panel that shows the data for both sexes together or are we better off to keep the figure separated by sex as that is how the histology images are shown?

I am trying to revise the paper for submitting to Science Translational Medicine. I think there is space to have two figures for the mouse data. Let me know what you think.

Thank you, Amy

From: "Gralinski, Lisa E" <lgralins@email.unc.edu>
Date: Monday, March 16, 2020 at 2:38 PM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: mers histo scoring

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Lisa

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Wed 3/18/2020 11:43:03 AM (UTC-07:00)
To: Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: mers histo scoring

Yes, things are nuts here too. Hugh filed for the invention report at PNNL and PNNL may be reaching out to UNC soon.

I have been revising the draft for Science Translation. I will get it to you by tomorrow morning. I am sorry it is taking forever but life is messy at home and at work. Brian is still in NC and one of our dogs has been very sick.

Garry Coulson send me your article in Bloomberg. You looked good but tired. I hope you get a break soon.

Thank you, Amy

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From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Sent: Wed 3/18/2020 7:28:54 PM (UTC-07:00)

To: Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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Please write back ASAP. They want this up ASAP.

Thanks!

Tim

From: Painter, George R.[george.r.painter@emory.edu]

Sent: Wed 3/18/2020 7:42:18 PM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Cc: Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: Re: [External] Your response needed: Submission of Paper to BioRxiv

I agree.

George Painter, M.S., Ph.D

Professor of Pharmacology, Emory University, School of Medicine
Director, Emory Institute for Drug Development |EIDD
Section Head, Yerkes National Primate Center
CEO, Drug Innovation Ventures at Emory |DRIVE

954 Gatewood Rd. NE |Atlanta, GA,USA 30329

Voice: +1-404-712-6886
email: grpaint@emory.edu

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original message (including attachments).

From: Natchus, Michael[mnatchu@emory.edu]

Sent: Wed 3/18/2020 7:43:58 PM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: Re: [External] Your response needed: Submission of Paper to BioRxiv

I agree,

Mike Natchus

On 3/18/20, 10:28 PM, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu> wrote:

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Please write back ASAP. They want this up ASAP.

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Tim

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From: Bluemling, Gregory R.[gblueml@emory.edu]

Sent: Wed 3/18/2020 7:50:19 PM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Cc: Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Natchus, Michael[mnatchu@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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I agree.

Sent from my iPhone

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From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Wed 3/18/2020 7:54:30 PM (UTC-07:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: Re: Your response needed: Submission of Paper to BioRxiv

I agree.

Get Outlook for iOS

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, March 18, 2020 7:29 PM
To: Baric, Ralph S; Zhou, Shuntai; Sims, Amy C; Hill, Collin Siva; Leist, Sarah Rebecca; Schaefer, Alexandra; Agostini, Maria L K; Pruijssers, Ardina; Brown, Ariane; Greg Bluemling; Natchus, Michael; msainda@emory.edu; a.kolykhalov@emory.edu; Painter, George R.; Denison, Mark; Swanstrom, Ronald I; Dinnon, Kenneth Harold III; Graham, Rachel; Thornburg, Natalie (CDC/OID/NCIRD); zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann; Chappell, Jim
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Please write back ASAP. They want this up ASAP.

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From: Zhou, Shuntai[shuntaiz@email.unc.edu]

Sent: Wed 3/18/2020 9:08:20 PM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]

Cc: Baric, Ralph S[rbaric@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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From: Baric, Ralph S[rbaric@email.unc.edu]

Sent: Thur 3/19/2020 3:16:23 AM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, March 18, 2020 10:29 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Greg Bluemling <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; msainda@emory.edu; a.kolykhalov@emory.edu; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: Your response needed: Submission of Paper to BioRxiv
Importance: High

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Please write back ASAP. They want this up ASAP.

Thanks!

Tim

From: Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]

Sent: Thur 3/19/2020 3:35:56 AM (UTC-07:00)

To: Baric, Ralph S[rbaric@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Chappell, Jim[jim.chappell@vumc.org]

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I agree

Stephanie A. Montgomery, PhD, DVM, Dipl. ACVP

Associate Professor, Dept. of Pathology and Laboratory Medicine
Director, Animal Histopathology & Laboratory Medicine Core
901 Brinkhous-Bullitt Bldg
Chapel Hill, NC 27599-7525
P 919-962-5345 E stephanie@med.unc.edu

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To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Greg Bluemling <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; msainda@emory.edu <msainda@emory.edu>; a.kolykhalov@emory.edu <a.kolykhalov@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov <zaq6@cdc.gov>; axt4@cdc.gov <axt4@cdc.gov>; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
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From: Thornburg, Natalie (CDC/DDID/NCIRD/DVD)[nax3@cdc.gov]

Sent: Thur 3/19/2020 3:38:55 AM (UTC-07:00)

To: Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Greg Bluemling[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; msainda@emory.edu[msainda@emory.edu]; a.kolykhalov@emory.edu[a.kolykhalov@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Harcourt, Jennifer (CDC/DDID/NCIRD/DVD)[zaq6@cdc.gov]; Tamin, Azaibi (CDC/DDID/NCIRD/DVD)[axt4@cdc.gov]; Chappell, Jim[jim.chappell@vumc.org]

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Associate Professor, Dept. of Pathology and Laboratory Medicine
Director, Animal Histopathology & Laboratory Medicine Core
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Tim

From: Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]

Sent: Thur 3/19/2020 4:49:39 AM (UTC-07:00)

To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Saindane, Manohar T.[msainda@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

Subject: RE: [External] Your response needed: Submission of Paper to BioRxiv

I agree
-Sasha

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Sent: Wednesday, March 18, 2020 10:29 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
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If you have received this message in error, please contact the sender by reply e-mail message and destroy all copies of the original message (including attachments).

From: Saindane, Manohar T.[msainda@emory.edu]

Sent: Thur 3/19/2020 6:32:20 AM (UTC-07:00)

To: Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/OID/NCIRD)[nax3@cdc.gov]; zaq6@cdc.gov[zaq6@cdc.gov]; axt4@cdc.gov[axt4@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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I agree
Manohar Saindane

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Sent: Thursday, March 19, 2020 7:50 AM
To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
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From: Tamin, Azaibi (CDC/DDID/NCIRD/DVD)[axt4@cdc.gov]

Sent: Thur 3/19/2020 10:43:11 AM (UTC-07:00)

To: Saindane, Manohar T.[msainda@emory.edu]; Kolykhalov, Alexander A.[a.kolykhalov@emory.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Baric, Ralph S[rbaric@email.unc.edu]; Zhou, Shuntai[shuntaiz@email.unc.edu]; Sims, Amy C[amy.sims@pnnl.gov]; Hill, Collin Siva[collinh@live.unc.edu]; Leist, Sarah Rebecca[leist@email.unc.edu]; Schaefer, Alexandra[aschaefe@email.unc.edu]; Agostini, Maria L K[maria.l.agostini.1@vumc.org]; Pruijssers, Ardina[ardina.pruijssers@vumc.org]; Brown, Ariane[ajbrown7@email.unc.edu]; Bluemling, Gregory R.[gblueml@emory.edu]; Natchus, Michael[mnatchu@emory.edu]; Painter, George R.[george.r.painter@emory.edu]; Denison, Mark[mark.denison@vumc.org]; Swanstrom, Ronald I[ron_swanstrom@med.unc.edu]; Dinnon, Kenneth Harold III[kdinnon@email.unc.edu]; Graham, Rachel[rlgraham@ad.unc.edu]; Thornburg, Natalie (CDC/DDID/NCIRD/DVD)[nax3@cdc.gov]; Harcourt, Jennifer (CDC/DDID/NCIRD/DVD)[zaq6@cdc.gov]; Montgomery, Stephanie Ann[stephanie_montgomery@med.unc.edu]; Chappell, Jim[jim.chappell@vumc.org]

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From: Saindane, Manohar T. <msainda@emory.edu>
Sent: Thursday, March 19, 2020 9:32:20 AM
To: Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/DDID/NCIRD/DVD) <nax3@cdc.gov>; Harcourt, Jennifer (CDC/DDID/NCIRD/DVD) <zaq6@cdc.gov>; Tamin, Azaibi (CDC/DDID/NCIRD/DVD) <axt4@cdc.gov>; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: RE: [External] Your response needed: Submission of Paper to BioRxiv

I agree
Manohar Saindane

-----Original Message-----
From: Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>
Sent: Thursday, March 19, 2020 7:50 AM
To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>;

Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: RE: [External] Your response needed: Submission of Paper to BioRxiv

I agree
-Sasha

-----Original Message-----
From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Wednesday, March 18, 2020 10:29 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Zhou, Shuntai <shuntaiz@email.unc.edu>; Amy Sims <amy.sims@pnnl.gov>; Hill, Collin Siva <collinh@live.unc.edu>; Leist, Sarah Rebecca <leist@email.unc.edu>; Schaefer, Alexandra <aschaefe@email.unc.edu>; Agostini, Maria L K <maria.l.agostini.1@vumc.org>; Pruijssers, Ardina <ardina.pruijssers@vumc.org>; Brown, Ariane <ajbrown7@email.unc.edu>; Bluemling, Gregory R. <gblueml@emory.edu>; Natchus, Michael <mnatchu@emory.edu>; Saindane, Manohar T. <msainda@emory.edu>; Kolykhalov, Alexander A. <a.kolykhalov@emory.edu>; Painter, George R. <george.r.painter@emory.edu>; Denison, Mark <mark.denison@vumc.org>; Swanstrom, Ronald I <ron_swanstrom@med.unc.edu>; Dinnon, Kenneth Harold III <kdinnon@email.unc.edu>; Graham, Rachel <rlgraham@ad.unc.edu>; Thornburg, Natalie (CDC/OID/NCIRD) <nax3@cdc.gov>; zaq6@cdc.gov; axt4@cdc.gov; Montgomery, Stephanie Ann <stephanie_montgomery@med.unc.edu>; Chappell, Jim <jim.chappell@vumc.org>
Subject: [External] Your response needed: Submission of Paper to BioRxiv
Importance: High

Dear All,

I need you all to reply to this message with "I Agree", to upload our paper to BioRxiv.

Science Translation Medicine as requested we upload the original submission of the NHC coronavirus paper to BioRxiv to:

1. Get the paper out there.
2. To comply with the Wellcome Trust data sharing agreement (https://wellcome.ac.uk/press-release/sharing-research-data-and-findings-relevant-novel-coronavirus-covid-19-outbreak)

Please write back ASAP. They want this up ASAP.

Thanks!

Tim

This e-mail message (including any attachments) is for the sole use of the intended recipient(s) and may contain confidential and privileged information. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distribution or copying of this message (including any attachments) is strictly prohibited.

If you have received this message in error, please contact the sender by reply e-mail message and destroy all copies of the original message (including attachments).

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Thur 3/19/2020 2:49:15 PM (UTC-07:00)
To: Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: mers histo scoring

I know you don't believe me but I am really working on the paper. I should be able to get it to you and Tim again tomorrow. I am trying to make sure I hit all the required elements in the Sci Trans Med template.

After you and Tim review it I will send that draft out to all collaborators. Once those comments are assembled we can call it a draft ready to submit.

My apologies for taking forever. It's been a messy transition. Thank you, Amy

---

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Wednesday, March 18, 2020 at 11:39 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: mers histo scoring

Hi Amy, Hope your doing well in all this madness. Can you send the revised manuscript to me with the new data? I filed a invention disclosure with you, me, Hugh and Katrina listed. They also will want to talk with PNNL at ome point. However, I need the revised draft with figures asap. Is this possible? Lab is a madhouse. ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Tuesday, March 17, 2020 4:52 PM
To: Gralinski, Lisa E <lgralins@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: mers histo scoring

Lisa,

Really great data. Thank you for sending it. Should we add in a panel that shows the data for both sexes together or are we better off to keep the figure separated by sex as that is how the histology images are shown?

I am trying to revise the paper for submitting to Science Translational Medicine. I think there is space to have two figures for the mouse data. Let me know what you think.

Thank you, Amy

From: "Gralinski, Lisa E" <lgralins@email.unc.edu>
Date: Monday, March 16, 2020 at 2:38 PM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sims, Amy C" <amy.sims@pnnl.gov>

Subject: mers histo scoring

I did the calculations with all of the mice today (instead of separated by sex) and to my surprise, the stats are still significant between groups. So that was a good question Ralph! I can add the combined data to the figure tomorrow but here is the current version so Ralph can see.
Lisa

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Fri 3/20/2020 8:38:42 AM (UTC-07:00)
To: Baric, Ralph S[rbaric@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Subject: FW: Greetings from BEI Resources!

Please the email below from BEI Resources. Sujatha is really great to work with! I can provide examples of the paperwork to assist with what level of details are needed if you are going to provide the reagent to them for distribute.

Tim suggested that Ben would be someone likely to assist with this but I don't I remember his last name or have his email address now that I don't have access to my UNC account.

Hope things are going well. Thank you, Amy

From: "Rashid, Sujatha" <srashid@atcc.org>
Date: Tuesday, March 17, 2020 at 7:18 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Cc: "deBruin, Christine" <cdebruin@atcc.org>
Subject: RE: Greetings from BEI Resources!

Hi Amy
Dr. Baric was supposed to give us an ic of Wuhan isolate according to NIAID program offoicer. Can you give another lab contact? so I can work on it like I used to keep pinging you 😊
Thanks
Best regards,
Sujatha

Sujatha Rashid, MS, PhD, PMP®
Program Manager, ATCC Federal Solutions
Virology Team Lead, BEI Resources

10801 University Boulevard
Manassas, VA 20110-2209
Tel: (703) 365-2700 ext. 2660

From: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Sent: Fri 3/20/2020 8:53:49 AM (UTC-07:00)
To: srashid@atcc.org[srashid@atcc.org]
Cc: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]
Subject: Re: Greetings from BEI Resources!

Hi Sujatha,

I think we met at ASM Biothreats. I can be your contact for this. Right now, we are still characterizing this clone. When we are sure of how this reagent behaves, we can talk about deposition at BEI. Talk soon,

Tim

From: Amy Sims <amy.sims@pnnl.gov>
Date: Friday, March 20, 2020 at 11:38 AM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: FW: Greetings from BEI Resources!

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Date: Tuesday, March 17, 2020 at 7:18 AM
To: "Sims, Amy C" <amy.sims@pnnl.gov>
Cc: "deBruin, Christine" <cdebruin@atcc.org>
Subject: RE: Greetings from BEI Resources!

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Thanks
Best regards,
Sujatha

Sujatha Rashid, MS, PhD, PMP®
Program Manager, ATCC Federal Solutions
Virology Team Lead, BEI Resources

10801 University Boulevard
Manassas, VA 20110-2209
Tel: (703) 365-2700 ext. 2660

From: Rashid, Sujatha[srashid@atcc.org]
Sent: Fri 3/20/2020 9:03:42 AM (UTC-07:00)
To: Sheahan, Timothy Patrick[sheahan@email.unc.edu]
Cc: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]; deBruin, Christine[cdebruin@atcc.org]
Subject: RE: Greetings from BEI Resources!

Thank you, Amy!

I do recall meeting you, Tim. Thank you for the update, I will pass this information on to NIAID.

Best regards,
Sujatha

Sujatha Rashid, MS, PhD, PMP®
Program Manager, ATCC Federal Solutions
Virology Team Lead, BEI Resources

10801 University Boulevard
Manassas, VA 20110-2209
Tel: (703) 365-2700 ext. 2660

From: Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Sent: Friday, March 20, 2020 11:54 AM
To: Rashid, Sujatha <srashid@atcc.org>
Cc: Sims, Amy C <amy.sims@pnnl.gov>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Re: Greetings from BEI Resources!

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Tim

From: Amy Sims <amy.sims@pnnl.gov>
Date: Friday, March 20, 2020 at 11:38 AM
To: "Baric, Ralph S" <rbaric@email.unc.edu>, "Sheahan, Timothy Patrick" <sheahan@email.unc.edu>
Subject: FW: Greetings from BEI Resources!

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Cc: "deBruin, Christine" <cdebruin@atcc.org>
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Best regards,
Sujatha

Sujatha Rashid, MS, PhD, PMP®
Program Manager, ATCC Federal Solutions
Virology Team Lead, BEI Resources

10801 University Boulevard
Manassas, VA 20110-2209
Tel: (703) 365-2700 ext. 2660

From: Sims, Amy C[amy.sims@pnnl.gov]

Sent: Fri 3/20/2020 2:26:08 PM (UTC-07:00)

To: Baric, Ralph S[rbaric@email.unc.edu]; Sheahan, Timothy Patrick[sheahan@email.unc.edu]; Mitchell, Hugh D[Hugh.Mitchell@pnnl.gov]; Waters, Katrina M[Katrina.Waters@pnnl.gov]

Subject: Draft on apoptosis manuscript

Attachment: Apoptosis Sci Trans 3_20_2020_2.docx

Ralph, Tim, Hugh and Katrina,

Here is the most up to date draft of the primary cell apoptosis manuscript.

Per Ralph's suggestion I have formatted it for the longer of Science Translational Medicine's articles.

Please make comments and return to me as I need to get this paper out to all of the authors and then get through PNNL's processing for information release before I can submit.

Figures are in the back of the word document.

If you think another journal is more appropriate please let me know.

Thank you, Amy

Science Translational Medicine AAAS

Submitted Manuscript: Confidential template updated: February 28 2012

Ralph and Tim,

My apologies for taking so long to get this back to you. Life has not gone as planned since I left UNC.

I thought it might be easier for you to start off by reading my responses to your specific comments in the results and discussion. I wasn't sure if there was time for a call or not as I am aware that both of you must be insanely busy.

Ralph, you asked about FB cytox in Figure 6A-B but there isn't any. We may have to talk about this one on the phone for you to show me what I am missing.

*Ralph you asked about the type of FB (*primary cultured human lung (HLFs) or airway fibroblasts (HAFs) or both *used. I believe they are derived from the deep lung tissue the same as the MVE. The MVE must be sorted by flow at least once and the FB just crawl out of the tissue and grow on the dish. I can talk to Scott and get more details if you want.*

Figure 1 virologic phenotypes and CPE no changes
Figure 2 transcriptomics and proteomics Hugh updated the labeling of both panels and it is much easier to see what we are focused on.
Figure 3 lipidomics (could combine 2 and 3 if need be) no changes
Figure 4 caspase no changes
Figure 5 UPR and three viral proteins

>Transcriptomics have been removed
>Hugh made graphs for several viral proteins and I thought the data looked the best for spike, ORF4a and membrane so I have included those graphs. These trend with the titer data and look the same for both cell types
>All UPR related proteins Hugh could find are included as data here. I asked again to make sure, but we did not see differences in CHOP or IRE1 or ATF6 or XBP1. This study was never designed to be an exhaustive look into the MERS vs the UPR it was only to validate the omics findings and we got more than we bargained for.
>For clarity: GRP78 and Bip are the same thing
>GRP94 and HSP90B1 are the same thing
>In a previous version Tim asked me to go down to one name per entity and I did but it was hard to figure out which name was most frequently used. I have them both listed now.

Figure 6 PERK inhibitor in lung cells no changes
Figure 7 Gralinski mouse data she added this missing axis
Figure 8 Gralinski mouse histology data (she just sent a pdf and I might need her to send me the graphs in another way to make the figure legends and titles line up

Science Translational Medicine Manuscript Template

General Instructions on using this template and submitting a manuscript to *Science Translational Medicine*:
Using this template will help to speed the processing of your paper. Our goal is to be able to identify each section of your manuscript so that we can accurately record the title, authors, abstract, etc. and also be able to enrich it by including reference links and an accurate layout.

Please use the actual template, which starts on page 2. When you are ready to submit, please delete the text on this cover page.

You can submit your paper at https://cts.sciencemag.org
Additional instructions are available at http://stm.sciencemag.org

More specific formatting instructions are provided in the actual template, which follows.

Title: Inhibition of the Unfolded Protein Response Reduces Middle East Respiratory Syndrome Coronavirus Induced Acute Lung Injury

Authors: Amy C. Sims[1*]†, Hugh Mitchell[2]†, Lisa E. Gralinski[1], Jennifer E. Kyle[2], Kristin E. Burnum-Johnson[2], Mariam Lam[3], M. Leslie Fulcher[3], Ande West[1], Richard D. Smith[2], Scott Randell[3], Thomas O. Metz[2], Timothy P. Sheahan[1]‡, Katrina Waters[2]‡, Ralph S. Baric[1]‡

Affiliations:
[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC.

[2]Biological Sciences Division, Pacific Northwest National Laboratories, Richland, WA.

[3]University of North Carolina Tissue Procurement and Cell Culture Core, University of North Carolina at Chapel Hill, Chapel Hill, NC.

*To whom correspondence should be addressed: Amy C. Sims amy.sims@pnnl.gov current address: National Security Directorate, Pacific Northwest National Laboratory Richland, WA.

†contributed equally to manuscript.

‡ co-senior author

One Sentence Summary: An unfolded protein response inhibitor reduces Middle East Respiratory Syndrome Coronavirus replication in primary human lung cells and improves respiratory functions and diminishes acute lung injury signatures in a lethal challenge rodent animal model.

Abstract: Currently, there are no approved treatment options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) induced acute respiratory distress syndrome (ARDS) and little is understood about how individual primary human lung cell types contribute to overall disease phenotypes. MERS-CoV replicates equivalently in primary human lung microvascular endothelial cells (MVE) and fibroblasts (FB) but only MVE demonstrate virus induced cytopathic effect. To explore potential mechanisms leading to reduced MVE viability, three sets of donor-matched human lung MVE and FB were infected and samples collected for transcriptomic, proteomic, and lipidomic analysis over time. Functional enrichment analysis results were validated and demonstrated that MERS-CoV-infected MVE were dying via an unfolded protein response (UPR) mediated apoptotic mechanism. Pharmacologic manipulation of the UPR in MERS-CoV infected MVE, FB, and mice confirmed its importance in virus replication and infection outcomes, resulting in improved respiratory functions and a reduction in the signatures of acute lung injury detected in infected untreated mice. These data support that infection and death of MVE, loss of endothelial barrier integrity and vascular leakage into the airway could be a potential trigger for ARDS commonly seen in MERS-CoV patients. Our systems biology approach provides new insight into how MERS-CoV infection of cells essential for lung structure and function may drive severe end stage lung disease while simultaneously

identifying novel host targets that can reduce hallmark symptoms of severe end stage lung disease.

[Main Text:]

Introduction

Coronaviruses (CoV) are important emerging pathogens associated with severe disease outcomes in humans and animals causing significant global morbidity and mortality. In 2003, severe acute respiratory coronavirus (SARS-CoV) emerged from closely related bat CoV strains, spread to 26 nations, and caused approximately 8,000 human cases and 800 deaths, worldwide (*1, 2*). In 2012, Middle East respiratory syndrome CoV (MERS-CoV) emerged, causing approximately 2,400 cases with a ~35% mortality rate in 27 countries and the outbreak is still ongoing (*3*). In 2020, the causative agent of coronavirus infectious disease 2019 was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) and to date more than 200,000 cases have been confirmed with a morality rate of ~4% in >160 countries with ongoing virus transmission resulting in significant economic losses and global public health concerns (WHO COVID 19 website). SARS-CoV, SARS-CoV 2 and MERS-CoV disease severity are strongly influenced by aging and other co-morbidities (e.g., diabetes, obesity) and mortality rates exceed 50% in aged individuals (>60 years)(*4*). These data underscore the highly pathogenic potential of emerging CoVs and reinforce the critical need for comprehensive experimental approaches that define pathogenic programs which could be targeted for antiviral therapy to reverse severe disease outcomes.

Acute Respiratory Distress Syndrome (ARDS) is a severe end stage lung disease characterized by rapid onset respiratory failure resulting from diffuse alveolar damage, vascular leakage into the airways and pulmonary fibrosis (*5-8*). ARDS is a complex syndrome with

multiple etiologies which complicates diagnosis and treatment. While not the most prevalent cause(*9*), severe respiratory infections can progress to ARDS including those by highly pathogenic avian influenza(*10*) (H5N1) and SARS-CoV, SARS-CoV 2 and MERS-CoV(*2, 11-14*). Dissecting the mechanisms of MERS-CoV-induced ARDS has been hampered human genetic variation, variable co-morbidities and limited human sample availability (*11, 15*). Highly pathogenic human coronaviruses have been observed to cause programmed cell death within in vitro and in vivo models of viral pathogenesis as well as in patient autopsy tissues (*4, 16-23*). Given that MERS-CoV replicates efficiently in multiple cell types essential for lung physiology (e.g. lung fibroblasts, epithelial and endothelial cells) (*24*), primary culture systems provide a biologically relevant platform to better understand virus and host interactions that may drive severe lung pathology.

Here we report a kinetic multi-omics analysis of MERS-CoV infected primary human lung fibroblasts (FB) and microvascular endothelial (MVE) cells from three different human donors. While MERS-CoV replication kinetics were similar among FB and MVE, the host responses as determined by transcriptomic, proteomic, and lipidomic analyses differed significantly by cell type and suggested that MVE cells were dying via apoptotic mechanisms initiated by the unfolded protein response (UPR) which helps monitor and maintain homeostasis in the endoplasmic reticulum (ER) following a stress response. Pharmacologic manipulation of UPR demonstrated that active/dimerized PERK was critical for viral replication in vitro. Of note, mice infected with MERS-CoV and treated with an inhibitor specific for PERK have reduced weight loss and improved respiratory functions validating that regulation of the UPR influences disease phenotypes in an animal model of lethal MERS-CoV infection. Our studies used analysis of multi-omics datasets derived from MERS-CoV infected primary human lung cells to identify

critical host pathways that regulate viral replication and cell survival outcomes and suggest that apoptosis of MERS-CoV infected MVE cells is mediated by the UPR and may represent one of the first breaches of the epithelial-endothelial cell barrier which may allow disease progression to ARDS.

Results

MERS-CoV induces cytopathic effect in primary human lung endothelial cells but not fibroblasts

Understanding critical MERS-CoV-host interactions in various primary human lung cells, each essential for architecture and physiology, provides a unique opportunity to better understand the contributions of individual cell types to disease phenotypes in the lung circumventing one of the biggest challenges in understanding MERS-CoV pathogenicity, a lack of available clinical samples for analysis. To characterize MERS-CoV infection in primary human lung microvascular endothelial cells (MVE) and primary human lung fibroblasts (FB), we obtained virologic and multi-omics data (transcriptomic, proteomic, and lipidomic) from infected cells from three matched human donors every 12 hours for 48 hours. Viral growth kinetics and peak titers (~10^7 plaque forming units (PFU)/mL) were nearly identical regardless of donor background (Figure 1A-B). We also determined infection frequency via microscopy by comparing the total number of cells (i.e. nuclei) to the number of MERS-CoV infected cells per high powered field (Figure 1C and D and Supplemental Figure 1). To simplify this process, we utilized a MERS-CoV expressing the red fluorescent protein (MERS-RFP) (Figure 1C and D). Unlike infection frequency in FB which increased over time, the numbers of total cells per field (Figure 1C) as well infection frequency decreased over time in MVE (Figure 1C-D). Since the number of cells per field in mock-infected MVE cultures did not diminish over time, this suggested that a virus induced cytopathic effect (CPE) was mediating the loss of cells in MERS-

CoV infected MVE (Figure 1C and D). To quantitate CPE in MERS-CoV infected MVE and FB over time, we performed a cell viability assay (CellTiter-Glo) which estimates the number of metabolically active viable cells by measuring the levels of adenosine triphosphate (ATP) in each well. Unlike FB which had similar levels of cell viability in mock- and MERS-CoV-infected cultures for most time points (Figure 1E), infected MVE viability decreased significantly over time as compared to mock (Figure 1F) displaying a similar trend to that observed in Figure 1C. Together, these data demonstrate that both primary MVE and FB are similarly susceptible to MERS-CoV infection but MVE cell viability is significantly reduced over time yet FB are relatively unaffected.

Cross-donor consensus transcriptomic, proteomic and lipidomic responses

To gain insight into the divergent outcomes in cell viability following MERS-CoV infection of FB and MVE, we analyzed donor matched kinetic multi-omic datasets. Functional enrichment was performed on transcriptomic and proteomic data across both cell types which showed distinct differences in the modulation of the transcriptome and proteome among infected FB and MVE (Figure 2). We found that pathways related to apoptosis (transcription, Figure 2A) and the unfolded protein response (UPR, transcripts and proteins, Figure 2A and 2B), were significantly enriched in MERS-CoV infected MVE at multiple timepoints which was not observed in similarly infected FB. Interestingly, increased hemoglobin protein expression levels in both FB and MVE were detected at 48hpi (arrow Figure 2B), which has been demonstrated to regulate endothelial and epithelial cell communication as well as to regulate the durability of vascular walls (*25-27*). We then investigated if mothers against decapentaplegic homolog 7 (SMAD7) and/or fibroblast growth factor 2 (FGF2) transcripts were differentially expressed in MERS-CoV infected MVE or FB as previous studies indicated that upregulated expression of SMAD7 and

FGF2 in MERS-CoV infected immortalized kidney and lung epithelial cells led to cellular apoptosis (*28*). Neither SMAD7 nor FGF2 expression levels were distinct following infection and did not appear to explain the differences in cytopathic effect seen in the current studies (Supplemental Figure S2). Finally, we sought to determine if MERS-CoV infection would alter the lipidome in FB or MVE. We classified lipids into broad categories for enrichment analysis, which revealed differential expression of ceramides and triglycerides in FB and MVE (Figure 3A). When analyzed at a per-lipid-species level, we found dramatic and significant differences in specific species of ceramides (Figure 3B, upper panel) and triglycerides (Figure 3B, lower panel) both of which are involved in activating apoptotic processes (*29*).

MERS-CoV activates Caspases 3 and 7 in infected MVE

To validate the complementary multi-omics observations suggesting that MERS-CoV infection induces apoptosis in MVE, we simultaneously measured death effector caspases 3 and 7 and cell viability in mock or MERS-CoV infected FB and MVE using the Promega Apotox Triplex kit. We included staurosporine (induces caspase 3/7 activation) or ionomycin (induces necrotic cell death with no caspase activation) treatment as controls. In addition, we added UV-inactivated MERS-CoV virions in order to control for effects on cultures independent of virus replication (i.e. entry, uncoating, etc.). Uninfected MVE and FB treated with staurosporine significantly induced caspase 3/7 activation as compared to mock and cells treated with UV-inactivated MERS-CoV (Figure 4A-B). As expected, ionomycin treatment did not induce caspase 3/7 activation. With MERS-CoV infection, significant caspase 3/7 activation was observed at both 24 and 48 hours post infection but only in MVE (Figure 4A) not in FB (Figure 4B). Caspase activation was not observed with UV-inactivated MERS-CoV treatment or in mock-infected cells for either cell type (Figure 4A-B). When measuring cell viability within the same assay,

neither mock infection nor treatment with UV-inactivated virions appreciably affected cell viability (Figure 4C-D). Importantly, treatment of both FB and MVE with control compounds (e.g. staurosporine or ionomycin) diminished cell viability but MERS-CoV infection only diminished cell viability in MVE (Figure 4C-D). Death of MERS-CoV infected MVE could lead to permeability at the epithelial/endothelial cell barrier one of the first steps of ARDS and viable MERS-CoV infected FB would continue to produce high levels of infectious virus both of which would contribute to the overall disease burden in the infected patient.

Expression of proteins indicative of the UPR pathway are increased in MERS-CoV infected MVE

Both systems data and confirmatory experimental validation studies suggested that MERS-CoV infected MVE were dying via apoptotic pathways. To better understand the initiation of this process, we re-analyzed our systems biology data focusing on specific mediators of apoptosis and UPR. We found increased protein expression of three well-established UPR markers, glucose regulated protein 78 (GRP78 also known as binding immunoglobulin protein (BiP)), heat shock protein 90kDa beta member 1 (HSP90B1 also known as GRP94) and calnexin (CANX) in MERS-CoV infected MVE but not infected FB (Figure 5A-C). GRP78/BiP is a master regulatory protein for the UPR that binds to regulatory enzymes within the UPR pathway keeping them inactive unless misfolded proteins accumulate triggering dissociation and enzyme activation. HSP90B1/GRP94 and CANX are ER protein chaperones that facilitate nascent protein folding. In support of the viral titer data, the expression of MERS-CoV structural proteins, spike glycoprotein and membrane protein as well as the accessory open reading frame protein 4a (ORF4a) were expressed to similar levels in both cell types for all donors by 12 hours post infection (Figure 5D-F). Cumulatively, these data suggest that MERS-CoV modulation of

the UPR is specific to a particular cellular environment (MVE) and may not be broadly applicable to all infected cells and tissues.

PERK activation is critical for MERS-CoV replication in primary human lung MVE and FB

To further validate the results thus far, which suggested that apoptosis of MVE was associated with the UPR, we pharmacologically perturbed the UPR in MERS-CoV infected MVE and FB using an inhibitor specific to the first enzyme activated following misfolded protein accumulation, protein kinase R-like endoplasmic reticulum kinase (PERK, AMG44). Activated PERK regulates phosphorylation of the key translation mediator, elongation initiation factor 2alpha (eIF2alpha). Following activation of the UPR and PERK, host translational shutoff serves to reestablish ER homeostasis and proper protein folding which if not achieved, results in the activation of apoptotic pathways. Dose response studies were performed in mock and MERS-CoV infected MVE and FB with PERK inhibitor (AMG 44 at 100 to 2 μM) to determine if pharmacologic perturbation of the PERK arm of the UPR would affect MERS-CoV replication and/or cell death (*30*). We utilized a MERS-CoV nanoluciferase reporter virus (MERS nanoluc) to increase accuracy and throughput of the assay (*31*). As shown in Figure 6, inhibition of PERK diminished MERS-CoV replication in both FB (Figure 6A and B) and MVE (Figure 6C and D) in a dose dependent manner when assayed at either 24 (Figure 6A and C) or 48 hours post infection (Figure 6B and D). In addition to monitoring changes in virus replication in the context of PERK inhibition, we also monitored cytotoxicity in drug treated uninfected cultures via CellTiter-Glo cell viability assay. Unlike FB in which we did not observe cytotoxicity at either timepoint (Figure 6A and B), in MVE we observed a dose dependent increase in cytotoxicity with PERK inhibition that was most notable at 48hpi (Figure 6D). Importantly, we found that at 24hpi MERS-CoV replication was inhibited at multiple drug doses that did not exhibit

cytotoxicity. These results suggest that primary human lung MVE are more sensitive to inhibition of the UPR in the absence of infection in contrast to the more tolerant primary lung FB. To determine if PERK inhibition modifies induction of apoptosis following MERS-CoV infection, we performed similar dose response assays as described in Figure 6A-D but then assayed for caspase 3 and 7 activation as in Figure 4 using similar UV inactivated and small molecule controls (i.e. staurosporin, ionomycin). No significant dose responsive change in caspase 3/7 activation above untreated infected cells was detected in either primary human lung MVE or FB following MERS-CoV infection and treatment with PERK inhibitor (Supplemental Figure S3).

PERK inhibition improves pulmonary function and diminishes MERS-CoV pathogenesis and ALI signatures Because *in vitro* PERK inhibition resulted in a significant decrease in MERS-CoV replication in both cell types, we sought to determine if *in vivo* inhibition would result in a change in viral replication and/or pathogenesis. To address this, we utilized a transgenic mouse model where the murine ortholog of the human MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), was humanized at residues 288 and 330 (hDPP4) facilitating high titer replication localized to the respiratory tract and lung pathology similar to that observed in humans(*32, 33*). We initiated treatment of hDPP4 mice with AMG44 or vehicle once per treatment at 24 hours prior to and post MERS-CoV infection. By three days post MERS-CoV infection, vehicle treated mice lost significantly (p value <0.05) more weight than AMG44 treated mice and this difference was maintained for the remainder of the study (Figure 7A). Interestingly, virus titer in the lung on day 3 post infection was similar regardless of treatment (Figure 7B). "Pulmonary hemorrhage", a gross pathological phenotype that increases coincident with MERS-CoV pathogenesis, was significantly diminished in AMG44 treated mice as compared to those

receiving vehicle treatment (Figure 7C). To determine if PERK inhibition through AMG44 treatment would affect pulmonary function, we performed whole body plethysmography (WBP) daily. Concordant with pulmonary hemorrhage, AMG44 treatment improved pulmonary function as compared to those receiving vehicle. For three WPB metrics typically induced following MERS-CoV infection (*32-34*), Pause, Penh and EF50, AMG44 treated mice had significantly improved values (p value <0.05) than vehicle treated animals at multiple timepoints (Figure 7D-F). Pause, PenH and EF50 are all measures of airway constriction or obstruction and indicate that AMG44 treatment is relieving or preventing lung pathology that negatively affects lung function. To quantitatively assess the improvement AMG44 treatment had on MERS-CoV infected mice, histological lung sections were assessed using the American Thoracic Society (ATS) scoring system designed to more closely relate data from small animal models of acute lung injury (ALI) to infected patient outcomes as previously described (*35, 36*). Hematoxylin and eosin stained fields of lung tissue were blindly scored for the presence of neutrophils in the alveolar and interstitial space, hyaline membranes, proteinaceous debris filling the airway spaces, and thickening of the alveolar septal (*35*). ATS lung injury scores were significantly reduced in male but not female MERS-CoV infected AMG44 treated mice (Figure 8A-E). Together with the wide variety of supportive data described above, the *in vivo* studies with AMG44 directly demonstrate the importance of PERK signaling in promoting MERS-CoV pathogenesis. Thus, with our unbiased systems biology-based approach, we identified a pathway modulated during MERS-CoV infection of primary human cells, validated the importance of this pathway for MERS-CoV replication and cell death *in vitro* and then demonstrated its importance in viral pathogenesis thus confirming the utility of this approach for identifying host factors/pathways that could be targeted as antiviral therapy.

Discussion

Viral pathogenesis is a multifactorial process driven by virus and host factors, responses in infected and neighboring cells, innate and adaptive immunity, host and viral genetics, and responses at the cellular, tissue, organ and organismal level. Due to this inherent complexity, defining the relative contribution of each of these factors to the disease state and the underlying cellular mechanisms that contribute to the progression towards severe disease is complicated. Thus, new models are needed to define cell and tissue host response patterns that play critical roles in viral pathogenesis. Both SARS- and MERS-CoV cause severe respiratory disease with replication and pathogenesis primarily limited to the lung. As shown in a recent pathologic evaluation of human tissue from a fatal case of MERS-CoV by Ng et al., diffuse alveolar damage, the pathological hallmark of acute lung injury (ALI), was noted along with viral antigen primarily found in alveolar pneumocytes with no extrapulmonary viral antigen detected (*4*). While the few post-mortem analyses of tissue samples from MERS-CoV patients have provided insight into the types of cells targeted by virus and the degree and severity of pathology in the lung, many basic questions related to the kinetics of virus replication, cell targeting, and the host response remain unknown. Primary cell cultures offer an opportunity to decrease the complexity of the intact organ to study how virus host interactions determine the fate of specific cell types following infection. While most studies with pneumotropic viruses have focused on airway epithelial cells or type II pneumocytes, MVE and FB play critical roles in maintaining lung architecture, compartmentalization and function (*37*). FB play a central role in the homeostasis of the extracellular matrix and are effector cells during injury repair, while the microvascular endothelium regulates vascular homeostasis, as vascular leakage can result in inefficient gas exchange in the lungs (*38*). In addition to MERS-CoV, H5N1 and other highly pathogenic

influenza viruses also replicate efficiently in endothelial cells, providing diverse model systems to investigate virus-host interactions and identify novel tissue specific response patterns that can be used to attenuate virus replication and/or disease (*24, 39, 40*). Understanding the fate of these cells after infection provides a unique opportunity to understand how MERS-CoV induced disease phenotypes manifest despite limited clinical sample availability. Death of MERS-CoV infected MVE and epithelial cells (*4, 16*) could result in the breakdown of the epithelial-endothelial cell barrier and allow vascular leakage of fluids into the lung, leading to alveolar flooding, a hallmark feature of ALI and ARDS often seen in MERS-CoV patients and mouse models of human disease (*11, 32, 41*). These findings support a more thorough examination of MERS-CoV lung cell tropism as clinical samples become available. The current findings also highlight that even within the same organ cell types can respond to infection with very different outcomes and emphasize the value of studying primary cell types in culture.

During viral infection, viral glycoproteins, unfolded and misfolded host and viral proteins accumulate in the endoplasmic reticulum (ER) disrupting ER homeostasis. ER stress is sensed by several ER chaperone proteins (GRP78, etc.), allowing the cells to activate pro-survival responses that are mediated in part by UPR signaling through PERK, the transmembrane protein inositol-requiring protein-1 (IRE1α), and the activating transcription factor-6 (ATF6) (*42, 43*). If the UPR response fails to restore ER homoeostasis, it promotes cell death through the induction of the specific proapoptotic genes like CHOP and various caspases (*44*). To date the impact of highly pathogenic human CoV infection on different lung cell types has been poorly studied in primary human lung cells. Analysis of systems biology datasets provides an unbiased approach to define host pathways that are crucial for virus replication and cell fate outcomes following infection. Functional enrichment analysis of transcriptomic, proteomic and lipidomic datasets

suggested that activation of the UPR promoted apoptotic cell death in MERS-CoV infected MVE, as compared with FB cells that displayed a minimal UPR response. Analysis of a single dataset would have hinted at either activated stress response or specific cell death pathways in MERS-CoV infected MVE. However, concordant findings across transcriptomic, proteomic and lipidomic datasets suggested key indicators of activated UPR and apoptotic pathways in MERS-CoV infected MVE cultures supporting the hypothesis that prolonged UPR signaling led to ER stress, PERK activation and programmed apoptotic cell death. As virus titers and viral protein expression are equivalent in both cell types, the robust activation of the UPR and apoptotic responses in MVE, but not in FB cells derived from the same individual is puzzling. UPR is activated when the influx of nascent, unfolded polypeptides exceeds the folding capacity of the ER, which may differ between MVE and FB cells, yet viral structural and accessory protein levels were similar in both cell types. We hypothesize that lung FB can maintain ER homeostasis longer than infected MVE due to higher endogenous levels of ER folding chaperone proteins or increased overall ER volume allowing continued cell viability after MERS-CoV infection. Future studies will probe how primary lung FB survive MERS-CoV infection. Importantly, ceremide and triglyceride are also potent stimulators of ER stress and apoptosis and these lipids are also highly upregulated following MERS-CoV infection of MVE, but much less so in FB cells. Increased expression of multiple triglyceride and ceramide species (*45, 46*) (products of sphingomyelinase pathways) is strongly correlative with virus induced CPE in mouse models demonstrating the *in vivo* relevance of these markers (*47*). Future studies will need to focus on evaluating the cell type specific UPR responses to various biochemical stimuli, after contemporary coronavirus and other respiratory virus infections, and identifying which

ceramides and triglycerides regulate the UPR and pro-apoptotic response in primary lung MVE and FB.

AMG44 is a selective and potent PERK inhibitor and treatment efficiently blocked MERS-CoV replication in FB and MVE cells *in vitro* (*30*). These studies validate the importance of PERK activation and the UPR response as being critical for MERS-CoV replication fitness early in infection, especially in MVE cells. The most likely mechanism for AMG44 inhibition of MERS-CoV growth is that the PERK signaling pathway and the UPR response promote increased membrane reorganizations and suppressed host translation that optimizes the environment for virus replication, maturation and egress. AMG44 would promote ER stress and translation of host proteins, potentially disrupting replication complexes, budding and release. Coronavirus infection is associated with extensive membrane reorganization (*48, 49*). In fact, coronavirus membrane-associated proteins nonstructural protein 3 (nsp3) and nsp4 have intrinsic membrane remodeling properties and usurp ER membranes to generate double membrane vesicles (DMVs) and other convoluted membrane structures that likely function as prominent sites of coronavirus replication (*48, 50-52*). Moreover, coronavirus egress occurs in a rER/Golgi intermediate compartment and coronavirus glycoproteins can induce ER stress and activate the UPR response (*17, 53-60*). Other coronaviruses respond to the PERK signaling cascade activation in a variety of ways including increased virus induced apoptosis (*54, 55*) or decreased viral titers (*58-60*). PERK activation was detected following overexpression of both SARS-CoV spike and ORF3a but the effects on replication were not determined (*17, 56, 57*). In contrast, the SARS-CoV E glycoprotein protected from UPR stress mediated by the IRE1 pathway (*61*). The role of MERS-CoV structural and nonstructural proteins are less certain although ORF4a has been reported to prevent activation of the stress response pathway via protein kinase R (PKR)

antagonism (*60*). AMG44 prophylactic treatment protected MERS-CoV infected mice from clinical disease as evidenced by reduced weight loss, lung hemorrhage, and ALI signatures as well as improved respiratory function. It is noteworthy that AMG44 treatment did not alter viral titers at day 3 post infection, perhaps reflecting the differential drug susceptibilities of the multiple cell types (e.g., airway epithelium, alveolar epithelial cells, FB and MVE) that are infected by MERS-CoV *in vivo*. In mice, PERK activation may not be pro-viral in all MERS-CoV susceptible cell types and/or the dosing regimen may not have been equivalent in all infected cell types. These results also suggest that PERK may play a role in a damaging pathogenic process *in vivo* where the individual cell types are part of a larger organ-based physiology and that treatment with the PERK inhibitor actually improves pulmonary function. Interestingly, a previous study in Huh7 cells that explored the temporal kinase following MERS-CoV infection did not identify PERK as important for MERS-CoV infection emphasizing the importance of using the most relevant primary human cells for global analysis studies (*62*).

Currently there are no approved therapeutics to treat highly pathogenic human coronavirus infection and with the ongoing MERS-CoV epidemic and novel SARS-CoV 2 pandemic methods to identify novel viral and host targets are recognized as a high priority by the WHO (*63*). Despite considerable progress, no therapy is presently available to reverse the widespread vascular leak that is observed during ARDS. Additional treatment studies with AMG44 in the MERS-CoV challenge model are needed to resolve and expand understanding of drug efficacy. Prophylactically treated male mice had a significant reduction in hallmark ALI disease phenotypes following MERS-CoV infection yet similarly treated female mice did not. Adding additional days of treatment or performing twice daily treatment may improve the outcomes noted in the current study. Determining the therapeutic window for AMG44

efficacy against MERS-CoV will also be required. Nevertheless, the comprehensive systems biology approach described herein led to identification and validation of critical host pathways that mediated MVE cell death, leading to potential protein kinase based therapeutic treatment options that were successful in limiting disease phenotypes in mouse models of MERS-CoV induced ALI. When coupled with the data presented here, modulating UPR responses provides a robust strategy to develop novel therapeutics to control infection mediated vascular permeability, inflammation and ALI, especially when linked with potent direct acting antiviral inhibitors of virus replication *in vivo* (*31, 36*).

Materials and Methods

Primary human lung cells and immortalized cells. Primary human lung cells were isolated from distal lung tissue and processed as described (*24*). Human lung microvascular endothelial cells (MVE) were cultured in Vasculife VEGF-MVE Endothelial Media (Lifeline Cell Tech). Human lung fibroblasts (FB) were cultured in DMEM-H Basal Medium (Corning), 1X penicillin/streptomycin (Sigma), 10% fetal bovine serum (Gemini Bio). Media fetal bovine serum concentrations were reduced to 4% prior to infection. Vero 81 cells were cultured in Dulbecco's modified essential media (DMEM Gibco) with 10% fetal clone II (Hyclone) and 1X antibiotic/antimycotic (Gibco).

Viruses and viral titration Wild-type MERS-CoV (EMC 2012 strain), MERS-CoV expressing nano luciferase (MERS nanoluc) and MERS-CoV expressing the red fluorescent protein (MERS-RFP) were rescued from infectious clones as previously described (*24, 31*). Vero C81 cells were used to generate viral stocks and to quantitate viral titers following infection (*24, 31*).

Infections to collect transcriptomic, proteomic, and lipidomic samples. Donor matched MVE and FB from three different human tissue donors were infected and samples harvested for

systems biology analysis. For transcriptomic analysis, five replicate wells of MVE or FB were either mock-infected or infected with wild type MERS-CoV at multiplicity of infection (MOI) 5. At 0, 12, 24, 36, and 48 hours post infection, 100uL of media/supernatant was collected for viral titration assays, media removed and then 1mL of Trizol (Invitrogen/ThermoFisher) added per well. Total RNA samples were sent to Arraystar for downstream analysis. In parallel, an additional five replicate wells were subjected to chloroform/methanol (2:1 mix) precipitation as previously described (*64, 65*). All proteomic and lipidomic samples were desiccated and frozen prior to shipment to Pacific Northwest National Laboratories for downstream analysis.

Transcriptomic Analysis Scanned images were analyzed using Agilent Feature Extraction Software (v11.0.1.1). The limma package for R (available on Bioconductor) was used to perform background correction, quantile normalization (normalizeBetweenArrays), and summarization (avereps) to derive a single normalized intensity value per probe. Outlier samples were detected using PCA and by visual inspection of heatmaps, and all data was re-processed after removing outlier samples. All data processing for each of the biological replicates was performed independently of the other.

Proteomic Analysis The algorithm RMD-PAV (*66*) was used to identify any outlier biological samples, which was confirmed via Pearson correlation. Peptides with inadequate data for either qualitative or quantitative statistical tests were also removed from the dataset (*67*). The SPANS algorithm (*67*) was used to identify the best normalization method for each dataset. Peptides were evaluated with Analysis of Variance (ANOVA) with a Dunnett test correction and a Bonferroni-corrected g-test to compare each virus to the associated mock within each time point. To perform signature-based protein quantification, BP-Quant (*68*), each peptide was categorized as a vector of length equal to the number of viruses being evaluated. If all comparisons for all

time points are 0 for a specific virus it is considered as non-changing and given a value of 0. If there are more time points with an increase in virus to mock than decreasing it is categorized as a +1 and the contrary -1 is given for the decrease in virus to mock. BP-Quant was run with a default parameter of 0.9. All proteins were then analyzed using the same methodology as for the peptides; ANOVA with a Dunnett test correction and a Bonferroni-corrected g-test to compare each virus to the associated mock within each time point.

Lipidomic Analysis The algorithm RMD-PAV (*66*) was used to identify any outlier biological samples, which was confirmed via Pearson correlation Lipids with inadequate data for either qualitative or quantitative statistical tests were also removed from the dataset (*67*). Median centering was used for normalization. Lipids were evaluated with a standard two sample t-test to compare each infected condition to the associated mock within each time point.

Functional Enrichment We identified significantly changed features (transcripts, proteins, lipids) by using an adjusted p-value of 0.05 as a threshold. For each experimental condition, perturbed features were divided into one list each of up- and down-regulated items. Each list was tested against the Gene Ontology (GO) database of gene sets using the EASE-adjusted one-sided Fisher exact test (*69*), such that each condition is tested for up- and down-regulation of each function/pathway in the ontology database. Results across multiple conditions were visualized in heatmaps using the log10 p-values of the significance tests, colored to indicate the direction of change. For lipids, feature sets were generated by categorizing the lipids observed in our experiments according to broad lipid classifications; these classifications were then used as "gene sets" and the enrichment analysis was then performed in the same manner as for transcripts and proteins.

Cell viability and percent infection assays To assess numbers of viable cells following MERS-CoV infection of FB and MVE, we used the CellTiter-Glo Luminescent Cell Viability Assay (Promega) at 24 and 48 hours post infection/treatment according to manufacturer's instructions and relative light units were determined by Spectromax plate reader (Molecular Devices), averaged and plotted. Percent infection was determined using MVE and FB infected with MERS-RFP (MOI 5) or mock-infected and counting nuclei (Horcht stain diluted 1:5,000 in media) in replicate wells at 0, 12, 24, 36, and 48 hours post infection. Cell numbers were determined using the Fiji (*70*) cell counter function and total number of cells versus number of red fluorescent cells were determined for at least three wells per condition per cell type. Statistical significance was determined by Manfield Whitney unpaired t test (performed in GraphPad Prism).

Apoptosis Assays Infected FB and MVE were assayed using either the Caspase-Glo 3/7 Kit (Promega) to measure caspase activation or using the ApoTox-Glo Triplex Assay (Promega) to assess cell viability, cytotoxicity and caspase 3/7 activation in a single set of samples at 24 and 48 hours post infection according to manufacturer's instructions. Control wells were treated with UV inactivated virus stocks, staurosporin (Sigma, 8uM for MVE or 10uM for FB) or ionomycin (ThermoFisher, 40uM for MVE and 60uM for FB). Relative light units or emission excitation wavelengths were determined by Spectromax plate reader (Molecular Devices). Statistical significance was determined by Manfield Whitney unpaired t test (performed in GraphPad Prism).

Inhibitor studies MERS-CoV infected MVE and FB were tested at 24 and 48 hours post infection following treatment with a dilution series PERK inhibitor (AMG 44(*30, 71*) 100 uM to 2 uM) and was evaluated for cytotoxicity with drug treatment alone (cell viability assay, no

virus), activation of the death caspases 3/7 (wild type MERS-CoV) and viral replication (detection of luciferase as a surrogate for replication, MERS nanoluc virus). All assay results were read by SpectraMax (Molecular Devices). Results are graphed as percent inhibition and toxicity (effective and cytotoxic concentration 50) as determined by GraphPad Prism.

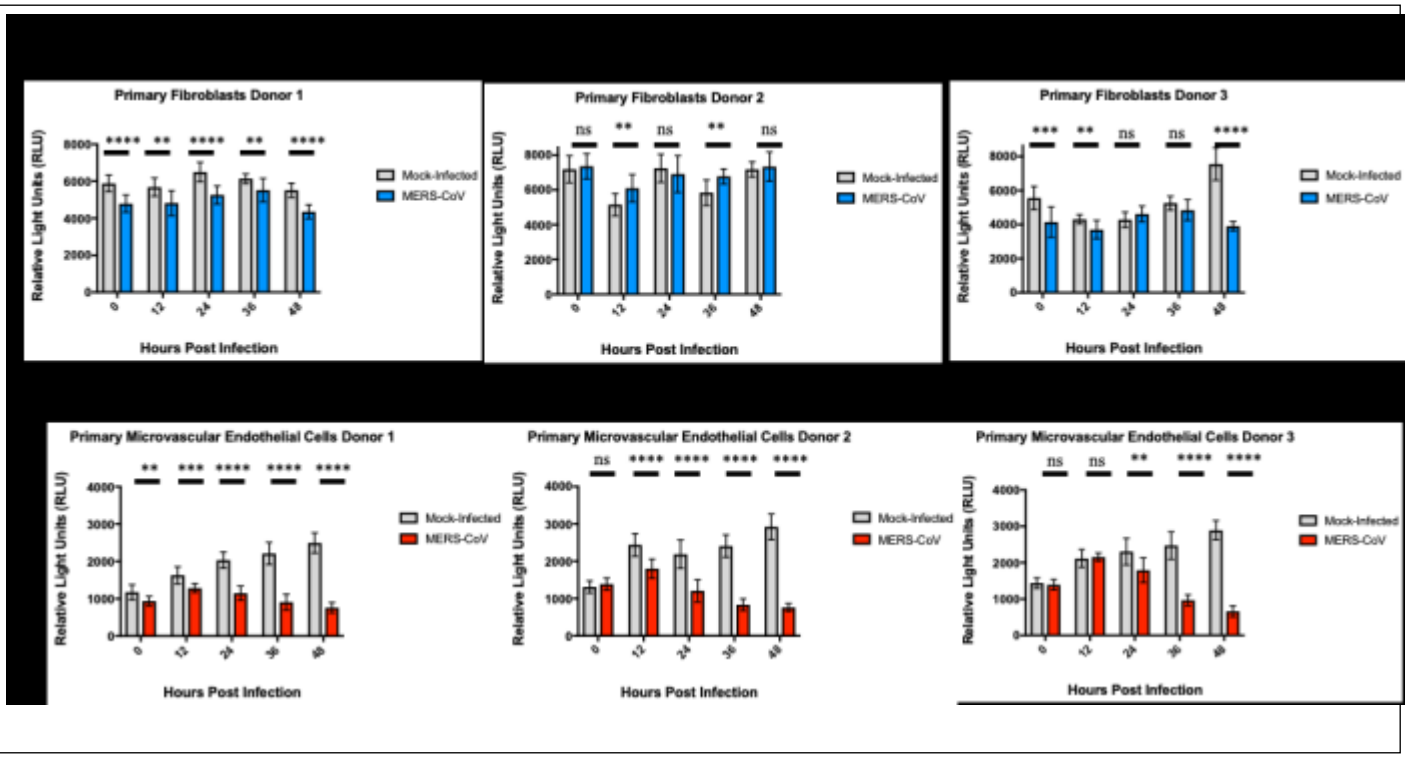
Mouse studies 288-330$^{+/+}$ mice (*32*) were housed and bred in accordance with the University of North Carolina Department of Comparative Medicine, AALAC #329. For a single group of mice, dosing occurred once a day 24 hours prior to infection and a second single dose was administered 24 hours post infection via the intraperitoneal route (12mg/kg of PERK AMG'44 suspended in water or with a sham control(*30, 71*)). Immediately prior to infection, mice were anesthetized with 50 uL of ketamine/xylazine mixture via intraperitoneal injection. 16-20 week old mice were intranasally infected with 10^4 PFU of mouse adapted MERS-CoV maM35c4 diluted in OPTIMEM (*33*), a total volume of 50 uL was given. Mice were weighed daily following infection and had their respiratory function measured one day prior to infection and at days two through six post infection using Buxco Whole Body Plethysmography (Data Sciences International) (*34*). Briefly, mice were allowed to acclimate for 30 minutes in the plethysmography chamber located within the biological safety cabinet after which a 5 minute measurement was taken. Readings were collected every 2 seconds for a total of 150 measurements per mouse per day. At days three and seven post infection mice were euthanized via isoflurane overdose after which lung tissue was harvested to determine viral replication titers. Gross pulmonary hemorrhage was observed and scored from zero (none) to four (severe and total) at the time of dissection.

Supplementary Materials

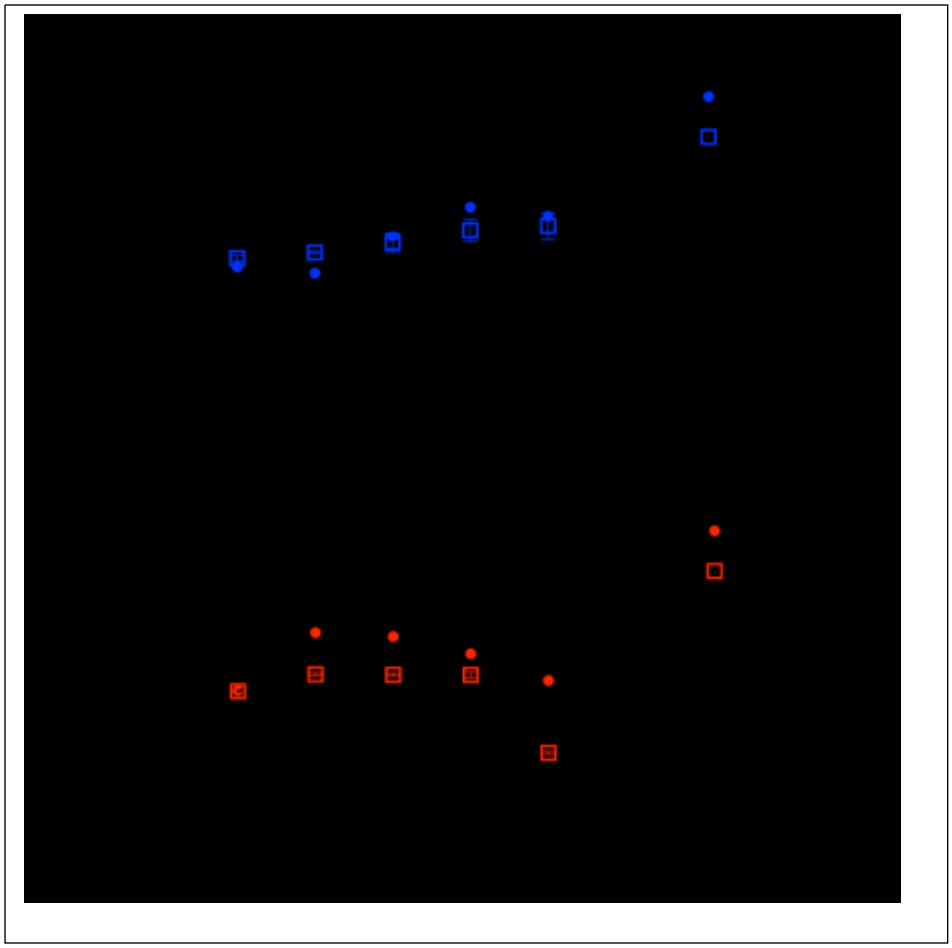
Supplementary Materials and Methods

All methodologies are described in the Materials and Methods section above.

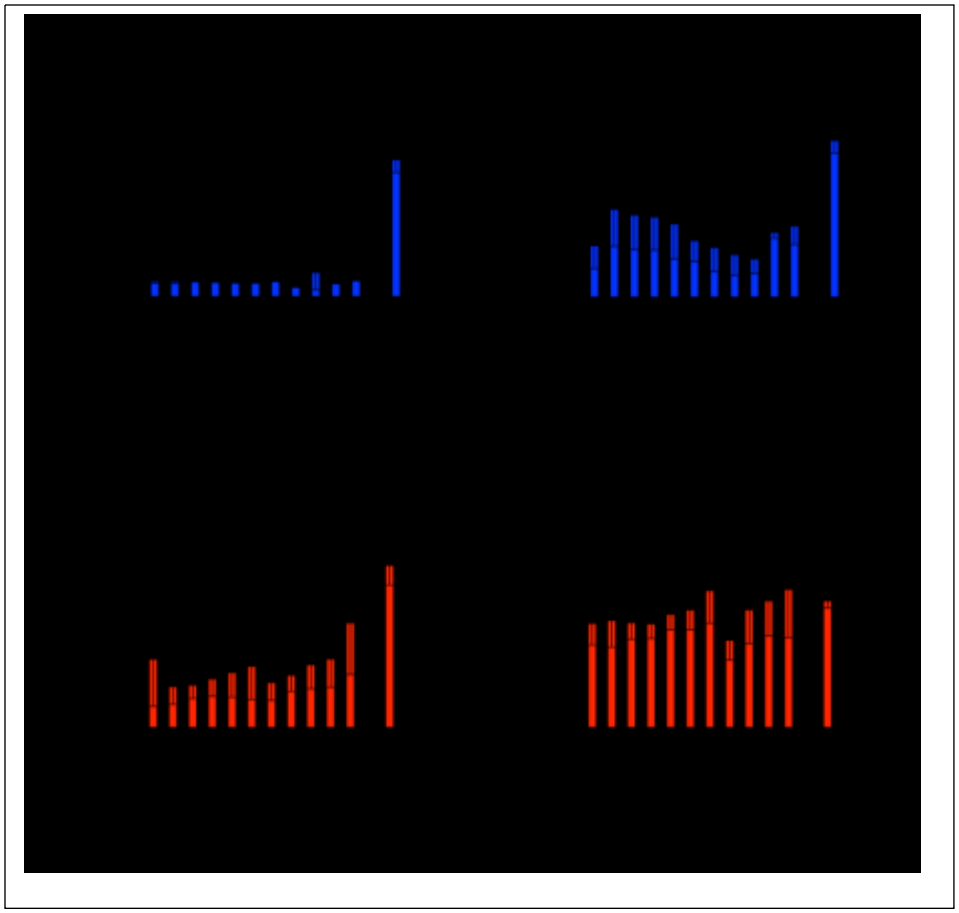
Supplementary Figures and Tables



Supplementary Fig. S1 MERS-CoV reduces cell viability for all three donors in MVE but not FB. Donor matched MVE and FB were infected with wild type MERS-CoV and assessed for cell viability using the CellTiter-Glo kit according to manufacturer's instructions (Promega) at the indicated times post infection. Relative light units (RLU) were graphed over time and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Gray bars- mock infected cells, red bars- MERS-CoV infected MVE, blue bars- MERS-CoV infected FB, **** p= <0.0001, ** p= <0.002, ns not statistically significant.



Supplementary Fig. S2 Neither SMAD7 nor FGF2 expression contribute to MERS-CoV induced cytopathic effect in primary human lung cells. A-B. Graphs show transcript expression levels for SMAD7 and FGF2 in MERS-CoV infected MVE and FB over the 48 hour time course (derived from microarray analysis and are from the same datasets used in Figure 2). Values graphed are fold change (log_2) and error bars are standard deviations from the mean. mothers against decapentaplegic homolog 7 (SMAD7); fibroblast growth factor 2 (FGF2)



Supplementary Fig. S3 Inhibition of PERK by AMG44 does not alter caspase 3/7 activation following MERS-CoV infection. A-D. Donor matched FB (A, B) and MVE (C, D) were plated and infected with UV-inactivated or wild type MERS-CoV and at 24 (A, C) and 48 (B, D) hours post infection caspase 3/7 activation was determined according to manufacturer's instructions using the Apotox Triplex kit. Control uninfected cells were treated with staurosporin (8 uM MVE/10 uM FB, activates caspase 3/7) or ionomycin (50 uM MVE/60 uM FB, does not activate caspase 3/7). Results are graphed as relative light units and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test.

Supplementary Table 1 Pathways contained within categories found by functional enrichment analysis of transcriptomic data in Figure 2

Please see separate Excel spreadsheet.

Supplementary Table 2 Pathways contained within categories found by functional enrichment analysis of proteomic data in Figure 2

Please see separate Excel spreadsheet.

References

1. R. L. Graham, E. F. Donaldson, R. S. Baric, A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol* **11**, 836-848 (2013).
2. J. S. Peiris, Y. Guan, K. Y. Yuen, Severe acute respiratory syndrome. *Nat Med* **10**, S88-97 (2004).
3. A. M. Zaki, S. van Boheemen, T. M. Bestebroer, A. D. Osterhaus, R. A. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* **367**, 1814-1820 (2012).
4. D. L. Ng *et al.*, Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. *Am J Pathol* **186**, 652-658 (2016).
5. R. Blondonnet, J. M. Constantin, V. Sapin, M. Jabaudon, A Pathophysiologic Approach to Biomarkers in Acute Respiratory Distress Syndrome. *Dis Markers* **2016**, 3501373 (2016).

6. A. D. T. Force *et al.*, Acute respiratory distress syndrome: the Berlin Definition. *JAMA* **307**, 2526-2533 (2012).

7. A. Husain, V. Kumar, in *Robbins and Cotran Pathologoic Basis of Disease*. (Saunders/Elsevier, Philadelphia, Pennsylvania, 2010), vol. 8th, pp. 715-716.

8. L. B. Ware, M. A. Matthay, The acute respiratory distress syndrome. *N Engl J Med* **342**, 1334-1349 (2000).

9. C. E. Luyt, A. Combes, J. L. Trouillet, A. Nieszkowska, J. Chastre, Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome. *Presse Med* **40**, e561-568 (2011).

10. C. Ramsey, A. Kumar, H1N1: viral pneumonia as a cause of acute respiratory distress syndrome. *Curr Opin Crit Care* **17**, 64-71 (2011).

11. Y. M. Arabi *et al.*, Middle East Respiratory Syndrome. *N Engl J Med* **376**, 584-594 (2017).

12. J. S. Peiris *et al.*, Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767-1772 (2003).

13. S. L. Smits *et al.*, Distinct severe acute respiratory syndrome coronavirus-induced acute lung injury pathways in two different nonhuman primate species. *J Virol* **85**, 4234-4245 (2011).

14. C. Huang *et al.*, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497-506 (2020).

15. J. H. Beigel *et al.*, Advances in respiratory virus therapeutics - A meeting report from the 6th isirv Antiviral Group conference. *Antiviral Res* **167**, 45-67 (2019).

16. R. W. Chan *et al.*, Tropism of and innate immune responses to the novel human betacoronavirus lineage C virus in human ex vivo respiratory organ cultures. *J Virol* **87**, 6604-6614 (2013).

17. H. Chu *et al.*, Middle East Respiratory Syndrome Coronavirus Efficiently Infects Human Primary T Lymphocytes and Activates the Extrinsic and Intrinsic Apoptosis Pathways. *J Infect Dis* **213**, 904-914 (2016).

18. A. H. de Wilde *et al.*, MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-alpha treatment. *J Gen Virol* **94**, 1749-1760 (2013).

19. A. C. Hocke *et al.*, Emerging human middle East respiratory syndrome coronavirus causes widespread infection and alveolar damage in human lungs. *Am J Respir Crit Care Med* **188**, 882-886 (2013).

20. X. Tao *et al.*, Bilateral entry and release of Middle East respiratory syndrome coronavirus induces profound apoptosis of human bronchial epithelial cells. *J Virol* **87**, 9953-9958 (2013).

21. H. Yan *et al.*, SARS coronavirus induces apoptosis in Vero E6 cells. *J Med Virol* **73**, 323-331 (2004).

22. Q. L. Zhang *et al.*, [Detection of cell apoptosis in the pathological tissues of patients with SARS and its significance]. *Di Yi Jun Yi Da Xue Xue Bao* **23**, 770-773 (2003).

23. J. Zhou *et al.*, Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Sci Adv* **3**, eaao4966 (2017).

24. T. Scobey *et al.*, Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. *Proc Natl Acad Sci U S A* **110**, 16157-16162 (2013).

25. C. Lechauve *et al.*, Endothelial cell alpha-globin and its molecular chaperone alpha-hemoglobin-stabilizing protein regulate arteriolar contractility. *J Clin Invest* **128**, 5073-5082 (2018).

26. A. C. Straub *et al.*, Endothelial cell expression of haemoglobin alpha regulates nitric oxide signalling. *Nature* **491**, 473-477 (2012).

27. A. C. Straub, A. C. Zeigler, B. E. Isakson, The myoendothelial junction: connections that deliver the message. *Physiology (Bethesda)* **29**, 242-249 (2014).

28. M. L. Yeung *et al.*, MERS coronavirus induces apoptosis in kidney and lung by upregulating Smad7 and FGF2. *Nat Microbiol* **1**, 16004 (2016).

29. A. M. Dart, J. P. Chin-Dusting, Lipids and the endothelium. *Cardiovasc Res* **43**, 308-322 (1999).

30. A. L. Smith *et al.*, Discovery of 1H-pyrazol-3(2H)-ones as potent and selective inhibitors of protein kinase R-like endoplasmic reticulum kinase (PERK). *J Med Chem* **58**, 1426-1441 (2015).

31. T. P. Sheahan *et al.*, Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* **9**, (2017).

32. A. S. Cockrell *et al.*, A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. *Nat Microbiol* **2**, 16226 (2016).

33. M. G. Douglas, J. F. Kocher, T. Scobey, R. S. Baric, A. S. Cockrell, Adaptive evolution influences the infectious dose of MERS-CoV necessary to achieve severe respiratory disease. *Virology* **517**, 98-107 (2018).

34. V. D. Menachery, L. E. Gralinski, R. S. Baric, M. T. Ferris, New Metrics for Evaluating Viral Respiratory Pathogenesis. *PLoS One* **10**, e0131451 (2015).

35. G. Matute-Bello *et al.*, An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* **44**, 725-738 (2011).

36. T. P. Sheahan *et al.*, Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222 (2020).

37. E. S. White, Lung extracellular matrix and fibroblast function. *Ann Am Thorac Soc* **12 Suppl 1**, S30-33 (2015).

38. J. Aman, E. M. Weijers, G. P. van Nieuw Amerongen, A. B. Malik, V. W. van Hinsbergh, Using cultured endothelial cells to study endothelial barrier dysfunction: Challenges and opportunities. *Am J Physiol Lung Cell Mol Physiol* **311**, L453-466 (2016).

39. S. Tundup *et al.*, Endothelial cell tropism is a determinant of H5N1 pathogenesis in mammalian species. *PLoS Pathog* **13**, e1006270 (2017).

40. H. Zeng *et al.*, Human pulmonary microvascular endothelial cells support productive replication of highly pathogenic avian influenza viruses: possible involvement in the pathogenesis of human H5N1 virus infection. *J Virol* **86**, 667-678 (2012).

41. K. M. Das, E. Y. Lee, R. D. Langer, S. G. Larsson, Middle East Respiratory Syndrome Coronavirus: What Does a Radiologist Need to Know? *AJR Am J Roentgenol* **206**, 1193-1201 (2016).

42. E. Dufey, D. Sepulveda, D. Rojas-Rivera, C. Hetz, Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 1. An overview. *Am J Physiol Cell Physiol* **307**, C582-594 (2014).

43. H. Malhi, R. J. Kaufman, Endoplasmic reticulum stress in liver disease. *J Hepatol* **54**, 795-809 (2011).

44. S. E. Logue, P. Cleary, S. Saveljeva, A. Samali, New directions in ER stress-induced cell death. *Apoptosis* **18**, 537-546 (2013).

45. E. Aflaki *et al.*, C16 ceramide is crucial for triacylglycerol-induced apoptosis in macrophages. *Cell Death Dis* **3**, e280 (2012).

46. Y. R. Kim *et al.*, Hepatic triglyceride accumulation via endoplasmic reticulum stress-induced SREBP-1 activation is regulated by ceramide synthases. *Exp Mol Med* **51**, 1-16 (2019).

47. S. E. Dautel *et al.*, Lipidomics reveals dramatic lipid compositional changes in the maturing postnatal lung. *Sci Rep* **7**, 40555 (2017).

48. K. Knoops *et al.*, SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol* **6**, e226 (2008).

49. H. Zhou *et al.*, The N-terminal region of severe acute respiratory syndrome coronavirus protein 6 induces membrane rearrangement and enhances virus replication. *J Virol* **84**, 3542-3551 (2010).

50. M. M. Angelini, M. Akhlaghpour, B. W. Neuman, M. J. Buchmeier, Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio* **4**, (2013).

51. D. Oudshoorn *et al.*, Expression and Cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronaviral RNA Replication. *mBio* **8**, (2017).

52. I. Romero-Brey, R. Bartenschlager, Endoplasmic Reticulum: The Favorite Intracellular Niche for Viral Replication and Assembly. *Viruses* **8**, (2016).

53. A. Perrier *et al.*, The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. *J Biol Chem* **294**, 14406-14421 (2019).

54. T. S. Fung, D. X. Liu, Coronavirus infection, ER stress, apoptosis and innate immunity. *Front Microbiol* **5**, 296 (2014).

55. Y. Liao *et al.*, Upregulation of CHOP/GADD153 during coronavirus infectious bronchitis virus infection modulates apoptosis by restricting activation of the extracellular signal-regulated kinase pathway. *J Virol* **87**, 8124-8134 (2013).

56. R. Minakshi *et al.*, The SARS Coronavirus 3a protein causes endoplasmic reticulum stress and induces ligand-independent downregulation of the type 1 interferon receptor. *PLoS One* **4**, e8342 (2009).

57. S. C. Sung, C. Y. Chao, K. S. Jeng, J. Y. Yang, M. M. Lai, The 8ab protein of SARS-CoV is a luminal ER membrane-associated protein and induces the activation of ATF6. *Virology* **387**, 402-413 (2009).

58. Y. Wang *et al.*, Triggering unfolded protein response by 2-Deoxy-D-glucose inhibits porcine epidemic diarrhea virus propagation. *Antiviral Res* **106**, 33-41 (2014).

59. M. Xue *et al.*, The PERK Arm of the Unfolded Protein Response Negatively Regulates Transmissible Gastroenteritis Virus Replication by Suppressing Protein Translation and Promoting Type I Interferon Production. *J Virol* **92**, (2018).

60. H. H. Rabouw *et al.*, Middle East Respiratory Coronavirus Accessory Protein 4a Inhibits PKR-Mediated Antiviral Stress Responses. *PLoS Pathog* **12**, e1005982 (2016).

61. M. L. DeDiego *et al.*, Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis. *PLoS Pathog* **7**, e1002315 (2011).

62. J. Kindrachuk *et al.*, Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother* **59**, 1088-1099 (2015).

63. G. V. Asokan, T. Ramadhan, E. Ahmed, H. Sanad, WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-PubMed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain. *Oman Med J* **34**, 184-193 (2019).

64. K. E. Burnum-Johnson *et al.*, MPLEx: a method for simultaneous pathogen inactivation and extraction of samples for multi-omics profiling. *Analyst* **142**, 442-448 (2017).

65. E. S. Nakayasu *et al.*, MPLEx: a Robust and Universal Protocol for Single-Sample Integrative Proteomic, Metabolomic, and Lipidomic Analyses. *mSystems* **1**, (2016).

66. M. M. Matzke *et al.*, Improved quality control processing of peptide-centric LC-MS proteomics data. *Bioinformatics* **27**, 2866-2872 (2011).

67. B. J. Webb-Robertson *et al.*, Combined statistical analyses of peptide intensities and peptide occurrences improves identification of significant peptides from MS-based proteomics data. *J Proteome Res* **9**, 5748-5756 (2010).

68. B. J. Webb-Robertson *et al.*, Bayesian proteoform modeling improves protein quantification of global proteomic measurements. *Mol Cell Proteomics* **13**, 3639-3646 (2014).

69. D. A. Hosack, G. Dennis, Jr., B. T. Sherman, H. C. Lane, R. A. Lempicki, Identifying biological themes within lists of genes with EASE. *Genome Biol* **4**, R70 (2003).

70. J. Schindelin *et al.*, Fiji: an open-source platform for biological-image analysis. *Nat Methods* **9**, 676-682 (2012).

71. D. Rojas-Rivera *et al.*, When PERK inhibitors turn out to be new potent RIPK1 inhibitors: critical issues on the specificity and use of GSK2606414 and GSK2656157. *Cell Death Differ* **24**, 1100-1110 (2017).

Acknowledgements: We thank Ernesto Nakayasu for expert assistance with proteomics data. **Funding:** This study was funded by NIH/NIAID U19 AI109761 and NIH U19-AI106772-01 grants and the Cystic Fibrosis and Pulmonary Diseases Research and Treatment Center (BOUCHE15RO and NIH P30DK065988). **Author contributions** ACS, SR, TOM, KW, RSB-designed in vitro systems biology experiments; ML, MLF, SR-harvested, isolated and characterized primary human lung cells; ACS, AW- performed in vitro systems biology experiment and phenotypic characterization; HM, JEK, KEBJ, RDS, TOM, KW-processed and analyzed systems biology samples/datasets; ACS, TPS, HM, RSB-designed cell viability and caspase assays; ACS- performed cell viability, caspase assays, PERK inhibitor assays; HM, JEK-functional enrichment analysis or transcript, protein and lipid datasets; LEG, TPS, ACS, RSB designed in vivo PERK inhibitor study; LEG performed PERK inhibitor study in vivo; ACS, TPS, RSB, HM, KW wrote the manuscript. **Competing interests**: All authors claim no competing interests. **Data and materials availability:**

Figures and Figure Legends

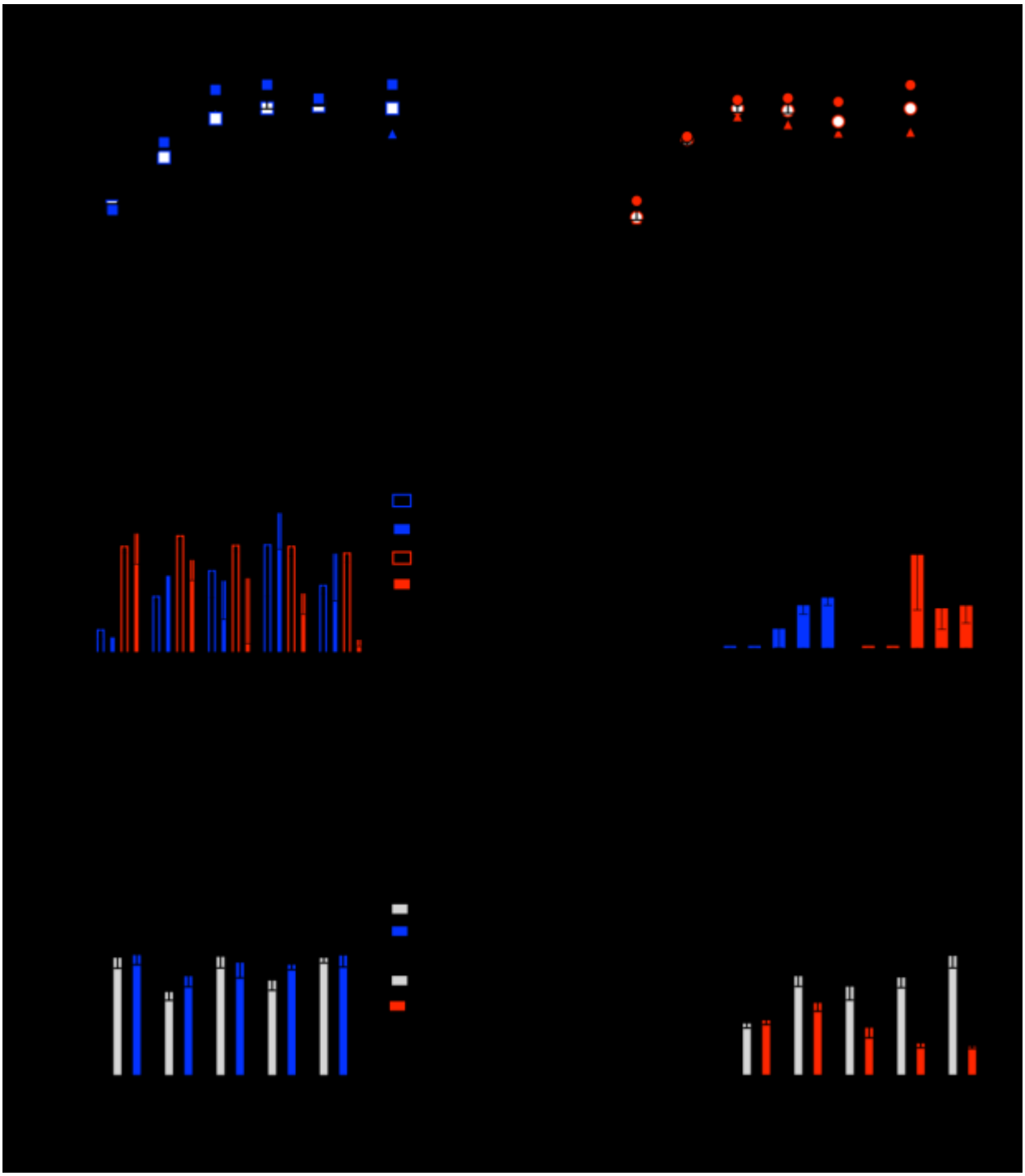


Figure 1. Viral growth kinetics, percent infected cells and cell viability following MERS-CoV infection of primary human lung fibroblasts and microvascular endothelial cells. A-B. Viral replication: Donor matched microvascular endothelial cells (MVE) and fibroblasts (FB) were infected with wild type MERS-CoV (MOI of 5) and supernatants collected at the indicated times and viral titers determined by plaque assay. Results are shown as plaque forming units (pfu) per mL over time. Each data point represents averaged data from supernatant collected from 10 different wells (5 wells harvested for RNA and 5 wells fractionated for proteins, metabolites and lipids). The graphs in A and B show levels of replication detected for all three tissue donors in both cell types. Error bars indicate standard deviation from the mean. Open and filled blue circles and blue triangles represent data from MERS-CoV infected FB, while open and filled red circles and red triangles represent MERS-CoV infected MVE. **C-D.** Percent MERS-CoV infected cells: Donor matched MVE and FB were mock-infected or infected with MERS-CoV expressing the red fluorescent protein (MERS-RFP), nuclei were stained with Hoechst stain, and images captured at the indicated times post infection. Total numbers of cells (shown for all conditions in **C**) and total numbers of infected (contained red fluorescence) cells were assessed for at least three fields per condition and total percent of infected cells determined and plotted (**D**). Representative data is shown for one of the three donors. Error bars indicate standard deviation from the mean. No statistical significance (ns) was found when comparing the percentage of infected FB and MVE at any specific timepoint. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Open blue bars- mock-infected FB, open red bars- mock-infected MVE, filled blue bars- MERS-RFP infected FB, filled red bars- MERS-CoV RFP infected MVE. **E-F.** Cell viability following MERS-CoV infection: Donor matched MVE and FB were infected with wild type MERS-CoV and assessed for cell viability

using the CellTiter-Glo kit according to manufacturer's instructions (Promega) at the indicated times post infection. Relative light units were graphed over time and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Gray bars- mock infected cells, red bars- MERS-CoV infected MVE, blue bars- MERS-CoV infected FB, **** p= <0.0001, ** p= <0.002, ns not statistically significant.

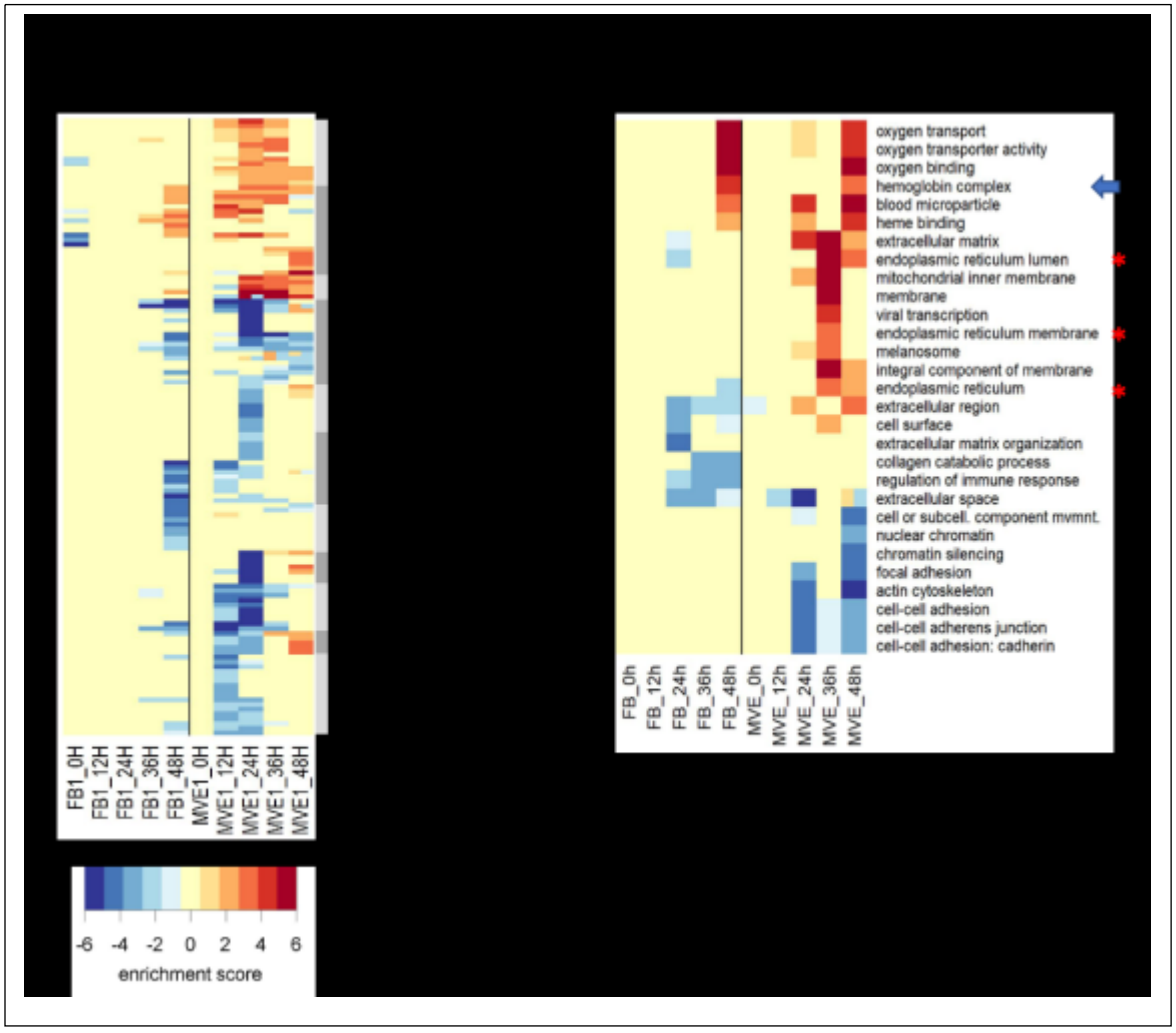


Figure 2. Transcriptomics and proteomics suggest activation of apoptotic pathways. A. Functional enrichment was performed on transcriptomic data from all three donor samples in both cell types, and results were only retained that were present in all three donors, keeping only

the least significant score. In this way a true consensus response is represented by all indicated functions. **B.** Protein expression for proteins associated with the GO term "positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway". All apoptosis-associated proteins are displayed across the three donors for fibroblasts and MVE. The blue arrow highlights proteins in the hemoglobin complex and red asterisks highlight apoptotic proteins from the endoplasmic reticulum.

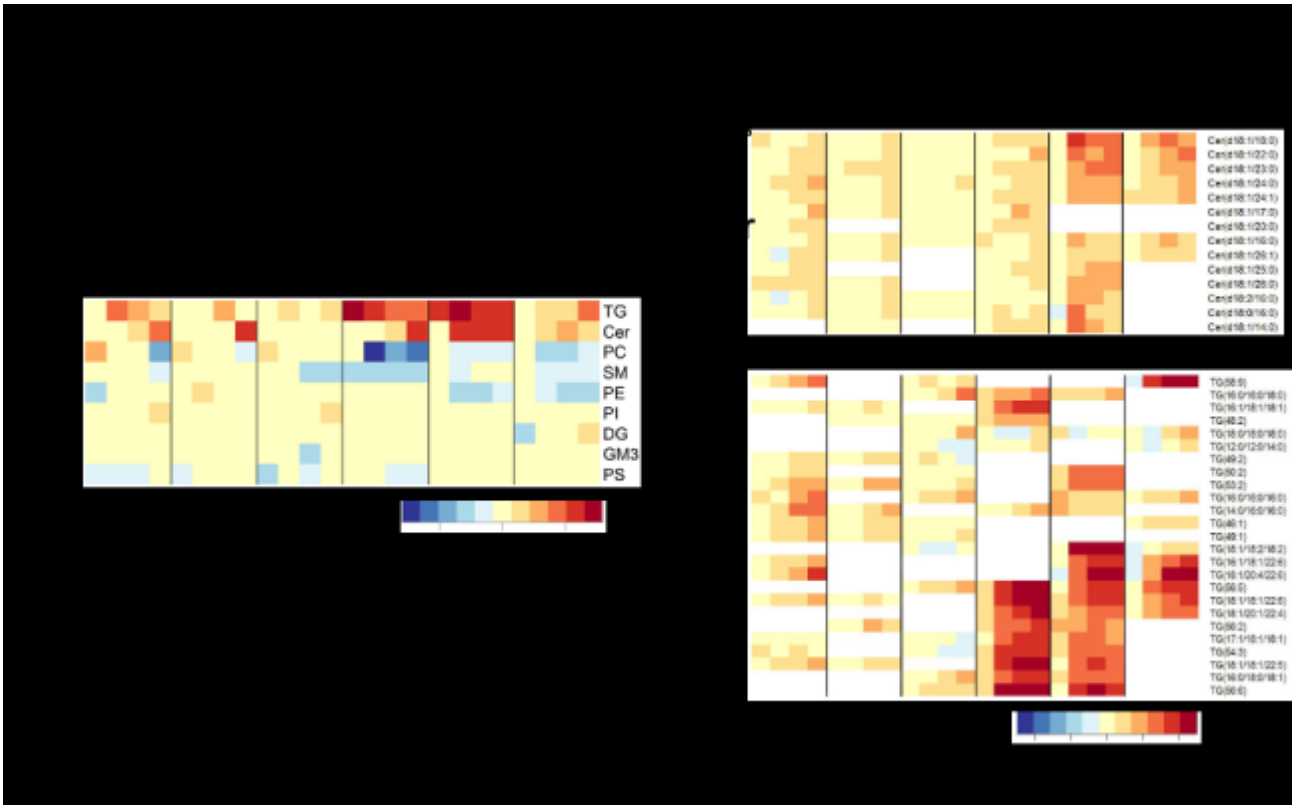


Figure 3. Lipid profiles suggest activation of apoptotic pathways. A. Enrichment analysis using lipid classes as enrichment sets. Cer-ceramide, TG-triglycerides, PC-phosphatidylcholine, PE-phosphatidylethanolamine, PS-phosphatidylserine, SM-sphingomyelin. **B.** Abundance of individual lipid species.

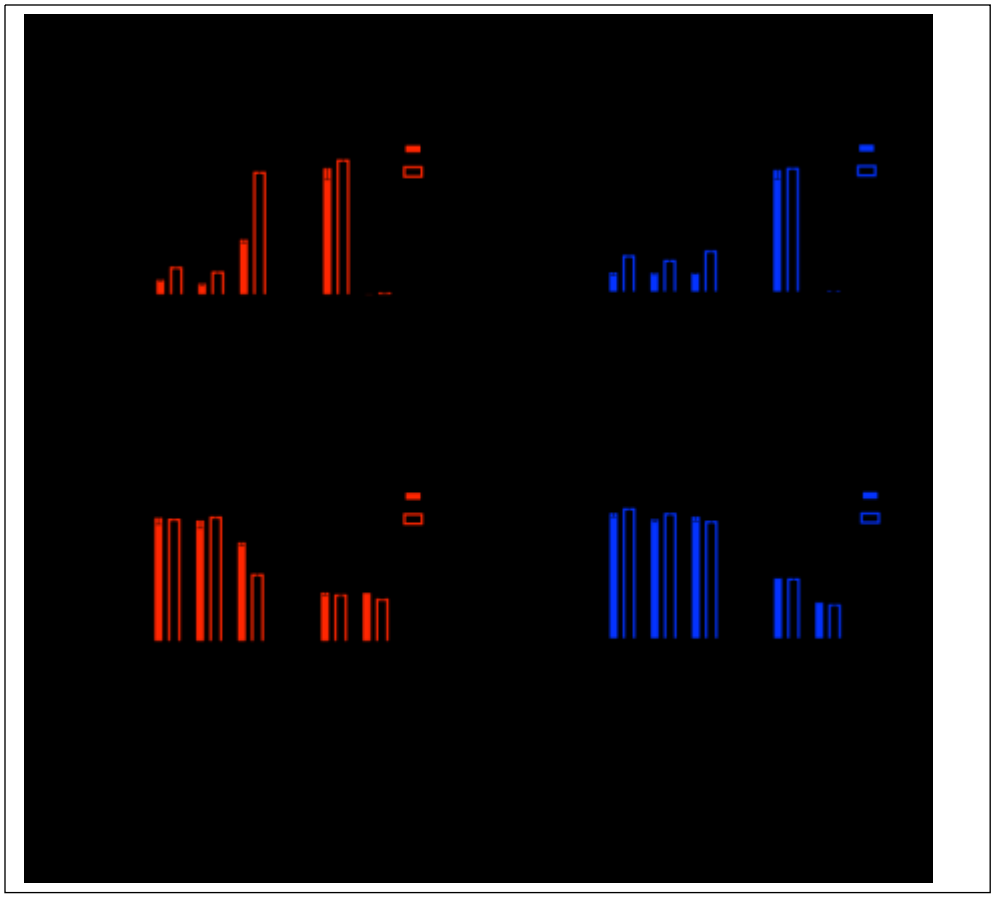


Figure 4 Caspases 3/7 are activated following MERS-CoV infection of primary human lung MVE but not primary lung FB. A-D. Donor matched MVE and FB were plated and mock-infected or infected with UV-inactivated or wild type MERS-CoV and at 24 and 48 hours post infection caspase 3/7 activation or cell viability was determined according to manufacturer's instructions using the Apotox Triplex kit (each well was measured for both parameters). Uninfected cells were treated with staurosporin (8 uM MVE/10 uM FB) to determine the maximal amount of caspase 3/7 activation. Uninfected cells were treated with ionomycin (50 uM MVE/60 uM FB) to demonstrate loss of cell viability via non-apoptotic pathway. Results are graphed as relative light units and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. **A-B**

Results from caspase 3/7 activation. **C-D.** Results from cell viability assay. Solid red bars- MVE 24 hour samples, open red bars- MVE 48 hour samples, solid blue bars- FB 24 hour samples, open blue bars- FB 48 hour samples. **** p=<0.0001, *** p= <0.0002, ns- not statistically significant.

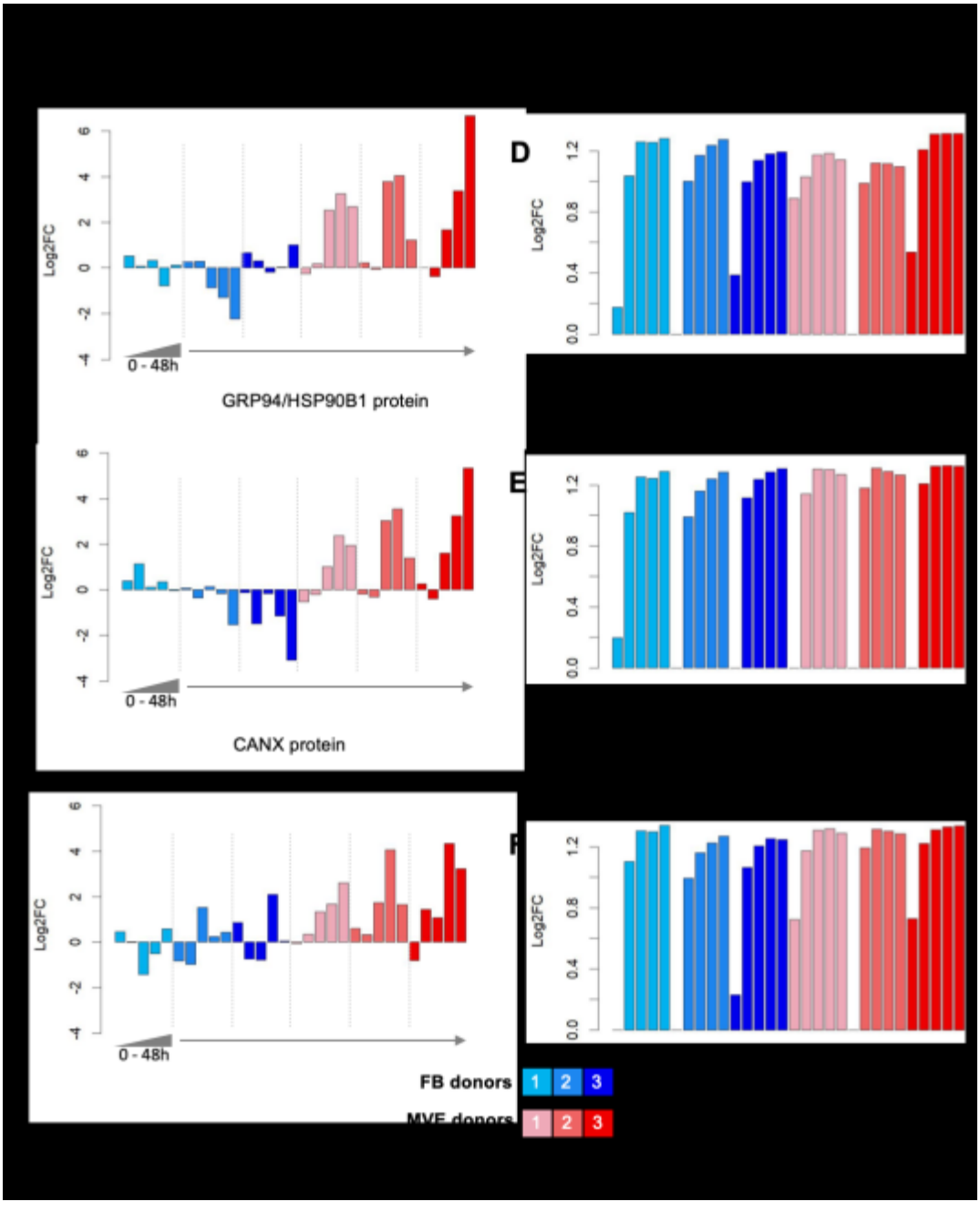


Figure 5 Protein markers suggest activation of unfolded protein response (UPR). A-C. Protein expression of markers of the unfolded protein response. Each figure shows the expression behavior of a UPR marker in FB (blues) and MVE (reds), with individual donors represented separately as individual color hues. For each donor, a time course of expression is shown that includes samples taken at 0, 12, 24, 36 and 48 hours post infection. Values are expressed as the log10 p-value of the change between the infection and control conditions, with sign assigned according to the direction of fold change. **D-F.** Viral protein expression. MERS-CoV spike, open reading frame 4a (ORF4a) and membrane protein abundances are represented as the ratio of each protein to the average abundance of all other proteins detected in each respective sample.

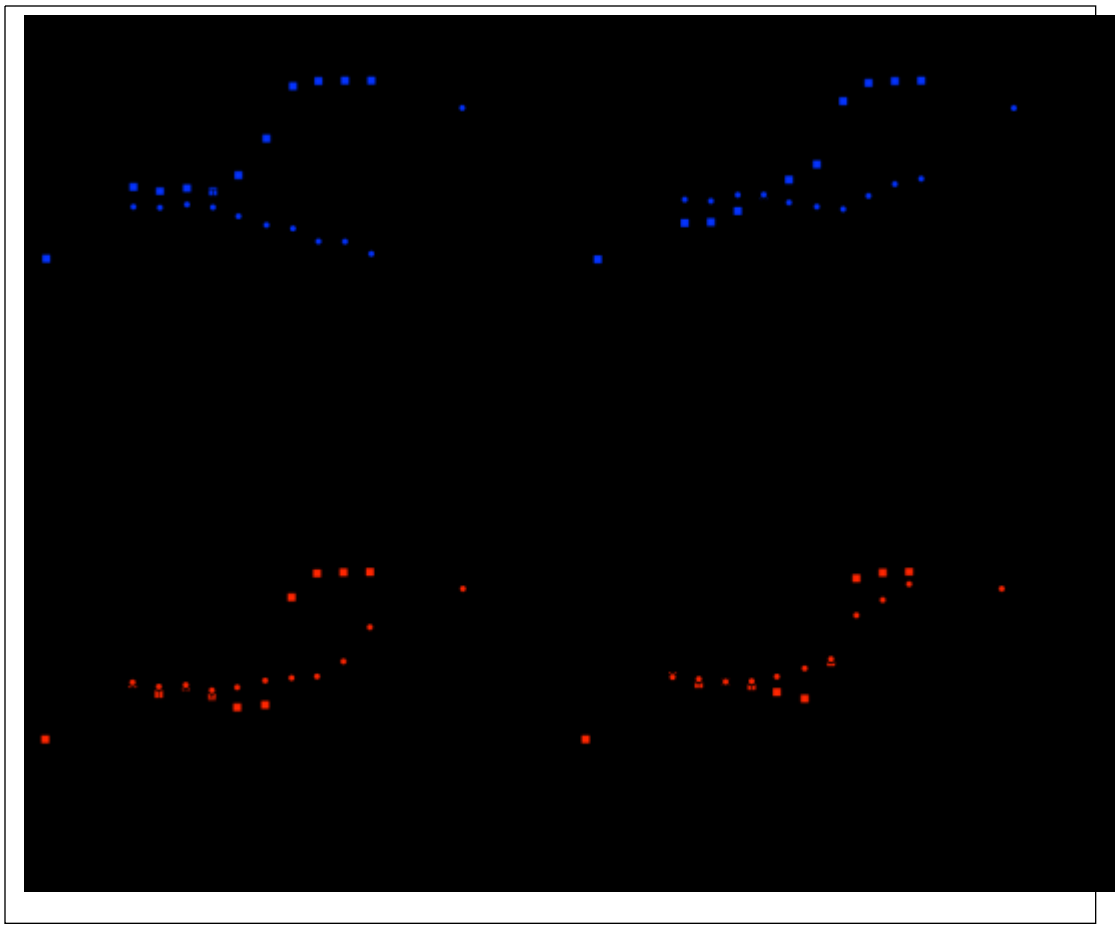


Figure 6 PERK inhibitor reduces MERS-CoV replication in infected primary human lung MVE and FB. A-D. Donor matched uninfected FB (circles, A, B) and MVE (circles, C, D) were treated with serial dilutions of PERK inhibitor (100 uM to 2 uM) and cell viability assessed at 24 (A, C) and 48 (B, D) hours post treatment using Promega's CellTiter Glo kit according to manufacturer's instructions. Each circle represents mean values from two experiments and are graphed as percent toxicity. Error bars indicate standard deviation from the mean. In parallel, the same donor matched FB (squares, A, B) and MVE (squares, C, D) were infected with MERS-nanoluc and simultaneously treated with the same serial dilutions of PERK inhibitor. Nanoluciferase expression was assayed at 24 (squares, A, C) and 48 (squares, B, D) hours post infection using Promega's NanoGlo kit according to manufacturer's instructions. Control wells were either treated with drug diluent and UV-inactivated virus or infected with MERS-nanoluc and treated with only drug diluent. Each square represents mean values from two experiments and are graphed as percent inhibition. Error bars indicate standard deviation from the mean. Blue squares- MERS-nanoluc infected FB treated with PERK inhibitor serial dilutions, blue circles- uninfected FB treated with PERK inhibitor serial dilutions, red squares- MERS-nanoluc infected MVE treated with PERK inhibitor serial dilutions, red circles- uninfected MVE treated with PERK inhibitor serial dilutions. PERK protein kinase R-like ER kinase, MVE primary human lung microvascular endothelial cell, FB primary human lung fibroblast, MERS-nanoluc MERS-CoV expressing nanoluciferase

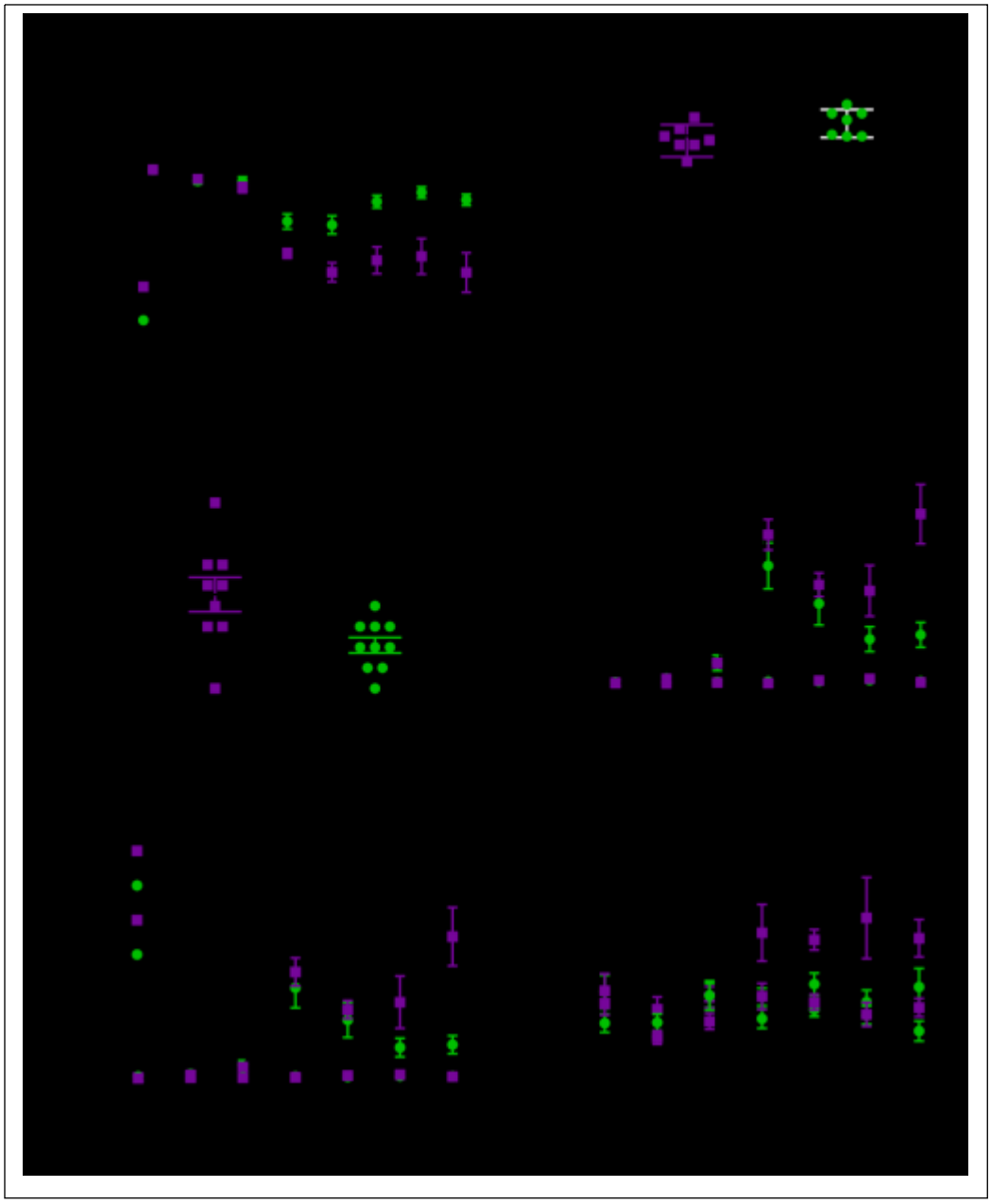


Figure 7 PERK inhibitor AMG44 treatment decreases MERS-CoV pathogenesis

A-F. 288/330+/+ mice were treated with PERK AMG'44 or sham control and infected with $5x10^4$ PFU of MERS-CoV MAm35c4 or PBS control. Weight loss was observed over the course of a seven day infection (A) and viral titers (B) and pulmonary hemorrhage was scored at the time of harvest (C). Daily respiratory function measurements (D-F) were taken via whole body

plethysmography. Error bars indicate standard error of the mean, # indicates a p value of < 0.1 and * indicates a p value of < 0.05.

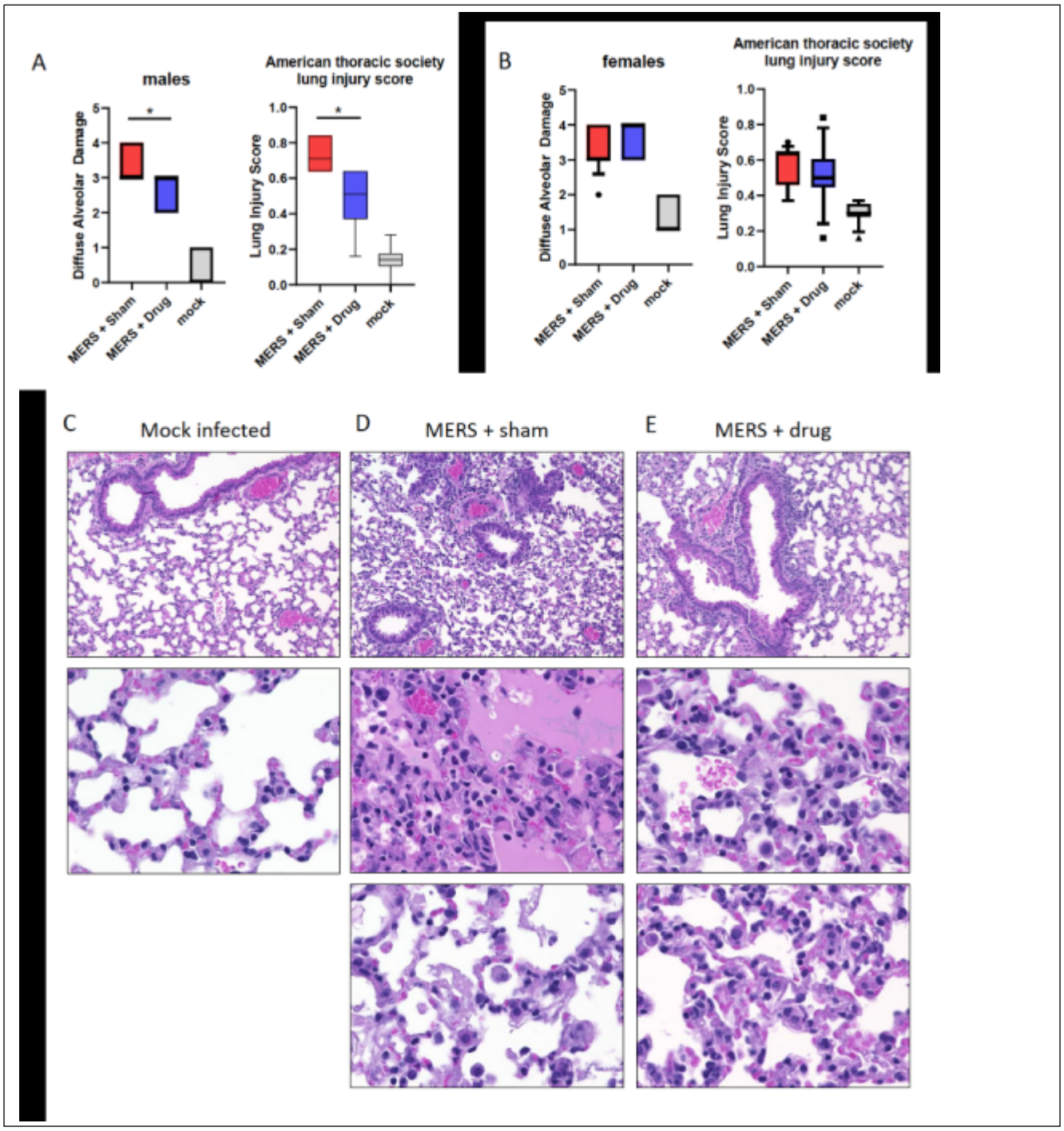


Figure 8 AMG44 reduces clinical signs of acute lung injury in MERS-CoV challenge model

A-E. The histological features of acute lung injury were blindly scored using the American Thoracic Society Lung Injury Scoring system by Matute-Bello, creating an aggregate score for: neutrophils in the alveolar and interstitial space, hyaline membranes, proteinaceous debris filling the air spaces, and alveolar septal thickening. **A-B.** Scoring for ALI and diffuse alveolar damage in male and female mice, respectively. Representative lung pathology for C) mock-infected, D) MERS-CoV infected and sham treated and E) MERS-CoV infected and AMG44 treated male mice at 7 days post infection. * indicates a p value of <0.001.

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Attachment: Apoptosis Sci Trans 3_20_2020_2-rsb.docx

Hi Amy, My comments, great paper. lets get it out soon! I pulled the figures so that I could send it. Pleasure to read. Hope your staying safe in Washington. Its going to be a terrible next 30 days. ralph

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From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 20, 2020 5:39 PM
To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Paper is too big to send

Hugh is working on breaking it up and sending it again.

Thank you, Amy

Science Translational Medicine AAAS

Submitted Manuscript: Confidential template updated: February 28 2012

Ralph and Tim,

My apologies for taking so long to get this back to you. Life has not gone as planned since I left UNC.

I thought it might be easier for you to start off by reading my responses to your specific comments in the results and discussion. I wasn't sure if there was time for a call or not as I am aware that both of you must be insanely busy.

Ralph, you asked about FB cytox in Figure 6A-B but there isn't any. We may have to talk about this one on the phone for you to show me what I am missing.

*Ralph you asked about the type of FB (*primary cultured human lung (HLFs) or airway fibroblasts (HAFs) or both *used. I believe they are derived from the deep lung tissue the same as the MVE. The MVE must be sorted by flow at least once and the FB just crawl out of the tissue and grow on the dish. I can talk to Scott and get more details if you want.*

Figure 1 virologic phenotypes and CPE no changes
Figure 2 transcriptomics and proteomics Hugh updated the labeling of both panels and it is much easier to see what we are focused on.
Figure 3 lipidomics (could combine 2 and 3 if need be) no changes
Figure 4 caspase no changes
Figure 5 UPR and three viral proteins

- *>Transcriptomics have been removed*
- *>Hugh made graphs for several viral proteins and I thought the data looked the best for spike, ORF4a and membrane so I have included those graphs. These trend with the titer data and look the same for both cell types*
- *>All UPR related proteins Hugh could find are included as data here. I asked again to make sure, but we did not see differences in CHOP or IRE1 or ATF6 or XBP1. This study was never designed to be an exhaustive look into the MERS vs the UPR it was only to validate the omics findings and we got more than we bargained for.*
- *>For clarity: GRP78 and Bip are the same thing*
- *>GRP94 and HSP90B1 are the same thing*
- *>In a previous version Tim asked me to go down to one name per entity and I did but it was hard to figure out which name was most frequently used. I have them both listed now.*

Figure 6 PERK inhibitor in lung cells no changes
Figure 7 Gralinski mouse data she added this missing axis
Figure 8 Gralinski mouse histology data (she just sent a pdf and I might need her to send me the graphs in another way to make the figure legends and titles line up

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Title: Inhibition of the Unfolded Protein Response Reduces Middle East Respiratory Syndrome Coronavirus Induced Acute Lung Injury

Authors: Amy C. Sims[1*]†, Hugh Mitchell[2]†, Lisa E. Gralinski[1], Jennifer E. Kyle[2], Kristin E. Burnum-Johnson[2], Mariam Lam[3], M. Leslie Fulcher[3], Ande West[1], Richard D. Smith[2], Scott Randell[3], Thomas O. Metz[2], Timothy P. Sheahan[1]‡, Katrina Waters[2]‡, Ralph S. Baric[1]‡

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One Sentence Summary: An unfolded protein response inhibitor reduced Middle East Respiratory Syndrome Coronavirus replication in primary human lung cells and reduced acute lung injury, leading to improved respiratory function, and survival in a lethal challenge rodent animal model.

Abstract: Currently, there are no approved treatment options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) induced pneumonia and acute respiratory distress syndrome (ARDS) and little is understood about how individual primary human lung cell types contribute to overall disease outcomes. MERS-CoV replicates equivalently in primary human lung microvascular endothelial cells (MVE) and fibroblasts (FB) but only MVE demonstrate virus induced cytopathic effect. To explore potential mechanisms leading to reduced MVE viability, three sets of donor-matched human lung MVE and FB were infected and samples collected for transcriptomic, proteomic, and lipidomic analysis over time. Functional enrichment analysis results were validated and demonstrated that MERS-CoV-infected MVE were likely dying via an unfolded protein response (UPR) mediated apoptotic mechanism. Pharmacologic manipulation of the UPR in MERS-CoV infected MVE, FB confirmed its importance in cell death, virus replication and infection outcomes. In infected mice, treatment resulted in improved respiratory function and reduced weight loss, with accompanying reductions in the pathologic signatures of acute lung injury and improved times to recovery. Using multi-omics systems biology and modeling, our data indicate that infection and death of MVE likely triggers loss of endothelial barrier integrity and vascular leakage into the airway, contributing to the ARDS and progressive end stage lung disease phenotypes commonly seen in emerging coronavirus patients.

[Main Text:]

Introduction

Coronaviruses (CoV) are important emerging pathogens associated with severe disease outcomes in humans and animals causing significant global morbidity and mortality. In 2003, severe acute respiratory coronavirus (SARS-CoV) emerged from closely related bat CoV strains, spread to 26 nations, and caused approximately 8,000 human cases and 800 deaths, worldwide (*1, 2*). In 2012, Middle East respiratory syndrome CoV (MERS-CoV) emerged, causing approximately 2,400 cases with a ~35% mortality rate in 27 countries and the outbreak is still ongoing (*3*). In 2020, the causative agent of coronavirus infectious disease 2019 was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) and to date more than 200,000 cases have been confirmed with a morality rate of ~4% in >160 countries with ongoing virus transmission resulting in significant economic losses and global public health concerns (WHO COVID 19 website). SARS-CoV 2, SARS-CoV, and MERS-CoV disease severity are strongly influenced by aging and other co-morbidities (e.g., diabetes, obesity) and mortality rates approach 15% or exceed 50% in aged individuals, respectively (>60 years)(*4*). These data underscore the highly pathogenic potential of emerging CoVs and reinforce the critical need for comprehensive experimental approaches that define the viral and host pathogenic programs which could be targeted by countermeasures to reverse severe disease outcomes.

Acute Respiratory Distress Syndrome (ARDS) is a severe end stage lung disease characterized by rapid onset respiratory failure resulting from diffuse alveolar damage, hyaline membrane formation, vascular leakage into the airways and pulmonary fibrosis (*5-8*). ARDS is a complex syndrome with multiple etiologies, which complicates diagnosis and treatment. While not the most prevalent cause(*9*), severe respiratory infections can progress to ARDS including

those by highly pathogenic avian influenza(*10*) (H5N1) and SARS-CoV, SARS-CoV 2 and MERS-CoV(*2, 11-14*). Dissecting the mechanisms of MERS-CoV-induced ARDS has been hampered human genetic variation, variable co-morbidities and limited human sample availability (*11, 15*). Highly pathogenic human coronaviruses oftentimes cause programmed cell death within in vitro and in vivo models of viral pathogenesis as well as in patient autopsy tissues (*4, 16-23*). Because MERS-CoV replicates efficiently in multiple cell types essential for lung physiology (e.g. lung fibroblasts, epithelial and endothelial cells) (*24*), primary culture systems provide a biologically relevant platform to better understand virus and virus-mediated-tissue specific host interactions that may drive severe lung pathology.

Here we report a kinetic multi-omics analysis of matched MERS-CoV infected primary human lung fibroblasts (FB) and microvascular endothelial (MVE) cells from three different human donors. While MERS-CoV replication kinetics were similar among FB and MVE, the host responses, as determined by multi-omic transcriptomic, proteomic, and lipidomic analyses differed significantly by cell type and suggested that MVE cells were dying via apoptotic mechanisms initiated by the unfolded protein response (UPR), which helps monitor and maintain homeostasis in the endoplasmic reticulum (ER) following a stress response. Pharmacologic manipulation of UPR demonstrated that active/dimerized PERK was critical for viral replication in vitro. More importantly, mice infected with MERS-CoV and treated with a PERK specific inhibitor demonstrated reduced weight loss, pneumonia and acute lung injury leading to improved respiratory function and time to recovery. These data not only articulate an important role for the epithelial-endothelial cell barrier in MERS-CoV pathogenesis and acute lung injury, but also reveal new strategies for the treatment of highly pathogenic emerging coronavirus infections in humans and animals. .

Results

MERS-CoV induces cytopathic effect in primary human lung endothelial cells but not fibroblasts

Understanding MERS-CoV pathogenic mechanisms requires a detailed understanding of the critical virus-host interactions in infected primary human lung cells that provide the critical structural and physiological requirements for lung function. As clinical samples for MERS-CoV are scarce, a reductionist approach using matched primary human lung cells from transplant recipients provides a novel opportunity to elucidate tissue specific changes that may explain organ specific disease phenotypes after infection. To characterize MERS-CoV infection in primary human lung microvascular endothelial cells (MVE) and primary human lung fibroblasts (FB), we infected cells from three matched human donors and obtained virologic and multi-omics samples (transcriptomic, proteomic, and lipidomic) at 0, 12, 24, 36 and 48 hours post infection. Viral growth kinetics and peak titers (~10^7 plaque forming units (PFU)/mL) were nearly identical regardless of donor background (Figure 1A-B). We also determined infection frequency via microscopy by comparing the total number of cells (i.e. nuclei) to the number of MERS-CoV infected cells per high powered field (Figure 1C and D and Supplemental Figure 1). To simplify this process, we utilized a MERS-CoV expressing the red fluorescent protein (MERS-RFP) (Figure 1C and D). Unlike infection frequency in FB which increased over time, the numbers of total cells per field (Figure 1C) as well infection frequency decreased over time in MVE (Figure 1C-D). Since the number of cells per field in mock-infected MVE cultures did not diminish over time, virus induced cytopathic effect (CPE) was likely mediating the loss of cells in MERS-CoV infected MVE (Figure 1C and D). To quantitate CPE in MERS-CoV infected MVE and FB over time, we performed a cell viability assay (CellTiter-Glo) which estimates the number of metabolically active viable cells by measuring the levels of adenosine

triphosphate (ATP) in each well. Unlike FB which had similar cell viability estimates in mock- and MERS-CoV-infected cultures for most time points (Figure 1E), infected MVE viability decreased significantly over time as compared to mock (Figure 1F), supporting a loss in cell viability. Together, these data demonstrate that both primary MVE and FB are similarly susceptible to MERS-CoV infection but MVE cell viability is significantly reduced over time yet FB are relatively unaffected.

Cross-donor consensus transcriptomic, proteomic and lipidomic responses

To gain insight into the divergent outcomes in cell viability following MERS-CoV infection of FB and MVE, we analyzed donor matched kinetic multi-omic datasets. Functional enrichment was performed on transcriptomic and proteomic data across both cell types, which showed distinct differences in the modulation of the transcriptome and proteome among infected FB and MVE (Figure 2). We found that pathways related to apoptosis (transcription, Figure 2A) and the unfolded protein response (UPR, transcripts and proteins, Figure 2A and 2B), were significantly enriched in MERS-CoV infected MVE at multiple timepoints which was not observed in similarly infected FB. Interestingly, increased hemoglobin protein expression levels in both FB and MVE were detected at 48hpi (arrow Figure 2B), which has been demonstrated to regulate endothelial and epithelial cell communication as well as to regulate the durability of vascular walls (*25-27*). We then investigated if mothers against decapentaplegic homolog 7 (SMAD7) and/or fibroblast growth factor 2 (FGF2) transcripts were differentially expressed in MERS-CoV infected MVE or FB as previous studies indicated that upregulated expression of SMAD7 and FGF2 in MERS-CoV infected immortalized kidney and lung epithelial cells led to cellular apoptosis (*28*). Neither SMAD7 nor FGF2 expression levels were distinct following infection and did not appear to explain the differences in cytopathic effect seen in the current studies

(Supplemental Figure S2). Finally, we sought to determine if MERS-CoV infection would alter the lipidome in FB or MVE. We classified lipids into broad categories for enrichment analysis, which revealed differential expression of ceramides and triglycerides in FB and MVE (Figure 3A). When analyzed at a per-lipid-species level, we found dramatic and significant differences in specific species of ceramides (Figure 3B, upper panel) and triglycerides (Figure 3B, lower panel) both of which are involved in activating apoptotic processes (*29*).

MERS-CoV activates Caspases 3 and 7 in infected MVE

To validate the complementary multi-omics observations suggesting that MERS-CoV infection induces apoptosis in MVE, we simultaneously measured death effector caspases 3 and 7 and cell viability in mock or MERS-CoV infected FB and MVE using the Promega Apotox Triplex kit. We included staurosporine (induces caspase 3/7 activation) or ionomycin (induces necrotic cell death with no caspase activation) treatment as controls. In addition, we added UV-inactivated MERS-CoV virions in order to control for effects on cultures independent of virus replication (i.e. entry, uncoating, etc.). Uninfected MVE and FB treated with staurosporine significantly induced caspase 3/7 activation as compared to mock and cells treated with UV-inactivated MERS-CoV (Figure 4A-B). As expected, ionomycin treatment did not induce caspase 3/7 activation. With MERS-CoV infection, significant caspase 3/7 activation was observed at both 24 and 48 hours post infection but only in MVE (Figure 4A) not in FB (Figure 4B). Caspase activation was not observed with UV-inactivated MERS-CoV treatment or in mock-infected cells for either cell type (Figure 4A-B). When measuring cell viability within the same assay, neither mock infection nor treatment with UV-inactivated virions appreciably affected cell viability (Figure 4C-D). Importantly, treatment of both FB and MVE with control compounds (e.g. staurosporine or ionomycin) diminished cell viability but MERS-CoV infection only

diminished cell viability in MVE (Figure 4C-D). Death of MERS-CoV infected MVE could lead to permeability at the epithelial/endothelial cell barrier as one of the early steps of ARDS and viable MERS-CoV infected FB would continue to produce high levels of infectious virus both of which would contribute to the overall disease burden in the infected patient.

Expression of proteins indicative of the UPR pathway are increased in MERS-CoV infected MVE

Both systems data and confirmatory experimental validation studies suggested that MERS-CoV infected MVE were dying via apoptotic pathways. To better understand the initiation of this process, we re-analyzed our systems biology data focusing on specific mediators of apoptosis and UPR. We found increased protein expression of three well-established UPR markers, glucose regulated protein 78 (GRP78 also known as binding immunoglobulin protein (BiP)), heat shock protein 90kDa beta member 1 (HSP90B1 also known as GRP94) and calnexin (CANX) in MERS-CoV infected MVE but not infected FB (Figure 5A-C). GRP78/BiP is a master regulatory protein for the UPR that binds to regulatory enzymes within the UPR pathway keeping them inactive unless misfolded proteins accumulate triggering dissociation and enzyme activation. HSP90B1/GRP94 and CANX are ER protein chaperones that facilitate nascent protein folding. In support of the viral titer data, the expression of MERS-CoV structural proteins, spike glycoprotein and membrane protein as well as the accessory open reading frame protein 4a (ORF4a) were expressed to similar levels in both cell types for all donors by 12 hours post infection (Figure 5D-F). Cumulatively, these data suggest that MERS-CoV modulation of the UPR is specific to a particular cellular environment (MVE) and may not be broadly applicable to all infected cells and tissues.

PERK activation is critical for MERS-CoV replication in primary human lung MVE and FB

To further validate the results thus far, which suggested that apoptosis of MVE was associated with the UPR, we pharmacologically perturbed the UPR in MERS-CoV infected MVE and FB using an inhibitor specific to the first enzyme activated following misfolded protein accumulation, protein kinase R-like endoplasmic reticulum kinase (PERK, AMG44). Activated PERK regulates phosphorylation of the key translation mediator, elongation initiation factor 2alpha (eIF2alpha). Following activation of the UPR and PERK, host translational shutoff serves to reestablish ER homeostasis and proper protein folding, which if not achieved, results in the activation of apoptotic pathways. Dose response studies were performed in mock and MERS-CoV infected MVE and FB with PERK inhibitor (AMG 44 at 100 to 2 μM) to determine if pharmacologic perturbation of the PERK arm of the UPR would affect MERS-CoV replication and/or cell death (*30*). We utilized a MERS-CoV nanoluciferase reporter virus (MERS nanoluc) to increase accuracy and throughput of the assay (*31*). As shown in Figure 6, inhibition of PERK diminished MERS-CoV replication in both FB (Figure 6A and B) and MVE (Figure 6C and D) in a dose dependent manner when assayed at either 24 (Figure 6A and C) or 48 hours post infection (Figure 6B and D). In addition to monitoring changes in virus replication in the context of PERK inhibition, we also monitored cytotoxicity in drug treated uninfected cultures via CellTiter-Glo cell viability assay. Unlike FB in which we did not observe cytotoxicity at either timepoint (Figure 6A and B), in MVE we observed a dose dependent increase in cytotoxicity with PERK inhibition that was most notable at 48hpi (Figure 6D). Importantly, we found that at 24hpi MERS-CoV replication was inhibited at multiple drug doses that did not exhibit cytotoxicity. These results suggest that primary human lung MVE are more sensitive to inhibition of the UPR in the absence of infection in contrast to the more tolerant primary lung FB. To determine if PERK inhibition modifies induction of apoptosis following MERS-CoV

infection, we performed similar dose response assays as described in Figure 6A-D but then assayed for caspase 3 and 7 activation as in Figure 4 using similar UV inactivated and small molecule controls (i.e. staurosporin, ionomycin). No significant dose responsive change in caspase 3/7 activation above untreated infected cells was detected in either primary human lung MVE or FB following MERS-CoV infection and treatment with PERK inhibitor (Supplemental Figure S3).

PERK inhibition improves pulmonary function and diminishes MERS-CoV pathogenesis and ALI. Because *in vitro* PERK inhibition resulted in a significant decrease in MERS-CoV replication in both cell types, we sought to determine if *in vivo* inhibition would result in a change in viral replication and/or pathogenesis. To address this, we utilized a transgenic mouse model where the murine ortholog of the human MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), was humanized at residues 288 and 330 (hDPP4) facilitating high titer virus replication localized to the respiratory tract and lung pathology similar to that observed in humans(*32, 33*). We initiated treatment of hDPP4 mice with AMG44 or vehicle once per treatment at 24 hours prior to and post MERS-CoV infection. By three days post MERS-CoV infection, vehicle treated mice lost significantly (p value <0.05) more weight than AMG44 treated mice. Importantlly, AMG44 treated mice also displayed an improved time to recovery over the remainder of the study (Figure 7A). Interestingly, virus titer in the lung on day 3 post infection was similar regardless of treatment (Figure 7B). "Pulmonary hemorrhage", a gross pathological phenotype that increases coincident with MERS-CoV pathogenesis, was significantly diminished in AMG44 treated mice as compared to those receiving vehicle treatment (Figure 7C). To determine if PERK inhibition through AMG44 treatment would affect pulmonary function, we performed whole body plethysmography (WBP) daily. Concordant with pulmonary hemorrhage,

AMG44 treatment improved pulmonary function as compared to those receiving vehicle. For three WPB metrics typically induced following MERS-CoV infection (*32-34*), Pause, Penh and EF50, AMG44 treated mice had significantly improved values (p value <0.05) than vehicle treated animals at multiple timepoints (Figure 7D-F). Pause, PenH and EF50 are all measures of airway constriction or obstruction and indicate that AMG44 treatment is relieving or preventing lung pathology that negatively affects lung function. To quantitatively assess the impact of AMG44 treatment on MERS-CoV infected mice, histological lung sections were assessed using the American Thoracic Society (ATS) scoring system designed to more closely relate data from small animal models of acute lung injury (ALI) to infected patient outcomes as previously described (*35, 36*). Hematoxylin and eosin stained fields of lung tissue were blindly scored for the presence of neutrophils in the alveolar and interstitial space, hyaline membranes, proteinaceous debris filling the airway spaces, and thickening of the alveolar septal (*35*). ATS lung injury scores were significantly reduced in male but not female MERS-CoV infected AMG44 treated mice (Figure 8A-E). Together with the wide variety of supportive data described above, the *in vivo* studies with AMG44 directly demonstrate the importance of PERK signaling in promoting MERS-CoV pathogenesis in mice. Our unbiased systems biology-based approach identified a pathway differentially modulated during MERS-CoV infection of primary human cells, validated the importance of this pathway for MERS-CoV replication and cell death *in vitro* and then demonstrated its importance in regulating viral pathogenic outcomes in vivo, leading to a targeted antiviral therapy.

Discussion

Viral pathogenesis is a multifactorial process driven by virus and host factors, responses in infected and neighboring cells, innate and adaptive immunity, host and viral genetics, and

responses at the cellular, tissue, organ and organismal level. Due to this inherent complexity, defining the relative contribution of each of these factors to the disease state and the underlying cellular mechanisms that contribute to the progression towards severe disease is complicated. Thus, new models are needed to define cell and tissue specific host response patterns that play critical roles in viral pathogenesis. Both SARS-CoV, SARS-CoV2 and MERS-CoV cause severe respiratory disease with replication and pathogenesis primarily limited to the lung. As shown in a recent pathologic evaluation of human tissue from a fatal case of MERS-CoV by Ng et al., diffuse alveolar damage, the pathological hallmark of acute lung injury (ALI), was noted along with viral antigen primarily found in alveolar pneumocytes with no extrapulmonary viral antigen detected (*4*). Similar findings have been reported following severe SARS-CoV and SARS-CoV2 infections, suggesting common mechanisms of coronavirus-induced ALI (PMID:32048163, PMID:31986264). While the few post-mortem analyses of tissue samples from MERS-CoV patients have provided insight into the types of cells targeted by virus and the degree and severity of pathology in the lung, many basic questions related to the kinetics of virus replication, cell targeting, and the host response remain unknown. Primary cell cultures offer an opportunity to decrease the complexity of the intact organ to study how virus host interactions determine the fate of specific cell types following infection. While most studies with pneumotropic viruses have focused on airway epithelial cells or type II pneumocytes, MVE and FB play critical roles in maintaining lung architecture, compartmentalization and function (*37*). FB play a central role in the homeostasis of the extracellular matrix and are effector cells during injury repair, while the microvascular endothelium regulates vascular homeostasis, as vascular leakage can result in inefficient gas exchange in the lungs (*38*). In addition to MERS-CoV, H5N1 and other highly pathogenic influenza viruses also replicate efficiently in endothelial cells,

providing diverse model systems to investigate virus-host interactions and identify novel tissue specific response patterns that can be used to attenuate virus replication and/or disease (*24, 39, 40*). Understanding the fate of these cells after infection provides a unique opportunity to understand how MERS-CoV induced disease phenotypes manifest despite limited clinical sample availability. Death of MERS-CoV infected MVE and epithelial cells (*4, 16*) could result in the breakdown of the epithelial-endothelial cell barrier and allow vascular leakage of fluids into the lung, leading to alveolar flooding, a hallmark feature of ALI and ARDS often seen in MERS-CoV, SARS-CoV and SARS-CoV2b patients and mouse models of human disease (*11, 32, 41*). These findings support a more thorough examination of MERS-CoV lung cell tropism as clinical samples become available. The current findings also highlight that even within the same organ cell types can respond to infection with very different outcomes and emphasize the value of studying primary cell types in culture.

During viral infection, viral glycoproteins, unfolded and misfolded host and viral proteins accumulate in the endoplasmic reticulum (ER) disrupting ER homeostasis. ER stress is sensed by several ER chaperone proteins (GRP78, etc.), allowing the cells to activate pro-survival responses that are mediated in part by UPR signaling through PERK, the transmembrane protein inositol-requiring protein-1 (IRE1α), and the activating transcription factor-6 (ATF6) (*42, 43*). If the UPR response fails to restore ER homoeostasis, it promotes cell death through the induction of the specific proapoptotic genes like CHOP and various caspases (*44*). To date the impact of highly pathogenic human CoV infection on different lung cell types has been poorly studied in primary human lung cells. Analysis of systems biology datasets provides an unbiased approach to define host pathways that are crucial for virus replication and cell fate outcomes following infection, providing novel insights into different tissue and cell specific responses to viral

infection. Functional enrichment analysis of transcriptomic, proteomic and lipidomic datasets suggested that activation of the UPR promoted apoptotic cell death in MERS-CoV infected MVE, as compared with FB cells that displayed a minimal UPR response. Analysis of a single dataset would have hinted at either activated stress response or specific cell death pathways in MERS-CoV infected MVE. However, concordant findings across transcriptomic, proteomic and lipidomic datasets in matched cell types across multiple patient codes suggested key indicators of activated UPR and apoptotic pathways in MERS-CoV infected MVE cultures supporting the hypothesis that prolonged UPR signaling led to ER stress, PERK activation and programmed apoptotic cell death. As virus titers and viral protein expression are equivalent in both cell types, the robust activation of the UPR and apoptotic responses in MVE, but not in FB cells derived from the same individual is puzzling. UPR is activated when the influx of nascent, unfolded polypeptides exceeds the folding capacity of the ER, which may differ between MVE and FB cells, yet viral structural and accessory protein levels were similar in both cell types. We hypothesize that lung FB can maintain ER homeostasis longer than infected MVE due to higher endogenous levels of ER folding chaperone proteins or increased overall ER volume, allowing continued cell viability after MERS-CoV infection. Future studies will probe how primary lung FB survive MERS-CoV infection. Importantly, ceremide and triglyceride are also potent stimulators of ER stress and apoptosis and these lipids are also highly upregulated following MERS-CoV infection of MVE, but much less so in FB cells. Increased expression of multiple triglyceride and ceramide species (*45, 46*) (products of sphingomyelinase pathways) is strongly correlative with virus induced CPE in mouse models demonstrating the *in vivo* relevance of these markers as well (*47*). Future studies will need to focus on evaluating the cell type specific UPR responses to various biochemical stimuli, after contemporary coronavirus and other respiratory

virus infections, and identifying which ceramides and triglycerides regulate the UPR and pro-apoptotic response in primary lung MVE and FB.

AMG44 is a selective and potent PERK inhibitor and treatment efficiently blocked MERS-CoV replication in FB and MVE cells *in vitro* (*30*). These studies validate the importance of PERK activation and the UPR response as being critical for MERS-CoV replication fitness early in infection, especially in MVE cells. The most likely mechanism for AMG44 inhibition of MERS-CoV growth is that the PERK signaling pathway and the UPR response promote increased membrane reorganizations and suppressed host translation that optimizes an environmental milieu for improved virus replication, maturation and egress. AMG44 would promote ER stress and translation of host proteins, potentially disrupting virus replication complexes, budding and release. Coronavirus infection is associated with extensive membrane reorganization (*48, 49*). In fact, coronavirus membrane-associated proteins nonstructural protein 3 (nsp3) and nsp4 have intrinsic membrane remodeling properties and usurp ER membranes to generate double membrane vesicles (DMVs) and other convoluted membrane structures that likely function as prominent sites of coronavirus replication (*48, 50-52*). Moreover, coronavirus egress occurs in a rER/Golgi intermediate compartment where coronavirus glycoproteins can induce ER stress and activate the UPR response (*17, 53-60*). Other coronaviruses respond to the PERK signaling cascade activation in a variety of ways including increased virus induced apoptosis (*54, 55*) or decreased viral titers (*58-60*). PERK activation was detected following overexpression of both SARS-CoV spike and ORF3a but the effects on replication were not determined (*17, 56, 57*). In contrast, the SARS-CoV E glycoprotein protected from UPR stress mediated by the IRE1 pathway (*61*). The role of MERS-CoV structural and nonstructural proteins are less certain although ORF4a has been reported to prevent activation of the stress

response pathway via protein kinase R (PKR) antagonism (*60*). AMG44 prophylactic treatment protected MERS-CoV infected mice from clinical disease as evidenced by reduced weight loss, lung hemorrhage, and ALI signatures, leading to improved respiratory function and time to recovery. It is noteworthy that AMG44 treatment did not alter viral titers at day 3 post infection, perhaps reflecting the differential drug susceptibilities of the multiple cell types (e.g., airway epithelium, alveolar epithelial cells, FB and MVE) that are infected by MERS-CoV *in vivo*. In mice, PERK activation may not be pro-viral in all MERS-CoV susceptible cell types and/or the dosing regimen may not have been equivalent in all infected cell types. These results also suggest that PERK may play a role in a damaging pathogenic process *in vivo* where the individual cell types are part of a larger organ-based physiology and that treatment with the PERK inhibitor actually improves pulmonary function. Interestingly, a previous study in Huh7 cells that explored the temporal kinase following MERS-CoV infection did not identify PERK as important for MERS-CoV infection, emphasizing the importance of using the most relevant primary human cells for global analysis studies (*62*).

Currently there are no approved therapeutics to treat highly pathogenic human coronavirus infections associated with the ongoing MERS-CoV epidemic or the 2019 SARS-CoV 2 pandemic, so methods to identify novel viral and host targets are recognized as a high priority by the WHO (*63*). Despite considerable progress, no therapy is presently available to reverse the widespread vascular leak that is observed during ARDS. Additional treatment studies with AMG44 in the MERS-CoV and the SARS-CoV2 challenge model are needed to resolve and expand upon the panel of disease-attenuating drug candidates. SARS-CoV, SARS-CoV2 and MERS-CoV cause more serious disease in males, so it is interesting that prophylactically treated male, but not female mice had a significant reduction in hallmark ALI disease phenotypes after

MERS-CoV infection. Adding additional days of treatment or performing twice daily treatment may improve the outcomes noted in the current study, using AMG44 in combination with robust antivirals (PMC6954302, PMC5567817, **doi:** https://doi.org/10.1101/2020.03.19.997890), and determining the therapeutic window for AMG44 efficacy against MERS-CoV and SARS-CoV2 are also critical research priorities of the future. Nevertheless, the comprehensive systems biology approach described herein led to identification and validation of critical host pathways that mediated MVE cell death, leading to potential protein kinase based therapeutic treatment options that were successful in limiting disease phenotypes in mouse models of MERS-CoV induced ALI. When coupled with the data presented here, modulating UPR responses provides a robust strategy to develop novel therapeutics to control infection mediated vascular permeability, inflammation and ALI, especially when linked with potent direct acting antiviral inhibitors of virus replication *in vivo* (*31, 36*).

Materials and Methods

Primary human lung cells and immortalized cells. Primary human lung cells were isolated from distal lung tissue and processed as described (*24*). Human lung microvascular endothelial cells (MVE) were cultured in Vasculife VEGF-MVE Endothelial Media (Lifeline Cell Tech). Human lung fibroblasts (FB) were cultured in DMEM-H Basal Medium (Corning), 1X penicillin/streptomycin (Sigma), 10% fetal bovine serum (Gemini Bio). Media fetal bovine serum concentrations were reduced to 4% prior to infection. Vero 81 cells were cultured in Dulbecco's modified essential media (DMEM Gibco) with 10% fetal clone II (Hyclone) and 1X antibiotic/antimycotic (Gibco).

Viruses and viral titration Wild-type MERS-CoV (EMC 2012 strain), MERS-CoV expressing nano luciferase (MERS nanoluc) and MERS-CoV expressing the red fluorescent protein (MERS-RFP) were rescued from infectious clones as previously described (*24, 31*). Vero C81 cells were used to generate viral stocks and to quantitate viral titers following infection (*24, 31*).

Infections to collect transcriptomic, proteomic, and lipidomic samples. Donor matched MVE and FB from three different human tissue donors were infected and samples harvested for systems biology analysis. For transcriptomic analysis, five replicate wells of MVE or FB were either mock-infected or infected with wild type MERS-CoV at multiplicity of infection (MOI) 5. At 0, 12, 24, 36, and 48 hours post infection, 100uL of media/supernatant was collected for viral titration assays, media removed and then 1mL of Trizol (Invitrogen/ThermoFisher) added per well. Total RNA samples were sent to Arraystar for downstream analysis. In parallel, an additional five replicate wells were subjected to chloroform/methanol (2:1 mix) precipitation as previously described (*64, 65*). All proteomic and lipidomic samples were desiccated and frozen prior to shipment to Pacific Northwest National Laboratories for downstream analysis.

Transcriptomic Analysis Scanned images were analyzed using Agilent Feature Extraction Software (v11.0.1.1). The limma package for R (available on Bioconductor) was used to perform background correction, quantile normalization (normalizeBetweenArrays), and summarization (avereps) to derive a single normalized intensity value per probe. Outlier samples were detected using PCA and by visual inspection of heatmaps, and all data was re-processed after removing outlier samples. All data processing for each of the biological replicates was performed independently of the other.

Proteomic Analysis The algorithm RMD-PAV (*66*) was used to identify any outlier biological samples, which was confirmed via Pearson correlation. Peptides with inadequate data for either

qualitative or quantitative statistical tests were also removed from the dataset (*67*). The SPANS algorithm (*67*) was used to identify the best normalization method for each dataset. Peptides were evaluated with Analysis of Variance (ANOVA) with a Dunnett test correction and a Bonferroni-corrected g-test to compare each virus to the associated mock within each time point. To perform signature-based protein quantification, BP-Quant (*68*), each peptide was categorized as a vector of length equal to the number of viruses being evaluated. If all comparisons for all time points are 0 for a specific virus it is considered as non-changing and given a value of 0. If there are more time points with an increase in virus to mock than decreasing it is categorized as a +1 and the contrary -1 is given for the decrease in virus to mock. BP-Quant was run with a default parameter of 0.9. All proteins were then analyzed using the same methodology as for the peptides; ANOVA with a Dunnett test correction and a Bonferroni-corrected g-test to compare each virus to the associated mock within each time point.

Lipidomic Analysis The algorithm RMD-PAV (*66*) was used to identify any outlier biological samples, which was confirmed via Pearson correlation Lipids with inadequate data for either qualitative or quantitative statistical tests were also removed from the dataset (*67*). Median centering was used for normalization. Lipids were evaluated with a standard two sample t-test to compare each infected condition to the associated mock within each time point.

Functional Enrichment We identified significantly changed features (transcripts, proteins, lipids) by using an adjusted p-value of 0.05 as a threshold. For each experimental condition, perturbed features were divided into one list each of up- and down-regulated items. Each list was tested against the Gene Ontology (GO) database of gene sets using the EASE-adjusted one-sided Fisher exact test (*69*), such that each condition is tested for up- and down-regulation of each function/pathway in the ontology database. Results across multiple conditions were visualized in

heatmaps using the log10 p-values of the significance tests, colored to indicate the direction of change. For lipids, feature sets were generated by categorizing the lipids observed in our experiments according to broad lipid classifications; these classifications were then used as "gene sets" and the enrichment analysis was then performed in the same manner as for transcripts and proteins.

Cell viability and percent infection assays To assess numbers of viable cells following MERS-CoV infection of FB and MVE, we used the CellTiter-Glo Luminescent Cell Viability Assay (Promega) at 24 and 48 hours post infection/treatment according to manufacturer's instructions and relative light units were determined by Spectromax plate reader (Molecular Devices), averaged and plotted. Percent infection was determined using MVE and FB infected with MERS-RFP (MOI 5) or mock-infected and counting nuclei (Horcht stain diluted 1:5,000 in media) in replicate wells at 0, 12, 24, 36, and 48 hours post infection. Cell numbers were determined using the Fiji (*70*) cell counter function and total number of cells versus number of red fluorescent cells were determined for at least three wells per condition per cell type. Statistical significance was determined by Manfield Whitney unpaired t test (performed in GraphPad Prism).

Apoptosis Assays Infected FB and MVE were assayed using either the Caspase-Glo 3/7 Kit (Promega) to measure caspase activation or using the ApoTox-Glo Triplex Assay (Promega) to assess cell viability, cytotoxicity and caspase 3/7 activation in a single set of samples at 24 and 48 hours post infection according to manufacturer's instructions. Control wells were treated with UV inactivated virus stocks, staurosporin (Sigma, 8uM for MVE or 10uM for FB) or ionomycin (ThermoFisher, 40uM for MVE and 60uM for FB). Relative light units or emission excitation wavelengths were determined by Spectromax plate reader (Molecular Devices).

Statistical significance was determined by Manfield Whitney unpaired t test (performed in GraphPad Prism).

Inhibitor studies MERS-CoV infected MVE and FB were tested at 24 and 48 hours post infection following treatment with a dilution series PERK inhibitor (AMG 44(*30, 71*) 100 uM to 2 uM) and was evaluated for cytotoxicity with drug treatment alone (cell viability assay, no virus), activation of the death caspases 3/7 (wild type MERS-CoV) and viral replication (detection of luciferase as a surrogate for replication, MERS nanoluc virus). All assay results were read by SpectraMax (Molecular Devices). Results are graphed as percent inhibition and toxicity (effective and cytotoxic concentration 50) as determined by GraphPad Prism.

Mouse studies 288-330$^{+/+}$ mice (*32*) were housed and bred in accordance with the University of North Carolina Department of Comparative Medicine, AALAC #329. For a single group of mice, dosing occurred once a day 24 hours prior to infection and a second single dose was administered 24 hours post infection via the intraperitoneal route (12mg/kg of PERK AMG'44 suspended in water or with a sham control(*30, 71*)). Immediately prior to infection, mice were anesthetized with 50 uL of ketamine/xylazine mixture via intraperitoneal injection. 16-20 week old mice were intranasally infected with 10^4 PFU of mouse adapted MERS-CoV maM35c4 diluted in OPTIMEM (*33*), a total volume of 50 uL was given. Mice were weighed daily following infection and had their respiratory function measured one day prior to infection and at days two through six post infection using Buxco Whole Body Plethysmography (Data Sciences International) (*34*). Briefly, mice were allowed to acclimate for 30 minutes in the plethysmography chamber located within the biological safety cabinet after which a 5 minute measurement was taken. Readings were collected every 2 seconds for a total of 150 measurements per mouse per day. At days three and seven post infection mice were euthanized

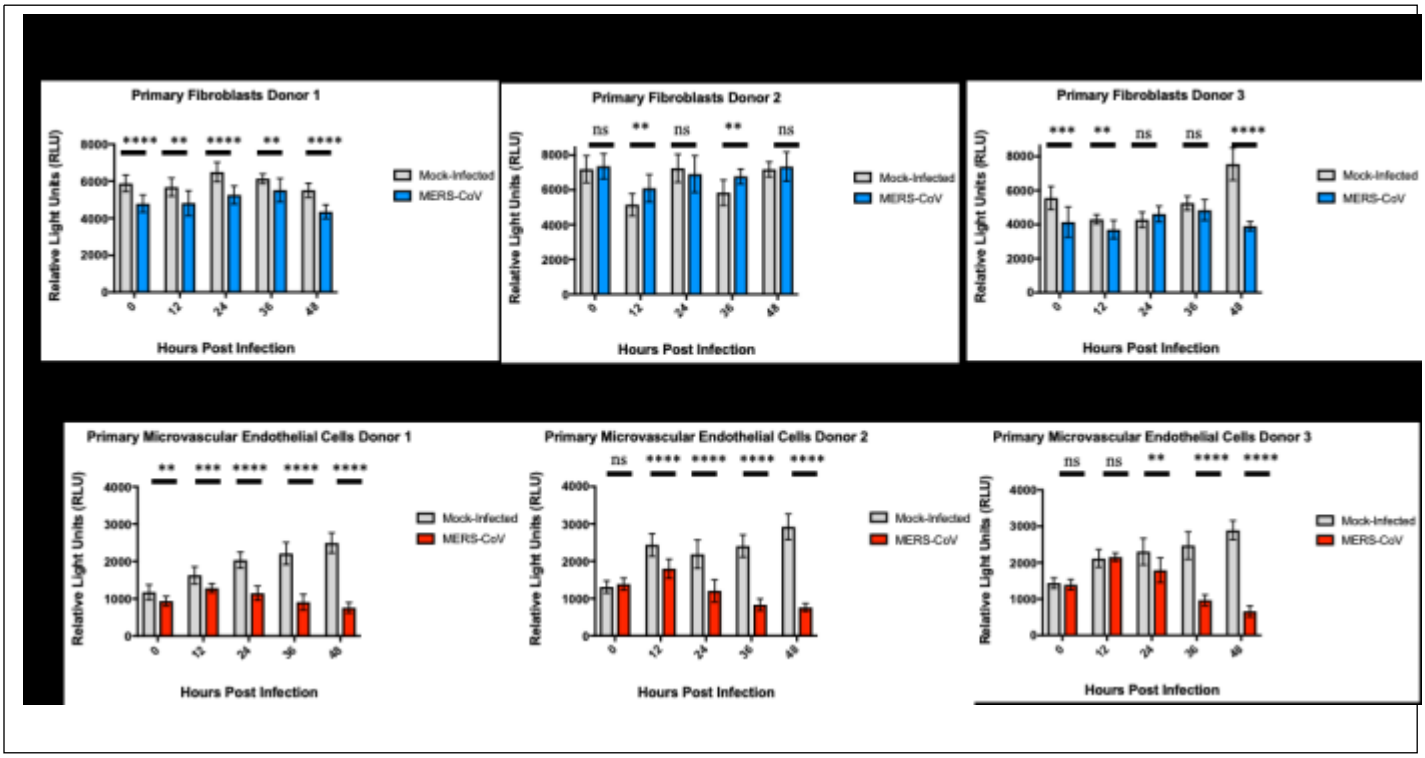
via isoflurane overdose after which lung tissue was harvested to determine viral replication titers. Gross pulmonary hemorrhage was observed and scored from zero (none) to four (severe and total) at the time of dissection.

Supplementary Materials

Supplementary Materials and Methods

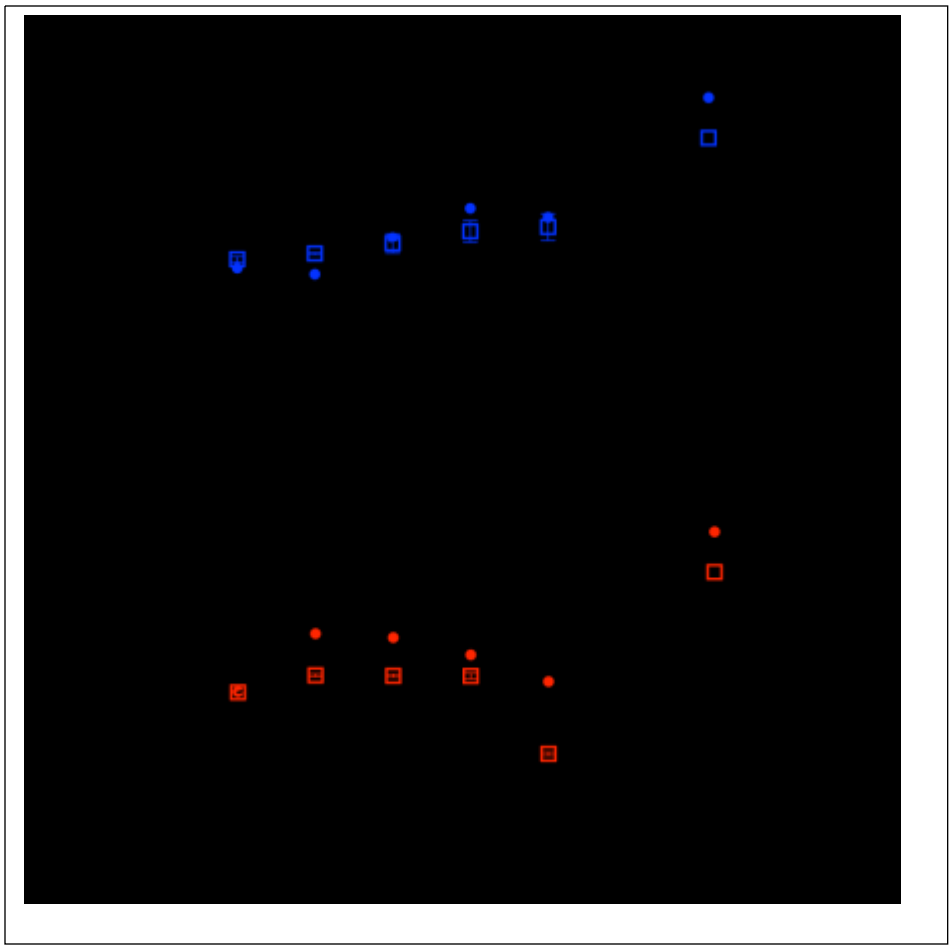
All methodologies are described in the Materials and Methods section above.

Supplementary Figures and Tables



Supplementary Fig. S1 MERS-CoV reduces cell viability for all three donors in MVE but not FB. Donor matched MVE and FB were infected with wild type MERS-CoV and assessed for cell viability using the CellTiter-Glo kit according to manufacturer's instructions (Promega) at

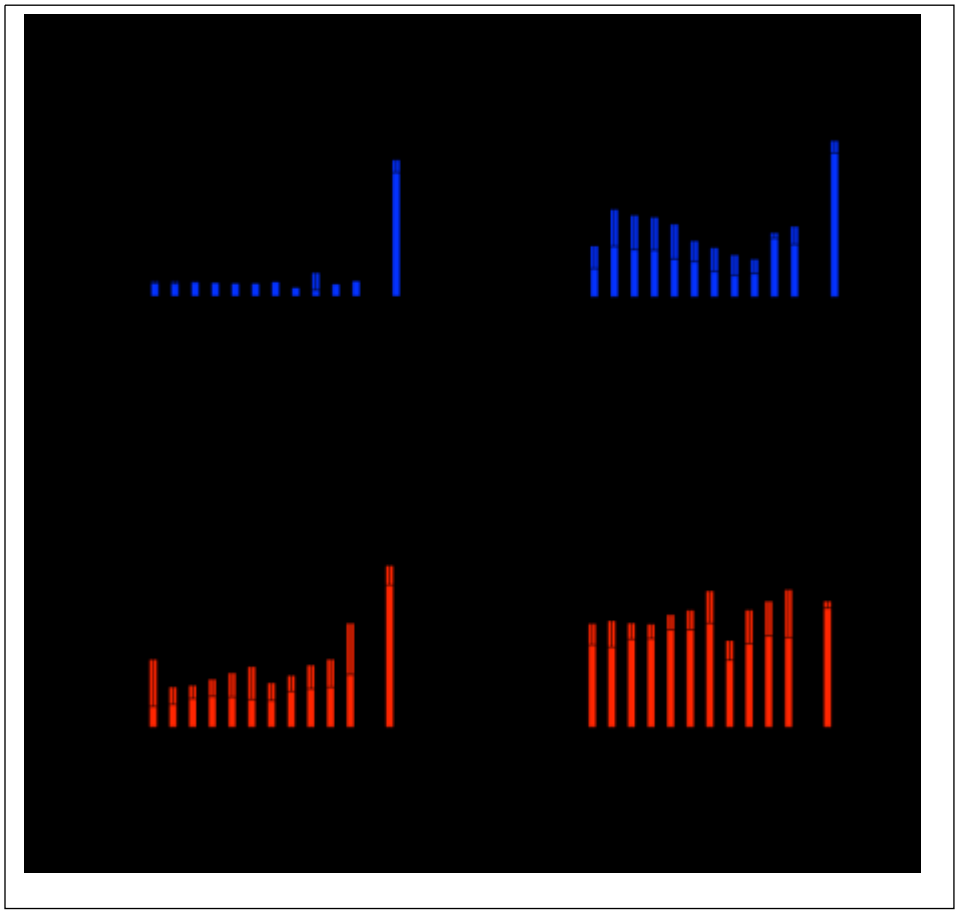
the indicated times post infection. Relative light units (RLU) were graphed over time and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Gray bars- mock infected cells, red bars- MERS-CoV infected MVE, blue bars- MERS-CoV infected FB, **** p= <0.0001, ** p= <0.002, ns not statistically significant.



Supplementary Fig. S2 Neither SMAD7 nor FGF2 expression contribute to MERS-CoV induced cytopathic effect in primary human lung cells. A-B. Graphs show transcript expression levels for SMAD7 and FGF2 in MERS-CoV infected MVE and FB over the 48 hour time course (derived from microarray analysis and are from the same datasets used in Figure 2).

Values graphed are fold change (log_2) and error bars are standard deviations from the mean.

mothers against decapentaplegic homolog 7 (SMAD7); fibroblast growth factor 2 (FGF2)



Supplementary Fig. S3 Inhibition of PERK by AMG44 does not alter caspase 3/7 activation following MERS-CoV infection. A-D. Donor matched FB (A, B) and MVE (C, D) were plated and infected with UV-inactivated or wild type MERS-CoV and at 24 (A, C) and 48 (B, D) hours post infection caspase 3/7 activation was determined according to manufacturer's instructions using the Apotox Triplex kit. Control uninfected cells were treated with staurosporin (8 uM MVE/10 uM FB, activates caspase 3/7) or ionomycin (50 uM MVE/60 uM FB, does not activate caspase 3/7). Results are graphed as relative light units and error bars indicate standard deviation

from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test.

Supplementary Table 1 Pathways contained within categories found by functional enrichment analysis of transcriptomic data in Figure 2

Please see separate Excel spreadsheet.

Supplementary Table 2 Pathways contained within categories found by functional enrichment analysis of proteomic data in Figure 2

Please see separate Excel spreadsheet.

References

1. R. L. Graham, E. F. Donaldson, R. S. Baric, A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol* **11**, 836-848 (2013).
2. J. S. Peiris, Y. Guan, K. Y. Yuen, Severe acute respiratory syndrome. *Nat Med* **10**, S88-97 (2004).
3. A. M. Zaki, S. van Boheemen, T. M. Bestebroer, A. D. Osterhaus, R. A. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* **367**, 1814-1820 (2012).
4. D. L. Ng *et al.*, Clinicopathologic, Immunohistochemical, and Ultrastructural Findings of a Fatal Case of Middle East Respiratory Syndrome Coronavirus Infection in the United Arab Emirates, April 2014. *Am J Pathol* **186**, 652-658 (2016).

5. R. Blondonnet, J. M. Constantin, V. Sapin, M. Jabaudon, A Pathophysiologic Approach to Biomarkers in Acute Respiratory Distress Syndrome. *Dis Markers* **2016**, 3501373 (2016).

6. A. D. T. Force *et al.*, Acute respiratory distress syndrome: the Berlin Definition. *JAMA* **307**, 2526-2533 (2012).

7. A. Husain, V. Kumar, in *Robbins and Cotran Pathologoic Basis of Disease*. (Saunders/Elsevier, Philadelphia, Pennsylvania, 2010), vol. 8th, pp. 715-716.

8. L. B. Ware, M. A. Matthay, The acute respiratory distress syndrome. *N Engl J Med* **342**, 1334-1349 (2000).

9. C. E. Luyt, A. Combes, J. L. Trouillet, A. Nieszkowska, J. Chastre, Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome. *Presse Med* **40**, e561-568 (2011).

10. C. Ramsey, A. Kumar, H1N1: viral pneumonia as a cause of acute respiratory distress syndrome. *Curr Opin Crit Care* **17**, 64-71 (2011).

11. Y. M. Arabi *et al.*, Middle East Respiratory Syndrome. *N Engl J Med* **376**, 584-594 (2017).

12. J. S. Peiris *et al.*, Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* **361**, 1767-1772 (2003).

13. S. L. Smits *et al.*, Distinct severe acute respiratory syndrome coronavirus-induced acute lung injury pathways in two different nonhuman primate species. *J Virol* **85**, 4234-4245 (2011).

14. C. Huang *et al.*, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497-506 (2020).

15. J. H. Beigel *et al.*, Advances in respiratory virus therapeutics - A meeting report from the 6th isirv Antiviral Group conference. *Antiviral Res* **167**, 45-67 (2019).

16. R. W. Chan *et al.*, Tropism of and innate immune responses to the novel human betacoronavirus lineage C virus in human ex vivo respiratory organ cultures. *J Virol* **87**, 6604-6614 (2013).

17. H. Chu *et al.*, Middle East Respiratory Syndrome Coronavirus Efficiently Infects Human Primary T Lymphocytes and Activates the Extrinsic and Intrinsic Apoptosis Pathways. *J Infect Dis* **213**, 904-914 (2016).

18. A. H. de Wilde *et al.*, MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-alpha treatment. *J Gen Virol* **94**, 1749-1760 (2013).

19. A. C. Hocke *et al.*, Emerging human middle East respiratory syndrome coronavirus causes widespread infection and alveolar damage in human lungs. *Am J Respir Crit Care Med* **188**, 882-886 (2013).

20. X. Tao *et al.*, Bilateral entry and release of Middle East respiratory syndrome coronavirus induces profound apoptosis of human bronchial epithelial cells. *J Virol* **87**, 9953-9958 (2013).

21. H. Yan *et al.*, SARS coronavirus induces apoptosis in Vero E6 cells. *J Med Virol* **73**, 323-331 (2004).

22. Q. L. Zhang *et al.*, [Detection of cell apoptosis in the pathological tissues of patients with SARS and its significance]. *Di Yi Jun Yi Da Xue Xue Bao* **23**, 770-773 (2003).

23. J. Zhou *et al.*, Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Sci Adv* **3**, eaao4966 (2017).

24. T. Scobey *et al.*, Reverse genetics with a full-length infectious cDNA of the Middle East respiratory syndrome coronavirus. *Proc Natl Acad Sci U S A* **110**, 16157-16162 (2013).

25. C. Lechauve *et al.*, Endothelial cell alpha-globin and its molecular chaperone alpha-hemoglobin-stabilizing protein regulate arteriolar contractility. *J Clin Invest* **128**, 5073-5082 (2018).

26. A. C. Straub *et al.*, Endothelial cell expression of haemoglobin alpha regulates nitric oxide signalling. *Nature* **491**, 473-477 (2012).

27. A. C. Straub, A. C. Zeigler, B. E. Isakson, The myoendothelial junction: connections that deliver the message. *Physiology (Bethesda)* **29**, 242-249 (2014).

28. M. L. Yeung *et al.*, MERS coronavirus induces apoptosis in kidney and lung by upregulating Smad7 and FGF2. *Nat Microbiol* **1**, 16004 (2016).

29. A. M. Dart, J. P. Chin-Dusting, Lipids and the endothelium. *Cardiovasc Res* **43**, 308-322 (1999).

30. A. L. Smith *et al.*, Discovery of 1H-pyrazol-3(2H)-ones as potent and selective inhibitors of protein kinase R-like endoplasmic reticulum kinase (PERK). *J Med Chem* **58**, 1426-1441 (2015).

31. T. P. Sheahan *et al.*, Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* **9**, (2017).

32. A. S. Cockrell *et al.*, A mouse model for MERS coronavirus-induced acute respiratory distress syndrome. *Nat Microbiol* **2**, 16226 (2016).

33. M. G. Douglas, J. F. Kocher, T. Scobey, R. S. Baric, A. S. Cockrell, Adaptive evolution influences the infectious dose of MERS-CoV necessary to achieve severe respiratory disease. *Virology* **517**, 98-107 (2018).

34. V. D. Menachery, L. E. Gralinski, R. S. Baric, M. T. Ferris, New Metrics for Evaluating Viral Respiratory Pathogenesis. *PLoS One* **10**, e0131451 (2015).

35. G. Matute-Bello *et al.*, An official American Thoracic Society workshop report: features and measurements of experimental acute lung injury in animals. *Am J Respir Cell Mol Biol* **44**, 725-738 (2011).

36. T. P. Sheahan *et al.*, Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222 (2020).

37. E. S. White, Lung extracellular matrix and fibroblast function. *Ann Am Thorac Soc* **12 Suppl 1**, S30-33 (2015).

38. J. Aman, E. M. Weijers, G. P. van Nieuw Amerongen, A. B. Malik, V. W. van Hinsbergh, Using cultured endothelial cells to study endothelial barrier dysfunction: Challenges and opportunities. *Am J Physiol Lung Cell Mol Physiol* **311**, L453-466 (2016).

39. S. Tundup *et al.*, Endothelial cell tropism is a determinant of H5N1 pathogenesis in mammalian species. *PLoS Pathog* **13**, e1006270 (2017).

40. H. Zeng *et al.*, Human pulmonary microvascular endothelial cells support productive replication of highly pathogenic avian influenza viruses: possible involvement in the pathogenesis of human H5N1 virus infection. *J Virol* **86**, 667-678 (2012).

41. K. M. Das, E. Y. Lee, R. D. Langer, S. G. Larsson, Middle East Respiratory Syndrome Coronavirus: What Does a Radiologist Need to Know? *AJR Am J Roentgenol* **206**, 1193-1201 (2016).

42. E. Dufey, D. Sepulveda, D. Rojas-Rivera, C. Hetz, Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 1. An overview. *Am J Physiol Cell Physiol* **307**, C582-594 (2014).

43. H. Malhi, R. J. Kaufman, Endoplasmic reticulum stress in liver disease. *J Hepatol* **54**, 795-809 (2011).

44. S. E. Logue, P. Cleary, S. Saveljeva, A. Samali, New directions in ER stress-induced cell death. *Apoptosis* **18**, 537-546 (2013).

45. E. Aflaki *et al.*, C16 ceramide is crucial for triacylglycerol-induced apoptosis in macrophages. *Cell Death Dis* **3**, e280 (2012).

46. Y. R. Kim *et al.*, Hepatic triglyceride accumulation via endoplasmic reticulum stress-induced SREBP-1 activation is regulated by ceramide synthases. *Exp Mol Med* **51**, 1-16 (2019).

47. S. E. Dautel *et al.*, Lipidomics reveals dramatic lipid compositional changes in the maturing postnatal lung. *Sci Rep* **7**, 40555 (2017).

48. K. Knoops *et al.*, SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol* **6**, e226 (2008).

49. H. Zhou *et al.*, The N-terminal region of severe acute respiratory syndrome coronavirus protein 6 induces membrane rearrangement and enhances virus replication. *J Virol* **84**, 3542-3551 (2010).

50. M. M. Angelini, M. Akhlaghpour, B. W. Neuman, M. J. Buchmeier, Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. *mBio* **4**, (2013).

51. D. Oudshoorn *et al.*, Expression and Cleavage of Middle East Respiratory Syndrome Coronavirus nsp3-4 Polyprotein Induce the Formation of Double-Membrane Vesicles That Mimic Those Associated with Coronaviral RNA Replication. *mBio* **8**, (2017).

52. I. Romero-Brey, R. Bartenschlager, Endoplasmic Reticulum: The Favorite Intracellular Niche for Viral Replication and Assembly. *Viruses* **8**, (2016).

53. A. Perrier *et al.*, The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. *J Biol Chem* **294**, 14406-14421 (2019).

54. T. S. Fung, D. X. Liu, Coronavirus infection, ER stress, apoptosis and innate immunity. *Front Microbiol* **5**, 296 (2014).

55. Y. Liao *et al.*, Upregulation of CHOP/GADD153 during coronavirus infectious bronchitis virus infection modulates apoptosis by restricting activation of the extracellular signal-regulated kinase pathway. *J Virol* **87**, 8124-8134 (2013).

56. R. Minakshi *et al.*, The SARS Coronavirus 3a protein causes endoplasmic reticulum stress and induces ligand-independent downregulation of the type 1 interferon receptor. *PLoS One* **4**, e8342 (2009).

57. S. C. Sung, C. Y. Chao, K. S. Jeng, J. Y. Yang, M. M. Lai, The 8ab protein of SARS-CoV is a luminal ER membrane-associated protein and induces the activation of ATF6. *Virology* **387**, 402-413 (2009).

58. Y. Wang *et al.*, Triggering unfolded protein response by 2-Deoxy-D-glucose inhibits porcine epidemic diarrhea virus propagation. *Antiviral Res* **106**, 33-41 (2014).

59. M. Xue *et al.*, The PERK Arm of the Unfolded Protein Response Negatively Regulates Transmissible Gastroenteritis Virus Replication by Suppressing Protein Translation and Promoting Type I Interferon Production. *J Virol* **92**, (2018).

60. H. H. Rabouw *et al.*, Middle East Respiratory Coronavirus Accessory Protein 4a Inhibits PKR-Mediated Antiviral Stress Responses. *PLoS Pathog* **12**, e1005982 (2016).

61. M. L. DeDiego *et al.*, Severe acute respiratory syndrome coronavirus envelope protein regulates cell stress response and apoptosis. *PLoS Pathog* **7**, e1002315 (2011).

62. J. Kindrachuk *et al.*, Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother* **59**, 1088-1099 (2015).

63. G. V. Asokan, T. Ramadhan, E. Ahmed, H. Sanad, WHO Global Priority Pathogens List: A Bibliometric Analysis of Medline-PubMed for Knowledge Mobilization to Infection Prevention and Control Practices in Bahrain. *Oman Med J* **34**, 184-193 (2019).

64. K. E. Burnum-Johnson *et al.*, MPLEx: a method for simultaneous pathogen inactivation and extraction of samples for multi-omics profiling. *Analyst* **142**, 442-448 (2017).

65. E. S. Nakayasu *et al.*, MPLEx: a Robust and Universal Protocol for Single-Sample Integrative Proteomic, Metabolomic, and Lipidomic Analyses. *mSystems* **1**, (2016).

66. M. M. Matzke *et al.*, Improved quality control processing of peptide-centric LC-MS proteomics data. *Bioinformatics* **27**, 2866-2872 (2011).

67. B. J. Webb-Robertson *et al.*, Combined statistical analyses of peptide intensities and peptide occurrences improves identification of significant peptides from MS-based proteomics data. *J Proteome Res* **9**, 5748-5756 (2010).

68. B. J. Webb-Robertson *et al.*, Bayesian proteoform modeling improves protein quantification of global proteomic measurements. *Mol Cell Proteomics* **13**, 3639-3646 (2014).

69. D. A. Hosack, G. Dennis, Jr., B. T. Sherman, H. C. Lane, R. A. Lempicki, Identifying biological themes within lists of genes with EASE. *Genome Biol* **4**, R70 (2003).

70. J. Schindelin *et al.*, Fiji: an open-source platform for biological-image analysis. *Nat Methods* **9**, 676-682 (2012).

71. D. Rojas-Rivera *et al.*, When PERK inhibitors turn out to be new potent RIPK1 inhibitors: critical issues on the specificity and use of GSK2606414 and GSK2656157. *Cell Death Differ* **24**, 1100-1110 (2017).

Acknowledgements: We thank Ernesto Nakayasu for expert assistance with proteomics data. **Funding:** This study was funded by NIH/NIAID U19 AI109761, U19100625 and NIH U19-AI106772-01 grants and the Cystic Fibrosis and Pulmonary Diseases Research and Treatment Center (BOUCHE15RO and NIH P30DK065988). **Author contributions** ACS, SR, TOM, KW, RSB- designed in vitro systems biology experiments; ML, MLF, SR-harvested, isolated and characterized primary human lung cells; ACS, AW- performed in vitro systems biology experiment and phenotypic characterization; HM, JEK, KEBJ, RDS, TOM, KW-processed and analyzed systems biology samples/datasets; ACS, TPS, HM, RSB-designed cell viability and caspase assays; ACS- performed cell viability, caspase assays, PERK inhibitor assays; HM, JEK-functional enrichment analysis or transcript, protein and lipid datasets; LEG, TPS, ACS, RSB designed in vivo PERK inhibitor study; LEG performed PERK inhibitor study in vivo; ACS,

TPS, RSB, HM, KW wrote the manuscript. **Competing interests**: All authors claim no competing interests. **Data and materials availability:**

Figures and Figure Legends

Figure 1. Viral growth kinetics, percent infected cells and cell viability following MERS-CoV infection of primary human lung fibroblasts and microvascular endothelial cells. A-B. Viral replication: Donor matched microvascular endothelial cells (MVE) and fibroblasts (FB) were infected with wild type MERS-CoV (MOI of 5) and supernatants collected at the indicated times and viral titers determined by plaque assay. Results are shown as plaque forming units (pfu) per mL over time. Each data point represents averaged data from supernatant collected from 10 different wells (5 wells harvested for RNA and 5 wells fractionated for proteins, metabolites and lipids). The graphs in A and B show levels of replication detected for all three tissue donors in both cell types. Error bars indicate standard deviation from the mean. Open and filled blue circles and blue triangles represent data from MERS-CoV infected FB, while open and filled red circles and red triangles represent MERS-CoV infected MVE. **C-D.** Percent MERS-CoV infected cells: Donor matched MVE and FB were mock-infected or infected with MERS-CoV expressing the red fluorescent protein (MERS-RFP), nuclei were stained with Hoechst stain, and images captured at the indicated times post infection. Total numbers of cells (shown for all conditions in **C**) and total numbers of infected (contained red fluorescence) cells were assessed for at least three fields per condition and total percent of infected cells determined and plotted (**D**). Representative data is shown for one of the three donors. Error bars indicate

standard deviation from the mean. No statistical significance (ns) was found when comparing the percentage of infected FB and MVE at any specific timepoint. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Open blue bars- mock-infected FB, open red bars- mock-infected MVE, filled blue bars- MERS-RFP infected FB, filled red bars- MERS-CoV RFP infected MVE. **E-F.** Cell viability following MERS-CoV infection: Donor matched MVE and FB were infected with wild type MERS-CoV and assessed for cell viability using the CellTiter-Glo kit according to manufacturer's instructions (Promega) at the indicated times post infection. Relative light units were graphed over time and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. Gray bars- mock infected cells, red bars- MERS-CoV infected MVE, blue bars- MERS-CoV infected FB, **** p= <0.0001, ** p= <0.002, ns not statistically significant.

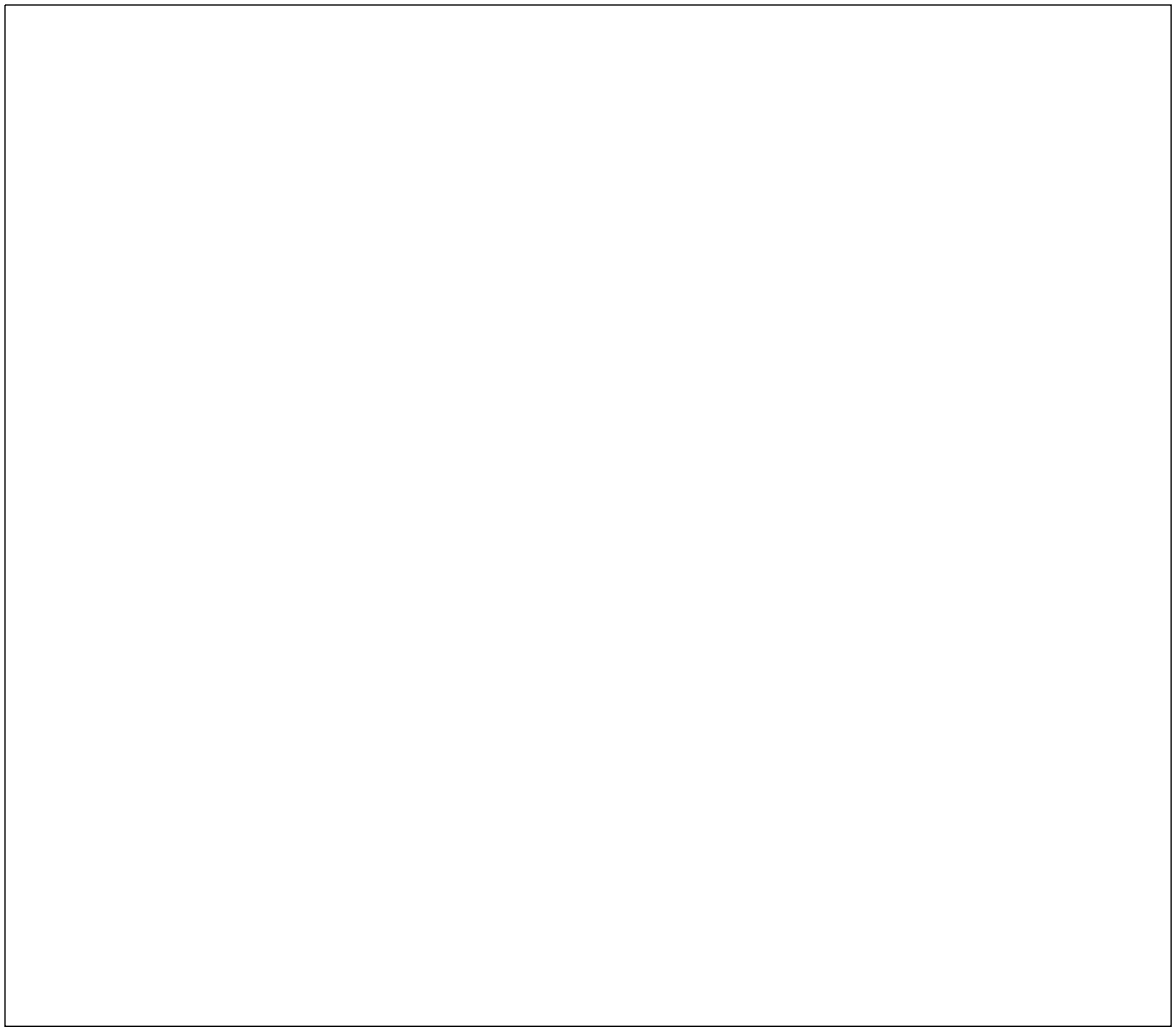


Figure 2. Transcriptomics and proteomics suggest activation of apoptotic pathways. A. Functional enrichment was performed on transcriptomic data from all three donor samples in both cell types, and results were only retained that were present in all three donors, keeping only the least significant score. In this way a true consensus response is represented by all indicated functions. **B.** Protein expression for proteins associated with the GO term "positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway". All apoptosis-associated proteins are displayed across the three donors for fibroblasts and MVE. The blue arrow highlights proteins in the hemoglobin complex and red asterisks highlight apoptotic proteins from the endoplasmic reticulum.

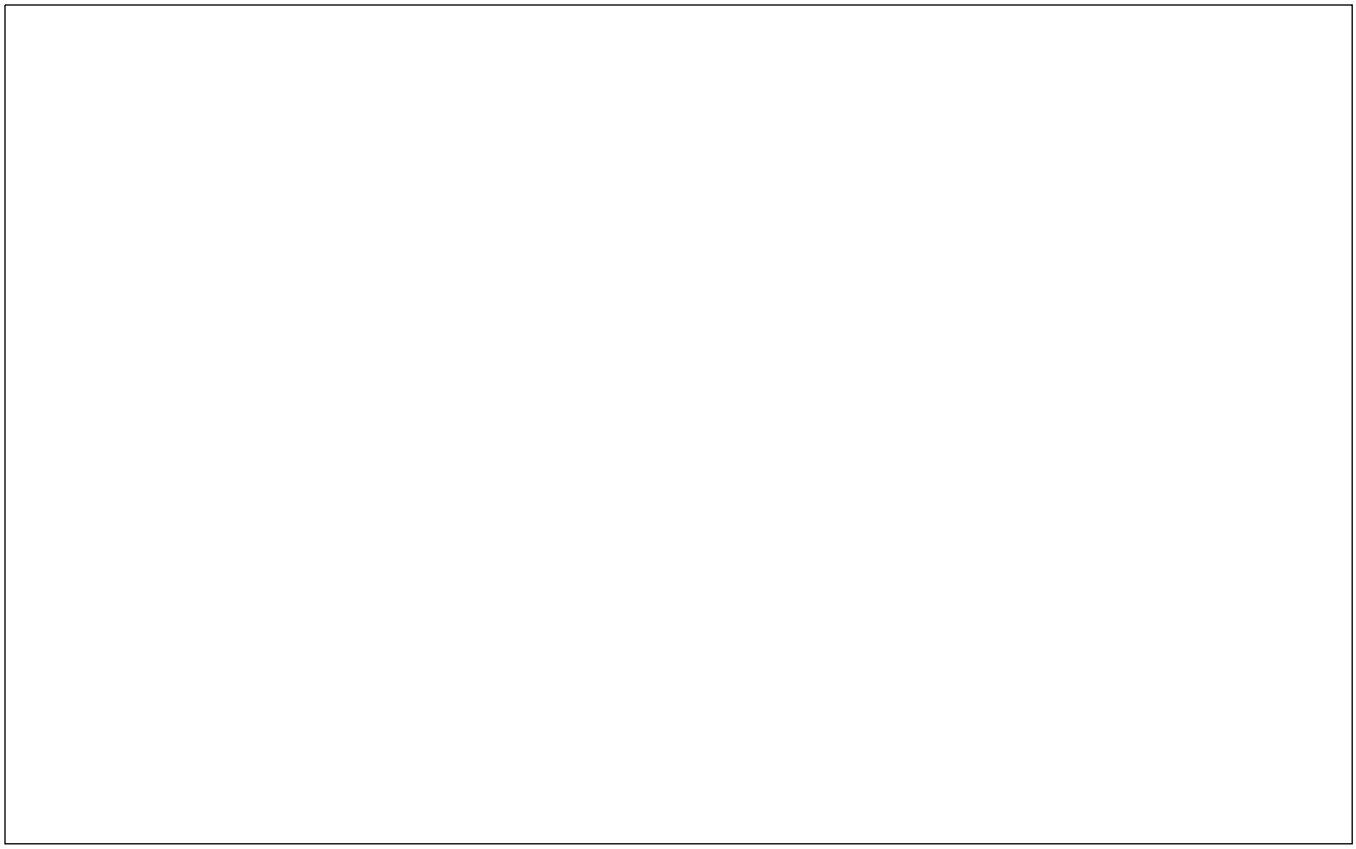


Figure 3. Lipid profiles suggest activation of apoptotic pathways. A. Enrichment analysis using lipid classes as enrichment sets. Cer-ceramide, TG-triglycerides, PC-phosphatidylcholine, PE-phosphatidylethanolamine, PS-phosphatidylserine, SM-sphingomyelin. **B.** Abundance of individual lipid species.

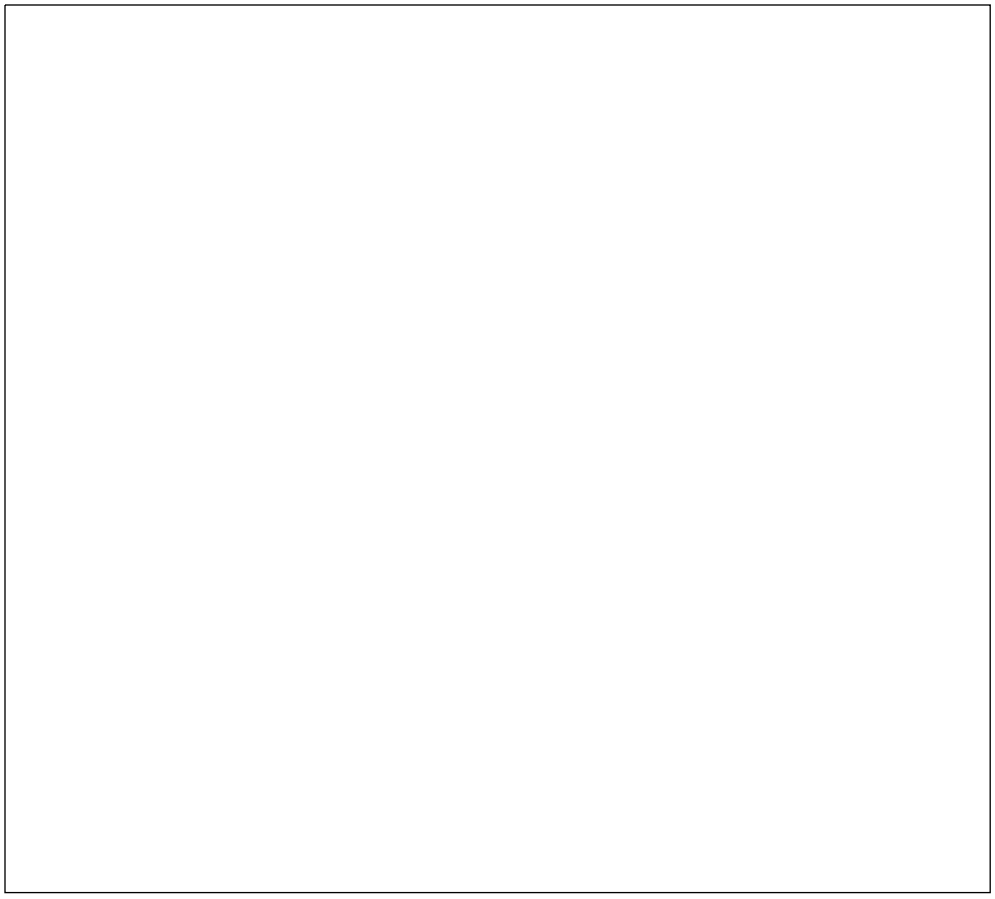


Figure 4 Caspases 3/7 are activated following MERS-CoV infection of primary human lung MVE but not primary lung FB. A-D. Donor matched MVE and FB were plated and mock-infected or infected with UV-inactivated or wild type MERS-CoV and at 24 and 48 hours post infection caspase 3/7 activation or cell viability was determined according to manufacturer's instructions using the Apotox Triplex kit (each well was measured for both parameters). Uninfected cells were treated with staurosporin (8 uM MVE/10 uM FB) to determine the maximal amount of caspase 3/7 activation. Uninfected cells were treated with ionomycin (50 uM MVE/60 uM FB) to demonstrate loss of cell viability via non-apoptotic pathway. Results are graphed as relative light units and error bars indicate standard deviation from the mean. Statistical analysis performed in GraphPad determined by Manfield Whitney unpaired t test. **A-B**

Results from caspase 3/7 activation. **C-D.** Results from cell viability assay. Solid red bars- MVE 24 hour samples, open red bars- MVE 48 hour samples, solid blue bars- FB 24 hour samples, open blue bars- FB 48 hour samples. **** p=<0.0001, *** p= <0.0002, ns- not statistically significant.

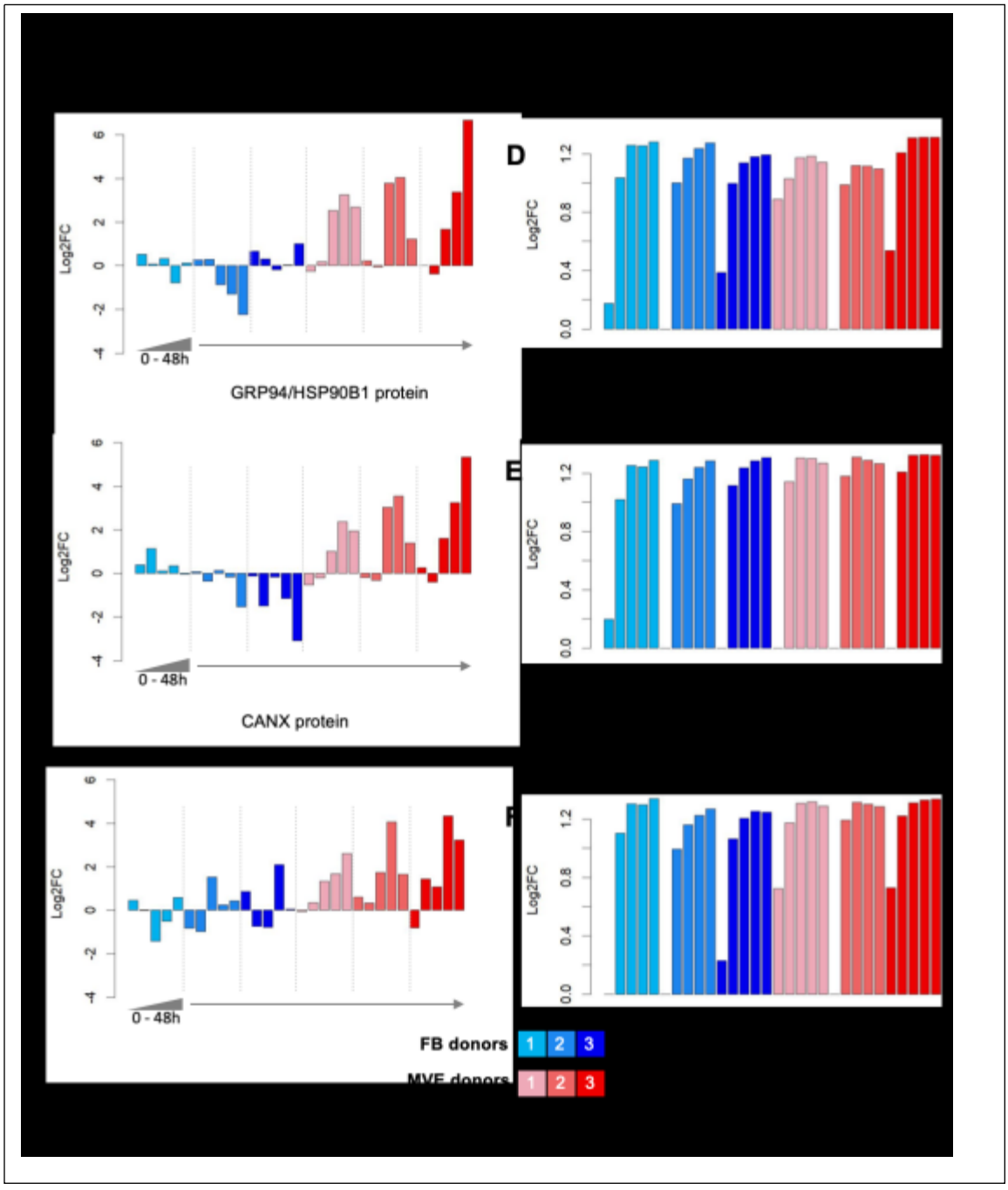


Figure 5 Protein markers suggest activation of unfolded protein response (UPR). A-C. Protein expression of markers of the unfolded protein response. Each figure shows the expression behavior of a UPR marker in FB (blues) and MVE (reds), with individual donors represented separately as individual color hues. For each donor, a time course of expression is shown that includes samples taken at 0, 12, 24, 36 and 48 hours post infection. Values are expressed as the log10 p-value of the change between the infection and control conditions, with sign assigned according to the direction of fold change. **D-F.** Viral protein expression. MERS-CoV spike, open reading frame 4a (ORF4a) and membrane protein abundances are represented as the ratio of each protein to the average abundance of all other proteins detected in each respective sample.

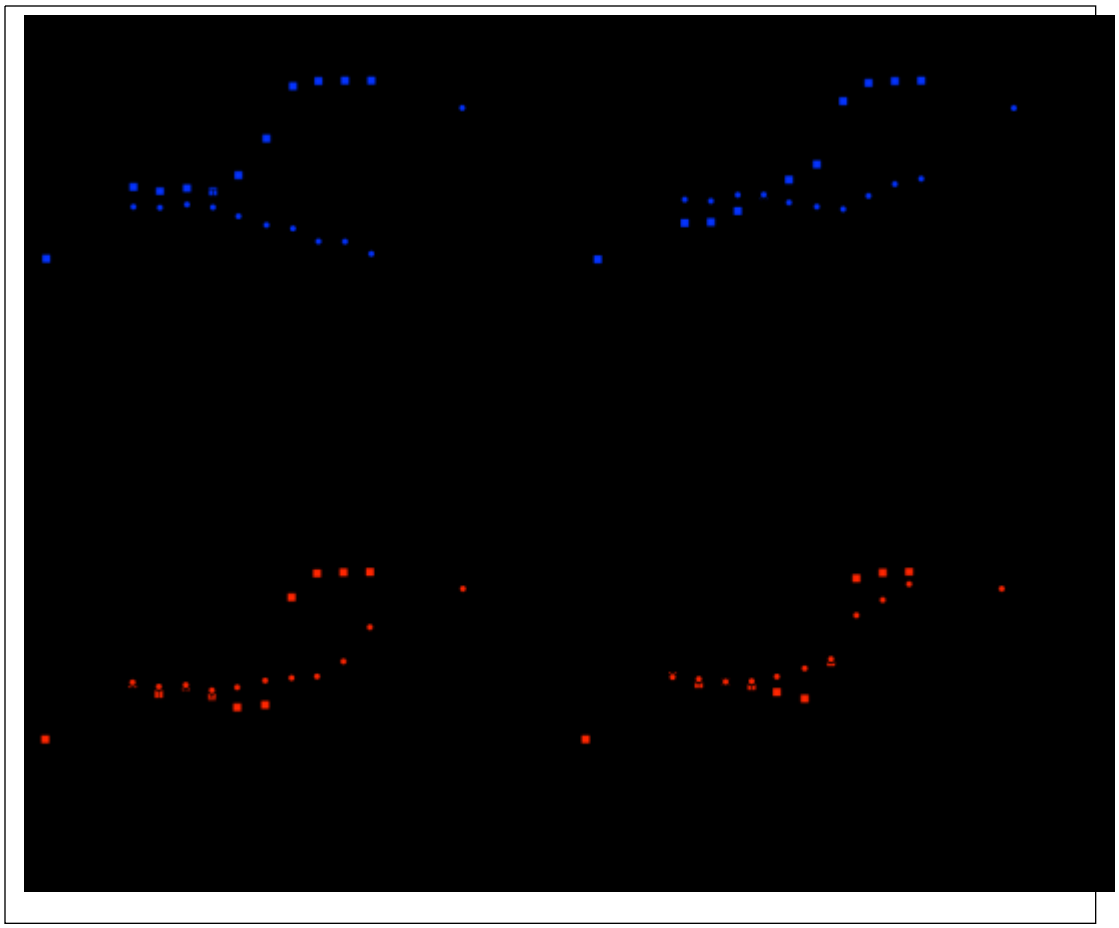


Figure 6 PERK inhibitor reduces MERS-CoV replication in infected primary human lung MVE and FB. A-D. Donor matched uninfected FB (circles, A, B) and MVE (circles, C, D) were treated with serial dilutions of PERK inhibitor (100 uM to 2 uM) and cell viability assessed at 24 (A, C) and 48 (B, D) hours post treatment using Promega's CellTiter Glo kit according to manufacturer's instructions. Each circle represents mean values from two experiments and are graphed as percent toxicity. Error bars indicate standard deviation from the mean. In parallel, the same donor matched FB (squares, A, B) and MVE (squares, C, D) were infected with MERS-nanoluc and simultaneously treated with the same serial dilutions of PERK inhibitor. Nanoluciferase expression was assayed at 24 (squares, A, C) and 48 (squares, B, D) hours post infection using Promega's NanoGlo kit according to manufacturer's instructions. Control wells were either treated with drug diluent and UV-inactivated virus or infected with MERS-nanoluc and treated with only drug diluent. Each square represents mean values from two experiments and are graphed as percent inhibition. Error bars indicate standard deviation from the mean. Blue squares- MERS-nanoluc infected FB treated with PERK inhibitor serial dilutions, blue circles- uninfected FB treated with PERK inhibitor serial dilutions, red squares- MERS-nanoluc infected MVE treated with PERK inhibitor serial dilutions, red circles- uninfected MVE treated with PERK inhibitor serial dilutions. PERK protein kinase R-like ER kinase, MVE primary human lung microvascular endothelial cell, FB primary human lung fibroblast, MERS-nanoluc MERS-CoV expressing nanoluciferase

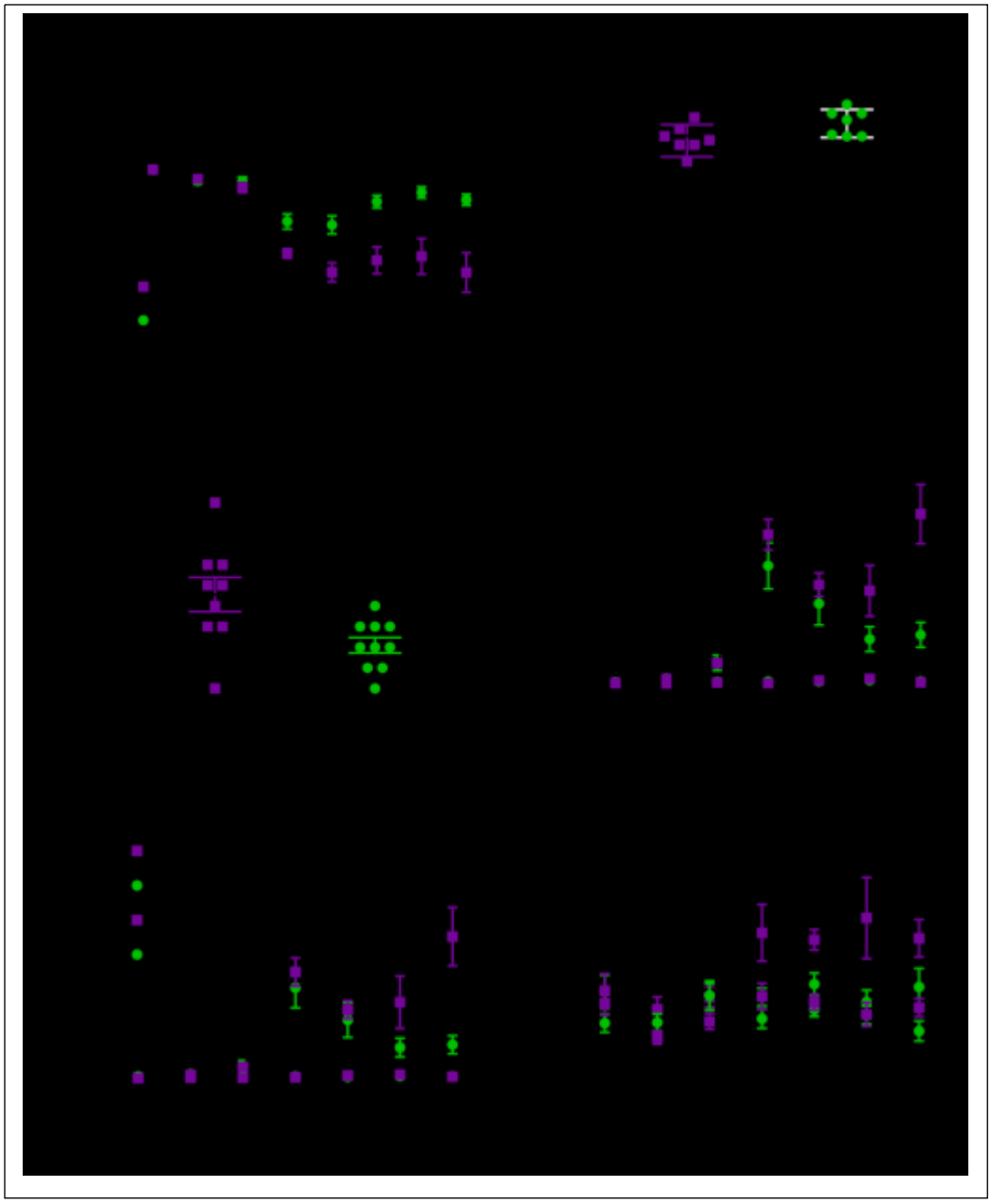


Figure 7 PERK inhibitor AMG44 treatment decreases MERS-CoV pathogenesis

A-F. 288/330+/+ mice were treated with PERK AMG'44 or sham control and infected with $5x10^4$ PFU of MERS-CoV MAm35c4 or PBS control. Weight loss was observed over the course of a seven day infection (A) and viral titers (B) and pulmonary hemorrhage was scored at the time of harvest (C). Daily respiratory function measurements (D-F) were taken via whole body

plethysmography. Error bars indicate standard error of the mean, # indicates a p value of < 0.1 and * indicates a p value of < 0.05.

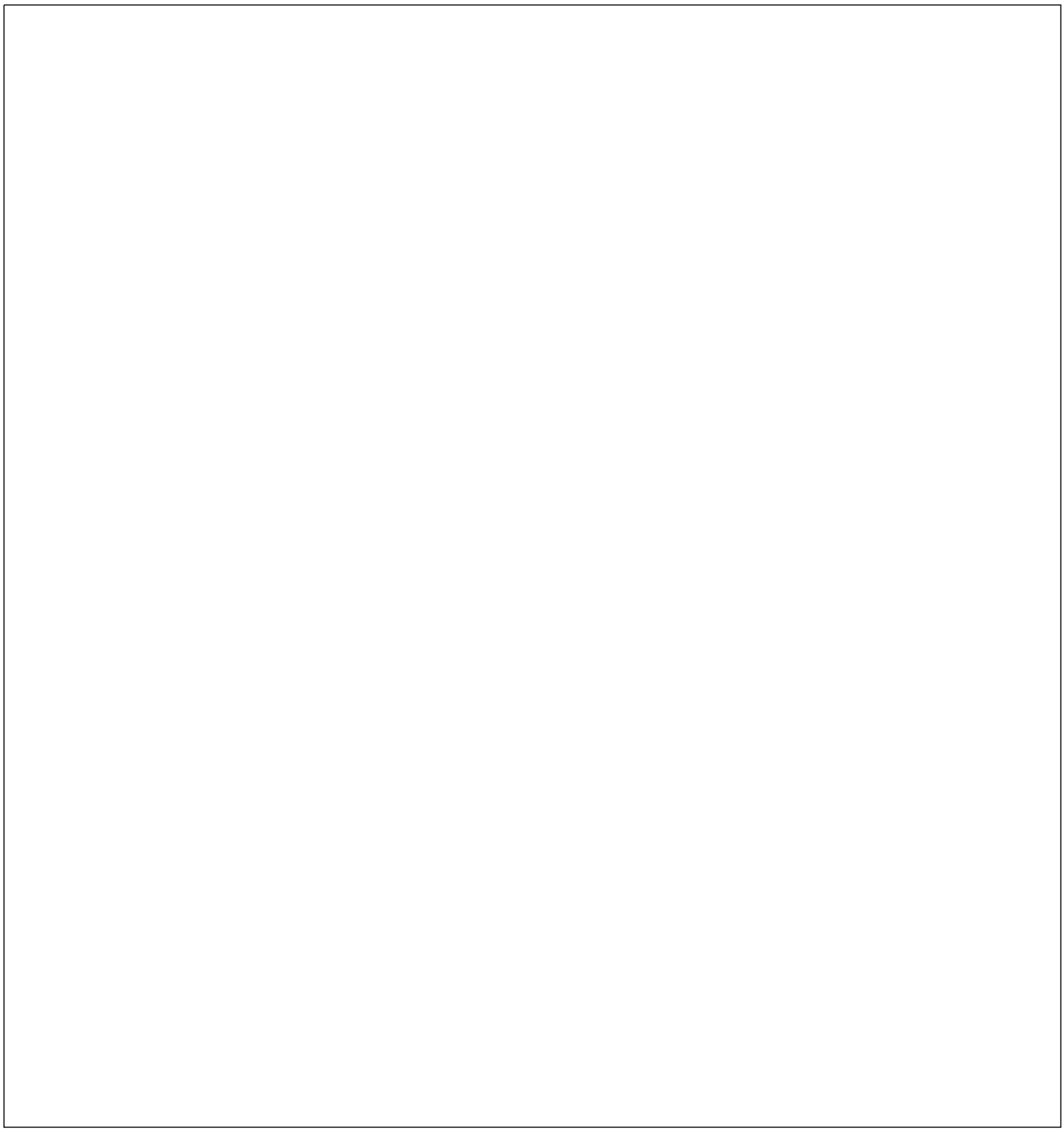


Figure 8 AMG44 reduces clinical signs of acute lung injury in MERS-CoV challenge model

A-E. The histological features of acute lung injury were blindly scored using the American Thoracic Society Lung Injury Scoring system by Matute-Bello, creating an aggregate score for: neutrophils in the alveolar and interstitial space, hyaline membranes, proteinaceous debris filling the air spaces, and alveolar septal thickening. **A-B.** Scoring for ALI and diffuse alveolar damage in male and female mice, respectively. Representative lung pathology for C) mock-infected, D) MERS-CoV infected and sham treated and E) MERS-CoV infected and AMG44 treated male mice at 7 days post infection. * indicates a p value of <0.001.

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Sat 3/21/2020 8:06:47 PM (UTC-07:00)
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Hi Amy, My comments, great paper. lets get it out soon! I pulled the figures so that I could send it. Pleasure to read. Hope your staying safe in Washington. Its going to be a terrible next 30 days. ralph

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Subject: Paper is too big to send

Hugh is working on breaking it up and sending it again.

Thank you, Amy

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Sun 3/22/2020 5:44:07 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Paper is too big to send

I take naps in the middle of the day

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Saturday, March 21, 2020 11:07 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Subject: Re: Paper is too big to send

Thank you very much. Sorry to see you were up so late. I will get this out to everyone ASAP.

Get Outlook for iOS

From: Baric, Ralph S <rbaric@email.unc.edu>
Sent: Saturday, March 21, 2020 7:39:46 PM
To: Sims, Amy C <amy.sims@pnnl.gov>; Sheahan, Timothy Patrick <sheahan@email.unc.edu>
Subject: RE: Paper is too big to send

Hi Amy, My comments, great paper. lets get it out soon! I pulled the figures so that I could send it. Pleasure to read. Hope your staying safe in Washington. Its going to be a terrible next 30 days. ralph

---

From: Sims, Amy C <amy.sims@pnnl.gov>
Sent: Friday, March 20, 2020 5:39 PM
To: Sheahan, Timothy Patrick <sheahan@email.unc.edu>; Baric, Ralph S <rbaric@email.unc.edu>
Subject: Paper is too big to send

Hugh is working on breaking it up and sending it again.

Thank you, Amy

From: Baric, Ralph S[rbaric@email.unc.edu]
Sent: Mon 3/23/2020 9:40:15 AM (UTC-07:00)
To: Schughart, Klaus[Klaus.Schughart@helmholtz-hzi.de]
Cc: Sims, Amy C[amy.sims@pnnl.gov]
Subject: RE: Manuscript with HAE data - please give feed-back asap

Hi Klaus, Amy and I would be fine. I have no problem with this, especially if she doesn't. Ralph

---

From: Schughart, Klaus <Klaus.Schughart@helmholtz-hzi.de>
Sent: Monday, March 23, 2020 9:51 AM
To: Baric, Ralph S <rbaric@email.unc.edu>
Subject: Manuscript with HAE data - please give feed-back asap

Hi Ralph,
my colleagues here in Memphis prepared a manuscript on the expression changes of Ace2 in the BXD population that I did some time ago. I enclose the first draft that I received today and on which I am working.

We would like to include the HAE expression data that I had analyzed together with Amy some time ago. The data is publically accessible. So I think that we do not need to include everyone who participated generating it (Katze etc.). Rather, you and Amy should be sufficient – or? Amy helped me with the analysis and it's interpretation. The methods should be described in Amy's Calu3 paper (enclosed)?
What do you think? Any other opinions, thoughts?

Hope you are otherwise doing ok and do not get flooded too much with all this activities.

Please give me feed-back asap.
Best regards,
Klaus

Prof. Dr. Klaus Schughart
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University of Veterinary Medicine Hannover,
University of Tennessee Health Science Center
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Stellvertreter: MinDirig Rüdiger Eichel, Niedersächsisches Ministerium für Wissenschaft und Kultur
Geschäftsführung: Prof. Dr. Dirk Heinz; Silke Tannapfel
Gesellschaft mit beschränkter Haftung (GmbH)
Sitz der Gesellschaft: Braunschweig
Handelsregister: Amtsgericht Braunschweig, HRB 477

From: Sims, Amy C[amy.sims@pnnl.gov]
Sent: Mon 3/23/2020 9:43:04 AM (UTC-07:00)
To: Baric, Ralph S[rbaric@email.unc.edu]; Schughart, Klaus[Klaus.Schughart@helmholtz-hzi.de]
Subject: Re: Manuscript with HAE data - please give feed-back asap

Thank you, Klaus. That sounds great. I really appreciate it. I hope everyone is doing well in these crazy times. Best wishes, Amy

---

From: "Baric, Ralph S" <rbaric@email.unc.edu>
Date: Monday, March 23, 2020 at 9:40 AM
To: "Schughart, Klaus" <Klaus.Schughart@helmholtz-hzi.de>
Cc: "Sims, Amy C" <amy.sims@pnnl.gov>
Subject: RE: Manuscript with HAE data - please give feed-back asap

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Gesellschaft mit beschränkter Haftung (GmbH)
Sitz der Gesellschaft: Braunschweig
Handelsregister: Amtsgericht Braunschweig, HRB 477

From: Schughart, Klaus[Klaus.Schughart@helmholtz-hzi.de]
Sent: Mon 3/23/2020 10:17:41 AM (UTC-07:00)
To: Sims, Amy C[amy.sims@pnnl.gov]; Baric, Ralph S[rbaric@email.unc.edu]
Subject: AW: Manuscript with HAE data - please give feed-back asap

Great.
Will do like this. Expect a revised version some time at the end of the week.
Klaus

Von: Sims, Amy C <amy.sims@pnnl.gov>
Gesendet: Montag, 23. März 2020 17:43
An: Baric, Ralph S <rbaric@email.unc.edu>; Schughart, Klaus <Klaus.Schughart@helmholtz-hzi.de>
Betreff: Re: Manuscript with HAE data - please give feed-back asap

Thank you, Klaus. That sounds great. I really appreciate it. I hope everyone is doing well in these crazy times. Best wishes, Amy

---

From: "Baric, Ralph S" <rbaric@email.unc.edu>
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Geschäftsführung: Prof. Dr. Dirk Heinz; Silke Tannapfel
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