From: [redacted]
To: [redacted]
Cc: [redacted]; [redacted]
Subject: Re: Gyrfalcon - 17 AA Mutant Paper
Date: Monday, September 9, 2019 3:33:45 AM

Dear [redacted],
In principle, I am of the opinion that AC methods are freely available to all, and anyone can publish maps representing their HI data. Thus, there would be no need to wait for our bigger H5 map.

However, there are a few points to consider.
1. We have not published our H5 map yet, because we want to make absolutely sure that it is right. We have been beating on this map for years and are still beating on it to make sure even the odd things are correct (e.g. the close proximity of 2.3.4.4 with classical strains is being investigated by analysis of the mutations causing it). We have beaten seriously on the 2004 H3N2 map, and are doing it again now for H5. It would be painful if someone else points out major errors in the map later.
2. Previously, we have seen differences between our H5 map and yours. In principle, only one map can be "right". I am not sure if [redacted] has beaten up on the Wisconsin map enough to make sure that that map is fine and in line with the [redacted] map. Otherwise we might end up publishing 2 different maps, with - in part - the same authors, which I think would be undesirable?
3. What will be the main message of the 17AA paper and where do you intend publishing it? Strategy-wise we have not yet put our H5 map in just a small publication, as it has the potential to represent substantial scientific progress for a high impact paper. To achieve that, I think we do need additional data to spice it up, such as regression analysis to align molecular basis of the map computationally and experimentally and/or antigen design of central/peripheral vaccine candidate(s) and/or other data. So a strategic decision on publication of these maps also seems appropriate?

Other thoughts are welcome.

Kind regards
[redacted]

Op 4 sep. 2019, om 17:05 heeft [redacted] > het volgende geschreven:

Dear All,

In the interest of time, I didn't want to bring it up in today's call. You can let me know your opinion by email, and/or we can discuss it during our next call.

Thanks,

[redacted]

From: [redacted]
Sent: Tuesday, September 3, 2019 8:48 PM
To: [redacted]
[redacted];
<[redacted]
Subject: RE: Gyrfalcon - 17 AA Mutant Paper

Dear All,

We've now drafted a manuscript for Huihui's 17AA gyrfalcon mutants, and [redacted] has finalized the antigenic map (please see attached; the 17AA mutants are shown in brown; clade 2.3.4.4 viruses are shown in blue).
This is a minimal map which preserves the relative positions of major clades without disclosing more information about other H5 viruses than necessary.

- Is it okay to publish this map before the bigger H5 papers from [redacted] group (antigenic map of H5 clades) and from our group (antigenic map of H5 mutants including data from the Gates and BARDA projects)?
- Or would you be concerned that we are disclosing too much information about the antigenic locations of H5 clades before the bigger papers are being submitted?

Maybe we can discuss this briefly at the end of our call on Wednesday.

Thanks,

[redacted]

<Gyrfalcon-17AA-Minimal Map.PNG>

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: H2N2 manuscript
Date: Saturday, September 21, 2019 3:36:00 PM

Dear [redacted]

Please find attached a manuscript describing the data obtained with your H2N2 viruses. The first author [redacted] who needs an acceptance letter from a journal by this November. Otherwise, he needs to wait another whole year. So, we will be submitting this manuscript to Viruses.

Please change the manuscript as you see fit. We made an antigenic map using [redacted] website. But, obviously, we are not that familiar with this type of analysis. Therefore, I would very much appreciate your help to ensure the accuracy of the map.

Thank you in advance for your help.
[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: H2N2 manuscript
Date: Wednesday, September 25, 2019 5:57:11 AM

Dear [redacted]
Thank you for including me as an author on this very interesting manuscript. It reads very well and I have only minor comments.
I have reran the map on my own laptop (not the website) and get the same results as yours. See attached. So I have no doubts about the accuracy.
Let me know if I can do more.
Kind regards
[redacted]

> Op 21 sep. 2019, om 22:37 heeft [redacted]
> <[redacted] het volgende geschreven:
>
> Dear [redacted]
>
> Please find attached a manuscript describing the data obtained with your H2N2 viruses. The first author [redacted] who needs an acceptance letter from a journal by this November. Otherwise, he needs to wait another whole year. So, we will be submitting this manuscript to Viruses.
>
> Please change the manuscript as you see fit. We made an antigenic map using [redacted] website. But, obviously, we are not that familiar with this type of analysis. Therefore, I would very much appreciate your help to ensure the accuracy of the map.
>
> Thank you in advance for your help.
> [redacted]
>
> <Figures (Antigenic drift of H2N2)0921.pptx><Manuscript (Antigenic drift of H2N2)0921.docx><Tables (Antigenic drift of H2N2)0921.docx>

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: H2N2 manuscript
Date: Wednesday, September 25, 2019 7:04:00 AM

Dear [redacted]

Thank you for taking the time to review our manuscript.
We will incorporate your suggestions and submit it shortly.
Acknowledging the CRIP funding is important for the renewal!

Yes. [redacted] and I discussed this point and came to the same conclusion that humans are like ferrets in this case; humans were immunologically exposed to H2N2 viruses only once or twice. We will add a paragraph about this to the manuscript.

Best,
[redacted]

From: [redacted] <[redacted]
Sent: Wednesday, September 25, 2019 8:10 PM
To: [redacted] <[redacted]
Cc: [redacted]
Subject: Re: H2N2 manuscript

By the way, it is amazing to see that the positions of the 4 antigens in the maps made with ferret and human sera come out so similar. This has been incredibly hard to prove for other influenza A virus subtypes (H1N1, H3N2, see references below) because humans undergo multiple re-infections over long time-spans. For H2N2 this is less of a problem (in just 10 years, humans are less likely to have 2 infections). Great to see, and perhaps worthwhile to mention ….
[redacted]

See:
Antigenic Maps of Influenza A(H3N2) Produced With Human Antisera Obtained After Primary Infection.
Fonville JM, Fraaij PL, de Mutsert G, Wilks SH, van Beek R, Fouchier RA, Rimmelzwaan GF.
J Infect Dis. 2016 Jan 1;213(1):31-8.

And:
Identification of amino acid substitutions supporting antigenic change of influenza A(H1N1)pdm09 viruses.
Koel BF, Mögling R, Chutinimitkul S, Fraaij PL, Burke DF, van der Vliet S, de Wit E, Bestebroer TM, Rimmelzwaan GF, Osterhaus AD, Smith DJ, Fouchier RA, de Graaf M.
J Virol. 2015 Apr;89(7):3763-75.

Op 25 sep. 2019, om 12:56 heeft [redacted] <[redacted]
het volgende geschreven:

Dear [redacted]
Thank you for including me as an author on this very interesting manuscript. It reads very well and I have only minor comments.
I have reran the map on my own laptop (not the website) and get the same results as yours. See attached. So I have no doubts about the accuracy.
Let me know if I can do more.
Kind regards
[redacted]

> Op 21 sep. 2019, om 22:37 heeft [redacted]
> <[redacted] het volgende geschreven:
>
> Dear [redacted]
>
> Please find attached a manuscript describing the data obtained with your H2N2 viruses. The first author [redacted] who needs an acceptance letter from a journal by this November. Otherwise, he needs to wait another whole year. So, we will be submitting this manuscript to Viruses.
>
> Please change the manuscript as you see fit. We made an antigenic map using [redacted] website. But, obviously, we are not that familiar with this type of analysis. Therefore, I would very much appreciate your help to ensure the accuracy of the map.
>
> Thank you in advance for your help.
> [redacted]
>
> <Figures (Antigenic drift of H2N2)0921.pptx><Manuscript (Antigenic drift of H2N2)0921.docx><Tables (Antigenic drift of H2N2)0921.docx>

<Manuscript (Antigenic drift of H2N2)0921 rf.docx><H2N2map.pdf>
<H2N2map.ps>

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: H2N2 manuscript
Date: Tuesday, October 1, 2019 2:58:00 PM
Attachments: H2N2 final version Manuscript.pdf

Dear [redacted]

Please find attached the final version of the H2N2 manuscript.

In both Fonville et al. (JID 2015) and Koel et al. (JV 2015), the human sera used were from infants. So, we discussed the results in that context.

Best,
[redacted]

From: [redacted] <[redacted]
Sent: Wednesday, September 25, 2019 8:10 PM
To: [redacted] <[redacted]
Cc: [redacted]
Subject: Re: H2N2 manuscript

By the way, it is amazing to see that the positions of the 4 antigens in the maps made with ferret and human sera come out so similar. This has been incredibly hard to prove for other influenza A virus subtypes (H1N1, H3N2, see references below) because humans undergo multiple re-infections over long time-spans. For H2N2 this is less of a problem (in just 10 years, humans are less likely to have 2 infections). Great to see, and perhaps worthwhile to mention ….
[redacted]

See:
Antigenic Maps of Influenza A(H3N2) Produced With Human Antisera Obtained After Primary Infection.
Fonville JM, Fraaij PL, de Mutsert G, Wilks SH, van Beek R, Fouchier RA, Rimmelzwaan GF.
J Infect Dis. 2016 Jan 1;213(1):31-8.

And:
Identification of amino acid substitutions supporting antigenic change of influenza A(H1N1)pdm09 viruses.
Koel BF, Mögling R, Chutinimitkul S, Fraaij PL, Burke DF, van der Vliet S, de Wit E, Bestebroer TM, Rimmelzwaan GF, Osterhaus AD, Smith DJ, Fouchier RA, de Graaf M.
J Virol. 2015 Apr;89(7):3763-75.

Op 25 sep. 2019, om 12:56 heeft [redacted] <[redacted]
het volgende geschreven:

Dear [redacted]
Thank you for including me as an author on this very interesting manuscript. It reads very well and I have only minor comments.
I have reran the map on my own laptop (not the website) and get the same results as yours. See attached. So I have no doubts about the accuracy.
Let me know if I can do more.
Kind regards
[redacted]

> Op 21 sep. 2019, om 22:37 heeft [redacted]
> <[redacted] het volgende geschreven:
>
> Dear [redacted]
>
> Please find attached a manuscript describing the data obtained with your H2N2 viruses. The first author [redacted] who needs an acceptance letter from a journal by this November. Otherwise, he needs to wait another whole year. So, we will be submitting this manuscript to Viruses.
>
> Please change the manuscript as you see fit. We made an antigenic map using [redacted] website. But, obviously, we are not that familiar with this type of analysis. Therefore, I would very much appreciate your help to ensure the accuracy of the map.
>
> Thank you in advance for your help.
> [redacted]
>
> <Figures (Antigenic drift of H2N2)0921.pptx><Manuscript (Antigenic drift of H2N2)0921.docx><Tables (Antigenic drift of H2N2)0921.docx>

<Manuscript (Antigenic drift of H2N2)0921 rf.docx><H2N2map.pdf>
<H2N2map.ps>

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Revised H2N2 manuscript
Date: Thursday, October 17, 2019 4:14:00 PM
Attachments: Revised-manuscript(antigenic drift of H2N2).docx
Response letter(antigenic drift of H2N2).docx

Dear [redacted]

Please find attached our response letter to the reviewers' comments and the revised manuscript.
Please let me know if you have any questions.
We will submit it on Oct 21 (Mon).

[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: Revised H2N2 manuscript
Date: Friday, October 18, 2019 1:38:17 AM

Dear [redacted]
Looks good to me. Attached few minor points in your rebuttal.
[redacted]

> Op 17 okt. 2019, om 23:15 heeft [redacted] < [redacted] het volgende geschreven:
>
> Dear [redacted]
>
> Please find attached our response letter to the reviewers' comments and the revised manuscript.
> Please let me know if you have any questions.
> We will submit it on Oct 21 (Mon).
>
> [redacted]
> <Revised-manuscript(antigenic drift of H2N2).docx><Response letter(antigenic drift of H2N2).docx>

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR Planning
Date: Wednesday, November 13, 2019 5:25:00 AM
Attachments: image001.png
image002.png
image003.png

I can join if it is late afternoon ET. But, if not, please do not worry about me. Please fill me in later.

[redacted]

From: [redacted]
Sent: Wednesday, November 13, 2019 8:24 PM
To: [redacted]
Cc: [redacted]
Subject: Re: CEIRR Planning

Agree [redacted]

Does anyone want to be on the call with [redacted], if so let me know your availability for 9–5 [redacted]–time please and I'll see if she can do one of those times. But if she can't then I'll ask her for any time so we can hopefully get some clarity today.

[redacted]

On Wed, Nov 13, 2019 at 11:21 AM [redacted] wrote:

> Yes, splitting is an option into pandemic work, basic research on seasonal flu and seasonal work towards clinical application. Hopefully, pandemic work will be funded again via BARDA, but this is uncertain. Hopefully, basic seasonal work will be funded through CEIRR but probably not everything, and this will be decided by [redacted], not us. For seasonal work towards the clinic, CEIRR will definitely not have sufficient funds. Given this, and in particular the uncertainties, it would be good to first discuss with [redacted] what they are thinking ….
>
> Yours sincerely,
>
> [redacted]
>
> [redacted]
>
> [redacted]
>
> **Van:** [redacted]
> **Verzonden:** woensdag 13 november 2019 12:10
> **Aan:** [redacted]
> **CC:** [redacted]
> **Onderwerp:** Re: CEIRR Planning

I agree we could not expect our seasonal work to be fully funded from the base CEIRR structure. I will see if I can talk with [redacted] today about how she sees things, given that much of what we we marked up in the Attachment 4 is directly related to our work.

My email yesterday was about the split you had suggested last week [redacted] when I was at EMC about proposing the more research-oriented, and extension, aspects of the for CEIRR call.

[redacted]

On Wed, Nov 13, 2019 at 7:19 AM [redacted] wrote:

> I agree that approaching [redacted] with this issue would be logical. Best to come from [redacted], also on behalf of Wisconsin and [redacted]
> Chances are close to zero that [redacted] would reserve sufficient budget for our work to continue at the current pace, if it all.
>
> Yours sincerely,
>
> [redacted]

Van: [redacted]
Verzonden: woensdag 13 november 2019 02:26
Aan: [redacted]
CC: [redacted]
Onderwerp: RE: CEIRR Planning

Dear [redacted] and [redacted]

Actually, my point is not about the actual science. Rather, how our BARDA/NIH seasonal virus project will be funded. [redacted] mentioned that the total "base" budget will be lower than the current funding period. Our BARDA/NIH seasonal virus project was added as an option to the "base" budget during the current funding period. Since the base budget is lower than what we currently have, there is no way we can include the BARDA/NIH seasonal virus project in the renewal proposal. Therefore, we need [redacted] input about how the BARDA/NIH seasonal virus project will be funded.

[redacted]

From: [redacted]
Sent: Tuesday, November 12, 2019 11:19 PM
To: [redacted]
Cc: [redacted]

[redacted]

Subject: Re: CEIRR Planning

Hi [redacted]

All we know from [redacted] is what she said in the call we were all on, that once we send her the cost to completion that they would figure out how to fund it.

I was in [redacted] on Tuesday last week, and [redacted] and I were discussing CEIRR, how we might split things between CEIRR and whatever NIH would come up with for our seasonal trials. Clearly there are numerous line items in the CEIRR attachment 4 that relate directly to the joint work of our three laboratories. In particular sections 5 A&B. Would you be interested in connecting on those in our responses to [redacted] as it relates to our joint work with [redacted] I asked [redacted] about this and he is positive about our three labs continuing to collaborate in this way.

[redacted] figured that there would likely be parts of what we are doing for the clinical trial that are more research-oriented, and would be less likely to be funded for just an H3 trial, and also work on H1 and the Bs. And also of course extensions of what we are doing.

I attach the "Attachment 4" from the CEIRRs call, marked up for the parts [redacted] could contribute to. In green is our core-active work, in blue are things that we can also do but are not pursuing will full intensity. Most relevant is the marking in section 5 parts A and B. The marking in section 2 is for the things we would need from cohorts, and that we currently have collaborations on in various cohorts.

[redacted]

On Mon, Nov 11, 2019 at 12:53 AM [redacted] wrote:

> [redacted] and [redacted]
>
> [redacted] and I had a call earlier today with [redacted] about the recently funded CIVIC contract, which we are part of.
>
> At the end of the call, [redacted] mentioned that he has started to plan for the CEIRR application.
> After I mentioned that [redacted] and I have been brainstorming about protects, [redacted] invited us to send these ideas, which may be a great opportunity to have some of these ideas included in the application.
> This brings up the question about future funding of the current 'seasonal' BARDA/CEIRS projects:
>
> - Would they be funded through CEIRR, with [redacted] and [redacted] and our group as subcontractors?
> - Or would they be funded through a different mechanism, outside of the basic CEIRR contract?
>
> [redacted] have you had a chance to discuss this with [redacted]? We should send our suggestions to [redacted] by the middle of the week.
>
> Please let us know if we should discuss this in more detail.
>
> Thanks,
>
> [redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR Planning
Date: Wednesday, November 13, 2019 9:51:33 AM
Attachments: image001.png
image002.png
image003.png

Yes, that works for me.

Yours sincerely,

[redacted]

Van: [redacted] >
Verzonden: woensdag 13 november 2019 16:47
Aan: [redacted]
CC: [redacted]
Onderwerp: Re: CEIRR Planning

[redacted], as [redacted] initially indicated he can't do until late afternoon DC time, do you think it would be OK if you [redacted] and I had a preliminary call say in 30 mins, so we can think a bit more for perhaps another call later or tomorrow? 5:15pm NL. 10:15am Madison.

[redacted] could that work for you?

[redacted]

On Wed, Nov 13, 2019 at 3:41 PM [redacted] > wrote:

> My preferred times are from 5 am – 9 pm Central Time. Since this is important, I can be available during the remaining hours as well.
>
> [redacted]
>
> **From:** [redacted]
> **Sent:** Wednesday, November 13, 2019 9:32 AM
> **To:** [redacted]
> **Cc:** [redacted]
> **Subject:** Re: CEIRR Planning
>
> Spoke with [redacted]. Would be good if we had a call to discuss.
>
> [redacted] I see you are available. [redacted] I see you are not for another maybe 6 hours. But you'd also said that you'd wanted to get something to [redacted] by mid-week. [redacted] what is your availability?

[redacted]

On Wed, Nov 13, 2019 at 11:27 AM [redacted] <[redacted]> wrote:

> No absolute need for me to be on the call, but if you wish I am available after 3 pm NL time.
>
> Yours sincerely,
>
> [redacted]
>
> [redacted]
>
> [redacted]
>
> **Van:** [redacted]>
> **Verzonden:** woensdag 13 november 2019 12:24
> **Aan:** [redacted] <[redacted]>
> **CC:** [redacted] <[redacted]> [redacted]
> **Onderwerp:** Re: CEIRR Planning
>
> Agree [redacted]
>
> Does anyone want to be on the call with [redacted], if so let me know your availability for 9-5 [redacted]-time please and I'll see if she can do one of those times. But if she can't then I'll ask her for any time so we can hopefully get some clarity today.
>
> [redacted]
>
> On Wed, Nov 13, 2019 at 11:21 AM [redacted] <[redacted]> wrote:
>
> > Yes, splitting is an option into pandemic work, basic research on seasonal flu and seasonal work towards clinical application. Hopefully, pandemic work will be funded again via BARDA, but this is uncertain. Hopefully, basic seasonal work will be funded through CEIRR but probably not everything, and this will be decided by [redacted] not us. For seasonal work towards the clinic, CEIRR will definitely not have sufficient funds. Given this, and in particular the uncertainties, it would be good to first discuss with [redacted] they are thinking ….
> >
> > Yours sincerely,
> >
> > [redacted]
> >
> > [redacted]
> >
> > [redacted]

[redacted]

Van: [redacted]
Verzonden: woensdag 13 november 2019 12:10
Aan: [redacted] <[redacted]
CC: [redacted] <[redacted] [redacted]
Onderwerp: Re: CEIRR Planning

I agree we could not expect our seasonal work to be fully funded from the base CEIRR structure. I will see if I can talk with [redacted] today about how she sees things, given that much of what we we marked up in the Attachment 4 is directly related to our work.

My email yesterday was about the split you had suggested last week [redacted] when I was at EMC about proposing the more research-oriented, and extension, aspects of the for CEIRR call.

[redacted]

On Wed, Nov 13, 2019 at 7:19 AM [redacted] <[redacted] wrote:

> I agree that approaching [redacted] with this issue would be logical. Best to come from [redacted], also on behalf of Wisconsin and [redacted]
> Chances are close to zero that [redacted] would reserve sufficient budget for our work to continue at the current pace, if it all.
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> Yours sincerely,
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> [redacted]
>
> [redacted]
>
> [redacted]
>
> **Van:** [redacted] <[redacted]
> **Verzonden:** woensdag 13 november 2019 02:26
> **Aan:** [redacted] >
> **CC:** [redacted] <[redacted] [redacted]
> **Onderwerp:** RE: CEIRR Planning
>
> Dear [redacted] and [redacted]
>
> Actually, my point is not about the actual science. Rather, how our BARDA/NIH seasonal virus project will be funded. [redacted] mentioned that the total "base" budget will be lower than the current funding period. Our BARDA/NIH seasonal virus project was added as an option to the "base" budget during the current funding period. Since the base budget is lower than what we currently have, there is no

way we can include the BARDA/NIH seasonal virus project in the renewal proposal. Therefore, we need [redacted]s input about how the BARDA/NIH seasonal virus project will be funded.

[redacted]

From: [redacted]
Sent: Tuesday, November 12, 2019 11:19 PM
To: [redacted] <[redacted]
Cc: [redacted] <[redacted] [redacted]
Subject: Re: CEIRR Planning

Hi [redacted]

All we know from [redacted] is what she said in the call we were all on, that once we send her the cost to completion that they would figure out how to fund it.

I was in [redacted] on Tuesday last week, and [redacted] and I were discussing CEIRR, how we might split things between CEIRR and whatever NIH would come up with for our seasonal trials. Clearly there are numerous line items in the CEIRR attachment 4 that relate directly to the joint work of our three laboratories. In particular sections 5 A&B. Would you be interested in connecting on those in our responses to [redacted] as it relates to our joint work with [redacted] I asked [redacted] about this and he is positive about our three labs continuing to collaborate in this way.

[redacted] figured that there would likely be parts of what we are doing for the clinical trial that are more research-oriented, and would be less likely to be funded for just an H3 trial, and also work on H1 and the Bs. And also of course extensions of what we are doing.

I attach the "Attachment 4" from the CEIRRs call, marked up for the parts [redacted] could contribute to. In green is our core-active work, in blue are things that we can also do but are not pursuing will full intensity. Most relevant is the marking in section 5 parts A and B. The marking in section 2 is for the things we would need from cohorts, and that we currently have collaborations on in various cohorts.

[redacted]

On Mon, Nov 11, 2019 at 12:53 AM [redacted] <[redacted] wrote:

> [redacted] and [redacted]
>
> [redacted] and I had a call earlier today with [redacted] about the recently funded CIVIC contract, which we are part of.
>
> At the end of the call, [redacted] mentioned that he has started to plan for the CEIRR application.
> After I mentioned that [redacted] and I have been brainstorming about protects, [redacted] invited us to send these ideas, which may be a great opportunity to have some of these ideas included in the application.
> This brings up the question about future funding of the current 'seasonal' BARDA/CEIRS projects:
>
> - Would they be funded through CEIRR, with [redacted] and [redacted] and our group as subcontractors?
> - Or would they be funded through a different mechanism, outside of the basic CEIRR contract?
>
> [redacted] have you had a chance to discuss this with [redacted]? We should send our suggestions to [redacted] by the middle of the week.
>
> Please let us know if we should discuss this in more detail.
>
> Thanks,
>
> [redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]

Subject: RE: Time to selecting CVVs
Date: Wednesday, November 13, 2019 4:07:00 PM

I will talk to [redacted] at the NIID; [redacted], who does all of the pathological analysis of our work now.
I think asking [redacted] is a great idea; [redacted] is a pathologist himself. I could talk to him. But, it may be a good idea to wait for BARDA's input first.

I agree with [redacted] about gravity. But, it appears to be a requirement in a WHO document for a CVV; [redacted] told me so.

[redacted]

From: [redacted] <[redacted]
Sent: Thursday, November 14, 2019 6:49 AM
To: [redacted]
Cc: [redacted] <[redacted] [redacted]
[redacted]
Subject: Re: Time to selecting CVVs

Well, I am surprised if any scientist would judge that these experiments in ferrets are really necessary. I have made the joke before: this is like testing everyday whether gravity exists before you step out of bed, out of fears of falling upwards. We know these PR8 strains without MBCS in HA are avirulent.

I will ask [redacted] was is needed and what would be the comparator.

[redacted]

> Op 13 nov. 2019, om 22:30 heeft [redacted]> het volgende geschreven:
>
> Also, do any of you think it would be worth a call with [redacted] to check if we would need to do the ferret pathogenicity testing? If it is worth it it does make more sense I think for either [redacted] or [redacted] to make the call.
>
> Or we could wait for BARDA's opinion first--it would likely be too late to reach [redacted] before the call tomorrow anyhow.

[redacted]

On Wed, Nov 13, 2019 at 9:27 PM [redacted] wrote:

> Can you check with NIID [redacted]
>
> I will check with [redacted].
>
> [redacted]
>
> On Wed, Nov 13, 2019 at 9:25 PM [redacted] <[redacted]> wrote:
>
> > Well, if NIBC is slow we should not use NIBSC. And if we think [redacted] we should not use them neither. Can we call NIID and St Jude for their estimates?
> > [redacted]
> >
> > Op 13 nov. 2019, om 20:37 heeft [redacted] <[redacted]> het volgende geschreven:
> >
> > [redacted],
> >
> > >If all labs would need a year total, then we could contract different labs for each of the CVVs to speed up the time. Do you agree that this would be OK, and would not introduce any variation we would need to be concerned about?
> >
> > Actually, contracting with different labs would be better. As I mentioned, the CDC tested one of our high-yield viruses in ferrets and they determined it to be neurotropic, which we could not reproduce in either of my labs (Tokyo and Madison) with 36 ferrets.
> >
> > >Seems to me it could be helpful for the discussion tomorrow re timeline that we send this to BARDA and present it in the call. Do you agree? And if so, I'm happy to present, or for one of you to present. Which do you prefer?
> >
> > I think it is a good idea for you to present the Gantt.

[redacted]

From: [redacted] >
Sent: Thursday, November 14, 2019 4:21 AM
To: [redacted]
Cc: [redacted] < [redacted]
[redacted]
Subject: Re: Time to selecting CVVs

Attached a Gantt based on the info we have from you and [redacted]. Do you agree with the timelines?

First slide is for one CVV. Second slide is for three. [redacted] sent a follow up email today saying that the ferret testing might take sufficiently longer than they'd need a year total for 3 CVVs based. The longer time being for any facility shutdowns, needing to do other CVVs, etc, I mentioned yesterday.

If all labs would need a year total, then we could contract different labs for each of the CVVs to speed up the time. Do you agree that this would be OK, and would not introduce any variation we would need to be concerned about?

Seems to me it could be helpful for the discussion tomorrow re timeline that we send this to BARDA and present it in the call. Do you agree? And if so, I'm happy to present, or for one of you to present. Which do you prefer?

[redacted]

On Wed, Nov 13, 2019 at 10:20 AM [redacted] wrote:

> Thanks [redacted]
>
> We'll put together a Gantt and send it back for your approval before sending on to BARDA.
>
> [redacted]
>
> On Wed, Nov 13, 2019 at 10:16 AM M.J. [redacted] wrote:

Hi [redacted] et al
On our side, we'll have serology data of vaccinated ferrets (6 ferrets per groups) with the [redacted], Anhui wt and Sichuan in about three weeks. We'd like to wait for this data before we can make our final call.
Cheers
[redacted]

From: [redacted]>
Date: Tuesday, 12 November 2019 at 18:41
To: "[redacted]
<[redacted]
<[redacted]
Subject: Re: Time to selecting CVVs

I spoke with [redacted] today re what has to be done to make CVVs, and timelines.

They would make CVVs synthetically. With HA and NA from our specification, and the rest PR8.

Once they have the DNA in hand, they say 1 month to make the virus. Then 1.5m for safety testing in ferrets.

If they were making three CVVs, that would be say 2 weeks for the HA and NA DNA synthesis, 1 month for making the first virus, then 3x1.5m for the ferret safety testing--the making of the remaining viruses would happen in parallel with the ferret safety testing of the virus earlier in the pipeline, but the ferret work needs to be done serially if all done at NIBSC. So for 3 CVVs 0.5+1+(3x1.5)=6m. Then 2 weeks to do a 2-way test to check little enough no antigenic change.

Their containment facility closes for inspection every 6 months, for a couple of weeks, longer if something needs to be fixed. So we also might have to factor that in. And if they are required to make a CVV for the WHO during that time, then that would also likely take priority at NIBSC.

[redacted] says that St Jude, CDC, and NIID also routinely make CVVs that meet the same standards.

I asked what is being tested in the ferret safety test, it is lower pathogenicity than the WT. As our CVVs are variant to their root WT, we would apparently need someone to agree that the comparator could be [redacted], and [redacted] is not sure who could do that, perhaps the regulatory authority in the country the vaccine would be made, but was not sure. He also mentioned that the chicken path test is now no longer required in the US, something [redacted] was substantially involved in apparently. [redacted] suggested we talk with [redacted] about what our comparator would have to be. I wonder if we would need a ferret safety test at all, as your labs have perhaps already done something like this? [redacted] did not know. Perhaps it makes sense that one of you call [redacted] to check because if [redacted] starts asking questions about what you have already done, I likely will not know in enough detail. or perhaps you already know without calling?

BARDAs pushing us to have our final choices for CVVs is related they tell us to us getting the CVVs made by the end of the contract. That there is an option fo that in the current contract. And that they will be in a stronger position to argue for the follow on contract if we have the CVVs from this contract already.

I suggest we put together a preliminary Gantt for presenting on Thursday for us getting to CVVs that uses the timing from [redacted] above, and has your labs timings for getting to our choices. Like we did with the seasonal Gantts, we might need to do for a range of dates. Can you give your estimates please of the steps, and what can be done in parallel. Either already in Gantt format, or in text, and [redacted] will make into a Gantt together with the info from [redacted]. If we can have this for our BARDA/NIH call on Thursday, then hopefully that will be helpful. What do you think?

I also asked [redacted] about reagents for potency testing, he figured that for the clincal trials we would likely be able to get away with something inhouse by the manufacturer. But that we should check with BARDA for what they needed that might ease the way into bridging studies for potential stockpiling.

[redacted]

On Mon, Nov 11, 2019 at 6:10 PM [redacted] wrote:

> All
>
> [redacted] has let [redacted] know that BARDA would like to have our CVV selections. Clearly we are not ready to selected all.
>
> This a heads up to expect the question (again) this month.
>
> [redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Fwd: CVV safety testing
Date: Friday, November 15, 2019 12:48:10 AM
Attachments: Chen el al rgH5N1 vaccine strains risk and safety IORV 2019 on line.pdf

---

Here's [redacted] response.
[redacted]

Begin doorgestuurd bericht:

Van: [redacted]>
Onderwerp: RE: CVV safety testing
Datum: 15 november 2019 om 03:07:52 CET
Aan: "[redacted] <[redacted]

[redacted]

The CVV you describe would meet the definition of LPAI without chicken testing. But to clarify, I am not in the regulatory side of USDA or CDC.
For USA generated isolates, the paperwork would be submitted to CDC/APHIS Select Agent program for determination of Low Pathogenicity based on in vitro cell culture requiring trypsin to cleave the HA, deep sequencing to confirm only the low virulent cleavage site is present and 6 internal protein gene segments from PR8 or similar human influenza vaccine strain. I am not aware of any ferret testing being require.
For none USA origin CVVs, I am not sure of the regulatory process for import and if a declaration by the Netherlands government authorities as to the CVV are LP would be adequate. Let me check with some contacts and get back to you.

Not sure if you have seen this paper in IORV about the change in USA testing requirement.

Best wishes

[redacted]

-----Original Message-----

From: [redacted] <[redacted]
Sent: Wednesday, November 13, 2019 5:02 PM
To: [redacted]
Subject: CVV safety testing

Hi [redacted],

How's life and science in [redacted]?

You may have heard that the labs of [redacted], [redacted] and mine are working on pre-pandemic H5 candidate vaccine viruses that should protect against infection with all H5s detected globally. BARDA wants to move them to clinical study. My question to you is what would need to be done in terms of safety testing? Our CVVs are 6:2 recombinants based on PR8, with wildtype HPAI NA, and a mutated cross-reactive/immunogenic H5 HA from which the MBCS was removed.

I have been told that chicken safety testing is no longer required with these viruses. Is that correct? And what needs to be done in ferrets? We have inoculated ferrets intranasally with these viruses to raise antisera and have tested experimental vaccines with boosting with live virus without any symptoms of disease.

I always joke that the continued re-testing of the safety of PR8 viruses with HA from which the MBCS is removed is like re-testing everyday whether gravity exists before you step out of bed, out of fears of falling upwards. But that is just me, and I am not a regulatory authority. So perhaps you know what would be required?

Thanks for your advice,
With kind regards,
[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: CVV safety testing
Date: Friday, November 15, 2019 4:23:00 AM

[redacted] and [redacted]

I talked to [redacted] regarding the possibility of the NIID, Japan doing ferret testing of CVVs.
He said he can except during their BSL-3 shutdown for 2 months every year.
He suggested we get an OK from [redacted]

So, if we decide to ask the NIID, we can go this route.

Best,
[redacted]

From: [redacted]
Sent: Friday, November 15, 2019 5:35 PM
To: [redacted]
Cc: [redacted]
Subject: Re: CVV safety testing

Yes I agree, asking both is good.

And yes [redacted] did say CDC might do it for free.

[redacted]

On Fri, Nov 15, 2019 at 7:48 AM [redacted] wrote:

> We need to ask both anyway about timelines if we would make CVVs through them?
> [redacted] said that CDC might do it for free?
> We might as well ask both of them what other requirements (ferret testing) there would be.
> It sounds like [redacted] thinks it will be easier to work with US partners, but that is worth checking with [redacted] also?
> [redacted]
>
> > Op 15 nov. 2019, om 08:37 heeft [redacted] het volgende geschreven:

Super.

What do you think is the next step [redacted] check with [redacted], or [redacted]? If so, seems to me is best if it were you who did that.

[redacted]

On Fri, Nov 15, 2019 at 6:48 AM [redacted] wrote:

> Here's [redacted] response.
> [redacted]
>
> Begin doorgestuurd bericht:
>
> Van: [redacted]
> Onderwerp: RE: CVV safety testing
> Datum: 15 november 2019 om 03:07:52 CET
> Aan: "[redacted]
>
> [redacted]
>
> The CVV you describe would meet the definition of LPAI without chicken testing. But to clarify, I am not in the regulatory side of USDA or CDC.
> For USA generated isolates, the paperwork would be submitted to CDC/APHIS Select Agent program for determination of Low Pathogenicity based on in vitro cell culture requiring trypsin to cleave the HA, deep sequencing to confirm only the low virulent cleavage site is present and 6 internal protein gene segments from PR8 or similar human influenza vaccine strain. I am not aware of any ferret testing being require.
> For none USA origin CVVs, I am not sure of the regulatory process for import and if a declaration by the Netherlands government authorities as to the CVV are LP would be adequate. Let me check with some contacts and get back to you.
>
> Not sure if you have seen this paper in IORV about the change in USA testing requirement.
>
> Best wishes
>
> 

-----Original Message-----
From: [redacted] <[redacted]
Sent: Wednesday, November 13, 2019 5:02 PM
To: [redacted]
Subject: CVV safety testing

Hi [redacted],

How's life and science in [redacted]

You may have heard that the labs of [redacted], [redacted] and mine are working on pre-pandemic H5 candidate vaccine viruses that should protect against infection with all H5s detected globally. BARDA wants to move them to clinical study. My question to you is what would need to be done in terms of safety testing? Our CVVs are 6:2 recombinants based on PR8, with wildtype HPAI NA, and a mutated cross-reactive/immunogenic H5 HA from which the MBCS was removed.

I have been told that chicken safety testing is no longer required with these viruses. Is that correct? And what needs to be done in ferrets? We have inoculated ferrets intranasally with these viruses to raise antisera and have tested experimental vaccines with boosting with live virus without any symptoms of disease.

I always joke that the continued re-testing of the safety of PR8 viruses with HA from which the MBCS is removed is like re-testing everyday whether gravity exists before you step out of bed, out of fears of falling upwards. But that is just me, and I am not a regulatory authority. So perhaps you know what would be required?

Thanks for your advice,
With kind regards,
[redacted]

From:
To:
Cc:
Subject: FW: CVV safety testing
Date: Monday, November 25, 2019 8:59:11 AM

[redacted],
Here's the first answer already.

Yours sincerely,

[redacted]

-----Oorspronkelijk bericht-----
Van: [redacted] >
Verzonden: maandag 25 november 2019 15:54
Aan: [redacted]
Onderwerp: RE: CVV safety testing

Hi [redacted]
All is good here thanks [redacted]

From the perspective of removal from US select agent status, a CVV such as you describe would need plaquing (in MDCK is OK) with and without trypsin and also nextgen sequencing with >1,000-fold coverage of the HA gene demonstrating absence of a polybasic cleavage site (or IVPI). These data need to be sent to USDA for official review and documentation. Until this is done it needs to be treated as select agent (in US) including any import etc. Once its done, it can be treated as BSL2 in US.

The ferret studies are a WHO recommendation (we tried to get them removed but as might be expected, WHO erred on side of caution...). Technically US-based manufacturers don't need this to handle the virus in BSL2, but im not sure what their internal policies are. The current recommendations are

Outbred ferrets 4–8 months of age are sedated either by intramuscular inoculation of a mixture of anaesthetics (e.g. ketamine (25 mg/kg), xyalazine
(2 mg/kg) and atropine (0.05 mg/kg)) or by a suitable inhalant. A standard dose of 107 EID50/TCID50 (as appropriate) (106, if the higher dose is not
possible) in 1 ml phosphate-buffered saline is slowly administered into the nares of the sedated animal, making sure that the virus is inhaled and not swallowed or expelled. A group of 4–6 ferrets should be infected. One group of ferrets (2–3 animals) should be killed on day 3 or 4 post-infection and the following tissues should be collected for estimation of virus replication:
nasal turbinates and/or swabs, lung (tissue samples from each of four lobes and pooled), brain (tissues from anterior and posterior sections sampled and pooled), spleen and intestine. Additional lung tissue may be collected and processed for haematoxylin and eosin staining for microscopic evaluation of histopathology. The remaining animals are observed for 14 days for signs of weight loss, lethargy (based on a previously published index (1)), and respiratory and neurological symptoms. Neurological involvement may be confirmed by collection of brain tissue on day 14 post-infection at the termination of the experiment and processing as above for histopathology.

Expected outcomes
Viral titres of the vaccine strain in respiratory tissues should be no greater than in either parental strain; a substantial decrease in lung virus replication is anticipated. Replication of the vaccine candidate should also be restricted to the respiratory tract and replication in the spleen or intestine is not expected. Although isolation of the vaccine strain from the brain is not desirable, if high viral titres are found in the nasal turbinates, there may be some detection of virus in the brain based on previous results with non299 virulent human H3N2 viruses (2). The significance of such a fi nding may be confirmed by performing a histopathological analysis of brain tissue on day
14 post-infection. Neurological lesions detected in heamatoxylin and eosinstained tissue sections confirm virus replication in the brain. Neurological symptoms and histopathology would indicate a lack of suitable attenuation of the vaccine candidate. Likewise clinical signs of disease such as weight loss and lethargy would indicate lack of attenuation in the vaccine strain, assuming that the wild-type avian virus also causes these symptoms.

The CVV needs to be compared to the respective wild type strain to show attenuation (this is changing, but not adopted yet from my understanding) which could be complicating in your case (perhaps using the backbone virus as comparator??).

So, make sure you don't fall up!!

Regards
[redacted]

-----Original Message-----
From: [redacted]
Sent: Monday, November 25, 2019 8:32 AM
To: [redacted] >
Subject: CVV safety testing

Caution: External Sender

Hi [redacted],

How's life and science in [redacted]

You may have heard that the labs o[redacted] and mine are working on pre-pandemic H5 candidate vaccine viruses aimed to protect against infection with all H5s detected globally. BARDA wants to move our candidates to clinical study. My question to you is what would need to be done in terms of safety testing? Our CVVs are 6:2 recombinants based on PR8, with wildtype HPAI NA, and a mutated cross-reactive/immunogenic H5 HA from which the MBCS was removed. If these were generated as CVVs at St Jude, what would be the next requirements?

I have been told that chicken safety testing is no longer required with these viruses. But what needs to be done in ferrets? We have inoculated ferrets intranasally with these viruses to raise antisera and have tested experimental vaccines with boosting with live virus without any symptoms of disease. Is any additional (safety) testing in ferrets required?

I always joke that the continued re-testing of the safety of PR8 viruses with HA from which the MBCS is removed is like re-testing everyday whether gravity exists before you step out of bed, out of fears of falling upwards. But that is just me, and I am not a regulatory authority. So perhaps you know what would be required?

Thanks for your advice,
With kind regards,
[redacted]

PS. Are the PR8 backbones in use at CDC, St Jude, Melbourne, NIID, NIBSC always the same or does each lab use their own vaccine backbone?

From: [redacted]
To: [redacted]
Subject: Fwd: CVV safety testing
Date: Thursday, December 12, 2019 10:30:34 PM

FYI

From: [redacted]
Sent: Thursday, December 12, 2019 7:22 PM
To: [redacted]
Subject: RE: CVV safety testing

Dear [redacted]

Forgive the delay on this, you probably have your questions answered. See below:

-----Original Message-----
From: [redacted] <[redacted]
Sent: Monday, November 25, 2019 9:34 AM
To: [redacted]>
Subject: CVV safety testing

Hi [redacted],

How's life and science in [redacted]?

As you know, the labs of [redacted], [redacted] and myself are working on pre-pandemic H5 candidate vaccine viruses aimed to protect against infection with all H5s detected globally. BARDA wants to move our candidates to clinical study. My question to you is what would need to be done in terms of safety testing? Our CVVs are 6:2 recombinants based on PR8, with wildtype HPAI NA, and a mutated cross-reactive/immunogenic H5 HA from which the MBCS was removed. If these were generated as CVVs at CDC, what would be the next requirements?

XX, it is best to see USDA guidance but they are interested in testing the specific stock that will be removed from BSL3 to BSL2, once in two we expand stocks from there. USDA will want proof that they are low path in Chickens or you have evidence of Trypsin dependent plaque formation and >1000X sequence coverage over the cleavage site. You will need to submit a request to USDA-APHIS with the summary and supporting data. We indicate the construct designed, data on chicken path or trypsin and seq.

I have been told that chicken safety testing is no longer required with these viruses. But what needs to be done in ferrets? We have inoculated ferrets intranasally with these viruses to raise antisera and have tested experimental vaccines with boosting with live virus without any symptoms of disease. Is any additional (safety) testing in ferrets required?

See above on SA exclusion with regard to chickens. There are WHO guidelines on the ferret testing on there website. There was a technical working group revising this so not sure what is now listed, probably still older guidelines.

I always joke that the continued re-testing of the safety of PR8 viruses with HA from which the MBCS is removed is like re-testing everyday whether gravity exists before you step out of bed, out of fears of falling upwards. But that is just me, and I am not a regulatory authority. So perhaps you know what would be required?

XX I know what you mean, but I have now seen things that different groups do that make me understand why they require some of this.

Thanks for your advice,
With kind regards,
[redacted]

PS. Are the PR8 backbones in use at CDC, St Jude, Melbourne, NIID, NIBSC always the same or does each lab use their own vaccine backbone?

XX no there are many versions of PR8 and this is another reason the authorities like the testing.

From: [redacted]
To: [redacted]
Cc: [redacted]

Subject: New CRIP paper
Date: Wednesday, December 18, 2019 3:54:56 AM
Attachments: SM_Richard_al_NComms.pdf
Richard_al_Ncomms.pdf

Accepted in Nature Communications. Collaboration with [redacted] CEIRS ([redacted]
[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: FW: CEIRR
Date: Tuesday, December 24, 2019 1:09:03 AM
Attachments: Pages 142-153. Project 4. Fouchier.docx
Example Vertebrate animals ags.docx
Example Select agents ags.docx
Example other key pesonnel brief biography.docx
Example CV.docx
Example little blurp connection with CRIP.docx
Example facilities and resources.docx

[redacted]

[redacted] Good news is that I will get back on January 3, before the deadlines. I hope you can assist with getting this done on time.

I take from [redacted] email below that I will be the PI on project 4) Pathogenesis and immune response, with a minimum of 3 projects. I propose the working title "Molecular mechanisms of viral emergence, virulence and evolution", with 3 subprojects on A) "Molecular determinants of virus emergence", B) "Host factors and severity of disease" and C) "Molecular mechanisms of antigenic evolution".

I did not see info sent to [redacted] I saw this in the mail from [redacted] :" You will have one aim on [redacted], [redacted]. [redacted] knows about it. The other project is led by [redacted] on [redacted]. You will have one aim on [redacted] [redacted] knows about it." From this it seems that we all get (slightly) different info. That is not a problem, as long as we coordinate what we end up proposing.

So please have a look at the main title and 3 subprojects, to see if everything you want to propose will fit in. Please adjust titles if that is not the case. I did not get direct information that indeed Wisconsin will have projects on "Host factors and severity of disease". As I have no intention to propose anything under this title, someone else would need to fill it, or it should be deleted and a new subproject proposed.

A) [redacted] will propose [redacted] research for some of the [redacted]. Maybe more, need to check with [redacted], but budgets are limiting.
[redacted] will study the [redacted], using our system in which virus populations exhaled into the air can be sampled and analyzed.
[redacted] will propose [redacted] work and maybe more.

B) [redacted] will propose [redacted] on [redacted]

C) [redacted] will propose the following [redacted], some assay development.
[redacted] will propose investigation of [redacted].
[redacted] work may fit here?

Let me know what you think, so we can divide up the work.

Happy holidays
[redacted]

Van: [redacted]
Datum: zaterdag 21 december 2019 om 20:23
Aan: [redacted]
CC: [redacted]>
Onderwerp: CEIRR

Dear [redacted]

I finally had a scheme of how to put together the new CRIP application, and your role on it.

First, budget for you: As discussed previously, I need to be very conservative with the budget to allow for everybody to be part of the new CRIP. I think I told you I would like to allocate 200K for you in direct costs per year for seven years. I know is not too much, but hopefully you can manage with this, and then as options and pilots come available with the years, they will be opportunities to increase budgets, including collaborations with other CEIRR. Have also in mind this is a 7 year budget, so you can try to pace experiments. But I'm sure you will need to draw from other sources and I really appreciate your willingness to do it.

Role in CRIP: As you know, the application asks for 4 component:; 1)Longitudinal human studies 2)Influenza surveillance, risk assessment and response research (4 possible projects) 3) Pandemic response and 4) Pathogenesis and immune response (minimal 3 projects)

You will be part of a few components in 2 and 3 (especially with animal models and risk assessment), but for now I will need you to focus on one of the Projects of Pathogenesis and Immune response, you the PI, in the area of viral emergence, evolution and tranmsission. This will be dedicated to antigenic evolution and determinants of transmission, in the balance that you prefer withing the budget constraints. [redacted] will also put in your proposal one aim on [redacted], and you will be copied in my email to him so you can work together in merging this

For the research component I will need from you:

1. Cell phone number we can reach you for any emergency. We promise we will only use it if really needed.
2. Title of your project (including [redacted] component)
3. Project. A copy of the previous project is included as a reference for how it should be the formatted. Including [redacted] component should not be more than 10 pages
4. Vertebrate animals (example included)
5. Select agent forms (example included)
6. Short CV. You are a main person in the grant, so I need a one page CV (see attached example from previous time)
7. Little blurb on your expertise in connection with CRIP(see attached example from previous time)
8. Brief descriptions of other key personnel (see attached example from previous time)
9. Brief description of facilities and other resources (see attached example from previous time)
10. Collaboration letters (if pertinent).

Format (note this is different than R01s!!!):
a. Proposal page layout shall be letter size 8.5" x 11" for all pages.
b. Proposals shall not include links to internet web site addresses (URLs) or otherwise direct readers to alternate sources of information.
c. Proposals shall not include audio or video files of any type.
d. Font : Arial 11 points
e. Single spacing
f. Margins must be one-inch on all sides.
g. References. Do not format references, just include PMID numbers of references when you want to reference a paper. We will insert the references according to the PMID numbers.
h. Collaboration letters. Get them in word format, with letterhead and signatures inserted as pictures in the word format, in arial 10 points, single space. This is important as letters are part of the 250 pages limitation, so if we collect them this way, one letter will not be one page, but only half a page.

Deadlines:
For 1, 2: December 28
For 6, 7, 8 and 9: January 4
For 3, 4, 5 and 10: January 18.

Compliance with this deadline will allow us to merge everybody and do several rounds of corrections and formatting.

[redacted] copied here, will send some other material we need from you required for the proposal (both technical and business), with also deadlines.

For administrative issues: Contact [redacted]

For anything else, including sending documents: Contact me and [redacted] the overall scientific manager of my lab who will help me in putting together the whole application. [redacted] will also take care of deadline compliance for the items requested in this email.

There will be a few more things needed, but for starters, this is all.

Let me know if OK with you and if you have any questions at this moment. I will be traveling to [redacted], but I will try to be available

Happy Holidays and thanks for helping to put our new CRIP.

[redacted]

[redacted]

A. Objectives (Specific Aims)

[redacted]

B. Background and Significance

Influenza A virus pandemics

Influenza A viruses are enzootic in wild migratory aquatic birds around the world (*1, 2*). They occasionally spill over from this avian "reservoir" into other animal hosts, including domestic poultry, pigs, horses, a variety of carnivores, and marine mammals. Sporadically, the viruses adapt to their new animal hosts, leading to enzootic virus circulation for years or decades (*2*). Although infrequent, avian-to-human transmissions do also occur but generally without serious consequences for public health. However, the introduction of "novel" influenza viruses from animals into humans and subsequent reassortment with contemporary human strains can result in pandemics, as was the case four times in the last century (*3*).

The influenza A virus hemagglutinin

New zoonotic viruses that emerge in humans may have different virulence and transmission properties compared to the contemporary circulating viruses. Both properties can largely be attributed to the influenza virus hemagglutinin protein (HA), i.e. the viral surface glycoprotein responsible for host cell attachment and entry. To date, 17 HA subtypes have been identified in birds and mammals (*4*). Accumulation of mutations in HA or the insertion of multiple basic amino acids in a protease cleavage site in HA (multi basic cleavage site; MBCS) is believed to yield viruses with increased virulence and transmissibility. The HA protein is initially synthesized as a single polypeptide precursor (HA0) which is cleaved to yield functional HA1 and HA2 subunits, by a trypsin-like endoprotease that is expressed in a limited range of cells. HA with a MBCS, however, is cleaved by intracellular furin-like proteases that are ubiquitously expressed. Low pathogenic avian influenza (LPAI) viruses can acquire a MBCS during circulation in poultry and become highly pathogenic avian influenza (HPAI) viruses. The MBCS motifs evolve by substitutions or (more frequently) by insertions of additional basic amino acid codons in poorly understood processes of virus polymerase slippage and RNA recombination (*5*). Importantly, such events have been detected in only two of 17 known subtypes, H5 and H7. However, experiments by others and us demonstrated that MBCS motifs are compatible with genes of other serotypes, such as H2, H4, H6, H8 and H14, inducing a HPAI phenotype (*6, 7*). This suggests that non-H5/H7 HA proteins can support an HPAI phenotype and that the observed exclusive emergence of H5 and H7 HPAI strains in nature may be determined by unique properties of their HA genes.

Antigenic evolution of influenza A virus HA

In humans, three subtypes of influenza A virus have become established in the last century: H1N1 (seasonal and 2009 pandemic), H2N2, and H3N2. Both H3N2 and pH1N1 are currently circulating in the human population to cause the yearly epidemics. For the HA and neuraminidase (NA) surface proteins, human host immunity is thought to be the main driving force of phenotypic and genetic evolution. In a process called antigenic drift, amino acid substitutions cause the virus to change antigenically, thereby escaping herd immunity (*2*).

Influenza virus receptor specificity

The first step of the influenza virus life cycle is attachment of HA to sialic acid (SA-) receptors, which can vary in structure and are species and tissue specific. Human influenza viruses prefer α2-6-Gal terminated SA-receptors, which are abundantly present on epithelial cells of the human upper respiratory tract, whereas avian viruses prefer those terminating in SA-α2-3-Gal which are found abundantly on avian epithelial cells and in the human lower respiratory tract (Fig. 1)(*8, 9*). These gross differences in receptor-binding properties of influenza viruses are important determinants of virus host range, virulence and transmissibility.

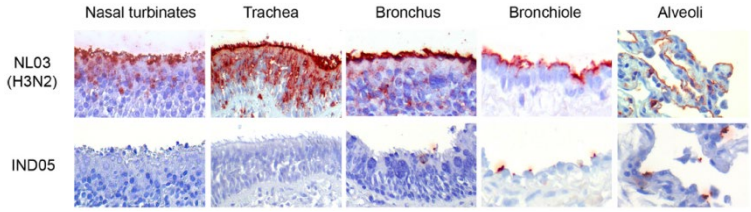
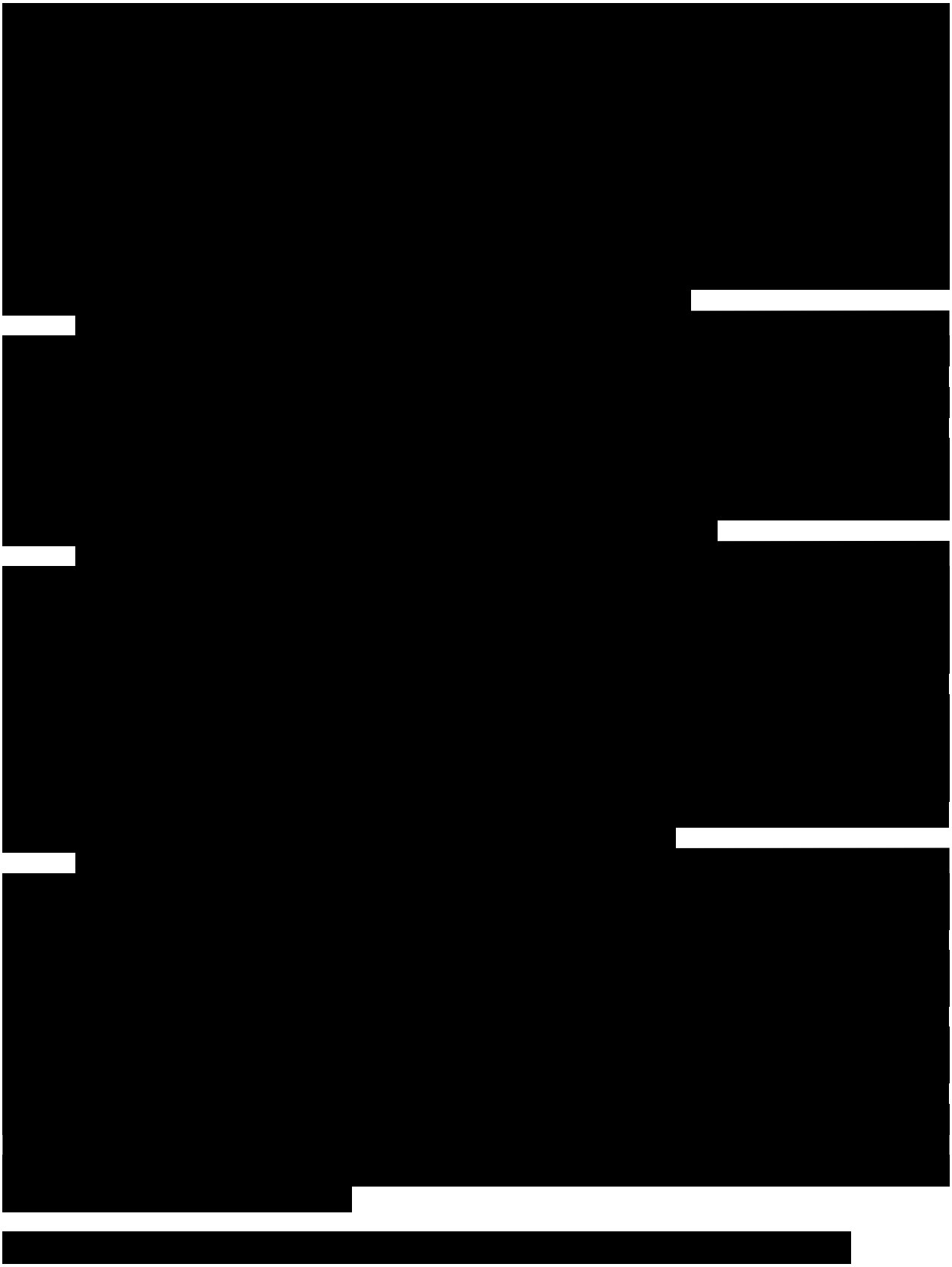


Fig. 1. Attachment of inactivated, FITC-labeled human (H3N2) and avian (H5N1, INDO5) influenza viruses to human respiratory tract tissue slides. The obtained signal was enhanced by incubation with secondary anti-FITC antibodies to yield a red precipitate (10).

Influenza A virus transmissibility.

Recent examples of zoonotic events include outbreaks of HPAI H5N1 viruses in the Eastern hemisphere since 1997, HPAI H7N7 virus in The Netherlands in 2003, and pandemic influenza H1N1 virus in 2009 (pH1N1). Since 1997, H5N1 viruses have continued to circulate in poultry in the Eastern hemisphere, causing occasional spill-overs to wild birds and mammals, including humans (*11*). The H5N1 viruses diversified into numerous distinct genetic “clades”, from which new sublineages or clades continue to emerge (*12*). Whether this ongoing evolution could eventually lead to the emergence of H5N1 viruses with pandemic potential, i.e. ability of virus to transmit between humans, has remained a key question. Human influenza viruses are well known for their ability to transmit efficiently via the airborne route (*3, 13*), however, what determines transmission has remained largely unknown.

[redacted]



[redacted]

virus populations that *emerge during replication in ferrets*, are *emitted from ferrets*, *"travel" via*

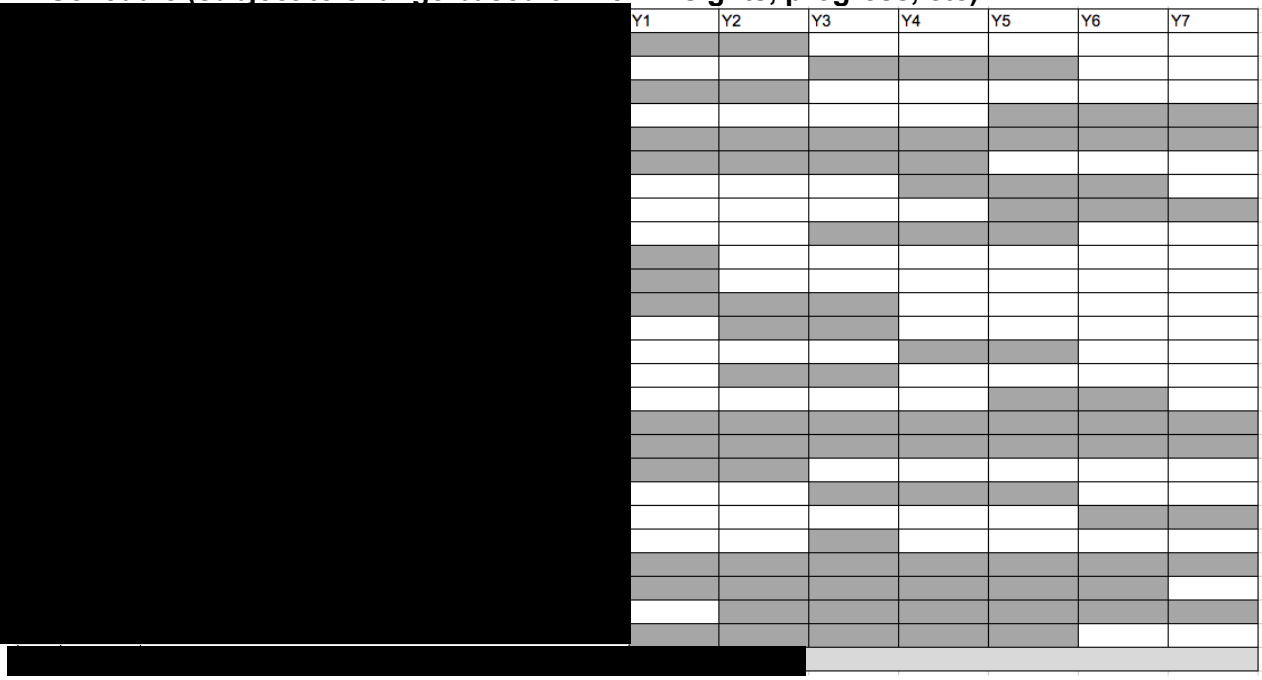
[redacted]

[redacted]

[redacted]

F. Schedule (subject to change based on new insights, progress, etc)

[redacted]



G. References (asterisk indicates references authored by CRIP investigators)

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[redacted]

[redacted]

Select agents

Specific experiments conducted at [redacted] will use challenges in mice with wild type highly pathogenic influenza viruses. These viruses are subjected to select agent regulation. [redacted] has appropriate enhanced BSL3 facilities to conduct this research and the facility, procedures and personnel involved in this work has been approved by CDC and USDA under the select agent program

Listing of agents:

[redacted]

Registration status:

The CDC and USDA have inspected and approved the [redacted] select agents and toxins program (Registration [redacted] expiration date of [redacted] according to select agent regulations.

[redacted]

[redacted]

[redacted]

[redacted]

BRIEF BIOGRAPHIES, OTHER INVESTIGATORS (in alphabetical order)

[redacted]

At [redacted] (20% dedication time), will continue to direct an extensive influenza surveillance program in different regions of the world, including Europe, Asia and Africa. He is also responsible of the phenotyping analysis in ferrets, and of the Research Project 4, HA determinants of virus phenotype: antigenicity, virulence, and transmission. [redacted] is a member of the CRIP EC. [redacted] is a renowned virologist with expertise on the evolution and molecular biology of respiratory viruses in humans and animals, with special emphasis on influenza virus zoonoses, pandemics and epidemics. Among his multiple collaborators, [redacted]

Facilities and Resources

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: CEIRR
Date: Tuesday, December 24, 2019 12:10:48 AM

Ok. But you also have a project on host factors and severity of disease, according to [redacted]?
[redacted]

From: [redacted] <[redacted]
Sent: Monday, December 23, 2019 6:39 AM
To: [redacted]
Cc: [redacted]
Subject: FW: CEIRR

Dear [redacted]

As far as we can tell from [redacted] emails, we will be contributing to the Research Project on antigenic evolution and transmission, with you taking the lead.
Regarding the component on antigenic evolution, we could propose to [redacted]
Regarding the component on transmission, we would study the [redacted]
Please let us know what documents you'd need, and what your deadlines are.
[redacted] will write the proposals and can coordinate the details with you.

Thanks and Happy Holidays,

[redacted]

From: [redacted] <[redacted]
Sent: Sunday, December 22, 2019 10:15 AM
To: [redacted]
Subject: FW: CEIRR

From: [redacted] <[redacted]
Sent: Sunday, December 22, 2019 4:55 PM

To: [redacted]
Cc: [redacted] <[redacted]
[redacted]
Subject: Re: CEIRR

[redacted]
Thanks.
Cell number is [redacted]
Let me know if you have a suggested title. Maybe we can have somewhat matching titles.
Something along the line of : [redacted]" for me…
Cheers
[redacted]

[redacted]
Datum: zaterdag 21 december 2019 om 22:07
Aan: [redacted]
[redacted]
[redacted] "[redacted] <[redacted]
[redacted] <[redacted]
Onderwerp: Re: CEIRR

1) Cell number [redacted]
2) [redacted] I will provide with aims on [redacted] If there is a chance of cross-collaboration on both of these aims, please let me know as the scope/complexities of the projects could be expanded depending on how much collaboration we could have.

Happy Holidays!

[redacted]

[redacted]

On Dec 21, 2019, at 2:45 PM, [redacted]

[redacted]

[External Sender]

Dear [redacted],

I finally had a scheme of how to put together the new CRIP application, and your role on it.

First, budget for you: As discussed previously, I need to be very conservative with the budget to allow for everybody to be part of the new CRIP. I think I told you I would like to allocate 200K for you in direct costs per year for seven years. I know is not too much, but hopefully you can manage with this, and then as options and pilots come available with the years, they will be opportunities to increase budgets, including collaborations with other CEIRR.

As you know, the application asks for 4 components:; 1)Longitudinal human studies 2)Influenza surveillance, risk assessment and response research (4 possible projects) 3) Pandemic response and 4) Pathogenesis and immune response (minimal 3 projects)

You will be part of a few components in 2 and 3 (especially with animal models and risk assessment), but for now I will need you to focus on two of the Projects of Pathogenesis and Immune response.
One project is led by [redacted] on antigenic evolution and transmission. You will have one aim on [redacted]. [redacted] knows about it.
The other project is led by [redacted] on host factors and severity of disease. You will have one aim on [redacted] knows about it.

For the research components I will need from you:

1. Cell phone number we can reach you for any emergency. We promise we will only use it if really needed.
2. Contact [redacted] and [redacted] to tell them you will provide them with these aims
3. Send to [redacted] and [redacted] after coordinating with them your science components
4. Vertebrate animals (example included)
5. Select agent forms (example included)
6. Short CV. You are a main person in the grant, so I need a one page CV (see attached example from previous time)

7. Little blurb on your expertise in connection with CRIP(see attached example from previous time)
8. Brief descriptions of other key personnel (see attached example from previous time)
9. Brief description of facilities and other resources (see attached example from previous time)
10. Collaboration letters (if pertinent).

Format (note this is different than R01s!!!):
a. Proposal page layout shall be letter size 8.5” x 11" for all pages.
b. Proposals shall not include links to internet web site addresses (URLs) or otherwise direct readers to alternate sources of information.
c. Proposals shall not include audio or video files of any type.
d. Font : Arial 11 points
e. Single spacing
f. Margins must be one-inch on all sides.
g. References. Do not format references, just include PMID numbers of references when you want to reference a paper. We will insert the references according to the PMID numbers.
h. Collaboration letters. Get them in word format, with letterhead and signatures inserted as pictures in the word format, in arial 10 points, single space. This is important as letters are part of the 250 pages limitation, so if we collect them this way, one letter will not be one page, but only half a page.

Deadlines:
For 1, 2: December 24
For 6, 7, 8 and 9: January 4
For 3: January 11 or whatever deadline is given to you by [redacted] and [redacted]
For 4, 5 and 10: January 18.

Compliance with this deadline will allow us to merge everybody and do several rounds of corrections and formatting.

[redacted], copied here, will send some other material we need from you required for the proposal (both technical and business), with also deadlines.

For administrative issues: Contact [redacted]
For anything else, including sending documents: Contact me and [redacted], the overall scientific manager of my lab who will help me in putting together the whole application. [redacted] will also take care of deadline compliance for the items requested in this email.

There will be a few more things needed, but for starters, this is all.

Let me know if OK with you and if you have any questions at this moment. I will be traveling to [redacted], but I will try to be available

Happy Holidays and thanks for helping to put our new CRIP.

[redacted]

From:
To:
Cc:
Subject: RE: CEIRR
Date: Tuesday, December 24, 2019 6:53:00 AM

Let me check with

From: <
Sent: Tuesday, December 24, 2019 9:54 PM
To: <
Subject: Re: CEIRR

We can submit 2 projects, 1 with you as PI and 1 with me, where all 3 labs can put in sub-aims for both projects. I think will be part of your project and you and are part of mine.
Or we can get clarification if we are uncertain.

From: <
Sent: Tuesday, December 24, 2019 3:22 PM
To:
Cc:
Subject: RE: CEIRR

OK. What are we going to do now?

From: <
Sent: Tuesday, December 24, 2019 6:16 PM
To: <
Cc:
Subject: Re: CEIRR

That is indeed another interpretation. I probably got it wrong then. Also good with me.

From:
Sent: Tuesday, December 24, 2019 1:10 PM
To:
Cc:
Subject: RE: CEIRR

Dear All,

As stated, we seem to have received slightly different information from
Here is an excerpt from mail to "I will need you to focus on one of the Projects of Pathogenesis and Immune response, you the PI, in the area of influenza disease and severity. This could go along the lines of what you proposed in your previous document to Identify host factors and pathways that affect the outcome of infection with seasonal and highly pathogenic influenza viruses. I will also put in your proposal one aim on ."

It was my impression that

- would lead a project that focuses on **virulence, transmission, and antigenic evolution**; aims would come from the ;
- would lead a project on "**Host factors and severity of diseases**"; aims would come from the

This is very different from structure below – I am just summarizing my understanding of the email I've seen to this point … but I may have misunderstood and/or plan.

Happy Holidays,

From: <
Sent: Tuesday, December 24, 2019 1:09 AM
To: <
Cc:
Subject: FW: CEIRR

, Good news is that I will get back on January 3, before the deadlines. I hope you can assist with getting this done on time.

I take from s email below that I will be the PI on project 4) Pathogenesis and immune response, with a minimum of 3 projects. I propose the working title "Molecular mechanisms of viral emergence, virulence and evolution", with 3 subprojects on A) "Molecular determinants of virus emergence", B) "Host factors and severity of disease" and C) "Molecular mechanisms of antigenic evolution".

I did not see info sent to I saw this in the mail from to " You will have one aim on , knows about it. The other project is led by on host factors and severity of disease. You will have one aim on knows about it." From this it seems that we all get (slightly) different info. That is not a problem, as long as we coordinate what we end up proposing.

So please have a look at the main title and 3 subprojects, to see if everything you want to propose will fit in. Please adjust titles if that is not the case. I did not get direct information that indeed Wisconsin will have projects on "Host factors and severity of disease". As I have no intention to propose anything under this title, someone else would need to fill it, or it should be deleted and a new subproject proposed.

A) will propose . Maybe more, need to check with , but budgets are limiting.
will study the .
will propose work and maybe more.

B) will propose

C) will propose the following , some assay development.

[redacted] will propose investigation of antigenic epitopes of human influenza viruses with human monoclonal antibodies.
[redacted] work may fit here?

Let me know what you think, so we can divide up the work.

Happy holidays
[redacted]

Van: [redacted] >
Datum: zaterdag 21 december 2019 om 20:23
Aan: [redacted] <[redacted]
CC: [redacted] [redacted] >
Onderwerp: CEIRR

Dear [redacted]

I finally had a scheme of how to put together the new CRIP application, and your role on it.

First, budget for you: As discussed previously, I need to be very conservative with the budget to allow for everybody to be part of the new CRIP. I think I told you I would like to allocate 200K for you in direct costs per year for seven years. I know is not too much, but hopefully you can manage with this, and then as options and pilots come available with the years, they will be opportunities to increase budgets, including collaborations with other CEIRR. Have also in mind this is a 7 year budget, so you can try to pace experiments. But I'm sure you will need to draw from other sources and I really appreciate your willingness to do it.

Role in CRIP: As you know, the application asks for 4 component:; 1)Longitudinal human studies 2)Influenza surveillance, risk assessment and response research (4 possible projects) 3) Pandemic response and 4) Pathogenesis and immune response (minimal 3 projects)

You will be part of a few components in 2 and 3 (especially with animal models and risk assessment), but for now I will need you to focus on one of the Projects of Pathogenesis and Immune response, you the PI, in the area of viral emergence, evolution and tranmsission. This will be dedicated to [redacted] in the balance that you prefer withing the budget constraints. [redacted] will also put in your proposal one aim on [redacted], and you will be copied in my email to him so you can work together in merging this

For the research component I will need from you:

1. Cell phone number we can reach you for any emergency. We promise we will only use it if really needed.
2. Title of your project (including [redacted] component)
3. Project. A copy of the previous project is included as a reference for how it should be the formatted. Including [redacted] component should not be more than 10 pages
4. Vertebrate animals (example included)
5. Select agent forms (example included)
6. Short CV. You are a main person in the grant, so I need a one page CV (see attached example from previous time)
7. Little blurb on your expertise in connection with CRIP(see attached example from previous time)
8. Brief descriptions of other key personnel (see attached example from previous time)
9. Brief description of facilities and other resources (see attached example from previous time)
10. Collaboration letters (if pertinent).

Format (note this is different than R01s!!!):
a. Proposal page layout shall be letter size 8.5" x 11" for all pages.
b. Proposals shall not include links to internet web site addresses (URLs) or otherwise direct readers to alternate sources of information.
c. Proposals shall not include audio or video files of any type.
d. Font : Arial 11 points
e. Single spacing
f. Margins must be one-inch on all sides.
g. References. Do not format references, just include PMID numbers of references when you want to reference a paper. We will insert the references according to the PMID numbers.
h. Collaboration letters. Get them in word format, with letterhead and signatures inserted as pictures in the word format, in arial 10 points, single space. This is important as letters are part of the 250 pages limitation, so if we collect them this way, one letter will not be one page, but only half a page.

Deadlines:
For 1, 2: December 28
For 6, 7, 8 and 9: January 4
For 3, 4, 5 and 10: January 18.

Compliance with this deadline will allow us to merge everybody and do several rounds of corrections and formatting.

[redacted] copied here, will send some other material we need from you required for the proposal (both technical and business), with also deadlines.

For administrative issues: Contact [redacted]
For anything else, including sending documents: Contact me and [redacted] the overall scientific manager of my lab who will help me in putting together the whole application. [redacted] will also take care of deadline compliance for the items requested in this email.

There will be a few more things needed, but for starters, this is all.

Let me know if OK with you and if you have any questions at this moment. I will be traveling to [redacted], but I will try to be available

Happy Holidays and thanks for helping to put our new CRIP.

[redacted]

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: Re: CEIRR
Date: Tuesday, December 24, 2019 7:57:53 AM

Thanks [redacted] and [redacted], this is helpful. There is also confusion about the deadlines. This is what I received, and will adhere to unless noted otherwise:

Deadlines:
For 1, 2: December 28
For 6, 7, 8 and 9: January 4
For 3, 4, 5 and 10: January 18.

Happy holidays!
[redacted]

From: [redacted]
Sent: Tuesday, December 24, 2019 5:42 PM
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR

Dear [redacted],

Thank you for the clarification!

[redacted]

From: [redacted]
Sent: Tuesday, December 24, 2019 10:36 PM
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR

1. Hi [redacted] for the component 2 this is more about capabilities for phenotyping viruses of interest, the same way we had it in the previous application, so there is not need right now for anything else.
2. If you think you can put a project under surveillance without increase the original budget allocated to you, let me know. If not, it will be premature at this moment, as we are already overbudgeted. As soon as I know, if you can do it, I will tell you how this will fit in the application.
3. It is option 2, sorry about the confusion. There will be two more projects, one from [redacted], and one from me or [redacted], mainly [redacted]

From: [redacted] [mailto:[redacted]
Sent: Tuesday, December 24, 2019 8:00 AM
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR

USE CAUTION: External Message.

Dear [redacted],

Thanks for the information. We will try to plan accordingly.
You mentioned in your mail that we will also be part of component #2 (flu surveillance, risk assessment and response research). Who will take the lead on the surveillance proposal? We'd like to contact the respective PI to provide information on our [redacted].

After communicating with [redacted], our groups are not entirely sure about the structure– which of the two options do you have in mind?

OPTION 1: [redacted] is PI on a project on Item 4 ("Pathogenesis and Immune Responses") with 3 subprojects:
- [redacted]
[redacted]
[redacted]

OPTION 2:
- [redacted] would lead a project that focuses on virulence, transmission, and antigenic evolution; aims would come from the [redacted] groups as described above;
- [redacted] would lead a project on"Host factors and severity of diseases"; aims would come from the [redacted] groups.

Yours,

[redacted]

From: [redacted]
Sent: Tuesday, December 24, 2019 6:10 PM
To: [redacted]
Cc: [redacted]
Subject: RE: CEIRR

Dear All,

As [redacted] stated, we seem to have received slightly different information from [redacted].
Here is an excerpt from [redacted] mail to [redacted] "I will need you to focus on one of the Projects of Pathogenesis and Immune response, you the PI, in the area of influenza disease and severity. This could go

along the lines of what you proposed in your previous document to Identify host factors and pathways that affect the outcome of infection with seasonal and highly pathogenic influenza viruses. [redacted] will also put in your proposal one aim on [redacted]."

It was my impression that

- [redacted] would lead a project that focuses on **virulence, transmission, and antigenic evolution**; aims would come from the [redacted]
- [redacted] would lead a project on "**Host factors and severity of diseases**"; aims would come from the [redacted] groups.

This is very different from [redacted] structure below – I am just summarizing my understanding of the email I've seen to this point … but I may have misunderstood [redacted] and/or [redacted] plan.

Happy Holidays,

[redacted]

From: [redacted] <[redacted]>
Sent: Tuesday, December 24, 2019 1:09 AM
To: [redacted] <[redacted]>
Cc: [redacted]
Subject: FW: CEIRR

[redacted], [redacted]

[redacted] Good news is that I will get back on January 3, before the deadlines. I hope you can assist with getting this done on time.

I take from [redacted] email below that I will be the PI on project 4) Pathogenesis and immune response, with a minimum of 3 projects. I propose the working title [redacted], with 3 subprojects on [redacted]

I did not see info sent to [redacted] I saw this in the mail from [redacted] to [redacted] "You will have one aim on [redacted], [redacted] knows about it. The other project is led by [redacted] on host factors and severity of disease. You will have one aim on [redacted] knows about it." From this it seems that we all get (slightly) different info. That is not a problem, as long as we coordinate what we end up proposing.

So please have a look at the main title and 3 subprojects, to see if everything you want to propose will fit in. Please adjust titles if that is not the case. I did not get direct information that indeed Wisconsin will have projects on "Host factors and severity of disease". As I have no intention to propose anything under this title, someone else would need to fill it, or it should be deleted and a new subproject proposed.

A) [redacted] will propose [redacted]. Maybe more, need to check with [redacted], but budgets are limiting.
[redacted] will study the [redacted].
[redacted] will propose [redacted] work and maybe more.

B) [redacted] will propose [redacted]

C) [redacted] will propose the following [redacted], some assay development.
[redacted] will propose [redacted].
[redacted] work may fit here?

Let me know what you think, so we can divide up the work.

Happy holidays
[redacted]

[redacted]
Datum: zaterdag 21 december 2019 om 20:23
Aan: [redacted] <[redacted]>
CC: [redacted]
Onderwerp: CEIRR

Dear [redacted]

I finally had a scheme of how to put together the new CRIP application, and your role on it.

First, budget for you: As discussed previously, I need to be very conservative with the budget to allow for everybody to be part of the new CRIP. I think I told you I would like to allocate 200K for you in direct costs per year for seven years. I know is not too much, but hopefully you can manage with this, and then as options and pilots come available with the years, they will be opportunities to increase budgets, including collaborations with other CEIRR. Have also in mind this is a 7 year budget, so you can try to pace experiments. But I'm sure you will need to draw from other sources and I really appreciate your willingness to do it.

Role in CRIP: As you know, the application asks for 4 component:; 1)Longitudinal human studies 2)Influenza surveillance, risk assessment and response research (4 possible projects) 3) Pandemic response and 4) Pathogenesis and immune response (minimal 3 projects)

You will be part of a few components in 2 and 3 (especially with animal models and risk assessment), but for now I will need you to focus on one of the Projects of Pathogenesis and Immune response, you the PI, in the area of viral emergence, evolution and tranmsission. This will be dedicated to [redacted] in the balance that you prefer withing the budget constraints. [redacted] will also put in your proposal one aim on [redacted], and you will be copied in my email to him so you can work together in merging this

For the research component I will need from you:

1. Cell phone number we can reach you for any emergency. We promise we will only use it if really needed.
2. Title of your project (including [redacted] component)
3. Project. A copy of the previous project is included as a reference for how it should be the formatted. Including [redacted] component should not be more than 10 pages
4. Vertebrate animals (example included)
5. Select agent forms (example included)
6. Short CV. You are a main person in the grant, so I need a one page CV (see attached example from previous time)
7. Little blurb on your expertise in connection with CRIP(see attached example from previous time)
8. Brief descriptions of other key personnel (see attached example from previous time)
9. Brief description of facilities and other resources (see attached example from previous time)
10. Collaboration letters (if pertinent).

Format (note this is different than R01s!!!):
a. Proposal page layout shall be letter size 8.5" x 11" for all pages.
b. Proposals shall not include links to internet web site addresses (URLs) or otherwise direct readers to alternate sources of information.
c. Proposals shall not include audio or video files of any type.
d. Font : Arial 11 points
e. Single spacing
f. Margins must be one-inch on all sides.
g. References. Do not format references, just include PMID numbers of references when you want to reference a paper. We will insert the references according to the PMID numbers.
h. Collaboration letters. Get them in word format, with letterhead and signatures inserted as pictures in the word format, in arial 10 points, single space. This is important as letters are part of the 250 pages limitation, so if we collect them this way, one letter will not be one page, but only half a page.

Deadlines:
For 1, 2: December 28
For 6, 7, 8 and 9: January 4
For 3, 4, 5 and 10: January 18.

Compliance with this deadline will allow us to merge everybody and do several rounds of corrections and formatting.

[redacted] copied here, will send some other material we need from you required for the proposal (both technical and business), with also deadlines.

For administrative issues: Contact[redacted]
For anything else, including sending documents: Contact me and[redacted] the overall scientific manager of my lab who will help me in putting together the whole application.[redacted] will also take care of deadline compliance for the items requested in this email.

There will be a few more things needed, but for starters, this is all.

Let me know if OK with you and if you have any questions at this moment. I will be traveling to[redacted], but I will try to be available

Happy Holidays and thanks for helping to put our new CRIP.

[redacted]