NIAID Response to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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NIAID, NIH, DHHS
SARS-CoV-2/COVID-19 Medical Countermeasures Task Force

SARS-CoV-2/COVID-19 MCM Task Force

- Therapeutics
- Vaccines
- Diagnostics
- Clinical Trials
NIAID Accelerating SARS-CoV-2 Research

- Improve understanding of SARS-CoV-2/COVID-19
- Evaluate potential cross-reactivity with existing SARS/MERS vaccine candidates (and antibodies)
- Develop SARS-CoV-2 vaccine candidates
- Provide resources to facilitate vaccine development
Current Funding Opportunities

- Notice of Special Interest Regarding the Availability of Urgent Competitive Revisions for Research on the 2019 Novel Coronavirus (2019-nCoV)*
  - Improve understanding of 2019-nCoV
  - Development of medical countermeasures
  - Development of animal models

- 2020 NIAID Omnibus Broad Agency Announcement solicits development of 2019-nCoV* vaccines, therapeutics and diagnostics

*SARS-CoV-2
Sharing Samples and Reagents

- Viral isolate from first U.S. patient available through BEI Resources (others soon)

- Patient samples as available (via USG sample sharing WG)

- Reagents including molecular clones, plasmids, pseudoviruses, recombinant protein in progress
Partnership between the VRC/NIAID and Moderna

GMP product expected in March 2020

2 proline (2P) mutations at apex of central helix result in S protein locked in prefusion conformation.

Prefusion-stabilized CoV S-2P is more immunogenic than wild-type S.
Ongoing Efforts Towards a Universal CoV Vaccine

- Optimize antigen design for potency and breadth
- Nanoparticles to display multiple CoV spike antigens and optimize immunogenicity
- Gene-based delivery for rapid response

Slide Adapted from Barney Graham
Vaccine Development For Emerging Coronaviruses

- Coronaviruses have pandemic potential and novel coronaviruses will likely continue to emerge

- NIAID rapidly advancing development of SARS-CoV-2 vaccine candidates

- Global collaboration and transparency are critical
2019-nHCoV

Baric Laboratory
University of North Carolina
Outline

• Introduction

• Emerging Coronaviruses
  – SARS-CoV
  – Pre-pandemic SARS-like Bat-CoV
  – Drivers of Epidemic Disease Outbreaks

• The Outbreak
  – Origins
  – 2019-HCoV
    • Genome Organization and relatedness
  – Disease

• Countermeasures
  – Vaccines

• Summary
## Timeline: Emerging Nidoviruses

<table>
<thead>
<tr>
<th>Virus</th>
<th>Species</th>
<th>Emergence</th>
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</thead>
<tbody>
<tr>
<td>HCoV-NL63</td>
<td>Human</td>
<td>500-800 years</td>
</tr>
<tr>
<td>HCoV-229E</td>
<td>Human</td>
<td>200-300 years</td>
</tr>
<tr>
<td>HCoV-OC43</td>
<td>Human</td>
<td>~120 years</td>
</tr>
<tr>
<td>PEDV</td>
<td>Porcine</td>
<td>~25 years</td>
</tr>
<tr>
<td>PRRSV</td>
<td>Porcine</td>
<td>~25 years</td>
</tr>
<tr>
<td>BCoV</td>
<td>Bovine</td>
<td>~20 years</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>Human</td>
<td>~16 years</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Human</td>
<td>~7 years</td>
</tr>
<tr>
<td>SADS-CoV (HKU2)</td>
<td>Porcine</td>
<td>~2 years</td>
</tr>
<tr>
<td>2019-nHCoV</td>
<td>Human</td>
<td>2 months</td>
</tr>
</tbody>
</table>

2012 in US

Accelerating Cross Species Movement

Drivers of CoV Evolution

- **CoV Genome Size:** 32Kb

- **CoV Mutation Rate**
  - $10^{-6}$
  - Regulated Fidelity (nsp14: ExoN)

- **Environmental Change**
  - Fidelity rates change

- **High Rates RNA Recombination**
  - 25% during mixed infections
  - Modular evolution

- **Plastic Surface Glycoprotein**
  - Tolerates high rates of mutation
  - Deletions and Insertions (tropism, antigenicity)
  - Recombination (modular evolution)

Origins of the Group 2B SARS and SARS-like CoV

- **SARS-CoV Origins (Yellow)**
  - bats
  - Open Markets and Civet Intermediate Hosts

- **SARS-like bat CoV (Pink)**
  - Pre-epidemic potential (high/low)
  - Bats, low level seroprevalence in people residing near bat hibernacula

- **2019-nHCoV**
  - Bats
  - Open Market Origins

Before Dec 2019
SARS-CoV Emergence in 2002 in China

8,096 cases, 774 deaths, in 32 countries, Nov 1 2002 - July 31 2003

Most Likely Model

Epidemic SARS-CoV

WIV-16 (98% Identical)

Bat to Human to Civet

Intermediate host

Is SARS-CoV Extinct?

BtCoV

Animals

Threat Level?
SARS MA15 Molecular Clone

Replicate like SARS-CoV on primary human airway epithelial cells
Use human receptor as well as SARS-CoV (if yes)
Synthesize full length genomes, recover full length virus

Rockx et al., JV 2007; Becker et al., PNAS 2008; Menachery et al., Nature Medicine, 2015; Menachery et al., PNAS 2017
Most Emerging Viruses

Zoonotic Reservoirs

SARS-like bat CoV
SARS-CoV
MERS-CoV

Heterogeneous Pools of related viruses (0-35+%) PrePandemic Strains

SARS-CoV 2003-04 0%

8,000 cases 774 deaths

10%

22%

2019-nCoV

High Risk Emergence Strains

2019-

Future Outbreak?

>60,000 cases 1360 deaths in 28 countries; Human transmission: Germany, US, Thailand, Japan, Vietnam, China

Sheahan et al., JV 2008; Becker PNAS 2008; Menachery V et al., Nature Medicine 2015, Menachery PNAS 2016; Simon et al., mBIO 2017
Known Group 2B SARS-like CoV Poised for Human Emergence

High Risk Features
- Use hACE2/entry
- Grow in Primary Human Airway Cells
- Cause ARDS
- Are-related Disease Severity (elderly ↑)
- Escape Existing Immune Therapeutics

Platform to develop/test broad based vaccines, hmAB and antiviral drugs
Known Group 2C MERS-like CoV Poised for Human Emergence

MERS-related Strains

MERS-like bat CoV (China) 65% Identity with MERS-CoV Spike
-Uses hDPP4 as a receptor for docking and entry
-Replicates efficiently in primary human airway epithelial cells
Zoonotic Virus Emergence Models

**Classic Model: Mutation Driven**

- Zoonotic Virus Pools
  - Host range mutation
- Random
- Rare

**3-4 Step Model Requiring Mutations**

- Secondary host (reservoir)
- Human infection
- Adaptation

- Epidemic strain

- Direct human infection
- Secondary host (reservoir)
- Adaptation

**Limited Mutation is Necessary**

- PreProgrammed Viruses
  - Generalists: receptor orthologs
- Recombination events
- Random

- May not require mutation-driven adaptation

- Direct human infection
- Secondary host (reservoir)

- Epidemic strain
2019-nHCoV

• Emerged Early Dec in Wuhan China (Dec 1)

• Began as Cluster of Cases Associated with Open Markets (Dec 31)
  – No Evidence of Human to Human Transmission
  – Not Very Pathogenic
  – Not SARS-CoV, Likely a Novel Virus

Lesson
Don’t under-estimate epidemic potential of an emerging virus

• Wuhan Open Fish Market Closed (Jan 1, 2020)

• Identified as a Coronavirus on Jan 7th, 2020
  – distant relative to the SARS-CoV (kissing cousin)

• Genome Length Sequence Reported (5 isolates) (~9-11th)

• 15 HCW infected, China Confirms Person to Person Spread (~20th)
## UPDATE ON NEWLY DISCOVERED CORONAVIRUS

<table>
<thead>
<tr>
<th></th>
<th>SARS CoV</th>
<th>MERS CoV</th>
<th>2019 nCo-V (SARI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virion Structure</strong></td>
<td>Enveloped RNA virus</td>
<td>Enveloped RNA virus</td>
<td>Enveloped RNA virus</td>
</tr>
<tr>
<td><strong>Outbreak period</strong></td>
<td>2003-2004</td>
<td>2012-present</td>
<td>2019-present</td>
</tr>
<tr>
<td><strong>Initial site of isolation</strong></td>
<td>Guangdong province, China</td>
<td>Saudi Arabia</td>
<td>Wuhan, China</td>
</tr>
<tr>
<td><strong>No. of countries/cases</strong></td>
<td>29</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td><strong>No. of cases (mortality)</strong></td>
<td>8,096 (9.6%)</td>
<td>2,494 (~34%)</td>
<td>~60,000 (N=1367)(2%)* &gt;8,243 critical (~16%)</td>
</tr>
<tr>
<td><strong>No. of cases U.S.</strong></td>
<td>8</td>
<td>2 (2014)</td>
<td>13 (WA, IL, CA, AZ, Mass, Wis)</td>
</tr>
<tr>
<td><strong>Reservoir (intermediate host)</strong></td>
<td>Bats (palm civet)</td>
<td>Bats (dromedary camels)</td>
<td>Bats (likely a zoonosis)</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>2-7 days (range, 2-21)</td>
<td>2-7 (range, 2-14 days)</td>
<td>2-14 days (mean 5-6)</td>
</tr>
<tr>
<td><strong>Infectivity, rho</strong></td>
<td>1.8-2.5</td>
<td>0.3-1.3</td>
<td>1.4-2.2 (WHO), 2.5-3.8*</td>
</tr>
<tr>
<td><strong>Super spreaders</strong></td>
<td>Yes</td>
<td>Yes (uncommon)</td>
<td>Yes (1 case infected 14 HCW)</td>
</tr>
<tr>
<td><strong>Asymptomatic/mild Spread</strong></td>
<td>No</td>
<td>Rare</td>
<td>Perhaps Yes?/Yes</td>
</tr>
<tr>
<td><strong>Attack Rate</strong></td>
<td>10.3% to 60%</td>
<td>4 to 20%</td>
<td>?, 80+% (one study)</td>
</tr>
<tr>
<td><strong>Transmission (including to HCP)</strong></td>
<td>Droplet/Direct, Airborne/Indirect?</td>
<td>Droplet/Direct, Airborne/Indirect?</td>
<td>Droplet/Direct, Airborne/Indirect?</td>
</tr>
<tr>
<td><strong>Treatment (PEP)</strong></td>
<td>Supportive (none)</td>
<td>Supportive (none)</td>
<td>Supportive (none)*</td>
</tr>
<tr>
<td><strong>Infection Prevention^</strong></td>
<td>Airborne, contact, face shield</td>
<td>Airborne, contact, face shield</td>
<td>Airborne, contact, face shield</td>
</tr>
</tbody>
</table>

*Wuhan is 4.1 percent and 2.8 percent in Hubei, compared to 0.17 percent elsewhere*
Phylogentic Relationships Between the Group 2B Coronaviruses

21st Century Emerging Human Coronaviruses
SARS-CoV 2003
MERS-CoV 2012
2019-nHCoV
21st Century
Emerging Human
Coronaviruses
SARS-CoV 2003
MERS-CoV 2012
2019-nCoV

Phylogenetic Relationships Between the Group 2B Coronaviruses

High Risk
SARS-like Bt CoV
3-10%
SARS/SHC041 Chimera

SARS-CoV
2003-04
(1-2%)
Spike

Low Risk
SARS-like Bt CoV
15-25%

New Clade of SARS-like Viruses

Differ by
>5,000 nts

RaTG13 was sequenced from a bat in a cave from Yunnan Province in China
(1200 nts)

96% nt
Identity

25% different

25% different

2019 nCoV

2019-nCoV/USA/IL1/2020 MN988713
2019-nCoV/USA/CA1/2020 MN994467
2019-nCoV/WW32 MN988527
2019-nCoV/WW36 V05 MN995529
2019-nCoV/WW4 MN988528
2019-nCoV/WHU01 MN988668
2019-nCoV/WHU02 MN988669
2019-nCoV/USA/CA2/2020 MN994468
2019-nCoV/Florida/12020 MT007544
2019-nCoV/WW06 MN988530
2019-nCoV/WW07 MN996531
2019-nCoV/Whuan Hu-1 MN989947
2019-nCoV/USA/AZ1/2020 MN997409
2019-nCoV/HKU-SZ-004 MN989364
2019-nCoV/USA/WU7/200 MN989325
2019-nCoV/HKU-SZ-005a MN975262

Rooted with
HCoV OC43
2019-nHCoV Genome Organization

Uses hACE2 Receptor for Entry

Zhou et al., bioRxiv 2020.01.22.914952
Immune Therapeutic Countermeasures

2003-2004 SARS-CoV Outbreak Strains

- Urbani (Late)
- CUHK-W1 (Middle)
- GZ02 (Early)
- GD03 2004

Group 2B SARS-like Bat Coronaviruses

- WIV16
- WIV1
- SHC014
- 2019 nHCoV
- HKU3

All Are Poised for Human Emergence

Antigenic Distance is Large, SARS-CoV Immune Therapeutics (hmAB) and Vaccines likely Fail

Broadly active drugs/vaccines are essential to control zoonotic CoV
Vaccine Targets

• Spike is a major target for neutralizing antibodies, a principle target for vaccine design for emerging and animal coronaviruses
  – SARS-CoV, SHC014, WIV1 and SARS-CoV 2.0

• Produce broadly cross reactive vaccines that target group 2b SARS-like CoV
  – Broadly cross neutralizing epitopes ill defined

• Stem is more conserved than head domain of spike glycoprotein—target for broad nAB

• Potent Neutralizing Antibodies
  – Globular Head
SARS Vaccine Complications

• Vaccine efficacy in aged populations can reduce performance

• Heterogeneous group 2b SARS-like CoV pool may vary by as much as 35% (compared with SARS)

• Th2 Immune Pathology after Vaccination

• Evidence for Enhancing Antibodies
  – Primates (ACS Infect Dis. 2016 May 13;2(5):361-76)
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  Kendra Gully
  Ariana Brown

Mark Denison Lab

Rich Whitley, UAB

National Institute of Allergy and Infectious Diseases
Developing Antivirals Against Coronaviruses

Denison Lab – Vanderbilt University Medical Center
Baric Lab – UNC Chapel Hill
Gilead Sciences
Emory University - DRIVE
The Coronavirus Antiviral Research Team

- **Vanderbilt University Medical Center:** Andrea Pruijssers, Jim Chappell, Maria Agostini, Laura Stevens, Xiaotao Lu, Tia Hughes, Amelia George, Mark Denison
- **University of North Carolina:** Tim Sheahan, Amy Sims, Rachel Graham, Boyd Yount, Ralph Baric
- **Gilead:** Joy Feng, Danielle Porter, Richard Mackman, Mike Clarke, Tomas Cihlar
- **Emory / EIDD / DRIVE:** Greg Bleumling, Mike Natchus, George Painter
- **NIH / NIAD – U19 (Whitley UAB) – CETR – AD3C**
Need for Antivirals against CoVs:

- Broad diversity of CoVs in bats with demonstrated capability to infect human cells animal models – “outbreak ready”
- Failure of antibodies to neutralize “future” zoonotic CoVs and loss of cross protection by vaccines
- Time to develop vaccines differs from trajectory of epidemic
- Universal vaccines across all CoV PPP groups will be difficult and potentially with gaps or not possible
- Potential for “off the shelf” use toward highly conserved functions
Goals for CoV antiviral development

• Broadly active against diverse coronaviruses
• High barrier to resistance - limited genetic paths, high fitness cost
• Extended therapeutic window for prevention, amelioration, treatment,
• Additional
  • decrease transmission,
  • oral administration
Coronavirus Replication

Essential functions and viral components:

- Entry - Spike
- Translation
- Proteolysis - nsp3 and nsp5
- Replication and Transcription - (nsp7-nsp14)
- Assembly and Release - structural proteins

Coronavirus amino acid and function is highly conserved in the core replicase proteins.
Coronaviruses assemble a multiprotein replicase complex

PLpro  3CLpro

Helicase ATPase

Endonuclease

2’O-Methyltransferase

3’-5’ Exoribonuclease

N7-Methyltransferase

2’O-Methytransferase

nsp7 - 8 Processivity

nsp-9 RNA-binding

nsp-10 14/16 cofactor

Polymerase

RdRP

3’-5’ Exoribonuclease

nsp8

nsp7

nsp12-RdRp

nsp14-ExoN

nsp10

nsp13

nsp9 RNA “clamp”
Coronaviruses assemble a multiprotein replicase complex

- Only RNA virus order (nidovirales) to encode proofreading ExoN
- Removes mis-incorporated nucleotides
- Confers high fidelity replication (up to 20-fold)
Coronaviruses encode a proofreading exoribonuclease (nsp14-ExoN)

- Only RNA virus to encode a proofreading exonuclease
- Removes mis-incorporated nucleotides
- Confers high fidelity replication (up to 20-fold)
Native resistance of coronaviruses to nucleoside analogues is due to ExoN-proofreading

MOI = 0.01 PFU/cell
24 h p.i.

Adapted from Smith et al. PLOS Path. 2013.
Remdesivir and β-D-\(N^4\)-Hydroxycytidine (EIDD-1931/2801, NHC) inhibit CoV replication

EC_50 = 0.03 μM

EC_50 = 0.17 μM

MOI = 0.01 PFU/cell
24 h p.i.

Agostini et al mBio 2017

Agostini et al J Virol 2019
Remdesivir inhibits other human CoVs and potential zoonotic CoVs

α-CoV

<table>
<thead>
<tr>
<th>HCoV-NL63</th>
</tr>
</thead>
<tbody>
<tr>
<td>[remdesivir] µM</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>10^7</td>
</tr>
</tbody>
</table>

β-2c MERS-like

<table>
<thead>
<tr>
<th>Bat-CoV HKU5</th>
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<tbody>
<tr>
<td>[remdesivir] µM</td>
</tr>
<tr>
<td>0</td>
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<td>10^7</td>
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β-2b SARS-like

<table>
<thead>
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<th>Bat-CoV HKU3</th>
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<tr>
<td>[remdesivir] µM</td>
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<td>10^7</td>
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</table>

<table>
<thead>
<tr>
<th>Bat-CoV SCH014</th>
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<tbody>
<tr>
<td>[remdesivir] µM</td>
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<tr>
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<td>10^7</td>
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</table>

<table>
<thead>
<tr>
<th>Bat-CoV WIV1</th>
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</thead>
<tbody>
<tr>
<td>[remdesivir] µM</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>10^7</td>
</tr>
</tbody>
</table>

MOI = 0.5 PFU/cell

48 h p.i.

Two mutations (F476L and V553L) selected in the nsp12-RdRp after 23 passages in the presence of Remdesivir.

6 fold resistance
In SARS-CoV
Remdesivir resistance mutations are less fit than WT in vitro and attenuated in vivo.
Remdesivir given before or 1 day post exposure mitigates disease in a mouse model of Lethal SARS-CoV infection
Remdesivir - IV

• Potently inhibits multiple divergent CoVs
• Mechanism includes RNA chain termination
• Resistance has high barrier – difficult to achieve
• Resistance mutations associated with fitness loss in vitro and attenuation in vivo.
• Efficacious for prophylaxis in mouse model of lethal SARS-CoV
• Decreases disease and virus titer when administered early in infection
Remdesivir - IV

- Potently inhibits multiple divergent CoVs
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EIDD-2801- NHC oral

- Mutagenesis
Coronavirus Countermeasures

Direct acting antivirals (DAA’s) - for treatment, prophylaxis, and decreasing transmission

Monoclonal antibodies - to block infection and act as “passive immunization” during an epidemic

Host Directed therapy - inhibitors or immunomodulators – modify disease – extend therapeutic window for DAA’s and mAbs

Combinations

• DAA’s + DAA’s: increase potency and efficacy, prevent resistance
• DAAs + mAbs: block infection and stop virus replication
• DAA’s + Host Directed Rx: target disease and extend therapeutic window