Summary of Discussions between NASEM and CAS on COVID-19, 13Oct 2020

1. CAS (George Gao) provided an overview of the COVID-19 vaccine efforts underway in China. Key points were as follows:
    a. 7 different vaccine approaches are underway (list was shared)
    b. Range from classic inactivated vaccines to live, attenuated candidates
    c. Vaccine underdeveloped based on modified "cold adapted" influenza vaccine as a live, attenuated vaccine for COVID-19 following nasal administration.
    d. Several candidates are in Phase 3 clinical trials (Brazil, Argentina and UAE mentioned, but perhaps other locations as well)
2. Human monoclonal antibody candidates are being developed for clinical use
    a. Multiple candidates are under study
    b. Collaborations with Lilly to create a 2 monoclonal antibody cocktail was mentioned. This product is in clinical trials (now on hold) in the USA.
    c. Several questions were raised:
        i. Protective efficacy of candidates
        ii. Impact on/activity in lungs
        iii. Duration of maby protection
        iv. Possibility of antibody dependent enhancement
        v. Possible impact on vaccination
3. A general discussion of the value and challenges associated with the creation of a universal coronavirus vaccine similar to ongoing discussions about a possible universal vaccine for influenza.
    a. Comment (Stanley Perlman) about the possibility of including T cell epitopes as a component of a universal coronavirus vaccine given demonstrated cross-reactivity among recognized coronaviruses.
4. NAS (Nancy Connell) shared an overview of the USA "Warp Speed" vaccine development efforts underway.
    a. 4 vaccine platforms are being developed with 2 candidates supported in each platform technology (list shared)
    b. Most candidates will require a prime/boost administration
    c. mRNA candidates will require an ultralow temperature cold chain that will be demanding to implement
    d. Many are in Phase 3 clinical trials with the mRNA candidates most advanced
    e. Selection of technologies was based in part on ease of production
    f. Results of clinical studies may be available incrementally with the mRNA candidates farthest along; results known perhaps by Nov-Dec 2020; others at roughly 2 month intervals with the replicating live vaccine results available in late 2021.
    g. Vaccine production is underway concurrent with clinical trials, with approximately 100 M doses of mRNA vaccine available around the end of 2020. Manufacturing costs provided by USG (BARDA).
5. Discussion of challenges associated with USA vaccine development and roll-out strategy.
    a. Key questions: is the candidate safe, is it effective in preventing infection/disease, and what is the duration of protection (Harvey's comments)

    b. How to manage multiple “successful” candidates with differing vaccination schedules and other requirements
    c. How to detect adverse events
    d. If EUA is granted early, those receiving placebo with receive the vaccine, leading to challenges in interpretation late onset adverse events (Ralph’s comment)
    e. For all candidate vaccines (USA and China), what is the strategy for select segments of the population—children, elderly, high risk occupations, others—still being addressed in China; Just released NASEM report on equitable distribution of vaccine discussed by Nancy and slide of 4 tiers of those to be vaccinated shared.
6. Review of vaccination efforts for animal diseases caused by coronaviruses (Linda Saif)
    a. Linda gave a comprehensive review of several vaccine development efforts, especially those associated with swine (list provided)
    b. Challenges encountered in producing protective vaccines for piglets
    c. Difficulties in generating mucosal immunity/IgA
7. Discussion of lessons learned from animal coronaviruses and how they might foretell problems with COVID-19 vaccination
    a. Relevance of past infection versus naïve populations on response to vaccines
    b. Mention of evidence of naturally occurring recombination of coronaviruses infecting swine in Europe.

To: 'relman@stanford.edu'[relman@stanford.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'saif.2@osu.edu'[saif.2@osu.edu]; 'stanley-perlman@uiowa.edu'[stanley-perlman@uiowa.edu]; 'daszak@ecohealthalliance.org'[daszak@ecohealthalliance.org]; 'harvey.fineberg@moore.org'[harvey.fineberg@moore.org]; 'dgriffi6@jhmi.edu'[dgriffi6@jhmi.edu]; 'peggy@hbfam.net'[peggy@hbfam.net]; 'jwleduc@UTMB.EDU'[jwleduc@UTMB.EDU]; 'peshi@UTMB.EDU'[peshi@UTMB.EDU]; Dzau, Victor J.[VDzau@nas.edu]; 'Nancy Connell'[NancyConnell@jhu.edu]; 'Dave Franz (davidrfranz@gmail.com)'[davidrfranz@gmail.com]
Cc: 'fsharples_3@hotmail.com'[fsharples_3@hotmail.com]; Lowenthal, Micah[mlowenth@nas.edu]; Baric, Toni C[antoinette_baric@med.unc.edu]; 'andre@ecohealthalliance.org'[andre@ecohealthalliance.org]; 'jennifer.ryan@moore.org'[jennifer.ryan@moore.org]; Bowman, Katherine[KBowman@nas.edu]; Kanarek, Morgan[MKanarek@nas.edu]; 'Raymond JEANLOZ'[jeanloz@berkeley.edu]; Hare, Hope[HHare@nas.edu]; Cervenka, Nicole[NCervenka@nas.edu]; Sharples, Fran[FSharples@nas.edu]; Block, Bruce[BBlock@nas.edu]
From: Rusek, Benjamin[BRusek@nas.edu]
Sent: Wed 10/14/2020 7:32:16 PM (UTC-04:00)
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links
NAS-CAS-Vaccine-20201014.pdf
Emerging CoVs Swine Vaccine China NAS diaglog LJSaif_10-13-20pdf.pdf
20201013Vaccines US update.pdf

Greetings,

Thank you for joining the dialogue session last night. I have attached the slides from the three presentations.

FYI CAS has invited two additional CCDC experts to the session tonight.

Dr. Huaqing Wang, PI, Immunization program, Chinese Center for Disease Control and Prevention
Dr. Zundong Yin, Director of National Immunization Program, Chinese Center for Disease Control and Prevention

Looking forward seeing and hearing from you all in a few hours.
Session 2: Wednesday October 14, **9-11 PM ET / 6-8 PM PT in U.S.**
Meeting Link: https://nasem.zoom.us/j/98420889232?pwd=NFlIKzF1eWgxT0xDZHQzQWxMbnJPdz09
Password: 375761

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Rusek, Benjamin
Sent: Monday, October 12, 2020 12:36 PM
To: 'relman@stanford.edu' <relman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidrfranz@gmail.com)' <davidrfranz@gmail.com>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSharples@nas.edu>; Block, Bruce <BBlock@nas.edu>
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links
Importance: High

Greetings,

I have attached what should be the final agenda for the U.S. China dialogue meeting sessions on Tuesday, October 13 and

Wednesday October 14. It includes the Chinese participant list at the end. Links to join the Zooms are also below.

Looking forward to seeing/talking to you all on Tuesday and Wednesday evening.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

***
Session 1: Tuesday, October 13, **9-11 PM ET / 6-8 PM PT in U.S.**
Meeting Link: https://nasem.zoom.us/j/92754903815?pwd=OUV2R3BPdDdibDdZZ24vcGd4VmJoUT09
Password: 833624

Session 2: Wednesday October 14, **9-11 PM ET / 6-8 PM PT in U.S.**
Meeting Link: https://nasem.zoom.us/j/98420889232?pwd=NFllKzF1eWgxT0xDZHQzQWxMbnJPdz09
Password: 375761

From: Rusek, Benjamin
Sent: Friday, October 9, 2020 5:43 PM
To: 'relman@stanford.edu' <relman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidrfranz@gmail.com)' <davidrfranz@gmail.com>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSharples@nas.edu>
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links
Importance: High

Greetings,

We are looking forward to the two virtual bio dialogue sessions set to take place on Tuesday, October 13 (9-11 PM ET / 6-8 PM PT) and Wednesday, October 14 (9-11 PM ET / 6-8 PM PT) next week. Like in previous sessions we expect that the Chinese expert participants will lead the discussion on the majority of the topics and that the format will be more of a discussion among the participants instead of a series of formal presentations. I have attached an agenda that includes the Zoom connection links for both days along with the U.S. participant list. If I get the Chinese participant list before the session I will send that out to you all.

Feel free to respond to this email with any thoughts, points of emphasis or issues that you would like to discuss among the U.S. group before the sessions. Also let me know if you have any questions or concerns.

Kind regards,

Ben

Benjamin Rusek
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From: Rusek, Benjamin
Sent: Monday, September 21, 2020 9:01 PM

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Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>
Subject: Virtual U.S. China dialogue meeting October 13 and 14
Importance: High

Greetings,

I hope you all had a good summer and are staying safe and healthy. The Chinese Academy of Sciences has agreed to hold another (4th) virtual bio dialogue meeting with NASEM on **1) vaccine development and delivery** and **2) immunity, testing and diagnostics.** The agreed topics for the session are below. **We have reserved Tuesday, October 13 (9-11 PM ET / 6-8 PM PT) and Wednesday, October 14 (9-11 PM ET / 6-8 PM PT**) to discuss the topics on the agenda.

We hope you are able to participate. Please let me know if you are available and if so save the dates and times on your calendar. We will get back to you with more information and a detailed agenda for the sessions soon.

Kind regards,

Ben

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***

Vaccine development and delivery

Human

1) **Current status of CoVID-19 vaccine development in China and the U.S.**
2) **Chinse vaccination of military personnel and other Chinese populations**
3) **Vaccination of pediatric populations**
4) **Active surveillance strategies for monitoring adverse events observed after vaccination (as well as immunogenicity)**
5) **Adapting current vaccine platforms to novel mass vax strategies and other mass vaccination strategic issues**
6) **Progress on a universal influenza vaccines**
7) **Vaccine for enterovirus D68**

Animal

1) **Status of corona virus vaccination for animals - kinds of vaccine, efficacy, complications, etc**
2) **ASF in China and ASF vaccine progress**
3) **New swine coronavirus**
4) **Vaccination strategy for H5N1 avian influenza and domestic poultry**

Immunity, testing and diagnostics

1) **Correlates of immunity including the possibility of background immunity from circulating "common cold" coronaviruses**
2) **Chinese diagnostic testing strategies for testing large populations quickly**
3) **Antibody and antibody testing topics, importance of T-cell responses**
4) **Long-term sequela following COVID-19 infection—lung function, neurologic issues, others**

From: Rusek, Benjamin
Sent: Thursday, June 4, 2020 1:25 PM

To: 'relman@stanford.edu' <relman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; 'davidrfranz@gmail.com' <davidrfranz@gmail.com>; 'Nancy Connell' <NancyConnell@jhu.edu>
Subject: RE: 3rd Virtual U.S. China dialogue meeting on COVID-19 Tuesday, June 9, 9-11PM ET
Importance: High

Greetings,

I have attached the American version of the agenda for the 3rd U.S. China virtual dialogue meeting on immunity and related topics set to take place on **Tuesday night, June 9 from 9:00-11:00 PM ET** (9-11 AM the next morning, Beijing time).

As you can see we have incorporated George Gao's questions into the agenda, we hope that **Harvey Fineberg** can provide information on and lead the discussion of 1) serologic investigation in the U.S. 2) strategy in the U.S. for the second half of this year 3) vaccine availability in the U.S. and that **Ralph Baric** can do the same re progress in the development of vaccine in the U.S. (especially mRNA vaccine).

We have also listed delegation member names after the other Immunity questions. Like previously, folks are listed simply so someone is responsible for getting an answer from the Chinese to each question during the discussion. I will send a version to CAS without those names listed but will let them know who we have asked to answer George's questions.

Please let us know if you have any thoughts or comments on the agenda or this plan. I will send you the Zoom link later tonight or tomorrow morning.

Kind regards,

Ben

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Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; 'davidrfranz@gmail.com' <davidrfranz@gmail.com>
Subject: RE: 3rd Virtual U.S. China dialogue meeting on COVID-19 Tuesday, June 9, 9-11PM ET
Importance: High

Greetings,

Good news, just heard back from CAS. They agreed to hold the 3rd dialogue meeting on the proposed immunity topics on **Tuesday, June 9 from 9:00-11:00 PM ET** (9-11 AM the next morning, Beijing time). Please hold that time on your calendar.

CAS let us know that George Gao wants to add the following questions to the discussion:

- Could any US participant introduce the progress in the development of vaccine in the US, especially mRNA vaccine?
- How is the overall situation of serologic investigation in the US?
- What is the COVID-19 prevention and control strategy in the US for the second half of this year? When do you expect COVID-19 vaccine to be available in the US ?

We will send out a new agenda and Zoom link for the meeting later in the week.

Kind regards,

Ben

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Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; 'davidrfranz@gmail.com' <davidrfranz@gmail.com>
Subject: RE: 3rd Virtual U.S. China dialogue meeting on COVID-19
Importance: High

Greetings,

Good news: Last night CAS leadership agreed to hold the 3rd virtual dialogue (Zoom meeting) on the list of Immunity topics we proposed. However they would like to push the dates for the 3rd meeting back to the first or second week of June (so no Zoom meeting on Tuesday night next week). Some of our Chinese counterparts are involved in China's National People's Congress taking place next week.

We are targeting **one night on June 1-4 or on June 8-11** (at 9-11 PM ET for the Americans, the following morning for the Chinese group.)

Please send your availability to participate on those nights (or maybe simply send the nights you can't participate) to Hope Hare [HHare@nas.edu] so we can propose a date or dates to CAS that works best for the American group.

Thanks again for your availability and willingness to participate in this initiative and I hope you have a good long weekend.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
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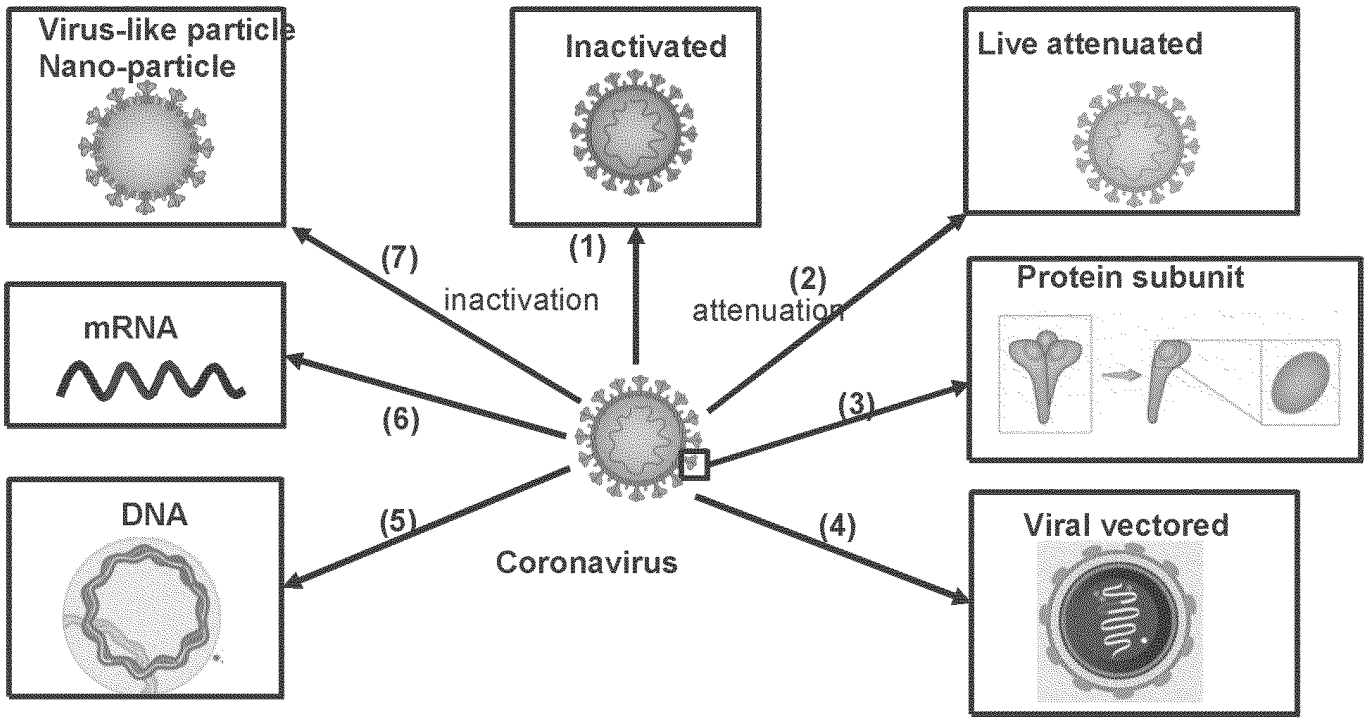
Vaccine development

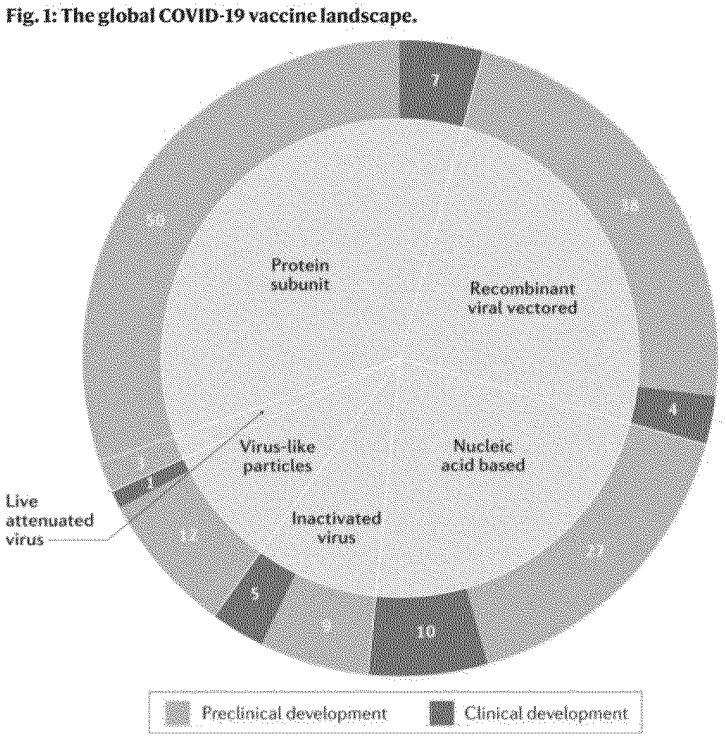
Future hope

Major forms of coronavirus vaccine



全球新冠疫苗研发现况（截至2020年9月9日，全球有180种候选疫苗）

- 35种进入人体临床试验，9种进入临床Ⅲ期
  - 非复制病毒载体（4）：Ad5 、ChAdOx1、 Ad5+ Ad26、 Ad26
  - RNA（2）：mRNA-1273、mRNA-BNT162b
  - 灭活疫苗（3）：中生北京所、中生武汉所、科兴
  - DNA：INO-4800等
  - 蛋白亚单位：NVX CoV2373等
- 145种在临床前研究阶段，主要技术路线：
  - 蛋白亚单位（51）
  - 非复制病毒载体（19）
  - 复制型病毒载体（19）
  - RNA（17），DNA（12）
  - 病毒样颗粒（12），灭活（9）
  - 减毒（3）



Jeyanathan, M., Afkhami, S., Smaill, F. et al. Immunological considerations for COVID-19 vaccine strategies. Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-00434-6
WHO: DRAFT landscape of COVID-19 candidate vaccines – 3 Sep 2020

我国新冠疫苗研发

企业	疫苗类型	临床试验	目标人群	剂次	进展
康希诺公司	Ad5载体疫苗	I期	18-60岁	1	完成
		II期	≥18岁	1	完成
		III期	≥18岁	1	俄罗斯
中生集团（武汉所）	灭活疫苗(Vero)+铝佐剂	I + II期	≥6岁	2	完成
		III期	≥18岁	2	阿联酋、秘鲁、摩洛哥、阿根廷、埃及
中生集团（北京所）	灭活疫苗(Vero))+铝佐剂	I + II期	≥3岁	2	完成
		III期	≥18岁	2	阿联酋、秘鲁、摩洛哥、阿根廷
北京科兴	灭活疫苗(Vero))+铝佐剂	I + II期	18-59岁;≥60岁	2	已完成
		III期	18-59岁, ≥60岁	2	巴西、印尼
医科院昆明所	灭活疫苗(Vero))+铝佐剂	I + II期	18-59岁	2	进行中
智飞龙科马	重组亚单位(CHO))+铝佐剂	I+ II期	18-59岁;≥60岁	2	进行中
华西医院	重组亚单位（Sf9）)+铝佐剂	I期	18-55岁;≥55岁	2	进行中
苏州艾博&沃森生物	mRNA疫苗	I期	18-59岁;≥60岁	2	进行中
复星医药/BioNTech	mRNA疫苗	I期	18-55岁;≥55岁	2	进行中
北京万泰	鼻喷流感病毒载体疫苗	I期	≥18岁	?	9月8日注册
艾棣维欣/Inovio	DNA疫苗	I期	18-59岁	2	9月11日注册

我国新冠疫苗研发进展

企业	类型	Ⅰ期	Ⅱ期	Ⅲ期	备注
艾棣维欣	DNA疫苗	9月11日			
北京万泰	流感病毒载体鼻喷疫苗	9月8日			
上海复星	mRNA疫苗	7月22日			
苏州艾博&云南沃森	mRNA疫苗	6月24日			
四川大学华西医院	重组蛋白疫苗（sf9）	8月28日			
智飞	重组蛋白疫苗（CHO）	6月25日	7月10日		
康希诺	Ad5腺病毒载体	3月18日	4月10日		
昆明所	灭活疫苗（vero）	6月4日			
北京科兴	灭活疫苗（vero）	4月28日			EUA
中生北京所	灭活疫苗（vero）	4月29日			EUA
中生武汉所	灭活疫苗（vero）	4月13日			

Hot Spot：ChAdOx1腺病毒载体疫苗（AZD1222）

- 由牛津大学与阿斯利康合作开发

- 腺病毒载体疫苗
- 以复制缺陷型猿猴腺病毒为载体，包含SARS-CoV-2的全长结构表面糖蛋白（S蛋白）的腺病毒载体疫苗
- 该平台尚未用于已批准的疫苗，但已在针对其他病毒（包括埃博拉病毒）的实验性疫苗中进行了测试。

- 临床试验分期：Ⅲ期临床试验

- 美国、英国、巴西、南非
- 18-55岁健康成人

※阿斯利康与深圳康泰公司签署了技术转让的合作协议

Folegatti et al., (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancet, https://doi.org/10.1016/S0140-6736(20)31604-4

AZD1222因疑似不良反应暂停临床试验

- 9月8日，阿斯利康表示一个英国受试者出现一种无法解释的疾病
  - 该公司该疫苗在全球临床试验都暂停，旨在确保受试者安全，
- 9月10日，阿斯利康CEO Pascal Soriot 在电话会议中表示
  - 患上无法解释疾病的受试者是否为**横贯性脊髓炎**仍正在检查
  - 今年7月也曾发现一名疫苗接种者出现了神经系统症状，也一度暂停临床试验，后被诊断患有多发性硬化症，独立审查小组结论为**多发性硬化症**与疫苗接种无关

9月12日，英国恢复了阿斯利康牛津冠状病毒疫苗AZD1222的临床试验

AstraZeneca 阿斯利康

Pascal Soriot 阿斯利康CEO

横贯性脊髓炎

- 脊髓局限性炎性病变过程，导致运动、感觉和自主神经功能障碍
  - 疼痛、肌肉无力、瘫痪、感觉问题或膀胱和肠道功能障碍
- 横贯性脊髓炎的确切病因不清楚
  - 一些影响脊髓的病毒、细菌和真菌感染可能导致横断性脊髓炎

Table 1 Cases of transverse myelitis following vaccination

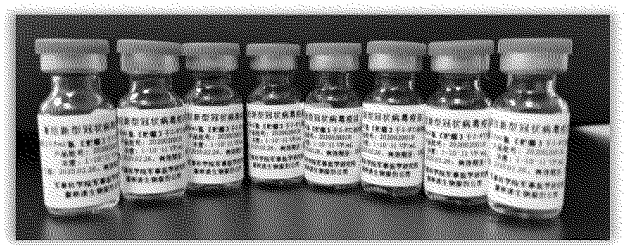
First author	*Year of publication*	*Vaccine*	*Age (years)*	*Time from vaccination*
Bir[69]	2007	Rabies	25	2 months
Das[67]	2007	Typhoid	19	5 days
Kelly[36]	2006	OPV + DT + Hib	0.5	7 days
Riel-Romero[43]	2006	DTP	0.7	17 days
Lim[68]	2004	Measles or Rubella	9	16 days
Kulkarni[51]	2004	Rabies	45	14 days
Fonseca[33]	2003	HBV	3	10 days
Nakamura[48]	2003	Influenza	70	7 days
Zanoni[69]	2002	MMR	1.25	21 days
Matsui[70]	2002	Japanese B encephalitis	4	14 days
Karaali-Savrun[34]	2001	HBV	42	2 months
		HBV	33	4 weeks
		HBV	40	3 weeks
		HBV	42	3 months
Larner[47]	2000	Influenza	42	Days9
Iñiguez[30]	2000	HBV	15	1 week
Renard[31]	1999	HBV	16	1 week
Tartaglino[28]	1995	HBV	40	2 weeks
Friedrich[38]	1995	OPV	12	6 years
		OPV	8	4 years
		OPV	13	9 years
Joyce[71]	1995	MMR	20	2 weeks
Abdul-Ghaffar[41]	1994	DT	13	3 days
Trevisani[72]	1993	HBV	11	3 weeks
Read[42]	1992	DTP	50	2weeks
D'Costa[37]	1990	Cholera, typhoid, OPV	24	2 days
Shaw[32]	1988	HBV	41.5	2 weeks
		HBV	*	12 weeks
		HBV	*	20 weeks
		HBV	*	27 weeks
Label[52]	1982	Rabies	50	2 days1
Clark[73]	1977	Rubella	16	13 days
Whittle[44]	1977	DTP	0.6	6 days
Holt[74]	1976	Rubella	17	2 weeks
	1976	Rubella	13	4 days
Kulenkampff[75]	1974	Pertussis	6	17 days
Harrington[60]	1971	Rabies	41	14 days

*41.5, average of all four cases presented by Shaw *et al.*[32]

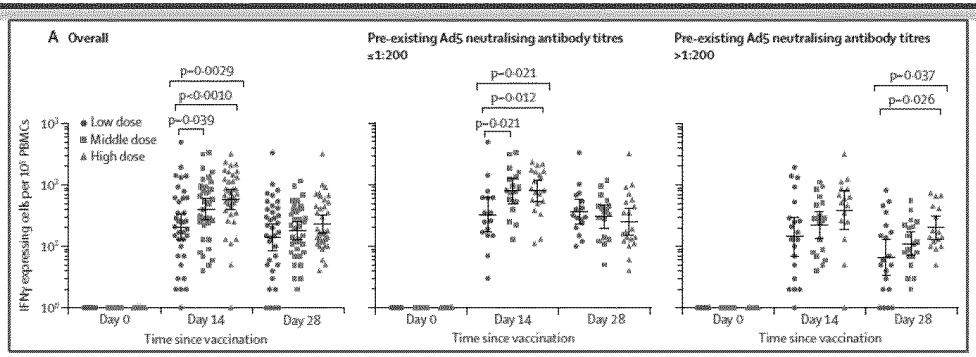
- **Johnson & Johnson: Ad26**

Virus vectored vaccine strategy: Ad5-COVID-19

CanSino Biological Inc. with Beijing Institute of Biotechnology



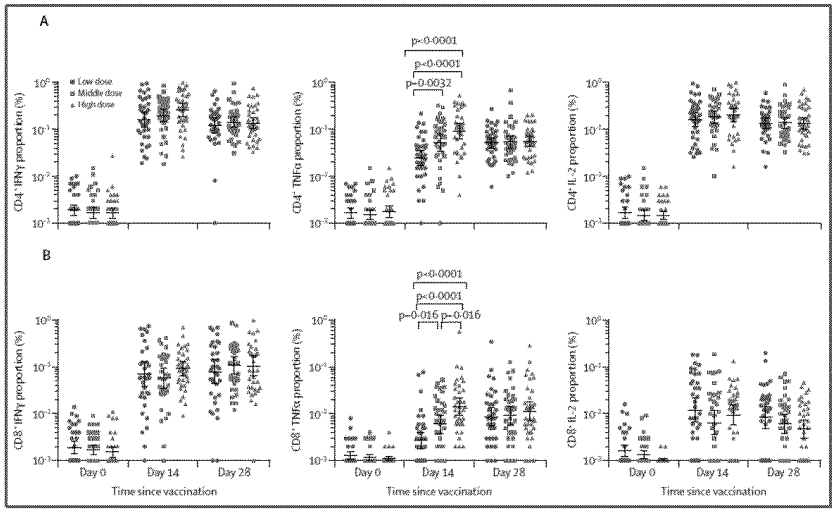
Approved for IND in China on17th, March, 2020



Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

Feng-Cai Zhu, Yu-Hua Li*, Xu-Hua Guan, Li-Hua Hou, Wen-Juan Wang, Jing-Xin Li, Shi-Po Wu, Bu-Sen Wang, Zhao Wang, Lei Wang, Si-Yue Jia, Hu-Dachuan Jiang, Ling Wang, Tao Jiang, Yi Hu, Jin-Bo Gou, Sha-Bei Xu, Jun-Jie Xu, Xue-Wen Wang, Wei Wang, Wei Chen*

In May, Lancet published the data for phase I clinical trials



Safety and immunogenic for both humoral and cellular responses

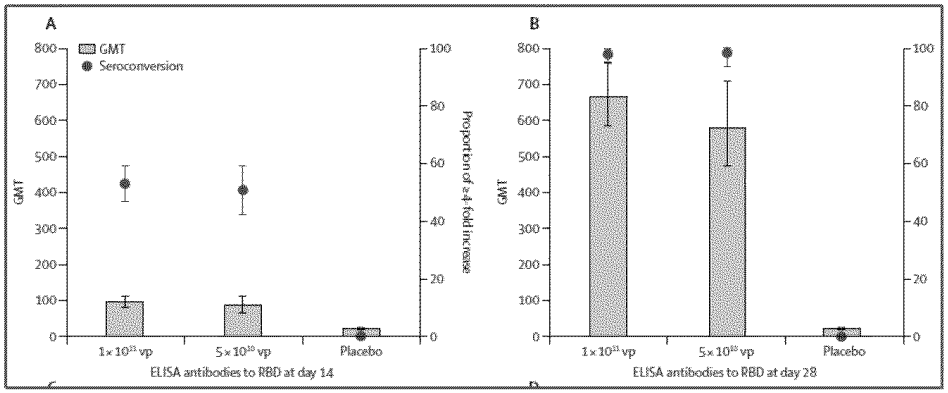
Virus vectored vaccine strategy: Ad5-COVID-19

CanSino Biological Inc. with Beijing Institute of Biotechnology

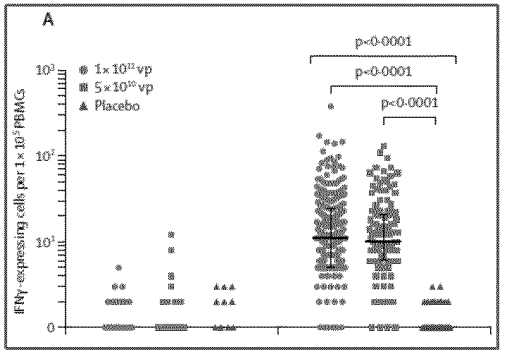
Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial

Feng-Cai Zhu, Xu-Hua Guan*, Yu-Hua Li, Jian-Ying Huang, Tao Jiang, Li-Hua Hou, Jing-Xin Li, Bei-Fang Yang, Ling Wang, Wen-Juan Wang, Shi-Pu Wu, Zhao Wang, Xiao-Hong Wu, Jun-Jie Xu, Zhe Zhang, Si-Yue Jia, Bo-Sen Wang, Yi Hu, Jing-Jing Liu, Jun Zhang, Xiao-Ai Qian, Qiong Li, Hong-Xing Pan, Hu-Dachuan Jiang, Peng Deng, Jin-Bo Gou, Xue-Wen Wang, Xing-Huan Wang, Wei Chen*

In Jul., Lancet published the data for phase II clinical trials



NCT04526990;
NCT04540419

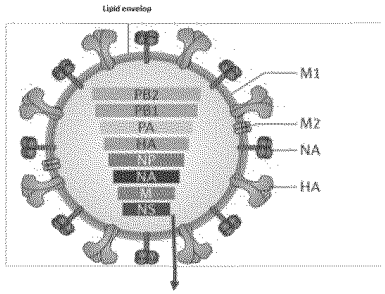


Safety and immunogenic for both humoral and cellular responses

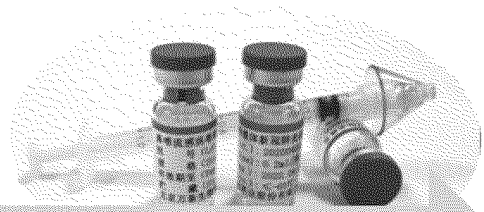
Currently under Phase III overseas multi-center clinical trials

鼻喷流感载体新冠肺炎疫苗

- 由厦门大学、香港大学和北京万泰生物药业股份有限公司共同研发
- 核心技术是CA4-DelNS1，是将California/04/2009(H1N1)流感病毒株的NS1基因敲除后再经低温适应获得的减毒且温度敏感的双重减毒流感载体，缺失NS1可显著增强T细胞免疫应答
- 该疫苗是在CA4-DelNS1内插入新冠病毒RBD基因片段研制而成的活病毒载体疫苗，是目前已获准开展临床试验的新冠肺炎候选疫苗中唯一采用鼻腔喷雾接种方式的疫苗



DelNS1-nCoV-RBD-OPT1



1月27日启动研发　　8月27日获批临床　　9月1日启动一期临床

鼻喷流感载体新冠肺炎疫苗

- 该疫苗在动物模型中呈现出对流感病毒和新冠病毒的双重保护效果：
  - ✓ 小鼠实验显示：对甲型H1N1流感病毒的致死性感染保护率为100%。
  - ✓ hACE2小鼠和仓鼠实验显示：攻毒对照组肺组织出现中至重度病理损伤且体重明显下降，疫苗免疫可明显减轻肺组织病理损伤，体重无明显下降。
- 该疫苗通过模拟呼吸道病毒天然感染途径激活局部和全身性免疫应答，在动物体内可诱导出较强的RBD特异性细胞应答，尤其以肺组织局部T细胞应答为突出特征，同时可检测到RBD特异性抗体应答，包括粘膜局部的IgA。
- 该疫苗于9月1日启动一期临床试验，已完成63名受试者接种，显示出良好安全性：
  - ✓ 正常年龄组 (18-59岁) 不良反应发生率为28.13% (9/32)，其中2级2人，1级7人。

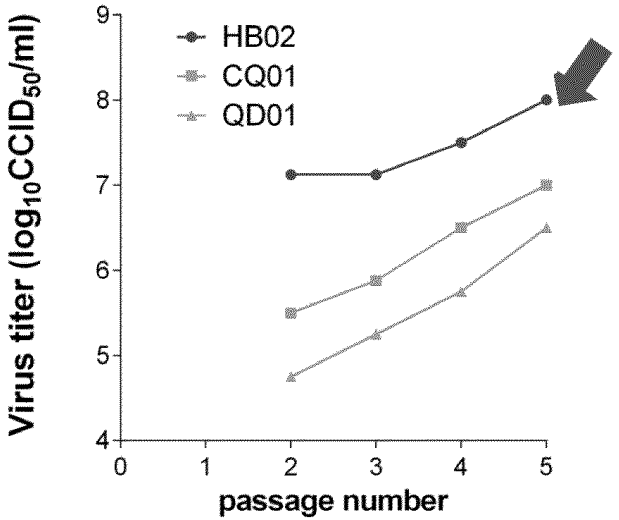
- **Inactivated vaccine, BBIBP-CorV**
- **Protein subunit vaccine**

Seed virus selection for COVID-19 vaccine

3 virus strains isolated from broncho-alveolar lavage samples or throat swabs of 3 hospitalized patients

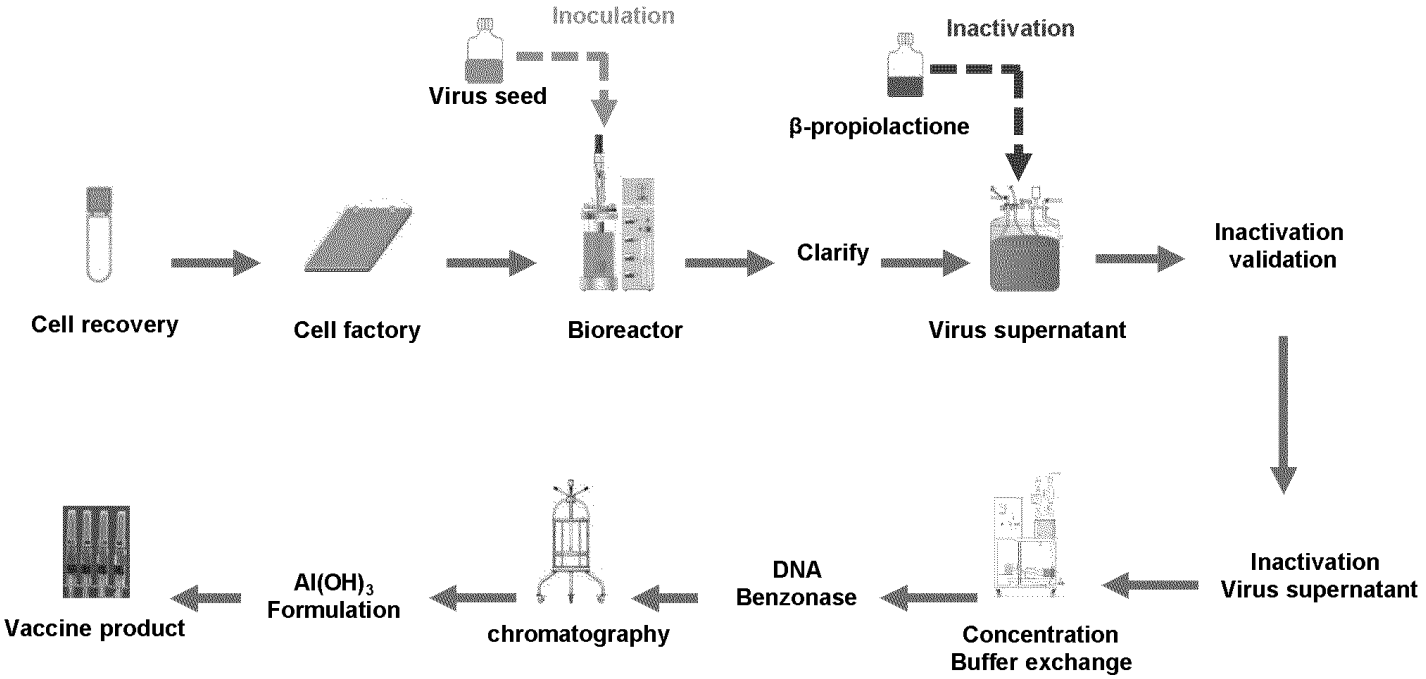
- 19nCoV-CDC-Tan-HB02
- 19nCoV-CDC-Tan-Strain03 (CQ01)
- 19nCoV-CDC-Tan-Strain 04

Lu et al, Lancet, 2020
Zhu et al, NEJM, 2020



Wang et al., Cell, 2020

Flowchart of preparing the inactivated COVID-19 virus vaccine, BBIBP-CorV



Wang et al., Cell, 2020

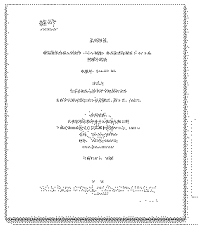
Time-course of the BBIBP-CorV vaccine development

COVID-19 vaccine started

2020.1.25

2020.2

Confirm the workshop design plan



Initiate animal safety evaluation studies

2020.3

The first batch of inactivated stock solution was prepared successfully

Start rolling submission of IND application

2020.4

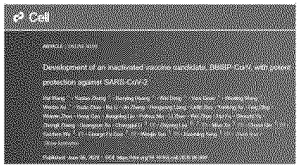
Many batches of samples obtained the qualified report of the Chinese People's Procuratorate

BBIBP-CorV vacine advanced into Phase II

2020.5

4.27 Obtain clinical trial approval

4.29 First subject inoculation



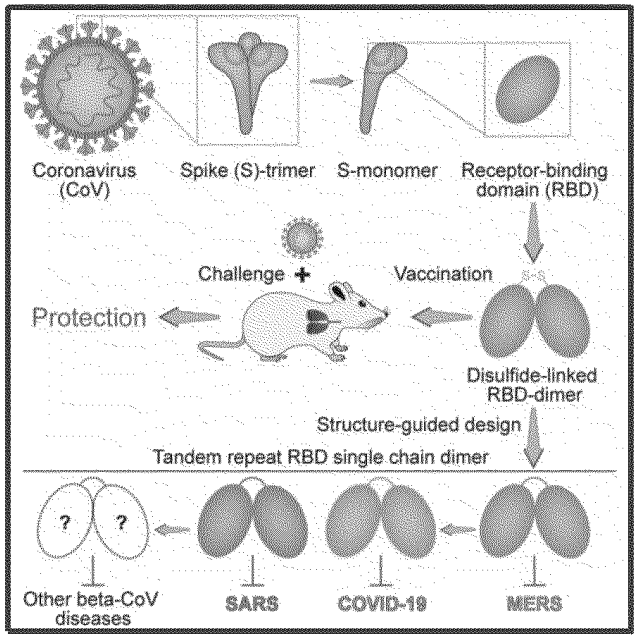
2020.6

Studies on BBIBP-CorV vacine published in Cell journal

6.28. Phase Ⅰ/Ⅱ clinical trials unblinding. Seroconversion of NAbs are 100% for the all receipients

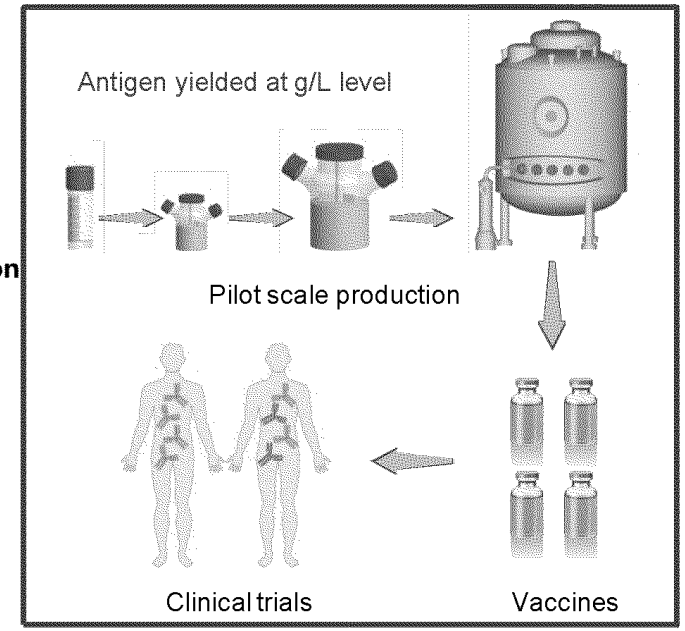
- **Inactivated vaccine, BBIBP-CorV**
- **Protein subunit vaccine**

Overview of the protein subunit COVID-19 vaccine



Translation

ZFSW

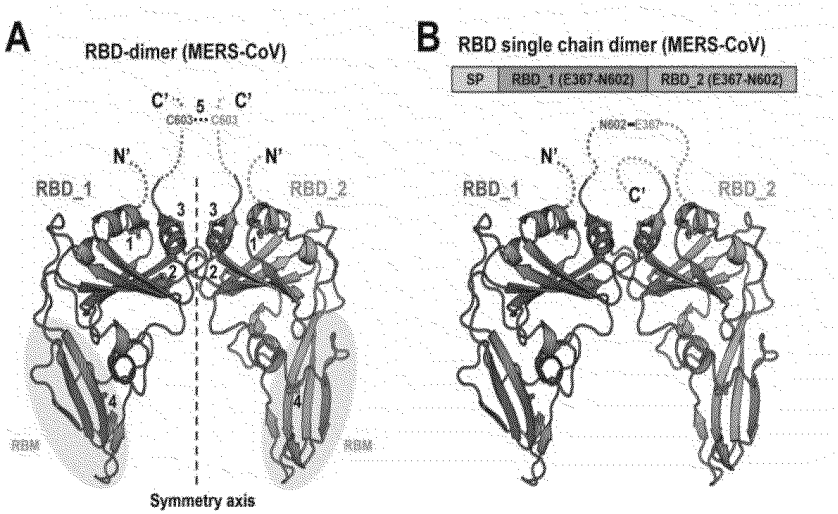


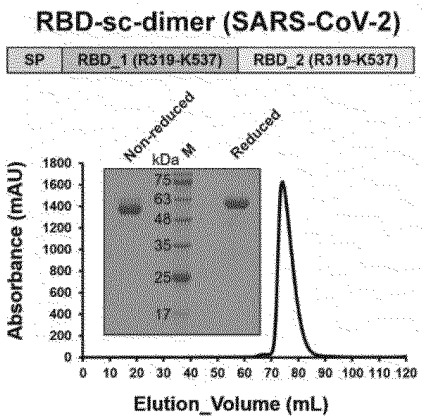
* A universal design of betacoronavirus vaccines

Dai et al., 2020, Cell

* The **first** protein subunit COVID-19 vaccine approved for clinical trials in China and the **second** in the world

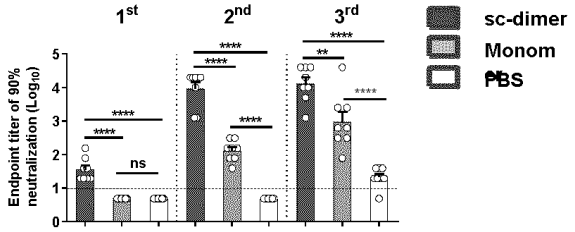
Rational design of tandem repeat RBD single chain dimer





A homogeneous RBD-dimer

- A generalizable strategy to design vaccines against MERS, COVID-19, SARS and other CoV diseases



- RBD-sc-dimer induced significantly higher NAbs compared to conventional monomer

Dai et al., 2020, Cell

Clinical trials of the first protein subunit vaccine in China

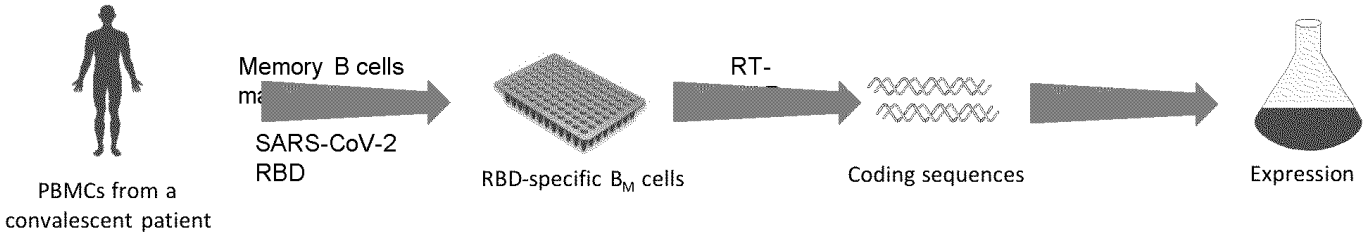
The first human volunteer in trial

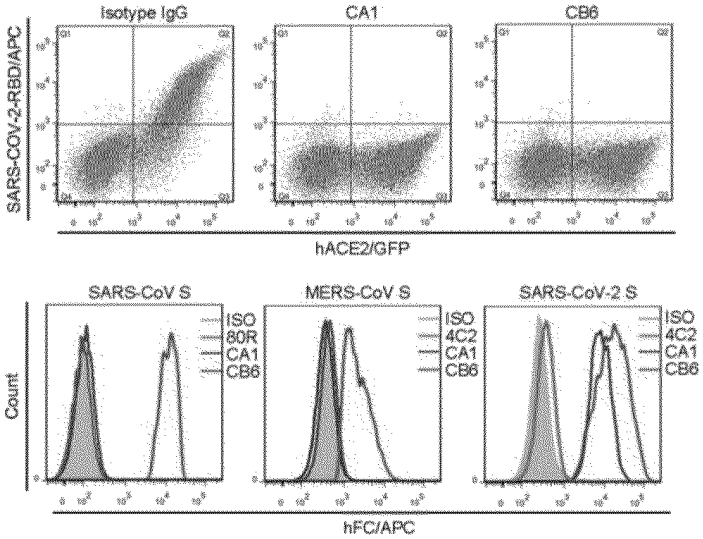
On 19 June 2020, vaccine was approved by the NMPA to enter Phase I clinical trials in China

On 10 July 2020, vaccine enters Phase II clinical trials in China

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/regulatory status-Coronavirus candidate	Same platform for non-Coronavirus candidates
Inactivated	Inactivated + alum	Sinovac	SARS-CoV2	Phase 3 NCT04456595 Phase 1/2 NCT04383574 NCT04352608	SARS
Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	SARS-CoV2	Phase 3 ISRCTN89951424 Phase2b/3 2020-001228-32 Phase 1/2 PACTR202006922165132 2020-001072-15	MERS, influenza, TB, Chikungunya, Zika, MenB, plague
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	SARS-CoV2	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906	Ebola
Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	SARS-CoV2	Phase 2 NCT04466085 Phase 1 NCT04445194	MERS

Isolation of RBD-specific memory B cells in a convalescent patient

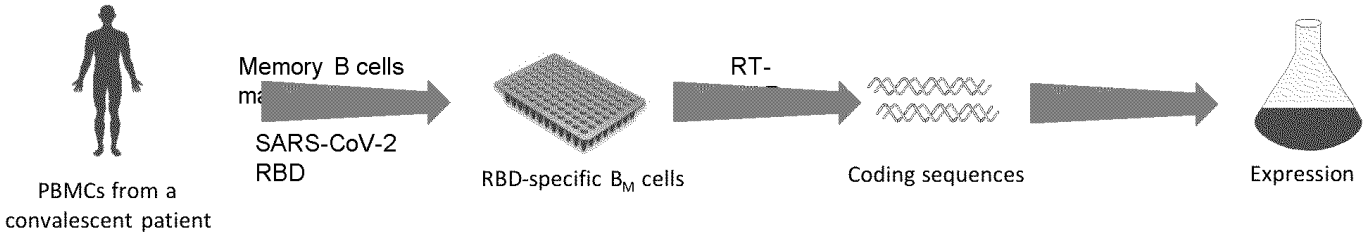


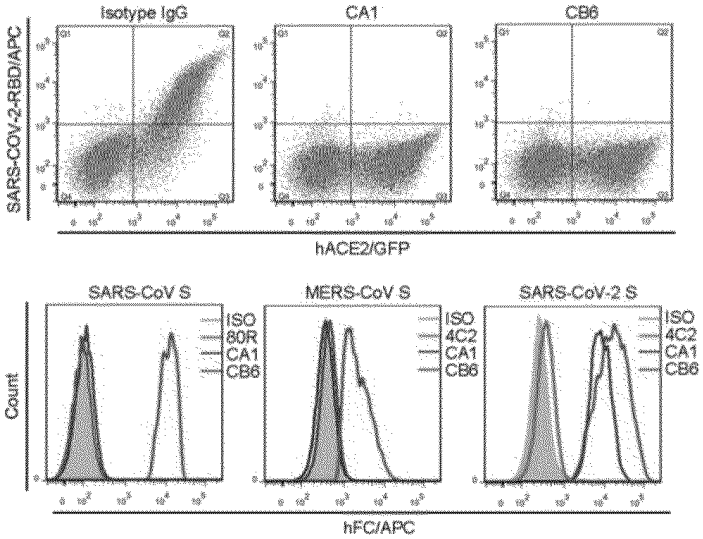


- Two mAbs-containing supernatant blocks the interaction between soluble COVID-19 virus RBD and 293T-hACE2 cells, respectively.
- Both CA1 and CB6 are specific to interact with COVID-19 virus S protein

Shi et al., 2020, Nature

Isolation of RBD-specific memory B cells in a convalescent patient

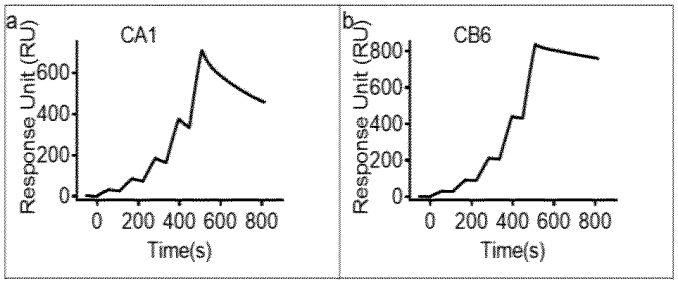




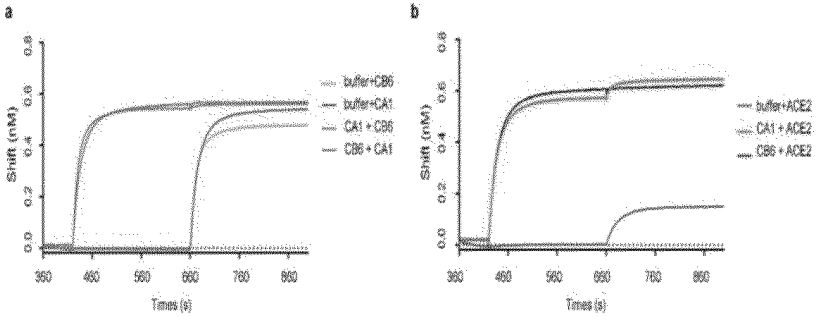
- Two mAbs-containing supernatant blocks the interaction between soluble COVID-19 virus RBD and 293T-hACE2 cells, respectively.
- Both CA1 and CB6 are specific to interact with COVID-19 virus S protein

Shi et al., 2020, Nature

Binding affinity between mAbs and RBD



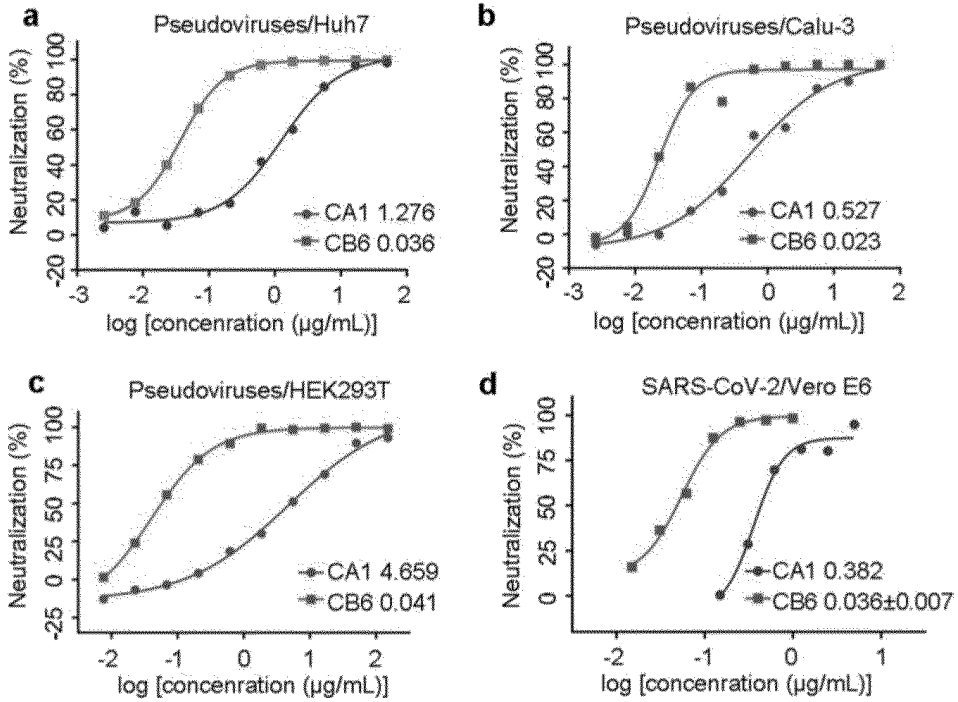
	ka (1/Ms)	kd (1/s)	K_D (M)
CA1/RBD	3.98E+06	1.16E-02	2.92E-09
CB6/RBD	8.95E+05	7.29E-04	0.82E-09
ACE2/RBD	3.82E+04	5.15E-03	133.3E-09



- The binding affinity between mAbs and RBD are stronger than that between the receptor and RBD
- CA1 and CB6 bind to the overlapped epitopes

Shi et al., 2020, Nature

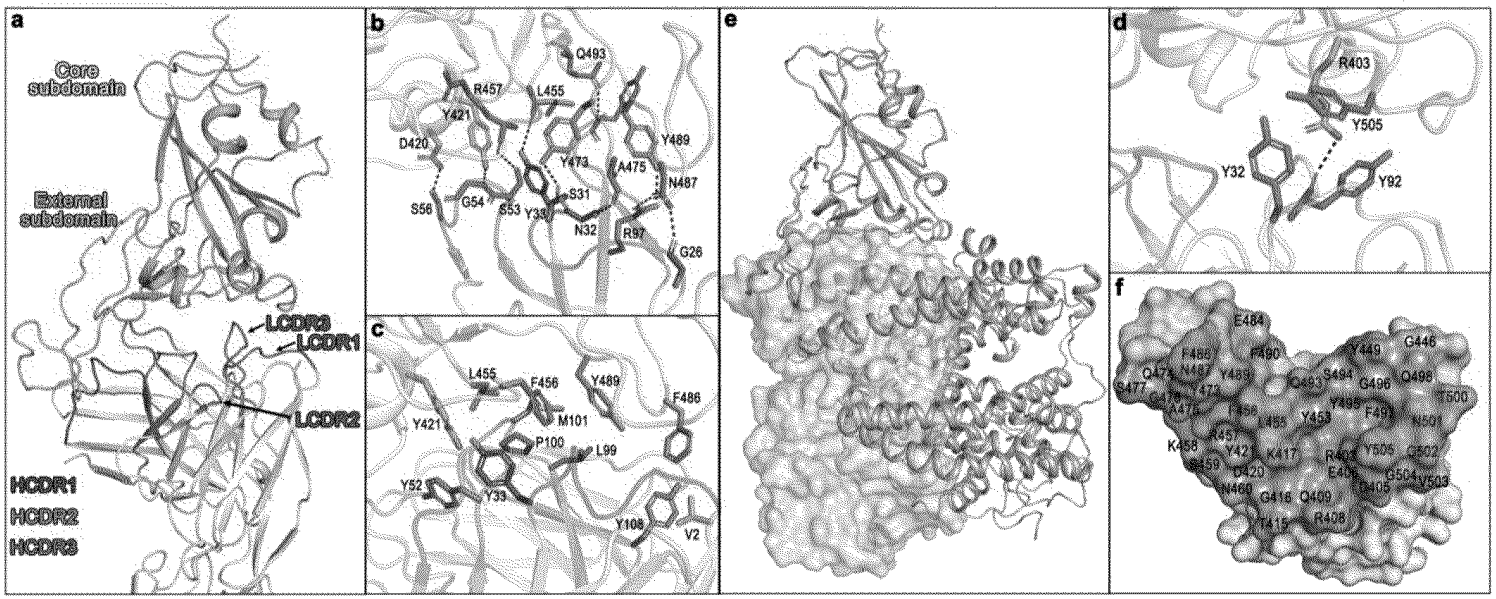
CB6 and CA1 can effectively neutralize COVID-19 virus



- CB6 and CA1 can effectively neutralize COVID-19 virus pseudovirus and live COVID-19 virus *in vitro*.

Shi et al., 2020, Nature

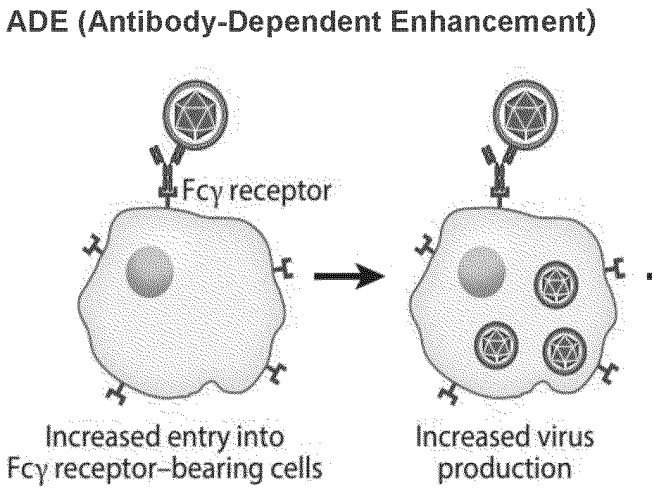
CB6 and CA1 can effectively neutralize COVID-19 virus

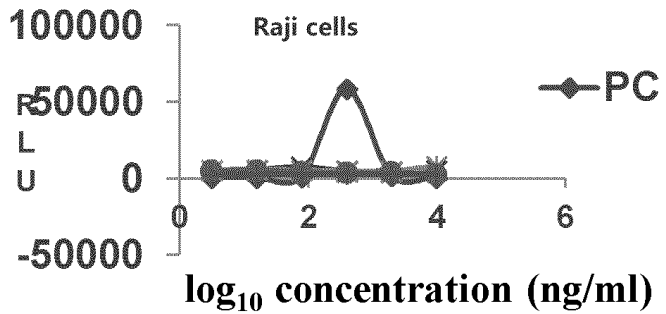


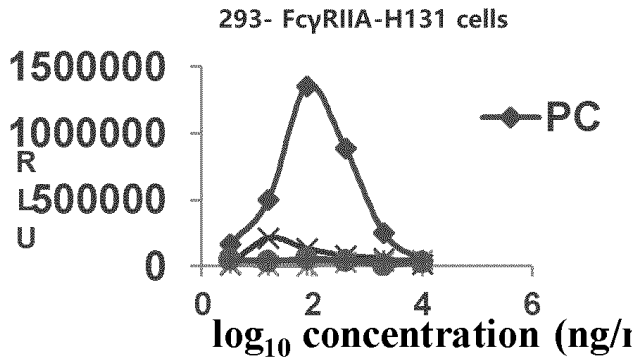
- CB6 competes with the receptor to interact with the same residues of COVID-19 virus RBD
- Both of CB6 heavy chain and light chain sterically hinder the interaction of COVID-19 virus RBD with hACE2

Shi et al., 2020, Nature

CB6-LALA to eliminate the potential ADE effect



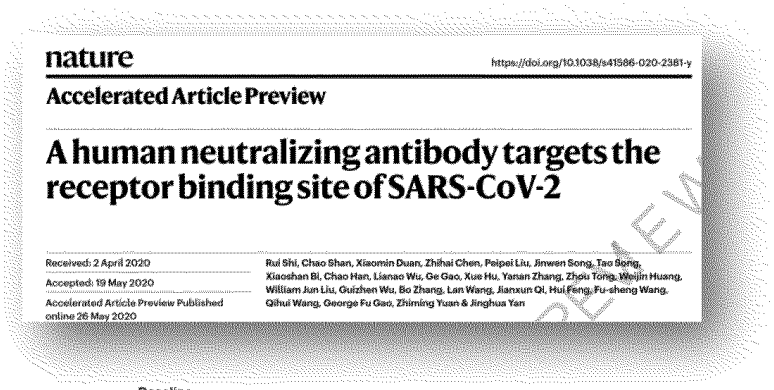


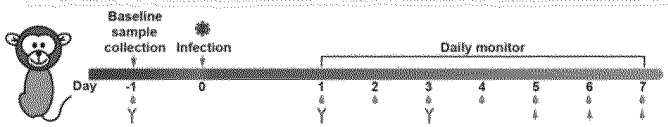


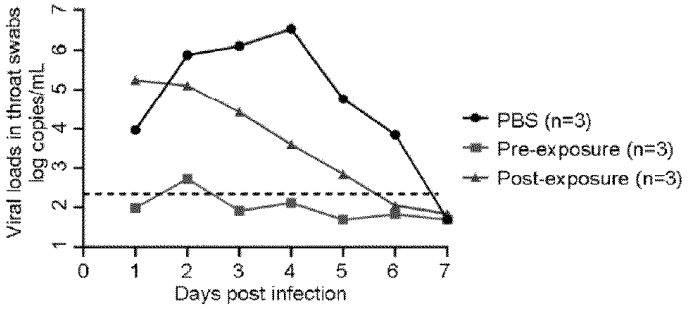
- No detectable ADE effect for CB6-LALA *in vitro*

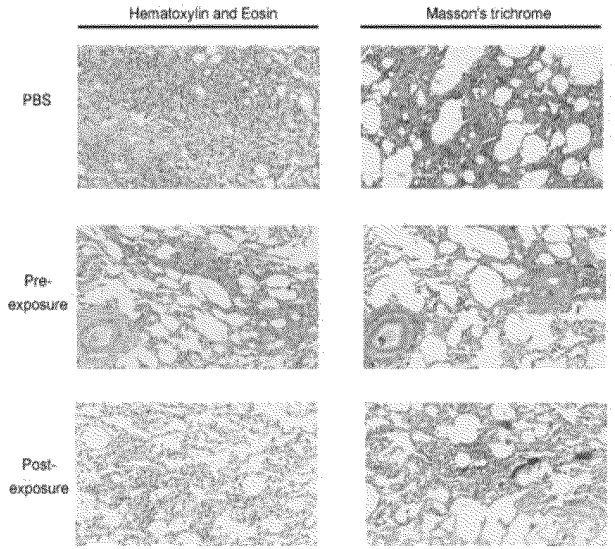
Unpublished data

CB6-LALA protects NHPs from COVID-19 virus infection





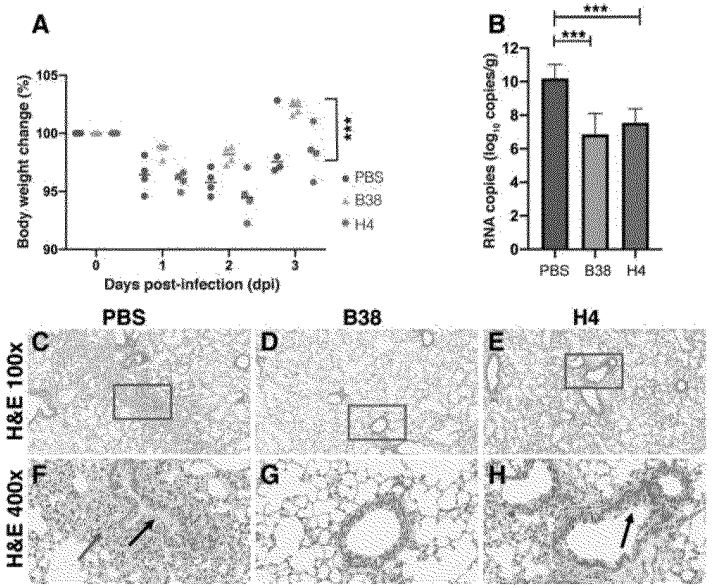


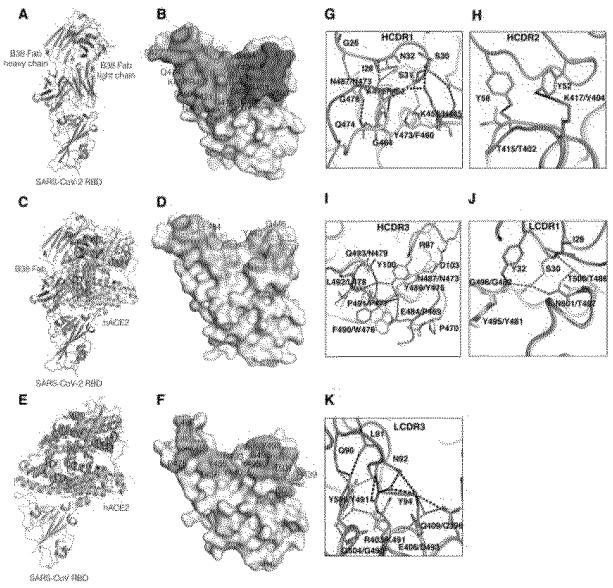


- CB6 decreased the viral loads in the throat swabs in NHPs at both prophylactic and treatment settings
- CB6 reduced the infection-related lung damage of challenged NHPs at both groups

Shi et al., 2020, Nature

Multiple neutralizing MAbs could prevent the escape mutations





- The protection efficiency of MAbs in hACE2 mice model post infection with COVID-19 virus
- Structural analysis of B38 and COVID-19 virus RBD complex and the epitope comparison between B38 and hACE2

Wu et al., 2020, Science

A pair of noncompeting human neutralizing MAbs against COVID-19 virus

Science

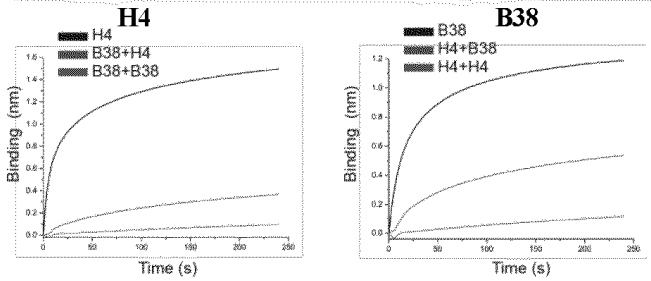
REPORTS

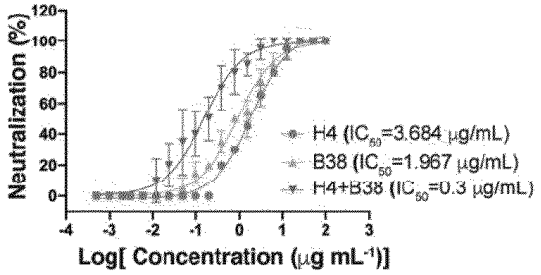
Cite as: Y. Wu et al., Science 10.1126/science.abc2241 (2020)

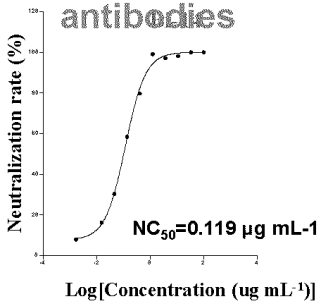
A noncompeting pair of human neutralizing antibodies block COVID-19 virus binding to its receptor ACE2

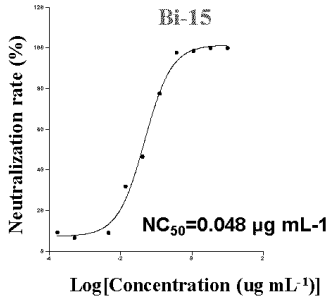
Yan Wu[1,2*†], Feiran Wang[3,4†], Chengyang Shen[5,6†], Weiyu Peng[5,6†], Delin Li[1,2,3*], Cheng Zhao[5,6], Zhaohui Li[7,8], Shihua Li[9], Yuhai Bi[9,10], Yang Yang[5], Yuhuan Gong[9,10], Haixia Xiao[7], Zheng Fan[5], Shuguang Tan[5], Guizhen Wu[11], Wenjie Tan[11], Xuancheng Lu[12], Changfa Fan[13], Qihui Wang[9], Yingxia Liu[9], Chen Zhang[5], Jianxun Qi[9], George Fu Gao[9,14], Feng Gao[7*], Lei Liu[5*]

- H4 and B38, a pair of noncompeting human neutralizing MAbs, synergistically prevent COVID-19 virus infection
- The neutralizing activity of bispecific antibody Bi-15 against COVID-19 pseudovirus is **10 times stronger** than those of parental monoclonal antibodies









Wu et al., 2020, Science

Unpublished data

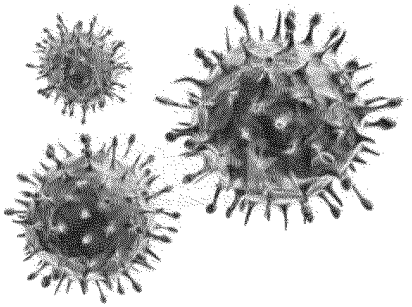
CB6 advanced into clinical trials in both China and America

- On 5 June 2020, CB6 was approved by the NMPA to enter Phase I clinical trials in China
- On 8 June 2020, CB6 was approved by the FDA to enter Phase I clinical trials in America

Name ▲	Target ▲	Format ▲	Status ▲	Developer/Reseacher ▲
REGN-COV2 (dual mAb cocktail)	SARS-CoV-2 S protein	mAb	Phase 1	Regeneron
LY-CoV555	SARS-CoV-2 S protein	mAb	Phase 1	AbCellera/Eli Lilly
JS016	SARS-CoV-2 S protein	mAb	Phase 1	Junshi Biosciences/Institute of Microbiology, Chinese Academy of Sciences/Eli Lilly
TY027	SARS-CoV-2 S protein	mAb	Phase 1	Tychan

Outstanding questions

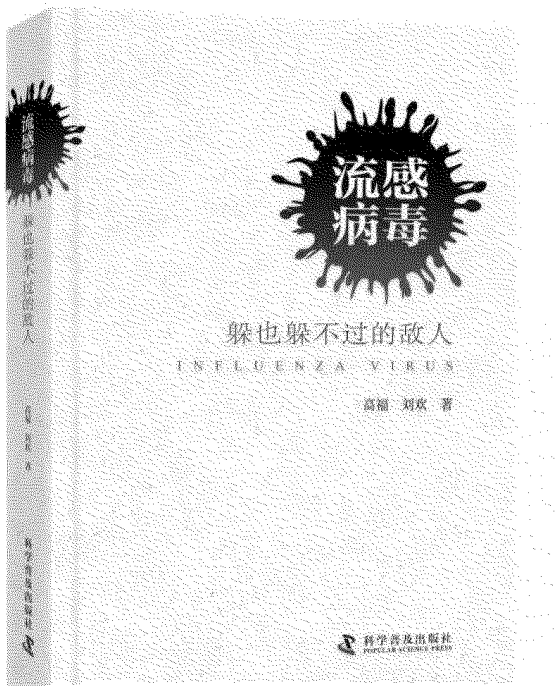
- Correlations of neutralizing MAbs with protection
- Reach of neutralizing MAbs to lung
- Lasting time of neutralizing MAbs in vivo
- Antibody-dependent enhancement (ADE) effect
- Best Immunization programs and the pro and con of all the vaccines
- Stratified/prioritized vaccination program



流感病毒

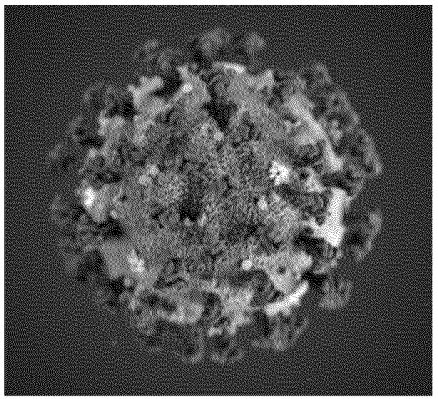
躲也躲不过的敌人

THANK YOU



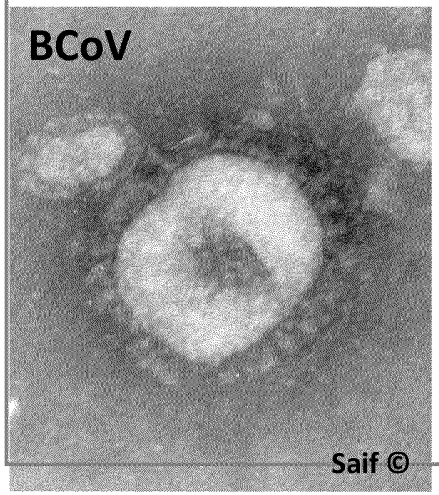
Emerging coronaviruses of humans and animals: Immunity and vaccines

SARS-CoV-2



Linda J. Saif

BCoV



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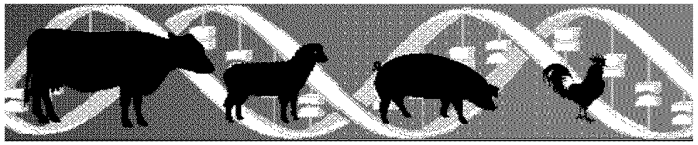
COLLEGE OF FOOD, AGRICULTURAL, AND ENVIRONMENTAL SCIENCES



Food Animal Health Research Program

College of Veterinary Medicine
The Ohio State University

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7 Human Coronviruses —Respiratory infections
6 Swine and 1 Bovine CoV —Enteric/respiratory infections

Human CoVs

- **Endemic--Common Cold** (Population has immunity, but lasts only ~1yr)
  - Alpha-CoVs- HC 229E,NL63
  - Beta-CoVs- HC OC43, HC HKU1
- **Epidemic/Pandemic-- Pneumonia** (Naïve population, no immunity)
  - Beta-CoVs- SARS, MERS, SARS-CoV-2

Bovine CoVs

- **Endemic—Respiratory/Diarrhea**
  - Beta-CoV- BCoV

Porcine CoVs

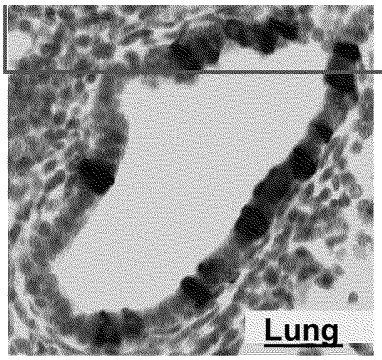
- **Endemic--Gastroenteritis**
  - Alpha-CoVs- TGEV, PEDV
- **Endemic--Respiratory**
  - Alpha-CoV- PRCV
- **Endemic--Encephalomyelitis**
  - Beta-CoV- HEV
- **Epidemic-- Diarrhea** (Naïve population, no immunity)
  - Alpha-CoV- SADS
  - Delta-CoV- PDCoV

Bovine and most human CoVs belong to the *betacoronavirus* genus; most swine CoVs belong to the *alphacoronavirus* genus

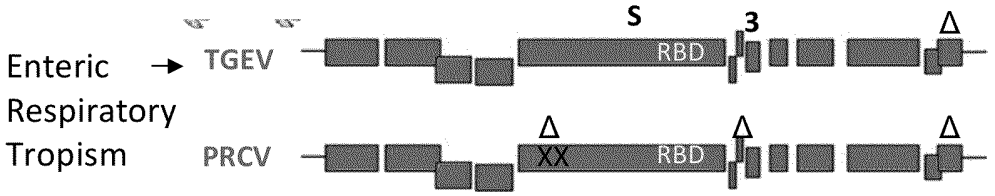
Questions Addressed:
SARS-CoV-2 and Porcine and Bovine CoVs

- How does SARS-CoV-2 cause disease compared with a porcine and bovine respiratory CoV?
- What are the unknowns/gaps for SARS-CoV-2 vaccines and lessons learned based on porcine and bovine CoV vaccines?

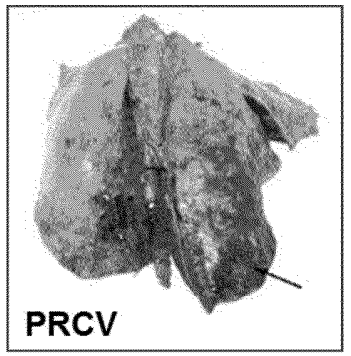
  -- What are the correlates of protection?
  -- What are the lessons for immunity from similar next Gen platform swine experimental CoV vaccines?
  -- What are the correlates of immunity based on immunity to bovine respiratory CoV infections?



Porcine respiratory CoV (PRCV) mutant of TGEV



XX S 681nt Δ
-Loss SA binding
ORF 3 Δ
-Nonfunctional



- TGEV causes fatal diarrhea in baby pigs
- PRCV--S gene deletion mutant of TGEV (621 – 682 bp, N-terminus) emerged in 1980s
- TGEV and PRCV share APN receptor; tissue tropisms differ due to loss of SA binding (gut mucins) by PRCV Spike *(Schultze et al 1996)*
- Lost of enteric tropism and virulence

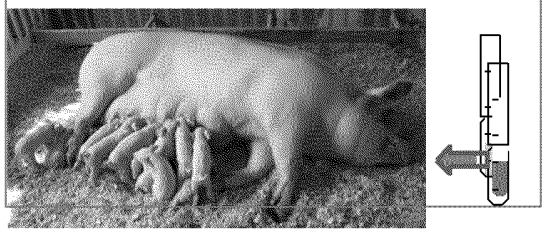
Similarities to SARS CoV-2 respiratory infections

- PRCV infects epithelial cells of upper/lower respiratory tract and type I and 2 pneumoctyes *(Jung/Saif et al 2007 JVI)*
- Most infections mild or subclinical— walking pneumonia like > 50% asymptomatic COVID-19 cases *(Long, QX et al 2020 Nat Med)*
- Atypical pneumonia in most pigs resembles SARS-CoV-2 lesions *(Saif, Jung, 2020 JCM)*: ***PRCV as a BSL2 respiratory CoV model for COVID-19***

Lessons from Swine Coronavirus Veterinary Vaccines

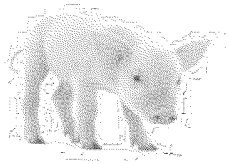
Swine Enteric/Respiratory Coronaviruses: TGEV/PRCV

- Only 2-3X attenuated oral enteric CoV vaccine induced gut/milk IgA Abs: Correlate of immune protection *(Chatta, Roth, Saif 2015 ARAB; Langel/Saif et al 2020 Pathogens)*
  - *GALT-Mammary gland SIgA axis*



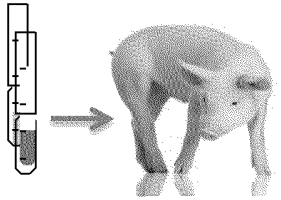
Mother

Gut IgA Ab- Immunity against CoV



Suckling piglet

Milk IgA Abs-Passive immunity



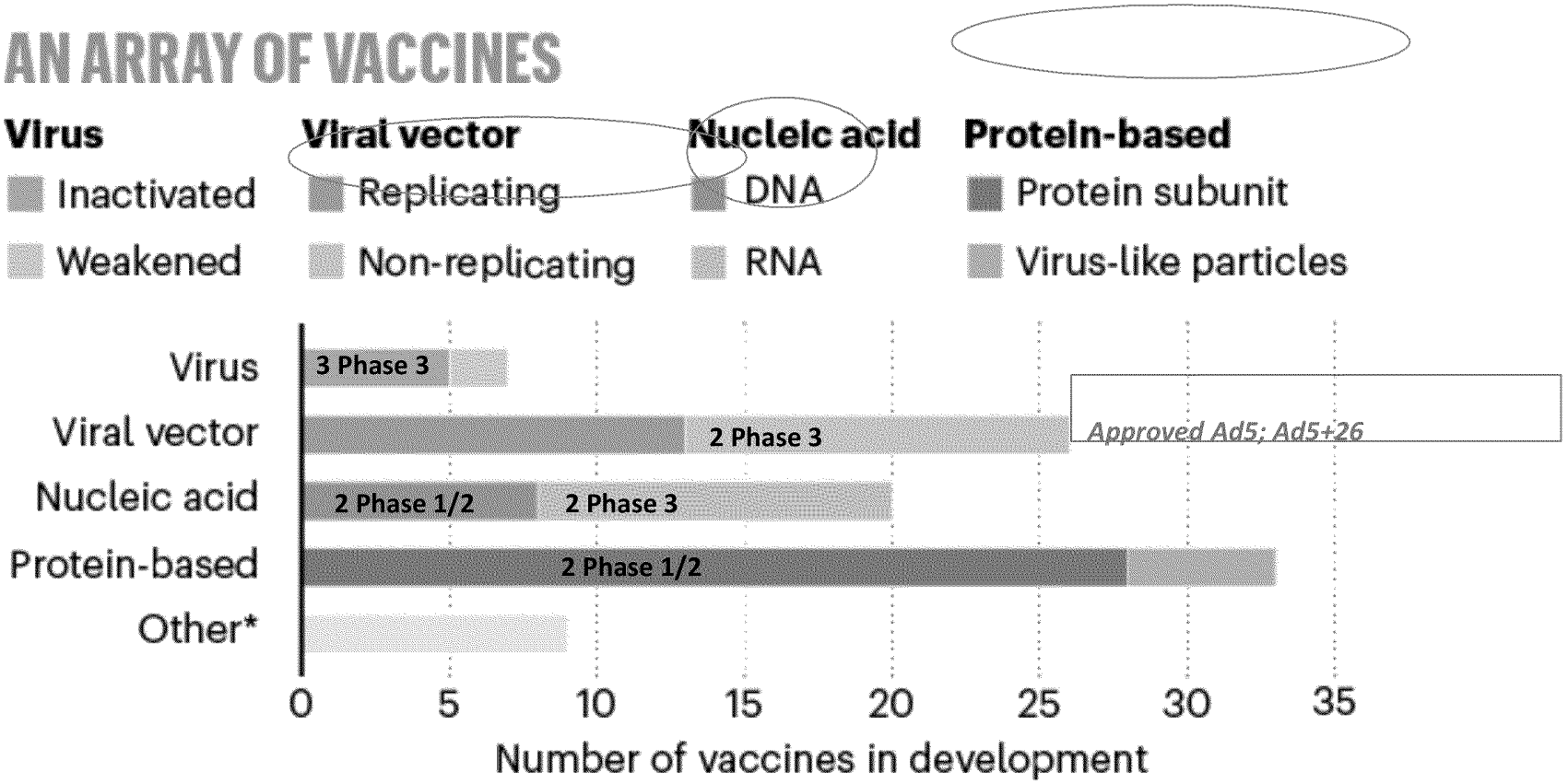
Weaned piglet

Gut IgA Ab-Active immunity: Prevent disease and infection

- Repeated PRCV infections induce IgA Abs and immunity to TGEV *(Sestak/Saif et al 1996 AJVR)*
  - *BALT-Mammary gland SIgA axis*

PRCV as naturally occurring TGEV vaccine

COVID-19 Vaccines



* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

(Modified E Callaway Nature 30 April 2020)

©nature

Lessons from Molecular Vaccines for Swine CoVs

➢ Molecular next Gen vaccines have advantages (if safe & effective)

-- Provide a platform for rapid production of vaccines for new emerging diseases

-- Backbone constructs to insert key antigens for new viruses with established manufacturing

Will these unproven vaccines be effective to prevent disease and shedding (transmission)?

Recombinant vector vaccines:

PRCV respiratory vaccine

— Recominant experimental human adenovirus (Ad)+PRCV S1

Enteric CoV vaccines — PEDV

— PEDV -Recominant experimental human Ad5+PEDV S1

— PEDV- iPEDV+ (PED RNA)vaccine—Viral Replicon Particle (VRP)= VEEV based replicon vaccine encoding PEDV S replicon RNA

- Non-replicating single cycle RNA in DCs

Recombinant Vector Vaccines: rAd vaccines for porcine CoVs

Antigen/ Vector	Route (dose)	Challenge Inoculum	VN Ab Serum	Protection against Morbidity	Protection against Infection
PRCV respir.			*(Callebaut et al, J Gen Virol 1996;4-wk-old pigs)*		
H Ad5 /S_{A+D} (1220aa) (A+)	**Oronasal 1x**	**PRCV**	**Yes (low)**	**NT**	**Partial (shorter)**
H Ad5 Control	**Oronasal 1x**	**PRCV**	**No**	**NT**	**None**
PEDV enteric			*(Crawford et al, Virus Res 2016; 8 and 20-wk-old pigs)*		
H Ad5/S1 PEDV	**IN 1X**	**PEDV**	**(PreC) No**	**Partial**	**No**
			(Post) Yes (3x)		
Control	**--**	**PEDV**	**No**	**No**	**No**
			Yes		

The human Adeno-S vaccine 1x elicited only partial respiratory immunity to PRCV and marginal enteric immunity to PEDV: multiple doses needed?

Lessons from Molecular Vaccines for Swine CoVs

Recombinant vector/virus and subunit vaccines:

Enteric CoV vaccines — TGEV and PEDV

— TGEV -S recombinant vaccine—ineffective in naïve pigs, but effective as booster vaccine after 1x oral attenuated vaccine *(Shoup/Saif et al, 1997; Park/Saif et al,1998)*

— PEDV -PED RNA (iPEDV+) vaccine—Viral Replicon Particle (VRP) VEEV+ PEDV S replicon RNA

- 1-3X IM doses in pregnant sows showed low efficacy (only 14-22% less mortality vs controls) in piglet protection in manufacturer's studies *(Crawford et al 2016)* and only 3% less in an independent study *(Greiner et al 2015)*
- Low milk VN Ab titers (50%+,<80) vs milk (100%,>320) of wt PEDV orally inoculated sows *(Sherba et al 2016)*

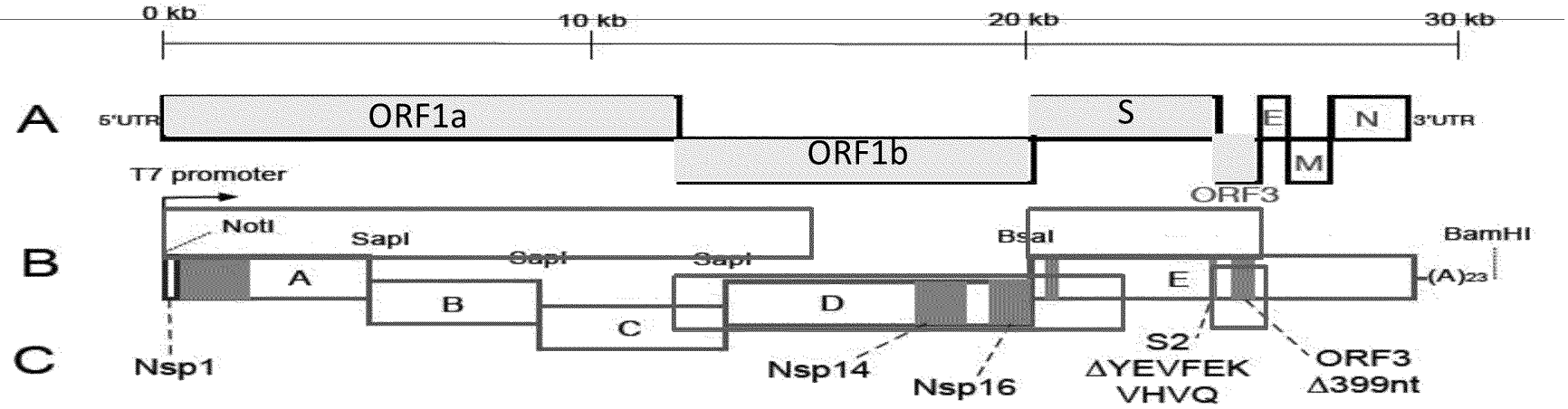
— PEDV -Recominant live attenuated virus vaccine developed by introduction of attenuating mutations into infectious clone (Lead PI: Dr Q. Wang, OSU)

Strategy to generate safe attenuated CoV vaccines using iclones

PEDV

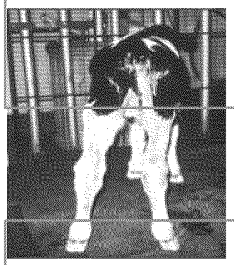
- Target genes that encode innate immune response modulators (nsp1,nsp16) and virus replication (nsp14), non-essential sequences of S protein and the accessory gene ORF3

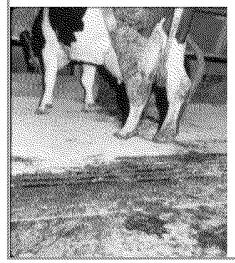
- Introduce at least 2 distinct mutations into separate genes that attenuate the virus to increase genetic stability

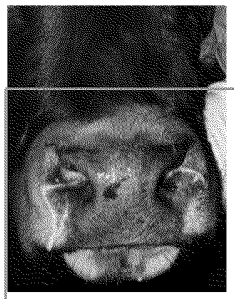


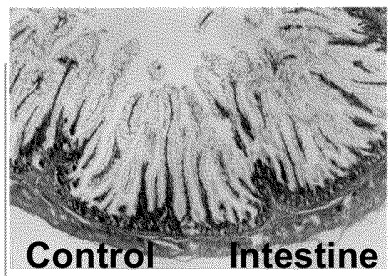
(Hou Y, Ke H, Kim J, Yoo D, Su Y, Boley P, Saif LJ, Wang Q. 2019. J Virol)

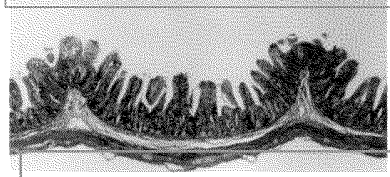
Three Clinical Syndromes Occur for Bovine Beta-CoV A Infections











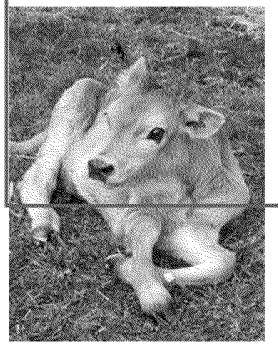
Enteric Infections Calf diarrhea • Diarrhea, dehydration • Intestinal villous atrophy	Age Groups/Vaccines Birth to 4 wks of age IM inact or atten virus vaccine in pregnant cow
Winter dysentery • Bloody diarrhea ± upper respiratory infection • Intestinal villous atrophy	Adults, but not calves *No Vaccine*
Respiratory Infections Calf respiratory disease Bovine respiratory disease complex (Shipping Fever) •Cough, nasal discharge, pneumonia	2 wks to 6 months 6-9-mo-old feedlot cattle *No Vaccine*

Saif ©

BCoVs are endemic, pneumoenteric, age effects for clinical syndromes *(Saif, Jung 2020 JCM)*

Some SARS-CoV-2 patients have diarrhea, shed virus in stools

Lessons from BCoV respiratory infection: Correlates of protective immunity in calves



- Strong correlation between serum antibody titers to BCoV and respiratory disease and IgA antibody titers in nasal secretions and nasal shedding in field studies

Calves (Heckert/Saif et al, 1990, 1991)

- *Calves (birth to 20 weeks) shed BCoV repeatedly in nasal secretions, often subclinically (short lived mucosal immunity?)*
- *Calves with IgA antibodies (titer >100) in nasal secretions did not show recurrent BCoV nasal shedding*
- *Correlation between serum antibody titers to BCoV at 24hrs of age and subsequent number of respiratory sick days*

Develop COVID-19 vaccines that elicit both systemic and mucosal immunity?

Lessons from BCoV respiratory infections: Correlates of protective immunity in feedlot cattle

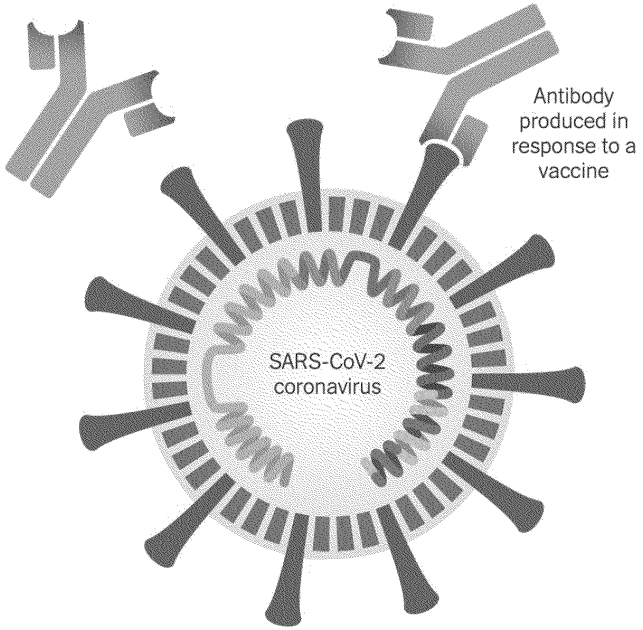
- In Feedlot cattle BCoV serum antibody titers may be a marker for respiratory protection
  - *Antibody isotype (IgG, IgA) and neutralizng titer in serum of cattle at arrival in feedlots were correlated with protection against respiratory disease, pneumonia or BCoV shedding* *(Cho/Saif et al, 2001; Lin et al, 2001; Hasoksuz/Saif et al 2002; Thomas/Saif et al, 2005)*

Strategy: Use vaccines to boost memory antibody responses to BCoV to rapidly increase antibody titers

- *Calves vaccinated IN with an attenuated BCoV vaccine at entry to feedlots had reduced risk for treatment for shipping fever pneumonia* *(Plummer et al, 2004)*

Challenges for COVID-19 Vaccines

- Rapidly deployed nucleic acid or viral vector vaccines may be a 1st generation vaccine to reduce mortality in high risk groups
  - May not prevent nasal shedding (NHP: ChAdOx1, BioRxiv; Inact vaccine, Sci)
  - May require annual booster doses to maintain immunity (common cold CoVs)
- 2^{nd} generation (more potent, efficacious) vaccines (attenuated) may be needed to prevent severe disease and reduce shedding
- Many vaccines have reduced efficacy in elderly (or those with chronic diseases)
  - Require higher dose like flu vaccines, better adjuvants or multiple doses
  - Animal models may not reflect vaccine responses in these high risk groups
- Vaccines will be used in two populations: naïve vs recovered individuals with variable levels of pre-existing immunity
  - Efficacy/adverse effects (ADE?) may vary



COVID-19 vaccines in the US an update

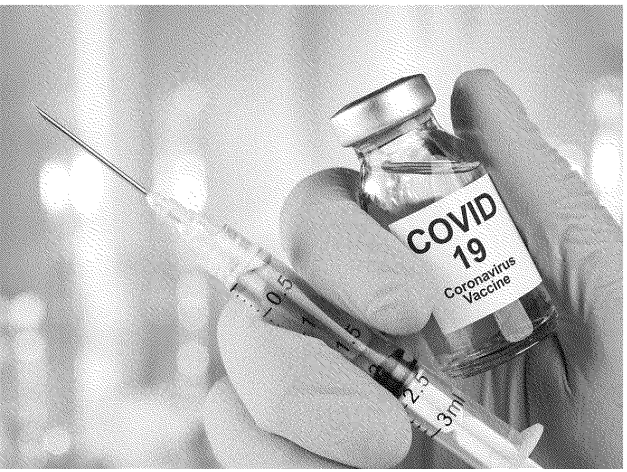
13 OCT 2020

Nancy Connell

Professor and Senior Scholar

Johns Hopkins Center for Health Security

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH | Center for Health Security



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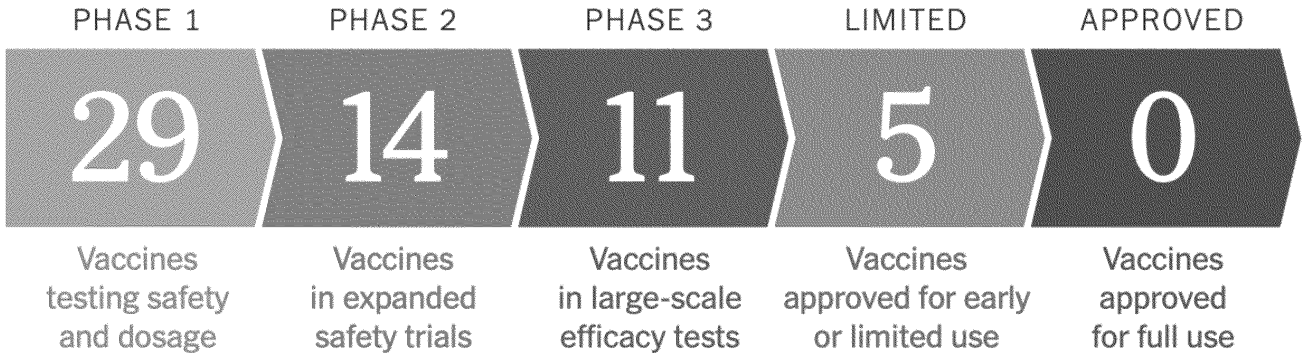
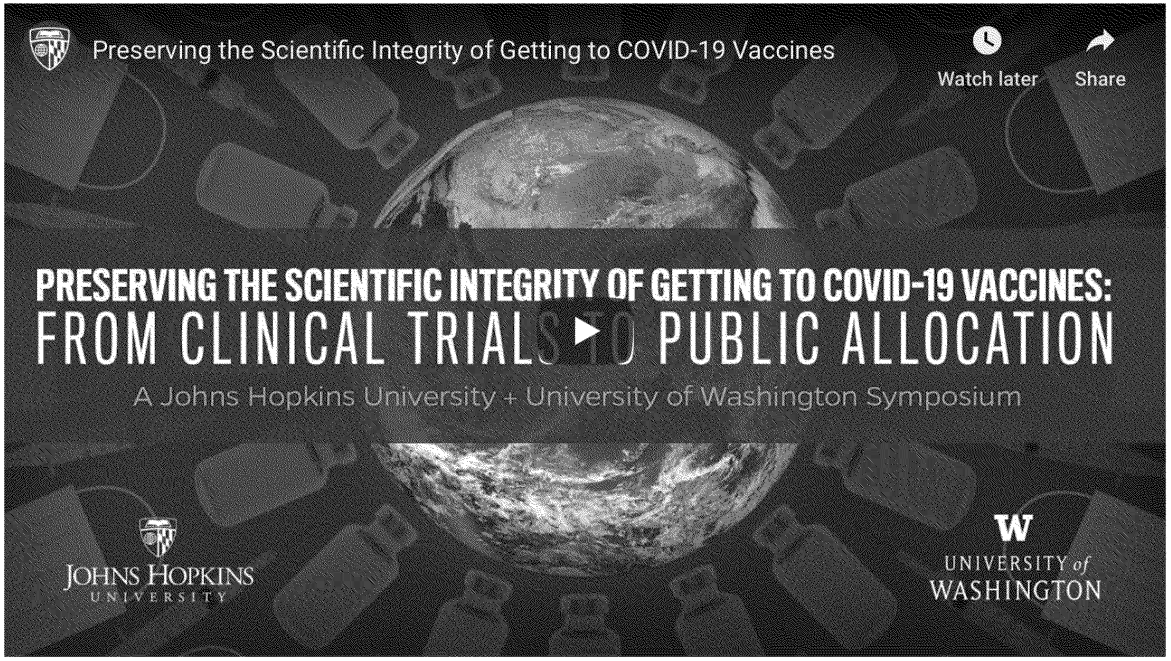
Draft landscape of COVID-19 candidate vaccines

2 October 2020 | Publication



NY Times Oct 12, 2020

Preserving the Scientific Integrity of Getting to COVID-19 Vaccines: From Clinical Trials to Public Allocation



Moncef Slaoui
Chief Advisor

Four platforms, 2 vaccines in each

- Parameters for choice
  - Speed of development
  - Likelihood of efficacy
  - Expected safety profile
  - Scaleup of manufacturing
  - Capacity of owners to execute

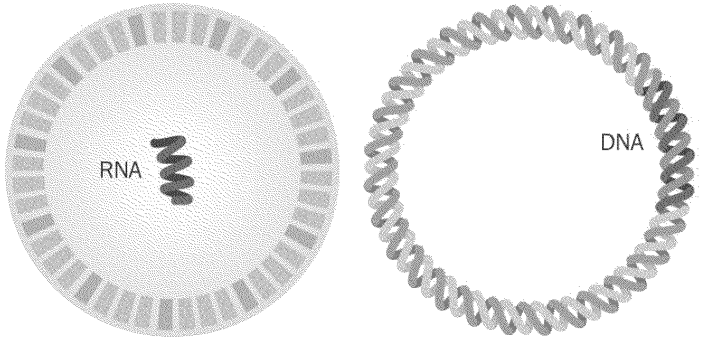
- 1. mRNA vaccine
- 2. non-replicating live vectored
- 3. adjuvanted recombinant protein
- 4. live replicating vectored vaccine
  - Oral? Single does?

mRNA vaccines

- Who?
  - Moderna
  - BioNtech/Pfizer/Fosun Pharma

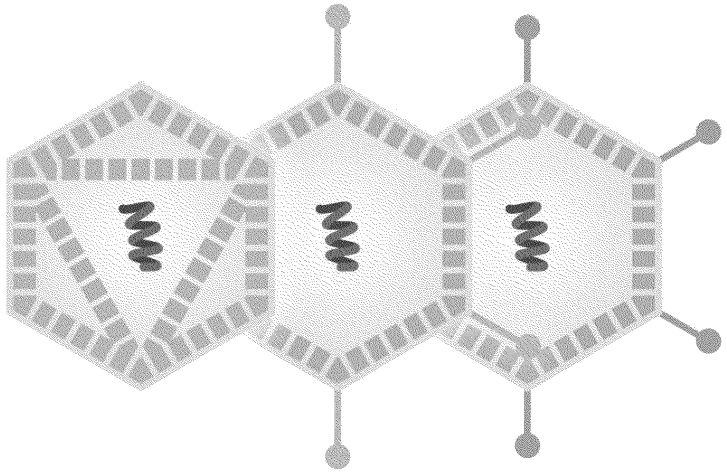
Previous uses?
- none

MF and dose availability:
- single digit millions Nov
- 10s millions – Dec
- 100s million - Jan



- Stuctures
  - mRNA encoding Spike protein
  - Encapsulated in lipid nanoparticles – to survive attack by blood cells
  - Pass through cell membranes
  - Chemicals – ease of manufacture
  - Ultracold chain required

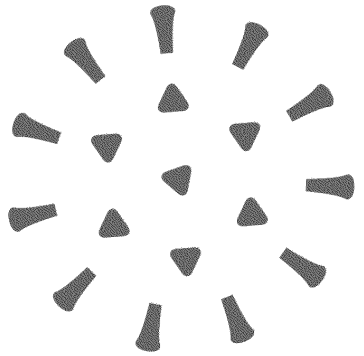
Non-replicative live vector



- Who?
  - Johnson & Johnson
  - Oxford/Astrazeneca
- Previous use?
  - Ebola
- MF and dose availability
  - Oxford 10s millions Jan
  - J&J 6-8 weeks behind

- Mechanism:
  - Virus infects one cell –induced viral immune response
  - Carries S protein gene
  - Immunity to vector?
    - J&J: Adenovirus Ad26 (obscure)
    - Oxford/AZ: (ChAdOx1) (chimp)

Adjuvanted recombinant protein



- Who?

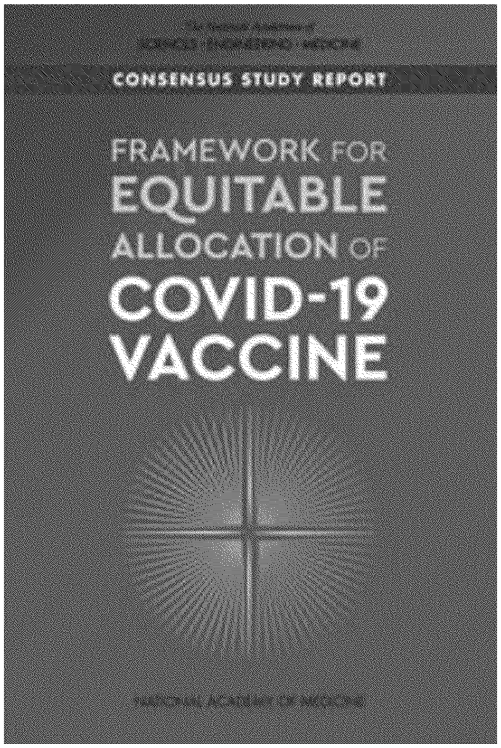
  Novovax

  Sanofi/GSK

- Previous use?
  - multiple
- MF and dose availability:
  - Doses available 1st Q 2021
  - Novovax: NC and TX
  - Sanofi: MA and NJ
- Mechanism
  - Each protein and expression system is different
  - Novovax: nanoparticle with adjuvant
  - Sanofi: based on flu vaccine technology (“FluBlock”)

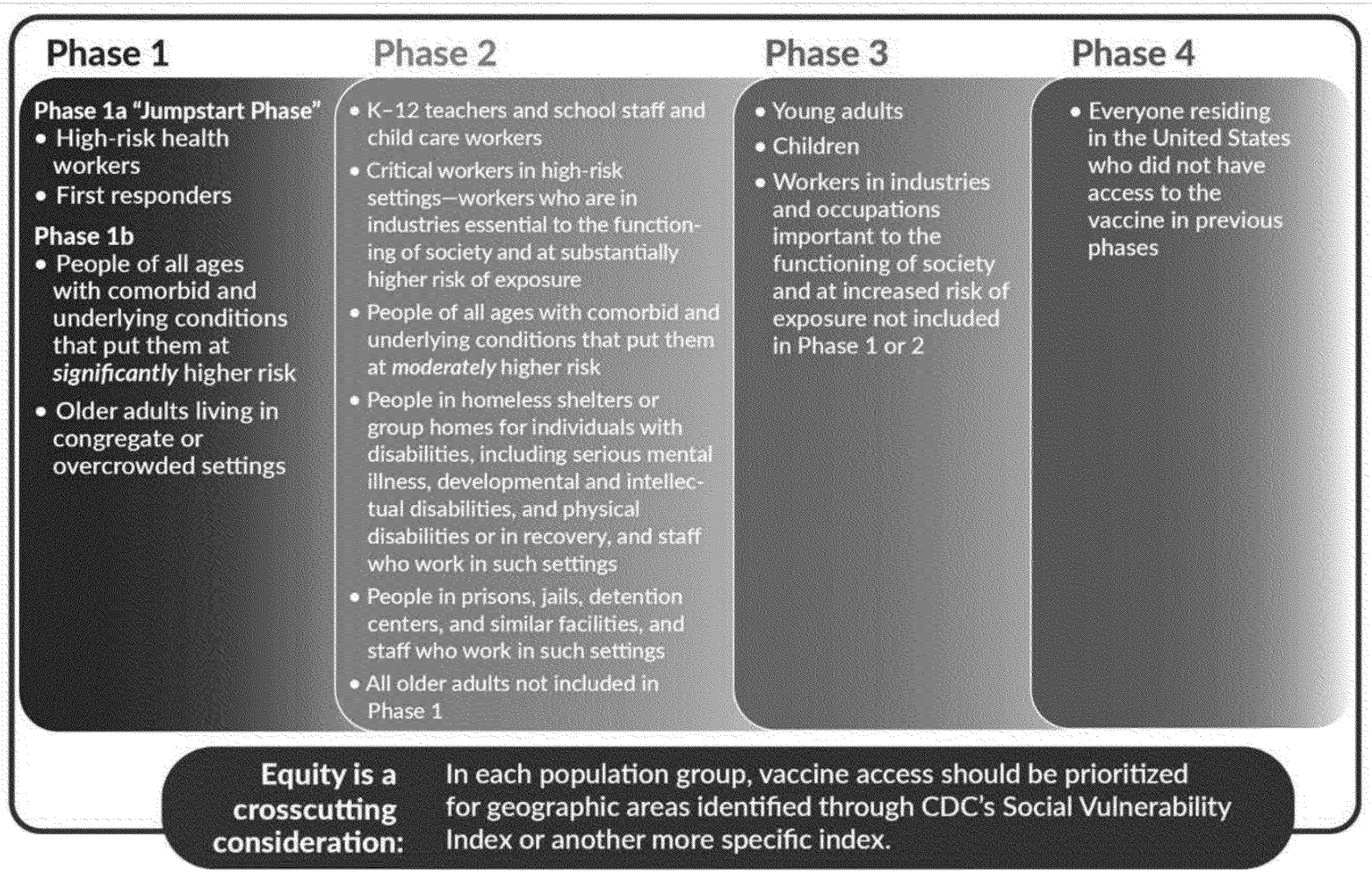
Four waves of roll-out

- RNA vaccines — November/December
- Non-replicating live vectors — January/February
- Adjuvanted proteins — March-April
- Replicating live vectors — mid-late 2021



Equitable allocation of COVID-19 vaccine

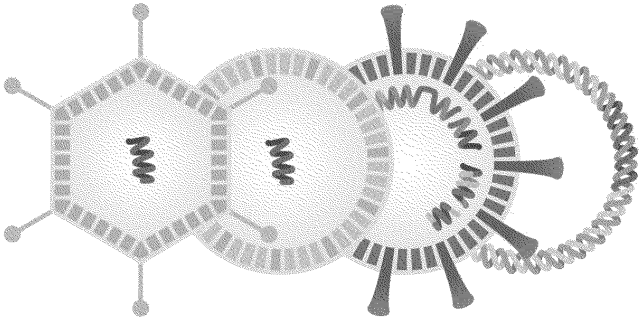
- Four-phased equitable framework, for state, tribal, local and territorial authorities (demand exceeds supply)
- Use existing programs;
- Promotion campaign with risk communication and engagement;
- Support of equitable global allocation



NATIONAL ACADEMY of MEDICINE

FIGURE: A Phased Approach to Vaccine Allocation for COVID-19

The National Academies of SCIENCES ENGINEERING MEDICINE



- *Fauci:* I could say… as a public health person, as a scientist, it will end. We will get through this for absolutely certain. We've already suffered through a lot of pain—a lot of economic and personal pain and inconvenience. But it will end. It will end because the public health efforts will succeed ultimately. And science will get us through this. We will get a vaccine. We will get therapies for early disease and for late disease. So the only message that I think we can jointly tell the American public and the global public is that we will get through this. Hang in there. It will end, we promise you.

Anthony Fauci, August 2020

To: 'Peter Daszak'[daszak@ecohealthalliance.org]; 'relman@stanford.edu'[relman@stanford.edu]; Baric, Ralph S[rbaric@email.unc.edu]; 'saif.2@osu.edu'[saif.2@osu.edu]; 'stanley-perlman@uiowa.edu'[stanley-perlman@uiowa.edu]; 'harvey.fineberg@moore.org'[harvey.fineberg@moore.org]; 'dgriffi6@jhmi.edu'[dgriffi6@jhmi.edu]; 'peggy@hbfam.net'[peggy@hbfam.net]; 'jwleduc@UTMB.EDU'[jwleduc@UTMB.EDU]; 'peshi@UTMB.EDU'[peshi@UTMB.EDU]; Dzau, Victor J.[VDzau@nas.edu]; 'Nancy Connell'[NancyConnell@jhu.edu]; 'Dave Franz (davidrfranz@gmail.com)'[davidrfranz@gmail.com]
Cc: 'fsharples_3@hotmail.com'[fsharples_3@hotmail.com]; Lowenthal, Micah[mlowenth@nas.edu]; Baric, Toni C[antoinette_baric@med.unc.edu]; Alison Andre[andre@ecohealthalliance.org]; 'jennifer.ryan@moore.org'[jennifer.ryan@moore.org]; Bowman, Katherine[KBowman@nas.edu]; Kanarek, Morgan[MKanarek@nas.edu]; 'Raymond JEANLOZ'[jeanloz@berkeley.edu]; Hare, Hope[HHare@nas.edu]; Cervenka, Nicole[NCervenka@nas.edu]; Sharples, Fran[FSharples@nas.edu]; Block, Bruce[BBlock@nas.edu]
From: Rusek, Benjamin[BRusek@nas.edu]
Sent: Mon 10/19/2020 11:57:43 PM (UTC-04:00)
Subject: RE: Some bullets following our US-China dialogue discussion on Friday
3-month follow-up-JP Weng.pdf

Greetings,

Thanks again for participating in the China bio dialogue sessions last week. And thank you Peter and others who sent me feedback and thoughts on the future of the dialogue. Additional thoughts and comments are welcome.

Re next steps: The general plan is to try and hold another two night session in 2-3 months, when we have more information to share on vaccines, durability of immunity and the evaluation and uses of different types of tests. More discussion on the origin or "natural history" of the virus focused on preventing future outbreaks (since George Gao seems to be open to it) might be possible as well.

PS I have attached the ppt on learning from Covid patients from the dialogue.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Monday, October 19, 2020 12:21 AM
To: Rusek, Benjamin <BRusek@nas.edu>; 'relman@stanford.edu' <relman@stanford.edu>; rbaric_email.unc <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidrfranz@gmail.com)' <davidrfranz@gmail.com>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; antoinette_baric.med <antoinette_baric@med.unc.edu>; Alison Andre <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSharples@nas.edu>; Block, Bruce <BBlock@nas.edu>
Subject: Some bullets following our US-China dialogue discussion on Friday
Importance: High

Thanks for a good discussion on Friday Ben,

I fully support a continued dialog and noted, as did some of those on the call, that George Gao and others were more open in their discussion of investigations into animal reservoirs of SARS-CoV-2 – i.e. discussion about the origin. We discussed ways we could frame a future topic that would allow us to talk about some important issues around the 'natural history' of SARS-CoV-2, that might also be comfortable for our Chinese colleagues. Here are a couple of bullets along the lines you asked me for:

1. Summary of recent findings re. the ability of SARS-CoV-2 to infect other species of animals in the lab, and in the wild, around the world (e.g. mink farm infections Europe and US, experimental infections of ferrets & raccoon dogs, risk

assessments of SARS-CoV-2 infecting bats in other countries)

2. From the natural history of the virus, what do we know about the diversity of alpha and beta CoVs in wildlife reservoirs, and in potential intermediate hosts in various countries in Asia.

3. What information can we identify from the receptor binding domain of SARS-related CoVs that might help us predict future potential for emergence of CoVs from other countries

I think a good strategy would be to have the US side give the opening slide deck so that we sort of set the parameters and open up some of the discussion that I'm sure would lead to interesting information. I'd be happy to help on the first 2 points, and I'm sure Ralph could talk to the 3rd point. Linda and Stanley have a great deal of knowledge and could provide supporting comments…

Cheers,

Peter

Peter Daszak
President

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EcoHealth Alliance develops science-based solutions to prevent pandemics and promote conservation

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Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; antoinette_baric.med <antoinette_baric@med.unc.edu>; Alison Andre <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSharples@nas.edu>; Block, Bruce <BBlock@nas.edu>
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links

Greetings,

Thank you for participating in the China bio dialogue sessions on Tuesday and Wednesday this week. We have scheduled a short hotwash session so the American participants can discuss the virtual dialogue discussions (from this week and earlier this year) and your get your ideas on future topics and other issues.

The session will take place tomorrow from 5:30-6:30 PM, Zoom link is below. Sorry for the short notice, if you can't make it tomorrow feel free to weigh in by email.

Topic: China Bio Post Dialogue Meeting Discussion
Time: Oct 16, 2020 5:30 PM ET / 4:30 PM CT / 2:30 PM PT
Meeting Link: https://nasem.zoom.us/j/92476126782?pwd=a0VUaDI1dEVORjlKOC9xaXRuTGpRdz09
Password: 604638

PS I have asked CAS for the ppts from last night, will send those out as soon as I get them.

Kind regards,

Ben

Benjamin Rusek
The U.S. National Academy of Sciences
1-202-334-3975

From: Rusek, Benjamin
Sent: Wednesday, October 14, 2020 7:32 PM
To: 'relman@stanford.edu' <relman@stanford.edu>; 'rbaric@email.unc.edu' <rbaric@email.unc.edu>; 'saif.2@osu.edu' <saif.2@osu.edu>; 'stanley-perlman@uiowa.edu' <stanley-perlman@uiowa.edu>; 'daszak@ecohealthalliance.org' <daszak@ecohealthalliance.org>; 'harvey.fineberg@moore.org' <harvey.fineberg@moore.org>; 'dgriffi6@jhmi.edu' <dgriffi6@jhmi.edu>; 'peggy@hbfam.net' <peggy@hbfam.net>; 'jwleduc@UTMB.EDU' <jwleduc@UTMB.EDU>; 'peshi@UTMB.EDU' <peshi@UTMB.EDU>; Dzau, Victor J. <VDzau@nas.edu>; 'Nancy Connell' <NancyConnell@jhu.edu>; 'Dave Franz (davidrfranz@gmail.com)' <davidrfranz@gmail.com>
Cc: 'fsharples_3@hotmail.com' <fsharples_3@hotmail.com>; Lowenthal, Micah <mlowenth@nas.edu>; 'antoinette_baric@med.unc.edu' <antoinette_baric@med.unc.edu>; 'andre@ecohealthalliance.org' <andre@ecohealthalliance.org>; 'jennifer.ryan@moore.org' <jennifer.ryan@moore.org>; Bowman, Katherine <KBowman@nas.edu>; Kanarek, Morgan <MKanarek@nas.edu>; 'Raymond JEANLOZ' <jeanloz@berkeley.edu>; Hare, Hope <HHare@nas.edu>; Cervenka, Nicole <NCervenka@nas.edu>; Sharples, Fran <FSharples@nas.edu>; Block, Bruce <BBlock@nas.edu>
Subject: RE: Virtual U.S. China dialogue meeting October 13 and 14 - agenda with zoom links

Greetings,

Thank you for joining the dialogue session last night. I have attached the slides from the three presentations.

FYI CAS has invited two additional CCDC experts to the session tonight.

Dr. Huaqing Wang, PI, Immunization program, Chinese Center for Disease Control and Prevention
Dr. Zundong Yin, Director of National Immunization Program, Chinese Center for Disease Control and Prevention

Looking forward seeing and hearing from you all in a few hours.
Session 2: Wednesday October 14, **9-11 PM ET / 6-8 PM PT in U.S.**
Meeting Link: https://nasem.zoom.us/j/98420889232?pwd=NFllKzF1eWgxT0xDZHQzQWxMbnJPdz09
Password: 375761

Kind regards,

Ben

Benjamin Rusek
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