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For Immediate Release

**DATA ON 53 PATIENTS TREATED WITH INVESTIGATIONAL ANTIVIRAL
REMDESIVIR THROUGH THE COMPASSIONATE USE PROGRAM PUBLISHED IN
NEW ENGLAND JOURNAL OF MEDICINE**

***-- Remdesivir treatment resulted in clinical improvement in 68 percent of patients
in this limited data set --***

Foster City, Calif., April 10, 2020— Gilead Sciences, Inc. (Nasdaq: GILD) today announced results from a cohort analysis of 53 patients hospitalized with severe complications of COVID-19 who were treated with the investigational antiviral remdesivir on an individual compassionate use basis. The majority of patients in this international cohort demonstrated clinical improvement and no new safety signals were identified with remdesivir treatment. Compassionate use data have limitations and multiple Phase 3 studies are ongoing to determine the safety and efficacy of remdesivir for the treatment of COVID-19. The detailed results of this analysis were published today in *The New England Journal of Medicine*.

Remdesivir is not yet licensed or approved anywhere globally and has not been demonstrated to be safe or effective for the treatment of COVID-19.

Nearly two thirds of patients (64 percent, n=34/53) in this cohort were on mechanical ventilation at baseline, including four patients also on extracorporeal membrane oxygenation (ECMO). Treatment with remdesivir resulted in an improvement in oxygen support class for 68 percent of patients (n=36/53) over a median follow-up of 18 days from the first dose of remdesivir. More than half of patients on mechanical ventilation were extubated (57 percent, n=17/30) and nearly half of all patients (47 percent, n=25/53) were discharged from the hospital following treatment with remdesivir. After 28 days of follow-up, the cumulative incidence of clinical improvement, defined as discharge from the hospital and/or at least a two-point improvement from baseline on a predefined six-point scale, was 84 percent according to Kaplan-Meier analysis. Clinical improvement was less frequent among patients on invasive ventilation versus noninvasive ventilation (HR: 0.33 [95 percent CI 0.16, 0.68]) and among patients at least 70 years of age (HR vs < 50 years: 0.29 [95 percent CI 0.11, 0.74]). Compassionate use data have limitations due to the small size of the cohort, the relatively short duration of follow-up, potential missing data due to the nature of the program and lack of a randomized control group.

“Currently there is no proven treatment for COVID-19. We cannot draw definitive conclusions from these data, but the observations from this group of hospitalized patients who received remdesivir are hopeful,” said Jonathan D. Grein, MD, Director of Hospital Epidemiology, Cedars-Sinai Medical Center, Los Angeles, and lead author of the journal article. “We look forward to the results of controlled clinical trials to potentially validate these findings.”

-more-

The overall mortality rate in this cohort was 13 percent (n=7/53). The mortality rate was higher in the subgroup of patients on invasive ventilation (18 percent, n=6/34), compared with patients on noninvasive oxygen support (5 percent, n=1/19). Factors associated with an increased risk of mortality included age greater than 70 years (HR vs < 70 years: 11.34 [95% CI 1.36, 94.17]) and higher baseline serum creatinine levels (HR per mg/dL: 1.91 [95% CI 1.22, 2.99]), indicating reduced kidney function.

Mild to moderate liver enzyme (ALT and/or AST) elevations (23 percent, n=12/53) were observed in this cohort. No new safety signals were detected during short-term remdesivir therapy.

Given the limitations of this data set and analysis, data from ongoing, randomized clinical studies of remdesivir are needed to provide a scientifically robust understanding of the clinical impact of remdesivir treatment.

“While the outcomes observed in this compassionate use analysis are encouraging, the data are limited,” said Merdad Parsey, MD, PhD, Chief Medical Officer, Gilead Sciences. “Gilead has multiple clinical trials underway for remdesivir with initial data expected in the coming weeks. Our goal is to add to the growing body of evidence as quickly as possible to more fully evaluate the potential of remdesivir and, if appropriate, support broader use of this investigational drug.”

Gilead is conducting two Phase 3 clinical trials of remdesivir, the SIMPLE studies, in countries with high prevalence of COVID-19. Data from the SIMPLE study in patients with severe disease are expected this month, followed by data from the SIMPLE study in patients with moderate disease in May. In addition, Gilead is supporting multiple clinical trials led by other organizations, including two studies conducted in Hubei Province, China. Gilead has been informed that the study in China in patients with severe disease was terminated early due to low enrollment; the company awaits the publication of these data to enable an in-depth review of the results. The study in China in patients with mild-to-moderate disease is ongoing. A global study of remdesivir led by NIAID continues to enroll patients and data from this study are anticipated in May. Finally, additional studies of remdesivir and other investigational treatments for COVID-19, based on a master protocol by the World Health Organization, have also begun to enroll patients in countries around the world.

About the Compassionate Use Cohort Analysis

Since January 25, 2020, Gilead has been providing emergency access to remdesivir for qualifying patients with severe complications of COVID-19 who are unable to enroll in ongoing clinical trials. More than 1,800 patients have been treated with remdesivir through individual compassionate use protocols.

This cohort evaluated data from 53 patients in the United States, Europe, Canada and Japan who received at least one dose of remdesivir on or before March 7, 2020, through Gilead’s compassionate use program. All patients were hospitalized with severe acute respiratory coronavirus 2 (SARS-CoV-2) infection and either an oxygen saturation of 94 percent or less, or a need for oxygen. The median duration of symptoms before initiation of remdesivir was 12 days. The majority of patients (75 percent) were men over the age of 60 years with comorbid conditions, including hypertension, diabetes, hyperlipidemia and asthma. Combined, all three of these factors have been associated with adverse outcomes of COVID-19.

The planned treatment was a 10-day course of remdesivir, consisting of a 200 mg loading dose administered intravenously on day 1, followed by 100 mg daily for the remaining nine treatment days. Of the 53 patients included in the analysis, 75 percent received the full 10-day course of remdesivir, 19 percent received 5-9 days of treatment, and 6 percent received fewer than 5 days of treatment. Follow-up continued through 28 days after initiation of remdesivir treatment. Four patients discontinued remdesivir prematurely, one due to worsening of pre-existing renal failure, one due to multiple organ failure and two due to elevated liver enzymes, including one patient with a maculopapular rash.

There were no prespecified endpoints for this program. As part of the analysis, rates of key clinical events were quantified, including change in oxygen support requirements, hospital discharge, reported adverse events leading to discontinuation of remdesivir treatment, and mortality. In addition, the analysis evaluated the proportion of patients with clinical improvement, defined as live discharge from the hospital and/or a clinical improvement of at least two points from baseline on a six-point scale reflecting hospitalization and oxygen support status, as recommended by the World Health Organization R&D Blueprint Group.

About Remdesivir

Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity both *in vitro* and *in vivo* in animal models against multiple emerging viral pathogens, including Ebola, Marburg, MERS and SARS. *In vitro* testing conducted by Gilead has demonstrated that remdesivir is active against the virus that causes COVID-19. The safety and efficacy of remdesivir to treat COVID-19 are being evaluated in multiple ongoing Phase 2 and 3 clinical trials. Initial clinical trial data are expected in mid-April.

About Gilead Sciences

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet medical need. The company strives to transform and simplify care for people with life-threatening illnesses around the world. Gilead has operations in more than 35 countries worldwide, with headquarters in Foster City, California.

For more information on Gilead's response to the coronavirus outbreak please visit the company's dedicated page: <https://www.gilead.com/purpose/advancing-global-health/covid-19>.

Forward Looking Statement

This press release includes forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors. Remdesivir is an investigational agent that has not been licensed or approved anywhere globally, and it has not been demonstrated to be safe or effective for any use, including for the treatment of COVID-19. There is the possibility of unfavorable results from clinical trials involving remdesivir and the possibility that Gilead may be unable to complete one or more of such trials in the currently anticipated timelines or at all. Further, it is possible that Gilead may make a strategic decision to discontinue development of remdesivir or that FDA and other regulatory agencies may not approve remdesivir, and any marketing approvals, if granted, may have significant limitations on its use. As a result, remdesivir may never be successfully commercialized. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. These risks, uncertainties and other factors could cause actual results to differ materially from those referred to in the forward-looking statements. The reader is cautioned not to rely on these forward-looking statements. These and other risks are described in detail in Gilead's Annual Report on Form 10-K for the year ended December 31, 2019, as filed with the U.S. Securities and Exchange Commission. All forward-looking statements are based on information currently available to Gilead, and Gilead assumes no obligation to update any such forward-looking statements.

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For more information about Gilead, please visit the company's website at www.gilead.com, follow Gilead on Twitter (@GileadSciences) or call Gilead Public Affairs at 1-800-GILEAD-5 or 1-650-574-3000.

From: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
To: Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Subject: RE: NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS
Date: 2020/06/25 16:48:33
Priority: Normal
Type: Note

Thanks, Gretta.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
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From: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>
Sent: Thursday, June 25, 2020 4:24 PM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: FW: NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS

Hi Gary,

You have received this email and corresponding letter and information from RAAS Nutritionals through Congressman Garcia's Office. I will ensure this information is sent to the CoronaWatch team. I have drafted a letter from you to the Congressman. Please feel free to edit and sign.

Thanks

g

From: Oxner, Julie (OS/ASPR/OEA) <Julie.Oxner@hhs.gov>
Sent: Thursday, June 25, 2020 8:40 AM
To: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>
Cc: Rybak, Bailey (OS/ASPR/OEA) <Bailey.Rybak@hhs.gov>
Subject: FW: NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS

Good morning,

Just an FYI, the staffer asked that I send these documents so I am ☺ I asked if they wanted a status update and am waiting for the response.

Julie

From: Morales, John (b)(6)
Sent: Wednesday, June 24, 2020 6:34 PM
To: Oxner, Julie (OS/ASPR/OEA) <Julie.Oxner@hhs.gov>
Subject: FW: NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS

Hi Julie,

Cristi Schwarcz from CDC pointed me your direction on an earlier email and I have a similar question to one I had then.

I work for Congressman Garcia out here in CA-25th district and we have a constituent with a nutritional supplement company (not sure of its size) that wants to get some of his application materials brought to the attention of Dr. Disbrow who made a recent comment about also searching for non-pharmaceutical remedies to COVID.

Please see his email and attachments below. He has already used the standard BARDA portal previously and felt that didn't go anywhere.

Let me know if I should direct this to someone else.

Thank you for your assistance.

Best Regards,

John Morales

Deputy District Director

Office of Congressman Mike Garcia (CA-25)

23734 Valencia Blvd, Ste 206, Santa Clarita, CA 91355

(661) 568-4857 (O)

(b)(6) (C)

From: Kieu Hoang <kieuhoang@raascorp.com>

Sent: Tuesday, June 16, 2020 4:45 PM

To: TechWatchInbox@hhs.gov

Cc: Sergio Gor <(b)(6)>; Mike Garcia <(b)(6)>; Morales, John <(b)(6)>; Costantini, Danielle <(b)(6)>; Robert Blackmon Patent Lawyer <rnb@blackmonlaw.com>; Ian Scally <ianscally@raascorp.com>; Milstein, Judit <Judit.Milstein@fda.hhs.gov>; Gordon, Jennifer (NIH/NIAID) [E] <jennifer.gordon2@nih.gov>; melinda.tibbals@nih.gov; ann.eakin@nih.gov; kraffta@niaid.nih.gov; CDCExecSec@cdc.gov; COVID19-productdevelopment <covid19-productdevelopment@fda.hhs.gov>; industry.biologics@fda.hhs.gov; bmulach@niaid.nih.gov; hoppdc@mail.nih.gov; Daria.Taydakova@cdph.ca.gov

Subject: NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS

Dear Dr. John Tegeris,

BARDA TechWatch Program Lead / nCoV MCM Task Force

As you may recall, Ian Scally, my assistant, and myself have tried to contact several different agencies of the US government including CDC which contacted me after receiving a letter from Senator Dr. Rand Paul on February 23rd, 2020. At that time in USA we had only 15 cases of COVID-19 and not a single American had died. CDC has referred me to NIAID which signed an agreement to conduct non clinical studies, but the problem NIAID was not able to test an extract from grapes, soy and rice. NIAID can only test the compounds. Dr. Jennifer Gordon informed us that we must get FDA approval and finally we ended up with Judit Milstein Chief, Project Management Staff, Division of Regulatory Operations for Specialty Medicine, FDA who told us according to the law it is a drug and encouraged us to apply for all the procedures to comply with drug regulations.

I have learned today that another spike in Wuhan with hundreds of people infected with COVID-19. In order to face the very critical pandemic like COVID-19, I have asked Senator Dr. Rand Paul, Congressman Mike Garcia and Congressman Tom McClintock to help to present my letter to Dr. Gary L. Disbrow, PhD who allow NON-PHARMACEUTICAL PRODUCTS NEEDED TO COMBAT HEALTH SECURITY THREATS.

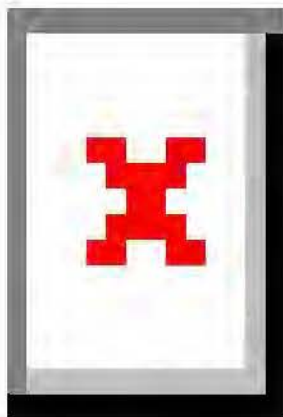
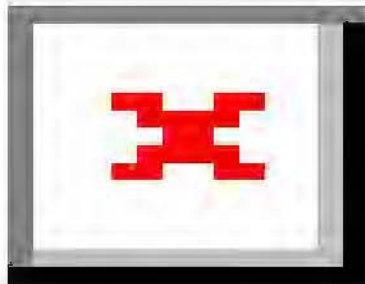
I was so happy when on March 12th, 2020 BARDA TechWatch Program Lead / nCoV MCM Task Force allowed a half an hour presentation but was so disappointed later on by the same agency informing us our products are not relevant to the immediate needs of the USG COVID-19 response. Therefore, we were not awarded a scheduled meeting.

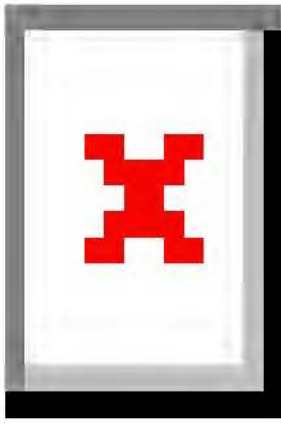
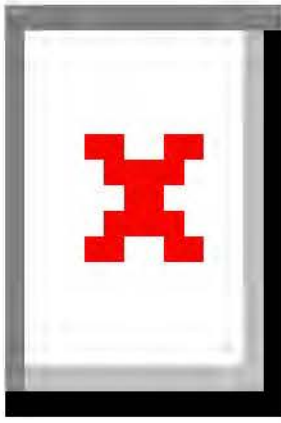
I am grateful for what BARDA has done for our country, millions of ventilators, COVID-19 test kits, drugs just Remdesivir and hydroxychloroquine, steroid drug dexamethasone and 32 vaccine candidates. My question to BARDA is, can these drugs and vaccines reduce the viral load in a COVID-19 patient from 1.1 billion down to non-detected just like our food functional dietary supplements?

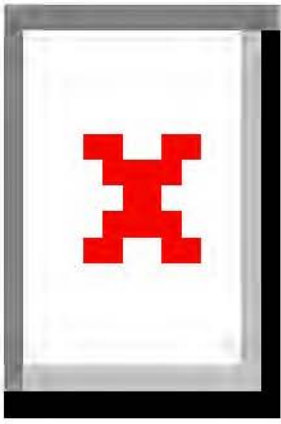
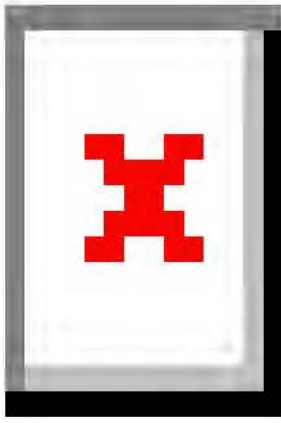
I beg you please, in order to rescue the United States and the world, I urge please allow us to have a presentation and help to test our products. Not only for the COVID-19 but also for other 92 kinds of viruses and bacteria including non-specified viruses and bacteria, along with the disease underlying with

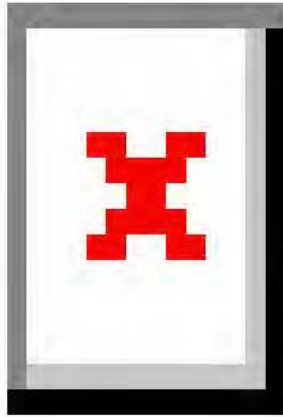
COVID-19 patients like diabetes, hypercholesterolemia, atherosclerosis, chronic kidney disease, hepatitis B and hepatitis C.

Thank you for your utmost attention to this request.









With thanks and best regards,

Kieu Hoang
Chairman & CEO

RAAS Nutritionals, LLC
3615 Old Conejo
Thousand Oaks, CA 91320
<https://protect2.fireeye.com/url?k=ae002c3f-f2540514-ae001d00-0cc47a6d17cc-761a1a1c90cd0f63&u=http://www.raasnutritionals.com/>
Tel: (818) 991-6117
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Kieu Hoang Winery, LLC
1285 Dealy Lane
Napa, CA 94559

<https://protect2.fireeye.com/url?k=4b0b8de3-175fa4c8-4b0bbcdc-0cc47a6d17cc-49de26dd86f78a8e&u=http://www.kieuhuongwinery.com/>

Rare Antibody Antigen Supply, Inc.

3615 Old Conejo Rd

Thousand Oaks, CA 91320

<https://protect2.fireeye.com/url?k=de1499f4-8240b0df-de14a8cb-0cc47a6d17cc-e0ebcab5602bd5dc&u=http://www.raascorp.com/>

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Sent Date: 2020/06/25 16:48:32

Delivered Date: 2020/06/25 16:48:33

From:	Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
To:	Ventura, Christy (OS/ASPR/BARDA) (CTR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9bb949caca464329823ca3cf77654a06-Ventura, Ch <Christy.Ventura@hhs.gov>
CC:	Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>; Boucher, David (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41293945651d475fa0413062a819aac5-Boucher, Da <David.Boucher@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Subject:	RE: MCM Task Force opinion: FOR YOUR REVIEW
Date:	2020/04/30 16:25:08
Priority:	Normal
Type:	Note

Team,

We cannot commit to a timeline for vaccine availability.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary

Director, Medical Countermeasure Programs

Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR

Department of Health and Human Services

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From: Ventura, Christy (OS/ASPR/BARDA) (CTR) <Christy.Ventura@hhs.gov>

Sent: Thursday, April 30, 2020 3:31 PM

To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>

Cc: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>; Boucher, David (OS/ASPR/BARDA) <David.Boucher@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>

Subject: MCM Task Force opinion: FOR YOUR REVIEW

Gary,

We received a request through FEMA from CISA to provide the "best estimated timeframe for broadly available antivirals and vaccines". The following response has been compiled with input from the MCM Task Force Agency Leads. Will you please review and provide comments/concurrence?

(b)(5)

(b)(5)

Thank you,
Christy

FOUO

--

Christy L. Ventura, Ph.D.
Tunnell Government Services
Executive Secretary, SARS-CoV-2 Medical Countermeasures Task Force
Project Manager, CBRN/BARDA/ASPR/HHS
O'Neill 23L05
Office: 202-730-8643
Cell: (b)(6)

Sender:	Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
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Sent Date:	2020/04/30 16:25:08

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(b)(5)

Withheld pursuant to exemption

(b)(3):42 U.S.C. § 247d-6b(d)

of the Freedom of Information Act

Withheld pursuant to exemption

(b)(3):42 U.S.C. § 247d-6b(d)

of the Freedom of Information Act

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Courses of Action (COAs) to Increase the Availability and Access
to Remdesivir for Trials and Potential Treatment of COVID-19

(b)(5)

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UNCLASSIFIED//FOUO

Back-up: BARDA funding commitments to date

	Company	Amount (\$M's)	Screening / pre-clinical	Devel't / clinical trial	MFG @ scale	Other	Notes on activities & funding to-date	Looking ahead
nAb	Regeneron†	85.9	✓	✓	✓		Screening, pre-clinical & phase 1 of mAb cocktail Start-up costs for human studies	(b)(3).42 U.S.C. § 247d-6b(d)
	AstraZeneca	23.7		✓			Phase 1 study of individual mAb candidates	
	SAB Biotherapeutics†	9.4		✓			Clin. dev. of polyclonal HIG derived from vaccinated cows	
Plasma & HIG	Mayo, ABC, ARC††	73.2		✓		✓	- Plasma collection and transfusion \$49M for EAP (Mayo); \$24.2M/0.75M for ABC / ARC plasma collection	- Current funding allocation also intended to support clinical trials (conducted by NIAID) - Current funding allocation also intended to support clinical trials (conducted by NIAID) No additional funding anticipated for Tocilizumab
	Emergent†	14.5		✓		✓	Funding being used to facilitate plasma collection	
	Grifols†	12.7		✓		✓	Funding being used to facilitate plasma collection	
IM	Genentech†	47.7		✓			\$25.1M for phase 2/3 study of Tocilizumab \$22.6M for phase 2 of MSTT1041A/UTTR1147A	(b)(3).42 U.S.C. § 247d-6b(d)
	Regeneron†	16.4		✓			Phase 2 / 3 study of Sarilumab	
Anti-viral	Janssen†	148.4	✓	✓			- Compound library screening - Identified Itraconazole as lead candidate	Allocated funding will support clinical trial of Itraconazole & other candidates (as identified)
Other	Phlow†	360			✓		PPP to repatriate MFG of raw materials & APIs	Allocated funding to support MFG of generics
	Alchem†	22		✓			RCT to evaluate hydroxychloroquine, standard of care & Fomatinine	Enrollment was paused when Remdesivir obtained EUA

1. ABC = America's Blood Centers; ARC = American Red Cross

† Award made prior to OWS

Note: Additional 4-5M funding for misc.

Recipient:

Stimson, Brian (HHS/OGC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=338aa495176d4c92bb314f8f3f51d118-Stimson, Br <Brian.Stimson@hhs.gov>;
Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>;
Kadlec, Robert (OS/ASPR/IO) (Robert.Kadlec@hhs.gov) <Robert.Kadlec@hhs.gov>;
Shuy, Bryan (OS/ASPR/IO) (Bryan.Shuy@hhs.gov) <Bryan.Shuy@hhs.gov>

Sent Date: 2020/03/05 17:08:25**Delivered Date:** 2020/03/05 17:08:00

Courses of Action (COAs) to Increase the Availability and Access
to Remdesivir for Trials and Potential Treatment of COVID-19

Objective: Secure Remdesivir to treat COVID-19 cases in the United States

Background: Remdesivir is an investigational, broad-spectrum antiviral developed by Gilead Science Inc. (Gilead), and is currently in clinical trials for COVID-19 in the United States and China. The drug is finished (final product) in the United States, however, its active pharmaceutical ingredients (API) are made in Canada with many ingredients from China. Remdesivir is not yet approved anywhere globally. See Tab A for more background information on Remdesivir.

Courses of Action (COAs) for national level policy

Policy options include:

- COA 1: Secure existing supply of Remdesivir and its API in the United States; and
- COA 2: Wait to stockpile Remdesivir and its API until results of clinical trials are available.

Recommend COAs 1; Do Not Recommend COA 2

COAs:

- (1) Secure existing supply of Remdesivir or its API, or both, within the United States before clinical trials show that the drug is safe and effective.

Potential Actions

- HHS accepts Gilead offered donation of 7,500 treatment courses (TCs) of Remdesivir (final product) from Gilead.
- HHS negotiates the rapid, sole-source procurement of entire domestic supply of Remdesivir and its API.
- If negotiations with Gilead are not successful:
 - HHS issues a rated order or contract for Remdesivir or an allocation order under the Defense Production Act (DPA) of 1950 (as amended), to include the entire domestic supply of finished product and API.
 - If necessary, HHS procures services to produce finished product from API for the American public.
 - Use International Emergency Economic Powers Act (IEEPA) to restrict export of existing U.S. supply of Remdesivir

UNCLASSIFIED//FOUO
DRAFT | DELIBERATIVE | PRE-DECISIONAL

and API. This would be a novel use of IEEPA and further assessment is needed.

PROs & CONs

a. PRO: *Demonstrate leadership*

b. CONs:

- o *Unknown safety and effectiveness:* Remdesivir not demonstrated safe or effective against COVID-19
- o *Unknown medical risk:* Previous trial data show toxicities which may limit use for those with underlying liver or kidney disease
- o *Risk of excessive cost:* One estimate is \$2,200 per TCs, for total of \$154 million for 70,000 TCs or 95 kg of API (total amount currently in United States); potential additional cost to convert API to finished product
- o *Risk of legal challenge:* Limited case law on using allocation (DPA) authorities for this purpose
- o *Unintended Consequences with Gilead:* Using DPA or other actions could lead the company to not bring API into the United States and simply send it to China
- o *Political ramifications:* Potential backlash from World Health Organization and other countries with a high incidence of disease
- o *Trade ramifications:* United States is net importer of pharmaceutical and medical supplies, including the materials used to make those supplies

- (2) Wait to stockpile Remdesivir and its API until Remdesivir is proven safe and effective through clinical trials that are underway.

Potential Action

- Monitor clinical trials for drug effectiveness

PROs & CONs

a. PROs:

- o *Cost savings:* No need to buy Remdesivir or its API, until Remdesivir is proven safe and effective.
- o *Will know medical risk of using Remdesivir.*

b. CONs:

- o *Product paucity:* Others could purchase entire supply
- o *Foreign reliance:* Determination of effectiveness could depend on China sharing results of the clinical trial in a timely manner

(b)(5)

TAB A

Background Information on Remdesivir

Drug information: Remdesivir, developed by the U.S. company Gilead Science Inc. (Gilead), is an investigational broad-spectrum antiviral being developed to treat multiple viral pathogens including Ebola, Marburg, MERS and SARS. Remdesivir is currently in clinical trials for COVID-19 in the United States and China. Remdesivir is not yet approved anywhere globally and has only early clinical data against Ebola and pre-clinical data against SARS and MERS.

Remdesivir supply chain: Gilead imports many of Remdesivir's raw materials from China to synthesize active pharmaceutical ingredients (API). Gilead synthesizes those ingredients into API at their facility in Alberta, Canada. Gilead ships the API to the United States for final formulation. Gilead has recently informed Health and Human Services (HHS) that it is establishing final formulation and filling capabilities in China, which could increase drug availability in China.

Existing stock of Remdesivir: There are ~5,000 treatment courses (TCs) in the United States. As of January 28, there were 135 kg of API in Canada that would yield ~90,000 TCs of finished product. On March 2, 2020, Gilead informed HHS that 95 kg of API was shipped to the United States for finishing, and ~12 kg of API was shipped to China--where Gilead is establishing product-finishing facilities. Of the original 135 kg of API, 28 kg (~70,000 TCs equivalents) remains in Canada. Gilead is planning to use the 95 kg of API in the United States to increase the amount of finished product by ~70,000 TCs by end of June 2020. The company is manufacturing additional material and examining ways to expand global stocks of both API and final drug product.

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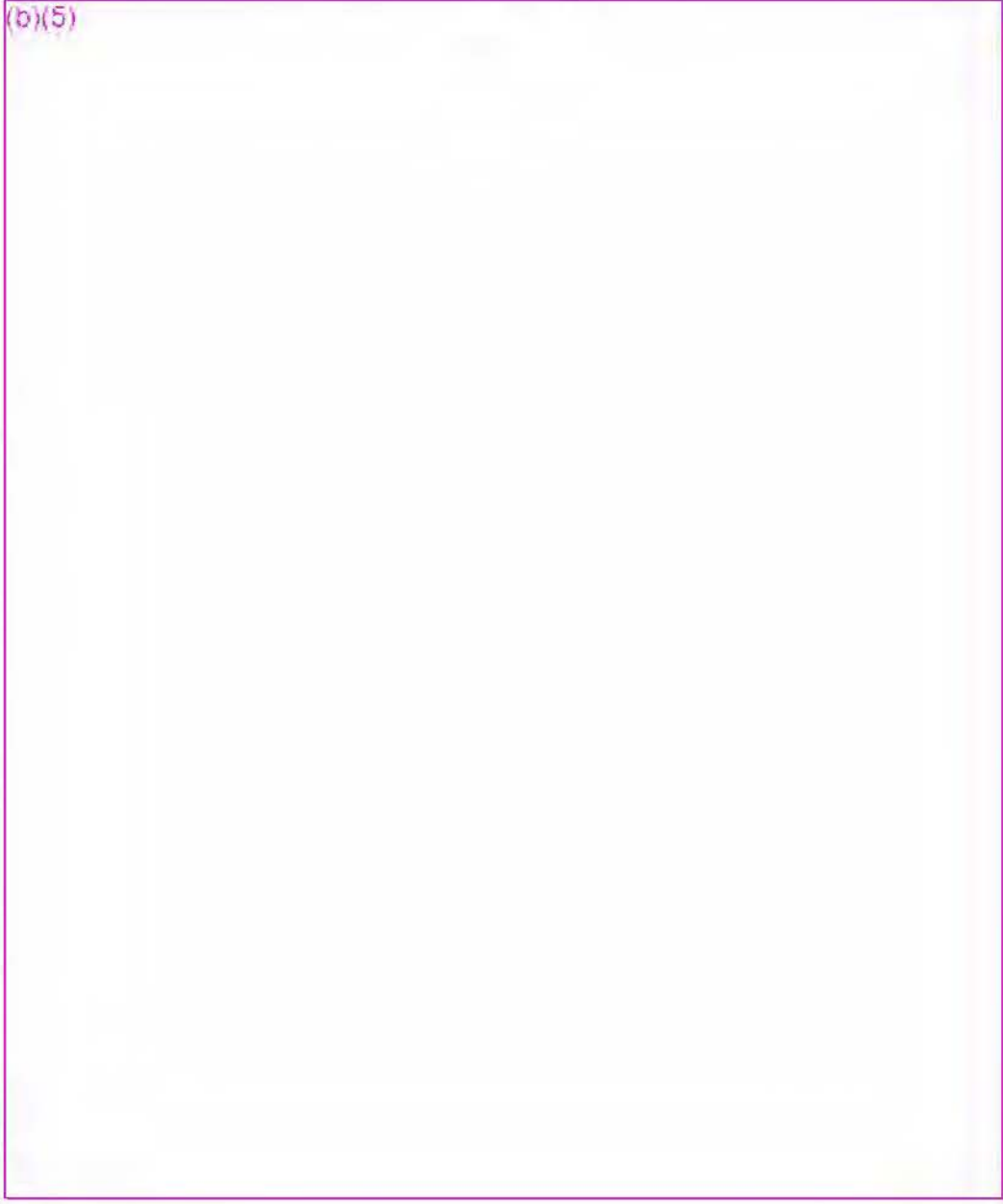
Committee on Health, Education, Labor and Pensions

Questions for the Record

Hearing: Shark Tank: New Tests for COVID-19

May 7th, 2020

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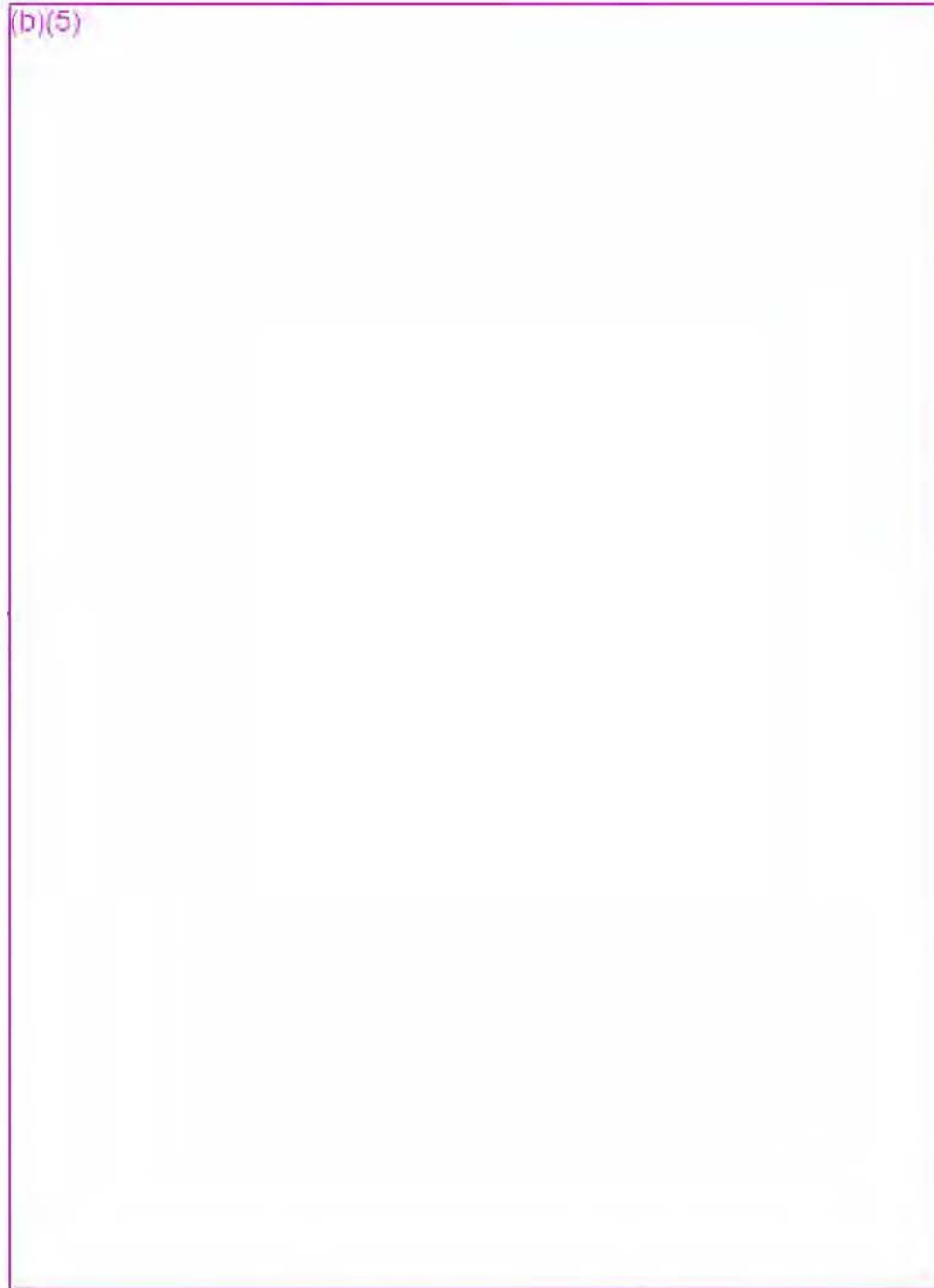
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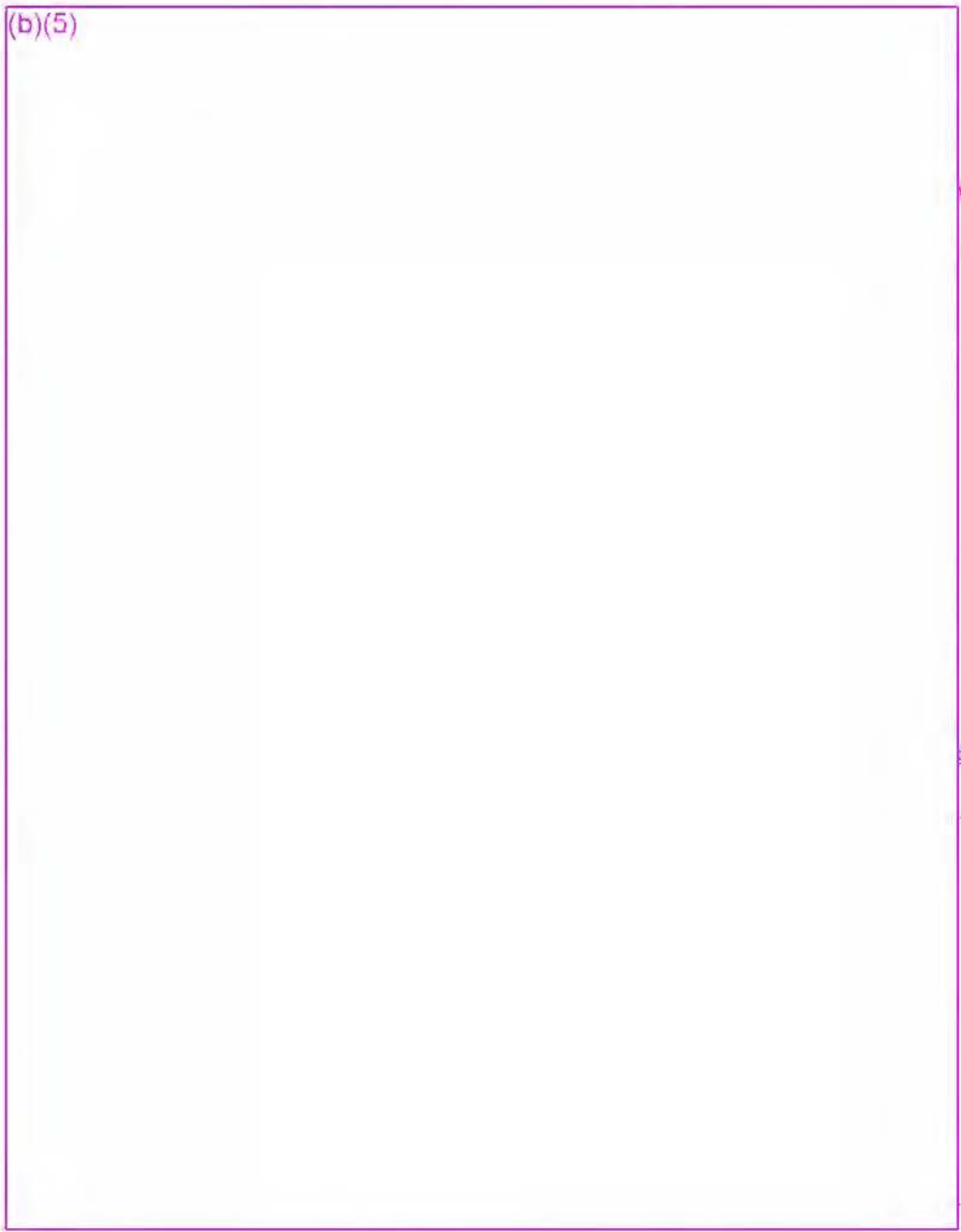


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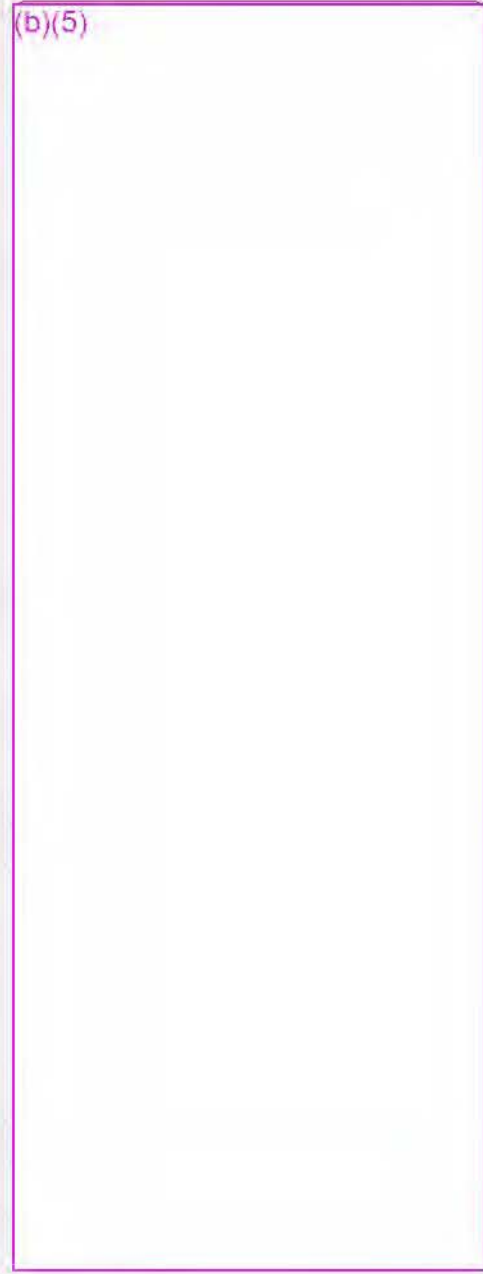
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ASPR

COVID-19 MEDICAL COUNTERMEASURE UPDATE FOCUS ON THERAPEUTICS AND VACCINES

XXX XX, 2020

FOUO INFORMATION

ASPR Mission

**Save Lives
and Protect
Americans from
21st Century
Health Security
Threats**



Speed is the critical component of **response**.
Even the most advanced countermeasures **fail** unless
present in **sufficient quantities** with **minimal delay**
at the **location of need**.



16
Years

3rd Coronavirus Outbreak
No Licensed products

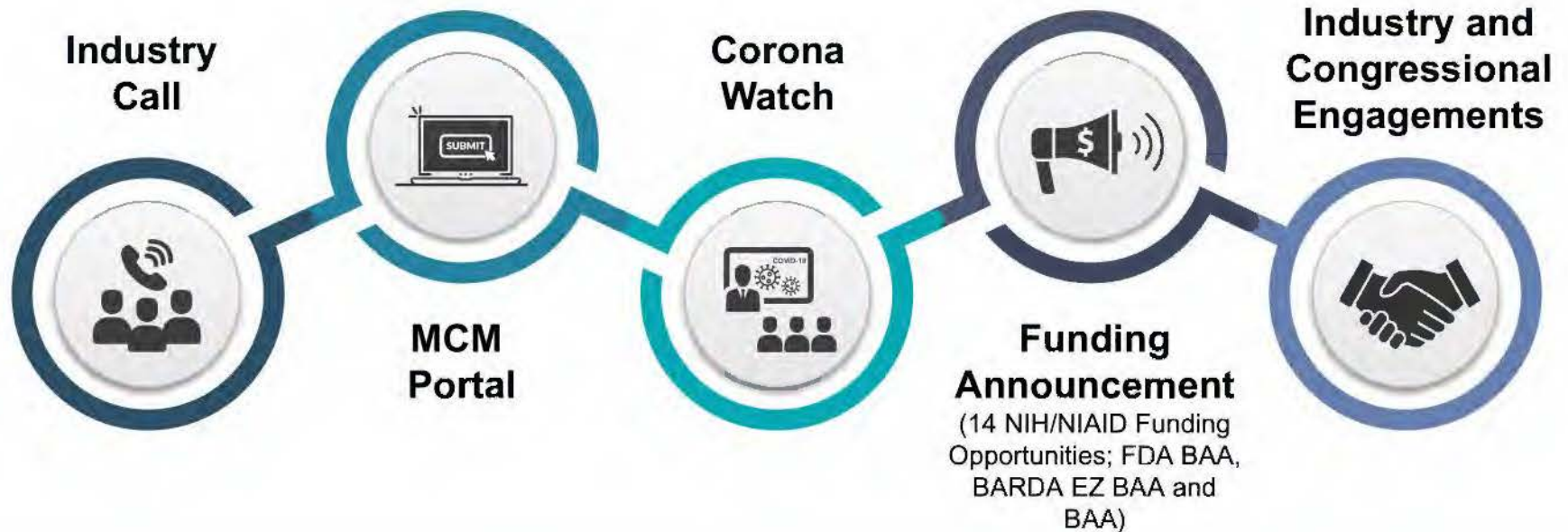
SARS-CoV-2 Medical Countermeasures Task Force

Align MCM and prioritize development across interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps

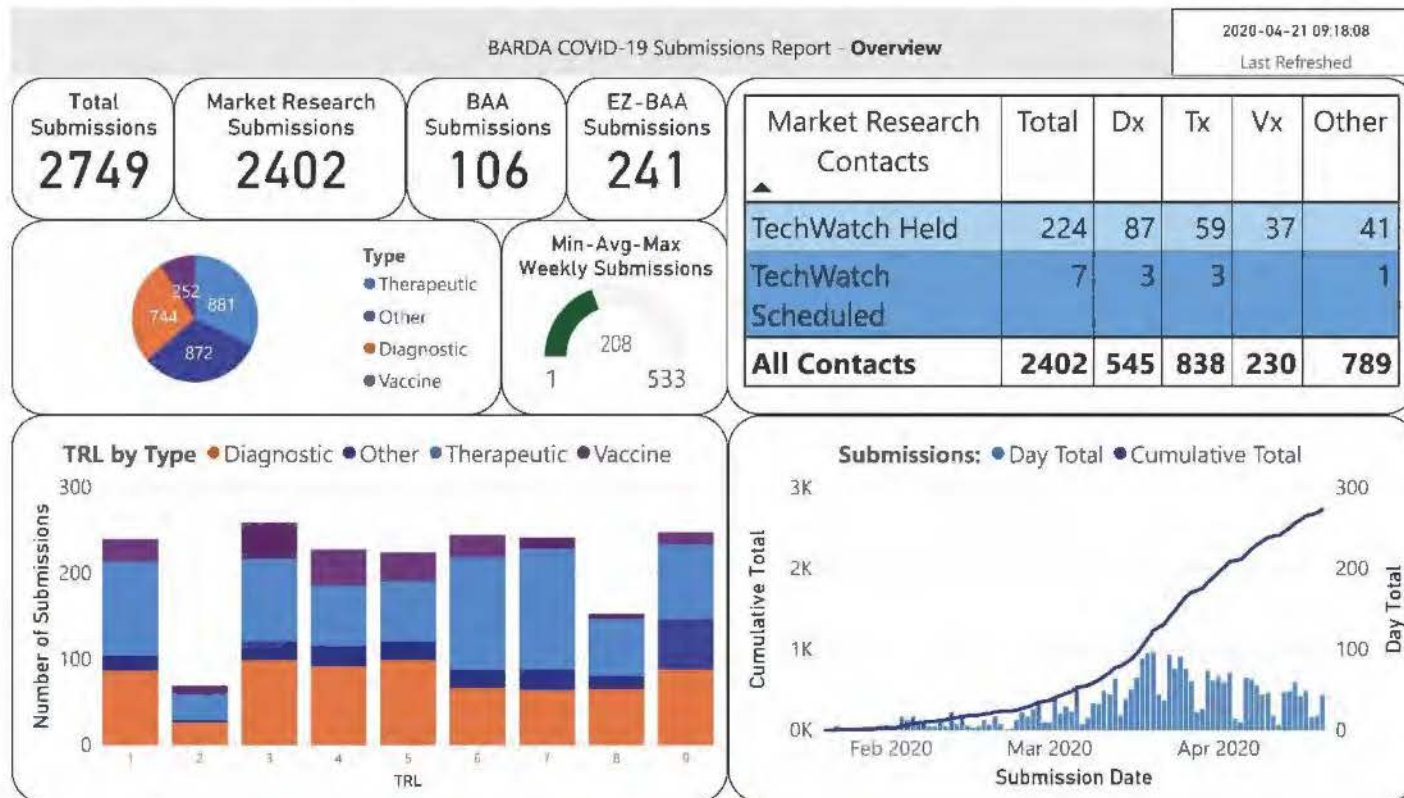


FOUO INFORMATION
Saving Lives. Protecting Americans.

Agency-Wide Engagement with Developers



COVID-19 Market Research Portal Submissions



COVID-19 MEDICAL COUNTERMEASURE DEVELOPMENT STRATEGY



ACCELERATE DEVELOPMENT

- Platform technologies
- Repurpose licensed products
- Parallel, not sequential, activities

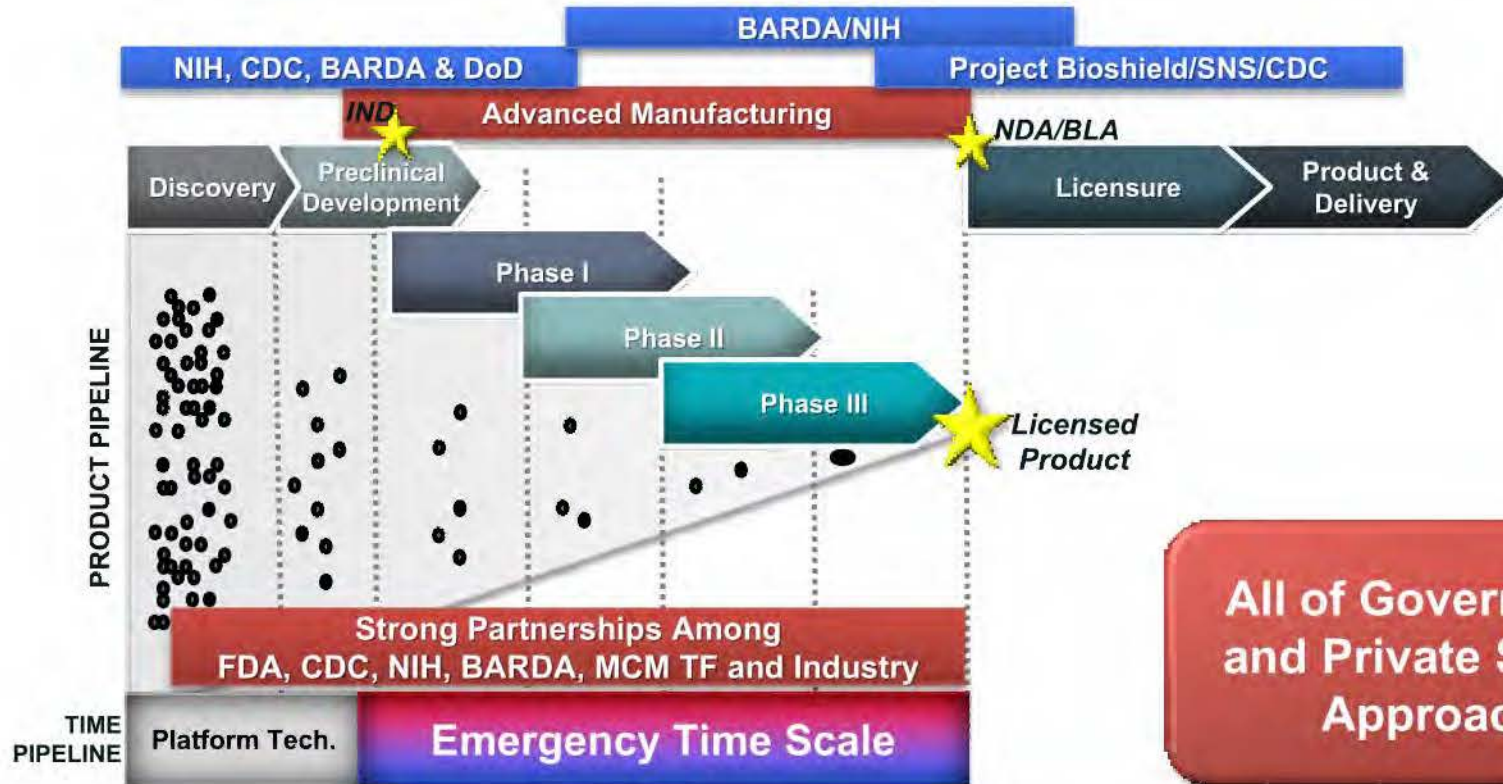
MITIGATE RISK

- Multiple technologies
- Multiple targets
- Redundancy

DOMESTIC MANUFACTURING

- Scale Up & Scale Out
- Raw materials and supply chains
- Leverage existing facilities

Emergency Vaccine & Drug Development



Therapeutics Development



FDA-approved therapeutics
licensed for other indications

- Ready for immediate
clinical testing

e.g., inhibitors of viral
activation, host pathway
modulators

e.g., 2019-CoV specific
monoclonal antibodies, small
molecule antivirals, and
immunoglobulins

Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

Repurposed Therapeutics



Thousands of compounds currently being screened-low cost/high impact
Many candidates identified and undergoing clinical evaluation

Allows rapid advancement to clinical trials (i.e. IL-6 monoclonal antibody trial started 2-weeks after identification)

Utilize existing facilities for production;
Expand capacity through partnerships with large pharmaceutical partners

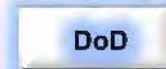
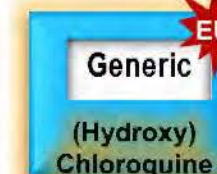
BARDA seeking to leverage existing infrastructure for rapid clinical trial initiation

USG-Supported SARS-CoV-2 Therapeutics

Pre-Clinical

Phase 1

Phase 2/3



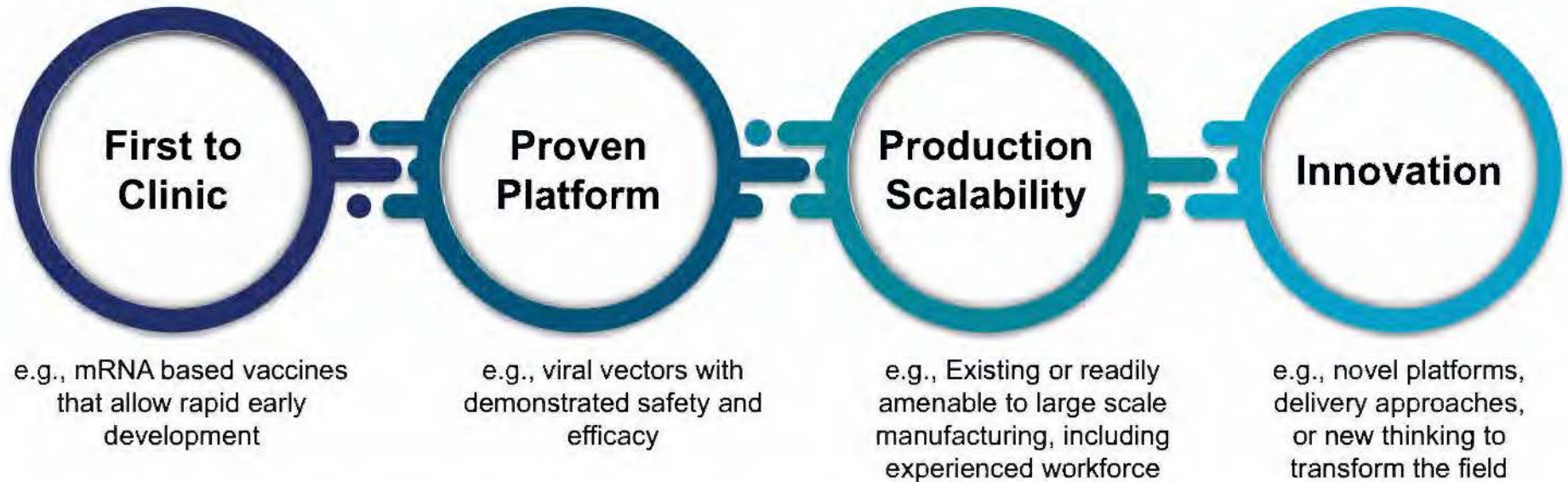
Active USG-sponsored Clinical Trials

Product Type	Product (Developer)	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	USG Sponsor
Therapeutic	Remdesivir (Gilead) and Baricitinib (Lilly)	Clinical status assessed at Day 15 using 8-point ordinal scale	700	Confidential	69	NIAID
	Sarilumab (Regeneron & Sanofi)	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	Confidential	53	BARDA
	Tocilizumab (Genentech & Roche)	Clinical status assessed at Day 28 using 7-point ordinal scale	330	Confidential	52	BARDA
	Hydroxy-chloroquine (Multiple)	Clinical status assessed at Day 15 using 7-point ordinal scale	510	Confidential	45	NHLBI
	Galidesivir (BioCryst)	Safety, viral load reduction, improvement in signs and symptoms, mortality	66	Enrolling	1	NIAID
	Hydroxy chloroquine + famotidine	Clinical status assessed at Day 15 using 7-point ordinal scale	1170	Confidential	111	BARDA

Active USG-sponsored Clinical Trials

Product Type	Product (Developer)	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	USG Sponsor
Vaccine	mRNA-1273 (Moderna)	Safety & Immunogenicity at 25µg, 100µg & 250µg; 3 age groups: 18-55 (15/dose) 56-70 and 71+ (10/dose)	105	Confidential	3	NIAID
	INO-4800 (Inovio)	Safety & Immunogenicity at 1 mg and 2 mg, administered days 0, 28	40	Enrolling	2	DoD
Natural History	n/a	Natural history: epi, lab, biomarker correlates with clinical outcomes	N/A	Confidential	5	DoD
	n/a	Retrospective and prospective study of hospitalized COVID-19 pts to collect clinical, biological, and imaging data	3000	TBD	20-40	NHLBI

Vaccine Development



Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

SARS-CoV-2 Vaccine Landscape

Pre-Clinical

Phase 1

Phase 2

Subunit



Nucleic Acid



Virus vector



Live attenuated



Plant



BARDA

DoD

NIH

Vaccine Approach

Accelerate Development



Rapid Vaccine Platform Approaches

- Nucleic Acid
- Vectors
- Recombinant protein



Repurpose Licensed Products

- Viral Vector
- Recombinant Protein



Parallel Activities

- Overlapping clinical trials
- Scale up in parallel with clinical development

Mitigate Risk



Multiple Platforms

- Address potential yield risks
- Address potential dose risk



Multiple Presentations (recombinant, vector, etc.)

- Disease enhancement mitigation
- Alternative routes of delivery



Redundancy

- Take multiple products through large scale clinical trials
- Multiple manufacturing facilities for each product

Domestic Manufacturing



Scale Up & Scale Out

- Validate large scale process (i.e. larger tanks)
- Technology transfer to more facilities
- Increase fill/finish capacity



Raw Materials Supply Chains

- Remove bottlenecks
- Establish stockpiles



Leverage Existing Facilities

- Facilities of large pharma partners
- CMOs

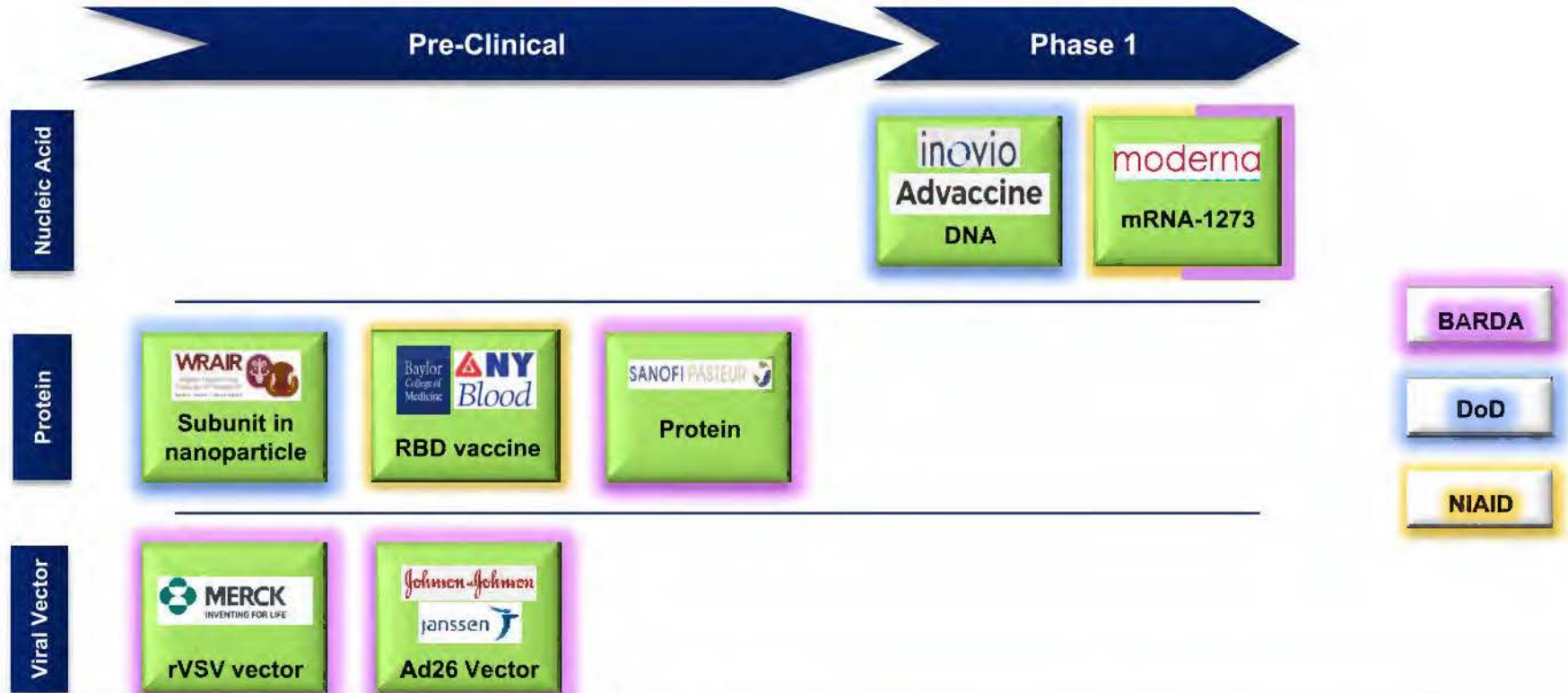
Two Parallel Tracks

- Push forward with the 4-5 technologies that were identified by the MCM Task force based on previous data with SARS or MERS-CoV, clinical exposure data for another infectious disease or scalability, well established manufacturing process
- Initiate screening of the additional candidates on the landscape
 - MCM task force is prioritizing candidates based on a 5 point scale for multiple desired characteristics for a desired vaccine(s)
 - USG alignment of BSL-3 space, development of animal models, assays, reagents and interface with prioritized list

Vaccine Assessment Tool

- Vaccine landscape assessment
 - 5 categories each with a five-point scale:
 1. Platform Development Status
 2. Platform Manufacturing Status
 3. Platform Dosing Regimen
 4. Pre-clinical development status for SARS-CoV-2
 5. Clinical development status for SARS-CoV-2
 - Consideration for
 1. Focus on US regulatory approvals for assessments
 2. Domestic manufacturing ability

USG-Supported SARS-CoV-2 Vaccines



BARDA Medical Countermeasures Response

Portfolio

Therapeutics

Johansen-Johnsen
janssen
Anti-viral Library
Screening

REGENERON
Anti-SARS-CoV-2
mAb

SAb
BIOTHERAPEUTICS
Polyclonal Ab

GRIFOLS
Hyperimmune
Globulin,
Convalescent
Plasma

REGENERON
Anti-IL6R mAb
(Kevzara®)

Roche Genentech
Anti-IL6R mAb
(Actemra®)

emergent
Hyperimmune
Globulin

American Red Cross
Convalescent
Plasma
Collection

Cantor BioConnect
Convalescent
Serum
Collection

ICON
Convalescent
Serum
Collection

Vaccines

Johansen-Johnsen
janssen
Ad26 Vector

SANOFI
Recombinant
Protein

moderna
mRNA-1273

MERCK
rVSV
Vaccine

Diagnostics

**TMA for Panther
Platform
EUA**

DiaSorin
RT-PCR
EUA

**POC / Lab RT-PCR
(GeneExpert)
EUA**

Antigen

**POC RT-PCR
EUA**

Luminex
NxTAG
EUA

GenMark
Respiratory Panel

**Portable
Molecular
Diagnostic**

Luminex
ARIES
EUA

**QIAstat Panel
EUA**

VELA
RT-PCR

DiaSorin
Antibody

nanomix
Antigen &
Antibody

**Antigen &
Antibody**

TANGEN
Diagnostic Assay

Cytovale
Sepsis Diagnostic

Supportin g Efforts

BATTELLE
Animal Model
Development

**LOVELACE
BIOMEDICAL**
Animal Model
Development

**SR SOUTHERN
RESEARCH**
Animal Model
Development

MRI Global D
Animal Model
Development

NYU
Clinical Sample
Collection

**UNIVERSITY OF
MARYLAND**
Therapeutic
Screening and
Animal Model Dev.

Berry Consultants
Statistical Support

ENVIGO
Animal Model
Support

**Reagent prep
to support
diagnostic
development**

Withheld pursuant to exemption

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of the Freedom of Information Act

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ASPR

COVID-19 MEDICAL COUNTERMEASURE UPDATE

April 5, 2020

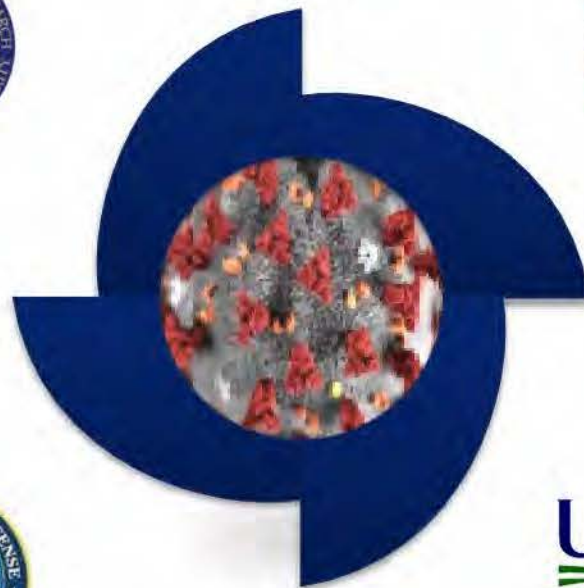
FOUO- FOR OFFICIAL USE ONLY- PRE-DECISIONAL

16
Years

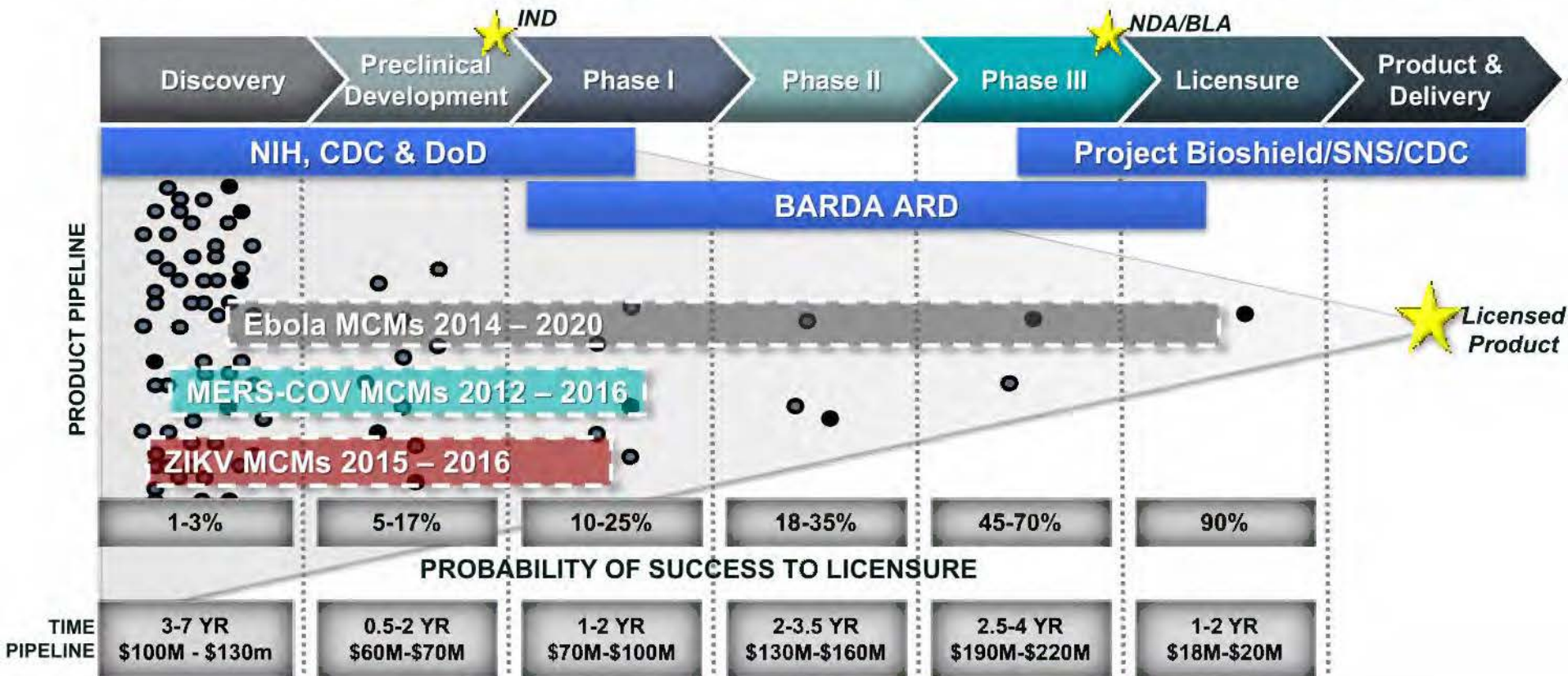
3rd Coronavirus Outbreak
No Licensed products

2019-nCoV Medical Countermeasures Task Force

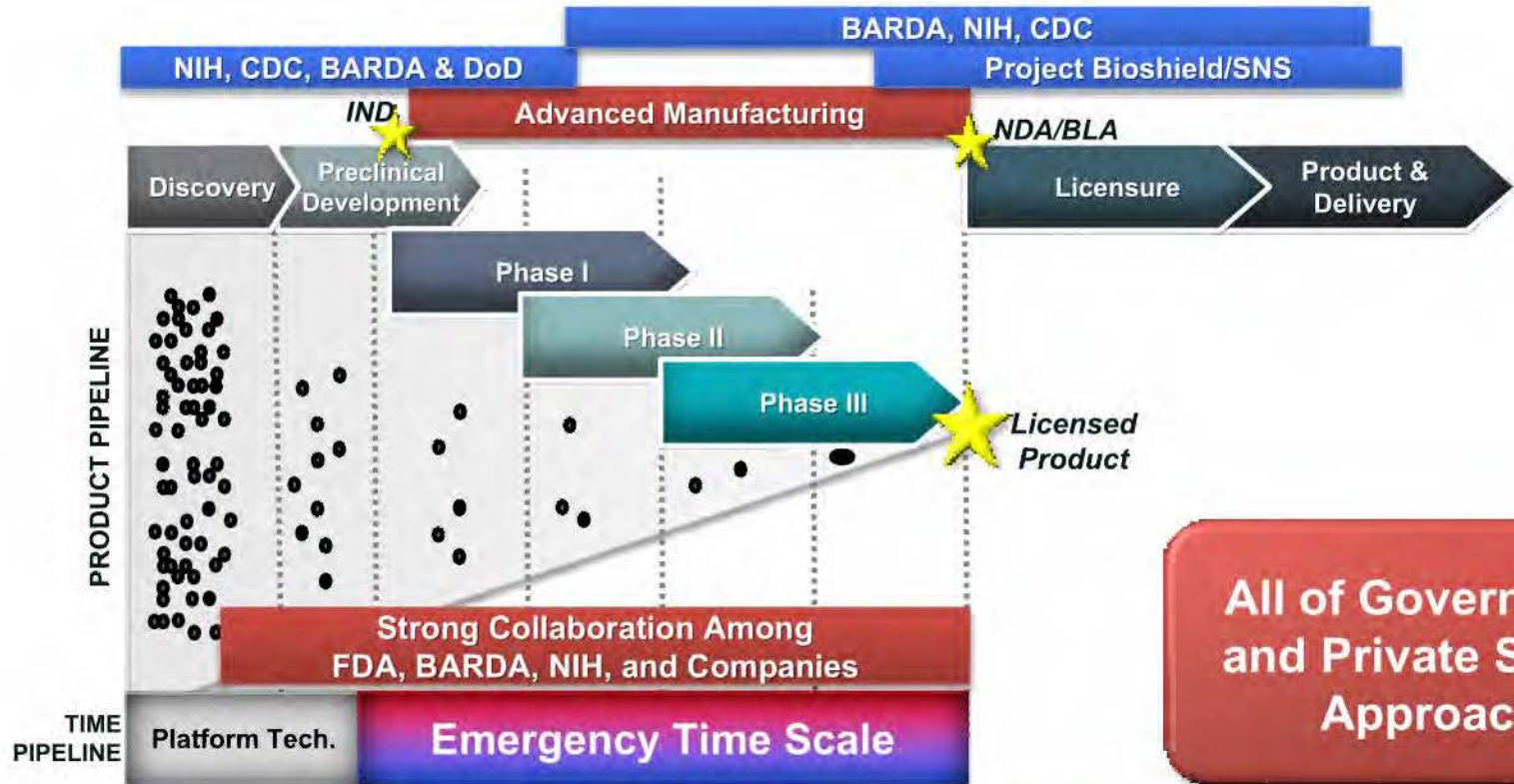
Align and prioritize MCM development across Interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps



Vaccine & Drug Development is Expensive, Risky and Lengthy



Emergency Vaccine & Drug Development



COVID-19 MEDICAL COUNTERMEASURE DEVELOPMENT STRATEGY



ACCELERATE DEVELOPMENT

- Platform technologies
- Repurpose licensed products
- Parallel, not sequential, activities

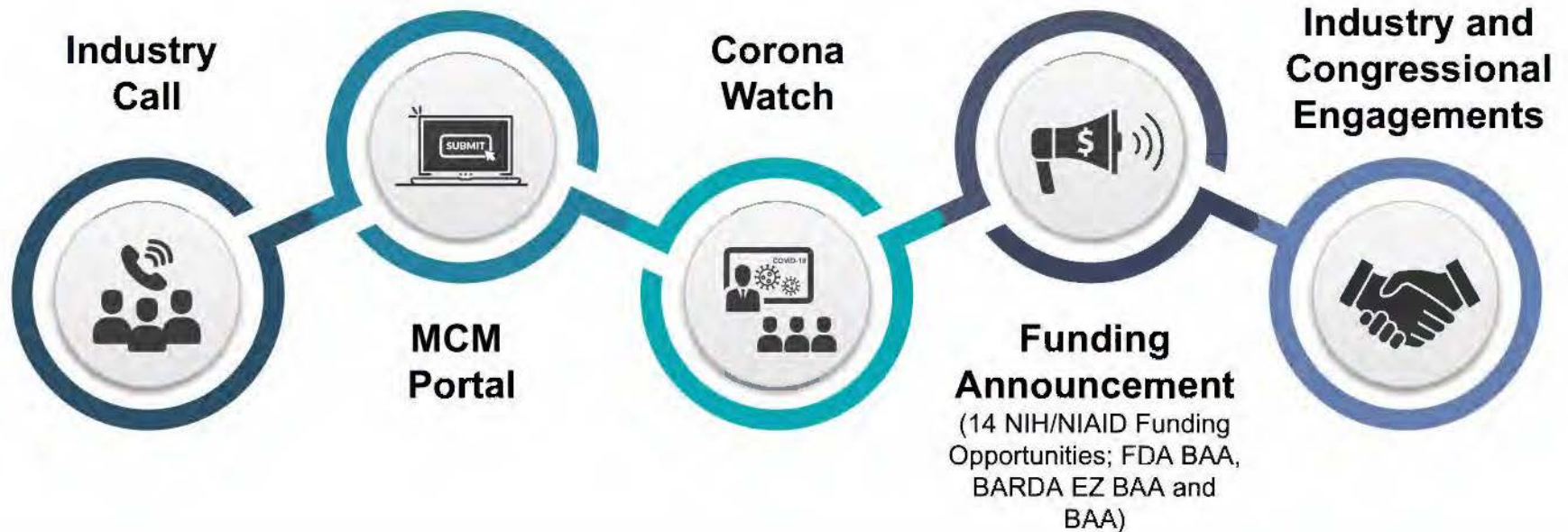
MITIGATE RISK

- Multiple technologies
- Multiple targets
- Redundancy

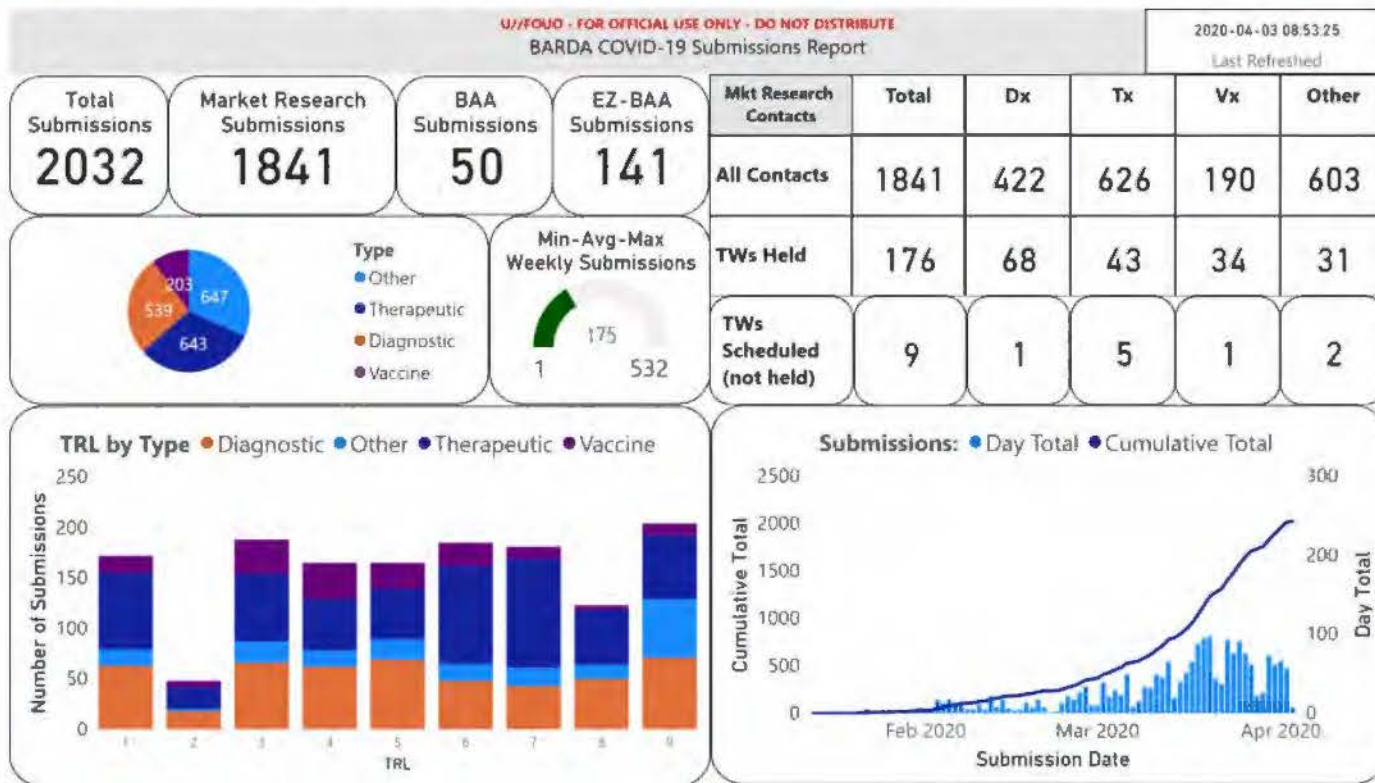
DOMESTIC MANUFACTURING

- Scale Up & Scale Out
- Raw materials and supply chains
- Leverage existing facilities

Agency-Wide Engagement with Developers



COVID-19 Market Research Portal Submissions



Therapeutics Development



FDA-approved therapeutics
licensed for other indications

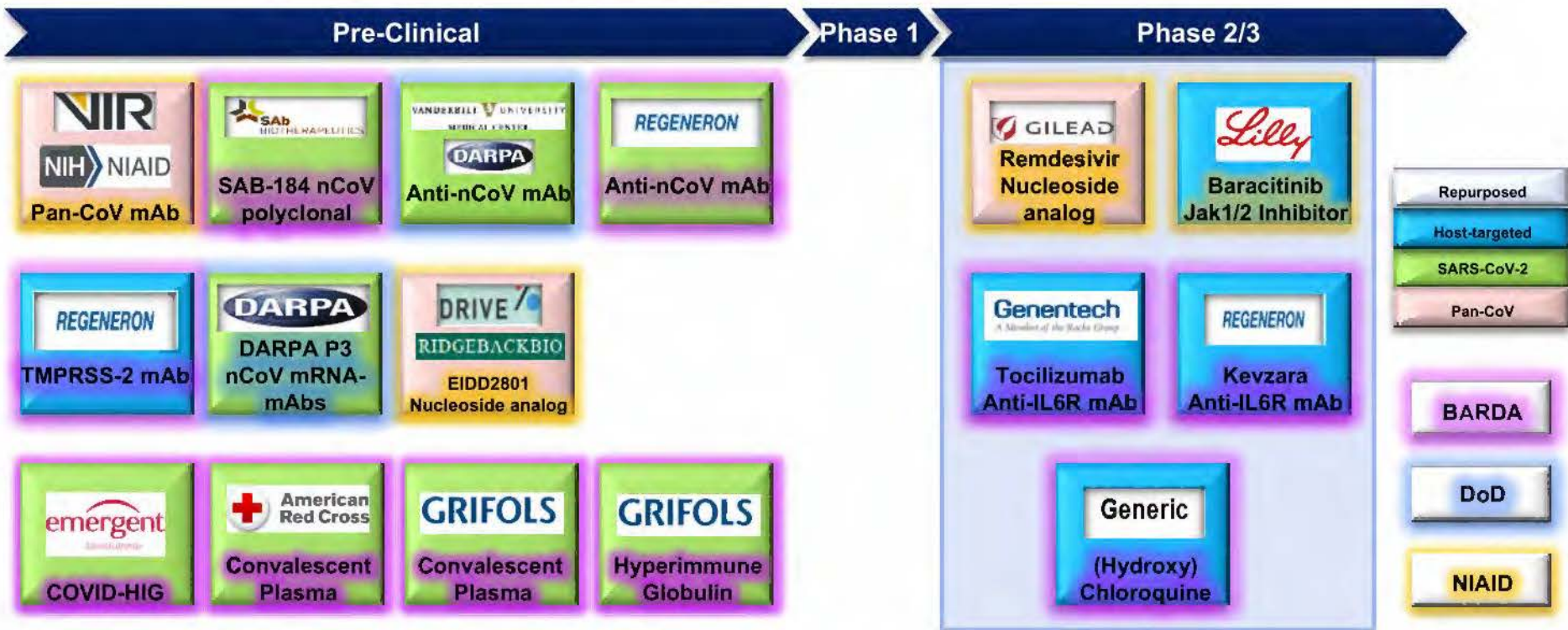
- Ready for immediate
clinical testing

e.g., inhibitors of viral
activation, host pathway
modulators

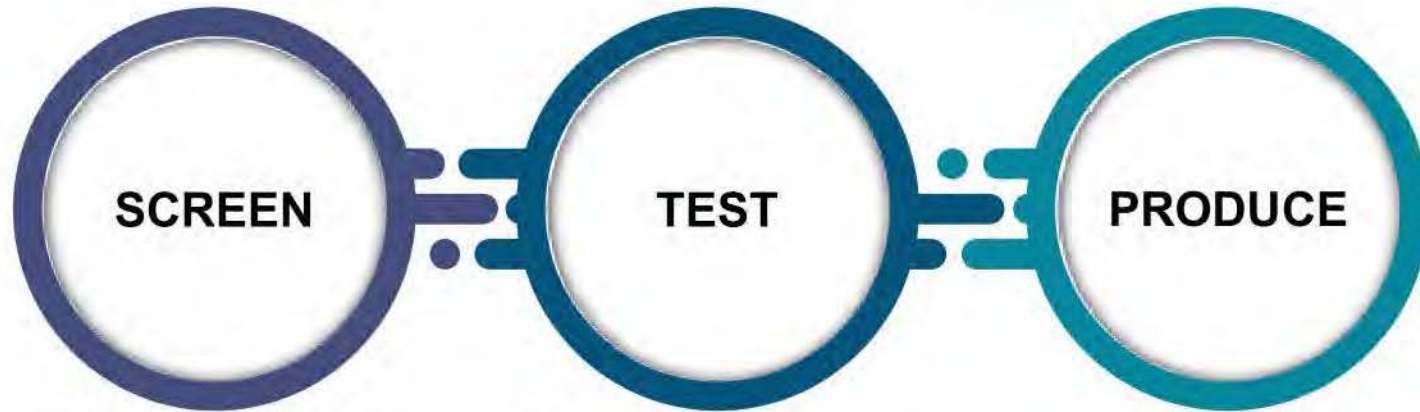
e.g., 2019-CoV specific
monoclonal antibodies, small
molecule antivirals, and
immunoglobulins

Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

USG-Supported SARS-CoV-2 Therapeutics



Repurposed Therapeutics



Thousands of compounds currently being screened-low cost/high impact
Many candidates identified and undergoing clinical evaluation

Allows rapid advancement to clinical trials (i.e. IL-6 monoclonal antibody trial started 2-weeks after identification)

Utilize existing facilities for production;
Expand capacity through partnerships with large pharmaceutical partners

BARDA seeking to leverage existing infrastructure for rapid clinical trial initiation

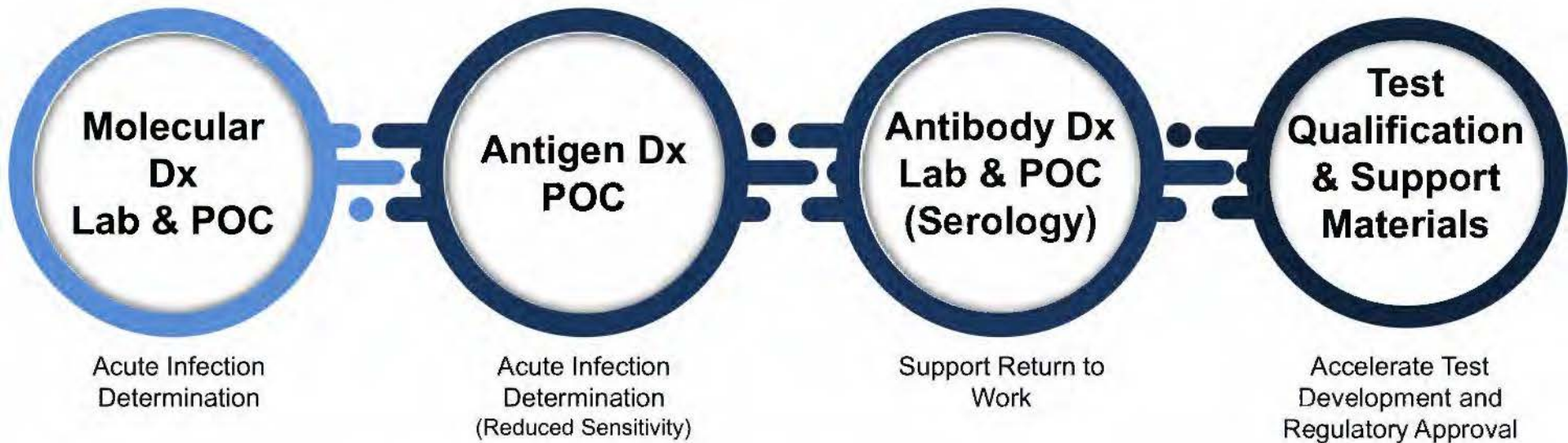
BARDA / DoD / NIAID Supported Studies

Product Type	Product (Developer)	Clinical Trials Identifier	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	Notes
Therapeutic	Remdesivir (Gilead)	NCT04280705	Clinical status assessed at Day 15 using 8-point ordinal scale	440 initially; increased to 700	426	49	Adaptive COVID-19 Treatment Trial; can add new candidates
Therapeutic	Sarilumab (Regeneron & Sanofi)	NCT04315298	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	730	51	Adaptive Phase 2/3 design; began enrolling March 19 and will enroll through 400 th patient follow up and data analysis
Therapeutic	Tolilizumab (Genentech & Roche)	NCT04320615	Clinical status assessed at Day 28 using 7-point ordinal scale	330	2	2	Phase 3 study; Scheduled to begin enrollment during the week of April 3
Vaccine	mRNA-1273 (Moderna)	NCT04283461	Safety & Immunogenicity at 25µg, 100µg & 250µg	45	30	2	Second cohort (100µg) dosed and in monitoring phase; dosing of 250µg expected to begin Apr 8
Observational	n/a	n/a	Observational study to collect pathological data on COVID-19	n/a	32	5	Department of Defense's "EPICC" Study; complementary studies in planning phases

Therapeutics Clinical Studies: US & ROW Summary

 Product Type	 US Trials	 US + International Trials
All therapeutics	30	231
Remdesivir	4	12
HCQ/CQ	7	46
Sarilumab (Kevzara)	1	6
Tocilizumab (Actemra)	1	10

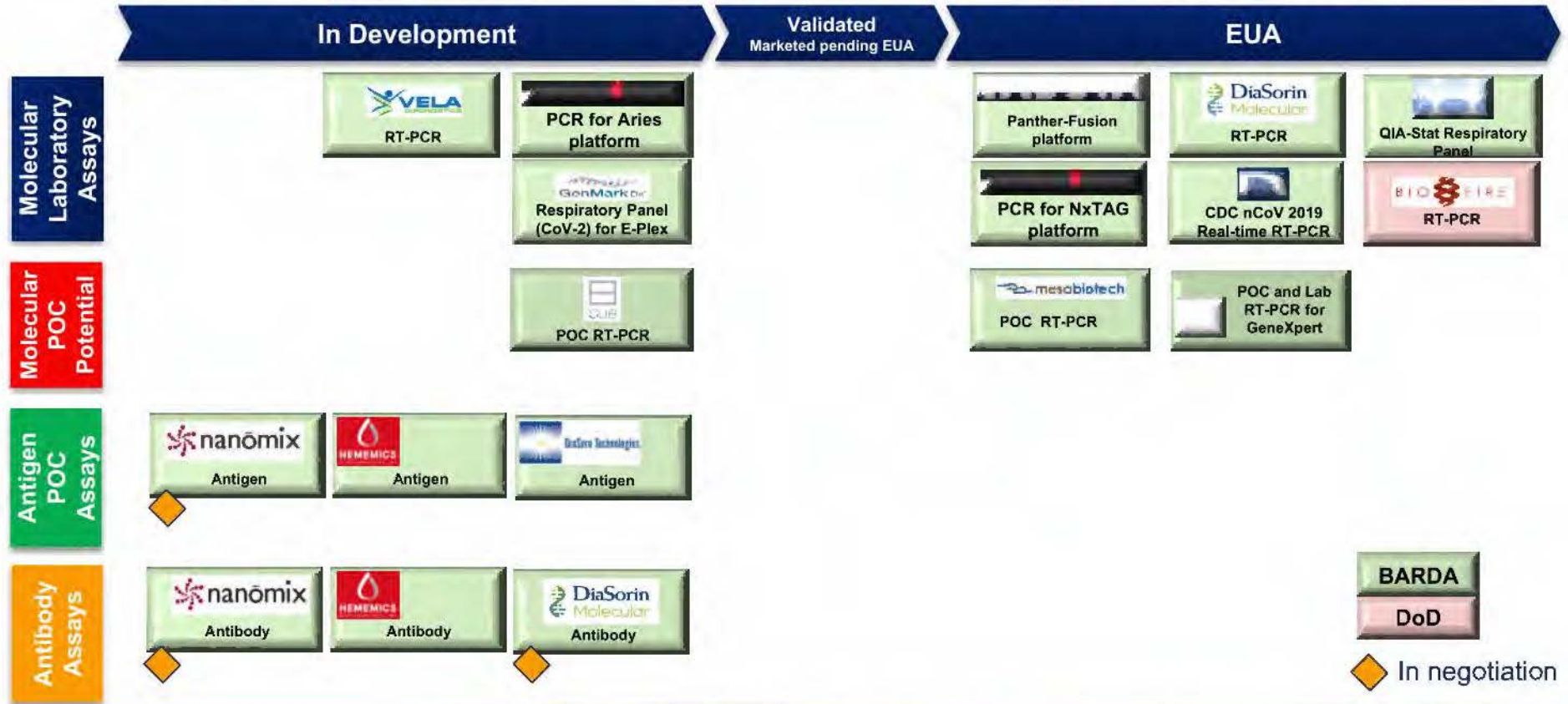
Diagnostics Development: Four-Pronged Approach



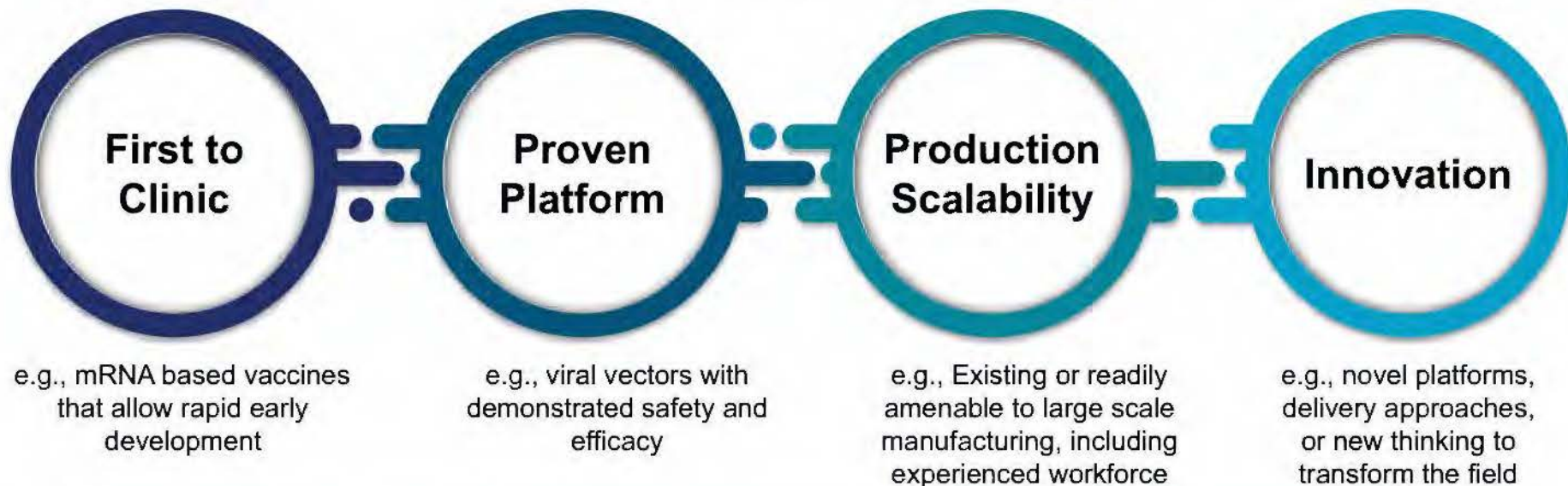
Leverage existing Laboratory Infrastructure & Equipment
Leverage Existing & Complete In-Development POC Equipment

04/02/20

USG-Sponsored SARS-CoV-2 Diagnostic Tests



Vaccine Development



Leverage existing infrastructure for rapid MCM generation and production through partnerships (contracts and OTA) including other USG agencies

SARS-CoV-2 Vaccine Landscape

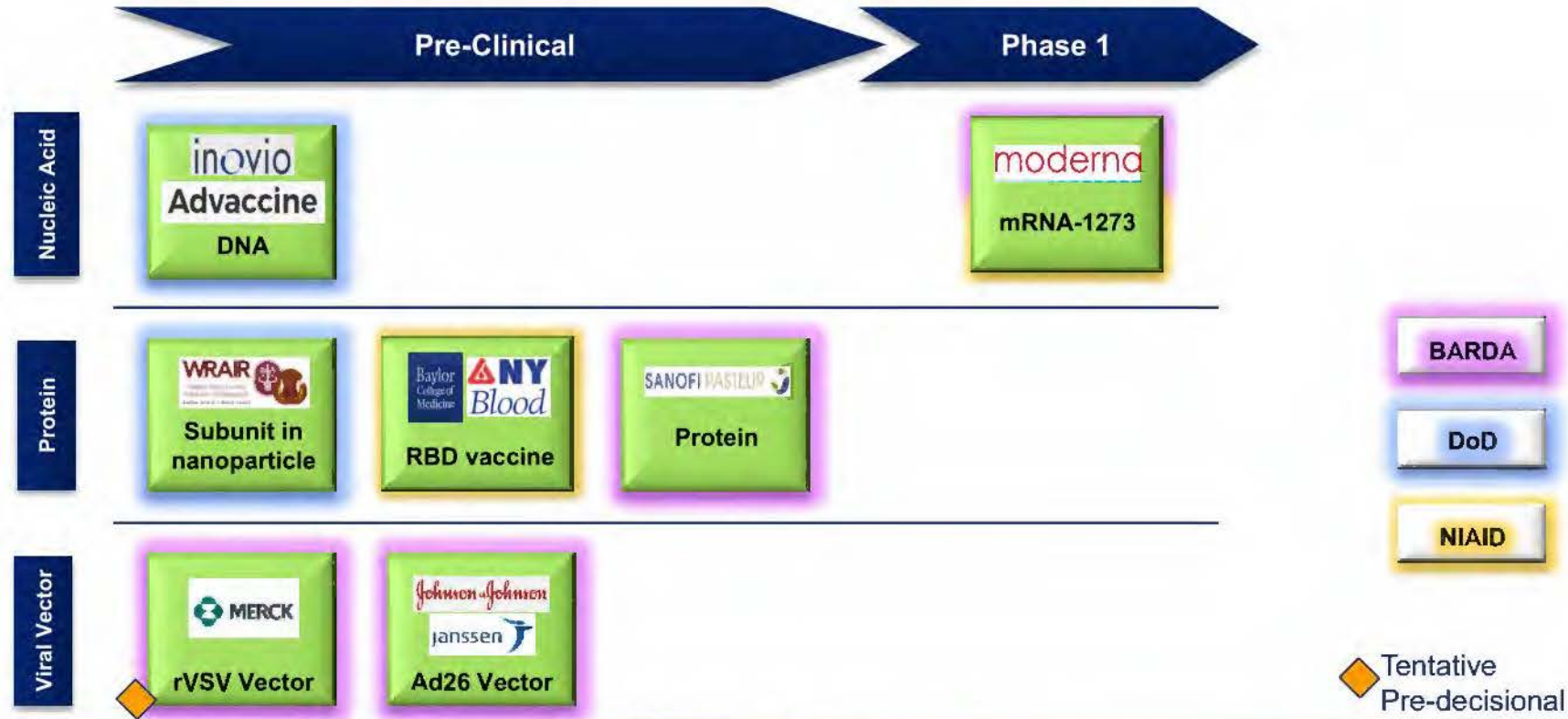
Pre-Clinical

Phase 1



USG Support

USG-Supported SARS-CoV-2 Vaccines



Vaccine Approach

Accelerate Development



Rapid Vaccine Platform Approaches

- Nucleic Acid
- Vectors
- Recombinant protein



Repurpose Licensed Products

- Viral Vector
- Recombinant Protein



Parallel Activities

- Overlapping clinical trials
- Scale up in parallel with clinical development

Mitigate Risk



Multiple Platforms

- Address potential yield risks
- Address potential dose risk



Multiple Presentations (recombinant, vector, etc.)

- Disease enhancement mitigation
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Redundancy

- Take multiple products through large scale clinical trials
- Multiple manufacturing facilities for each product

Domestic Manufacturing



Scale Up & Scale Out

- Validate large scale process (i.e. larger tanks)
- Technology transfer to more facilities
- Increase fill/finish capacity



Raw Materials Supply Chains

- Remove bottlenecks
- Establish stockpiles



Leverage Existing Facilities

- Facilities of large pharma partners
- CMOs

Moderna



DEVELOPMENT

- First to clinic (1Q 2020)
- Phase 2 (2Q 2020)



RISK

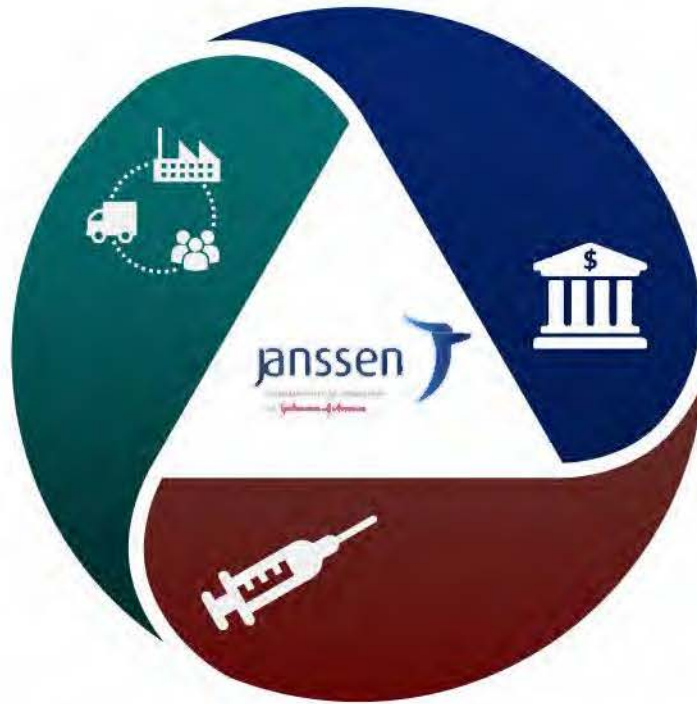
- Unlicensed platform
- Scale-up constraints and limited experience
- Raw materials
- Required Dose



DOMESTIC MANUFACTURING

- Scale up (limited) and out
- Secure supply chain

Janssen



DEVELOPMENT

- Parallel Work Streams
- Robust preclinical screening
- Phase 1 by 3Q2020

RISK

- Production yield
- Required Dose

DOMESTIC MANUFACTURING

- Technology transfer to domestic facility
- Significant manufacturing experience mitigates risk

Sanofi Pasteur



DEVELOPMENT

- FDA-licensed vaccine platform
- Parallel Work Streams
- Phase 1 by 3Q2020



RISK

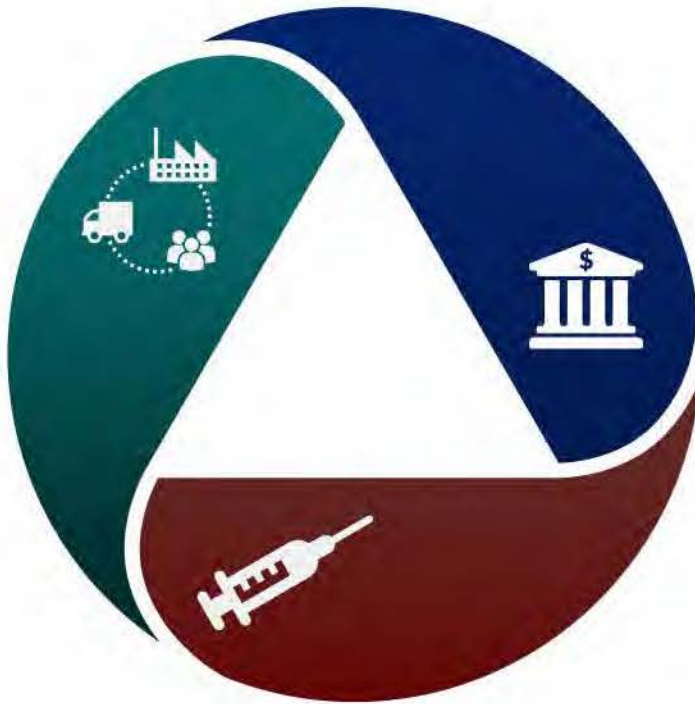
- Production yield
- Adjuvant likely required



DOMESTIC MANUFACTURING

- Licensed manufacturing facility available
- Production levels likely to be robust
- Experienced manufacturing team

Innovation



AREAS OF INTEREST

- Product yield enhancement
- Faster time to protection
- Operational improvements

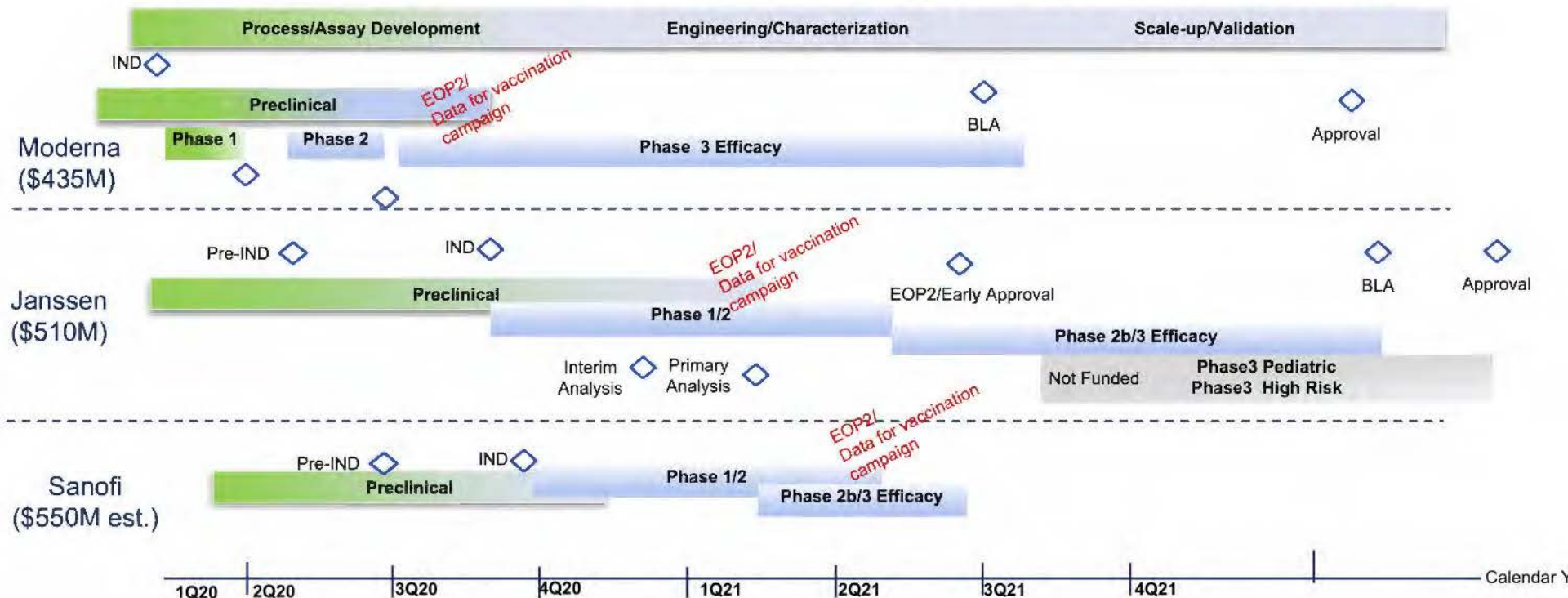
IDENTIFICATION

- Handoff from other Government agencies
- High ranking from MCM review panels
- Leveraging opportunities (within and outside of Government)
- Assess timelines and domestic manufacturing capability

TARGETED STRATEGY

- Initial 'seed' funding to assess feasibility
- Flexible funding approaches
- Cost Share

Estimated Vaccine Development Timelines



From: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
To: Wallace, Rodney (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b4654f8f0c0f4623b9e47465e9e1037a-Wallace, Ro <Rodney.Wallace@hhs.gov>
Subject: RE: Mask Manufacturing Capacity Increase
Date: 2020/03/20 12:11:00
Priority: Normal
Type: Note

Let them know this is a WH directive and it was sent to you because the person did not know who to contact at the SNS

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-0899
Mobile: (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

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From: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Sent: Friday, March 20, 2020 12:10 PM
To: Wallace, Rodney (OS/ASPR/BARDA) <Rodney.Wallace@hhs.gov>
Cc: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: RE: Mask Manufacturing Capacity Increase

Please forward the slide deck to Steve Adams and Makoto Braxton for their consideration.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
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From: Wallace, Rodney (OS/ASPR/BARDA) <Rodney.Wallace@hhs.gov>
Sent: Friday, March 20, 2020 12:08 PM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: Mask Manufacturing Capacity Increase

Gary: Has there been any determination on what organization will lead the mask manufacturing capacity increase efforts the white house approached manufacturers about? You can detect the frustration in Mike Bowen's tone in the email below. Halyard will be in the same state soon, unless the white house reaches out to them directly.

Rod

+(b)(6)

From: (b)(6) >
Sent: Friday, March 20, 2020 11:41 AM
To: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>; Wallace, Rodney (OS/ASPR/BARDA) <Rodney.Wallace@hhs.gov>
Subject: If ASPR needs us, you know where we are.

We don't have time to find out what, if anything, the government wants from us.

Mike Bowen

Phone: (b)(6)
Fax: 817-886-2733

(b)(6)

(b)(6)

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Confidencialidad de Correo Electronico de (b)(6)

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Sender: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>

Recipient: Wallace, Rodney (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b4654f8f0c0f4623b9e47465e9e1037a-Wallace, Ro <Rodney.Wallace@hhs.gov>

Sent Date: 2020/03/20 12:11:37

Delivered Date: 2020/03/20 12:11:00

From: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
To: Houchens, Christopher (HHS/ASPR) (Christopher.Houchens@hhs.gov) /o=HHS EES/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=Christopher.Houchens.os <Christopher.Houchens@hhs.gov>
Subject: Remdesivir trials
Date: 2020/04/02 13:06:00
Priority: Normal
Type: Note

<https://clinicaltrials.gov/ct2/results?cond=COVID&term=Remdesivir&cntry=&state=&city=&dist=>

There are 9 trials ongoing or to be started.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary

Director, Medical Countermeasure Programs

Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR

Department of Health and Human Services

330 Independence Avenue, S.W. Room 640 G

Washington, D.C. 20201

Office: 202-260-0899

Mobile: (h/v/s)

Fax: 202-205-0873

email: Gary.Disbrow@HHS.gov

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Sender: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>

Recipient: Houchens, Christopher (HHS/ASPR) (Christopher.Houchens@hhs.gov) /o=HHS EES/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=Christopher.Houchens.os <Christopher.Houchens@hhs.gov>

Sent Date: 2020/04/02 13:06:01

Delivered Date: 2020/04/02 13:06:00

From: Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>

'Marik, Paul E.' <MarikPE@EVMS.EDU>;
Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>;
Robert Malone <[REDACTED]>;
vinu arumugham <vaccine.safety@aol.com>;
Sestili, Piero <piero.sestili@uniurb.it>;
<def2004@cumc.columbia.edu>;
<jconigliaro@northwell.edu>;
<ddm1@cumc.columbia.edu>;
<ag3786@cumc.columbia.edu>;
<mo2130@cumc.columbia.edu>;
<jl1333@cumc.columbia.edu>;
<dtuveson@cshl.edu>;
<zj7@cumc.columbia.edu>;
<wt62@cumc.columbia.edu>;
<dw11@cumc.columbia.edu>;
<tcw21@cumc.columbia.edu>;
<kjtracey@northwell.edu>;
mvcallahan@mgh.harvard.edu /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=20f0e9a3ebeb4ef99d30a96386fb2627-Guest_945f5
<mvcallahan@mgh.harvard.edu>;
<ja660@cumc.columbia.edu>;
<janowitz@cshl.edu>;
<djp65@cam.ac.uk>;
<yongfeng@email.unc.edu>;
<xphuang@unc.edu>;
<kris.white@mssm.edu>;
To: <elena.morenodelolmo@mssm.edu>;
<Assaf_Alon@hms.harvard.edu>;
<Andrew_Kruse@hms.harvard.edu>;
<anthony.mittermaier@mcgill.ca>;
<Julianne.Hall@quinnipiac.edu>;
<Robert.Bona@quinnipiac.edu>;
<h.clark@ucl.ac.uk>;
<bryan_roth@med.unc.edu>;
<Victor.Francone@quinnipiac.edu>;
<Norbert.Herzog@quinnipiac.edu>;
<Maurice.Fremont-Smith@quinnipiac.edu>;
Commins, Scott P <scommins@email.unc.edu>;
Lawrence Steinman <steiny@stanford.edu>;
<ngkounis@otenet.gr>;
Matzinger, Polly <pcm@helix.nih.gov>;
<pconti@unich.it>;
Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob
<Robert.Kadlec@hhs.gov>;
HHS Secretary (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=5e3fce8f00194d8d94fc91094888d811-HHS Secreta
<secretary@hhs.gov>;
Christine Laine <claine@acponline.org>;
<fgodlee@bmj.com>;
<howard.bauchner@jamanetwork.org>;
<richard.horton@lancet.com>;
<erubin@hsph.harvard.edu>

Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Date: 2020/07/08 14:38:28

Priority: Normal

Type: Note

Please remove me from this email distribution list.

Regards

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
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Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

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From: Marik, Paul E. <MarikPE@EVMS.EDU>

Sent: Wednesday, July 8, 2020 8:40 AM

To: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <(b)(6)>;
vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>;
def2004@cumc.columbia.edu; jconigliaro@northwell.edu; ddm1@cumc.columbia.edu;
ag3786@cumc.columbia.edu; mo2130@cumc.columbia.edu; jl1333@cumc.columbia.edu;
dtuveson@cshl.edu; zj7@cumc.columbia.edu; wt62@cumc.columbia.edu; dwl1@cumc.columbia.edu;
tcw21@cumc.columbia.edu; kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu;
ja660@cumc.columbia.edu; janowitz@cshl.edu; djp65@cam.ac.uk; yongfeng@email.unc.edu;
xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu;
Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca;
Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk;
bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu;
Maurice.Fremont-Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence
Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>;
pconti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS)
<secretary@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Christine Laine
<claine@acponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org;

richard.horton@lancet.com; erubin@hsph.harvard.edu

Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

To add to the discussion it has been known for a long time that Vitamin C stabilizes mast cells and, inhibits histamine synthesis and inactivates histamine.

PM

Paul E. Marik MD, FCCP, FCCM |

Eastern Virginia Medical School |

Department of Internal Medicine |

Chief, Pulmonary and Critical Care Medicine |

825 Fairfax Ave, Rm 575, Norfolk, VA 23507 |

☎ 757.446.8910 | 📠 757.446.5242 |

✉ marikpe@evms.edu | 🌐 <https://protect2.fireeye.com/url?k=af60a9f4-f335a024-af6098cb-0cc47a6a52de-11162424aad75683&u=http://www.evms.edu/>

Teaching. Discovering. Caring.

From: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>

Sent: Wednesday, July 8, 2020 8:27 AM

To: Robert Malone <rmalone@biomimicry.com>; vinu arumugham <yaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; df2004@cumc.columbia.edu; jconigliaro@northwell.edu; ddm1@cumc.columbia.edu; ag3786@cumc.columbia.edu; mo2130@cumc.columbia.edu; jl1333@cumc.columbia.edu; dtuveson@cshl.edu; zj7@cumc.columbia.edu; wt62@cumc.columbia.edu; dwl1@cumc.columbia.edu; tcw21@cumc.columbia.edu; kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu; ja660@cumc.columbia.edu; janowitz@cshl.edu; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf Alon@hms.harvard.edu; Andrew Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Marik, Paul E. <MarikPE@EVMS.EDU>; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it; Robert.Kadlec@hhs.gov; Secretary@HHS.gov; Gary.Disbrow@hhs.gov; Christine Laine <claine@acponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu

Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

All,

The following preprint on Kawasaki Disease and Multisystem Inflammatory Syndrome in Children: An Antibody-Induced Mast Cell Activation Hypothesis is posted here: <https://www.ll.mit.edu/research/publications/kawasaki-disease-and-multisystem-inflammatory-syndrome-children-antibody-induced> is now in press: J Pediatrics & Pediatr Med. 2020; 4(2): 1-7 (attached draft).

I would be interested in contributing to the proposed efforts.

Sincerely,

Darrell

Darrell O. Ricke, Ph.D.
Group 49 Biological and Chemical Technologies
Lincoln Laboratory, Massachusetts Institute of Technology
244 Wood Street
Lexington, MA 02421-6426

Phone: 781-981-8323 (voice messages only)

Work cell: (617) 253-3333

E-mail: Darrell.Ricke@ll.mit.edu

From: Robert Malone <(617) 253-3333>
Date: Tuesday, July 7, 2020 at 6:12 PM
To: vinu arumugham <vaccine.safety@aol.com>
Cc: "Sestili, Piero" <piero.sestili@uniurb.it>, "def2004@cumc.columbia.edu" <def2004@cumc.columbia.edu>, "jconigliaro@northwell.edu" <jconigliaro@northwell.edu>, "ddm1@cumc.columbia.edu" <ddm1@cumc.columbia.edu>, "ag3786@cumc.columbia.edu" <ag3786@cumc.columbia.edu>, "mo2130@cumc.columbia.edu" <mo2130@cumc.columbia.edu>, "jl1333@cumc.columbia.edu" <jl1333@cumc.columbia.edu>, "dtuveson@cshl.edu" <dtuveson@cshl.edu>, "zj7@cumc.columbia.edu" <zj7@cumc.columbia.edu>, "wt62@cumc.columbia.edu" <wt62@cumc.columbia.edu>, "dwl1@cumc.columbia.edu" <dwl1@cumc.columbia.edu>, "tcw21@cumc.columbia.edu" <tcw21@cumc.columbia.edu>, "kjtracey@northwell.edu" <kjtracey@northwell.edu>, "mvcallahan@mgh.harvard.edu" <mvcallahan@mgh.harvard.edu>, "ja660@cumc.columbia.edu" <ja660@cumc.columbia.edu>, "janowitz@cshl.edu" <janowitz@cshl.edu>, "djp65@cam.ac.uk" <djp65@cam.ac.uk>, "Ricke, Darrell - 0449 - MITLL" <darrell.ricke@ll.mit.edu>, "yongfeng@email.unc.edu" <yongfeng@email.unc.edu>, "xphuang@unc.edu" <xphuang@unc.edu>, "kris.white@mssm.edu" <kris.white@mssm.edu>, "elena.morenodelolmo@mssm.edu" <elena.morenodelolmo@mssm.edu>, "[Assaf Alon@hms.harvard.edu](mailto:Assaf_Alon@hms.harvard.edu)" <[Assaf Alon@hms.harvard.edu](mailto:Assaf_Alon@hms.harvard.edu)>, "[Andrew Kruse@hms.harvard.edu](mailto:Andrew_Kruse@hms.harvard.edu)" <[Andrew Kruse@hms.harvard.edu](mailto:Andrew_Kruse@hms.harvard.edu)>, "anthony.mittermaier@mcgill.ca" <anthony.mittermaier@mcgill.ca>, "Julianne.Hall@quinnipiac.edu" <Julianne.Hall@quinnipiac.edu>, "Robert.Bona@quinnipiac.edu" <Robert.Bona@quinnipiac.edu>, "h.clark@ucl.ac.uk" <h.clark@ucl.ac.uk>, "bryan_roth@med.unc.edu" <bryan_roth@med.unc.edu>, "Victor.Francone@quinnipiac.edu" <Victor.Francone@quinnipiac.edu>, "Norbert.Herzog@quinnipiac.edu" <Norbert.Herzog@quinnipiac.edu>, "Maurice.Fremont-Smith@quinnipiac.edu" <Maurice.Fremont-Smith@quinnipiac.edu>, "marikpe@evms.edu"

<marikpe@evms.edu>, "Commins, Scott P" <scommins@email.unc.edu>, Lawrence Steinman <steiny@stanford.edu>, "ngkounis@otenet.gr" <ngkounis@otenet.gr>, "Matzinger, Polly" <pcm@helix.nih.gov>, "pconti@unich.it" <pconti@unich.it>, "Robert.Kadlec@hhs.gov" <Robert.Kadlec@hhs.gov>, "Secretary@HHS.gov" <Secretary@hhs.gov>, "Gary.Disbrow@hhs.gov" <Gary.Disbrow@hhs.gov>, Christine Laine <claine@acponline.org>, "fgodlee@bmj.com" <fgodlee@bmj.com>, "howard.bauchner@jamanetwork.org" <howard.bauchner@jamanetwork.org>, "richard.horton@lancet.com" <richard.horton@lancet.com>, "erubin@hsph.harvard.edu" <erubin@hsph.harvard.edu>
Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham <vaccine.safety@aol.com>wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this [one](#)?) requesting that authorities rapidly consider and promote the clinical exploitation of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

<https://doi.org/10.3389/fphar.2020.00854>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

<https://www.researchsquare.com/article/rs-30934/v2>

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

<https://pubmed.ncbi.nlm.nih.gov/32013309/>

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell

stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin
<https://doi.org/10.5281/zenodo.3748303>

As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

<https://protect2.fireeye.com/url?k=e18ec594-bddbcc44-e18ef4ab-0cc47a6a52de-44d3aa827e434ccc&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen. Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

<https://doi.org/10.3389/fphar.2020.00854>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili
Full Professor in Pharmacology,
University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham <vaccine.safety@aol.com>ha scritto:

----- Forwarded Message -----

Subject: Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers

Date: Thu, 14 May 2020 09:42:05 -0700

From: vinu arumugham <vaccine.safety@aol.com>

To: nchoueit@montefiore.org <nchoueit@montefiore.org>, Brett.Giroir@hhs.gov <Brett.Giroir@hhs.gov>, ufficiostampa@asst-pg23.it <ufficiostampa@asst-pg23.it>, ldantiga@hpg23.it <ldantiga@hpg23.it>, letters@nytimes.com <letters@nytimes.com>, nytnews@nytimes.com <nytnews@nytimes.com>, inytletters@nytimes.com <inytletters@nytimes.com>, editorial@nytimes.com <editorial@nytimes.com>, corrections@nytimes.com <corrections@nytimes.com>, books@nytimes.com <books@nytimes.com>, magazine@nytimes.com <magazine@nytimes.com>, travelmail@nytimes.com <travelmail@nytimes.com>, edu@nytimes.com <edu@nytimes.com>, eileen.murphy@nytimes.com <eileen.murphy@nytimes.com>, danielle.rhoades-ha@nytimes.com <danielle.rhoades-ha@nytimes.com>, booking@nytimes.com <booking@nytimes.com>, bizday@nytimes.com <bizday@nytimes.com>, foreign@nytimes.com <foreign@nytimes.com>, sports@nytimes.com <sports@nytimes.com>, washington@nytimes.com <washington@nytimes.com>, national@nytimes.com <national@nytimes.com>, thearts@nytimes.com <thearts@nytimes.com>, metropolitan@nytimes.com <metropolitan@nytimes.com>, tips@nytimes.com <tips@nytimes.com>, public@nytimes.com <public@nytimes.com>, sarah.mervosh@nytimes.com <sarah.mervosh@nytimes.com>, pam.belluck@nytimes.com <pam.belluck@nytimes.com>, reed.abelson@nytimes.com <reed.abelson@nytimes.com>, n.walsh@medpagetoday.com <n.walsh@medpagetoday.com>, tips@medpagetoday.com <tips@medpagetoday.com>, c.bankhead@medpagetoday.com <c.bankhead@medpagetoday.com>, c.phend@medpagetoday.com <c.phend@medpagetoday.com>, m.walker@medpagetoday.com <m.walker@medpagetoday.com>, ehlavinka@medpagetoday.com <ehlavinka@medpagetoday.com>, iingram@medpagetoday.com <iingram@medpagetoday.com>, k.fiore@medpagetoday.com <k.fiore@medpagetoday.com>, n.lou@medpagetoday.com <n.lou@medpagetoday.com>, Press.Office@exec.ny.gov, r.viner@ucl.ac.uk <r.viner@ucl.ac.uk>, e.whittaker@imperial.ac.uk <e.whittaker@imperial.ac.uk>, m.levin@imperial.ac.uk <m.levin@imperial.ac.uk>, JPIDS.EditorialOffice@oup.com <JPIDS.EditorialOffice@oup.com>, gerberj@email.chop.edu <gerberj@email.chop.edu>, sarah.parker@ucdenver.edu <sarah.parker@ucdenver.edu>, greemd@chp.edu <greemd@chp.edu>, ravi.jhaveri@northwestern.edu <ravi.jhaveri@northwestern.edu>, samir.shah@cchmc.org <samir.shah@cchmc.org>, ashane@emory.edu <ashane@emory.edu>, ilan.youngster@childrens.harvard.edu <ilan.youngster@childrens.harvard.edu>, storch@wustl.edu <storch@wustl.edu>, jsbradley@ucsd.edu <jsbradley@ucsd.edu>, penelope.bryant@mcri.edu.au <penelope.bryant@mcri.edu.au>, chchiu@adm.cgmh.org.tw <chchiu@adm.cgmh.org.tw>, lara.danziger-isakov@cchmc.org <lara.danziger-isakov@cchmc.org>, dhunstad@wustl.edu <dhunstad@wustl.edu>, Huskins.Charles@mayo.edu <Huskins.Charles@mayo.edu>, mлаufer@medicine.umaryland.edu <mлаufer@medicine.umaryland.edu>

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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

<https://twitter.com/ArumughamVinu/status/1259659169046474753?s=20>

One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303>

As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1>

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

<https://doi.org/10.5281/zenodo.3766462>

My comment posted in the Annals of Internal Medicine:

Please see comments section:

<https://protect2.fireeye.com/url?k=89b04da4-d5e54474-89b07c9b-0cc47a6a52de-0d3acbf2316abfbb&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping. <https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients>

Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example. <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

<https://www.bmj.com/content/360/bmj.k1378/rr-15>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)

There is an increase in mast cell density during infections:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435071/>

IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

[https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749\(17\)32622-2/fulltext](https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749(17)32622-2/fulltext)

Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF- κ B Pathways in Nasal Fibroblasts

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214978/>

Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/17158962>

The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

<https://www.ncbi.nlm.nih.gov/pubmed/1578094>

<https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus>

Also, azithromycin reduces histamine induced inflammation.

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

<https://www.ncbi.nlm.nih.gov/pubmed/29888693>

Hydroxychloroquine helps in allergic asthma.

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma.

<https://www.ncbi.nlm.nih.gov/pubmed/9723661>

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

<https://www.sciencedirect.com/science/article/pii/S0924857920300996>

<https://protect2.fireeye.com/url?k=2ff8f995-73adf045-2ff8c8aa-0cc47a6a52de-d6f7d13655de4261&u=https://www.mediterranee-infection.com/covid-19/>

So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

--

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<https://protect2.fireeye.com/url?k=2959cd27-750cc4f7-2959fc18-0cc47a6a52de-f0896a6017734c49&u=http://www.rwmalonemd.com/>

"Tread lightly, take only pictures, leave only footprints, kill only time"

Sender:	Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
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Sent Date: 2020/07/08 14:38:27

Delivered Date: 2020/07/08 14:38:28

From:	Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
To:	Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>
CC:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: Remdesivir Donation
Date:	2020/04/07 19:33:00
Priority:	Normal
Type:	Note

Team,

This was shared with the WH and very broadly, almost a week ago. There is nothing for us to do. There is an entire email train going around with no less than 25 emails in the last 30 minutes. I have responded to Elleen. Please don't get sucked into the emails.

The FDA is going to issuance guidance for companies to pursue IND path. They want to donate their supply so they do not have to respond to expanded access request and transfer it to the USG. Let SNS and CDC accept the product and support the EUA.

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR
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From: Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Sent: Tuesday, April 7, 2020 7:26 PM
To: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: RE: Remdesivir Donation

Donations such as this are handled by SNS. Looping in Gary and Rick in case they know something I don't that makes this different. Thanks.

Robert Johnson, Ph.D.
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From: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Sent: Tuesday, April 7, 2020 6:36 PM
To: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA)

<Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>

Subject: RE: Remdesivir Donation

If you are asking if BARDA should also file the EUA for Remdesivir, my answer would be (b)(5)

(b)(5)

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services (DHHS)
Office: 202-205-3633
BB: (b)(6)
Christopher.houchens@hhs.gov

From: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>

Sent: Tuesday, April 7, 2020 5:08 PM

To: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>

Subject: RE: Remdesivir Donation

Sorry, Chris, I should have been clearer. I'm asking whether there is a plan for BARDA and the working group to manage this EUA, similar to how we are managing (H)CQ? (I'm hoping that's not the case) The OGC lawyer is including me in her questions, but I don't know what my role is with this one.

Bob

From: Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>

Sent: Tuesday, April 7, 2020 4:32 PM

To: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>

Subject: RE: Remdesivir Donation

Bob – Thanks. Are you specifically asking about the following the position of the BARDA and/or the MCM TF? I cannot address the former but can engage the MTF to develop a position on the latter. Chris

"At least initially, supply of the drug is going to be very limited, so use of the product should be restricted to only the sickest patients. We anticipate that there will be need for some mechanism to assess which hospitals have the greatest need based on the number of severely ill patients and allocate supply to them."

Christopher Houchens, PhD
Director (Acting) Division of CBRN Countermeasures
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
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From: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Sent: Tuesday, April 7, 2020 4:13 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Subject: FW: Remdesivir Donation

Linda, Robert, Chris
Just received this. Wanted to make certain you are aware and clarify what our role (BARDA and interagency working group) is.

Bob

From: Mantoan, Patricia (HHS/OGC) <Patricia.Mantoan@HHS.GOV>
Sent: Tuesday, April 7, 2020 3:50 PM
To: Gorman, Susan (ASPR/SNS) <spg4@cdc.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Ottem, Ronald (Ron) (ASPR/SNS) <rco9@cdc.gov>; Mabry, Shirley (ASPR/SNS) <aiq8@cdc.gov>; Adams, Steven A. (ASPR/SNS) <saa1@cdc.gov>
Cc: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Waters, Cicely (OS/ASPR/OEA) <Cicely.Waters@hhs.gov>
Subject: FW: Remdesivir Donation

SNS and BARDA colleagues: Hi, I wanted to make you aware of a proposed donation from Gilead for 140,000 courses of Remdesivir. I'm assuming you would want this donation, but please let me know otherwise. My team is working on a draft donation agreement. I wanted to flag for you some preliminary issues that Gilead raised below. If any of these issues would be problematic to SNS or BARDA, please let me know so we can work through those issues with Gilead.

Thanks,
Patty

From: Chuck Clapton <Chuck.Clapton@gilead.com>
Sent: Tuesday, April 7, 2020 3:27 PM
To: Mantoan, Patricia (HHS/OGC) <Patricia.Mantoan@HHS.GOV>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>
Cc: Jennifer Alton <jenn.alton@pathwaypolicy.com>; Michael Boyd <michael.boyd1@gilead.com>
Subject: RE: Remdesivir Donation

<Joseph.Hamel@hhs.gov>

Cc: Jennifer Alton <jenn.alton@pathwaypolicy.com>

Subject: [EXTERNAL] RE: Remdesivir Donation

Chuck: I will call you at 2:30 today.

Thanks,
Patty

From: Chuck Clapton <Chuck.Clapton@gilead.com>

Sent: Tuesday, April 7, 2020 2:03 PM

To: Mantoan, Patricia (HHS/OGC) <Patricia.Mantoan@HHS.GOV>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>

Cc: Jennifer Alton <jenn.alton@pathwaypolicy.com>

Subject: RE: Remdesivir Donation

Thanks Joe and Patty. Yes, 2:30 works. My direct is (b)(6)

From: Mantoan, Patricia (HHS/OGC) <Patricia.Mantoan@HHS.GOV>

Sent: Tuesday, April 7, 2020 1:58 PM

To: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Chuck Clapton <Chuck.Clapton@gilead.com>

Cc: Jennifer Alton <jenn.alton@pathwaypolicy.com>

Subject: [EXTERNAL] RE: Remdesivir Donation

Chuck: I can contact you so I can get the particulars of the donation and then send you a donation agreement. Can you talk with me at 2:30 today?

Thanks,
Patty

From: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>

Sent: Tuesday, April 7, 2020 1:56 PM

To: Mantoan, Patricia (HHS/OGC) <Patricia.Mantoan@HHS.GOV>

Cc: Jennifer Alton <jenn.alton@pathwaypolicy.com>; chuck.clapton@gilead.com

Subject: Remdesivir Donation

Importance: High

Patty,

Jenn just reached out to me and let me know that Chuck at Gilead (CC'd) is interested in making a donation of Remdesivir to HHS. Please connect with him and let's get this teed up.

Chuck,

THANK YOU so much for your consideration with this at this critical time in our Nation's history.

Best,
Joe Hamel

Strategic Innovation and Emerging Technology Manager
Assistant Secretary for Preparedness and Response
Office: 202-969-3852
Cell: (b)(6)

Sender:	Disbrow, Gary (OS/ASPR/BARDA) </O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA>
Recipient:	Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/04/07 19:33:56
Delivered Date:	2020/04/07 19:33:00

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Carnation Ambulatory Monitor (CAM™) Extended Wear ECG Patch:

Only Patch Monitor Clinically Validated to Monitor QT Intervals

BARDA / MedTech Innovator – April 2020

Ken Nelson

*Chief Commercial Officer
Bardy Diagnostics*

The Bardy Diagnostics Solution: QT Interval & Arrhythmia Detection Monitor (14 Day ECG)



Carnation Ambulatory Monitor (CAM™) Patch

- Remotely monitor life-threatening QT Prolongation in COVID-19 patients using hydroxychloroquine with the only patch monitor with a peer-reviewed, clinically validated QT interval measurement compared to a 7-lead Holter
- Facilitate transition to telehealth with a disposable, single-use patch monitor to reduce unnecessary contact and possible exposure to COVID-19



Comfort for the Patient



Convenience for the Organization



Clarity for the Physician

Core Advantages of CAM Patch



Advanced Diagnostic Accuracy

- Patented P-wave centric ECG detection technology
- Diagnostic accuracy never seen before, proven in 2 peer-reviewed clinical trials (Holter and leading Patch)
- Designed to dramatically improve visualization of the entire ECG
- 14-Day continuous recording

Patient-Friendly Design

- Simple, easy-to-use, disposable
- Convenient, compact, and comfortable
- Unique, narrow, hourglass-shape especially comfortable for women



Note vector and location ideal for sensing T-waves directly over the heart.

COVID-19 Monitoring Solutions & Value

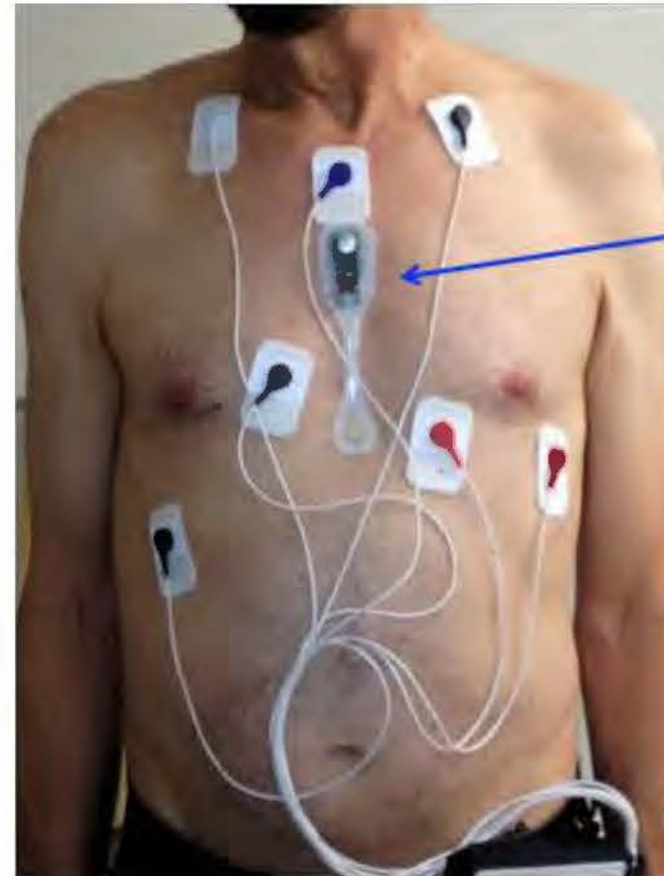
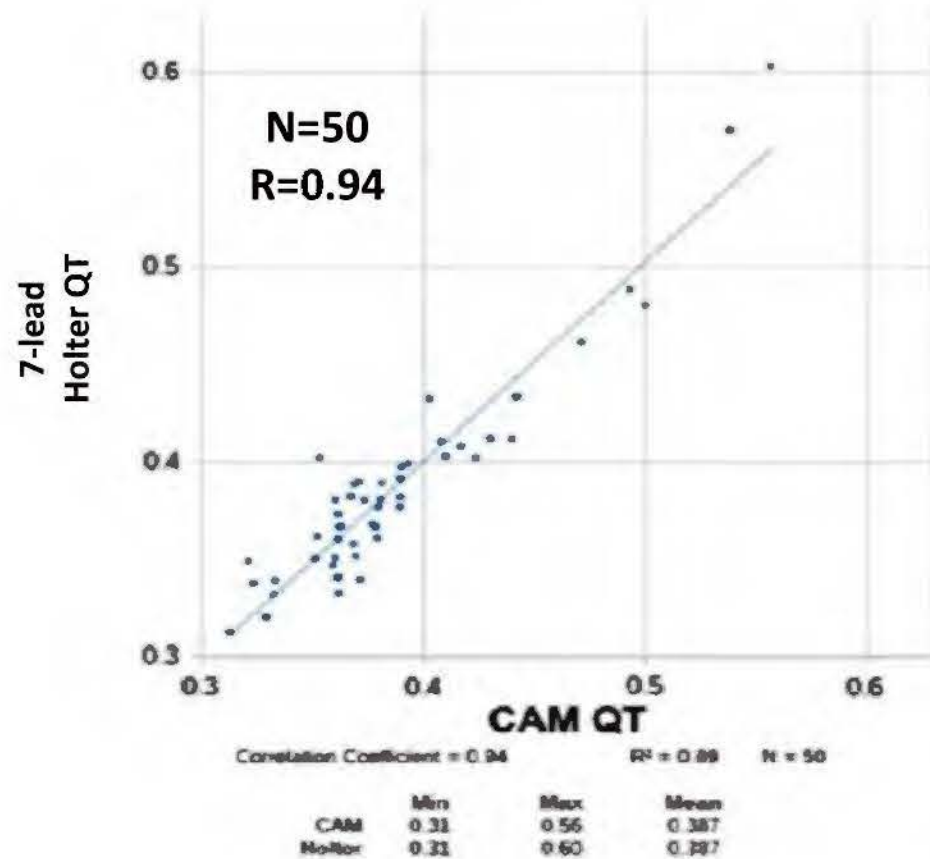


1. Mail-To-Patient home application of CAM patches
2. One-time use (Disposable)
3. Continuous monitoring of QT interval, critical when looking for change and monitoring drug side effects on repolarization
4. Excellent vector and proximity to the ventricles, critical for T-wave visualization
5. Unique ability to record low frequency content during repolarization both allowing visualization of the T wave and distinction between the T-wave and the U-wave.
6. Peer-reviewed published data confirming QT interval validity in addition to FDA approval
7. Use in 3 University ongoing trials for QT interval monitoring in COVID-19 infected patients, including Walter Reed Hospital in Bethesda.
8. Professor Mark Haigney, who is conducting the Walter Reed study, is an expert on QT prolongation and chose the Carnation Ambulatory monitor for his work because of its unique capabilities in recording all aspects of the ECG including low amplitude, low frequency content.

The only peer-reviewed, clinically validated QT interval measurement compared to a 7-lead Holter



Figure 3 C



CAM

Holter/Event with cassette and cables

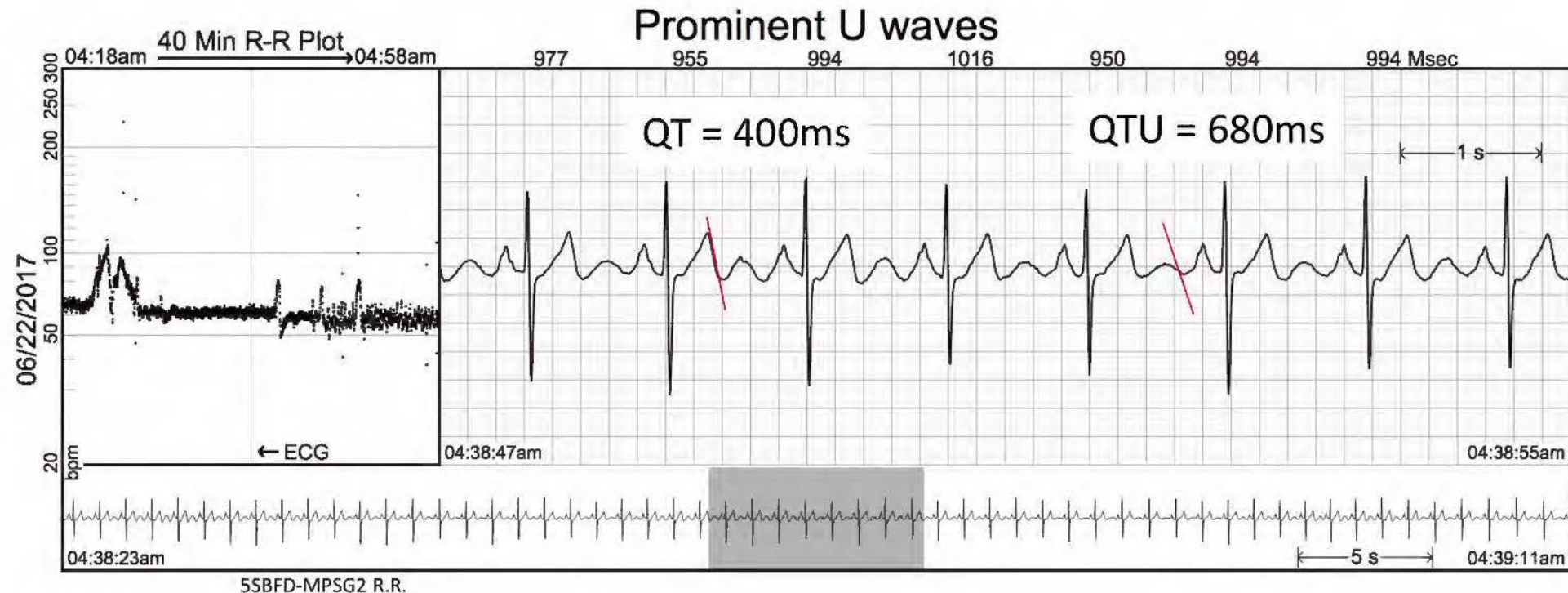
SOURCE = Smith WM., et al. Comparison of diagnostic value using a small, single channel, P-wave centric sternal ECG monitoring patch with a standard Holter. American Heart Journal. March 2017 (See Figure 3-c)

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QT Prolongation Is Distinct From QTU Prolongation



53 year old treated for AF with amiodarone



QT prolongation is distinct from QTU prolongation

COVID-19 Patient QT Intervals on CAM Reports



COVID-19 patients, or any others needing QT interval monitoring, can now receive the following QT measurements on CAM Reports:

- Average QT interval measurement
- Minimum Sinus Heart Rate QT Interval measurement
- Longest R to R interval QT measurement
- QT strips and measurements 2 hours after COVID-19 therapy dosing
- QTU measurements when pertinent

Commercial Mission = "The Standard of Care in Cardiac Monitoring"

2020



Selected to Present at the HRS 2020 Imagineer Tech Showcase



Selected as part of Journal of mHealth's Global Digital Health 100

CARDIOLOGY 2.0

Selected as part of Cardiology 2.0's Cardiac Monitoring Leaders 2020

MedCity INVEST Digital Health

Finalist for MedCity INVEST Digital Health Pitch Perfect Competition



Finalist for the Medtech Insight Award for Best Diagnostics Innovation: & Best Proof-of-Value of an Innovation



Winner of the ESC Congress Pitch Session in Remote Patient Monitoring in Arrhythmias Category



Winner of the MedTech Breakthrough Award for Best New Diagnostic Tech.



Selected into the HealthTech Arkansas Accelerator Program

2018

FROST & SULLIVAN

Winner of the Frost & Sullivan Technology Innovation Award: Remote Cardiac Monitoring



Showcase Program Finalist for MedTech Innovator Pitch Competition



Winner of the Impact Pediatric Health Competition @ SXSW 2019

GeekWire

Winner of the GeekWire Award in the Hardware of the Year Category



Winner of the Fierce Innovation Award - Life Sciences Edition: Medical Devices



Winner of the Children's National Pediatric Medical Device Innovation Competition

MED TECH TOP 10 CARDIO VASCULAR DEVICE COMPANIES - 2018

Recognized by MedTech Outlook as one of the Top 10 Cardiovascular Device Companies



Recognized by CIOReview as one of the 10 Most Promising Patient Monitoring Solution Providers

2017

Questions?

Ken Nelson

Chief Commercial Officer
Bardy Diagnostics

knelson@bardydx.com

Cell: (b)(6)



Bardy Diagnostics (BDx) Overview



Industry-Leading Monitoring Technology

- Proprietary, disruptive P-wave centric technology
- Only technology capable of diagnosing arrhythmias precisely

Proprietary Platform & Back-End Analytics

- Founded and invented by Electrophysiologist Dr. Gust Bardy
- Platform technology addresses short and long-term monitoring

Strong Clinical Evidence

- Peer-reviewed publications demonstrating clear clinical superiority over existing monitors (head to head studies)

Flexible Billing & Workflow Options

- Split billing & workflow options address the clinical and financial needs of customers

Solid Commercialization Path

- FDA 510(k) cleared, CE Marked, Health Canada cleared
- Utilizes existing reimbursement codes

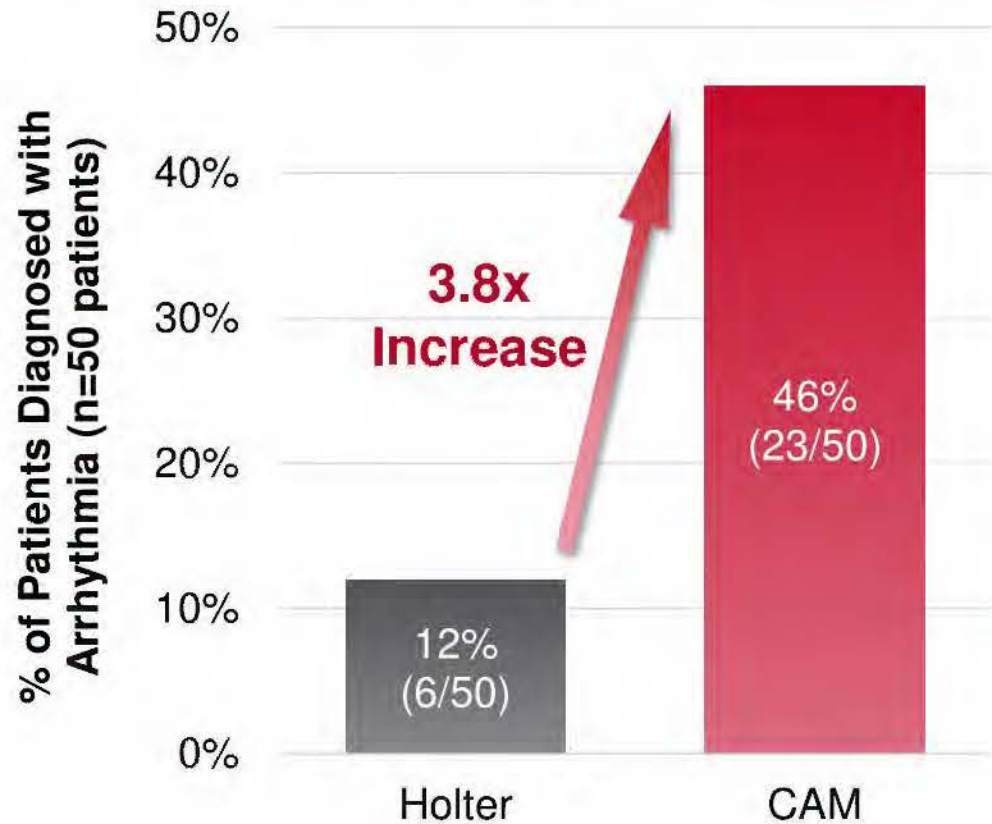
Accelerating Commercial Traction

- 500+ Accounts; 150,000+ CAM Patch patients to date
- 70+ U.S. Patents & Additional Patents Pending

Compelling Clinical Evidence



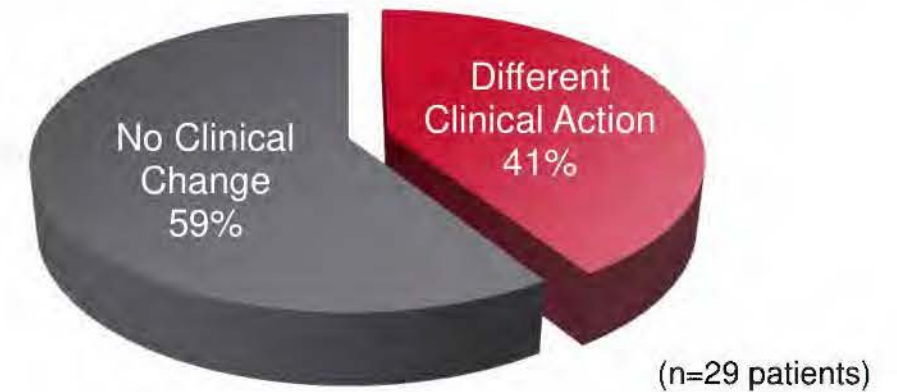
CAM Patch vs. Holter Study



Source: Smith W, et al. Comparison of diagnostic value using a small single channel, P-wave centric sternal ECG monitoring patch with a standard 3-lead Holter system over 24 hours. *American Heart Journal*. 2016.

CAM Patch vs. iRhythm Zio Patch Study

- CAM patch reported **40% more arrhythmias** than the Zio XT patch.
- Increased diagnostic accuracy of the CAM patch resulted in a **different, more informed, clinical action in 12 of 29 patients (41%)**:



Source: Rho R, Vossler M, Blancher S, Poole JE. Comparison of two ambulatory patch ECG monitors: The benefit of the P-wave and signal clarity. *American Heart Journal*. 2018.

Who is BardyDx?

- Bardy Diagnostics, Inc. ("BardyDx") is an innovator in digital health and remote patient monitoring, with a focus on providing the most diagnostically-accurate and patient-friendly cardiac monitors in the industry.
- BardyDx has FDA 510(k) clearance and CE Mark approval to market the Carnation Ambulatory Monitor (CAM) Patch.
- BardyDx generates revenue through sales of the CAM Patch and ECG analyses of the CAM (covered commercially by existing CPT codes)

What is the Carnation Ambulatory Monitor?

- Non-invasive, P-wave centric™ ambulatory cardiac monitor and arrhythmia detection device that is designed to improve patient compliance with its lifestyle-enabling patch design.
- Designed to be worn comfortably and discreetly for up to 14 days by men, women, and children (suitable for pediatric patients >22 lbs).
- Placed on the center of the chest, directly over the heart for optimal ECG signal collection.
- Distinguished from other products by its state-of-the-art sensing technology, the CAM provides optimal detection and clear recording of the entire ECG waveform, especially the P-wave, the part of the signal that is essential for accurate arrhythmia diagnosis.



Problems with Current Cardiac Monitors

The current standard of care is the Holter monitor, which was introduced into clinical practice in the mid-1960s, lacks the sensitivity for comprehensive cardiac rhythm analysis due to its poor detection of the entire ECG waveform, particularly the P-wave:

1. Unreliable Diagnostics Lead to Repeat Testing

- 4 of 5 Holter tests fail to detect clinical events or diagnose disease.¹
- Approximately 23% will undergo repeat monitoring.²

2. Incomplete Diagnostics Result in Ineffective Therapies

- Inaccurate or incomplete detection provided by current monitors contributes to the decreased success rate of cardiac ablation procedures and medications.
- For example, 5-year outcome studies have shown a recurrence of atrial fibrillation (AF) in more than 60% of patients undergoing ablation therapy³ likely due to other underlying arrhythmias missed by current monitors.

Mobile Cardiac Telemetry
0.7MM Tests



**US Ambulatory Cardiac
Monitor Market⁴**
(\$1B)

The Solution: BardyDx CAM Patch

The CAM is the industry's only P-wave centric ambulatory cardiac monitor and arrhythmia detection device, designed to address the limitations of current products on the market.



Value Proposition



Clarity for Physicians

- Patented P-wave centric ECG detection technology designed to drastically improve clinical decision-making
- Demonstrated in head-to-head studies to be superior to current products:
 - 3.8x increase in clinically-significant arrhythmias compared to a Holter⁵
 - 40% more arrhythmias than the first-to-market iRhythm Zio Patch⁶



Convenience for Practices

- Simple-to-use, disposable patch avoids headaches with coordinating Holter lending & returns
- Fits into existing workflows, including option to perform ECG analysis in-house or outsource to BardyDx
- Strong practice applications in cardiology, emergency medicine, neurology (stroke), internal medicine, pediatrics



Comfort for Patients

- Improved patient compliance with its lifestyle-enabling patch design (no need to remove while showering or sleeping)
- Patient-friendly design that is discreet, compact, and comfortable
- 96% of patients preferred wearing the CAM patch compared to a 3-lead standard Holter monitor⁶



Gust Bardy, MD

Founder & CEO

- 38 years as a cardiac electrophysiologist
- 400+ peer-reviewed publications
- 240+ US Patents
- Founder of Cameron Health's (acquired by Boston Scientific) revolutionary S-ICD device

Executive Team

Gust H. Bardy, MD: CEO
 Ken Nelson: CCO
 Ed Vertatschitsch: COO
 Mark Handfelt: CAO
 Mark Query: CFO

Board of Directors

Gust H. Bardy, MD
 Garheng Kong, MD, PhD
 Alan Levy, PhD
 Paul LaViolette
 Dave Tamburri
 Rik Vandevenne
 Warren Watson

¹ Steinberg J, et al. 2017 ISHNE-HRS Expert Consensus on Ambulatory ECG and External Cardiac Monitoring/ Telemetry. *Heart Rhythm*. 2017;14(7).

² Arnold R, et al. Cost Analysis and Clinical Outcomes of Ambulatory Care Monitoring in Medicare Patients: Describing the Diagnostic Odyssey. *Journal of Health Economics and Outcomes Research*. 2015;2(2):161-9.

³ Bunch T, et al. Five-Year Outcomes of Catheter Ablation in Patients with Atrial Fibrillation and Left Ventricular Systolic Dysfunction. *Journal of Cardiovascular Electrophysiology*. 2015;26(4):363-370.

⁴ Bracciodeita, E. Ambulatory Electrocardiography Monitoring Devices – 2019 US Market Analysis. Decision Resources Group. 2018.

⁵ Smith W, et al. Comparison of diagnostic value using a small single channel, P-wave centric sternal ECG monitoring patch with a standard 3-lead Holter system over 24 hours. *Am Heart J* 2016;185:67-73.

⁶ Rho R, et al. Comparison of two ambulatory patch ECG monitors: The benefit of the P-wave and signal clarity. *American Heart Journal*. 2018;203:109-117.

From: Janowitz, Tobias <janowitz@cshl.edu>

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HHS Secretary (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5e3fce8f00194d8d94fc91094888d811-HHS Secreta <secretary@hhs.gov>;
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Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Date: 2020/07/08 14:42:56

Priority: Normal

Type: Note

I would also like to unsubscribe from this list.

Regards,

Tobias

From: "Disbrow, Gary (OS/ASPR/BARDA)" <Gary.Disbrow@hhs.gov>

Date: Wednesday, July 8, 2020 at 2:38 PM

To: "Marik, Paul E." <MarikPE@EVMS.EDU>, "Ricke, Darrell - 0449 - MITLL"

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Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Please remove me from this email distribution list.

Regards

Gary

Gary L. Disbrow Ph.D.
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Director, Medical Countermeasure Programs
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Sent: Wednesday, July 8, 2020 8:40 AM
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Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

To add to the discussion it has been known for a long time that Vitamin C stabilizes mast cells and, inhibits histamine synthesis and inactivates histamine.

PM

Paul E. Marik MD, FCCP, FCCM|
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Chief, Pulmonary and Critical Care Medicine|
825 Fairfax Ave, Rm 575, Norfolk, VA 23507|
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• marikpe@evms.edu<mailto:marikpe@evms.edu%7C> • <https://protect2.fireeye.com/url?k=2532f565-7966ec19-2532c45a-0cc47adc5fa2-04f2d488c3d4e004&u=https://protect2.fireeye.com/url?k=af60a9f4-f335a024-af6098cb-0cc47a6a52de-11162424aad75683&u=http://www.evms.edu/><https://protect2.fireeye.com/url?k=69605350-35344a2c-6960626f-0cc47adc5fa2-5050f27c666d1875&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3D456a8f77-2D193f86a7-2D456abe48-2D0cc47a6a52de-2D2a48786653d90e0b-26u-3Dhttp-3A__www.evms.edu-257c_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=HsgHWSdc56o6HYznVALb7C88k0O98NgiCJOkeGARaXo&e=>>

Teaching. Discovering. Caring.

From: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu<mailto:darrell.ricke@ll.mit.edu>>
Sent: Wednesday, July 8, 2020 8:27 AM
To: Robert Malone <(b)(6)><mailto:(b)(6)>>; vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>; Sestili, Piero <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>; def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>; jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>; ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>; ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>; mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>; jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>; dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>; zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>; wt62@cumc.columbia.edu<mailto:wt62@cumc.columbia.edu>; dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>; tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>; kjtracey@northwell.edu<mailto:kjtracey@northwell.edu>; mvcallahan@mgh.harvard.edu<mailto:mvcallahan@mgh.harvard.edu>; ja660@cumc.columbia.edu<mailto:ja660@cumc.columbia.edu>; janowitz@cshl.edu<mailto:janowitz@cshl.edu>; djp65@cam.ac.uk<mailto:djp65@cam.ac.uk>; yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>; xphuang@unc.edu<mailto:xphuang@unc.edu>; kris.white@mssm.edu<mailto:kris.white@mssm.edu>; elena.morenodelolmo@mssm.edu<mailto:elena.morenodelolmo@mssm.edu>; Assaf_Alon@hms.harvard.edu<mailto:Assaf_Alon@hms.harvard.edu>; Andrew_Kruse@hms.harvard.edu<mailto:Andrew_Kruse@hms.harvard.edu>; anthony.mittermaier@mcgill.ca<mailto:anthony.mittermaier@mcgill.ca>; Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>; Robert.Bona@quinnipiac.edu<mailto:Robert.Bona@quinnipiac.edu>; h.clark@ucl.ac.uk<mailto:h.clark@ucl.ac.uk>; bryan_roth@med.unc.edu<mailto:bryan_roth@med.unc.edu>; Victor.Francone@quinnipiac.edu<mailto:Victor.Francone@quinnipiac.edu>;

Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>; Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>; Marik, Paul E. <MarikPE@EVMS.EDU<mailto:MarikPE@EVMS.EDU>>; Commins, Scott P <scommins@email.unc.edu<mailto:scommins@email.unc.edu>>; Lawrence Steinman <steiny@stanford.edu<mailto:steiny@stanford.edu>>; ngkounis@otenet.gr<mailto:ngkounis@otenet.gr>; Matzinger, Polly <pcm@helix.nih.gov<mailto:pcm@helix.nih.gov>>; pconti@unich.it<mailto:pconti@unich.it>; Robert.Kadlec@hhs.gov<mailto:Robert.Kadlec@hhs.gov>; Secretary@HHS.gov<mailto:Secretary@HHS.gov>; Gary.Disbrow@hhs.gov<mailto:Gary.Disbrow@hhs.gov>; Christine Laine <claine@acponline.org<mailto:claine@acponline.org>>; fgodlee@bmj.com<mailto:fgodlee@bmj.com>; howard.bauchner@jamanetwork.org<mailto:howard.bauchner@jamanetwork.org>; richard.horton@lancet.com<mailto:richard.horton@lancet.com>; erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>
Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

All,

The following preprint on Kawasaki Disease and Multisystem Inflammatory Syndrome in Children: An Antibody-Induced Mast Cell Activation Hypothesis is posted here: <https://www.ll.mit.edu/r-d/publications/kawasaki-disease-and-multisystem-inflammatory-syndrome-children-antibody-induced><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ll.mit.edu_r-2Dd_publications_kawasaki-2Ddisease-2Dand-2Dmultisystem-2Dinflammatory-2Dsyndrome-2Dchildren-2Dantibody-2Dinduced&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjStIj0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=u3v4W6qCXVmTQPIezDmD_L9wfr79xipLeHDgnM20g_g&c=>> is now in press: J Pediatrics & Pediatr Med. 2020; 4(2): 1-7 (attached draft).

I would be interested in contributing to the proposed efforts.

Sincerely,

Darrell

Darrell O. Ricke, Ph.D.
Group 49 Biological and Chemical Technologies
Lincoln Laboratory, Massachusetts Institute of Technology
244 Wood Street
Lexington, MA 02421-6426

Phone: 781-981-8323 (voice messages only)

Work cell: (b)(6)

E-mail: Darrell.Ricke@ll.mit.edu<mailto:Darrell.Ricke@ll.mit.edu>

From: Robert Malone <(b)(6)> <mailto:(b)(6)>>

Date: Tuesday, July 7, 2020 at 6:12 PM

To: vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>

Cc: "Sestili, Piero" <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>,
"def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>"
<def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>>,
"jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>"
<jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>>,
"ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>"
<ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>>,
"ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>"
<ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>>,
"mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>"
<mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>>,
"jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>"
<jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>>,
"dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>" <dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>>,
"zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>"
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"wt62@cumc.columbia.edu<mailto:wt62@cumc.columbia.edu>"
<wt62@cumc.columbia.edu<mailto:wt62@cumc.columbia.edu>>,
"dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>"
<dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>>,
"tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>"
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"kjtracey@northwell.edu<mailto:kjtracey@northwell.edu>"
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"ja660@cumc.columbia.edu<mailto:ja660@cumc.columbia.edu>"
<ja660@cumc.columbia.edu<mailto:ja660@cumc.columbia.edu>>,
"janowitz@cshl.edu<mailto:janowitz@cshl.edu>" <janowitz@cshl.edu<mailto:janowitz@cshl.edu>>,
"djp65@cam.ac.uk<mailto:djp65@cam.ac.uk>" <djp65@cam.ac.uk<mailto:djp65@cam.ac.uk>>,
"Ricke, Darrell - 0449 - MITLL" <darrell.ricke@ll.mit.edu<mailto:darrell.ricke@ll.mit.edu>>,
"yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>"
<yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>>,
"xphuang@unc.edu<mailto:xphuang@unc.edu>" <xphuang@unc.edu<mailto:xphuang@unc.edu>>,
"kris.white@mssm.edu<mailto:kris.white@mssm.edu>"
<kris.white@mssm.edu<mailto:kris.white@mssm.edu>>,
"elena.morenodelolmo@mssm.edu<mailto:elena.morenodelolmo@mssm.edu>"
<elena.morenodelolmo@mssm.edu<mailto:elena.morenodelolmo@mssm.edu>>,
"Assaf_Alon@hms.harvard.edu<mailto:Assaf_Alon@hms.harvard.edu>"
<Assaf_Alon@hms.harvard.edu<mailto:Assaf_Alon@hms.harvard.edu>>,
"Andrew_Kruse@hms.harvard.edu<mailto:Andrew_Kruse@hms.harvard.edu>"
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"anthony.mittermaier@mcgill.ca<mailto:anthony.mittermaier@mcgill.ca>"
<anthony.mittermaier@mcgill.ca<mailto:anthony.mittermaier@mcgill.ca>>,
"Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>"
<Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>>,
"Robert.Bona@quinnipiac.edu<mailto:Robert.Bona@quinnipiac.edu>"
<Robert.Bona@quinnipiac.edu<mailto:Robert.Bona@quinnipiac.edu>>,
"h.clark@ucl.ac.uk<mailto:h.clark@ucl.ac.uk>" <h.clark@ucl.ac.uk<mailto:h.clark@ucl.ac.uk>>,
"bryan_roth@med.unc.edu<mailto:bryan_roth@med.unc.edu>"
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 "Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>"
 <Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>>, "Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>" <Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>>,
 "marikpe@evms.edu<mailto:marikpe@evms.edu>" <marikpe@evms.edu<mailto:marikpe@evms.edu>>,
 "Commins, Scott P" <scommins@email.unc.edu<mailto:scommins@email.unc.edu>>, Lawrence Steinman <steiny@stanford.edu<mailto:steiny@stanford.edu>>,
 "ngkounis@otenet.gr<mailto:ngkounis@otenet.gr>"
 <ngkounis@otenet.gr<mailto:ngkounis@otenet.gr>>, "Matzinger, Polly"
 <pcm@helix.nih.gov<mailto:pcm@helix.nih.gov>>, "pconti@unich.it<mailto:pconti@unich.it>"
 <pconti@unich.it<mailto:pconti@unich.it>>,
 "Robert.Kadlec@hhs.gov<mailto:Robert.Kadlec@hhs.gov>"
 <Robert.Kadlec@hhs.gov<mailto:Robert.Kadlec@hhs.gov>>,
 "Secretary@HHS.gov<mailto:Secretary@HHS.gov>"
 <Secretary@hhs.gov<mailto:Secretary@hhs.gov>>,
 "Gary.Disbrow@hhs.gov<mailto:Gary.Disbrow@hhs.gov>"
 <Gary.Disbrow@hhs.gov<mailto:Gary.Disbrow@hhs.gov>>, Christine Laine
 <claine@acponline.org<mailto:claine@acponline.org>>,
 "fgodlee@bmj.com<mailto:fgodlee@bmj.com>" <fgodlee@bmj.com<mailto:fgodlee@bmj.com>>,
 "howard.bauchner@jamanetwork.org<mailto:howard.bauchner@jamanetwork.org>"
 <howard.bauchner@jamanetwork.org<mailto:howard.bauchner@jamanetwork.org>>,
 "richard.horton@lancet.com<mailto:richard.horton@lancet.com>"
 <richard.horton@lancet.com<mailto:richard.horton@lancet.com>>,
 "erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>"
 <erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>>
 Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham
 <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>> wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this one<https://urldefense.proofpoint.com/v2/url?u=https-3A__academic.oup.com_cid_article_doi_10.1093_cid_ciaa939_5867798&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=MYgdONPADt-JwIncB1Vw5AnbwEquKEL1Qxinmhextcw&e=?>) requesting that authorities rapidly consider and promote the clinical exploitation of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020

because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

<https://doi.org/10.3389/fphar.2020.00854><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

<https://www.researchsquare.com/article/rs-30934/v2><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.researchsquare.com_article_rs-2D30934_v2&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=j68Y6W2t8A2NNC5IJjGlzj9rlbVLzfBv_Xco53SNFVg&e=>

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

<https://pubmed.ncbi.nlm.nih.gov/32013309/><https://urldefense.proofpoint.com/v2/url?u=https-3A__pubmed.ncbi.nlm.nih.gov_32013309_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=6_trPnBT2XreYZjRCzTs4p42rSLclGk-7AH1qMDopMo&e=>

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.5281_zenodo.3748303&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wq82Sv_ttg4saUpfNx275-fC4xfxjhQMZEff7VfTZ8E&e=>

As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

<https://protect2.fireeye.com/url?k=58c2e722-0496fe5e-58c2d61d-0cc47adc5fa2-d81810ddd19db6b3&u=https://protect2.fireeye.com/url?k=e18ec594-bddbcc44-e18ef4ab-0cc47a6a52de-44d3aa827e434ccc&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician><[https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Deb474ef1-2Db7124721-2Deb477fce-2D0cc47a6a52de-2Dcf07498f50d73e08-26u-3Dhttps-3A__annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-](https://protect2.fireeye.com/url?k=494a73b1-151e6acd-494a428e-0cc47adc5fa2-e38003e3191aa9e0&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Deb474ef1-2Db7124721-2Deb477fce-2D0cc47a6a52de-2Dcf07498f50d73e08-26u-3Dhttps-3A__annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-)

e8IgWakoRNvkw5IZR_bQ&s=DYt7c7-R65Cpzq8v4RXbAa3dIJPBm2luohhZmMlnqec&e=>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen.
Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

<https://doi.org/10.3389/fphar.2020.00854><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili

Full Professor in Pharmacology,
University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham

<vaccine.safety@aol.com<<mailto:vaccine.safety@aol.com>>> ha scritto:

www.bmj.com/content/368/bmj.m1252/rr-1<https://urldefense.proofpoint.com/v2/url?u=http-3A__www.bmj.com_content_368_bmj.m1252_rr-2D1&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=EGoliAD_qufMBM4NxxwJEaYdnoRoc8WDWu7CT2IJdg48&e=>

----- Forwarded Message -----

Subject:

Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers

Date:

Thu, 14 May 2020 09:42:05 -0700

From:

vinu arumugham <vaccine.safety@aol.com><mailto:vaccine.safety@aol.com>

To:

nchoueit@montefiore.org<mailto:nchoueit@montefiore.org>
<nchoueit@montefiore.org><mailto:nchoueit@montefiore.org>,
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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

<https://twitter.com/ArumughamVinu/status/1259659169046474753?s=20><<https://urldefense.proofpoint.c>

om/v2/url?u=https-3A__twitter.com_ArumughamVinu_status_1259659169046474753-3Fs-3D20&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=pnGu5AyahOEN7R2OQ5ZswzoWK8DdK5VPJFPtfmgTLUo&c=>

One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.5281_zenodo.3748303&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wq82Sv_ttg4saUpfNx275-fC4xfxjhQMZEff7VfTZ8E&c=>

As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.medrxiv.org_content_10.1101_2020.05.01.20086694v1&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=SdocmnvkWuC9GxFjSeluKdp2X3478rCrePpVHDAAdRX0&c=>

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

<https://doi.org/10.5281/zenodo.3766462><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.5281_zenodo.3766462&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=cj8LcUAnK9z6xldvx_K67Av3BgybJKis7cXjWS6teUQ&c=>

My comment posted in the Annals of Internal Medicine:

Please see comments section:

<https://protect2.fireeye.com/url?k=5d1e21bb-014a38c7-5d1e1084-0cc47adc5fa2->

0ac0d75398a557bf&u=https://protect2.fireeye.com/url?k=89b04da4-d5e54474-89b07c9b-0cc47a6a52de-0d3acbf2316abfbb&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician<https://protect2.fireeye.com/url?k=b8c1393e-e4952042-b8c10801-0cc47adc5fa2-96a7fa50a9822538&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3De18f1fc2-2Dbdda1612-2De18f2efd-2D0cc47a6a52de-2Dd03b63f3ad8596bf-26u-3Dhttps-3A__annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=QrwjMplMCw-gYAwRoZoBxxzIFDIIdGJmefJnVOFKD99A&e=>

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping. <https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.npr.org_sections_health-2Dshots_2020_04_02_826105278_ventilators-2Dare-2Dno-2Dpanacea-2Dfor-2Dcritically-2Dill-2Dcovid-2D19-2Dpatients&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=ns_rDtrq5q1sozVBGVyffAeePW4EpuKhWO1UUB8HYMM&e=>

Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example. <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.cdc.gov_vaccines_pubs_pinkbook_downloads_appendices_b_excipient-2Dtable-2D2.pdf&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=TFHoxIH57zLMFMv8B1cU3L7N-aeSGInUothbCDoARbQ&e=>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

<https://www.bmj.com/content/360/bmj.k1378/rr-15><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.bmj.com_content_360_bmj.k1378_rr-2D15&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=PgG9dxWbyXeGbCJaAKep6p5ciUcZWGi4XAqTsBmA0lHo&e=>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)<[There is an increase in mast cell density during infections:](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.thelancet.com_journals_lancet_article_PIIS0140-2D6736-2820-2930628-2D0_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=qz0bFEmcdkWmTZV2GeYiQs67uaKO3FBnKCwwBhxKwwM&e=></p></div><div data-bbox=)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435071/><[IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4435071_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=fuFR9xaEo90-eSb0eDhAMxtzrEzT3L6il6_7wkpQjEw&e=></p></div><div data-bbox=)

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

[https://protect2.fireeye.com/url?k=94e789a7-c8b390db-94e7b898-0cc47adc5fa2-2bf8daf9ceb0b18e&u=https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749\(17\)32622-2/fulltext](https://protect2.fireeye.com/url?k=94e789a7-c8b390db-94e7b898-0cc47adc5fa2-2bf8daf9ceb0b18e&u=https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749(17)32622-2/fulltext)<[Histamine promotes release of IL-6.](https://protect2.fireeye.com/url?k=d270a622-8e24bf5e-d270971d-0cc47adc5fa2-8f836775ec588417&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Dd17dc1e1-2D8d28c831-2Dd17df0de-2D0cc47a6a52de-2D24d8d9d7adeedda7-26u-3Dhttps-3A__www.jacionline.org_article_S0091-2D6749-2817-2932622-2D2_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=oqnmFUHUhOKPfjgIVB-uzpr2KNXjax_w9CXXPY1-EE&e=></p></div><div data-bbox=)

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF-κB Pathways in Nasal Fibroblasts

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214978/><[Also, neutrophils recruited to the lung during infection can release histamine.](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4214978_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wsLUle3V45G_Ra2-A-21xEpUGFdR6ngbytk5APv67NU&e=></p></div><div data-bbox=)

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/17158962><[The antihistamine effect of Vitamin C IV seems to help.](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_17158962&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=WCztb1O-3QkxBbaZJTfVacQFDIApcJFizGA9brC_g&e=></p></div><div data-bbox=)

<https://www.ncbi.nlm.nih.gov/pubmed/1578094><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_1578094&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEgX7YxisEG8VjS1tJ0oxmu_lk&m=f_laRuzze9NBCIPdMzJCrb-e8IgWakoRNvkW5IZR_bQ&s=NGj4Z6fuUBOazJKs-2yUiZvtQVXSrdsHzzHN3uTqPNY&e=>

Also, azithromycin reduces histamine induced inflammation.

<https://www.ncbi.nlm.nih.gov/pubmed/29888693><https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_29888693&d=DwMGaQ&c=mkpgQs82XaCKIWNV8b32dmVOMERqJc4bB0tF0CetP9Y&r=6BEXLumDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrB-e8IgWakoRNvkw5IZR_bQ&s=SHet5h_swdJ1uS2s-O8OvUbkkJc1LTcjMkTXt-WxY8o&e=>

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So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

—
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From: vinu arumugham <vaccine.safety@aol.com>

Sent: Tuesday, July 7, 2020 2:41 PM

To: Sestili, Piero <piero.sestili@uniurb.it>; def2004@cumc.columbia.edu

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Subject: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this [one](#)?) requesting that authorities rapidly consider and promote the clinical exploitation

of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

<https://doi.org/10.3389/fphar.2020.00854>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

<https://www.researchsquare.com/article/rs-30934/v2>

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

<https://pubmed.ncbi.nlm.nih.gov/32013309/>

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303>

As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

<https://protect2.fireeye.com/url?k=a59a2530-f9cf2c23-a59a140f-0cc47adb5650-90e476868a577354&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen. Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof. Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

<https://doi.org/10.3389/fphar.2020.00854>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili
Full Professor in Pharmacology,
University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham <vaccine.safety@aol.com>ha scritto:
www.bmj.com/content/368/bmj.m1252/rr-1

----- Forwarded Message -----

SubjectKawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers,
:H1/H2 blockers

Date:Thu, 14 May 2020 09:42:05 -0700

From:vinu arumugham <vaccine.safety@aol.com>

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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

<https://twitter.com/ArumughamVinu/status/1259659169046474753?s=20>

One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303>

As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.
Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1>

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

<https://doi.org/10.5281/zenodo.3766462>

My comment posted in the Annals of Internal Medicine:

Please see comments section:

<https://protect2.fireeye.com/url?k=ebfab2d7-b7afb4c4-ebfa83e8-0cc47adb5650-f6ba0a653f975305&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping.

<https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients>

Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines. for example.

<https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease

severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

<https://www.bmj.com/content/360/bmj.k1378/rr-15>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)

There is an increase in mast cell density during infections:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435071/>

IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

[https://protect2.fireeye.com/url?k=fcc8fca1-a09df5b2-fcc8cd9e-0cc47adb5650-4ff4360b0b9a8d34&u=https://www.jacionline.org/article/S0091-6749\(17\)32622-2/fulltext](https://protect2.fireeye.com/url?k=fcc8fca1-a09df5b2-fcc8cd9e-0cc47adb5650-4ff4360b0b9a8d34&u=https://www.jacionline.org/article/S0091-6749(17)32622-2/fulltext)

Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF-κB Pathways in Nasal Fibroblasts

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214978/>

Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/17158962>

The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

<https://www.ncbi.nlm.nih.gov/pubmed/1578094>

[https://protect2.fireeye.com/url?k=43b90bf7-1fec02e4-43b93ac8-0cc47adb5650-](https://protect2.fireeye.com/url?k=43b90bf7-1fec02e4-43b93ac8-0cc47adb5650-f00265bd76be54f9&u=https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus)

[f00265bd76be54f9&u=https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus](https://protect2.fireeye.com/url?k=43b90bf7-1fec02e4-43b93ac8-0cc47adb5650-f00265bd76be54f9&u=https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus)

Also, azithromycin reduces histamine induced inflammation.

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

<https://www.ncbi.nlm.nih.gov/pubmed/29888693>

Hydroxychloroquine helps in allergic asthma.

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma.

<https://www.ncbi.nlm.nih.gov/pubmed/9723661>

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

<https://www.sciencedirect.com/science/article/pii/S0924857920300996>

<https://protect2.fireeye.com/url?k=756b68f1-293e61e2-756b59ce-0cc47adb5650-4dd2cfe5d4d951f6&u=https://www.mediterranee-infection.com/covid-19/>

So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

--

Prof. Piero Sestili

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Sender: Lawrence Steinman <steiny@stanford.edu>

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<erubin@hsph.harvard.edu>

Sent Date: 2020/07/08 14:57:33

Delivered Date: 2020/07/08 14:58:40

Thank you for your support, the data seem to be heading in the right direction.
Jonathan

Any guidance would be more than welcome.

From: Jonathan Javitt
Sent: Friday, July 10, 2020 3:23 PM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Azar, Alex (alex.azar@hhs.gov) <alex.azar@hhs.gov>
Cc: McBride, Dennis ((b)(6)); cunnion@mac.com
Subject: RE: RLF-100 (aviptadil) for treatment of Critical COVID-19
Importance: High

Dear Dr. Disbrow,

I appreciate the focus on partnership and procedure. We have submitted our information to ACTIV. However, we have a clinical trial in the field that is saving lives today and we need a miniscule (by BARDA standards) amount of emergency support today. We proceeded at risk in good faith because we believed we had a lifesaving solution and the science is coming our way. In my previous email I sent you information on 3 cases of rapid clinical recovery being observed in NCT04311697. More than 10 such cases have now been identified with the first 30 randomized patients. The DSMB will be reviewing the first unblinded data in a few days.

In the meantime, I hope you will read the attached report of the first patient treated under open-label named-patient FDA Emergency Access IND, a 54 year old man with rejection of a double lung transplant and Critical COVID-19 with respiratory failure. He had exhausted all other therapeutic options, including Tocilizumab and had a NIAID Score of 2. He was treated with RLF-100. Within 3 days, his pneumonitis cleared on x-ray and chest CT. His oxygen saturation rapidly improved, and he was discharged from the ICU after 4 days on room air.

<https://protect2.fireeye.com/url?k=d569d8b5-893cd1a6-d569e98a-0cc47adb5650-a804c4e5b000ad06&u=https://www.preprints.org/manuscript/202007.0178/v1>

History will remember us by what we do today. Not by our adherence to administrative procedure. The death knell of the Roman Empire was the Justinian plague. The end of the Renaissance was sparked by the bubonic plague. Spanish flu killed more people than combat in World War I. In the past week, 3 of our study coordinators have been put out of action by COVID-19 and the ICUs at our study sites are once again full.

Yesterday, the FDA pulmonary division requested that I file a blanket (i.e. not named-patient) Emergency Access IND for patients who don't qualify for our clinical trial. In my 30 years of dealing with FDA, I never imagined that they would ask a sponsor to make an unapproved medication more widely available rather than the other way around.

You have control of an open quantity contract with ICONgphs that has more than \$500 million of available ceiling. Their teaming agreement with us is documented in the BARDA White Paper. Please direct resources to ICON sufficient to generate definitive efficacy data in NCT04311697 and to institute CMC scaleup. I'm looking to you for definitive data. Not to line our corporate treasury.

A \$25 million initial task order within your existing, congressionally-funded contract will prove whether we have a game-changing, lifesaving solution or whether we should fold our tent and go home. If we hand you data, we will ask you to support rapid scaleup. If another 100,000 Americans die needlessly because we are caught up in an administrative SNAFU, history will be unforgiving. I know you are committed to anything and everything that has the potential to save lives. Two colleagues whom you respect of USUHS and the National Defense University are cc'd. They would not be on cc if this was not the right thing to do.

Respectfully,
Jonathan

From: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Sent: Friday, July 10, 2020 2:27 PM
To: Jonathan Javitt <jjavitt@neurorxpharma.com>
Cc: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: RE: RLF-100 (aviptadil) for treatment of Critical COVID-19

Dr. Javitt,

I appreciate your email and dedication to your company and development of potential treatments for COVID-19 disease. As you are aware, under Operation Warp Speed (OWS), the NIH ACTIV Partnership is establishing multiple clinical trials, each under a master protocol to quickly evaluate; neutralizing monoclonal antibodies, immune modulators, antivirals and anticoagulants. This necessitated the closing of area of interest 9.3 since OWS would be funding these large clinical trials. Therapeutics are a high priority for OWS and this includes immune modulators. The ACTIV Partnership is actively reviewing submission of candidate products for potential inclusion into various clinical trials. The submission portal can be found at the link below. If you have not already, I encourage you to submit your information to allow the ACTIV Partnership to quickly review your data and provide you with feedback.

<https://grants.nih.gov/grants/rfi/rfi.cfm?ID=107>

As you are aware, BARDA is not able to receive submissions under area of interest 9.3. All parties are encouraged to engage with ACTIV as the clinical trials will be supported by OWS.

Regards,

Gary

Gary L. Disbrow Ph.D.

Deputy Assistant Secretary

Director, Medical Countermeasure Programs

Biomedical Advanced Research and Development Authority

BARDA

Assistant Secretary for Preparedness and Response ASPR

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Woodcock, Janet (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group
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Sent Date: 2020/07/16 10:07:53

Delivered Date: 2020/07/16 10:09:46

Back-up: BARDA funding commitments to date

	Company	Amount (\$M's)	Screening / pre-clinical	Devel't / clinical trial	MFG @ scale	Other	Notes on activities & funding to-date	Looking ahead
nAb	Regeneron†	85.9	✓	✓	✓		Screening, pre-clinical & phase 1 of mAb cocktail Start-up costs for human studies	(b)(3):42 U.S.C. § 247d-6b(d)
	AstraZeneca	23.7		✓			Phase 1 study of individual mAb candidates	
	SAB Biotherapeutics†	9.4		✓			Clin. dev. of polyclonal HIG derived from vaccinated cows	
Plasma & HIG	Mayo, ABC, ARC††	73.2		✓		✓	- Plasma collection and transfusion \$49M for EAP (Mayo); \$24.2M/0.75M for ABC / ARC plasma collection	
	Emergent†	14.5		✓		✓	Funding being used to facilitate plasma collection	Current funding allocation also intended to support clinical trials (conducted by NIAID)
	Grifols†	12.7		✓		✓	Funding being used to facilitate plasma collection	Current funding allocation also intended to support clinical trials (conducted by NIAID)
IM	Genentech†	47.7		✓			\$25.1M for phase 2/3 study of Tocilizumab \$22.6M for phase 2 of MTT1041A/UTTR1147A	No additional funding anticipated for Tocilizumab
	Regeneron†	16.4		✓			Phase 2 / 3 study of Sarilumab	(b)(3):42 U.S.C. § 247d-6b(d)
Anti-viral	Janssen†	148.4	✓	✓			- Compound library screening - Identified Itraconazole as lead candidate	Allocated funding will support clinical trial of Itraconazole & other candidates (as identified)
Other	Phlow†	360			✓		PPP to repatriate MFG of raw materials & APIs	Allocated funding to support MFG of generics
	Alchem†	22		✓			RCT to evaluate hydroxychloroquine, standard of care & Fomatinine	Enrollment was paused when Remdesivir obtained EUA

1. ABC = America's Blood Centers; ARC = American Red Cross

† Award made prior to OWS

Note: Additional 4-5M funding for misc.

Current and Innovative Pipelines for COVID-19 Therapeutics, Vaccines, and Diagnostics

Introduction. The COVID-19 outbreak has now spread to 134 countries or territories. The Secretary of Health and Human Services declared a Public Health Emergency (Jan 31, 2020), The World Health Organization (WHO) declared a pandemic (March 11, 2020), and the President declared a national emergency (March 13, 2020). The cause of the COVID-19 outbreak was determined to be a novel coronavirus, called SARS-CoV-2.

Although the U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorization (EUA) for some SARS-CoV-2 diagnostic tests, there are currently no FDA-approved diagnostics, therapeutics, or vaccines for COVID-19. Given that there are now over 1600 cases and 41 deaths in the U.S., it is imperative for the USG to develop safe and effective COVID-19 medical countermeasures rapidly.

Interagency 2019-Novel Coronavirus Medical Countermeasures Task Force. On 25 January 2020, the Assistant Secretary for Preparedness and Response (ASPR), in the Department of Health and Human Services (HHS), requested that the Biomedical Advanced Research and Development Authority (BARDA) stand up an interagency SARS-CoV-2 Medical Countermeasures (MCM) Task Force. The following USG agencies are partners in the Task Force: ASPR, BARDA, Centers for Disease Control and Prevention (CDC), Department of Defense (DoD), Department of Homeland Security (DHS), Food and Drug Administration (FDA), National Institute of Allergy and Infectious Diseases (NIAID), Office of Science and Technology Policy (OSTP), and United States Department of Agriculture (USDA).

The Interagency Task Force developed a market research initiative to solicit concept papers about COVID-19 diagnostics, therapeutics, vaccines, and other technologies from potential industry partners. The portal has received over 700 submissions and held meetings with 75 companies.

In addition, the MCM Task Force clinical trial working group has enabled coordination to establish clinical trials networks to collect samples and clinical data, as well as to understand the infection with respect to disease progression and viral shedding, to inform all aspects of the response. Additionally, this framework will allow for comparison of many of the products discussed in this document.

Current Pipelines for Diagnostics, Therapeutics, and Vaccines. The MCM Task Force Working Groups continue to survey the landscapes of potential diagnostics, therapeutics, and vaccines for COVID-19 (see Appendix 1 for an overview of each of these landscapes). The technologies described below have been prioritized by the Task Force according to specific criteria for each MCM type.

Current Diagnostics Pipeline. Accurate, rapid diagnostics are critical for identifying and rapidly isolating COVID-19 cases, tracking spread of the virus, managing patient care, and supporting clinical trials. Augmenting SARS-CoV-2 testing capacity in healthcare settings - including point-of-care (POC), hospital, clinical, and commercial laboratories - is a top priority. USG technical, regulatory, and financial support has a track record of accelerating diagnostic development in recent emerging disease outbreaks (2009H1N1 influenza, Zika, Ebola).

The Interagency MCM Task Force Diagnostic Working Group recommended prioritizing development and use of molecular assays (e.g., RT-PCR) specifically designed to detect SARS-CoV-2 RNA in respiratory samples for several reasons:

- Molecular assays are generally more sensitive and specific than immunoassays (i.e., lateral flow tests that detect viral proteins).
- Tests with high sensitivity, especially when a new disease emerges and there is limited information about the best specimen types and amount of virus that can be detected in these samples, are important to reduce the risk of false negative results.

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- Existing FDA-cleared molecular diagnostic platforms that are widely available for infectious disease testing can be leveraged to expedite development of and access to SARS-CoV-2 tests. Some of these platforms are designed for use in POC settings and others for use in laboratories with high-throughput testing capacity.
- The timeline to develop and validate molecular assays is shorter than that for immunoassays because the FDA has already evaluated the platform and specimen collection components, and the pathway for EUA is straightforward.
- [Note: additional information about lateral flow tests as well as hand-held and home-use diagnostic tests can be found in the Innovative Diagnostics section below.]

This focus has borne out as several molecular assays are now available for diagnostic purposes. The MCM Task Force has been an integral part of this effort by enabling reagent preparation and distribution and by funding multiple diagnostic development efforts. USG efforts to expedite the availability of molecular diagnostic tests for SARS-CoV-2 include the following:

- FDA is expediting the review of EUA submissions and utilizing flexible enforcement discretion where appropriate to accelerate the availability of diagnostic tests.
 - EUAs have been issued for the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel and two tests developed by industry partners
- BARDA and DoD are partnering with six companies to develop assays for existing and widely available FDA-cleared platforms
- NIH accelerated the availability of viral RNA that is needed for assay validation for EUA through its viral repositories.
- DoD is working with two large diagnostics companies capable of pushing the highest throughput molecular detection assays to large, high complexity DoD testing sites that are already linked into the Military Health System and could be expanded to other USG sites.

Current Therapeutics Pipeline. While there are no therapeutics currently shown to be safe and effective for the treatment of COVID-19 infections, a variety of therapeutic strategies can be used to accelerate development of products for potential use in the current pandemic. The USG and its partners have initiated simultaneous development of multiple therapeutic candidates with different attributes to increase the likelihood of success. The strategy for prioritization of therapeutic candidates includes the following criteria: 1) preclinical safety and efficacy data, 2) risk/benefit considerations, 3) risks, costs, and burdens of drug administration across populations, and 4) domestic manufacturing capabilities.

Small molecule-based antivirals. Broad-spectrum antivirals that are already approved or in clinical development for other indications can be repurposed by the USG to evaluate their safety and efficacy for treatment of COVID-19 patients.

- *Remdesivir* is a nucleotide analogue developed by Gilead Sciences, in conjunction with DoD, as a treatment for Ebola virus disease. Remdesivir has been evaluated in Phase 1 studies and as part of a Phase 2/3 study for Ebola virus disease. NIAID, in cooperation with an interagency team, initiated a randomized controlled trial (RCT) that will initially compare remdesivir with a placebo in the U.S. and at international sites. As of March 14, 2020, it has activated 8 US and 2 international sites and has enrolled 10 US and 1 international patients, and is progressively expanding clinical trial sites in the US and other countries. DoD is setting up military hospital sites for participation in the RCT and has established an agreement with Gilead for emergency use in Service Members on a case-by-case basis if the RCT is not available. Gilead is evaluating US-based manufacturing options to expand capabilities.
- *KALETRA® (lopinavir and ritonavir)* is an FDA-approved treatment for HIV infection marketed by AbbVie Inc. It is an orally-dosed fixed combination of two protease inhibitor antivirals now being evaluated in China as a potential treatment for COVID-19.

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- *Chloroquine* is an oral drug that is FDA-approved and widely used for pre-exposure prophylaxis and treatment of malaria. It is inexpensive to produce and has human safety data. Chloroquine is being tested as prophylaxis for healthcare workers and other high-risk individuals in Thailand.
- *Library screening*: BARDA and DoD are working with Janssen and Merck to screen libraries of compounds for antiviral activity against SARS-CoV-2. Some of these compounds have been tested in humans for other diseases, so some clinical safety data are available.

Antibody-based approaches. Recent breakthroughs in antibody identification, production, and domestic manufacturing allow for the development of specific antibody-based therapeutics on a faster time scale than ever before. The USG has previously invested in platform technologies that can be rapidly adapted to new and emerging infectious diseases.

- Convalescent plasma contains antibodies against SARS-CoV-2 that could provide a therapeutic benefit. Unverified information provided by China to FDA indicates that convalescent plasma may have a benefit, but further evaluation of this strategy is needed.
- BARDA expanded an existing partnership with Regeneron Pharmaceuticals to develop monoclonal antibodies that target SARS-CoV-2. The antibodies will be developed using an FDA-licensed “plug and play” platform technology that BARDA supported for development of therapeutics to treat the related MERS and Ebola; the Ebola antibodies are being studied in a randomized controlled trial in the ongoing outbreak in the Democratic Republic of the Congo.
- DoD is supporting several partners in rapid identification and production of monoclonal antibodies. Partners are isolating antibodies from SARS-CoV-2 survivors and working with the DoD and NIAID to characterize their properties.
- Sab Biotherapeutics is developing human polyclonal antibodies in its transchromosomal bovines by vaccinating with SARS-CoV-2 antigens. This technology was successfully used to create a MERS-CoV product that is ready for Phase 2 clinical studies.

Host-targeted therapeutics that modulate the immune response or promote tissue repair. Therapeutics acting on host processes such as tissue repair or the immune response, rather than directly targeting the virus, could be beneficial for enhancing recovery in severely ill patients; however, they may also have potential to cause harm, thus highlighting the need for carefully controlled and monitored study.

- *Tocilizumab (Actemra®)* and *sarilumab (Kevzara®)* are IL-6 receptor antagonists that are being tested for COVID-19 treatment in China and Italy. Elevated IL-6 levels have been noted in patients with COVID-19 and tend to correlate with disease severity in some reports. Randomized controlled trials of these therapies are expected to be implemented in the US by the end of March 2020.
- Agents such as *non-steroidal anti-inflammatories*, *‘statins’*, *metformin*, and *jak inhibitors*, as well as a large number of *interferons* and *cytokine-directed therapeutics*, are being considered. The level of scientific and clinical data underpinning these agents for use in COVID-19 vary greatly. Preclinical models of COVID-19 disease are being developed but may take some time to establish and validate as effective tools for prioritization of host target-directed therapies.

Current Vaccines Pipeline. Vaccination is often the most effective measure for the control of infectious diseases. The best strategy for rapid development, production, and administration of a COVID-19 vaccine entails leveraging existing vaccine platform technologies. Development efficiency is accelerated by drawing on approaches used for related coronaviruses. Diverse platform attributes (e.g., number of doses, safety, immunogenicity, manufacturability) are critical to de-risk the product development portfolio and to accelerate the time to first-in-human clinical trials.

Strategically, it is critical to initiate development of multiple candidates with different attributes. At each development stage, poorly performing candidates will be down-selected and resources transferred to better performers to maintain momentum towards late stage development. As such, multiple candidates

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will be supported in parallel with each platform, rather than sequentially, to expedite development of a successful vaccine. The major criteria for prioritization of vaccine candidates are as follows: 1) preclinical (potential) efficacy and safety data; 2) potential use in target populations; 3) risk/benefit analysis; 4) regimen, including adjuvants and number of doses; and 5) clinical development timelines and domestic manufacturing capability.

The following noteworthy vaccine candidates and platforms are being supported or considered by the USG:

- NIAID has partnered with Moderna, Inc. to produce a messenger RNA (mRNA) vaccine candidate in Moderna's domestic manufacturing facilities. The vaccine will be administered to normal healthy volunteers in a Phase 1 clinical trial beginning in mid-March 2020.
- BARDA expanded its existing partnerships with Janssen and Sanofi-Pasteur to use their platform technologies to rapidly develop vaccine candidates for SARS-CoV-2. The platforms have been used successfully to advance vaccines for Ebola and influenza.
- Additional candidates are in preliminary development by academic and industry developers. NIAID and BARDA are jointly evaluating contract support to de-risk development of these investigational vaccines. These include the following:
 - (b)(3); 42 U.S.C. § 247d-6b(d)
 - (b)(5)

Innovative Technologies for COVID-19 Medical Countermeasures.

USG Advanced Development and Manufacturing (ADM) facilities, housed at HHS and DoD, are strategic assets that are well-coordinated under the BioMAP initiative. It is intended that manufacturing of a number of vaccines and therapeutics will be accelerated utilizing these ADMs.

Innovative Diagnostics. Since molecular tests are generally the most sensitive and specific testing technology available to detect pathogens in acute stage of disease, significant research and development investments have been made to reduce the size and complexity of molecular testing platforms to allow use in POC and limited resource settings. There are 5 FDA-cleared small, simple to use molecular testing platforms that produce results in 20-30 minutes and are CLIA-waived (FDA has determined that an untrained person can get accurate results by reading the instructions). While each of these are small enough to use in Emergency Departments, clinics, and triage sites, they are not designed for high-throughput testing. SARS-CoV-2 tests are being developed for 3 of these systems with USG support.

Novel Approaches

- Several "hand-held" platforms that may be suitable for home use are in development. Efforts are underway to simplify these tests further by employing single-use disposable devices or cartridges for a small reusable base, with analysis and results directed to a cell phone app. BARDA is in discussions to fund adding SARS-CoV-2 tests to two of these platforms.
- Novel amplification-free technologies such as nanopores, nanofluidic enrichment of biomolecules, and CRISPR/Cas13a, as well as some signal amplification approaches, are also in development.
- While some are in advanced stages of development, most are at least 1-2 years from the market; investments being made to include SARS-CoV-2 may accelerate development but still likely to have only medium term impact.

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Lateral flow (dip stick) assays. Lateral flow (dip stick) assays to detect virus antigens and antibodies produce results in <20 minutes and are often seen as the best way to improve access to testing. Antigen tests for infectious diseases are typically less sensitive than molecular tests, and may require use of a reading device to reduce risk of false negatives. Moreover, there are limited data regarding the presence of various antigens in different sites of the body over the course of infection. Antibody tests, if highly specific for the new virus, may be useful for surveillance, transmission, or vaccine studies, but not useful for diagnosis of acute infection when antibodies are not yet present, and are therefore not currently a pressing clinical diagnostic need. Such tests are being developed by CDC and NIH for research purposes and BARDA opened its Broad Agency Announcement to accept proposals for antibody tests.

Innovative Therapeutics. Antibodies provide robust protection for many diseases, but natural antibodies take days to weeks to develop and are not as robust in older adults.

- Current plans include manufacturing antibodies and administering them to COVID-19 patients to “jump-start” the immune system. Proposals also include using monoclonal antibodies (mAbs) to pre-treat high-risk subjects, such as healthcare workers, to provide immediate and potent protection that can last months with a single dose.
- A promising new technology proposes to inject mRNA that is specific for a neutralizing antibody into humans and turn the body into a factory to produce millions of antibodies that provide rapid protection. As with any new concept, manufacturing development needs to occur to reduce production costs and to expand the number of domestic manufacturing sites.

Adjunctive Technologies. BARDA and DoD are considering adjunctive technologies that can be rapidly deployed to delay, lower, and control the epidemiological peak for COVID-19. These include the use of telemedicine (including tele-ICU), novel sensor technology, and host severity triage technologies to ultimately reduce the impact that will be faced by the healthcare system. During emergency response where resources are constrained, hospitals and healthcare providers must be able to identify individuals at higher risk upon admission, allowing discharge of unnecessary admissions and reducing risk of additional transmission. Technologies that can alleviate the COVID-19 disease burden on the healthcare system will provide positive externality effects to those that need to treat critically ill affected individuals.

- *Telemedicine approaches* (through use of mobile based Apps) can connect potentially infected individuals to a physician remotely
- *Continuous/Near Continuous Sensors, Wearable technologies, and other self-monitoring technologies* provide real-time information on host physiological markers so exposed individuals can monitor their health status and seek care if their health deteriorates. In addition, host markers can be monitored passively, continuously, and/or non-invasively using breathalyzers or blood/interstitial/sweat-based sensing to aid in identifying those who are sick or at risk.
- *Digital health tools* have the potential to determine the risk of health deterioration or sepsis, or predict outcome before onset and can be integrated into remote monitoring platforms (Tele-ICU). Machine learning and artificial intelligence approaches can integrate into the electronic health record (EHR) and utilize patient vital signs and clinical data. Digital health tools can be easily scalable, are interoperable, and can increase the number of patients that can be monitored concurrently and/or remotely, creating a physical safety barrier and reducing the burden on needed resources.
- *Host-based in vitro diagnostics (Critical Care Triage):* host biomarkers that can inform on disease severity and predict or identify sepsis or outcomes could be utilized to triage critically ill for ICU care.

There is an opportunity to assess and validate these technologies for impact in any EID scenario, as many are agnostic to a given threat. The utility specifically for COVID-19 has yet to be determined, but, utilization by the USG may encourage adoption for regional public health strategies.

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CC:	Lawler, James V <james.lawler@unmc.edu>; Redd, John (OS/ASPR/SPPR) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9ba3fed4ee8646ec849a5a87136a24f6-Redd, John <John.Redd@hhs.gov>; Hunt, Richard (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a104469df5184cc38bf02034af7eca04-Hunt, Richa <Richard.Hunt@hhs.gov>; Yeskey, Kevin (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6fe6cf13518445fd9c3a1c254e166b3f-Yeskey, Kev <Kevin.Yeskey@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Adams, Steven A. (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f98462fe8d124743a437c7a80b3f60dd-Adams, Stev <saa1@cdc.gov>
Subject:	Re: NEJM Remdesivir
Date:	2020/04/12 16:37:04
Priority:	Normal
Type:	Note

- Median interval of RMDV and Death was 15 days. That combined with only 68% efficacy for this duration of treatment today's is not a positive industry predictor
- 41% were older than 70 years
- too small a study

We are all hoping for this medication, even that it is IV and costs \$40k a treatment course, so maybe the larger RCT will prove it's efficacy.

FOUO: unfortunately or fortunately GILD is planning on dumping remdesivir for the new ER oral version, going into clinic in the next weeks. The bad news is we may lose momentum with IV remdesivir.

Michael Callahan MD MSPH DTM&H, DMCC (UK)
Director, Mass-Casualty Infection Operations
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Special Advisor to the Assistant Secretary of Public Health Preparedness and Response
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On Apr 12, 2020, at 10:49, Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov> wrote:

External Email - Use Caution

James thanks messy data with no clear information implications except. Maybe the adverse event rates

Sent from my iPhone

On Apr 12, 2020, at 12:45 PM, Lawler, James V <james.lawler@unmc.edu> wrote:

Cannot see how anybody can draw definitive conclusions from this "study". Looking at the baseline characteristics, these folks were somewhat younger and with fewer comorbidities than what I would consider a high-risk population. Certainly, they look like a better protoplasm than our Diamond Princess cohort. But I imagine the fact that they were people you would more likely expect to survive but who were very sick was one reason why they received compassionate use drug. The degree of improvement and survival is not dramatically different from what I would expect without a drug. Just confirms why RCT research response is so important in PHE.

James Lawler, MD, MPH, FIDSA

m: 
james.lawler@unmc.edu

From: "Kadlec, Robert (OS/ASPR/IO)" <Robert.Kadlec@hhs.gov>

Date: Sunday, April 12, 2020 at 8:47 AM

To: "Redd, John (OS/ASPR/SPPR)" <John.Redd@hhs.gov>, "Hunt, Richard (OS/ASPR/EMMO)" <Richard.Hunt@hhs.gov>, "Yeskey, Kevin (OS/ASPR/IO)" <Kevin.Yeskey@hhs.gov>, "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>, "Disbrow, Gary (OS/ASPR/BARDA)" <Gary.Disbrow@hhs.gov>, "Adams, Steven A. (ASPR/SNS)" <saa1@cdc.gov>, "Callahan, m." <mvcallahan@mgh.harvard.edu>, "Lawler, James V" <james.lawler@unmc.edu>

Subject: NEJM Remdesivir

Non-UNMC email

Here is the NEJM about compassionate use of Remdesivir. I would benefit from what you all think about the data

<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007016?articleTools=true> [nejm.org]

Bob

The information in this e-mail may be privileged and confidential, intended only for the use of the addressee(s) above. Any unauthorized use or disclosure of this information is prohibited. If you have received this e-mail by mistake, please delete it and immediately contact the sender.

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Hunt, Richard (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a104469df5184cc38bf02034af7eca04-Hunt, Richa <Richard.Hunt@hhs.gov>;

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Sent Date: 2020/04/12 16:36:53

Delivered Date: 2020/04/12 16:37:04

From: Robert Malone <[REDACTED]>

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Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Date: 2020/07/07 18:12:49

Priority: Normal

Type: Note

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham <vaccine.safety@aol.com>wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this [one](#)?) requesting that authorities rapidly consider and promote the clinical exploitation of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

<https://doi.org/10.3389/fphar.2020.00854>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

<https://www.researchsquare.com/article/rs-30934/v2>

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

<https://pubmed.ncbi.nlm.nih.gov/32013309/>

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303>

As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

<https://protect2.fireeye.com/url?k=198a4909-45de6022-198a7836-0cc47a6d17cc-952e80ee382a9fcf&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen. Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article
<https://doi.org/10.3389/fphar.2020.00854>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili

Full Professor in Pharmacology,

University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham <vaccine.safety@aol.com> ha scritto:

www.bmj.com/content/368/bmj.m1252/rr-1

----- Forwarded Message -----

Subject Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, :H1/H2 blockers

Date: Thu, 14 May 2020 09:42:05 -0700

From: vinu arumugham <vaccine.safety@aol.com>

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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

<https://twitter.com/ArumughamVinu/status/1259659169046474753?s=20>

One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303>

As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1>

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

<https://doi.org/10.5281/zenodo.3766462>

My comment posted in the Annals of Internal Medicine:

Please see comments section:

<https://protect2.fireeye.com/url?k=a2e1ec5b-feb5c570-a2e1dd64-0cc47a6d17cc-73e55e3ed851f510&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician>

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping.

<https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients>

Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example.

<https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

<https://www.bmj.com/content/360/bmj.k1378/rr-15>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)

There is an increase in mast cell density during infections:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435071/>

IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

<https://protect2.fireeye.com/url?k=52079293-0e53bbb8-5207a3ac-0cc47a6d17cc->

[33645de24e109e07&u=https://www.jacionline.org/article/S0091-6749\(17\)32622-2/fulltext](https://www.jacionline.org/article/S0091-6749(17)32622-2/fulltext)

Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF- κ B Pathways in Nasal Fibroblasts

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214978/>

Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/17158962>

The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

<https://www.ncbi.nlm.nih.gov/pubmed/1578094>

<https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus>

Also, azithromycin reduces histamine induced inflammation.

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

<https://www.ncbi.nlm.nih.gov/pubmed/29888693>

Hydroxychloroquine helps in allergic asthma.

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with

moderate symptomatic asthma.

<https://www.ncbi.nlm.nih.gov/pubmed/9723661>

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

<https://www.sciencedirect.com/science/article/pii/S0924857920300996>

[https://protect2.fireeye.com/url?k=4d662048-11320963-4d661177-0cc47a6d17cc-](https://protect2.fireeye.com/url?k=4d662048-11320963-4d661177-0cc47a6d17cc-07b97a53415a1fc5&u=https://www.mediterranee-infection.com/covid-19/)

[07b97a53415a1fc5&u=https://www.mediterranee-infection.com/covid-19/](https://protect2.fireeye.com/url?k=4d662048-11320963-4d661177-0cc47a6d17cc-07b97a53415a1fc5&u=https://www.mediterranee-infection.com/covid-19/)

So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

Prof. Piero Sestili
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<https://protect2.fireeye.com/url?k=6f54d9a4-3300f08f-6f54e89b-0cc47a6d17cc-b236feac930375fe&u=http://www.rwmalonemd.com/>

"Tread lightly, take only pictures, leave only footprints, kill only time"

Sender: Robert Malone <(b)(6)>

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Sent Date: 2020/07/07 18:13:50

Delivered Date: 2020/07/07 18:12:49

Dual-Histamine Blockade with Cetirizine - Famotidine Reduces Pulmonary Symptoms in COVID-19 Patients

Running Title: Treatment of COVID-19 with Cetirizine - Famotidine

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Acknowledgements: The authors gratefully acknowledge the assistance of the clinical staff and administrators of Baptist Health Systems (including Dr. Mike Byers) and Jackson Pulmonary Associates. This work was not supported financially by a sponsor or a grant.

Conflicts of Interest: Dr. Hogan II discloses a US patent application on dual-histamine blockade in the treatment of COVID-19 and issued patents on the treatment of diarrhea, plus ownership in a biomedical business related to the latter; Dr. Cannon has nothing to disclose; Dr. Rappai

has nothing to disclose; Dr. Studdard reports personal fees from American College of Chest Physicians, unrelated to the submitted work; Dr. Hogan III has nothing to disclose; Dr. Paul discloses ownership in unrelated biomedical-related businesses and consulting with numerous pharmaceutical companies; and Dr. Dooley discloses ownership in unrelated biomedical-related businesses.

Abstract

Background: The COVID-19 pandemic due to SARS-CoV-2 infection can produce Acute Respiratory Distress Syndrome as a result of a pulmonary cytokine storm. Antihistamines are safe and effective treatments for reducing inflammation and cytokine release. Combinations of Histamine-1 and Histamine-2 receptor antagonists have been effective in urticaria, and might reduce the histamine-mediated pulmonary cytokine storm in COVID-19. Can a combination of Histamine-1 and Histamine-2 blockers improve COVID-19 inpatient outcomes?

Methods: A physician-sponsored cohort study of cetirizine and famotidine was performed in hospitalized patients with severe to critical pulmonary symptoms. Pulmonologists led the inpatient care in a single medical center of 110 high-acuity patients that were treated with cetirizine 10 mg and famotidine 20 mg *b.i.d.* plus standard-of-care.

Results: Of all patients, including those with Do Not Resuscitate directives, receiving the dual-histamine blockade for at least 48 hours, the combination drug treatment resulted in a 16.4% rate of intubation, a 7.3% rate of intubation after a minimum of 48 hours of treatment, a 15.5% rate of inpatient mortality, and 11.0 days duration of hospitalization. The drug combination exhibited reductions in symptom progression when compared to published reports of COVID-19 patients. Concomitant medications were assessed and hydroxychloroquine was correlated with worse outcomes.

Conclusions: This physician-sponsored cohort study of cetirizine and famotidine provides proof-of-concept of a new safe and effective method to reduce the progression in symptom severity, presumably by minimizing the histamine-mediated cytokine storm. Further clinical

studies in COVID-19 are warranted of the repurposed off-label combination of two historically-safe histamine blockers.

Key words: COVID, ARDS, histamine, antihistamine, lung, cytokine storm, treatment

Introduction

Histamine and mast cells play a fundamental role in modulating inflammation through increased capillary blood flow and vascular permeability, as well as cytokine release. Histamine-1 (H1) receptor antagonists (e.g., cetirizine) are administered for allergies. Histamine-2 (H2) receptor antagonists (e.g., famotidine) are used to control heart burn. Prescription branded, generic, and over-the-counter (OTC) drugs of both classes are safe and commercially available worldwide.

Humans have been treated using dual-histamine blockade. Urticaria (hives) has been successfully treated with dual-histamine blockade since the 1970's¹⁻³. And, a few reports have begun to demonstrate that diarrhea can be treated similarly^{4,5}. At present no H1-H2 combination drug has been US FDA-approved.

COVID-19 (SARS-CoV-2) emerged in late 2019 in China, and nucleic acid sequence results indicate that it was very likely from a bat vector. The disease can manifest as a hyper-immune response with pulmonary cytokine release resembling that of other respiratory infections, such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and influenza. Studies from China have defined the COVID-19 cytokine profile⁶ and identified risk factors that increase mortality⁷. These retrospective studies suggest mortality may be linked to inflammatory processes caused by a “cytokine storm”, which was very common in patients with severe to critical symptoms⁸. Pulmonary pathology in early-phase COVID-19 pneumonia has

shown acute lung injury⁹. In the later stage of disease, patients can develop Acute Respiratory Distress Syndrome (ARDS) or ARDS-like conditions and multi-organ failure¹⁰.

According to the Centers for Disease Control (CDC), the disease severity from China is 14% severe and 5% critical, and the critical patients displayed a fatality rate of 49%.

(www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).

Furthermore the CDC reports, *"Among U.S. COVID-19 cases with known disposition, the proportion of persons who were hospitalized was 19%. Among all hospitalized patients, a range of 26% to 32% of patients were admitted to the ICU. Among all patients, a range of 3% to 17% developed ARDS compared to a range of 20% to 42% for hospitalized patients and 67% to 85% for patients admitted to the ICU. Mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study. The median length of hospitalization among survivors was 10 to 13 days."*

Because of the sudden emergence of COVID-19, rapid research efforts are being conducted to repurpose existing drugs or biologic immunotherapies, as these are more likely to have near-term benefit during the pandemic. A major goal of many of these initiatives is to prevent or reduce the cytokine storm in pulmonary tissue¹¹⁻¹³.

Animal model studies are informative at this juncture. Sars-CoV-infected mice have shown that T-cell responses are required for protection from disease and for virus clearance¹⁴. The immunomodulation by histamine depends mostly on its influence of T-cells¹⁵. Histamine

stimulates inflammation, cytokine release, and can lead to tissue damage, including lung ¹⁶. A porcine study evaluating H1N1 influenza demonstrated the accumulation of histamine in severe pneumonia ¹⁷. Furthermore, the histamine H1 receptor antagonist, ketotifen, decreased inflammatory cytokines and severe pneumonia ¹⁷.

Dual-histamine blockade has been effective in animal models of bacterial ARDS and allergy. A porcine animal model study has shown successful treatment of *Pseudomonas*-induced ARDS with diphenhydramine and cimetidine ¹⁸. In this model for the treatment of hypoxemia, pulmonary hypertension, and pulmonary microvascular injury, the combination of diphenhydramine and cimetidine was essential, and was augmented somewhat by ibuprofen. In a guinea pig model, treatment with clemastine and cimetidine protected against allergen-induced bronchial obstruction ¹⁹.

Therefore, we believe it is reasonable to bridge into humans infected by COVID-19 using dual-histamine blockade, in order to prevent or diminish the cytokine storm. Furthermore, the safety and efficacy of dual-histamine blockade previously evidenced in human urticaria (and diarrhea) makes this an appealing approach. Therefore, the major goals of the present proof-of-principle study include to decrease the progression of severe and critical (high-acuity) hospitalized patients to ventilation dependence and/or death.

Methods

This physician-sponsored cohort study was led by a team of board certified pulmonologists from a single practice group in Jackson, MS. All patients were treated in a single hospital operated by Baptist Health Systems, with IRB approval (IRB # 20-49 exemption) for retrospective access to patient data. The first dual drug-treated patient date was 3 April 2020 and the study period for this cohort concluded on 13 June 2020. The study was motivated by the principle of compassionate care use of repurposed medications (in view of the rationale, above) by the attending pulmonologists during the COVID-19 pandemic. Conditions included open-label drug use, without a placebo control or randomization. In lieu of a placebo control group, for comparison the control(s) consisted of published SOC patient results that were not administered the dual-histamine blockade from the USA and China.

Inclusion and Exclusion Criteria: The inclusion criteria were: (a) Males or females of minimum age of 17; (b) Admission to the hospital with suspected or confirmed pulmonary symptoms of COVID-19. All patients were confirmed COVID-19 positive by RT-PCR within several days of admission. The exclusion criteria were: (a) The patient is negative for COVID-19 by RT-PCR diagnostic test; (b) Sensitivity or allergy to cetirizine or famotidine, if known; (c) Duration of stay of less than 48 hours; and (d) Treatment with the drug combination for less than 48 hours. The investigators anticipated that any patient who was subject to a Do Not Resuscitate (DNR) directive may be a confounding factor (e.g., with regard to old age or the extent of aggressive life-sustaining care provided). Therefore, the DNR patients' results were parsed in the analyses for comparison to all patients.

Standard-of-Care Procedures & Medications: On admission to hospital, the patient was diagnosed for suspected COVID-19 based primarily upon pulmonary symptoms, and located within a COVID-19 ward. Treatment was initiated in ER with SOC per admitting provider. The patient was confirmed positive for COVID-19 by RT-PCR diagnostic test. SOC included radiologic assessments, supplemental oxygen when necessary, and intravenous (IV) hydration when necessary. SOC concomitant treatments included the antimalarial drug hydroxychloroquine (84.5%), the anti-IL6 biologic tocilizumab (50.9%), the glucocorticoid drug methylprednisolone (30.9%), and convalescence plasma (30.0%). The cumulative rate of intubation in this cohort was 16.4%.

Cetirizine - Famotidine Treatment: The H1 receptor antagonist was cetirizine. The H2 receptor antagonist was famotidine. Given the current challenge of market availability of oral H2 antagonists, whenever the oral dosage form was not available or appropriate the clinicians used famotidine IV. Cetirizine and famotidine administration was preferably (a) oral, when feasible; then (b) gastric via nasogastric tube; then (c) by IV injection, based upon clinical assessments. The first dose of the therapy was administered in the ER, or upon arrival to the COVID ward, or when our trial started. Famotidine 20 mg IV and cetirizine 10 mg IV (or alternatively PO) was administered. Subsequent doses consisted of famotidine 20 mg q 12 hrs and cetirizine 10 mg q 12 hrs PO.

Study Endpoints: The major endpoints were: (a) Increased rate of discharge; (b) Reduced ventilation requirements (i.e., reduced number of intubations overall and after receiving a

minimum of 48 hours of dual drug treatment); (c) Reduced inpatient mortality rate; and (d) Reduced duration of hospitalization.

The study endpoints were compared to SOC patient outcomes from Atlanta, GA²⁰, Louisiana²¹, New York City, NY²², and Wuhan, China^{23,24}. This comparison to external sources is informative, as the number of available SOC-only patients was limited in this medical center during the rapidly-evolving SOC in the COVID-19 pandemic. This new dual drug treatment paradigm was rapidly adopted as SOC in this hospital.

Results

The patient demographics for the cetirizine - famotidine treatment group consisted of 110 patients age 17 to 97; mean age of 63.7 (SD 18.1); Female 59% and male 41%; and racial composition of 36.4% White, 59.1% African American or Black, 4.5% other. According to the US Census Bureau the racial demographics for the state of Mississippi are 59.1% White, 37.8% African American or Black, 3.1% other, and the median age is 36.7 years. Thus, our treated patients in this medical center represented an inversion in racial demographics with regard to the state's statistics vis-à-vis African-American or Black versus White.

The 110 COVID-19-positive patients with severe and critical pulmonary symptoms were treated in an inpatient setting with cetirizine and famotidine for a minimum of 48 hours, in addition to SOC. This group of patients manifested an average of 2.7 comorbidities (Table I). The most

common comorbidities were hypertension (78.2%), obesity plus morbid obesity (58.2%), diabetes (42.7%), and cardiac disease (26.4%).

The results of dual drug treatment are summarized with regard to all patients including DNR and the subset excluding DNR (**Table II**). The investigators anticipated DNR patients would be a confounding factor, and there were 13 DNR patients. The endpoints were: (a) discharge rate; (b) intubation rate; (c) intubation rate after a minimum of 48 hours of dual drug treatment; (d) inpatient mortality rate; and (e) average number of days to discharge. The rate of discharge during the study period (10 weeks plus 1 day) was 84.5% (and 91.8% excluding DNR). The intubation rate was 16.4% (and 16.5% excluding DNR). The intubation rate after a minimum of 48 hours of drug treatment was 7.3% (and 6.2% excluding DNR). The inpatient mortality rate was 15.5% (and 8.2% excluding DNR). The average number of days to discharge was 11.0 (and 10.9 days excluding DNR).

Concomitant administration of other drugs, biologics, or treatments in the SOC of the severe to critical patients are potential confounding factors (**Table III**). For instance, 84.5% of the patients were administered hydroxychloroquine (HCQ). Based upon recent publications²⁵⁻²⁷, one may assert that HCQ likely provided no therapeutic benefit, and might have had an adverse effect on the outcomes in this cohort of 110 patients, as it correlated with worse outcomes (i.e., higher rates of intubation and death).

In some of the patients, and especially those who progressed to ventilation dependence, a biologic (tocilizumab in 50.9% of patients), a glucocorticoid (methylprednisolone in 30.9% of patients), or convalescent plasma (in 30.0% of patients) were used at the discretion of the

pulmonologist-led critical care team as concomitant treatments (**Table III**). At those junctures in patient management, the concomitant treatments were anticipated to possibly provide some benefit to the patients. However, the high degree of correlation of use of methylprednisolone, tocilizumab, and/or convalescent plasma with intubation per se hampered measurement.

It is interesting to note the clinical nature of the intubated patients and deaths associated with intubation. Of the 18 intubated patients, 9 died (50.0%). Of the group of 10 patients intubated prior to completing 48 hours of combination drug therapy, 9 were subsequently successfully extubated, 5 of whom were extubated within 2 to 4 days. Of the 8 patients intubated after completing a minimum of 48 hours of cetirizine and famotidine use, all 8 patients died and all received tocilizumab and convalescence plasma, whereas only 2 of the 8 patients received methylprednisolone. This particular patient subpopulation ($n = 8$) was critically ill and included 2 leukemia patients, a cirrhotic patient, a 91 year old with chronic kidney disease, a 79 year old former smoker with chronic kidney disease stage 3, an end stage renal disease patient, and a multiple sclerosis patient with chronic kidney disease in cardiogenic shock.

Limitations

There are multiple limitations to any physician-sponsored cohort (or case series) study. Within this initial study the limitations were most notably: (a) This proof-of-principle study was not a prospective, placebo-controlled, randomized, and blinded study that is customary for a regulatory registration trial; and (b) The study lacked a sufficiently high number of untreated

SOC patients for use as a retrospective control cohort. However, the investigators have provided comparisons to the published SOC cohorts from other regions in the USA and China.

However, offsetting these limitations it should be noted that this work was performed in April through June 2020 during an intense season within the COVID-19 pandemic crisis, at a time-is-of-the-essence season when pulmonologists, emergency room physicians, critical care specialists, and hospitalists were eager to attempt rational repurposing of previously FDA-approved medications. Thus, the physicians desired near-term improved outcomes, compassionate care, and to identify new proof-of-concept off-label therapies for COVID-19 ARDS patients. This resulted in the vast majority of all COVID-19 positive patients in this medical center being treated with cetirizine plus famotidine as the “new” SOC.

Discussion and Conclusions

Here we describe an initial study of dual-histamine blockade to retard the histamine-cytokine network and with the intention of blunting the cytokine storm. The safety profile of dual-histamine blockade makes this an appealing consideration for COVID-19-positive patients. If dual-histamine blockade is able to blunt the cytokine system, the risk of progressing to severe and/or critical disease should lessen.

The results of this initial physician-sponsored study provide a proof-of-principle that it can reduce disease severity and the need for ventilators, and save lives. The results of patients who received at least 48 hours of the combination drug treatment demonstrated reduced rates of intubation (16.4%), of intubation after 48 hours of dual drug treatment (7.3%), of inpatient mortality (15.5%), and of duration of hospitalization (11.0 days). If DNR patients were excluded, then the inpatient mortality rate was only 8.2%. These clinical outcomes represent reductions in the anticipated symptom severity expressed as ventilator dependence and lethality relative to SOC reported in Atlanta, Georgia ²⁰, Louisiana ²¹, New York City, New York ²², and Wuhan, China ^{23,24} (see below).

Outside of the dual-histamine blockade cohort group, preliminary results were noted by the same group of pulmonologists in the same medical center with an independent group of 12 SOC-only COVID-19 patients. The SOC-only patients (lacking cetirizine and famotidine) resulted in 5 intubations (41.7%), 5 deaths (41.7%), and 18.0 average days to discharge (data not shown). These SOC-only preliminary results are consistent with high symptom severity and

high rate of inpatient fatality in the overall admitted patient population. Furthermore, a small group of 7 famotidine-only patients resulted in 3 intubations (42.9%), 1 death (14.3%), and 16.2 average days to discharge (data not shown). Due to the limited number of patients in each of these two groups, they were not deemed sufficient for comparative analysis, relative to 110 cohort patients receiving cetirizine and famotidine for a minimum of 48 hours.

The 15.5% inpatient fatality rate or 8.2% excluding DNR patients compares favorably to a published inpatient fatality rates from other regions — 25.8% in Atlanta, GA²⁰, 23.6% in Louisiana²¹, 21% in New York City, NY²², and 21.9 and 28.3% in Whuan, China^{23,24}. In other words, we experienced a reduction in inpatient fatalities of approximately one fourth to one third relative to these reference locations.

The reports of inpatient mortality rate can be dependent on multiple variables, such as inclusion/exclusion criteria (e.g., regarding DNR patients), diagnosis (e.g., presumptive COVID-19 vs. PCR-confirmed for viral RNA), demographics of patients in the study, the duration of the study period, symptom severity and comorbidities at the time of admission, as well as rapidly evolving SOC treatments influenced by media, governmental agencies, and clinical reports. During this crisis it should be noted that many of the “publications” on COVID-19 were available only in preprint form, in view of time-is-of-the-essence. And, in some instances the information was only presented as an assertion in the media, without any supporting scientific information.

That being said, in our cohort 17 fatalities had an average age of 70.6 and our 9 DNR deaths had an average of 75.8 years. *[Note that one DNR death was due to a cirrhotic patient aged 38; if this individual had been excluded the DNR deaths would have averaged 80.5 years.]* Our overall and DNR deaths were predominantly among the elderly. Furthermore, the small group of 12 SOC-only patients treated by our pulmonologists exhibited a high case fatality rate of 41.7% in the same medical center (data not shown). These two findings (i.e., elderly patient deaths and a small SOC-only group with a high rate of inpatient fatality), suggest that our inpatient fatality rate of 15.5% with DNR was adversely impacted by patient age and multiple comorbidities (average of 2.7) in Central Mississippi. In other words, our dual-histamine blockade treatment effects were favorable even in an unfavorable context.

With regard to ventilator dependence, the observed intubation rate of 16.4% overall in the cohort of 110 patients (including DNR directives) in Jackson, Mississippi and especially only 7.3% intubation rate after a minimum of 48 hours of treatment with cetirizine plus famotidine compares favorably to 26.3% in Louisiana ²¹, 12.2% in New York City ²², and 33.3% in Wuhan, China ²³.

How does this H1-H2 drug combination treatment compare with other recent therapeutic developments in COVID-19? There are three noteworthy examples that have received attention at this juncture in the scientific literature and media, namely hydroxychloroquine, remdesivir, and famotidine.

First, hydroxychloroquine (HCQ) rapidly received general acceptance as a SOC medication for COVID-19 patients. The risk-benefit reward analysis of HCQ rapidly evolved to a highly unfavorable impression, based upon controlled clinical trials. The efficacy of HCQ in COVID-19 is now seriously doubted, and at least one cardio-toxic side effect has been noted ²⁵. This study consisted of 75 patients per arm, comparing SOC vs SOC + HCQ. The authors concluded that HCQ was not beneficial and resulted in more adverse events. Hydroxychloroquine was also ineffective in inpatients who required oxygen; 84 patients were treated with HCQ within 48 hours of admission vs 97 patients receiving SOC without HCQ ²⁷. There were no benefits to HCQ when assessing: (a) survival without transfer to ICU; (b) survival at 21 days; (c) survival without ARDS at 21 days; and (d) percentage of patients requiring oxygen at 21 days. Furthermore, 10% of the HCQ-treated patients manifested ECG anomalies requiring discontinuation of HCQ treatment. A randomized trial of hydroxychloroquine in COVID-19 patients attempted to detect a prophylactic benefit, and it was unsuccessful ²⁶. In aggregate these studies confirm that HCQ was not effective in preventing or treating disease progression in COVID-19 patients. The US FDA rescinded the Emergency Use Authorization (EUA) for this drug. Therefore, it should be noted that HCQ was administered to most of the patients in our study, and it is reasonable to speculate that it impaired patients in our cohort, in view of the correlation with worse outcomes.

Second, remdesivir was developed prior to the COVID-19 pandemic as a retroviral replication inhibitor. A well-designed placebo-controlled trial suggested a reduction in the time to clinical

improvement²⁸. However, the study was not sufficiently powered statistically²⁹. Thus, there was no improvement with regard to patient deaths or viral load. This trial did not provide convincing evidence of a substantial therapeutic benefit of remdesivir. Regardless, the US FDA granted EUA for this prescription medication, which is expected to be expensive in the USA.

And third, famotidine has been evaluated in a large retrospective association study of COVID-19 patients in New York City³⁰. A total of 84 hospitalized patients out of 1,620 total received famotidine within 24 hours of hospitalization. The doses ranged from 10-40 mg. Famotidine use was associated with a reduced risk of death or intubation, whereas by comparison proton pump inhibitors (that reduce gastric acid independent of a histamine mechanism) were not associated with reduced risk of death or intubation. This suggests a possible histamine-mediated effect in the COVID-19 patients. The authors also noted no benefit of HCQ. In addition very high doses of famotidine have been proposed elsewhere for COVID-19 outpatients³¹. A case series of only 10 outpatients administered high dose famotidine (most of them received 80 mg t.i.d. = 240 mg daily) perhaps suggested the possibility of a benefit³¹. For comparison our inpatient study of 110 patients used only 20 mg b.i.d. (40 mg daily) of famotidine, within the FDA-approved OTC dosage levels. The cetirizine amount (10 mg b.i.d.) is double the daily FDA-approved dosage as an OTC medication.

Given (a) the recent emergence of COVID-19, (b) the rapid need for safe and effective treatments deployable immediately, and (c) the rapid evolution in the SOC treatments, recent

innovations might not permit sufficient time for the statistically robust clinical trials that are customary for an FDA regulatory approval process. In this time-is-of-the-essence pandemic context, the results of this dual-histamine blockade treatment compares favorably to current SOC patients.

Although this study provides initial evidence in support of a safe and effective treatment, many questions remain to be addressed. Randomized prospective trials are warranted with inpatients and outpatients. We have planned a randomized placebo-controlled outpatient trial to begin to address this question in PCR-confirmed asymptomatic or mild-to-moderate severity patients. Furthermore, is the beneficial effect dependent on this particular combination of active pharmaceutical ingredients? And, would some patients benefit (more) from alternative doses or dosage schedules? It would also be highly beneficial to exclude HCQ as a confounding factor in prospective trials, as it might have been a handicap to our cohort

The present clinical investigation provides a new method of treatment for this unmet medical need. If the results reported here are replicated in other trials, the medications can provide safe and effective means to rapidly affect patient outcomes worldwide, which are anticipated to save lives. The favorable circumstances of having commercially-available branded, generic, and OTC drugs of both H1 and H2 receptor types provides another distinct advantage relative to other experimental drug and biologic research programs in COVID-19, some of which may take numerous years to develop and commercialize. This new approach could be rapidly deployed worldwide and should be affordable, even for under-served populations, not just for the economically advantaged.

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Table I: Comorbidities in 110 hospitalized COVID-19 patients treated with famotidine and cetirizine for a minimum of 48 hours.

Comorbidities:	%
Diabetes	42.7%
Hypertension	78.2%
COPD	13.6%
Cardiac Disease	26.4%
Arrhythmia	16.4%
Asthma	10.9%
Smoker	20.0%
Obesity (excluding Morbid Obesity)	41.8%
Morbid Obesity	16.4%
Total Comorbidities Per Patient	Mean = 2.7

Table II: Clinical outcomes in 110 hospitalized COVID-19 patients treated with famotidine and cetirizine for a minimum of 48 hours

Key Metric:	Including DNR	Excluding DNR
Total Patients Admitted	110	97
Total Patients Discharged	93	89
Discharge Rate	84.5%	91.8%
Total Patients Intubated	18	16
Intubation Rate	16.4%	16.5%
Total Patients Intubated After a Minimum of 48 hrs of Treatment	8	6
Intubation Rate After a Minimum of 48 hrs of Treatment	7.3%	6.2%
Total Deaths	17	8
Death Rate %	15.5%	8.2%
Average Days to Discharge	11.0	10.9

Table III: Clinical outcomes in 110 famotidine and cetirizine-treated COVID-19 patients and concomitant treatments

Concomitant Treatments	Total #	% of Total	Intubated %	Death %
Hydroxychloroquine - YES	93	84.5%	18.3%	17.2%
Hydroxychloroquine - NO	17	15.5%	5.9%	5.9%
Methylprednisolone - YES	34	30.9%	29.4%	14.7%
Methylprednisolone - NO	76	69.1%	10.5%	15.8%
Tocilizumab - YES	56	50.9%	30.4%	21.4%
Tocilizumab - NO	54	49.1%	1.9%	9.3%
Convalescent Plasma - YES	33	30.0%	30.3%	33.3%
Convalescent Plasma - NO	77	70.0%	10.4%	7.8%

From: Bartrum, John J Brig Gen USAF AF-SG (USA) <(b)(6)>
Hamel, Joseph (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=96d2c1602dfa45e5a5e21452a098b96d-Hamel, Jose <Joseph.Hamel@hhs.gov>;
Adams, Steven A. (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f98462fe8d124743a437c7a80b3f60dd-Adams, Stev <saa1@cdc.gov>;
Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob <Robert.Kadlec@hhs.gov>;
Shuy, Bryan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdeb5ca04b6b4ed19fec2209b5f571e7-Shuy, Bryan <Bryan.Shuy@hhs.gov>;
To: Hayes, Jonathan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8cdfb7232de4428794f2901218bc1360-Hayes, Jona <Jonathan.Hayes@hhs.gov>;
Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>;
Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>;
Greene, Jonathan (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1b692a4d6cff4afabbbee99d35336ece-Greene, Jon <Jonathan.Greene@hhs.gov>
CC: Harper, Victor (OS/ASPR/ORM) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user0bdee7e8 <Victor.Harper@hhs.gov>
Subject: RE: [Non-DoD Source] FW: Ops center calls re remdesivir
Date: 2020/05/05 11:08:15
Priority: Normal
Type: Note.SMIME.MultipartSigned

I added Victor who would like to know who in HHS or ASPR is doing the prioritization of remdesivir? If ASPR is involved, he wants to ensure the team has the appropriate coverage/follow through. Please advise.

From: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>
Sent: Saturday, May 2, 2020 11:03 AM
To: Adams, Steven A. (ASPR/SNS) <saa1@cdc.gov>; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Bartrum, John J Brig Gen USAF AF-SG (USA) <(b)(6)>; Hayes, Jonathan (OS/ASPR/IO) <Jonathan.Hayes@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Subject: [Non-DoD Source] FW: Ops center calls re remdesivir

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(FYDIBOHF23SPDLT)/cn=Recipients/cn=8cdfb7232de4428794f2901218bc1360-Hayes, Jona
<Jonathan.Hayes@hhs.gov>;
Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga
<Gary.Disbrow@hhs.gov>;
Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob
<Robert.Walker@hhs.gov>;
Greene, Jonathan (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=1b692a4d6cff4afabbbee99d35336ece-Greene, Jon
<Jonathan.Greene@hhs.gov>;
Harper, Victor (OS/ASPR/ORM) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=user0bdee7e8 <Victor.Harper@hhs.gov>

Sent Date: 2020/05/05 11:05:49

Delivered Date: 2020/05/05 11:08:15

From: Turner, William C. <wt62@cumc.columbia.edu>

Markowitz, David D. <ddm1@cumc.columbia.edu>;
Abrams, Julian A. <ja660@cumc.columbia.edu>;
Tracey, Kevin <KJTracey@northwell.edu>;
Landry, Donald W. <dw11@cumc.columbia.edu>;
Janowitz, Tobias <janowitz@cshl.edu>;
Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga
<Gary.Disbrow@hhs.gov>;
'Marik, Paul E.' <MarikPE@EVMS.EDU>;
Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>;
Robert Malone <[REDACTED]>;
vinu arumugham <vaccine.safety@aol.com>;
Sestili, Piero <piero.sestili@uniurb.it>;
Freedberg, Daniel E. <def2004@cumc.columbia.edu>;
Conigliaro, Joseph <Jconigliaro@northwell.edu>;
Gupta, Aakriti <ag3786@cumc.columbia.edu>;
O'Donnell, Max R. <mo2130@cumc.columbia.edu>;
Li, Jianhua <jl1333@cumc.columbia.edu>;
Tuveson, David <dtuveson@cshl.edu>;
Jin, Zhezhen <zj7@cumc.columbia.edu>;
Wang, Timothy C. <tcw21@cumc.columbia.edu>;
mvcallahan@mgh.harvard.edu /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=20f0e9a3ebeb4ef99d30a96386fb2627-Guest_945f5
<mvcallahan@mgh.harvard.edu>;
<djp65@cam.ac.uk>;
<yongfeng@email.unc.edu>;
<xphuang@unc.edu>;

To: <kris.white@mssm.edu>;
<elena.morenodelolmo@mssm.edu>;
<Assaf_Alon@hms.harvard.edu>;
<Andrew_Kruse@hms.harvard.edu>;
<anthony.mittermaier@mcgill.ca>;
<Julianne.Hall@quinnipiac.edu>;
<Robert.Bona@quinnipiac.edu>;
<h.clark@ucl.ac.uk>;
<bryan_roth@med.unc.edu>;
<Victor.Francone@quinnipiac.edu>;
<Norbert.Herzog@quinnipiac.edu>;
<Maurice.Fremont-Smith@quinnipiac.edu>;
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Lawrence Steinman <steiny@stanford.edu>;
<ngkounis@otenet.gr>;
Matzinger, Polly <pcm@helix.nih.gov>;
<pconti@unich.it>;
Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob
<Robert.Kadlec@hhs.gov>;
HHS Secretary (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=5e3fce8f00194d8d94fc91094888d811-HHS Secreta
<secretary@hhs.gov>;
Christine Laine <claine@acponline.org>;
<fgodlee@bmj.com>;
<howard.bauchner@jamanetwork.org>;
<richard.horton@lancet.com>;
<erubin@hsph.harvard.edu>

Subject: Re: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Date: 2020/07/08 16:37:42

Priority: Normal

Type: Note

unsubscribe

From: Markowitz, David D. <ddm1@cumc.columbia.edu>

Sent: Wednesday, July 8, 2020 4:17 PM

To: Abrams, Julian A. <ja660@cumc.columbia.edu>; Tracey, Kevin <KJTracey@northwell.edu>; Landry, Donald W. <dw11@cumc.columbia.edu>; Janowitz, Tobias <janowitz@cshl.edu>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <(b)(6)>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; Conigliaro, Joseph <Jconigliaro@northwell.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>; mvcallahan@mgh.harvard.edu <mvcallahan@mgh.harvard.edu>; djp65@cam.ac.uk <djp65@cam.ac.uk>; yongfeng@email.unc.edu <yongfeng@email.unc.edu>; xphuang@unc.edu <xphuang@unc.edu>; kris.white@mssm.edu <kris.white@mssm.edu>; elena.morenodelolmo@mssm.edu <elena.morenodelolmo@mssm.edu>; Assaf_Alon@hms.harvard.edu <Assaf_Alon@hms.harvard.edu>; Andrew_Kruse@hms.harvard.edu <Andrew_Kruse@hms.harvard.edu>; anthony.mittermaier@mcgill.ca <anthony.mittermaier@mcgill.ca>; Julianne.Hall@quinnipiac.edu <Julianne.Hall@quinnipiac.edu>; Robert.Bona@quinnipiac.edu <Robert.Bona@quinnipiac.edu>; h.clark@ucl.ac.uk <h.clark@ucl.ac.uk>; bryan_roth@med.unc.edu <bryan_roth@med.unc.edu>; Victor.Francone@quinnipiac.edu <Victor.Francone@quinnipiac.edu>; Norbert.Herzog@quinnipiac.edu <Norbert.Herzog@quinnipiac.edu>; Maurice.Fremont-Smith@quinnipiac.edu <Maurice.Fremont-Smith@quinnipiac.edu>; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr <ngkounis@otenet.gr>; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it <pconti@unich.it>; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Christine Laine <claine@acponline.org>; fgodlee@bmj.com <fgodlee@bmj.com>; howard.bauchner@jamanetwork.org <howard.bauchner@jamanetwork.org>; richard.horton@lancet.com <richard.horton@lancet.com>; erubin@hsph.harvard.edu <erubin@hsph.harvard.edu>

Subject: Re: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

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David D. Markowitz, MD

Associate Clinical Professor of Medicine

Columbia University, College of Physicians and Surgeons

Phone 212-305-1024

Fax 212-305-1039

From: Abrams, Julian A. <ja660@cumc.columbia.edu>

Sent: Wednesday, July 8, 2020 4:14 PM

To: Tracey, Kevin <KJTracey@northwell.edu>; Landry, Donald W. <dw11@cumc.columbia.edu>; Janowitz, Tobias <janowitz@cshl.edu>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert

Malone (b)(6); vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; Conigliaro, Joseph <Jconigliaro@northwell.edu>; Markowitz, David D. <ddm1@cumc.columbia.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>; mvcallahan@mgh.harvard.edu <mvcallahan@mgh.harvard.edu>; djp65@cam.ac.uk <djp65@cam.ac.uk>; yongfeng@email.unc.edu <yongfeng@email.unc.edu>; xphuang@unc.edu <xphuang@unc.edu>; kris.white@mssm.edu <kris.white@mssm.edu>; elena.morenodelolmo@mssm.edu <elena.morenodelolmo@mssm.edu>; Assaf_Alon@hms.harvard.edu <Assaf_Alon@hms.harvard.edu>; Andrew_Kruse@hms.harvard.edu <Andrew_Kruse@hms.harvard.edu>; anthony.mittermaier@mcgill.ca <anthony.mittermaier@mcgill.ca>; Julianne.Hall@quinnipiac.edu <Julianne.Hall@quinnipiac.edu>; Robert.Bona@quinnipiac.edu <Robert.Bona@quinnipiac.edu>; h.clark@ucl.ac.uk <h.clark@ucl.ac.uk>; bryan_roth@med.unc.edu <bryan_roth@med.unc.edu>; Victor.Francone@quinnipiac.edu <Victor.Francone@quinnipiac.edu>; Norbert.Herzog@quinnipiac.edu <Norbert.Herzog@quinnipiac.edu>; Maurice.Fremont-Smith@quinnipiac.edu <Maurice.Fremont-Smith@quinnipiac.edu>; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr <ngkounis@otenet.gr>; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it <pconti@unich.it>; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Christine Laine <claïne@acponline.org>; fgodlee@bmj.com <fgodlee@bmj.com>; howard.bauchner@jamanetwork.org <howard.bauchner@jamanetwork.org>; richard.horton@lancet.com <richard.horton@lancet.com>; erubin@hsph.harvard.edu <erubin@hsph.harvard.edu>

Subject: RE: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Unsubscribe

Julian Abrams, MD, MS
Associate Professor of Medicine and Epidemiology at CUMC
Division of Digestive and Liver Diseases
Columbia University Medical Center

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

From: Tracey, Kevin <KJTracey@northwell.edu>

Sent: Wednesday, July 8, 2020 3:00 PM

To: Landry, Donald W. <dw11@cumc.columbia.edu>; Janowitz, Tobias <janowitz@cshl.edu>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone (b)(6); vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; Conigliaro, Joseph <Jconigliaro@northwell.edu>; Markowitz, David D. <ddm1@cumc.columbia.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>; mvcallahan@mgh.harvard.edu; Abrams, Julian A. <ja660@cumc.columbia.edu>; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu;

Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Christine Laine <claine@acponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu
Subject: Re: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

I would also like to unsubscribe

Kevin J. Tracey, MD
President & CEO
Karches Family Distinguished Chair
Feinstein Institutes for Medical Research

Professor of Molecular Medicine and Neurosurgery
Associate Dean for Research
Zucker School of Medicine

Executive Vice President, Research
Northwell Health

350 Community Drive
Manhasset, NY 11030

(b)(6)
kjtracey@northwell.edu

On 7/8/20, 2:55 PM, "Landry, Donald W." <dwll@cumc.columbia.edu> wrote:

External Email. Use Caution.

I would also like to unsubscribe
Don Landry

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

From: Janowitz, Tobias <janowitz@cshl.edu>
Sent: Wednesday, July 8, 2020 2:41 PM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <(b)(6)>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; jconigliaro@northwell.edu; Markowitz, David D. <ddm1@cumc.columbia.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Landry, Donald W. <dwll@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>;

kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu; Abrams, Julian A.
<ja660@cumc.columbia.edu>; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu;
kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf_Alon@hms.harvard.edu;
Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu;
Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu;
Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-
Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman
<steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it;
Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS)
<secretary@hhs.gov>; Christine Laine <claine@acponline.org>; fgodlee@bmj.com;
howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu
Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

I would also like to unsubscribe from this list.

Regards,

Tobias

From: "Disbrow, Gary (OS/ASPR/BARDA)" <Gary.Disbrow@hhs.gov>
Date: Wednesday, July 8, 2020 at 2:38 PM
To: "'Marik, Paul E.'" <MarikPE@EVMS.EDU>, "Ricke, Darrell - 0449 - MITLL"
<darrell.ricke@ll.mit.edu>, Robert Malone <[REDACTED]> vinu arumugham
<vaccine.safety@aol.com>, "Sestili, Piero" <piero.sestili@uniurb.it>, "def2004@cumc.columbia.edu"
<def2004@cumc.columbia.edu>, "jconigliaro@northwell.edu" <jconigliaro@northwell.edu>,
"ddm1@cumc.columbia.edu" <ddm1@cumc.columbia.edu>, "ag3786@cumc.columbia.edu"
<ag3786@cumc.columbia.edu>, "mo2130@cumc.columbia.edu" <mo2130@cumc.columbia.edu>,
"jl1333@cumc.columbia.edu" <jl1333@cumc.columbia.edu>, "Tuveson, David" <dtuveson@cshl.edu>,
"zj7@cumc.columbia.edu" <zj7@cumc.columbia.edu>, "wt62@cumc.columbia.edu"
<wt62@cumc.columbia.edu>, "dwl1@cumc.columbia.edu" <dwl1@cumc.columbia.edu>,
"tcw21@cumc.columbia.edu" <tcw21@cumc.columbia.edu>, "kjtracey@northwell.edu"
<kjtracey@northwell.edu>, "mvcallahan@mgh.harvard.edu" <mvcallahan@mgh.harvard.edu>,
"ja660@cumc.columbia.edu" <ja660@cumc.columbia.edu>, "Janowitz, Tobias" <janowitz@cshl.edu>,
"djp65@cam.ac.uk" <djp65@cam.ac.uk>, "yongfeng@email.unc.edu" <yongfeng@email.unc.edu>,
"xphuang@unc.edu" <xphuang@unc.edu>, "kris.white@mssm.edu" <kris.white@mssm.edu>,
"elena.morenodelolmo@mssm.edu" <elena.morenodelolmo@mssm.edu>,
"Assaf_Alon@hms.harvard.edu" <Assaf_Alon@hms.harvard.edu>, "Andrew_Kruse@hms.harvard.edu"
<Andrew_Kruse@hms.harvard.edu>, "anthony.mittermaier@mcgill.ca"
<anthony.mittermaier@mcgill.ca>, "Julianne.Hall@quinnipiac.edu" <Julianne.Hall@quinnipiac.edu>,
"Robert.Bona@quinnipiac.edu" <Robert.Bona@quinnipiac.edu>, "h.clark@ucl.ac.uk"
<h.clark@ucl.ac.uk>, "bryan_roth@med.unc.edu" <bryan_roth@med.unc.edu>,
"Victor.Francone@quinnipiac.edu" <Victor.Francone@quinnipiac.edu>,
"Norbert.Herzog@quinnipiac.edu" <Norbert.Herzog@quinnipiac.edu>, "Maurice.Fremont-
Smith@quinnipiac.edu" <Maurice.Fremont-Smith@quinnipiac.edu>, "Commins, Scott P"
<scommins@email.unc.edu>, Lawrence Steinman <steiny@stanford.edu>, "ngkounis@otenet.gr"
<ngkounis@otenet.gr>, "Matzinger, Polly" <pcm@helix.nih.gov>, "pconti@unich.it" <pconti@unich.it>,
"Kadlec, Robert (OS/ASPR/IO)" <Robert.Kadlec@hhs.gov>, "HHS Secretary (HHS/IOS)"
<secretary@hhs.gov>, Christine Laine <claine@acponline.org>, "fgodlee@bmj.com"
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"richard.horton@lancet.com" <richard.horton@lancet.com>, "erubin@hsph.harvard.edu"

<erubin@hsph.harvard.edu>

Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Please remove me from this email distribution list.

Regards

Gary

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary
Director, Medical Countermeasure Programs
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330 Independence Avenue, S.W. Room 640 G
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email: Gary.Disbrow@HHS.gov<mailto:Gary.Disbrow@HHS.gov>

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From: Marik, Paul E. <MarikPE@EVMS.EDU>
Sent: Wednesday, July 8, 2020 8:40 AM
To: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <(b)(6)>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; def2004@cumc.columbia.edu; jconigliaro@northwell.edu; ddm1@cumc.columbia.edu; ag3786@cumc.columbia.edu; mo2130@cumc.columbia.edu; jl1333@cumc.columbia.edu; dtuveson@cshl.edu; zj7@cumc.columbia.edu; wt62@cumc.columbia.edu; dwl1@cumc.columbia.edu; tcw21@cumc.columbia.edu; kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu; ja660@cumc.columbia.edu; janowitz@cshl.edu; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pem@helix.nih.gov>; pconti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS)

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Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

To add to the discussion it has been known for a long time that Vitamin C stabilizes mast cells and, inhibits histamine synthesis and inactivates histamine.

PM

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From: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu<mailto:darrell.ricke@ll.mit.edu>>

Sent: Wednesday, July 8, 2020 8:27 AM

To: Robert Malone <(b)(6)><(b)(6)>; vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>; Sestili, Piero <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>; def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>; jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>; ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>; ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>; mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>; jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>; dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>; zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>; wt62@cumc.columbia.edu<mailto:wt62@cumc.columbia.edu>; dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>; tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>;

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Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

All,

The following preprint on Kawasaki Disease and Multisystem Inflammatory Syndrome in Children:
 An Antibody-Induced Mast Cell Activation Hypothesis is posted here:
https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ll.mit.edu_r-2Dd_publications_kawasaki-2Ddisease-2Dand-2Dmultisystem-2Dinflammatory-2Dsyndrome-2Dchildren-2Dantibody-2Dinduced&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FedVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=sBllxlji43B4ile9C3ai9zTRAwbxTbHEDb3p2AGDUqo&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ll.mit.edu_r-2Dd_publications_kawasaki-2Ddisease-2Dand-2Dmultisystem-2Dinflammatory-2Dsyndrome-2Dchildren-2Dantibody-2Dinduced&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjSltJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=u3v4W6qCXVmTQPIezDmD_L9wfr79xipLeHDgnM20g_g&e=>
 is now in press: J Pediatrics & Pediatr Med. 2020; 4(2): 1-7 (attached draft).

I would be interested in contributing to the proposed efforts.

Sincerely,

Darrell

Darrell O. Ricke, Ph.D.
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Lincoln Laboratory, Massachusetts Institute of Technology
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Phone: 781-981-8323 (voice messages only)

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From: Robert Malone (b)(6) <mailto:(b)(6)>
Date: Tuesday, July 7, 2020 at 6:12 PM
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Cc: "Sestili, Piero" <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>,
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 Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham
 <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>> wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this one https://urldefense.proofpoint.com/v2/url?u=https-3A_academic.oup.com_cid_article_doi_10.1093_cid_ciaa939_5867798&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrbe8IgWakoRNvkw5IZR_bQ&s=MYgdONPADt-JwIncB1Vw5AnbwEquKEL1Qxinmhextcw&e=>?) requesting that authorities rapidly consider and promote the clinical exploitation of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

https://urldefense.proofpoint.com/v2/url?u=https-3A_doi.org_10.3389_fphar.2020.00854&d=DwJGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=F505tdPeS9p3B4QQ3TuXmZT3nBrEiTmVOvA2LtaTNQY&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A_doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrbe8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfDRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

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Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

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Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

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As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

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Please respond if you would like to be a coauthor and please share any other ideas to make this happen. Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:
Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

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Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili
Full Professor in Pharmacology,
University of Urbino, Italy

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----- Forwarded Message -----
Subject:

Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers

Date:

Thu, 14 May 2020 09:42:05 -0700

From:

vinu arumugham <vaccine.safety@aol.com><<mailto:vaccine.safety@aol.com>>

To:

nchoueit@montefiore.org<<mailto:nchoueit@montefiore.org>><nchoueit@montefiore.org><<mailto:nchoueit@montefiore.org>>, Brett.Giroir@hhs.gov<<mailto:Brett.Giroir@hhs.gov>><Brett.Giroir@hhs.gov><<mailto:Brett.Giroir@hhs.gov>>, ufficiostampa@asst-pg23.it<<mailto:ufficiostampa@asst-pg23.it>> <ufficiostampa@asst-pg23.it><<mailto:ufficiostampa@asst-pg23.it>>, ldantiga@hpg23.it<<mailto:ldantiga@hpg23.it>><ldantiga@hpg23.it><<mailto:ldantiga@hpg23.it>>, letters@nytimes.com<<mailto:letters@nytimes.com>><letters@nytimes.com><letters@nytimes.com>, nytnews@nytimes.com<<mailto:nytnews@nytimes.com>><nytnews@nytimes.com><<mailto:nytnews@nytimes.com>>, inytletters@nytimes.com<<mailto:inytletters@nytimes.com>><inytletters@nytimes.com><<mailto:inytletters@nytimes.com>>, editorial@nytimes.com<<mailto:editorial@nytimes.com>><editorial@nytimes.com><<mailto:editorial@nytimes.com>>, corrections@nytimes.com<<mailto:corrections@nytimes.com>><corrections@nytimes.com><<mailto:corrections@nytimes.com>>, books@nytimes.com<<mailto:books@nytimes.com>><<mailto:books@nytimes.com>>, magazine@nytimes.com<<mailto:magazine@nytimes.com>><magazine@nytimes.com><<mailto:magazine@nytimes.com>>, travelmail@nytimes.com<<mailto:travelmail@nytimes.com>><travelmail@nytimes.com><<mailto:travelmail@nytimes.com>>, edu@nytimes.com<<mailto:edu@nytimes.com>><<mailto:edu@nytimes.com>><<mailto:edu@nytimes.com>>, eileen.murphy@nytimes.com<<mailto:eileen.murphy@nytimes.com>><eileen.murphy@nytimes.com><<mailto:eileen.murphy@nytimes.com>>, danielle.rhoades-ha@nytimes.com<<mailto:danielle.rhoades-ha@nytimes.com>><<mailto:danielle.rhoades-ha@nytimes.com>><<mailto:danielle.rhoades-ha@nytimes.com>>, booking@nytimes.com<<mailto:booking@nytimes.com>><booking@nytimes.com><<mailto:booking@nytimes.com>>, bizday@nytimes.com<<mailto:bizday@nytimes.com>><<mailto:bizday@nytimes.com>><<mailto:bizday@nytimes.com>>, foreign@nytimes.com<<mailto:foreign@nytimes.com>><foreign@nytimes.com><<mailto:foreign@nytimes.com>>, sports@nytimes.com<<mailto:sports@nytimes.com>><<mailto:sports@nytimes.com>><<mailto:sports@nytimes.com>>, washington@nytimes.com<<mailto:washington@nytimes.com>><washington@nytimes.com><<mailto:washington@nytimes.com>>, national@nytimes.com<<mailto:national@nytimes.com>><national@nytimes.com><<mailto:national@nytimes.com>>, thearts@nytimes.com<<mailto:thearts@nytimes.com>><thearts@nytimes.com><<mailto:thearts@nytimes.com>>, metropolitan@nytimes.com<<mailto:metropolitan@nytimes.com>><metropolitan@nytimes.com><<mailto:metropolitan@nytimes.com>>, tips@nytimes.com<<mailto:tips@nytimes.com>><<mailto:tips@nytimes.com>><<mailto:tips@nytimes.com>>, public@nytimes.com<<mailto:public@nytimes.com>><<mailto:public@nytimes.com>><<mailto:public@nytimes.com>>

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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

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One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

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As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

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Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

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My comment posted in the Annals of Internal Medicine:

Please see comments section:

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Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping.

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Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example.

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3A [www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b_excipient-2Dtable-2D2.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=8NmQRK8guQYSLV3b8wIGq_inbHm_Jp0TU0om-mHPkN8&e=<https://urldefense.proofpoint.com/v2/url?u=https-](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b_excipient-2Dtable-2D2.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=8NmQRK8guQYSLV3b8wIGq_inbHm_Jp0TU0om-mHPkN8&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.cdc.gov_vaccines_pubs_pinkbook_downloads_appendices_b_excipient-2Dtable-2D2.pdf&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=TFHoxIH57zLMFMv8B1cU3L7N-aeSGInUothbCDoARbQ&e=>)

3A www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b_excipient-2Dtable-2D2.pdf&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=TFHoxIH57zLMFMv8B1cU3L7N-aeSGInUothbCDoARbQ&e=>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

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There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

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There is an increase in mast cell density during infections:

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IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

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Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF-κB Pathways in Nasal Fibroblasts

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Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

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The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

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3A_www.nutraingredients.com_Article_2020_03_25_Hospital-2Dturns-2Dto-2Dhigh-2Ddose-
2Dvitamin-2DC-2Dto-2Dfight-
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3A_www.nutraingredients.com_Article_2020_03_25_Hospital-2Dturns-2Dto-2Dhigh-2Ddose-
2Dvitamin-2DC-2Dto-2Dfight-
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Also, azithromycin reduces histamine induced inflammation.

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

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Hydroxychloroquine helps in allergic asthma.

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma.

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3A_www.ncbi.nlm.nih.gov_pubmed_9723661&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6Fcd
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[Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial](https://urldefense.proofpoint.com/v2/url?u=https-3A_www.sciencedirect.com_science_article_pii_S0924857920300996&d=DwIGaQ&c=G2MiLl7SX E3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=5REC7nOKfqsCcJISfMzHlp_pqYp0NEJ62ioGHwvhCo&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.sciencedirect.com_science_article_pii_S0924857920300996&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=huP8akSYLDbnDaDUlaGd8L8hJbCrbAmQL0zeL2IErs4&e=>https://protect2.fireeye.com/url?k=754674f2-29137d22-754645cd-0cc47a6a52de-063dcd6fdd69c8e&u=https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3D2ff8f995-2D73ad045-2D2ff8c8aa-2D0cc47a6a52de-2Dd6f7d13655de4261-26u-3Dhttps-3A_www.mediterranee-2Dinfection.com_covid-2D19_&d=DwIGaQ&c=G2MiLl7SX E3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=Zpo0nBdwzr4bq2fMDg5zzRb_rHzAJb7nvaFW7_vxbA&e=<https://protect2.fireeye.com/url?k=bf0e7300-e35b7ad0-bf0e423f-0cc47a6a52de-f61480fb3d563f3f&u=https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3D1028eb31-2D4c7de2e1-2D1028da0e-2D0cc47a6a52de-2D1917dbc24e7b0a50-26u-3Dhttps-3A_www.mediterranee-2Dinfection.com_covid-2D19_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=46jxOuAhs4zOw9tALUI_WrQI5PKdUvuWYMI mkrkkFhM&e=></p></div><div data-bbox=)

[So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.](https://urldefense.proofpoint.com/v2/url?u=https-3A_www.sciencedirect.com_science_article_pii_S0924857920300996&d=DwIGaQ&c=G2MiLl7SX E3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=5REC7nOKfqsCcJISfMzHlp_pqYp0NEJ62ioGHwvhCo&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.sciencedirect.com_science_article_pii_S0924857920300996&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=huP8akSYLDbnDaDUlaGd8L8hJbCrbAmQL0zeL2IErs4&e=>https://protect2.fireeye.com/url?k=754674f2-29137d22-754645cd-0cc47a6a52de-063dcd6fdd69c8e&u=https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3D2ff8f995-2D73ad045-2D2ff8c8aa-2D0cc47a6a52de-2Dd6f7d13655de4261-26u-3Dhttps-3A_www.mediterranee-2Dinfection.com_covid-2D19_&d=DwIGaQ&c=G2MiLl7SX E3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=Zpo0nBdwzr4bq2fMDg5zzRb_rHzAJb7nvaFW7_vxbA&e=<https://protect2.fireeye.com/url?k=bf0e7300-e35b7ad0-bf0e423f-0cc47a6a52de-f61480fb3d563f3f&u=https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3D1028eb31-2D4c7de2e1-2D1028da0e-2D0cc47a6a52de-2D1917dbc24e7b0a50-26u-3Dhttps-3A_www.mediterranee-2Dinfection.com_covid-2D19_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=46jxOuAhs4zOw9tALUI_WrQI5PKdUvuWYMI mkrkkFhM&e=></p></div><div data-bbox=)

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

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(FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob
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Sent Date: 2020/07/08 16:23:20

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From: Abrams, Julian A. <ja660@cumc.columbia.edu>

Tracey, Kevin <KJTracey@northwell.edu>;
Landry, Donald W. <dw11@cumc.columbia.edu>;
Janowitz, Tobias <janowitz@cshl.edu>;
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mvcallahan@mgh.harvard.edu /o=ExchangeLabs/ou=Exchange Administrative Group
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Matzinger, Polly <pcm@helix.nih.gov>;
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Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob
<Robert.Kadlec@hhs.gov>;
HHS Secretary (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group
(FYDIBOHF23SPDLT)/cn=Recipients/cn=5e3fce8f00194d8d94fc91094888d811-HHS Secreta
<secretary@hhs.gov>;
Christine Laine <claine@acponline.org>;
<fgodlee@bmj.com>;
<howard.bauchner@jamanetwork.org>;
<richard.horton@lancet.com>;
<erubin@hsph.harvard.edu>

Subject: RE: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Date: 2020/07/08 16:15:35

Priority: Normal

Type: Note

Unsubscribe

Julian Abrams, MD, MS
Associate Professor of Medicine and Epidemiology at CUMC
Division of Digestive and Liver Diseases
Columbia University Medical Center

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

From: Tracey, Kevin <KJTracey@northwell.edu>
Sent: Wednesday, July 8, 2020 3:00 PM
To: Landry, Donald W. <dw11@cumc.columbia.edu>; Janowitz, Tobias <janowitz@cshl.edu>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <[REDACTED]>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; Conigliaro, Joseph <Jconigliaro@northwell.edu>; Markowitz, David D. <ddm1@cumc.columbia.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>; mycallahan@mgh.harvard.edu; Abrams, Julian A. <ja660@cumc.columbia.edu>; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Christine Laine <claine@aeponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu
Subject: Re: [EXTERNAL] RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

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kjtracey@northwell.edu

On 7/8/20, 2:55 PM, "Landry, Donald W." <dwll@cumc.columbia.edu> wrote:

External Email. Use Caution.

I would also like to unsubscribe
Don Landry

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

From: Janowitz, Tobias <janowitz@cshl.edu>
Sent: Wednesday, July 8, 2020 2:41 PM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; 'Marik, Paul E.' <MarikPE@EVMS.EDU>; Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <(b)(6)>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; Freedberg, Daniel E. <def2004@cumc.columbia.edu>; jconigliaro@northwell.edu; Markowitz, David D. <ddm1@cumc.columbia.edu>; Gupta, Aakriti <ag3786@cumc.columbia.edu>; O'Donnell, Max R. <mo2130@cumc.columbia.edu>; Li, Jianhua <jl1333@cumc.columbia.edu>; Tuveson, David <dtuveson@cshl.edu>; Jin, Zhezhen <zj7@cumc.columbia.edu>; Turner, William C. <wt62@cumc.columbia.edu>; Landry, Donald W. <dwll@cumc.columbia.edu>; Wang, Timothy C. <tcw21@cumc.columbia.edu>; kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu; Abrams, Julian A. <ja660@cumc.columbia.edu>; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Commins, Scott P <scommins@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; pconti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Christine Laine <claine@acponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu
Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

I would also like to unsubscribe from this list.

Regards,

Tobias

From: "Disbrow, Gary (OS/ASPR/BARDA)" <Gary.Disbrow@hhs.gov>
Date: Wednesday, July 8, 2020 at 2:38 PM
To: "'Marik, Paul E.'" <MarikPE@EVMS.EDU>, "Ricke, Darrell - 0449 - MITLL" <darrell.ricke@ll.mit.edu>, Robert Malone <(b)(6)>, vinu arumugham

<vaccine.safety@aol.com>, "Sestili, Piero" <piero.sestili@uniurb.it>, "def2004@cumc.columbia.edu" <def2004@cumc.columbia.edu>, "jconigliaro@northwell.edu" <jconigliaro@northwell.edu>, "ddm1@cumc.columbia.edu" <ddm1@cumc.columbia.edu>, "ag3786@cumc.columbia.edu" <ag3786@cumc.columbia.edu>, "mo2130@cumc.columbia.edu" <mo2130@cumc.columbia.edu>, "jl1333@cumc.columbia.edu" <jl1333@cumc.columbia.edu>, "Tuveson, David" <dtuveson@cshl.edu>, "zj7@cumc.columbia.edu" <zj7@cumc.columbia.edu>, "wt62@cumc.columbia.edu" <wt62@cumc.columbia.edu>, "dw11@cumc.columbia.edu" <dw11@cumc.columbia.edu>, "tcw21@cumc.columbia.edu" <tcw21@cumc.columbia.edu>, "kjtracey@northwell.edu" <kjtracey@northwell.edu>, "mvcallahan@mgh.harvard.edu" <mvcallahan@mgh.harvard.edu>, "ja660@cumc.columbia.edu" <ja660@cumc.columbia.edu>, "Janowitz, Tobias" <janowitz@cshl.edu>, "djp65@cam.ac.uk" <djp65@cam.ac.uk>, "yongfeng@email.unc.edu" <yongfeng@email.unc.edu>, "xphuang@unc.edu" <xphuang@unc.edu>, "kris.white@mssm.edu" <kris.white@mssm.edu>, "elena.morenodelolmo@mssm.edu" <elena.morenodelolmo@mssm.edu>, "Assaf_Alon@hms.harvard.edu" <Assaf_Alon@hms.harvard.edu>, "Andrew_Kruse@hms.harvard.edu" <Andrew_Kruse@hms.harvard.edu>, "anthony.mittermaier@mcgill.ca" <anthony.mittermaier@mcgill.ca>, "Julianne.Hall@quinnipiac.edu" <Julianne.Hall@quinnipiac.edu>, "Robert.Bona@quinnipiac.edu" <Robert.Bona@quinnipiac.edu>, "h.clark@ucl.ac.uk" <h.clark@ucl.ac.uk>, "bryan_roth@med.unc.edu" <bryan_roth@med.unc.edu>, "Victor.Francone@quinnipiac.edu" <Victor.Francone@quinnipiac.edu>, "Norbert.Herzog@quinnipiac.edu" <Norbert.Herzog@quinnipiac.edu>, "Maurice.Fremont-Smith@quinnipiac.edu" <Maurice.Fremont-Smith@quinnipiac.edu>, "Commins, Scott P" <scommins@email.unc.edu>, Lawrence Steinman <steiny@stanford.edu>, "ngkounis@otenet.gr" <ngkounis@otenet.gr>, "Matzinger, Polly" <pcm@helix.nih.gov>, "pconti@unich.it" <pconti@unich.it>, "Kadlec, Robert (OS/ASPR/IO)" <Robert.Kadlec@hhs.gov>, "HHS Secretary (HHS/IOS)" <secretary@hhs.gov>, Christine Laine <claine@acponline.org>, "fgodlee@bmj.com" <fgodlee@bmj.com>, "howard.bauchner@jamanetwork.org" <howard.bauchner@jamanetwork.org>, "richard.horton@lancet.com" <richard.horton@lancet.com>, "erubin@hsph.harvard.edu" <erubin@hsph.harvard.edu>

Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

Please remove me from this email distribution list.

Regards

Gary

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From: Marik, Paul E. <MarikPE@EVMS.EDU>
Sent: Wednesday, July 8, 2020 8:40 AM
To: Rieke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu>; Robert Malone <rmal@mit.edu>; vinu arumugham <vaccine.safety@aol.com>; Sestili, Piero <piero.sestili@uniurb.it>; def2004@cumc.columbia.edu; jconigliaro@northwell.edu; ddm1@cumc.columbia.edu; ag3786@cumc.columbia.edu; mo2130@cumc.columbia.edu; jl1333@cumc.columbia.edu; dtuveson@cshl.edu; zj7@cumc.columbia.edu; wt62@cumc.columbia.edu; dw11@cumc.columbia.edu; tcw21@cumc.columbia.edu; kjtracey@northwell.edu; mvcallahan@mgh.harvard.edu; ja660@cumc.columbia.edu; janowitz@cshl.edu; djp65@cam.ac.uk; yongfeng@email.unc.edu; xphuang@unc.edu; kris.white@mssm.edu; elena.morenodelolmo@mssm.edu; Assaf_Alon@hms.harvard.edu; Andrew_Kruse@hms.harvard.edu; anthony.mittermaier@mcgill.ca; Julianne.Hall@quinnipiac.edu; Robert.Bona@quinnipiac.edu; h.clark@ucl.ac.uk; bryan_roth@med.unc.edu; Victor.Francone@quinnipiac.edu; Norbert.Herzog@quinnipiac.edu; Maurice.Fremont-Smith@quinnipiac.edu; Commings, Scott P <scommings@email.unc.edu>; Lawrence Steinman <steiny@stanford.edu>; ngkounis@otenet.gr; Matzinger, Polly <pcm@helix.nih.gov>; peonti@unich.it; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; HHS Secretary (HHS/IOS) <secretary@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Christine Laine <claine@acponline.org>; fgodlee@bmj.com; howard.bauchner@jamanetwork.org; richard.horton@lancet.com; erubin@hsph.harvard.edu
Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

To add to the discussion it has been known for a long time that Vitamin C stabilizes mast cells and, inhibits histamine synthesis and inactivates histamine.

PM

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<https://protect2.fireeye.com/url?k=3d94eb5c-61c0f220-3d94da63-0cc47adc5fa2-0a62e59e49b2a902&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3D456a8f77-2D193f86a7-2D456abe48-2D0cc47a6a52de-2D2a48786653d90e0b-26u-3Dhttp-3A__www.evms.edu-257c_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEgX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=HsgHWSDc56o6HYznVALb7C88k0O98NgiCJOkeGARaXo&e=>

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From: Ricke, Darrell - 0449 - MITLL <darrell.ricke@ll.mit.edu<mailto:darrell.ricke@ll.mit.edu>>
Sent: Wednesday, July 8, 2020 8:27 AM
To: Robert Malone <(b)(6)><mailto:(b)(6)>>; vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>; Sestili, Piero <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>; def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>; jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>; ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>; ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>; mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>; jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>; dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>; zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>; wt62@cumc.columbia.edu<mailto:wt62@cumc.columbia.edu>; dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>; tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>; kjtracey@northwell.edu<mailto:kjtracey@northwell.edu>; mvcallahan@mgh.harvard.edu<mailto:mvcallahan@mgh.harvard.edu>; ja660@cumc.columbia.edu<mailto:ja660@cumc.columbia.edu>; janowitz@cshl.edu<mailto:janowitz@cshl.edu>; djp65@cam.ac.uk<mailto:djp65@cam.ac.uk>; yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>; xphuang@unc.edu<mailto:xphuang@unc.edu>; kris.white@mssm.edu<mailto:kris.white@mssm.edu>; elena.morenodelolmo@mssm.edu<mailto:elena.morenodelolmo@mssm.edu>; Assaf_Alon@hms.harvard.edu<mailto:Assaf_Alon@hms.harvard.edu>; Andrew_Kruse@hms.harvard.edu<mailto:Andrew_Kruse@hms.harvard.edu>; anthony.mittermaier@mcgill.ca<mailto:anthony.mittermaier@mcgill.ca>; Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>; Robert.Bona@quinnipiac.edu<mailto:Robert.Bona@quinnipiac.edu>; h.clark@ucl.ac.uk<mailto:h.clark@ucl.ac.uk>; bryan_roth@med.unc.edu<mailto:bryan_roth@med.unc.edu>; Victor.Francone@quinnipiac.edu<mailto:Victor.Francone@quinnipiac.edu>; Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>; Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>; Marik, Paul E. <MarikPE@EVMS.EDU<mailto:MarikPE@EVMS.EDU>>; Commings, Scott P <scommings@email.unc.edu<mailto:scommings@email.unc.edu>>; Lawrence Steinman <steiny@stanford.edu<mailto:steiny@stanford.edu>>; ngkounis@otenet.gr<mailto:ngkounis@otenet.gr>; Matzinger, Polly <pcm@helix.nih.gov<mailto:pcm@helix.nih.gov>>; pconti@unich.it<mailto:pconti@unich.it>; Robert.Kadlec@hhs.gov<mailto:Robert.Kadlec@hhs.gov>; Secretary@HHS.gov<mailto:Secretary@HHS.gov>;

Gary.Disbrow@hhs.gov<mailto:Gary.Disbrow@hhs.gov>; Christine Laine
<claine@acponline.org<mailto:claine@acponline.org>>; fgodlee@bmj.com<mailto:fgodlee@bmj.com>;
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richard.horton@lancet.com<mailto:richard.horton@lancet.com>;
erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>

Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

All,

The following preprint on Kawasaki Disease and Multisystem Inflammatory Syndrome in Children:
An Antibody-Induced Mast Cell Activation Hypothesis is posted here:
https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ll.mit.edu_r-2Dd_publications_kawasaki-2Ddisease-2Dand-2Dmultisystem-2Dinflammatory-2Dsyndrome-2Dchildren-2Dantibody-2Dinduced&d=DwlGaQ&c=G2MiLl7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=sBllx1ji43B4il9C3ai9zTRAWbxTbHEDb3p2AGDUqo&c=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ll.mit.edu_r-2Dd_publications_kawasaki-2Ddisease-2Dand-2Dmultisystem-2Dinflammatory-2Dsyndrome-2Dchildren-2Dantibody-2Dinduced&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjStJ0oxmu_lk&m=f_laRuzze9NBCIPdMzJCrb-e8IgWakoRNvkW5IZR_bQ&s=u3v4W6qCXVmTQPlzDmD_L9wfr79xipLeHDgnM20g_g&c=>
is now in press: J Pediatrics & Pediatr Med. 2020; 4(2): 1-7 (attached draft).

I would be interested in contributing to the proposed efforts.

Sincerely,

Darrell

Darrell O. Ricke, Ph.D.
Group 49 Biological and Chemical Technologies
Lincoln Laboratory, Massachusetts Institute of Technology
244 Wood Street
Lexington, MA 02421-6426

Phone: 781-981-8323 (voice messages only)

Work cell: (b)(6)

E-mail: Darrell.Ricke@ll.mit.edu<mailto:Darrell.Ricke@ll.mit.edu>

From: Robert Malone (b)(6) <mailto:(b)(6)>
Date: Tuesday, July 7, 2020 at 6:12 PM
To: vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>
Cc: "Sestili, Piero" <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>, "def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>" <def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>>, "jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>" <jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>>, "ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>"

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 "ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>"
 <ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>>,
 "mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>"
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 "jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>"
 <jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>>,
 "dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>" <dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>>,
 "zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>"
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 "dwl1@cumc.columbia.edu<mailto:dwl1@cumc.columbia.edu>"
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 "tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>"
 <tcw21@cumc.columbia.edu<mailto:tcw21@cumc.columbia.edu>>,
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 "mvcallahan@mgh.harvard.edu<mailto:mvcallahan@mgh.harvard.edu>"
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 "Ricke, Darrell - 0449 - MITLL" <darrell.ricke@ll.mit.edu<mailto:darrell.ricke@ll.mit.edu>>,
 "yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>"
 <yongfeng@email.unc.edu<mailto:yongfeng@email.unc.edu>>,
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 "Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>"
 <Julianne.Hall@quinnipiac.edu<mailto:Julianne.Hall@quinnipiac.edu>>,
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 <bryan_roth@med.unc.edu<mailto:bryan_roth@med.unc.edu>>,
 "Victor.Francone@quinnipiac.edu<mailto:Victor.Francone@quinnipiac.edu>"
 <Victor.Francone@quinnipiac.edu<mailto:Victor.Francone@quinnipiac.edu>>,
 "Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>"
 <Norbert.Herzog@quinnipiac.edu<mailto:Norbert.Herzog@quinnipiac.edu>>, "Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>" <Maurice.Fremont-Smith@quinnipiac.edu<mailto:Maurice.Fremont-Smith@quinnipiac.edu>>,

"marikpe@evms.edu<mailto:marikpe@evms.edu>" <marikpe@evms.edu<mailto:marikpe@evms.edu>>,
 "Commins, Scott P" <scommins@email.unc.edu<mailto:scommins@email.unc.edu>>, Lawrence
 Steinman <steiny@stanford.edu<mailto:steiny@stanford.edu>>,
 "ngkounis@otenet.gr<mailto:ngkounis@otenet.gr>"
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 "erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>"
 <erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>>
 Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham
 <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>> wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this one<https://urldefense.proofpoint.com/v2/url?u=https-3A_academic.oup.com_cid_article_doi_10.1093_cid_ciaa939_5867798&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMeRqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrB-e8IgWakoRNvkw5IZR_bQ&s=MYgdONPADt-JwIncB1Vw5AnbwEquKEL1Qxinmhextcw&e=>) requesting that authorities rapidly consider and promote the clinical exploitation of medications that address inappropriate mast cell activation and the resulting immune cascade in COVID-19 (these include mast cell stabilizers, histamine H1/H2 blockers, leukotriene antagonists and leukotriene receptor antagonists, Vitamin C, etc.)

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=F505tdPeS9p3B4QQ3TuXmZT3nBrEiTmVOvA2LtaTNQY&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.researchsquare.com_article_rs-2D30934_v2&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=i82YCRm_pOUozl5J9S928H9BdGGMMkACcQNAox8T6Cg&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.researchsquare.com_article_rs-2D30934_v2&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=j68Y6W2t8A2NNC5IJjGlzj9rlbVLzfBv_Xco53SNFVg&e=>

Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy

https://urldefense.proofpoint.com/v2/url?u=https-3A__pubmed.ncbi.nlm.nih.gov_32013309_&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=gulJKE-VFryEtTrJQjKpd39V3w1jknfrQDAMc_Kd6Nw&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__pubmed.ncbi.nlm.nih.gov_32013309_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=6_trPnBT2XreYZjRCzTs4p42rSLclGk-7AH1qMDoPMo&e=>

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.5281_zenodo.3748303&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=45ahY7NckOLG7xSCBrKt8vAdX6S1lQmHWBUqTxLN-Fo&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.5281_zenodo.3748303&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wq82Sv_ttg4saUpfNx275-fC4xfxjhQMZEff7VfTZ8E&e=>

As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

https://protect2.fireeye.com/url?k=55971602-09c30f7e-5597273d-0cc47adc5fa2-9ea8d2ec5b19cf69&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3De18ec594-2Dbddbccc44-2De18ef4ab-2D0cc47a6a52de-2D44d3aa827e434ccc-26u-3Dhttps-3A__annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=Fxen-UZuKpsxodmB4gXAwTEhE7MA6bPMiOFd0bCpTAc&e=<https://protect2.fireeye.com/url?k=409d8b77-1cc9920b-409dba48-0cc47adc5fa2-e98b744594e732eb&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Deb474ef1-2Db7124721-2Deb477fce-2D0cc47a6a52de-2Dcf07498f50d73e08-26u-3Dhttps-3A__annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=DYt7c7-R65Cpzq8v4RXbAa3dIJPBm2luohhZmMlnqec&e=>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen. Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=F505tdPeS9p3B4QQ3TuXmZT3nBrEiTmVOvA2LtaTNQY&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili
Full Professor in Pharmacology,
University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham
<vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>> ha scritto:

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----- Forwarded Message -----

Subject:

Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers

Date:

Thu, 14 May 2020 09:42:05 -0700

From:

vinu arumugham <vaccine.safety@aol.com><mailto:vaccine.safety@aol.com>

To:

nchoueit@montefiore.org<mailto:nchoueit@montefiore.org>
<nchoueit@montefiore.org><mailto:nchoueit@montefiore.org>,
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Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

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One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

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As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

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Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

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My comment posted in the Annals of Internal Medicine:

Please see comments section:

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Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping.

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Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example.

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 <https://urldefense.proofpoint.com/v2/url?u=https-
 3A__www.cdc.gov_vaccines_pubs_pinkbook_downloads_appendices_b_excipient-2Dtable-
 2D2.pdf&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLU
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 e8IgWakoRNvkW5IZR_bQ&s=TFHoxIH57zLMFMv8B1cU3L7N-aeSGInUothbCDoARbQ&e=>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of

subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.bmj.com_content_360_bmj.k1378_rr-2D15&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=n6e1GCeeuF9J51zCvHnsilIuNJ_VjT_R9BMkluSZJJw&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.bmj.com_content_360_bmj.k1378_rr-2D15&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=PgG9dxWbyXeGbCJAaKe6p5ciUcZWGi4XAqTsBmA0IH0&e=>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.thelancet.com_journals_lancet_article_PIIS0140-2D6736-2820-2930628-2D0_fulltext&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=V4H11cbxNkb16r1Zp-xf9zyZq5XF6S0nb60zXtDWDCs&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.thelancet.com_journals_lancet_article_PIIS0140-2D6736-2820-2930628-2D0_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=qz0bFEmcdkWmTZV2GeYiQs67uaKO3FBnKCwwBhxKwwM&e=>

There is an increase in mast cell density during infections:

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4435071_&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=F2o6e0t3LvlyCrt5jr7Xzc8fQtIPqXRwiZggFCD7QYM&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4435071_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=fuFR9xaEo90-seB0eDhAMxtzrEzT3L6il6_7wkpQjEw&e=>

IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

https://protect2.fireeye.com/url?k=d48601ab-88d218d7-d4863094-0cc47adc5fa2-7a17afd1ad2e8a59&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Da8f577aa-2Df4a07e7a-2Da8f54695-2D0cc47a6a52de-2D0c20b4f854efc630-26u-3Dhttps-3A__www.jacionline.org_article_S0091-2D6749-2817-2932622-2D2_fulltext&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=QqA624rnsou24Dqx9N2Iu_8mKklRCedFU9u6HTVjFgg&e=<https://protect2.fireeye.com/url?k=c012606c-9c467910-c0125153-0cc47adc5fa2-61578fa0aa657399&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3Dd17dc1e1-2D8d28c831-2Dd17df0de-2D0cc47a6a52de-2D24d8d9d7adeedda7-26u-3Dhttps-3A__www.jacionline.org_article_S0091-2D6749-2817-2932622-2D2_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=qz0bFEmcdkWmTZV2GeYiQs67uaKO3FBnKCwwBhxKwwM&e=>

UmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=oqnmFUhUHaOKPfjgIVB-uzpr2KNXjax_w9CXXPY1-EE&e=>

Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF- κ B Pathways in Nasal Fibroblasts

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4214978_&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=ZPUOZq_aEak79M9GA9jrZM-Vck3Mx6_OcDceOaFuWJM&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pmc_articles_PMC4214978_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVomERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=wsLUle3V45G_Ra2-A-21xEpUGFdR6ngbytk5APv67NU&e=>

Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_17158962&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=mDiJEfdJWrYToVIP_RlRmnQusN3PwTnjZRRxS9ZFguQ&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_17158962&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVomERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=Wcztb1O-3QkxjBbaZJTfVacQFDIApcJFizGA9brC_g&e=>

The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

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cx bq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=iiCXrSRZ9AdV8UjakESj92dWuyjfr9B5_JYHTHiaqw&e=<[Also, azithromycin reduces histamine induced inflammation.](https://protect2.fireeye.com/url?k=9d637ef9-c1376785-9d634fc6-0cc47adc5fa2-9cdfa9fdf90f0cc3&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__www.nutraingredients.com_Article_2020_03_25_Hospital-2Dturns-2Dto-2Dhigh-2Ddose-2Dvitamin-2DC-2Dto-2Dfight-2Dcoronavirus&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=IQcZYeRKOPVvenMIHJX15PpN6p25jHzmumO_ArPtNE&e=></p></div><div data-bbox=)

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

[Hydroxychloroquine helps in allergic asthma.](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_29888693&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6Fc dVjSsBSbw6gcR0U&r=22kP0O04-cx bq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=fDXb-YRe6rsmzpxcXQuG5itp8h4wSjBjCf9mXbTuWfs&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_29888693&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=SHet5h_swdJ1uS2s-O8OvUbkkJc1LTcjMkTXt-WxY8o&e=></p></div><div data-bbox=)

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma.

[Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial](https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_9723661&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6Fc dVjSsBSbw6gcR0U&r=22kP0O04-cx bq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=w8v5PIWjSrxz_zlDBHmiRWvQyAU2-_j7r7lXcfb8_Mc&e=<https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ncbi.nlm.nih.gov_pubmed_9723661&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=_3HS7BagYtpR0FQgGzFNMgy1ZtNoPn3WLPHyuhH1exk&e=></p></div><div data-bbox=)

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e8IgwakoRNvkw5IZR_bQ&s=huP8akSYLDbnDaDUlaGd8L8hJbCrbAmQL0zeL2IErs4&e=>
[So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.](https://protect2.fireeye.com/url?k=8a27d38d-d673caf1-8a27e2b2-0cc47adc5fa2-9855fac097d017cf&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3D2ff8f995-2D73adf045-2D2ff8c8aa-2D0cc47a6a52de-2Dd6f7d13655de4261-26u-3Dhttps-3A__www.mediterranee-2Dinfection.com_covid-2D19_&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR0U&r=22kP0O04-cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U_o&s=Zpo0nBdwzr4bq2fMDg5zzRb_rHzAJb7nvaFW7_vxbA&e=<https://protect2.fireeye.com/url?k=10590563-4c0d1c1f-1059345c-0cc47adc5fa2-c27a9038abe45d01&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-3Fk-3D1028eb31-2D4c7de2e1-2D1028da0e-2D0cc47a6a52de-2D1917dbc24e7b0a50-26u-3Dhttps-3A__www.mediterranee-2Dinfection.com_covid-2D19_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgwakoRNvkw5IZR_bQ&s=46jxOuAhs4zOw9tALUI_WrQ15PKdUvuWYMIImkrkkFhM&e=></p></div><div data-bbox=)

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

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3A__www.linkedin.com_in_rwmalonemd&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSs
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3A__www.linkedin.com_in_rwmalonemd&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe
4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCI
PdMzJCrb-
e8IgWakoRNvkw5IZR_bQ&s=UfUC850fbT_T90mGXmr8UIY7yXQ0MwSgb0fh5ExOj0U&e=>
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3b080e68d83f2e15&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-
3Fk-3D2959cd27-2D750cc4f7-2D2959fc18-2D0cc47a6a52de-2Df0896a6017734c49-26u-3Dhttp-
3A__www.rwmalonemd.com_&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcR
0U&r=22kP0O04-
cxbq2uHLN567gn_jmYZt5B29PSwWt9O8Hk&m=hkDX7i7ai2mPodTtSVes5gVtelXtrKGRMFqirZi6U
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<https://protect2.fireeye.com/url?k=9844c8c1-c410d1bd-9844f9fe-0cc47adc5fa2-
7081fd19c775a6cb&u=https://urldefense.proofpoint.com/v2/url?u=https-3A__protect2.fireeye.com_url-
3Fk-3Dc7719d48-2D9b249498-2Dc771ac77-2D0cc47a6a52de-2D27d4adf0be64098f-26u-3Dhttp-
3A__www.rwmalonemd.com_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0C
etP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_laruzze9NBCIPdMzJCrb-
e8IgWakoRNvkw5IZR_bQ&s=kkya7BXAB_cvnMsMML2tCf0Wy6CwjtTY7-gXqxFcQmA&e=>

"Tread lightly, take only pictures, leave only footprints. kill only time"

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Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

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Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

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Subject: RE: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

To add to the discussion it has been known for a long time that Vitamin C stabilizes mast cells and, inhibits histamine synthesis and inactivates histamine.

PM

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Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

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Sincerely,

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Group 49 Biological and Chemical Technologies
Lincoln Laboratory, Massachusetts Institute of Technology
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Work cell: (b)(6)

From: Robert Malone <(b)(6)> <mailto:(b)(6)>
Date: Tuesday, July 7, 2020 at 6:12 PM
To: vinu arumugham <vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>
Cc: "Sestili, Piero" <piero.sestili@uniurb.it<mailto:piero.sestili@uniurb.it>>, <def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>>, <def2004@cumc.columbia.edu<mailto:def2004@cumc.columbia.edu>>, <jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>>, <jconigliaro@northwell.edu<mailto:jconigliaro@northwell.edu>>, <ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>>, <ddm1@cumc.columbia.edu<mailto:ddm1@cumc.columbia.edu>>, <ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>>, <ag3786@cumc.columbia.edu<mailto:ag3786@cumc.columbia.edu>>, <mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>>, <mo2130@cumc.columbia.edu<mailto:mo2130@cumc.columbia.edu>>, <jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>>, <jl1333@cumc.columbia.edu<mailto:jl1333@cumc.columbia.edu>>, <dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>> <dtuveson@cshl.edu<mailto:dtuveson@cshl.edu>>, <zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>>, <zj7@cumc.columbia.edu<mailto:zj7@cumc.columbia.edu>>.

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"erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>"
<erubin@hsph.harvard.edu<mailto:erubin@hsph.harvard.edu>>
Subject: Re: Use mast cell stabilizers, histamine H1/H2 blockers in COVID-19

you may not be aware that this is now posted?

On Tue, Jul 7, 2020 at 5:42 PM vinu arumugham
<vaccine.safety@aol.com<mailto:vaccine.safety@aol.com>>wrote:

Prof. Sestili,

Thank you for your quick response and suggestion.

All,

As Prof. Sestili has suggested, I agree that we should coauthor a paper (or perhaps an open letter like this one<

We have been able to correctly predict the beneficial effects of these medications since late January 2020 because the mechanism was understood. Hundreds of thousands of lives could have been saved if these medications had been used. If we do not act now, hundreds of thousands more lives will be lost.

Many authors have described the mechanism and role of mast cell dysregulation in severe COVID-19:

Repositioning Chromones for Early Anti-inflammatory Treatment of COVID-19

<https://doi.org/10.3389/fphar.2020.00854><https://urldefense.proofpoint.com/v2/url?u=https-3A_doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrB-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cb9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms

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Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy
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Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin
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As I wrote in my comment posted in the Annals of Internal Medicine,

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Please see comments section:

https://protect2.fireeye.com/url?k=d912276e-85460e45-d9121651-0cc47a6d17cc-e09445ddb7ab6597&u=https://protect2.fireeye.com/url?k=e18ec594-bddbcc44-e18ef4ab-0cc47a6a52de-44d3aa827e434ccc&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician<https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3Deb474ef1-2Db7124721-2Deb477fce-2D0cc47a6a52de-2Dcf07498f50d73e08-26u-3Dhttps-3A_annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=DYt7c7-R65Cpzq8v4RXbAa3dIJPBm2luohhZmMlnqec&e=>

Please respond if you would like to be a coauthor and please share any other ideas to make this happen.
Please include coworkers who may be interested.

Thanks,

Vinu

On 7/7/20 12:11 AM, Sestili, Piero wrote:

Dear Vinu,

I wrote a paper in March proposing mast cell stabilizers to treat COVID-19 soon after its early clinical presentation.

I am elated to see that many colleagues around the world independently formulated similar thoughts and that evidences are accumulating strengthening this hypothesis.

We could collectively prepare a paper coauthorized by all of us (I see that you have a wide list where Prof. Conti, Prof. Kritas and their coworkers could be included) pushing authorities to rapidly consider and promote the clinical exploitation of MCS against COVID.

Here is the DOI of my article

<https://doi.org/10.3389/fphar.2020.00854><https://urldefense.proofpoint.com/v2/url?u=https-3A__doi.org_10.3389_fphar.2020.00854&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=-HCK5bQfdRS0Cbp9qF3MGwTFnd5dzkmMccHmEZPfzRw&e=>

Please, if you think it might be useful, forward this message to your MCS mail list.

Truly yours and thanks for your relevant effort, ciao

Piero Sestili
Full Professor in Pharmacology,
University of Urbino, Italy

Il giorno mar 7 lug 2020 alle 02:46 vinu arumugham
<vaccine.safety@aol.com<<mailto:vaccine.safety@aol.com>>> ha scritto:

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----- Forwarded Message -----

Subject:

Kawasaki disease and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers

Date:

Thu, 14 May 2020 09:42:05 -0700

From:

vinu arumugham <vaccine.safety@aol.com><<mailto:vaccine.safety@aol.com>>

To:

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dhunstad@wustl.edu<<mailto:dhunstad@wustl.edu>><dhunstad@wustl.edu><mailto:dhunstad@wustl.edu>,
Huskins.Charles@mayo.edu<mailto:Huskins.Charles@mayo.edu><Huskins.Charles@mayo.edu><mailto:Huskins.Charles@mayo.edu>,
mlaufer@medicine.umaryland.edu<mailto:mlaufer@medicine.umaryland.edu><mlaufer@medicine.umaryland.edu><mailto:mlaufer@medicine.umaryland.edu>,
latania_logan@rush.edu<mailto:latania_logan@rush.edu><latania_logan@rush.edu><mailto:latania_logan@rush.edu>,
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Lrubin@lij.edu<<mailto:Lrubin@lij.edu>><Lrubin@lij.edu><mailto:Lrubin@lij.edu>

Ls5@cumc.columbia.edu<mailto:Ls5@cumc.columbia.edu><Ls5@cumc.columbia.edu><mailto:Ls5@cumc.columbia.edu>,
 mike.sharland@stgeorges.nhs.uk<mailto:mike.sharland@stgeorges.nhs.uk><mike.sharland@stgeorges.nhs.uk><mailto:mike.sharland@stgeorges.nhs.uk>,
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 CGIDRadmin@seattlechildrens.org<mailto:CGIDRadmin@seattlechildrens.org><CGIDRadmin@seattlechildrens.org><mailto:CGIDRadmin@seattlechildrens.org>,
 danielle.zerr@seattlechildrens.org<mailto:danielle.zerr@seattlechildrens.org><danielle.zerr@seattlechildrens.org><mailto:danielle.zerr@seattlechildrens.org>

Kawasaki disease (KD) and COVID-19 are iatrogenic diseases; Try mast cell stabilizers, H1/H2 blockers.

KD shock syndrome is same mechanism as influenza and dengue shock syndrome covered below ("slow rolling anaphylaxis").

<https://twitter.com/ArumughamVinu/status/1259659169046474753?s=20><https://urldefense.proofpoint.com/v2/url?u=https-3A_twitter.com_ArumughamVinu_status_1259659169046474753-3Fs-3D20&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=pnGu5AyahOEN7R2OQ5ZswzoWK8DdK5VPJFPtfingTLUo&e=>

One can also expect peripheral blood eosinophilia. Have you checked? RCPCH case definition does not include it.

That would be consistent with the body's (iatrogenically induced) anti-parasite response against SARS-CoV-2, instead of just an antiviral response. Consider IgE/IgG4 responses against heat shock proteins.

Immunological mechanisms explaining the role of IgE, mast cells, histamine, elevating ferritin, IL-6, D-dimer, VEGF levels in COVID-19 and dengue, potential treatments such as mast cell stabilizers, antihistamines, Vitamin C, hydroxychloroquine, ivermectin and azithromycin

<https://doi.org/10.5281/zenodo.3748303><https://urldefense.proofpoint.com/v2/url?u=https-3A_doi.org_10.5281_zenodo.3748303&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wq82Sv_ttg4saUpfNx275-fC4xfxjhQMZEf7VfTZ8E&e=>

As I have been predicting for 3+ months, there is now evidence that Famotidine (antihistamine, H2-blocker) helps in COVID-19. Study below. The mechanism involved is explained above.

Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

<https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1><<https://urldefense.proofpoint.com/v2/>

[url?u=https-3A_www.medrxiv.org_content_10.1101_2020.05.01.20086694v1&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=SdocmnvkWuC9GxFjSeluKdp2X3478rCrePpVHDAAdRX0&e=>](https://www.medrxiv.org/content/10.1101/2020.05.01.20086694v1&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=SdocmnvkWuC9GxFjSeluKdp2X3478rCrePpVHDAAdRX0&e=>)

Root cause of COVID-19? Biotechnology's dirty secret: Contamination. Bioinformatics evidence demonstrates that SARS-CoV-2 was created in a laboratory, unlikely to be a bioweapon but most likely a result of sloppy experiments

https://doi.org/10.5281/zenodo.3766462<https://urldefense.proofpoint.com/v2/url?u=https-3A_doi.org_10.5281_zenodo.3766462&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=cj8LcUAnK9z6xldvx_K67Av3BgybJKis7cXjWS6teUQ&e=>

My comment posted in the Annals of Internal Medicine:

Please see comments section:

https://protect2.fireeye.com/url?k=f0bd2ce6-ace905cd-f0bd1dd9-0cc47a6d17cc-ab8bbbd8e2144f8c&u=https://protect2.fireeye.com/url?k=89b04da4-d5e54474-89b07c9b-0cc47a6a52de-0d3acbf2316abfbb&u=https://annals.org/aim/fullarticle/2764199/use-hydroxychloroquine-chloroquine-during-covid-19-pandemic-what-every-clinician<https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3De18f1fc2-2Dbdda1612-2De18f2efd-2D0cc47a6a52de-2Dd03b63f3ad8596bf-26u-3Dhttps-3A_annals.org_aim_fullarticle_2764199_use-2Dhydroxychloroquine-2Dchloroquine-2Dduring-2Dcovid-2D19-2Dpandemic-2Dwhat-2Devery-2Dclinician&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=QrwjMplMCw-gYAwRoZoBxxzIFDIIdGJmefJnVOFKD99A&e=>

Understanding mechanisms is better than demanding clinical trials in the middle of a pandemic

Hydroxychloroquine and azithromycin use in COVID-19 have been dismissed as "unproven" or "anecdotal", by the medical establishment. But the benefit of ventilators in COVID-19 is equally unproven. Why the clamor for ventilators? And now there are reports that ventilators are not helping.

https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.npr.org_sections_health-2Dshots_2020_04_02_826105278_ventilators-2Dare-2Dno-2Dpanacea-2Dfor-2Dcritically-2Dill-2Dcovid-2D19-2Dpatients&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_larRuzze9NBCIPdMzJCrb-e8lgWakoRNvkw5IZR_bQ&s=ns_rDtrq5q1sozVBGVyFfAeePW4EpuKhWO1UUB8HYMM&e=>

Running protein sequence analysis with the SARS-CoV-2, MERS, SARS viruses, there is a strong similarity to a pig spike protein (coronavirus infected pig). Accession number QGV12786 vs. QHD43416.1 for SARS-CoV-2.

Since vaccines contain porcine proteins derived from pigs infected with any number of diseases, one could develop IgE mediated sensitization to coronavirus spike proteins. We have entire, viable porcine circoviruses in the rotavirus vaccines, for example.

<https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.cdc.gov_vaccines_pubs_pinkbook_downloads_appendices_b_excipient-2Dtable-2D2.pdf&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=TFHoxIH57zLMFMv8B1cU3L7N-aeSGInUothbCDoARbQ&e=>

Upon infection with any of these viruses, the concurrent allergic reaction can increase disease severity. In such cases, antihistamines and other allergy treatments such as mast cell stabilizers may help reduce infection severity.

This is similar to influenza vaccine induced allergy to the influenza virus, increasing the severity of subsequent influenza infection as described here:

Influenza vaccines and dengue-like disease

<https://www.bmj.com/content/360/bmj.k1378/rr-15><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.bmj.com_content_360_bmj.k1378_rr-2D15&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=PgG9dxWbyXeGbCJaAKep5ciUcZWGi4XAqTsBmA0IHo&e=>

There have been reports that elevated ferritin and IL-6 levels are predictors of fatality in COVID-19.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30628-0/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext)<https://urldefense.proofpoint.com/v2/url?u=https-3A_www.thelancet.com_journals_lancet_article_PIIIS0140-2D6736-2820-2930628-2D0_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=qz0bFEmcdkWmTZV2GeYiQs67uaKO3FBnKCwwBhxKwwM&e=>

There is an increase in mast cell density during infections:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435071/><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pmc_articles_PMC4435071_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=fuFR9xaEo90-sEb0eDhAMxtzrEzT3L6il6_7wkpQjEw&e=>

IgE mediated mast cell degranulation results in increased ferritin levels as well as histamine levels.

Ferritin Particles Accumulate in Human Mast Cell Secretory Granules and Are Released upon FcεRI-mediated Activation

[https://protect2.fireeye.com/url?k=af0a3a8a-f35e13a1-af0a0bb5-0cc47a6d17cc-91215676bc8afd01&u=https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749\(17\)32622-2/fulltext](https://protect2.fireeye.com/url?k=af0a3a8a-f35e13a1-af0a0bb5-0cc47a6d17cc-91215676bc8afd01&u=https://protect2.fireeye.com/url?k=a8f577aa-f4a07e7a-a8f54695-0cc47a6a52de-0c20b4f854efc630&u=https://www.jacionline.org/article/S0091-6749(17)32622-2/fulltext)<https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3Dd17dc1e1-2D8d28c831-2Dd17df0de-2D0cc47a6a52de-2D24d8d9d7adeedda7-26u-3Dhttps-3A_www.jacionline.org_article_S0091-2D6749-2817-2932622-2D2_fulltext&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUMDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=oqnmFUHUhAOKPfgIVB-uzpr2KNXjax_w9CXXPY1-EE&e=>

Histamine promotes release of IL-6.

Histamine Promotes the Release of Interleukin-6 via the H1R/p38 and NF- κ B Pathways in Nasal Fibroblasts

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4214978/><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pmc_articles_PMC4214978_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=wsLUle3V45G_Ra2-A-21xEpUGFdR6ngbytk5APv67NU&e=>

Also, neutrophils recruited to the lung during infection can release histamine.

Neutrophil histamine contributes to inflammation in mycoplasma pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/17158962/><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pubmed_17158962&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=WCztb1O-3QkxjBbaZJTIVacQFDIApeJFizGA9brC_g&e=>

The antihistamine effect of Vitamin C IV seems to help.

Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis

<https://www.ncbi.nlm.nih.gov/pubmed/1578094/><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pubmed_1578094&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=NGj4Z6fuUBOazJKs-2yUiZvtQVXSrdsHzzHN3uTqPNY&e=>

<https://protect2.fireeye.com/url?k=8df3fd39-d1a7d412-8df3cc06-0cc47a6d17cc-cad96f3ec39c3c65&u=https://www.nutraingredients.com/Article/2020/03/25/Hospital-turns-to-high-dose-vitamin-C-to-fight-coronavirus><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.nutraingredients.com_Article_2020_03_25_Hospital-2Dturns-2Dto-2Dhigh-2Ddose-2Dvitamin-2DC-2Dto-2Dfight-2Dcoronavirus&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=IQcZYeRKOPVvenMIHJZX15PpN6p25jHzmumO_ArPtNE&e=>

Also, azithromycin reduces histamine induced inflammation.

The anti-inflammatory effects of erythromycin, clarithromycin, azithromycin and roxithromycin on histamine-induced otitis media with effusion in guinea pigs.

<https://www.ncbi.nlm.nih.gov/pubmed/29888693/><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pubmed_29888693&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOmERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=SHet5h_swdJ1uS2s-O8OvUbkkJc1LTcjMkTXt-WxY8o&e=>

Hydroxychloroquine helps in allergic asthma.

Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma.

<https://www.ncbi.nlm.nih.gov/pubmed/9723661><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.ncbi.nlm.nih.gov_pubmed_9723661&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=3HS7BagYtpR0FQgGzFNMgy1ZtNoPn3WLpHyuhHlexk&e=>

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

<https://www.sciencedirect.com/science/article/pii/S0924857920300996><https://urldefense.proofpoint.com/v2/url?u=https-3A_www.sciencedirect.com_science_article_pii_S0924857920300996&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=huP8akSYLDbnDaDUlaGd8L8hJbCrbAmQL0zeL2IErs4&e=>
<https://protect2.fireeye.com/url?k=a96152d5-f5357bfe-a96163ea-0cc47a6d17cc-d8c9bb2ecc9c22fd&u=https://protect2.fireeye.com/url?k=2ff8f995-73adf045-2ff8c8aa-0cc47a6a52de-d6f7d13655de4261&u=https://www.mediterranee-infection.com/covid-19/><https://urldefense.proofpoint.com/v2/url?u=https-3A_protect2.fireeye.com_url-3Fk-3D1028eb31-2D4c7de2e1-2D1028da0e-2D0cc47a6a52de-2D1917dbc24e7b0a50-26u-3Dhttps-3A_www.mediterranee-2Dinfection.com_covid-2D19_&d=DwMGaQ&c=mkpgQs82XaCKIwNV8b32dmVOMERqJe4bBOtF0CetP9Y&r=6BEXLUmDIROBW3umLQEGX7YxisEG8VjS1tJ0oxmu_lk&m=f_IaRuzze9NBCIPdMzJCrb-e8IgWakoRNvkw5IZR_bQ&s=46jxOuAhs4zOw9tALUI_WrQ15PKdUvuWYMIlnkrkkFhM&e=>

So there are many indicators pointing to the role of mast cell degranulation/histamine release being a major component of COVID-19.

Antihistamines, mast cell stabilizers, Vitamin C, hydroxychloroquine, azithromycin may all address different aspects of this same problem.

Focusing on only the antiviral actions of hydroxychloroquine or azithromycin, will lead us into blind alleys.

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"Tread lightly, take only pictures, leave only footprints, kill only time"

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Sent Date: 2020/07/08 14:44:29

Delivered Date: 2020/07/08 14:45:06

From:	Horwith, Gary (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F57CE90784EE45BB8261427305AB14C6-HORWITH, GA <Gary.Horwith@hhs.gov>
To:	Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
CC:	Faison, Tremel (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2bbab0bceb1342fbbdbbcc94deeb80f-Faison, Tre <Tremel.Faison@hhs.gov>
Subject:	RE: HCQ CQ EUA risk benefit summary [FOUO]
Date:	2020/06/15 09:03:36
Priority:	Normal
Type:	Note

Bob,

The internal memo you sent seems to have been generated without add-ins, so the endnote references were not created. Attached with endnote references.

Gary

From: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Sent: Monday, June 15, 2020 8:15 AM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Cc: Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>; Horwith, Gary (OS/ASPR/BARDA) <Gary.Horwith@hhs.gov>
Subject: HCQ CQ EUA risk benefit summary [FOUO]

Gary

For the record, please see the attached internal memo regarding the HCQ CQ EUA. This memo provides a summary from BARDA DCD's perspective on the available data that inform a reassessment of the risk-benefit of use of these drugs under the terms of the EUA.

Bob

<<File: HCQ CQ EUA_Summary of Risk-Benefit_20200615.docx >>

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Sent Date: 2020/06/15 09:03:19

Delivered Date: 2020/06/15 09:03:36



DATE: June 15, 2020

TO: Gary Disbrow, PhD
Acting Director, BARDA

THROUGH: Tremel Faison
Director, Regulatory and Quality Affairs, BARDA

FROM: Robert Walker, MD
Director, Division of Clinical Development, BARDA

Gary Horwith, MD
Senior Clinical Analyst, BARDA

RE: Hydroxychloroquine – Chloroquine Emergency Use Authorization: Review of
Risk/Benefit based on new findings

ISSUE

This memo summarizes recent information, both published and unpublished, that informs the current assessment of risk/benefit for hydroxychloroquine sulfate (HCQ) and chloroquine phosphate (CQ) treatment for COVID-19 under the existing Emergency Use Authorization. The currently available data indicate that neither HCQ nor CQ provide benefit and are potentially harmful in this setting. Therefore, BARDA's Division of Clinical Development recommends that BARDA leadership request that FDA withdraw the Emergency Use Authorization pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.

Data from Randomized Clinical Trials

Boulware, et al., recently published results of a randomized, double-blinded trial of HCQ as postexposure prophylaxis for COVID-19.¹ The trial was conducted in the U.S. and parts of Canada. Within 4 days of exposure to a person with confirmed COVID-19, subjects were assigned by a randomization table to receive HCQ (800mg once followed by 600mg in 6 to 8 hours, then 600mg for 4 additional days). The primary outcome was the incidence of either laboratory-confirmed COVID-19 or illness compatible with COVID-19 within 14 days. Overall, 87.6% of the participants (719 of 821 asymptomatic subjects) reported a high-risk exposure to a confirmed COVID-19 contact. The incidence of new illness compatible with COVID-19 did not differ significantly between participants who received HCQ (49 of 414 [11.8%]) and those who received placebo (58 of 407 [14.3%]); the absolute difference was -2.4% (95% confidence interval, -7.0% to 2.2; P=0.35). Adverse events were more common among HCQ participants (respectively, 40.1%, and 16.8%). No serious adverse events were reported. The

authors concluded that HCQ did not prevent COVID-19-compatible illness or confirmed infection when used for postexposure prophylaxis within 4 days after exposure.

Professors Peter Horby and Martin Landry, the chief investigators of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) Trial on hydroxychloroquine reported on June 5, 2020 that there was no clinical benefit from the use of HCQ in hospitalized patients with COVID-19.² This trial enrolled over 11,000 patients from 175 NHS hospitals in the UK. Throughout the trial, the independent Data Monitoring Committee (IDMC) reviewed the emerging data about every two weeks to determine if there was evidence that would be strong enough to affect national and global treatment of COVID-19. On June 4, in response to a request from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), the IDMC conducted a further review of the data. The Committee recommended the chief investigators review the unblinded data on the hydroxychloroquine arm of the trial. Upon review, the chief investigators concluded that there is no beneficial effect of hydroxychloroquine in patients hospitalized with COVID-19. They therefore decided to stop enrolling participants to the HCQ arm of the RECOVERY trial, and released the preliminary results. A total of 1,542 patients were randomized to HCQ compared with 3,132 patients randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% HCQ vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; $p=0.10$). There was also no evidence of beneficial effects on hospital stay duration or other outcomes.

For this particular analysis, follow-up was complete for just over 80% of participants. The lower bound of the confidence interval ruled out any meaningful benefit.

The RECOVERY Trial is a large, randomized controlled trial of possible treatments for patients admitted to hospital with COVID-19. Over 11,000 patients have been randomized to the following treatment arms, or no additional treatment. Treatment arms include:

- Lopinavir-ritonavir
- Low-dose dexamethasone
- HCQ
- Azithromycin
- Tocilizumab
- Convalescent plasma

In summary, recently reported results from large, well-designed, randomized clinical trials indicate no clinical improvement associated with HCQ in hospitalized patients with COVID-19 and no reduction in rates of SARS-CoV-2 infection or illness in the setting of post-exposure prophylaxis.

The Lancet article authored by Drs. Mehra, Ruschitzka, and Patel³, a multinational registry analysis of data from 671 hospitals on six continents contained data on 96,032 patients. They reported that there was no benefit of HCQ or CQ and an increased hazard for clinically significant occurrence of ventricular arrhythmias and death with COVID-19. The authors retracted the article due to several concerns with respect to the veracity of the data and analysis conducted by Surgisphere Corporation and its founder and co-author of the article.⁴ This study is not being considered in BARDA's evaluation and request for withdrawal of the EUA.

Outcome Data from EUA Submitted to BARDA (as of June 8, 2020)

As part of the EUA, health care providers who prescribe HCQ or CQ for their hospitalized patients are required to submit outcomes data via an electronic web link survey form. Instructions for this process

- **Baseline Characteristics:**
 - The mean (SD) age was 62.9 (15.77) years
 - Sex: 33.3% male, 23.5% female, 43.2% missing
 - Baseline severity of illness: 5.1% mild, 31.1% moderate, 47.9% severe, 15.9% critical
 - Comorbidities: 7% had cardiovascular disease, 23.8% had HTN, 19.1% had DM, and 2.8% had chronic renal disease
- **Clinical Characteristics**
 - The mean (SD) number of days patients received a dose was 4.2 (2.26), maximum number of days was 23
 - The mean (SD) number of days hospitalized was 9.7 (11.93)
 - 69.6% of patients were discharged and 30.4% of patients were deceased
 - Ventricular arrhythmias were reported in 6 (0.3%) subjects
 - Other cardiac AEs were reported in 31 (1.56%) subjects
- **Treatment Outcomes and Characteristics**
 - The mean number of days of dosing was the same in the discharged and deceased groups
 - The rate of ventricular arrhythmia was similar in the discharged and deceased groups
 - Other cardiac AEs were reported in 17 (1.23%) of discharged patients and 14 (2.32%) or deceased patients

In summary, limited data on outcomes reported in hospitalized patients treated with HCQ or CQ under the EUA indicate a mortality rate of approximately 30%, which is within range expected from published reports on COVID-19 associated mortality in hospitalized patients in the US.

Clinical Pharmacology

- The HCQ dosing regimen suggested in the EUA (800 mg on the first day followed by 400 mg daily for 4-7 days) was based on simulations published by Yao C, et al.⁵ The simulations predicted that lung concentrations would be many fold greater than the EC50 value, but the simulations assumed high intracellular accumulation of drug while the EC50 values were based on extracellular concentration. However, when EC50 values of extracellular drug concentrations are compared to in vivo free drug concentration in the plasma, the calculated free lung concentrations resulting from the proposed HCQ dosing regimen are well below in vitro EC50/EC90 values for SARS-CoV-2. Due to dose –dependent safety concerns (namely QT prolongation) adequate drug concentrations for antiviral activity are not likely achievable with a safe oral dosing regimen of HCQ. Potential immunomodulatory activity of HCQ is not considered.
- Confidential information shared by Gilead Sciences indicates evidence of in vitro interference between HCQ and remdesivir. In a respiratory syncytial virus system, HCQ resulted in

interference in the formation of the triphosphate active moiety of remdesivir and reduced antiviral activity. These findings are likely to be extrapolated to SARS-CoV-2. This finding has major clinical importance, because remdesivir is the only drug currently proved to have in vivo antiviral activity against SARS-CoV-2 in clinical trial

Viral Shedding

Results from eight published papers (2 randomized prospective trials, and 6 retrospective observational trials) showed that there was no decrease in the duration of virus shedding among recipients of HCQ, ⁶⁻¹³

Summary and Recommendations

For the following reasons it is no longer reasonable to believe that, as authorized for this use, CQ and HCQ may be effective in treating COVID-19:

- The suggested dosing regimens for CQ and HCQ as detailed in the Fact Sheets are unlikely to produce an antiviral effect.
- Earlier observations of decreased viral shedding with HCQ or CQ treatment have not been consistently replicated and recent data from a randomized controlled trial assessing probability of negative conversion showed no difference between HCQ and standard of care alone.
- Current NIH treatment guidelines recommend against the use of HCQ or CQ for the treatment of COVID-19 except in a clinical trial.
- Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.

Furthermore, ongoing reports of serious cardiac adverse events make it evident that the known and potential benefits of CQ and HCQ do not outweigh the known and potential risks associated with the authorized use. Therefore, we recommend that BARDA leadership request that FDA withdraw this EUA.

References

1. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med* 2020.
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9. Huang M, Tang T, Pang P, et al. Treating COVID-19 with Chloroquine. *J Mol Cell Biol* 2020;12:322-5.
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13. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849.

- **Reminder: For Official Use Only** information will be discussed at this meeting
- **All participants must have signed the Confidentiality Agreement of the PHEMCE MOU in order to participate in this call**
 - If you have not signed the Agreement and submitted it to Christy.ventura@hhs.gov, you will need to drop from the call at this time
 - PHEMCE MOU is attached to the meeting invite



ASPR

SARS-CoV-2

Medical Countermeasures Task Force

1 April 2020

1000-1100

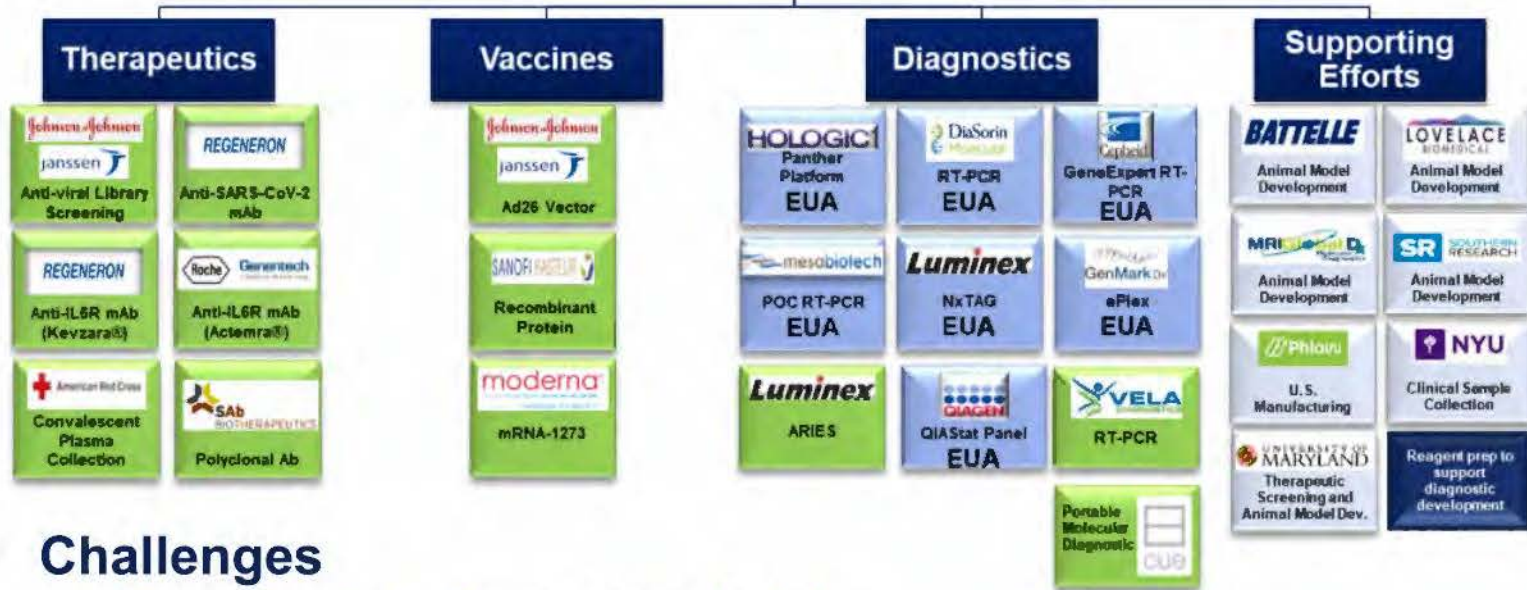
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Agenda

- **Opening Remarks**
- **Agency Updates**
- **Working Group Updates**
- **Next Steps/Closing Remarks**

BARDA

Portfolio



- **Challenges**
 - Supply chain for raw materials
 - PPE for manufacturing lines

CDC

Highlights

- COCA Call: Clinical Management of Critically Ill Adults with COVID-19
- PPE burn rate calculator and strategies to optimize use of PPE and ventilators:
 - <https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html>
- 2 deployments for IPC support in New Orleans, LA

Challenges

- Technical support for IPC at state and local level
- Support for IPC at LTCF

DoD

- **Highlights**
 - **Diagnostics – Biofire/Cepheid EUAs**
 - **Vaccines – JPEO/Inovio Manufacturing Effort**
 - **Therapeutics – JPEO/Vanderbilt Antibody Development & Manufacturing Effort**
 - **Clinical Trials – COVID-19 Observational Trials in MTFs**
- **Challenges**
 - **Funding/sample availability**

DHS

- Highlights
- Challenges

FDA

- Highlights
- Challenges

NIAID

- **Animal models**
 - Preprint of rhesus macaque model available
 - Cynomolgus model in progress; task orders awarded
- **Natural history studies:** Protocols for pediatric asthma and natural history of infection (including immunophenotyping) prepared to launch
- **Therapeutics:**
 - ACTT Remdesivir trial >50% enrolled
 - Azithromycin-(hydroxyl)chloroquine treatment trial underwent scientific review
 - IVIG planning underway
- **Vaccines:** First two dose groups enrolled in Phase 1
- **Challenges:** Medical supplies for trials

USDA

- **Highlights**

- Agricultural Research Service (ARS) is conducting infection studies to investigate the potential for a reverse zoonosis in livestock and poultry
- ARS is planning to investigate the stability of SARS-CoV-2 in foods that could be contaminated by SARS-CoV-2 positive food handlers.

- **Challenges**

- None at this time

Therapeutics Working Group

- **Accomplishments**

- Subgroup (members from therapeutic & clinical WGs) formed for prioritizing candidates for clinical studies and preclinical testing
- In vitro testing has commenced at BARDA & NIAID contractors, intramural NIAID and USAMRIID labs
- Rhesus model developed and initial testing of remdesivir completed (NIAID-RML)
- Additional small animal and NHP models being established (NIAID & BARDA contracts, NIAID intramural, USAMRIID)

- **Ongoing Tasks and Challenges**

- Data sharing between the agencies – working well
- Consensus on design and purpose of additional clinical studies – challenging
- Animal models require additional development before candidate testing; unclear whether animals will manifest late-stage disease or mainly viremia

Vaccines

- **Accomplishments**

- Awarded Janssen Ad26 development project
- DMID and BARDA small animal and NHP task orders awarded
- BEI Resources Reagent Availability

- **Ongoing Tasks and Challenges**

- In negotiations with Moderna for mRNA vaccines
- Expanding development scope with Sanofi Pasteur for recombinant Spike + Adjuvant vaccine
- Pre-submission discussion with Pfizer
- Need to address fill finish and cold-chain distribution challenges

Diagnostics

- **Accomplishments**

- Working Group call 3/26
 - ✓ Alternate sample types
 - ✓ Role of Serology tests
- S1 request 3/28 - use of serology tests for return to work
 - ✓ “Imperative to Develop a Coordinated COVID Serology Testing Plan”
 - Science/Knowledge gaps/R+D needs
 - Scaling and Production Issues
 - Policy Issues/Utilization Guidance
 - ✓ Outcome:
 - Serology WG established under FEMA/HHS Laboratory Testing TF
 - Need: serum to evaluate tests currently on market under FDA Policy, and test in development for EUA

Imperative to Develop a Coordinated COVID-19 Serology Testing Plan

Key deliverables to achieve ambitious 30-day goals

Research & Development

- Obtain serum
- Validate serum
- Prioritize tests to evaluate
- Testing and evaluation of multiple assays (rapid and lab-based)
- FDA EUA
- Diagnostic algorithms
- Research questions

Production and Scale-up

- Model demand and capacity
- Understand supply issues and barriers
- Support companies to scale-up

Operations and Deployment

- Test kits
- Education and campaign materials
- Mobilize commercial laboratory testing (drop-off/drive-thrus)
- Database
- Certificates

Policy

- How do we prioritize testing?
- Access?
 - Use of home tests?
- ConOps?
- Legal Considerations?

Clinical Trials

- **Accomplishments**
 - Emergency Use Authorization for chloroquine/hydroxychloroquine authorized on March 28
- **Ongoing tasks and challenges**
 - Natural History
 - ✓ NIAID INSIGHT study pending enrollment; HPCI Immunophenotyping study planned
 - Treatment
 - ✓ First draft HHS Clinical Treatment Guidelines drafted, under review
 - ✓ DAIDS-sponsored RCT of hydroxychloroquine and azithromycin protocol drafted; scientific review complete
 - ✓ Plan next intervention(s) to be used in NIAID ACTT study
 - Vaccines
 - ✓ Develop phase 2/3 vaccine trials
 - Emergency Use Authorization
 - ✓ Develop and publicly post FAQs and other educational materials
 - ✓ Agree on plan for responding to requests for clinical trial material
 - ✓ Implement outcomes data collection

Sample Sharing

- **Accomplishments**

- BARDA purchase agreement in place with Mark Mulligan (NYC) for PBMC/sera/virus
- NIH has PBMC/sera from DC patients

- **Ongoing Tasks and Challenges**

- BEI will make viral isolate from Hong Kong available next week
- CDC deposited 5 isolates in BEI- will go into production this week
- NIH working to get samples from Italy, UK, France, Germany, Canada
- CDC isolate from Thailand- isolate contaminated; expect mid-April
- CDC working on getting a lethal isolate
- URGENT NEED: PBMC/sera samples

QUESTIONS?

Next Meeting: 4/8/2020 at 1000

An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 and multiple
endemic, epidemic and bat coronavirus

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Abstract (153)

Coronaviruses (CoVs) traffic frequently between species resulting in novel disease
outbreaks, most recently exemplified by the newly emerged SARS-CoV-2. Herein, we
show that the ribonucleoside analog β -D-N⁴-hydroxycytidine (NHC, EIDD-1931) has
broad spectrum antiviral activity against SARS-CoV 2, MERS-CoV, SARS-CoV, and

related zoonotic group 2b or 2c Bat-CoVs, as well as increased potency against a coronavirus bearing resistance mutations to another nucleoside analog inhibitor. In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801, an orally bioavailable NHC-prodrug (β -D-N⁴-hydroxycytidine-5'-isopropyl ester), improved pulmonary function, and reduced virus titer and body weight loss. Decreased MERS-CoV yields *in vitro* and *in vivo* were associated with increased transition mutation frequency in viral but not host cell RNA, supporting a mechanism of lethal mutagenesis. The potency of NHC/EIDD-2801 against multiple coronaviruses, its therapeutic efficacy, and oral bioavailability *in vivo*, all highlight its potential utility as an effective antiviral against SARS-CoV-2 and other future zoonotic coronaviruses.

Introduction

The genetically diverse *Orthocoronavirinae* (coronavirus, CoV) family circulates in many avian and mammalian species. Phylogenetically, CoVs are divided into 4 genera: alpha (group 1), beta (group 2), gamma (group 3) and delta (group 4). Three new human CoV have emerged in the past 20 years with severe acute respiratory syndrome CoV (SARS-CoV) in 2002, Middle East respiratory syndrome CoV (MERS-CoV) in 2012, and now SARS-CoV-2 in 2019¹⁻³. The ongoing SARS-CoV-2 epidemic (referred to as COVID-19, Coronavirus disease 2019) has caused over 89,000 infections and over 3,000 deaths in 71 countries. Like SARS- and MERS-CoV, the respiratory disease caused by SARS-CoV-2 can progress to acute lung injury (ALI), an end stage lung disease with limited treatment options and very poor prognoses³⁻⁵. This emergence paradigm is not limited to humans. A novel group 1 CoV called swine acute diarrhea syndrome CoV (SADS-CoV) recently emerged from bats causing the loss of over 20,000 pigs in Guangdong Province, China⁶. More alarmingly, many group 2 SARS-like and MERS-like coronaviruses are circulating in bat reservoir species that can use human receptors and replicate efficiently in primary human lung cells without adaptation⁶⁻⁹. The presence of these “pre-epidemic” zoonotic strains foreshadow the emergence and epidemic potential of additional SARS-like and MERS-like viruses in the future. Given the diversity of CoV strains in zoonotic reservoirs and a penchant for

emergence, broadly active antivirals are clearly needed for rapid response to new CoV outbreaks in humans and domesticated animals.

Currently, there are no approved therapies specific for any human CoV. β -D-N⁴-hydroxycytidine (NHC, EIDD-1931) is orally bioavailable ribonucleoside analog with broad-spectrum antiviral activity against various unrelated RNA viruses including influenza, Ebola, CoV and Venezuelan equine encephalitis virus (VEEV)¹⁰⁻¹³. For VEEV, the mechanism of action (MOA) for NHC has been shown to be through lethal mutagenesis where deleterious transition mutations accumulate in viral RNA^{11,14}. Here, we demonstrate that NHC exerts potent, broad-spectrum activity against SARS-CoV, MERS-CoV and their related bat-CoV in primary human airway epithelial cell cultures (HAE), a biologically relevant model of the human conducting airway. In addition, we show that NHC is potently antiviral against the newly emerging SARS-CoV-2 as well as against coronavirus bearing resistance mutations to the potent nucleoside analog inhibitor, remdesivir (RDV). In SARS- or MERS-CoV infected mice, both prophylactic and therapeutic administration EIDD-2801, an oral NHC-prodrug (β -D-N⁴-hydroxycytidine-5'-isopropyl ester) improved pulmonary function and reduced virus titer and ameliorated disease severity. In addition, therapeutic EIDD-2801 reduced the pathological features of ALI in SARS-CoV infected mice. Using a high-fidelity deep sequencing approach (Primer ID), we found that increased mutation rates coincide with decreased MERS-CoV yields *in vitro* and protective efficacy *in vivo* supporting the MOA of lethal mutagenesis against emerging CoV¹³. The broad activity and therapeutic efficacy of NHC/EIDD-2801 highlight its potential to diminish epidemic disease today and limit future emerging CoV outbreaks.

Results

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

To determine whether NHC blocks the replication of highly pathogenic human CoV, we performed antiviral assays in continuous and primary human lung cell cultures. We first assessed the antiviral activity of NHC against MERS-CoV in the human lung epithelial cell line Calu-3 2B4 ("Calu3" cells). Using a recombinant MERS-CoV

expressing nanoluciferase (MERS-nLUC)¹⁵, we measured virus replication in cultures exposed to a dose range of drug for 48hr. NHC was potently antiviral with an average half-maximum effective concentration (IC₅₀) of 0.15μM and no observed cytotoxicity in similarly treated uninfected cultures across the dose range (50% cytotoxic concentration, CC₅₀, >10μM) (Fig. 1A). The therapeutic index for NHC was >100. Similarly, NHC strongly inhibited SARS-CoV-2 replication in Vero cells with an IC₅₀ of 0.3μM and CC₅₀ of >10μM (Fig. 1B). Human primary airway epithelial (HAE) cell cultures model the architecture and cellular complexity of the conducting airway and are readily infected by multiple human and zoonotic CoV, including SARS- and MERS-CoV¹⁶. We first assessed cytotoxicity of NHC in HAE treated with an extended dose range for 48hr using quantitative PCR of cell death-related gene transcripts as our metric. NHC treatment did not appreciably alter gene expression even at doses up to 100μM (Supplementary Figure 1). In MERS-CoV infected HAE, NHC dramatically reduced virus production with maximal titer reduction of > 5 logs at 10μM (average IC₅₀ = 0.024 μM), which correlated with reduced genomic (ORF1) and subgenomic (ORFN) RNA in paired samples (Fig. 1C). We observed similar trends in titer reduction (> 3 log at 10μM, average IC₅₀ = 0.14 μM) and levels of genomic and subgenomic RNA in SARS-CoV infected HAE (Fig. 1D). Thus, NHC was potently antiviral against MERS-CoV and SARS-CoV-2 in cell lines and MERS-CoV and SARS-CoV in human primary HAE cell cultures without cytotoxicity.

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

All human CoV are thought to have emerged as zoonoses most recently exemplified by SARS-CoV, MERS-CoV and SARS-CoV-2¹⁷⁻¹⁹. Although taxonomically divided into multiple genogroups (alpha , beta , gamma , delta), human CoV are found in only the alpha and beta subgroups thus far (Fig. 2A). There is high sequence conservation in the RdRp across CoV (Fig. 2A). For example, the RdRp of SARS-CoV-2 has 99.1% similarity and 96% amino acid identity to that of SARS-CoV (Fig. 2A). To gain insight into structural conservation of RdRp across the CoV family, we modeled the variation reflected in the RdRp dendrogram in Fig. 2A onto the structure of the SARS-

CoV RdRp²⁰ (Fig. 2B). The core of the RdRp molecule and main structural motifs that all RdRp harbor (Fig. 2B and Supplementary Figure 2) are highly conserved among CoV including SARS-CoV-2. We previously reported that CoV resistance to another broad spectrum nucleoside analog, remdesivir (RDV) was mediated by RdRp residues F480L and V557L in a model coronavirus mouse hepatitis virus (MHV) and in SARS-CoV, resulting in a 5-fold shift in IC₅₀ (Fig. 2C)²¹. Consequently, we tested whether RDV resistance mutations in MHV conferred cross resistance to NHC (Figure 2D). In fact, the two RDV resistance mutations, alone or together conferred increased sensitivity to inhibition by NHC. As our previous studies have demonstrated a high genetic barrier to NHC for VEEV, influenza and coronavirus¹¹⁻¹³, the lack of cross resistance further suggests that NHC and RDV may select for exclusive and mutually sensitizing resistance pathways.

To explore the breadth of antiviral efficacy against zoonotic CoV, we performed antiviral assays in HAE with three zoonotic Bat-CoV, SHC014, HKU3 and HKU5. Closely related to the beta 2b SARS-CoV, Bat-CoV SHC014 is capable of replicating in human cells without adaptation⁸ suggesting its potential for zoonotic emergence. More distantly related SARS-like beta 2b CoV, recombinant Bat-CoV HKU3 has a modified receptor binding domain to facilitate growth in cell culture²². Lastly, Bat-CoV HKU5 is a MERS-like beta 2c CoV²³. NHC diminished infectious virus production and the levels of genomic/subgenomic viral RNA in HAE in a dose-dependent manner for all three Bat-CoVs (Fig. 3). Therefore, the antiviral activity of NHC was not limited by natural amino acid variation in the RdRp, which among the group 2b and group 2c CoV can vary by almost 20% (Fig. 2A). Moreover, these data suggest that if another SARS- or MERS-like virus were to spillover into humans in the future, they would likely be susceptible to the antiviral activity of NHC.

NHC antiviral activity is associated with increased viral mutation rates.

It has recently been shown that NHC treatment increases the mutation rate in viral genomic RNA of RSV²⁴, VEEV¹¹, influenza²⁴, and our previous study used RNA seq to show that overall transition mutation frequency is increased during NHC treatment of MHV and MERS-CoV during infection in continuous cell lines¹³. We sought

to determine if NHC would increase the mutation frequency during MERS-CoV infection in human primary human airway epithelial cells (HAE). Using MERS-CoV infected HAE treated with either vehicle or a dose range of NHC or RDV, we show that both drugs reduced virus titers in a dose-dependent manner (Fig. 4A). We then employed a highly-sensitive high-fidelity deep sequencing approach (Primer ID NGS), which uses barcoded degenerate primers and Illumina indexed libraries to determine accurate mutation rates after antiviral treatment on viral RNA production²⁵. Using this approach, we analyzed a 538bp region of viral genomic RNA in nonstructural protein 15 (nsp15). The error rates (#mutations/10,000 bases) in vehicle (0.01) or RDV (0.01) treated cultures were very low. RDV is reported to act via chain termination of nascent viral RNA, and thus the low error rates in RDV-treated cultures are in line with the proposed MOA²⁶. In contrast, the error rate was significantly increased in NHC-treated MERS-CoV RNA in a dose-dependent manner (10-fold at 10 μ M and 5-fold at 1 μ M) at both 24 and 48hpi (Fig. 4C). The magnitude of the error rate in NHC-treated cultures correlated with virus titer reduction. At 48hpi the respective error rate and virus titer was 0.015 and 3.96E+06 pfu/mL for vehicle treatment, 0.045 and 2.86E+04 pfu/mL with 1 μ M NHC; and 0.090 and 1.5E+02 pfu/mL 10 μ M NHC. Thus, with 1 μ M NHC a 3-fold increase in error rate resulted in a 138-fold decrease in virus titer, while with 10 μ M NHC a 6-fold increase in error rate resulted in a 26,000-fold decrease in virus titer.

We then examined the mutational spectra induced by NHC, which can be incorporated into viral RNA as a substitution for either cytosine (C) or Uracil (U). RNA-mutagenic antivirals may incorporate in both nascent negative and positive sense RNA during genome replication (Fig. 4D). Adenine-to-guanine (A-to-G) and uracil-to-cytosine (U-to-C) transitions were enriched in MERS-CoV genomic RNA in an NHC dose-dependent manner (Fig. 4E). Collectively, these data used high-fidelity sequence analysis to demonstrate a specific enrichment for A:G and C:U transitions in MERS-CoV RNA after NHC treatment of primary HAE cell cultures.

Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis.

Given the promising antiviral activity of NHC *in vitro*, we next evaluated its *in vivo* efficacy using EIDD-2801, an orally bioavailable prodrug of NHC (β -D-N⁴-

hydroxycytidine-5'-isopropyl ester), designed for improved *in vivo* pharmacokinetics and oral bioavailability in humans and non-human primates¹². Importantly, the plasma profiles of NHC and EIDD-2801 were similar in mice following oral delivery¹². We first performed a prophylactic dose escalation study in C57BL/6 mice where we orally administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or 50, 150 or 500 mg/kg EIDD-2801 2hr prior to intranasal infection with 5E+04 PFU of mouse-adapted SARS-CoV (SARS-MA15), and then every 12hr thereafter. Beginning on 3dpi and through the end of the study, body weight loss compared to vehicle treatment was significantly diminished (50mg/kg) or prevented (150, 500mg/kg) with EIDD-2801 prophylaxis ($P < 0.0001$) (Supplemental Figure 2A). Lung hemorrhage was also significantly reduced 5dpi with 500mg/kg EIDD-2801 treatment (Supplemental Figure 2B). Interestingly, there was a dose-dependent reduction in SARS-CoV lung titer (median titers: 50mg/kg = 7E+03 pfu/mL, 150mg/kg = 2.5E+03 pfu/mL, 500mg/kg = 50 pfu/mL, vehicle = 6.5E+04 pfu/mL) with significant differences among the vehicle, 150 mg/kg ($P = 0.03$) and 500mg/kg ($P = 0.006$) groups. Thus, prophylactic orally administered EIDD-2801 was robustly antiviral and able to prevent SARS-CoV replication and disease.

Since only the 500mg/kg group significantly diminished weight loss, hemorrhage and reduced lung titer to near undetectable levels, we tested this dose under therapeutic treatment conditions to determine if EIDD-2801 could improve the outcomes of an ongoing CoV infection. As a control, we initiated oral vehicle or EIDD-2801 2hr prior to infection with 1E+04 pfu SARS-MA15. For therapeutic conditions, we initiated EIDD-2801 treatment 12, 24, or 48hr after infection. After initiating treatment, dosing for all groups was performed every 12hr for the duration of the study. Both prophylactic treatment initiated 2hr prior to infection and therapeutic treatment initiated 12hr after infection significantly prevented body weight loss following SARS-CoV infection on 2dpi and thereafter (-2hr: $P = 0.0002$ to <0.0001 ; +12hr: $P = 0.0289$ to <0.0001) (Fig. 5A). Treatment initiated 24hpi also significantly reduced body weight loss (3-5dpi, $P = 0.01$ to <0.0001) although not to the same degree as the earlier treatment initiation groups. When initiated 48hpi, body weight loss was only different from vehicle on 4dpi ($P = 0.037$, Fig. 5A). Therapeutic EIDD-2801 significantly reduced lung hemorrhage when

initiated up to 24hr after infection mirroring the body weight loss phenotypes (Fig. 5B). Interestingly, all EIDD-2801 treated mice had significantly reduced viral loads in the lungs even in the +48hr group (Fig. 5C), which experienced the least protection from body weight loss and lung hemorrhage. We also measured pulmonary function via whole body plethysmography (WBP). In Figure 5D, we show the WBP PenH metric, which is a surrogate marker for bronchoconstriction or pulmonary obstruction²⁷, was significantly improved throughout the course of the study if treatment was initiated up to 12hr after infection, although the +24hr group showed sporadic improvement as well (Fig. 5D). Lastly, we blindly evaluated hematoxylin and eosin stained lung tissue sections for histological features of ALI using two different and complementary scoring tools¹⁵, which show that treatment initiated up to +12hr significantly reduced ALI (Fig. 5E). Altogether, therapeutic EIDD-2801 was potently antiviral against SARS-CoV *in vivo* but the degree of clinical benefit was dependent on the time of initiation post infection.

Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis.

After obtaining promising *in vivo* efficacy data with SARS-CoV, we investigated whether EIDD-2801 would be effective against MERS-CoV. As the murine ortholog of the MERS-CoV receptor, dipeptidyl peptidase 4 (DPP4), does not support viral binding and entry, all *in vivo* studies were performed in genetically modified mice encoding a murine DPP4 receptor encoding two human residues at positions 288 and 330 (hDPP4 288/330 mice)^{15,28}. Similar to our SARS-CoV data (Supplementary Figure 3), all doses of prophylactic EIDD-2801 (50, 150 and 500mg/kg) protected hDPP4 288/330 mice from significant body weight loss ($P = 0.03$ to < 0.0001), lung hemorrhage ($P = 0.01$ to < 0.0001), and virus replication which was undetectable ($P < 0.0001$) regardless of drug dose following intranasal infection with $5E+04$ PFU mouse-adapted MERS-CoV (Supplementary Figure 4).

We then evaluated the therapeutic efficacy EIDD-2801 following the promising results of our prophylactic studies. Similar to our SARS-CoV study, EIDD-2801 treatment administered before or 12hr after intranasal mouse-adapted MERS-CoV infection ($5E+04$ PFU) prevented body weight loss from 2 through 6dpi (Fig. 6A, $P =$

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

Therapeutic efficacy correlates with an increased MERS-CoV mutation rate *in vivo*, without increased mutations in cellular RNA.

To study the molecular mechanisms associated with drug performance *in vivo*, we investigated the correlation between infectious virus production and EIDD-2801-mediated mutagenesis of MERS-CoV RNA under therapeutic treatment conditions. Using Primer ID NGS, we measured the mutation rates of both viral genomic RNA (i.e. non-structural protein 10, nsp10) and host interferon stimulated gene 15 (ISG15) mRNA, a highly upregulated innate immune related gene after MERS-CoV infection (Fig. 6F). Primer ID NGS measures the mutational frequency in single RNA molecules each of which are represented by a single template consensus sequence (TCS, See Fig. 4B)²⁵. Viral TCS were significantly reduced in a treatment initiation time-dependent manner (Fig. 6G) similar to viral genomic RNA measured by qRT-PCR (Fig. 6D). In contrast, the numbers of ISG15 TCS were similar ($P = 0.2$ to 0.8) for all groups indicating that neither vehicle nor drug treatment significantly affected the levels of or mutated ISG15 mRNA transcripts (Fig. 6G). Similar to our TCS data in Figure 6G, the

total error rate in viral nsp10 was significantly increased in groups where treatment was initiated prior to (-2hr, median error rate = 10.5 errors/10,000 bases, $P < 0.0001$) and up to 24hr post infection (12hr, median error rate = 8.2 errors/10,000 bases, $P < 0.0001$; +24hr, median error rate = 5.4 errors/10,000 bases, $P = 0.0003$) but the error rates in ISG15 remained at baseline for all groups (Fig. 6H). In addition, nucleotide transitions observed in MERS-CoV genomes *in vitro* (i.e. C to U transitions, Fig. 3), were also observed *in vivo* in groups where treatment was initiated prior to and up to 12hr post infection ($P = 0.0003$ to < 0.0001) (Fig. 5I). Importantly, these transitions were not observed in host ISG15 mRNA (Fig. 5I). Lastly, the EIDD-2801 dose-dependent mutagenesis of viral RNA correlated with an increase in codon change frequency, including stop codons, in mice where treatment was initiated 12hr or before (vehicle median = 3.4; -2hr median = 22.8, $P = 0.0035$; +12hr median = 20.0, $P = 0.0004$, Fig. 5I). Thus, approximately 20% of the mutations observed in the -2hr and +12hr groups resulted in a codon change and alteration of the nsp10 protein sequence. When extrapolating our results from nsp10 to the entirety of the 30kb MERS-CoV genome, EIDD-2801 likely causes between 15 (+24hr treatment) and 30 (-2hr treatment) mutations per genome 10-20% of which result in amino acid coding changes. Altogether, our data demonstrates that EIDD-2801-driven mutagenesis correlates well with the reductions in viral load, strongly suggestive of an error catastrophe-driven mechanism of action under therapeutic conditions.

Discussion

In the past 20 years, three novel human coronaviruses have emerged^{29,30}. The group 2b SARS-like CoV represent an existential and future threat to global health as evidenced by the emergence of SARS-CoV and SARS-CoV2 and zoonotic SARS-like bat CoV strains that can use human ACE2 receptors, grow well in primary human airway cells and vary by as much as 25% in key therapeutic and vaccine gene targets^{8,31}. Thus, to address the current public health emergency of COVID-19 and to maximize pandemic preparedness in the future, broad-based vaccines and therapeutics, which are active against the higher risk RNA virus families prone to emergence are desperately needed.

We recently reported the broad-spectrum potency of the nucleoside prodrug, remdesivir (RDV), against an array of epidemic, contemporary and zoonotic CoV both *in vitro* and *in vivo*^{15,16,21,31}. Currently RDV therapeutic efficacy is under investigation in several human clinical trials in China, the United States and elsewhere³². Here, we report the broad-spectrum antiviral activity of NHC and its orally bioavailable prodrug EIDD-2801, against SARS-CoV, MERS-CoV and related bat-CoV in primary human airway epithelial cells, as well as against the current pandemic strain SARS-CoV-2. In addition, NHC is broadly active against multiple genetically distinct viruses including coronaviruses, Venezuelan equine encephalitis (VEE), influenza A and B, Ebola, and Chikungunya viruses^{10-13,16,21,24,33-35}. Here, we show that prophylactic and therapeutic EIDD-2801 significantly reduced lung viral loads and improved pulmonary function in mouse models of both SARS- and MERS-CoV pathogenesis. Although the improvement in both SARS- and MERS-CoV outcomes diminished with the increase of treatment initiation time, it is important to note that the kinetics of disease in mice are compressed as compared to that in humans. While SARS- and MERS-CoV lung titers peak on 2dpi in mice concurrent with the onset of clinical signs and notable damage to the lung epithelium, in humans this occurs 7-10 days after the onset of symptoms^{16,28,36,37}. Thus, in mice, the window within which to treat emerging CoV infection prior to peak replication is compressed (e.g., 24-48hr) but should be much longer in humans. Although speculative, the SARS- and MERS-CoV *in vivo* data provided herein suggest that 2019-nCoV will prove highly vulnerable to NHC treatment modalities *in vivo*, critical experiments that must be performed as animal models become available. The data provided in this manuscript suggest that NHC should be quickly evaluated in primate models of human disease, using immediate models for MERS-CoV and SARS-CoV pathogenesis^{38,39}.

Small molecule antivirals can exert their antiviral effect through multiple mechanisms including blocking viral entry, inhibiting a virally encoded enzyme, blocking virus particle formation, or targeting a host factor required for replication⁴⁰. For VEE, EIDD-2801 exerts its antiviral activity on the RNA-dependent RNA polymerase leading to error catastrophe by inducing an error rate of replication that surpasses the error threshold allowed to sustain a virus population^{11,12}. This process occurs when NHC is

incorporated during RNA synthesis then subsequently misread thus increasing mutation rates. Therefore, the NHC MOA would appear less likely to be affected by the RNA proofreading activity encoded by the nsp14 exonuclease function that otherwise limits misincorporation⁴¹. Here, we present data using Primer ID NGS, a state of the art deep sequencing-based approach, to quantitate the frequency and identity of the mutational spectra in the MERS-CoV genome in both drug treated primary human airway cells and in mice at single genome resolution²⁵. As CoV are positive sense RNA viruses that replicate through a negative sense RNA intermediate, NHC incorporation as a "C" or a "U" can occur in both polarities of RNA. Using Primer ID NGS, we found increased nucleotide transitions (A to G, G to A, C to U, U to C) consistent with those reported after influenza and VEE infections^{11,12}. Under identical conditions, remdesivir did not alter the mutation rate in MERS-CoV genomic RNA, supporting its reported mechanism of action as a chain terminator of viral RNA synthesis²⁶. In primary human lung cell cultures and mice infected with MERS-CoV, the NHC mutation rates inversely correlated with a reduction in infectious virus. In addition, we found a positive correlation between increased mutation rates and the frequency of nonsynonymous mutations and the degree of therapeutic efficacy in mice. To explore the potential off-target effect in host mRNA which may contribute to drug toxicity, we also examined the impact of NHC treatment on transcripts from the highly MERS-CoV induced interferon stimulated gene 15 (ISG15). While ISG15 is present in great abundance, an accumulation of mutations was not observed in ISG15 in this model even at 500mg/kg dosing. These data also support previous studies using RNAseq to demonstrate that the model coronavirus MHV displayed increased mutation frequencies following NHC treatment *in vitro*¹³. All together, these data strongly support the notion that EIDD-2801 and its active nucleoside analog NHC, exert their antiviral effect through the induction of error catastrophe in the targeted virus. While our data suggest that the MERS-CoV nsp14 proofreading activity appeared ineffective against NHC *in vitro* and EIDD-2801 *in vivo*, future studies should investigate the antiviral activity of NHC in the presence or absence of the nsp14 proofreading activity, as loss of this activity increased the sensitivity of MHV and SARS-CoV replication to remdesivir treatment⁴¹.

Together, our data support the continued development of EIDD-2801 as a potent broad spectrum antiviral that could be useful in treating contemporary, newly emerged and emerging coronavirus infections of the future.

Materials and Methods

Compounds. The parental compound β -D-N⁴-hydroxycytidine (NHC, all *in vitro* studies) and its prodrug EIDD-2801 (all *in vivo* studies) was supplied by Emory University Institute for Drug Discovery (EIDD). NHC was supplied as a 10mM stock in DMSO and EIDD-2801 as a solid and solubilized in vehicle containing 10% PEG400, 2.5% Cremophor RH40 in water (10/2.5/87.5%, all v/v) prior to use. Remdesivir (RDV) was solubilized in 100% DMSO and provided by Gilead Sciences, Inc as previously described^{15,16}.

Virus strains. All viruses used for these studies were derived from infectious clones and isolated as previously described⁴². Virus strains for *in vitro* experiments include SARS-CoV expressing the green fluorescent protein (GFP) in place of open reading frames 7a/b (ORF7a/b, SARS-GFP)⁴², bat-spike receptor binding domain (Bat-SRBD)²² is a chimeric CoV strain derived from the HKU3 SARS-like bat coronavirus genomic sequence that has the wild type (Urbani SARS-CoV strain) RBD in the HKU3 spike gene to allow for virus replication in non-human primate cell lines and HAE cultures, SHC014 SARS-like bat coronavirus⁸, MERS-CoV expressing nanoluciferase in the place of ORF3 (MERS-nLUC)¹⁶ and MERS-CoV expressing the red fluorescent protein gene in the place of ORF 5 (RFP, MERS-RFP)⁴³. The virus stock utilized for MERS-CoV *in vivo* studies was derived from a plaque purified isolate of the mouse-adapted MERS-CoV p35C4 strain⁴⁴. The virus stock utilized for SARS-CoV *in vivo* studies was derived from the infectious clone of the mouse-adapted SARS-CoV MA15 (MA15) strain⁴⁵.

***In vitro* experiments** Calu3: At 48hrs prior to infection, Calu3 2B4 cells were plated in a 96-well black walled clear bottom plate at 5×10^4 cells/well. A 10mM stock of NHC was serially diluted in 100% DMSO in 3-fold increments to obtain a ten-point dilution series. MERS-nLUC was diluted in DMEM supplemented with 10% FBS, and 1% Antibiotic-

Antimycotic to achieve a multiplicity of infection (MOI) of 0.08. Cells were infected and treated with NHC in triplicate per drug dilution for 1hr, after which viral inoculum was aspirated, cultures were rinsed once and fresh medium containing drug or vehicle was added. At 48hrs post infection, nanoluciferase expression as a surrogate for virus replication was quantitated on a Spectramax (Molecular Devices) plate reader according to the manufacturer's instructions (Promega, NanoGlo). For our 100% inhibition control, diluted MERS-nLUC was exposed to short-wave UV light (UVP, LLC) for 6 minutes to inhibit the ability of the virus to replicate. For our 0% inhibition control, cells were infected in the presence of vehicle only. DMSO was kept constant in all conditions at 0.05%. Values from triplicate wells per condition were averaged and compared to controls to generate a percent inhibition value for each drug dilution. The IC₅₀ value was defined as the concentration at which there was a 50% decrease in luciferase expression. Data was analyzed using GraphPad Prism 8.0 (La Jolla, CA). The IC₅₀ values were calculated by non-linear regression analysis using the dose-response (variable slope) equation (four parameter logistic equation): $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) * \text{HillSlope}))}$. To measure cell viability to determine if there was any NHC induced cytotoxicity, Calu3 2B4 cells were plated and treated with NHC only as described above. Cells were exposed to the same ten-point dilution series created for the in vitro efficacy studies. As above, 0.05% DMSO-treated cells served as our 0% cytotoxicity control. Wells without cells served as our 100% cytotoxic positive control. After 48hr, cell viability was measured on a Spectramax (Molecular Devices) via Cell-Titer Glo Assay (Promega) according to the manufacturer's protocol. Similar data was obtained in three independent experiments.

HAE: Human tracheobronchial epithelial cells were obtained from airway specimens resected from patients undergoing surgery under University of North Carolina Institutional Review Board-approved protocols by the Cystic Fibrosis Center Tissue Culture Core. Primary cells were expanded to generate passage 1 cells and passage 2 cells were plated at a density of 250,000 cells per well on Transwell-COL (12mm diameter) supports. Human airway epithelium cultures (HAE) were generated by provision of an air-liquid interface for 6 to 8 weeks to form well-differentiated, polarized cultures that resembled *in vivo* pseudostratified mucociliary epithelium⁴⁶. At 48 hours

prior to infection the apical surface of the culture was washed with 500 μ L PBS for 1.5 hours at 37°C and the cultures moved into fresh air liquid interface (ALI) media. Immediately prior to infection, apical surfaces were washed twice with 500 μ L of PBS with each wash lasting 30 minutes at 37°C and HAE cultures were moved into ALI media containing various concentrations of NHC ranging from 10 μ M to 0.0016 μ M as indicated for each experiment (final % DMSO < 0.05%). Upon removing the second PBS wash, 200 μ L of viral inoculum (multiplicity of infection of (MOI) 0.5) was added to the apical surface and HAE cultures were incubated for 3 hours at 37°C. Viral inoculum was then removed, and the apical surface of the cultures were washed three times with 500 μ L PBS and then incubated at 37°C until 48 hours post infection (hpi). For all HAE cultures, infectious virus produced was collected by washing the apical surface of the culture with 100 μ L PBS. Apical washes were stored at -80 °C until analysis and titered by plaque assay as previously described¹⁶.

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

Primer ID and Deep Sequencing

Primer ID NGS is designed to specifically identify and remove RT-PCR mutations, while facilitating highly accurate sequence determination of single RNA molecules, because each cDNA is created with a barcoded degenerate primer (N10, 4¹⁰ combinations) from which Illumina indexed libraries are made. We used a multiplexed Primer ID library prep approach and MiSeq sequencing to investigate the presence of mutations in the viral genomes and murine mRNA. We designed cDNA primers targeting multiple regions on the viral genome and murine mRNA, each with a block of random nucleotides (11 bp

long) as the Primer ID^{25,47} (**Supplementary Table 2**). Viral RNA was extracted using QIAamp viral RNA kit. A pre-amplification titration of templates was performed to estimate the amount of template to use. We used SuperScript III to make cDNA with multiplexed cDNA primers based on the regions to be sequenced. We used 41R_PID11 for the pilot sequencing and titration determination. For the MERS-CoV sequencing, we multiplexed nsp10_PID11, nsp12_PID11 and nsp14_PID11 for the cDNA reaction; for the murine mRNA sequencing, we used mixed primers of nsp10_PID11, ifit3_PID11, isg15_PID11. After bead purification, we amplified the cDNA with a mixture of forward primers (based on the described schemes) and a universal reverse primer, followed by another round of PCR to incorporate Illumina sequencing adaptors and barcodes in the amplicons. After gel-purification and quantification, we pooled 24 libraries for MiSeq 300 base paired-end sequencing. The TCS pipeline version 1.38 (<https://github.com/SwanstromLab/PID>) was used to process the Primer ID sequencing data and construct template consensus sequences (TCSs) to represent each individual input templates, and the sequences of each region in the pool was de-multiplexed. The RUBY package viral_seq version 1.0.6 (https://rubygems.org/gems/viral_seq) was used to calculate the mutation rate at each position.

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

500,000 Vero E6 cells/well were seeded in 6-well plates. The following day, medium was removed and serial dilutions of clarified lung homogenate were added per plate (10^{-1} to 10^{-6} dilutions) and incubated at 37°C for 1hr after which wells were overlayed with 1X DMEM, 5% Fetal Clone 2 serum, 1X antibiotic/antimycotic, 0.8% agarose. Two days after, plaques were enumerated to generate a plaque/ml value. Lung hemorrhage is a gross pathological phenotype readily observed by the naked eye driven by the degree of virus replication where the coloration of the lung changes from pink to dark red^{48,49}. The large left lobe was placed in 10 % buffered formalin and stored at 4°C for 1-3 weeks until histological sectioning and analysis. For MERS-CoV, the prophylactic dose escalation studies we performed exactly as done for SARS-CoV with the following exceptions. First, MERS-CoV binds the human receptor dipeptidyl peptidase 4 (DPP4) to gain entry into cells and two residues (288 and 330) in the binding interface of mouse DPP4 prevent infection of mice. We recently developed a mouse model for MERS-CoV through the mutation of mouse DPP4 at 288 and 330 thus humanizing the receptor (*hDPP4*) and rendering mice susceptible to MERS-CoV infection²⁸. We performed all *in vivo* studies with EIDD-2801 in equivalent numbers of 10-14 week old female and male C57BL/6J *hDPP4* mice. Second, we intranasally infected mice with $5E+04$ PFU mouse-adapted MERS-CoV strain M35C4 in 50 μ l. Third, to titer lungs by plaque assay, Vero CCL81 cells were used and plaques were enumerated 3 days post infection.

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

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

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

Acute lung injury histological assessment tools. Two different and complementary quantitative histologic tools were used to determine if antiviral treatments diminished the histopathologic features associated with lung injury. Both analyses and scoring were performed by a Board Certified Veterinary Pathologist who was blinded to the treatment groups.

American Thoracic Society Lung Injury Scoring Tool. In order to help quantitate histological features of ALI observed in mouse models and increase their translation to the human condition, we used the ATS scoring tool⁴⁹. In a blinded manner, we chose three random diseased fields of lung tissue at high power (60 ×), which were scored for the following: (A) neutrophils in the alveolar space (none = 0, 1–5 cells = 1, > 5 cells = 2), (B) neutrophils in the interstitial space/ septae (none = 0, 1–5 cells = 1, > 5 cells = 2), (C) hyaline membranes (none = 0, one membrane = 1, > 1 membrane = 2), (D) Proteinaceous debris in air spaces (none = 0, one instance = 1, > 1 instance = 2), (E) alveolar septal thickening (< 2× mock thickness = 0, 2–4× mock thickness = 1, > 4× mock thickness = 2). To obtain a lung injury score per field, the scores for A–E were then put into the following formula, which contains multipliers that assign varying levels of importance for each phenotype of the disease state.: score = [(20× A) + (14 × B) + (7

$\times C) + (7 \times D) + (2 \times E)]/100$. The scores for the three fields per mouse were averaged to obtain a final score ranging from 0 to and including 1.

Diffuse Alveolar Damage (DAD) Tool. The second histological tool to quantitate lung injury was reported by Schmidt et al.⁵⁰. DAD is the pathological hallmark of ALI^{49,50}. Three random diseased fields of lung tissue were score at high power (60 ×) for the following in a blinded manner: 1 = absence of cellular sloughing and necrosis, 2 = Uncommon solitary cell sloughing and necrosis (1–2 foci/field), 3 = multifocal (3 + foci) cellular sloughing and necrosis with uncommon septal wall hyalinization, or 4 = multifocal (>75% of field) cellular sloughing and necrosis with common and/or prominent hyaline membranes. The scores for the three fields per mouse were averaged to get a final DAD score per mouse.

MERS-CoV genomic RNA qRT-PCR. Mouse lungs were stored in RNeasy (ThermoFisher) at -80°C until processed via homogenization in TRIzol (Invitrogen). Total RNA was isolated using Direct-zol RNA MiniPrep kit (Zymo Research). Previously published TaqMan primers were synthesized by Integrated DNA Technologies (IDT) to quantify MERS genomic RNA (targeting orf1a. Forward: 5'-GCACATCTGTGGTTCTCCTCTCT-3', Probe (6-FAM/ZEN/IBFQ): 5'-TGCTCCAACAGTTACAC-3', Reverse: 5'-AAGCCCAGGCCCTACTATTAGC)⁵¹. qRT-PCR was performed using 100ng total RNA compared to an RNA standard curve using TaqMan Fast Virus 1-Step Master Mix (ThermoFisher) on a Quant Studio 3 (Applied Biosystems).

nsp12 phylogenetic analysis and conservation modeling. Coronavirus RdRp (nsp12) protein sequence alignments and phylogenetic trees were generated using Geneious Tree Builder in Geneious Prime (version 2020.0.5) and visualized using Evolview (<https://www.evolgenius.info/evolview/>). Protein similarity scores were calculated using Blossum62 matrix. The accession numbers used were : PDCoV (KR265858), AIBV (NC_001451), HCoV-229E (JX503060), PEDV (NC_003436), MHV (AY700211), HCoV-HKU1 (DQ415904), HCoV-NL63 (JX504050), HCoV-OC43 (AY903460), HKU5-1 (NC_009020), MERS-CoV (JX869059), HKU9-4 (EF065516), 2019-nCoV (MN996528), HKU3-1 (DQ022305), SHC014 (KC881005), WIV1

(KF367457), SARS-CoV (AY278741). Amino acid conservation scores of coronavirus RdRp were generated using ConSurf Server (<https://consurf.tau.ac.il/>) using the protein alignment described above and visualized on the SARS-CoV RdRp structure (PDB: 6NUR) in PyMol (version 1.8.6.0)^{20,52}.

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

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

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Author contributions: A.C.S., T.P.S, designed *in vitro* efficacy studies. A.C.S., A.J.B., T.P.S. and R.L.G. executed and/or analyzed *in vitro* efficacy studies. J.H., A.T. and N.J.T. providing the clinical isolate of SARS-CoV-2. T.P.S., A.A.K., M.G.N., G.P. and R.S.B. designed *in vivo* efficacy studies. T.P.S., A.C.S., S.Z., C.S.H, and R.S. designed, executed and/or analyzed the Primer ID NGS data. K.H.D 3rd performed structural

modeling and phylogenetics and sequence alignments. M.L.A., A.J.P., J.D.C. and M.R.D. designed, performed and/or executed the construction of RDV resistant MHV and performed cross-resistance studies. T.P.S., A.S. and S.R.L. executed and analyzed *in vivo* efficacy studies. A.S. and S.R.L. performed whole body plethysmography for *in vivo* studies. S.A.M. assessed all lung pathology. G.R.B., and M.S., were responsible for synthesis, and scale-up of small molecules. T.P.S., A.C.S., S.Z., S.R.L., A.S., K.H.D. 3rd, M.L.A., A.J.P., J.D.C., G.R.B., A.A.K., G.P., R.S. M.R.D., and R.S.B., wrote the manuscript.

Disclaimers

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Names of specific vendors, manufacturers, or products are included for public health and informational purposes; inclusion does not imply endorsement of the vendors, manufacturers, or products by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

Competing financial interests: A.C.S. received a contract from NIAID to support the *in vitro* and *in vivo* efficacy studies reported herein. UNC is pursuing IP protection for Primer ID and R.S. has received nominal royalties.

Figures

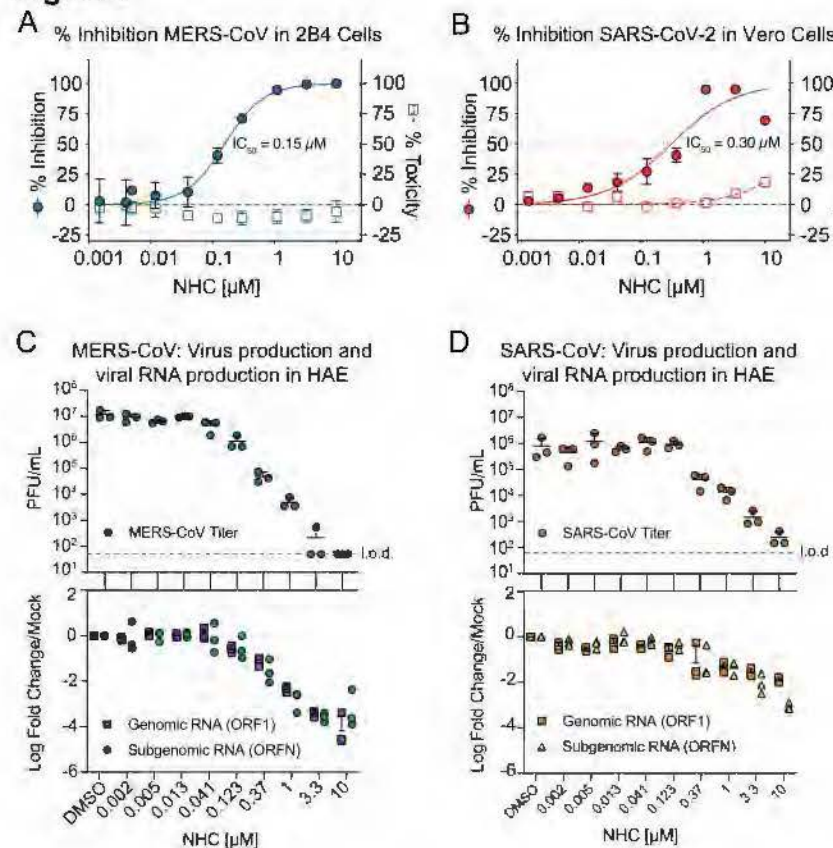


Figure 1: NHC potentially Inhibits MERS-CoV, SARS-CoV and newly emerging SARS-CoV-2

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

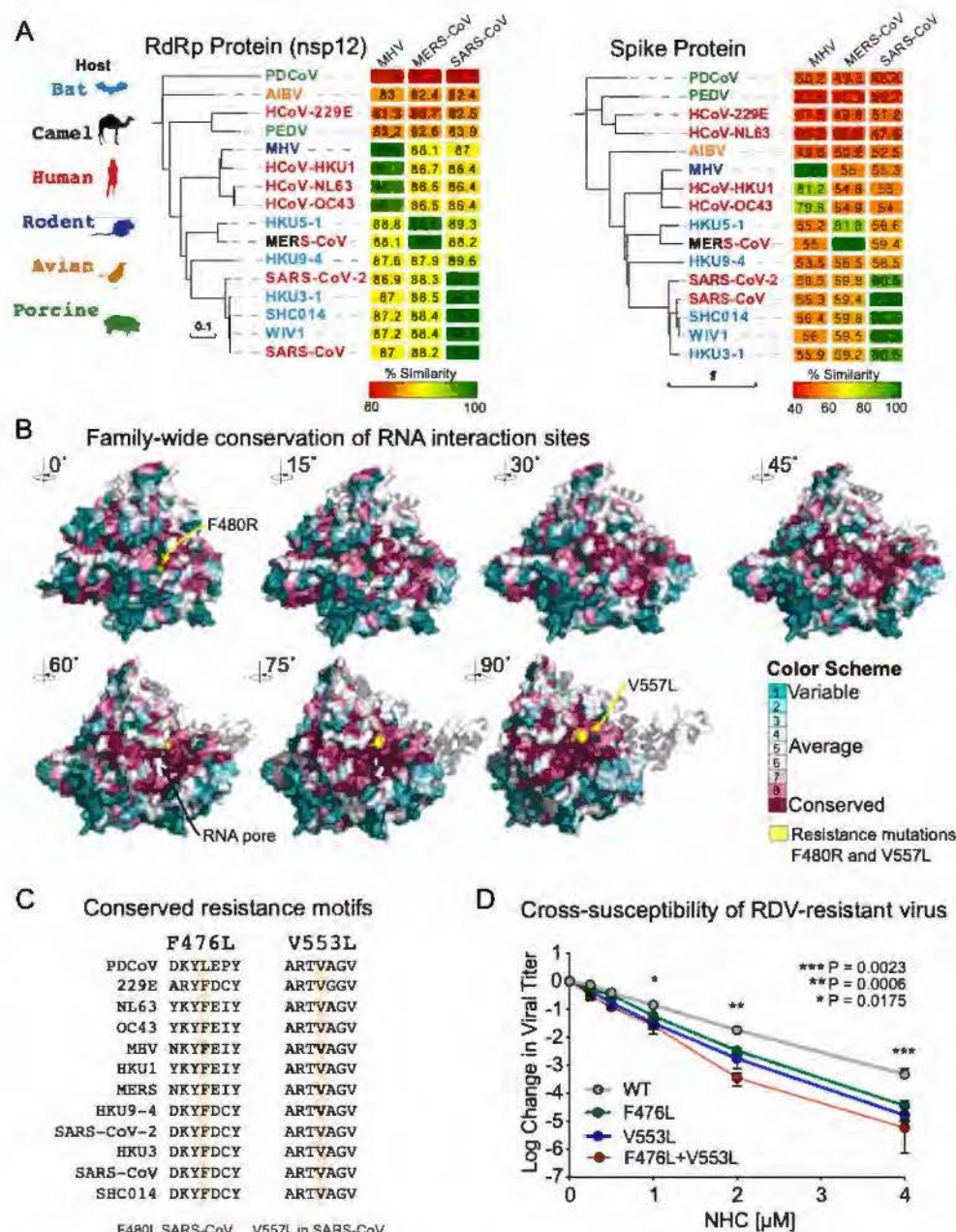


Figure 2

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

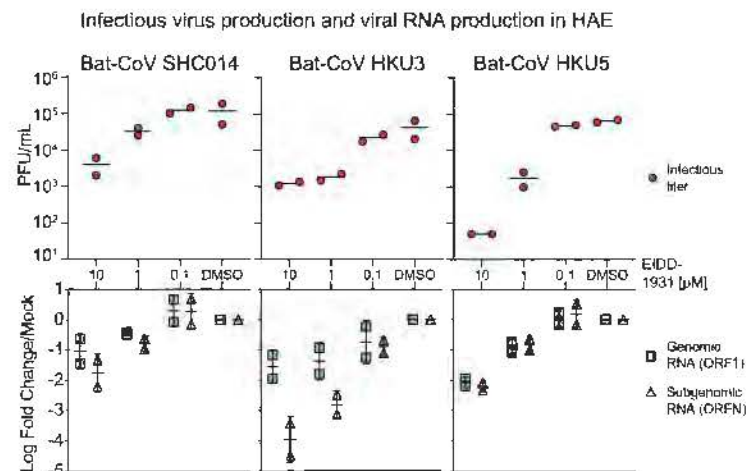


Figure 3: NHC is effective against multiple genetically distinct Bat-CoV. Top: Antiviral efficacy of NHC in HAE cells against SARS-like (HKU3, SHC014, group 2b) and MERS-like (HKU5, group 2c) bat-CoV. HAE cells were infected at an MOI of 0.5 in the presence of NHC in duplicate. After 48 hours, virus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

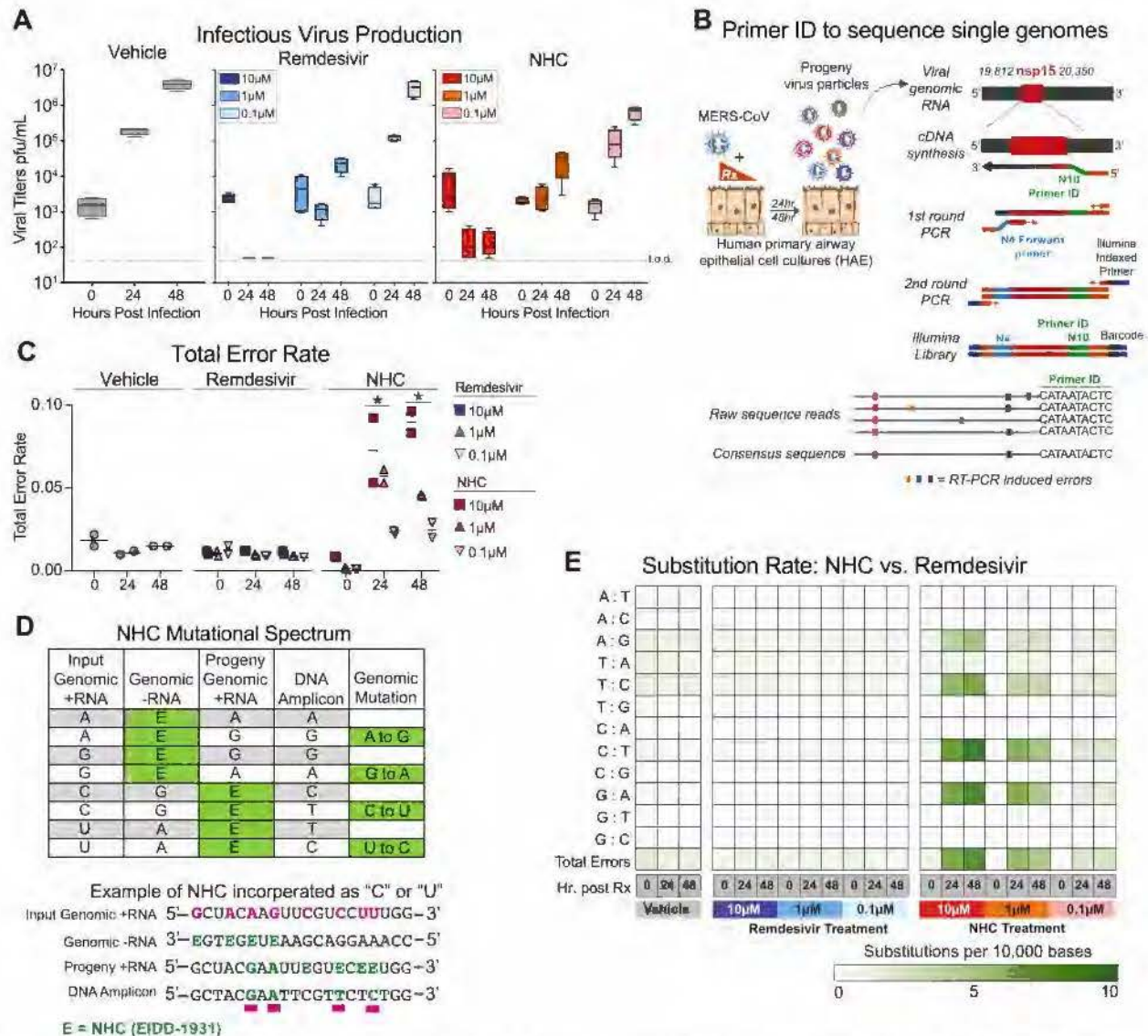


Figure 4: NHC antiviral activity is associated with increased viral mutation rates. **a**, Both remdesivir (RDV) and NHC reduce MERS-CoV infectious virus production in primary human HAE. Cultures were infected with MERS-CoV red fluorescent protein (RFP) at an MOI of 0.5 in duplicate in the presence of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

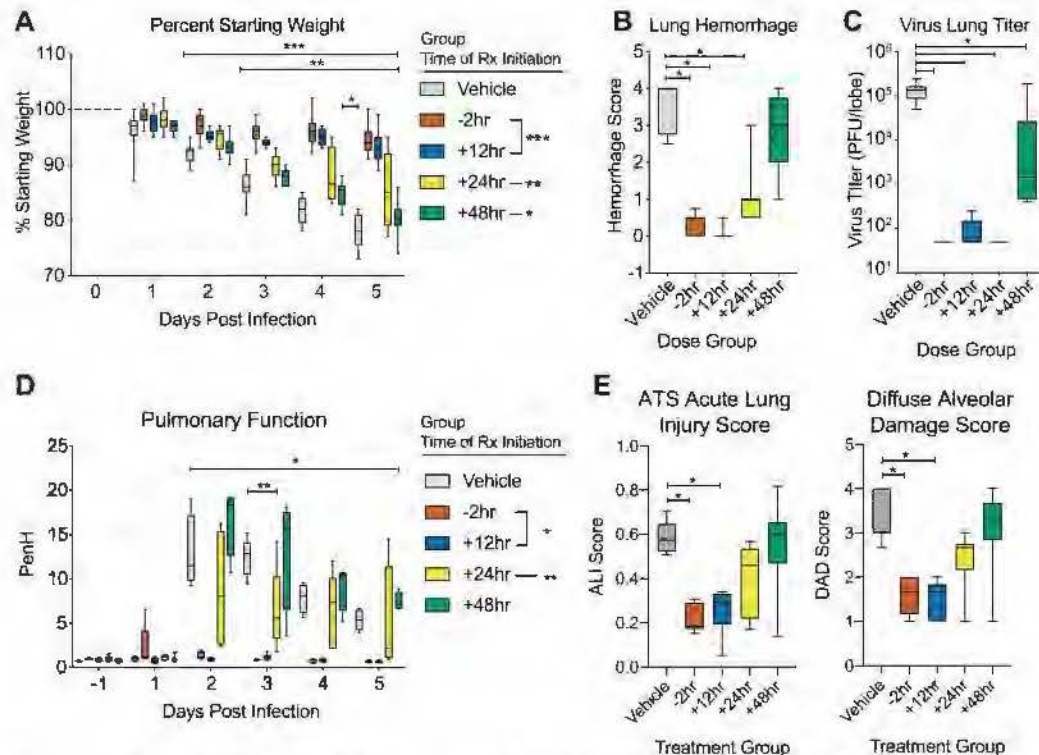


Figure 5: Prophylactic and Therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis. Equivalent numbers of 25-29 week old male and female C57BL/6 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801 beginning at -2hr, +12, +24 or +48hr post infection and every 12hr thereafter by oral gavage (n = 10/group). Mice were intranasally infected with 1E+04 PFU mouse-adapted SARS-CoV MA15 strain. **a**, Percent starting weight. Asterisks indicate differences by two-way ANOVA with Tukey's multiple comparison test. **b**, Lung hemorrhage in mice from panel **a** scored on a scale of 0-4 where 0 is a normal pink healthy lung and 4 is a diffusely discolored dark red lung. **c**, Virus lung titer in mice from panel **a** as determined by plaque assay. Asterisks in both panel **b** and **c** indicate differences by one-way ANOVA with a Dunnett's multiple comparison test. **d**, Pulmonary function by whole body plethysmography was performed daily on five animals per group. Asterisks indicate differences by two-way ANOVA with a Dunnett's multiple comparison test. **e**, Therapeutic EIDD-2801 reduces acute lung injury (ALI). The histological features of ALI were blindly scored using the American Thoracic Society Lung Injury Scoring system and a Diffuse Alveolar Damage Scoring System. Three randomly chosen high power (60X) fields of diseased lung were assessed per mouse. The numbers of mice scored per group: Vehicle N = 7, -2hr N = 9, +12hr N = 9, +24hr N = 10, +48hr N = 9. Asterisks indicate statistical significance by Kruskal-Wallis with a Dunn's multiple comparison test. For all panels, the boxes encompass the 25th to 75th percentile, the line is at the median, while the whiskers represent the range.

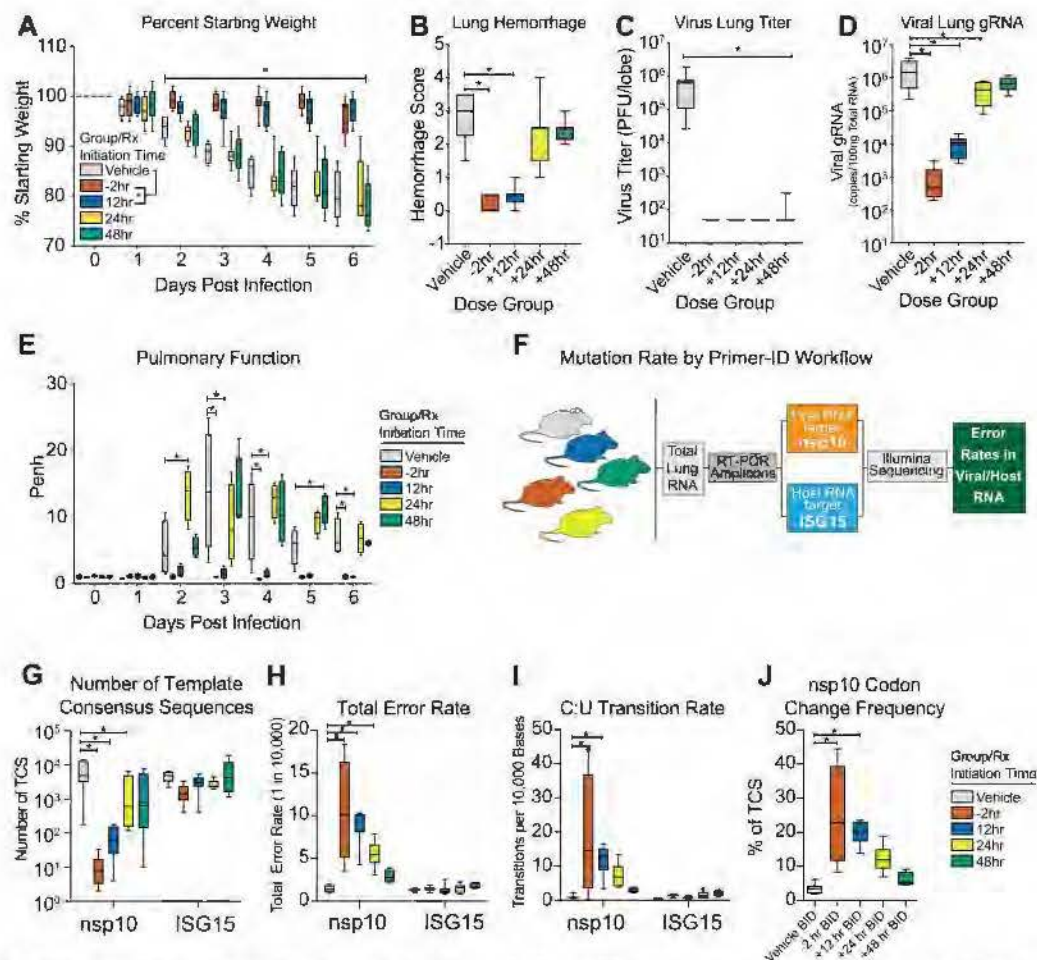
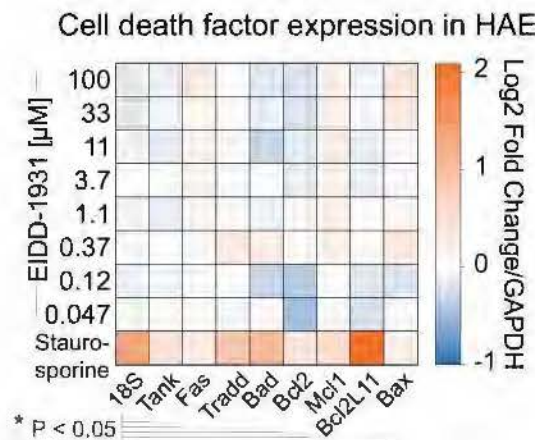
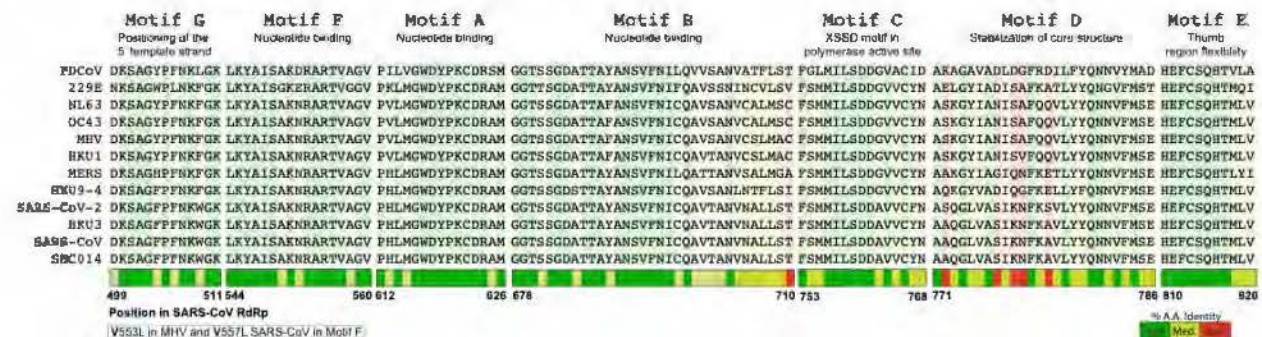


Figure 6: Prophylactic and therapeutic EIDD-2801 reduces MERS-CoV replication and pathogenesis coincident with increased viral mutation rates. Equivalent numbers of 10-14 week old male and female C57BL/6 hDPP4 mice were administered vehicle (10% PEG, 2.5% Cremophor RH40 in water) or NHC prodrug EIDD-2801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

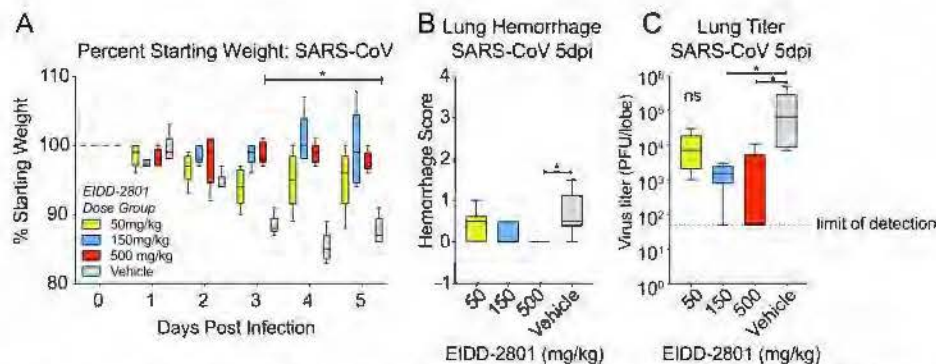


Supplementary Figure 1: Assessment of cytotoxicity of NHC in primary human epithelial cell cultures by qRT-PCR. Companion figure to Figure 1c and d. Primary human epithelial cell cultures were exposed to positive control 1 μ M staurosporine or a dose response of NHC for 48hr. Cytotoxicity was assessed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

Conservation of key RdRp motif residues

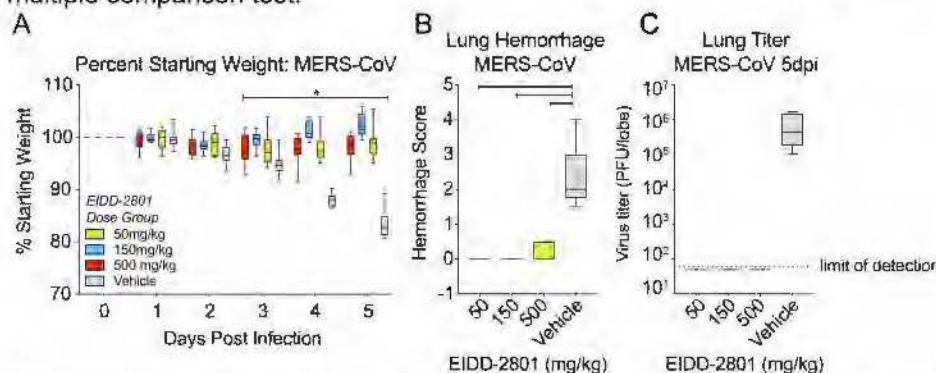


Supplementary Figure 2: High conservation of RdRp functional domains for SARS-CoV-2. Companion figure to Figure 2a. Multiple sequence alignment of the RNA dependent RNA polymerase (RdRp) from viruses in the dendrogram in Figure 2a showing high conservation in the RdRp structural motifs A-G.



Supplementary Figure 3: Prophylactic EIDD-2801 reduces SARS-CoV replication and

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



Supplementary Figure 4: Prophylactic EIDD-2801 reduces MERS-CoV replication and

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

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

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

* Validated assays available from Life Technologies

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

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

Primer	5'-3'	Comment
41R_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTATGACCTTCCTGTTGCTTCT	cDNA primer. Targeting 20331-20350 on the reference genome.
nsp10_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTCCTAAAGACGACATCAGTGG	cDNA primer. Targeting 13488-13507 on the reference genome.
nsp12_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTATAGCCAAAGACACAAACCG	cDNA primer. Targeting 15983-16002 on the reference genome.
nsp14_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTGAACATCGACAAAGAAAGGG	cDNA primer. Targeting 18715-18734 on the reference genome.
ifit3_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTTTCAGCCACTCCTTATCCC	cDNA primer. Targeting mice IFIT3 mRNA.
isg15_PID11	GTGACTGGAGTTCAGACGTGTGCTCTTCCGATCTNNNNNNNNNNNC AGTGGGGCTTTAGGCCATACTC	cDNA primer. Targeting mice ISG15 mRNA.
41F_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNGCTA CAAGTTCGTCCTTTGG	1 st round PCR forward primer. Targeting 19812-19831 on the reference genome
nsp10_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNTGCT CAGGTGCTAAGCGAAT	1 st round PCR forward primer. Targeting 12983-13002 on the reference genome
nsp12_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATAG GCTTCGATGTTGAGGG	1 st round PCR forward primer. Targeting 15388-15407 on the reference genome
nsp14_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNNATTG CAAGCTGGTTCTAACA	1 st round PCR forward primer. Targeting 18260-18279 on the reference genome
ifit3_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNCGAT CCACAGTGAACAACAG	1 st round PCR forward primer. Targeting mice IFIT3 mRNA.
isg15_AD	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAGNNNTGG GACCTAAAGGTGAAGATG	1 st round PCR forward primer. Targeting mice ISG15 mRNA.
Adapter R	GTGACTGGAGTTCAGACGTGTGCTC	1 st round PCR reverse primer
Universal Adapter	AATGATACGGGACCACCGAGATCTACACGCCTCCCTCGCGCCATC AGAGATGTG	2 nd round PCR forward primer with Illumina adapter sequence
Indexed Adapter	CAAGCAGAAGACGGCATACGAGATNNNNNNNGTACTGGAGTTCAG ACGTGTGCTC	2 nd round PCR reverse primer with Illumina adapter sequence and indices (NNNNNNN)
Old Nextera	GCCTCCCTCGCGCCATCAGAGATGTGTATAAGAGACAG	Customized sequencing primer

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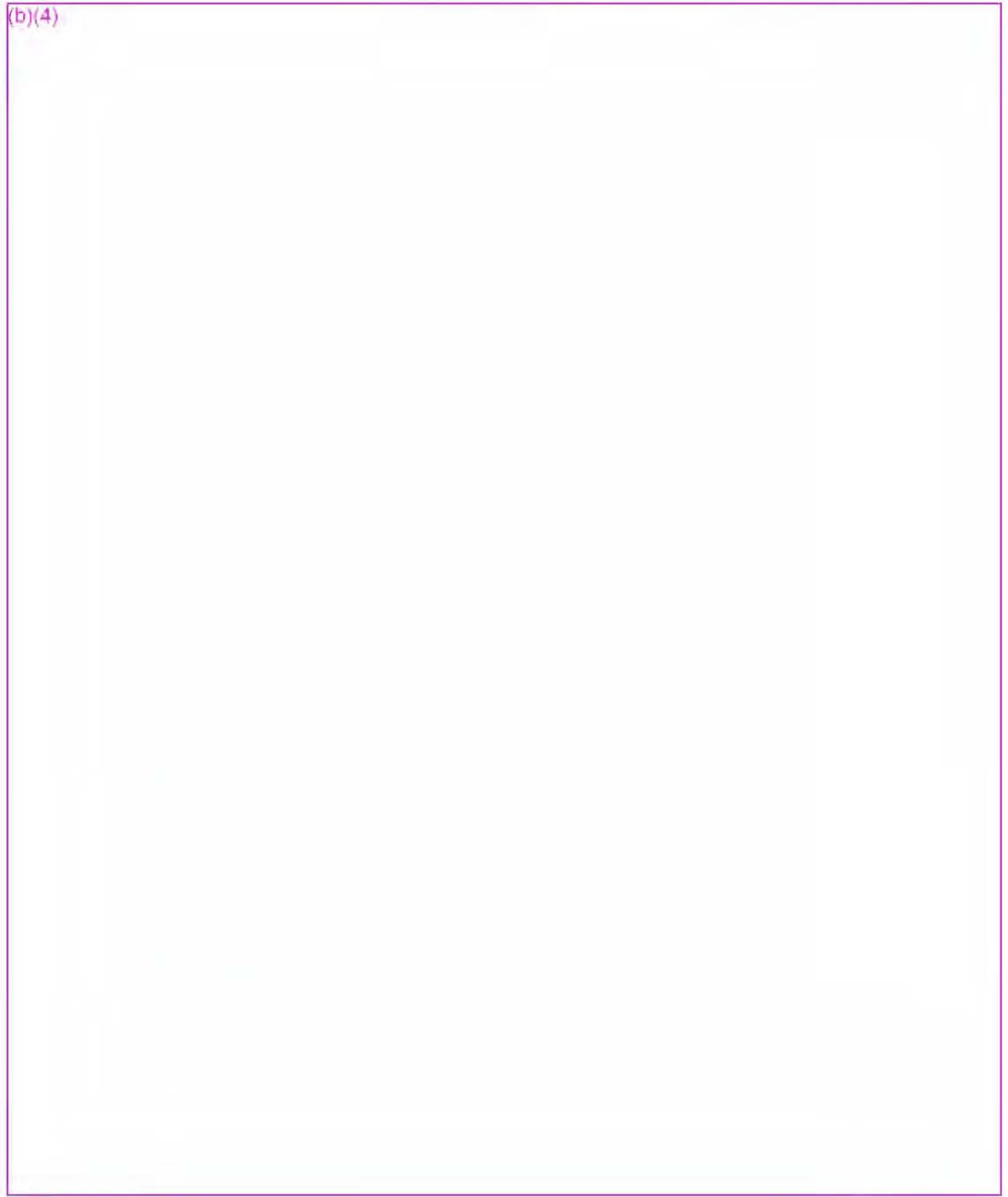
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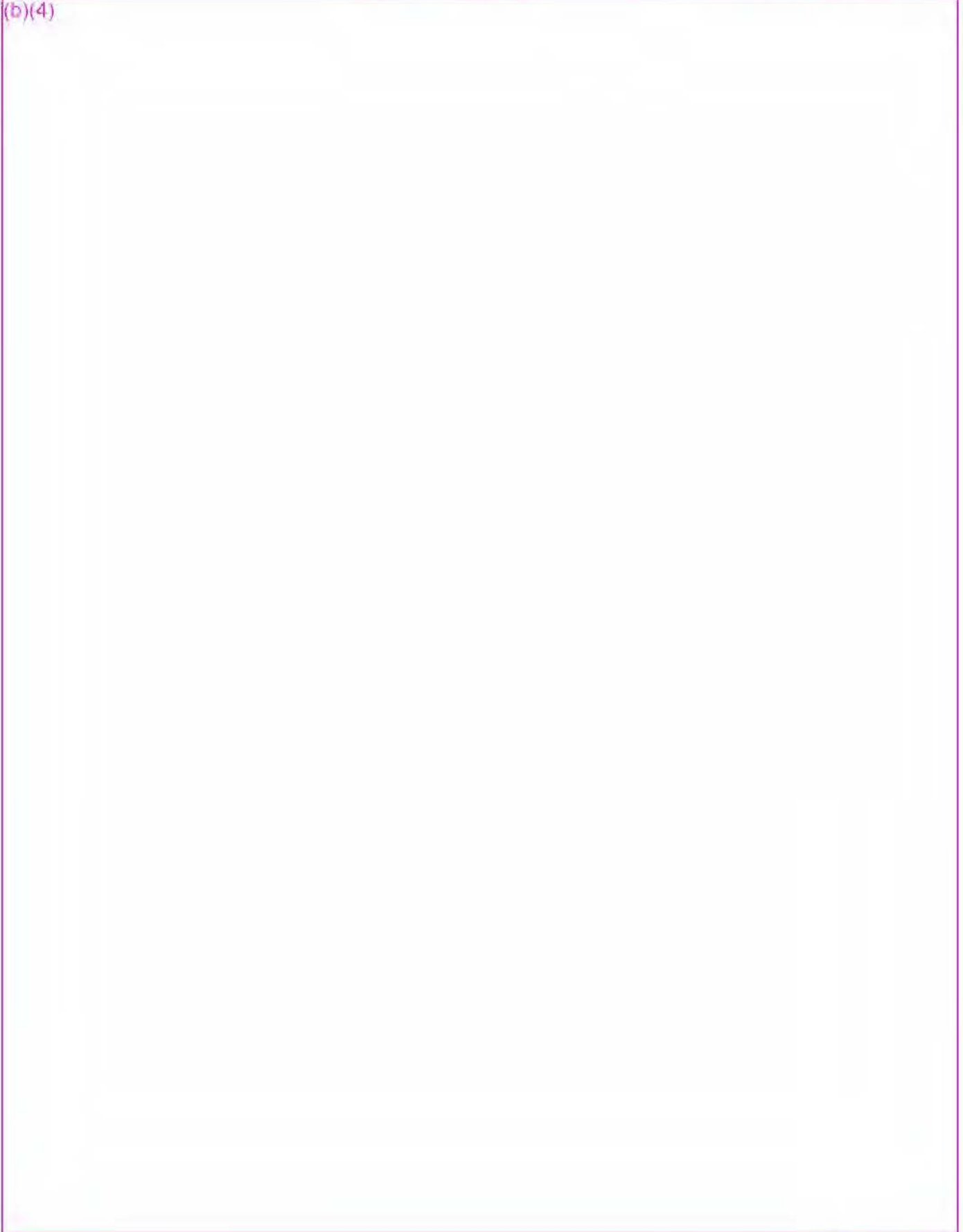
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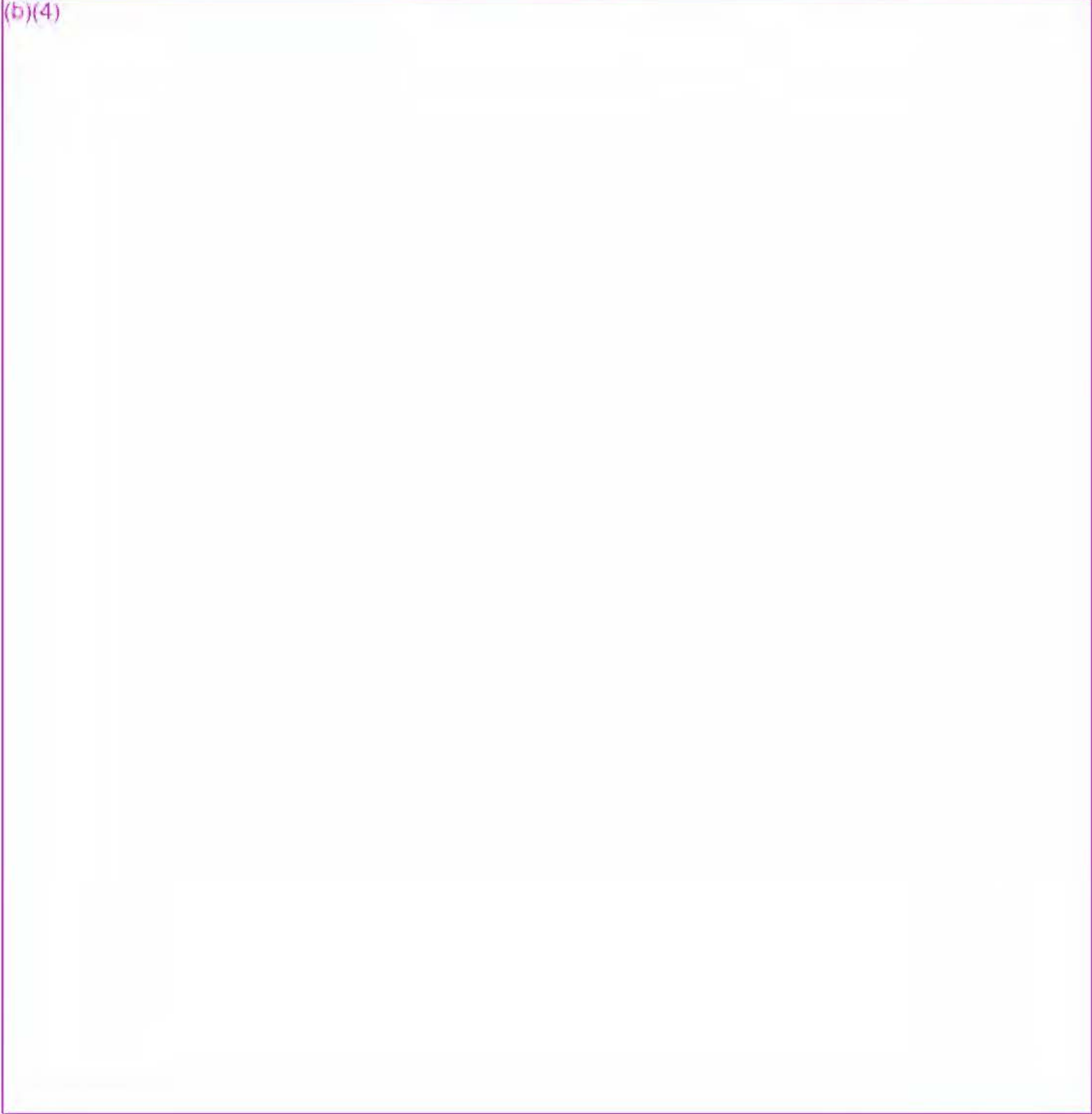
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'Pottol' (b)(6);
Hopkins, Svetlana A CTR USARMY (USA (b)(6);
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Pilia, Marcello CTR USARMY MEDCOM USAMRMC (US (b)(6);
West, Therese A CIV USARMY MEDCOM USAMRMC (US (b)(6);
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Michael Ingram (b)(6);
Rachel Overman (b)(6);
Megan Henline (b)(6);
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Selimovic, Seila (NIH/NIBIB) [E] /o=ExchangeLabs/ou=Exchange Administrative Group
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(FYDIBOHF23SPDLT)/cn=Recipients/cn=649aa75c91dc4824938df63c66e50158-dan.stought
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MacGill, Tracy (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group
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Hunt, Richard (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group
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 O'rourke, Anna (OS/ASPR/BARDA) (CTR) Anna.O'rourke@hhs.gov </o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1b485d31924b40269c895ec4ef27027c-O'rourke, A>;
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 Craig, Michael R. (CDC/DDID/NCEZID/DHQP) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=69fc1c441e114adab2ab338abba9afa5-Craig, Mich
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Subject: nCOV TechWatch, Humanigen, Thereapeutic

Date: 2020/03/24 14:19:00

Start Date: 2020/03/30 13:00:00

End Date: 2020/03/30 13:30:00

Priority: Normal

Type: Appointment

Location: WebEX

OS - ASPR - BARDA - ALL; OS - ASPR - VTC Support; Williams, Deitra (OS/ASPR/BARDA);
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 Tom.winters@nih.gov; <(b)(6)> Hrdina, Chad (OS/ASPR/SPPR); Jones, Juanita
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 Robert (FDA/OC); <(b)(6)> <(b)(6)> Wong, Diana
 (OS/ASPR/SIIM); Butts, Keane (OS/ASPR/BARDA); <(b)(6)> Gorman, Susan
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 (OS/ASPR/SPPR); Cliffer, Kenneth (OS/ASPR/SPPR); Post, Diane (NIH/NIAID) [E]; Shabman, Reed
Attendees: (NIH/NIAID) [E]; Uyeki, Timothy M. (CDC/DDID/NCIRD/ID); Gin, Julia (OS/ASPR/SPPR); Delaney, Lisa
 (CDC/NIOSH/OD); Peterson, Jeff (CDC/NIOSH/NPPTL/CVSDB); Dowell, Chad (CDC/NIOSH/OD);
 D'Alessandro, Maryann M. (CDC/NIOSH/NPPTL); Miller, Colleen S. (CDC/NIOSH/NPPTL/CVSDB);
 Pallansch, Mark A. (CDC/DDID/NCIRD/DVD); Gerber, Susan I. (CDC/DDID/NCIRD/DVD);
 <(b)(6)>
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 <(b)(6)> Marston, Hilary (NIH/NIAID) [E]; Bozick, Brooke (NIH/OD) [E];
 kimberly.taylor3@nih.gov; Sciotti, Rick (NIH/NIAID) [E]; Beanan, Maureen (NIH/NIAID) [E]; Patel,

Anita (CDC/DDID/NCIRD/OD); Mair, Michael (FDA/OC); Measer, Gregory (FDA/OC) (CTR); Carroll, Darin (CDC/DDID/NCEZID/OD); Kuhnert-Tallman, Wendi (CDC/DDID/OD); Osorio, Manuel (FDA/CBER); Florence, Clint (NIH/NIAID) [E]; (b)(6) Honey, Kristen (OS/IOS); Eloff, Benjamin (FDA/CDRH); (b)(6) (b)(6) Tous, Guillermo (OS/ASPR/BARDA) (CTR); Appler, Jessica (OS/ASPR/IO); Weinbaum, Cindy (CDC/DDID/NCIRD/ISD); Davenport, Matthew (OS/ASPR/BARDA); Ulbrandt, Nancy (NIH/NIAID) [E]; Evenhagen, Stuart (OS/ASPR/SPPR); (b)(6) Bentley, Lisa Marie (OS/ASPR/SIIM) (CTR); (b)(6) (b)(6) (b)(6) Loiseau, Jacqueline (OS/ASPR/BARDA) (CTR); Andrews, Sean (OS/ASPR/EMMO); (b)(6) Torrens, Luis (OS/ASPR/EMMO); Deckhut, Alison (NIH/NIAID) [E]; Breen, Joseph (NIH/NIAID) [E]; Flowers, Artensie (OS/ASPR/EMMO); Ramirez, Gabriela (OS/ASPR/EMMO); Lee, Sherline (OS/ASPR/EMMO); Parkinson, Elizabeth (OS/ASPR/EMMO); Marks, Lucia (OS/ASPR/EMMO); Staley, Michael (OS/ASPR/EMMO); Miron, Claudia (OS/ASPR/EMMO); White, Catalina (OS/ASPR/EMMO); Mittar, Dev (OS/ASPR/BARDA) (CTR); Howell, David (OS/ASPR/SPPR); (b)(6) Michelle.holko@pif.gov; Vaught, Andrea (OS/ASPR/BARDA) (CTR); (b)(6) (b)(6) Ezernack, Paige (OS/ASPR/SPPR); Hamel, Joseph (OS/ASPR/IO); Lombardini, Eric (OS/ASPR/IO); Leary, Adam (OS/ASPR/SPPR); (b)(6) Clay, Matt (OS/ASPR/SIIM) (CTR); keith.bayha@associates.hq.dhs.gov; Silverman, Matthew (FDA/ORA); (b)(6) Regan, Patrick M (FDA/ORA); michael.staley@cdc.hhs.gov; Cioce, Vittoria (OS/ASPR/BARDA) (CTR); Lee, Sherline (ASPR/SNS); Parkinson, Elizabeth (ASPR/SNS); Marks, Lucia K. 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(CDC/DDPHSIS/CPR/DSLRL); Torosian, Stephen (FDA/ORA); Bader, Judith (NIH/NCI) [V]; Asher, Jason (OS/ASPR/SIIM) (CTR); Durham, David (OS/ASPR/SIIM) (CTR); Burney, Tabinda (OS/ASPR/OEM) (CTR); Singer, Lawrence (OS/ASPR/BARDA) (CTR); Peavy, Rosha (OS/ASPR/MFHC); Volkow, Nora (NIH/NIDA) [E]; (b)(6) Sazonova, Irina (NIH/NIDA) [E]; (b)(6) (b)(6) Mu, Lillian (OS/ASPR/BARDA) (CTR); (b)(6) (b)(6) (b)(6); (b)(6) Hogdahl, Thomas (OS/ASPR/BARDA) (CTR); Harvath, Liana (OS/ASPR) (CTR); Gautreau, Marc (HHS/ASPR) (CTR); Jubelt, Lindsay (HHS/ASPR; OS CIP (HHS/OS); Dicarlo-Cohen, Andrea (NIH/NIAID) [E]; Sheoran, Anita (NIH/NIAID) [E]; Nguyen, Tam (NIH/NIAID) [E]; Bryant, Paula (NIH/NIAID) [E]; Cassatt, David (NIH/NIAID) [E]; Zeituni, Erin (NIH/NIAID) [E]; Kincaid, Randall (NIH/NIAID) [E]; Higgs, Elizabeth (NIH/NIAID) [E]; Leitner, Wolfgang (NIH/NIAID) [E]; Brown, Lilliana (NIH/NIAID) [E]; Krafft, Amy (NIH/NIAID) [E]; Macchiarini, Francesca (NIH/NIAID) [E]; Salomon, Rachelle (NIH/NIAID) [E]; Rios, Carmen (NIH/NIAID) [E]; Roberts, Chris (NIH/NIAID) [E]; Broughton, Robin (NIH/NIAID) [E]; Hollingsworth, Brynn (NIH/OD) [E]; Davis, Mindy (NIH/NIAID) [E]; Sanz, Patrick (NIH/NIAID) [E]; Schiltz, Helen (NIH/NIAID) [E]; 'Raymond Harris'; Coburn, James (FDA/OC); Lane, Cliff (NIH/NIAID) [E]; Spinelli, Beth (NIH/NIAID) [E]; Spiro, David (NIH/NIAID) [E]; Taliaferro, Lany (NIH/NIAID) [E]; Guina, Tina (NIH/NIAID) [E]; Vedamony, Merriline (NIH/NIAID) [E]; Davey, Richard (NIH/NIAID) [E]; Dowling, William (NIH/NIAID) [E]; Klein, Harvey (NIH/CC/DTM) [V]; Spriggs, Shardell (NIH/NINDS) [E]; Nuzum, Ed (NIH/NIAID) [E]; Jett, David (NIH/NINDS) [E]; Yeung, David (NIH/NINDS) [E]; Eakin, Ann (NIH/NIAID) [E]; O'Connor, Thomas (FDA/CDER); Daniel Harris; Cho, David S (CBER) (FDA/CBER); Hu-Primmer, Jean (FDA/OC); Lee, Sau (FDA/CDER); Scott, Dorothy (FDA/CBER); Schwartz, Suzanne (FDA/CDRH); Graitcer, Samuel B. (CDC/DDID/NCIRD/ISD); Anthony Macaluso; Edward Clayson; Eric Midboe; Erin Milner; George Christopher; Jonathan Phillips; Juanita Grimsley; 'Kimberly Wallace'; 'Melanie Eacho'; 'Sangeeta Underwood'; 'Clayson, Edward T CIV USARMY DOD JPEOCBD (US'; 'Dean, Wendy K CIV USARMY MEDCOM USAMMDA (US'; 'Ramsburg, Katherine J CTR USARMY MEDCOM USAMRMC (US'; 'Pottol'; Hopkins, Svetlana A CTR USARMY (USA; Crowder, Alicia T CIV USARMY MEDCOM USAMRMC (US; Davis, Michael R Col USAF USARMY MEDCOM USAMRMC (US; Johnston, David S LTC USARMY MEDCOM USAMRMC (US; Pilia, Marcello CTR USARMY MEDCOM USAMRMC (US; West, Therese A CIV USARMY MEDCOM USAMRMC (US; Cosing, Sheryl G CTR DHA J-9 (US; (b)(6) Michael Ingram; Rachel Overman; Megan Henline; (b)(6) (b)(6) Selimovic, Seila (NIH/NIBIB) [E]; Gordon, Jennifer (NIH/NIAID) [E]; Stemmy, Erik (NIH/NIAID) [E]; Stoughton, Daniel (NIH/NIAID) [E]; (b)(6) MacGill, Tracy (FDA/OC); Pickett, Thames (NIH/NIAID) [E]; mark.williams4@nih.gov; Ross, Jennifer (FDA/OC); Greene, Carolyn M. 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Lenzilumab: The Only Phase III Ready Asset to Prevent COVID-19 Cytokine Storm and Improve Morbidity and Mortality Lenzilumab is a proprietary Humaneered® anti-human-GM-CSF mAb in development to prevent cytokine storm resulting from CAR-T therapy and graft-versus-host disease (GvHD). The product is owned by Humanigen, Inc. (Humanigen) Lenzilumab has been tested in 113 patients, including severe respiratory disease, and is safe and well-tolerated. Lenzilumab prevents cytokine storm in animal models and this has been published in peer reviewed journals (attached). Humanigen is enrolling patients in a registrational clinical study to demonstrate lenzilumab's ability to prevent cytokine storm associated with CAR-T therapy in collaboration with Kite Pharma, Inc., a Gilead company. We are also in the late planning stages to start a phase III trial with lenzilumab for early treatment of cytokine storm associated with acute GvHD in high risk patients. We are requesting your assistance to repurpose lenzilumab to prevent cytokine storm associated with COVID-19. According to the World Health Organization (WHO), SARS-CoV-2 and its associated clinical syndrome (COVID-19) is a viral pandemic resulting in 15% severe infections (requiring oxygen) and 5% critical infections (requiring mechanical ventilation). WHO estimates the current case fatality rate to be 3-4%. Interventions are urgently needed to prevent severe and critical cases and to prevent ICU stay and mortality resulting from cytokine storm. Although it is not currently known why some patients experience mild or asymptomatic disease, the severe clinical features associated with COVID-19 and other coronaviruses appear to result from a hyper-reactive immune response triggered by the virus that results in cytokine storm even after viral titers begin to fall. This cytokine storm results in an inflammation-induced lung injury. A recent pre-publication, entitled "Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus", supports the hypothesis that cytokine storm-induced immune mechanisms contribute to patient mortality with COVID-19 (attached). The authors note that steroid treatment in such cases has been disappointing in terms of outcome, but suggest that a monoclonal antibody that targets GM-CSF may prevent or curb the hyper-active immune response caused by COVID-19 in this setting. Humanigen believes that the authors' findings are clearly worthy of further investigation, suggesting that to reduce or eradicate ICU care and prevent deaths from COVID-19, an intervention may be needed to prevent cytokine storm. Although tocilizumab has been approved for treatment of cytokine storm based on anecdotal case reports showing limited utility, this agent has no effect on prevention of cytokine storm and can exacerbate cytokine storm in the CNS when given as a preventative measure. Additionally, this and other IL-6 antagonists have black box warnings for the risk of serious infections in patients with pulmonary disease. Safer options to prevent cytokine storm in at-risk patients and prevent ICU admission are urgently needed. Lenzilumab offers a safe, scalable, phase III ready asset that could prevent cytokine storm in at-risk patients and make a significant impact on morbidity, mortality, and healthcare resource utilization

Humanigen	
Host: Ralph Balsamo	
When it's time, start your meeting from here:	
Start the meeting	
When: Monday, March 30, 2020, 1:00 pm (30 mins), Eastern Daylight Time (New York, GMT-04:00).	
Access Information	
Meeting Number:	
(b)(6)	
Password:	
(This meeting does not require a password.)	
Host Key:	
367401 (Use this key during the meeting if you ever need to reclaim the host role.)	
Audio Connection	
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Butts, Keane (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group
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Koerner, John (OS/ASPR/SPPR) /o=ExchangeLabs/ou=Exchange Administrative Group
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Cliffer, Kenneth (OS/ASPR/SPPR) /o=ExchangeLabs/ou=Exchange Administrative Group
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FEMA

Medical Countermeasures Task Force

15 April 2020

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SARS-CoV-2 Medical Countermeasures Task Force

Align MCM development across interagency partners to avoid duplication of effort, identify opportunities for synergy, and fill potential gaps



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MCM Task Force Objectives

- Collaborate across the USG to share data and information critical to accelerate the development, manufacture, and availability of COVID-19 MCMs
- Provide real-time information to leadership for decision-making
- Identify approaches and opportunities to coordinate with interagency partners to accelerate MCM research & development
- Address questions regarding use of currently available MCMs

SARS-CoV-2 Medical Countermeasures Task Force

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Executive Secretary: Christy Ventura, BARDA

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(David) Chris Hassell

DHS Lead
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DoD Lead
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USDA Lead
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**Therapeutic
Prioritization
Sub-Working Group**
Lead: TBD

**NIAID RCT
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Diagnostics Working Group
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Vaccines Working Group
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Dan Wolfe, BARDA

Therapeutics Working Group
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Tina Guina, BARDA

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National Guard LNOs
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LTC Luis Rodriguez, USA
LTC John Syprunowicz, USA
LTC Alisa Englert, USA

Assistant Secretary for Preparedness & Response

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



Biomedical Advanced Research & Development Authority

- Activities (3 bullets)
 - Established and expanding diverse MCM portfolio
 - Working with product developers and USG partners to shorten development timelines
 - Implementing blood products strategy for convalescent and hyperimmune products.
- Major Accomplishments/Contributions
 - Improving diagnostics: Diagnostic funding resulted in 7 EUAs (as of 4/11)
 - Improving therapeutic options: Multiple treatment trials ongoing
 - Over twenty products under development, as well as multiple support efforts (model development, sample collection, etc.)
- Challenges
 - Compressing therapeutic and vaccine development timelines
 - MCM manufacturing scale up/out to include advance acquisition of raw materials

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National Institute of Allergy and Infectious Diseases

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



Food and Drug Administration

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



Centers for Disease Control and Prevention

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



Department of Defense

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



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Department of Homeland Security

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



United States Department of Agriculture

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



Partnering to Improve Preparedness

VACCINES

- Proven platforms
- Large scale manufacturability
- Speed
- Multiple approaches



THERAPEUTICS

- Platform-based monoclonal antibodies
- Repurposed therapeutics
- Host targeted therapeutics



DIAGNOSTICS

Faster and easier to use
More accurate



Earlier Identification



Earlier Treatment

DOMESTIC MANUFACTURING

- Expand production
- Increase fill/finish capacity

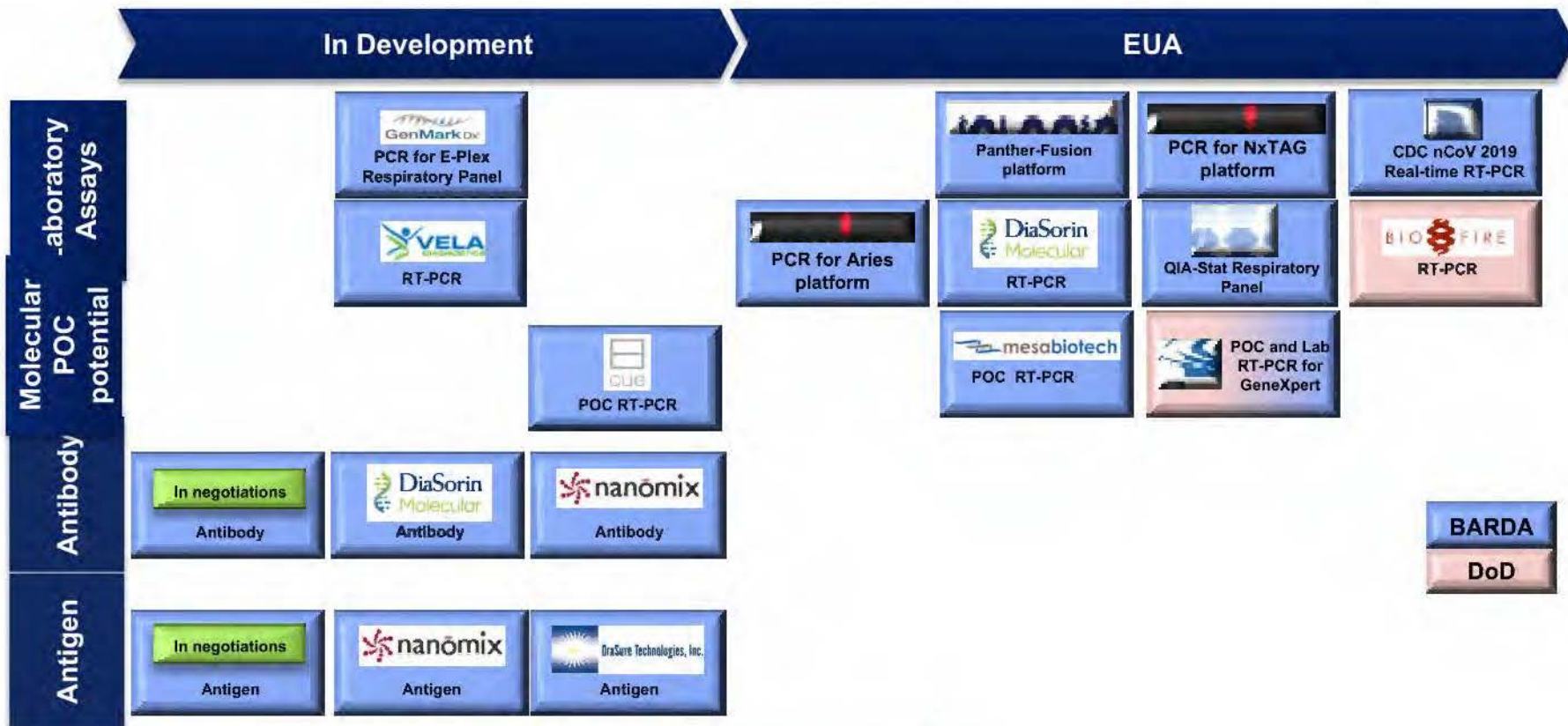


Diagnostics Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



USG-Sponsored SARS-CoV-2 Diagnostic Tests



BARDA
DoD

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Therapeutics Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

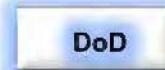


USG-Supported SARS-CoV-2 Therapeutics

Pre-Clinical

Phase 1

Phase 2/3



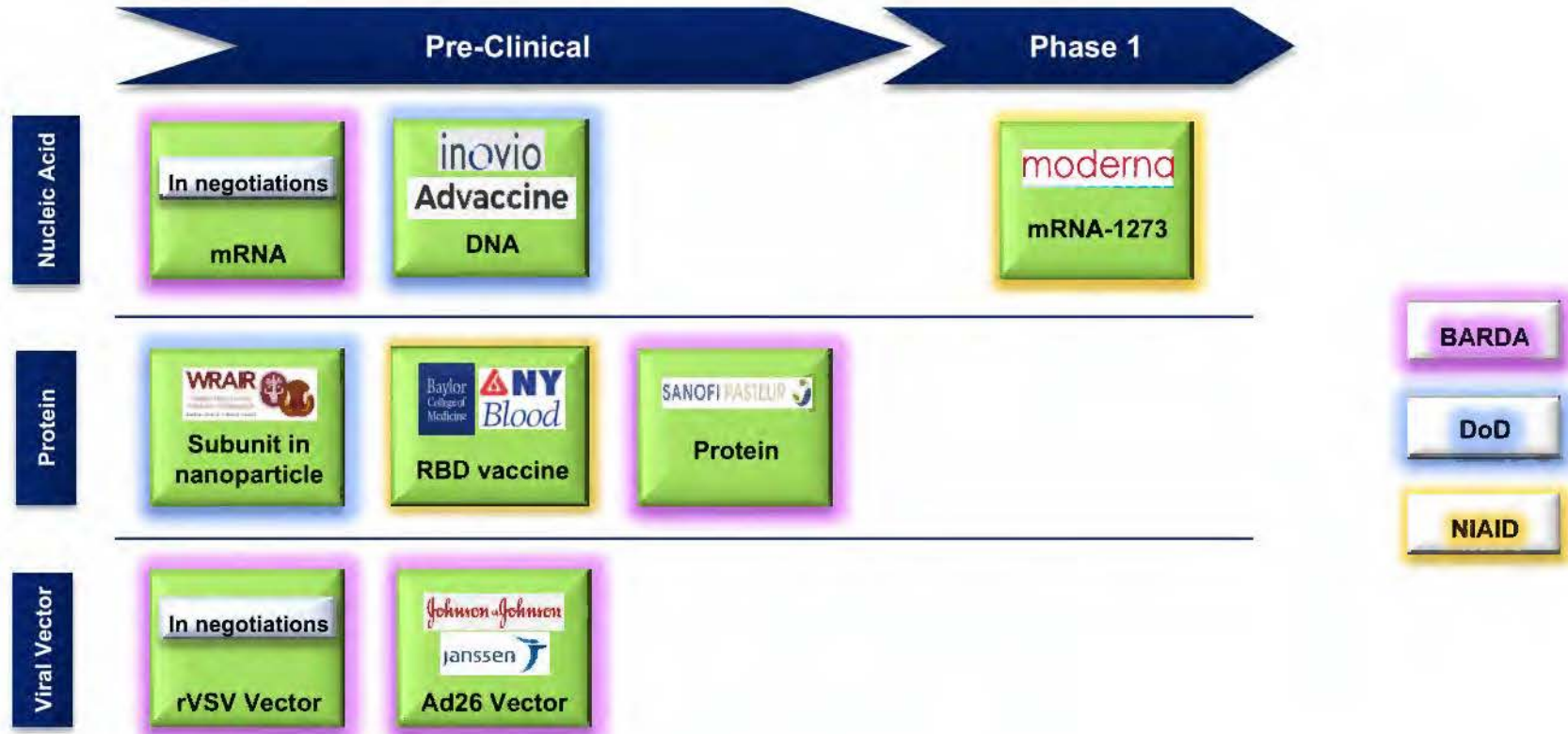
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Vaccines Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)



USG-Supported SARS-CoV-2 Vaccines



Clinical Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Clinical Trials Table

Product Type	Product (Developer)	Primary Endpoint	Target Enrollment	Current Enrollment	Number of Sites	Notes
Therapeutic	Remdesivir (Gilead)	Clinical status assessed at Day 15 using 8-point ordinal scale	700	604	64	Adaptive COVID-19 Treatment Trial; can add new candidates
	Sarilumab (Regeneron & Sanofi)	Phase 2: Time to resolution of fever for 48h Phase 3: Time to improvement (2 points) using 7-point ordinal scale	400	991	53	Adaptive Phase 2/3 design; continuing enrollment beyond initial target
	Tolilizumab (Genentech & Roche)	Clinical status assessed at Day 28 using 7-point ordinal scale	330	9	11	Phase 3 study for COVID-19
	Hydroxy-chloroquine	Clinical status assessed at Day 15 using 7-point ordinal scale	510	44	12	Phase 3 study for COVID-19
Vaccine	mRNA-1273 (Moderna)	Safety & Immunogenicity at 25µg, 100µg & 250µg	45	34	2	Third cohort (250µg) sentinels dosed and in monitoring phase
	INO-4800 (Inovio)	Safety & Immunogenicity at 1 mg and 2 mg, administered days 0, 28	40	Enrolling	2	First cohort
Observational	n/a	Observational study to collect pathological data on COVID-19	N/A	41	5	Department of Defense's "EpiCC" Study; complementary studies in planning phases

Sample Sharing Working Group

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Serology Project Team

- Activities (3 bullets)
- Major Accomplishments/Contributions (3 bullets)
- Challenges (1-2 bullets)

Supply Chain Task Force

- Activities (3 bullets)
 - Major Accomplishments/Contributions (3 bullets)
 - Challenges (1-2 bullets)
-
- providing information about PPE and supply shortages for MCM development, manufacturing, and clinical studies

Manufacturing Scale-up and Procurement

- L