From: Handley, Gray (NIH/NIAID) [E]
Sent: Wed, 8 Jan 2020 21:52:25 +0000
To: Dominique, Joyelle (NIH/NIAID) [E];Chen, Ping (NIH/NIAID) [E];Bernabe, Gayle (NIH/NIAID) [E]
Cc: Lu, Tami (NIH/NIAID) [E];Rosa, William (NIH/NIAID) [E]
Subject: FW: coronavirus countermeasures
Attachments: Current Wuhan Pneumonia Update 1-8-2020.docx

Very good summary. Good to keep. Gray

From: Rojas, Cynthia (NIH/NIAID) [E] (b) (6)
Sent: Wednesday, January 8, 2020 4:37 PM
To: Marston, Hilary (NIH/NIAID) [E] (b) (6)
Cc: Embry, Alan (NIH/NIAID) [E] (b) (6); Folkers, Greg (NIH/NIAID) [E] (b) (6); Lerner, Andrea (NIH/NIAID) [E] (b) (6); Eisinger, Robert (NIH/NIAID) [E] (b) (6); Handley, Gray (NIH/NIAID) [E] (b) (6); Bushar, Nicholas (NIH/NIAID) [E] (b) (6); NIAID BUGS (b) (6)
Subject: RE: coronavirus countermeasures

Good Afternoon Hilary,

The updated summary is attached. We were also able to confirm that the information from the landscape document can be shared publicly. Please let us know if you have any questions or if you need any more information.

Thank you,

Cynthia Rojas

Cynthia M. Rojas, MPH
Communications Health Specialist
Office of Scientific Coordination and Program Operations
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
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5601 Fishers Lane, Room 7G74
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From: Marston, Hilary (NIH/NIAID) [E] (b) (6)
Sent: Wednesday, January 8, 2020 10:15 AM
To: Rojas, Cynthia (NIH/NIAID) [E] (b) (6)
Cc: Embry, Alan (NIH/NIAID) [E] (b) (6); Folkers, Greg (NIH/NIAID) [E] (b) (6); Lerner, Andrea (NIH/NIAID) [E] (b) (6); Eisinger, Robert

(NIH/NIAID) [E] (b) (6); Handley, Gray (NIH/NIAID) [E] (b) (6);
Bushar, Nicholas (NIH/NIAID) [E] (b) (6); NIAID BUGS (b) (6)
Subject: Re: coronavirus countermeasures

Thanks so much! We'll review and noted about NIAID only.

On Jan 8, 2020, at 9:58 AM, Rojas, Cynthia (NIH/NIAID) [E] (b) (6) wrote:

Good Morning Hilary,

The attached document is a landscape analysis for MERS and CEPI produced for us under a TO with OBRRTR. It's a good summary of the current status of the MERS field, including animal models. It can be shared within NIAID, but we have not yet verified if it can be shared publicly, we will circle back once we know whether or not it can be shared.

We are working on gathering additional information for you and will send it to you ASAP.

Thank you,

Cynthia Rojas

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From: Rojas, Cynthia (NIH/NIAID) [E] (b) (6)
Sent: Monday, January 6, 2020 4:26 PM
To: Marston, Hilary (NIH/NIAID) [E] (b) (6); NIAID BUGS (b) (6)
Cc: Embry, Alan (NIH/NIAID) [E] (b) (6); Folkers, Greg (NIH/NIAID) [E] (b) (6); Lerner, Andrea (NIH/NIAID) [E] (b) (6); Eisinger, Robert (NIH/NIAID) [E] (b) (6); Handley, Gray (NIH/NIAID) [E] (b) (6);
Bushar, Nicholas (NIH/NIAID) [E] (b) (6)
Subject: Re: coronavirus countermeasures

Good Afternoon Hilary,

We will look into this for you and will do our best to meet the requested deadline.

Thank you,

Cynthia M. Rojas, MPH
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From: "Marston, Hilary (NIH/NIAID) [E]" (b) (6)
Date: Monday, January 6, 2020 at 3:58 PM
To: NIAID BUGS (b) (6)
Cc: "Embry, Alan (NIH/NIAID) [E]" (b) (6), "Folkers, Greg (NIH/NIAID) [E]" (b) (6), "Lerner, Andrea (NIH/NIAID) [E]" (b) (6), "Eisinger, Robert (NIH/NIAID) [E]" (b) (6), "Handley, Gray (NIH/NIAID) [E]" (b) (6), "Bushar, Nicholas (NIH/NIAID) [E]" (b) (6)
Subject: coronavirus countermeasures

With the caveat that the China pneumonia syndrome etiology is still unreported/unknown to us, ASF is starting to field questions about coronavirus research, esp countermeasures. Would you be able to assemble a summary of diagnostics, therapeutics and vaccine efforts for the viral family, particularly therapeutics? It would also be helpful to know what animal models we have available if needed for testing (should a viral isolate become available).

If it is possible to put something together by the end of the week, we would appreciate it.

Thanks so much,

Hilary

Hilary D. Marston, MD, MPH
Medical Officer and Policy Advisor for Global Health
Immediate Office of the Director
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<MERS-CoV Landscape Analysis_HHSN272201800010I_75N93019F00131_Final 10172019.pdf>

Updated 1/8/2020

Information listed as "pers comm" reflects personal comments from investigators, and may not be verified from public health authorities.

Wuhan Pneumonia Update

Background

- In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause.
- On December 31st the WHO China Country Office was notified of 44 patients with pneumonia of unknown etiology, 11 of which were severely ill.
- As of January 5th, 2020 there are 59 patients with a diagnosis of unknown viral pneumonia is Wuhan, 7 of which are severely ill. At least one patient is on ECMO (Peiris, pers comm 1/6/2020). The earliest case was reported December 12th, and the latest onset was December 29th. All patients are isolated and receiving treatment in Wuhan medical institutions. 163 close contacts have been identified for ongoing medical observation.
- Case-patients in the outbreak are reported to have fever, difficulty breathing, and bilateral lung infiltrates on chest radiography (CDC, http://bit.ly/36GxY3y).
- Hong Kong has added Wuhan Pneumonia to the list of notifiable diseases. As of January 7th, 2020 the Hong Kong Center for Health Protection has reports of 30 cases under enhanced surveillance with recent travel history to Wuhan. https://www.chp.gov.hk/files/pdf/enhanced_sur_pneumonia_wuhan_eng.pdf
- Epidemiological investigation showed that some patients operated businesses in the Wuhan South China Seafood City. As of January 1st, 2020 the market has been closed for environmental sanitation and disinfection.
- There is currently no clear evidence of human-to-human transmission, however one family cluster has been identified. No nosocomial transmission has been seen (Peiris, pers comm 1/6/2020).
- Fragments of coronavirus RNA with an 86% homology to SARS has been found in one patient (Peiris, pers comm 1/6/2020).
- News reports on 1/8/2020 the virus is a novel coronavirus, sequenced in one patient and identified in others.

Related Coronavirus Basic Research

- M51C CoV portfolio has 20 grants (13 basic, 2 Tx, 5 Vx).
- Peter Daszak (R01AI110964-06) is funded for work to understand how coronaviruses evolve and jump to human populations, with an emphasis on bat CoVs and high-risk populations at the human-animal interface. Main foreign sites are in China (including co-investigators at the Wuhan Institute of Virology). Main aims of the award are to characterize the diverse SARS-related CoVs in bat populations, conduct surveillance in human populations, and to characterize the spillover risk of novel CoVs.
    - Work under previous award has identified over 50 SARS-related CoVs, some of which can infect human cells and cause disease in humanized mouse models.
    - This group identified the Swine Acute Diarrheal Syndrome CoV (SADS-CoV), an alpha CoV that caused the death of >20,000 pigs in China.

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- Fang Li (R01AIAI089728-09) is funded to investigate the receptor recognition and cell entry in coronaviruses using structural approaches using spike proteins in complex with receptors. This award found the first evidence of a MERS-related CoV that uses the human receptor and provides evidence of a natural recombination event between bat CoVs.
- Stanley Perlman (P01AI060699-11) leads a team of investigators using mouse models of SARS and MERS to investigate CoV pathogenesis and develop vaccines and therapeutics. Projects focus on age-dependent differences in CoV pathogenesis, cell entry pathways as targets for antiviral strategies, and viral pathogenesis and lung disease.
- Animal Model development:
    - NIAID has directly supported several animal models of MERS-CoV, including adenovirus vector, transgenic human receptor knock-in, humanized mouse, and NHP.
    - Small animal models of MERS-CoV are widely used to understand viral pathogenesis and to test medical countermeasures. Mouse models are most common, particularly Crispr-Cas9 humanized and transgenic strains. Mouse models of MERS-CoV may also require use of a mouse-passaged strain to observe severe disease. Ongoing work by NIAID grantees continues to refine mouse models of MERS-CoV, including expanding to collaborative cross mice.
    - Three NHP species have been used as models of MERS-CoV: the rhesus macaque, common marmoset, and African Green Monkey. Generally, MERS-CoV infection results in viral replication and mild disease, and severity can vary by route of administration. The most severe disease is seen in marmosets.
    - NIAID has an IAA in place with USAMRIID for further development of the African Green Monkey model.
- CEIRS MERS Basic Research Projects:
    - MERS Surveillance (Egypt, Lebanon, Jordan, Tunisia, Algeria, Ethiopia). Ghazi Kayali & Richard Webby (St. Jude Children's Research Hospital); Mohamed Ali (National Research Centre, Egypt). Ongoing surveillance and genomic sequencing of virus from camels in 5 Middle Eastern countries including, Egypt, Tunisia, Algeria, Jordan, and Lebanon; as well as surveillance and sequencing of virus from bats in Lebanon and Ethiopia.
    - Development of methods and their application for the investigation of the animal sources of human infection with MERS CoV. Malik Peiris (University of Hong Kong); Richard Webby (St. Jude Children's Research Hospital). Longitudinal seroepdemiology studies of humans and animals in the Middle East and North Africa will investigate seasonality, routes of transmission, and geographic distribution or MERS-CoV.

Related Coronavirus Diagnostics:

- MERS diagnostics focus on serological evidence of infection and PCR sequencing of samples from patients.
- Developing advanced MERS diagnostics is a portfolio gap, and there is a need to focus on developing rapid, sensitive point-of-care diagnostics (PMCID: PMC6361340).

Related Coronavirus Medical Countermeasures:

Updated 1/8/2020

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- NIAID continues to support the preclinical and clinical development of MERS-CoV vaccines and therapeutics through both grant and contract mechanisms.
- NIAID has developed mouse models of MERS-CoV via both grant and contract mechanisms that can be used for efficacy studies of MERS-CoV MCMs.
- NIAID preclinical services can provide *in vitro* and *in* vivo screening of vaccines and therapeutics for MERS and SARS.

Vaccines. Work on vaccines has identified several candidates that produce a robust neutralizing antibody response. One vaccine candidate has completed a Phase I trial and three others are beginning Phase I or II trials.

- Vaccine candidates in Phase I trials: ChAdOx1 (NCT04170829, NCT03399578, Oxford Univ), MVA-MERS-S (NCT04119440, IDT), BVRS-GamVac (NCT04128059, Russian MoH).
- Vaccine Candidates in Phase II trials: GLS-5300 (Inovio), BVRS-GamVac (NCT04130594, Russian MoH).
- CEPI is supporting MERS vaccine development with candidates from Inovio (DNA Spike), Themis (measles vector), IDT (MVA vector), and Oxford University (ChAd vector).
- A Phase I clinical trial of a MERS DNA vaccine (Inovio) was conducted at WRAIR finding the vaccine was safe and well-tolerated.
- The VRC and collaborators have stabilized the MERS-CoV spike protein in its prefusion conformation. The stabilized spike protein is potently immunogenic and elicits protective antibodies to the receptor binding domain, n-terminal domain and other surfaces of the spike protein. The stabilized coronavirus spike protein, and mRNA expressing the spike protein through collaboration with Moderna Therapeutics, is currently being evaluated in the humanized DPP4 mouse model at UNC.
- Extramural grantees are developing MERS vaccine candidates including recombinant spike receptor binding domain protein (Lanying Du, NY Blood Center; Hotez, Baylor; Jason McLellan UT Austin), vaccine/adjuvant combinations (Ralph Baric, UNC), viral-like particles and live-attenuated MERS-CoV vaccines (Gallagher, Enjuanes; P01 to University of Iowa), Rabies virus vectored (Schnell, Frieman; Jefferson U, UMD)

Therapeutics. Currently no therapeutics approved. Overall candidates are in early stages along the drug development pipeline, however two antibody therapeutics have been tested in Phase I clinical trials.

- NIAID grants and contracts have supported efforts to develop a monoclonal antibody therapeutics for MERS-CoV (REGN3048 and REGN3051; PMC4507189). Efficacy studies were supported via DMID TO and NHP studies performed at RML (PMID: 29885377). A Phase I clinical trial was conducted at NIAID's Phase I Clinical Trial Units, and was completed in 2019 (NCT03301090).
- NIAID supported GLP toxicology and tissue cross reactivity studies for an IND for a human polyclonal antibody produced in transchromosomic cows (SAB 301). A Phase I trial was conducted at DCR (PMCID: PMC5871563). NIAID will hold the US IND for a Phase II/III trial to be conducted in the Kingdom of Saudi Arabia. Currently the protocol is under development and the trial is anticipated to start in Q3/Q4 2020.

Updated 1/8/2020

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- A number of other therapeutic strategies have been tested (convalescent plasma, lopinavir/ritonavir, ribavirin, interferon), however small case numbers have made it difficult to assess their impact on morbidity and mortality in infected patients (PMID: 3023653).

Updated 1/8/2020

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Appendix 1: Currently funded M51C CoV Grants

PI Name	Title	Grant	Proj Start	Proj End	Abs	Objective
SIMS, AMY C	How MERS-CoV Regulates Innate Immunity in Primary Human Lung Cells	1 R21 AI146872-01	2019/06/05	2021/05/31	Abs	Basic
KIRCHDOERFER, ROBERT NICHOLAS	Structural Studies of the Coronavirus Life Cycle	4 R00 AI123498-03	2019/12/18	2021/11/30	Abs	Basic
GRAEPEL, KEVIN WHITTLE	Roles of replication fidelity in viral RNA synthesis, population diversity, and overall fitness of coronaviruses	5 F30 AI129229-03	2017/01/13	2020/10/12	Abs	Basic
FEHR, ANTHONY R	Investigating How ADP-ribosylation Impacts Innate Immunity During Coronavirus Infection	5 K22 AI134993-02	2018/12/07	2020/11/30	Abs	Basic
BAKER, SUSAN C	Mechanisms of viral proteases in coronavirus replication and pathogenesis	5 R01 AI085089-10	2010/07/01	2020/06/30	Abs	Basic
LI, FANG	Receptor recognition and cell entry of coronaviruses	5 R01 AI089728-09	2016/06/07	2021/05/31	Abs	Basic
BARIC, RALPH S	Determinants of Coronavirus Fidelity in Replication and Pathogenesis	5 R01 AI108197-07	2013/08/01	2023/02/28	Abs	Basic
BARIC, RALPH S	Mechanisms of MERS-CoV Entry, Cross-species Transmission and Pathogenesis	5 R01 AI110700-05	2015/04/20	2020/03/31	Abs	Basic
MAKINO, SHINJI	New Paradigm for Host and Viral Gene Regulation by MERS Coronavirus nsp1	5 R01 AI114657-05	2015/05/01	2020/04/30	Abs	Basic
PERLMAN, STANLEY	Role of eicosanoids in pathogenic human CoV infections	5 R01 AI129269-04	2016/09/23	2021/08/31	Abs	Basic
DANIEL, SUSAN	Structural and functional analysis of the coronavirus spike protein fusion peptide	5 R01 AI135270-02	2018/08/09	2022/07/31	Abs	Basic
WEISS, SUSAN R	MERS coronavirus: antagonism of double-stranded RNA induced host response by accessory proteins	5 R01 AI140442-02	2018/05/24	2023/04/30	Abs	Basic

Updated 1/8/2020

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PERLMAN, STANLEY	PPG: SARS-CoV-host cell interactions and vaccine development	5 P01 AI060699-13	2004/07/01	2022/07/31	Abs	Basic/Vx
CHANG, KYEONG-OK	Small Molecule Protease Inhibitors against MERS-CoV	5 R01 AI130092-02	2018/05/15	2023/04/30	Abs	Tx
BARIC, RALPH S	Broad-spectrum antiviral GS-5734 to treat MERS-CoV and related emerging CoV	5 R01 AI132178-03	2017/08/09	2022/07/31	Abs	Tx
BARIC, RALPH S	Respiratory Virus Vaccine and Adjuvant Exploration	1 U01 AI149644-01	2019/04/19	2024/03/31	Abs	Vx
MCLELLAN, JASON SCOTT	Structure, Function and Antigenicity of Coronavirus Spike Proteins	5 R01 AI127521-03	2017/02/09	2022/01/31	Abs	Vx
DU, LANYING	Rational design and evaluation of novel mRNA vaccines against MERS-CoV	5 R01 AI137472-02	2018/02/13	2023/01/31	Abs	Vx
DU, LANYING	Structure-based design of coronavirus subunit vaccines	5 R01 AI139092-02	2018/05/21	2023/04/30	Abs	Vx
WHITTAKER, GARY R	Development of a subunit vaccine for MERS-CoV and other emerging coronaviruses	5 R21 AI135373-02	2018/06/06	2020/05/31	Abs	Vx