Beyond COVID-19: Preparing for future pandemic threats

(Building the Plane While Flying: Research in the Time of COVID)

Sumit Chanda
Professor of Immunology and Microbiology
Our Response - Understanding the Virus to Build Antivirals

- How SARS-CoV-2 enters human cells
- How SARS-CoV-2 is detected by the immune system
- How our cells defend against SARS-CoV-2 infection
- Strategies to prevent severe disease

November 9, 2020
A Brief Timeline

December 2019: Xin Yin returns to China for the Christmas Holidays

Mid-Jan 2020: Assembly of a Virology “Dream Team” : Ren Sun (UCLA), Shuofeng Yuan & Kwok-Yung Yuen (HKU), Adolfo Garcia-Sastre (MSSM)

Late Jan 2020: Arnab Chatterjee @ Scripps/Calibr commits to providing 12k Repurposing Library

Early February: Laura Riva cancels trip to Hong Kong due to travel ban
There’s an App for That

Mid-February: Drug Discovery by iPhone

Can ‘Team Science’ Yield a Covid-19 Treatment?
*New York Times Magazine*, Kim Tingley
May 13, 2020
ReFRAME: The Repurposing, Focused Rescue, and Accelerated Medchem Initiative

- Calibr’s library of more than 12,000 drug compounds known to be safe in humans, with well-characterized therapeutic properties

- Open-source database containing preclinical and clinical data on these drugs

- Established in 2018 with support from the Bill & Melinda Gates Foundation
The Initial Antiviral Map

Riva et al. Nature (2020)
Getting our Hands on the Virus
SARS-Related Coronavirus 2, Isolate USA-WA1/2020 was received early March 2020

Compounds → Vero seeding → SARS-COV-2 infection → IFA
Narrowing the Haystack

Vero E6 (CPE/IF)
Selected by Z-score, GSEA (CPE)
>40% inhibition of infectivity at 2.5 µM (IF)

Vero E6 (Dose-response)
EC50 < 1 uM, SI > 10

293T-Ace2 and/or Huh7-Ace2 cells
EC50 < 1 uM, SI > 10

Remdesivir Synergy/Impact on viral life cycle

Inhibition of Replication in Human primary pneumocytes

Inhibition of replication in a complex disease tissue

Decrease in viral titers and attenuation of disease severity in an animal model (hamster, mouse, cats, NHPs)
21 Known Drugs Inhibit SARS-CoV-2 Replication

Riva et al. Nature (2020)
Evaluation in Disease-Relevant Cells

Riva et al. Nature (2020)
Evaluation in Disease-Relevant Tissue

Ex vivo lung tissues
Intracellular RNA

E

Ex vivo lung tissues
plaque assay

F

Relative RNA level
DMSO  Aplimod  Remdesivir

Viral titer (PFU/ml)
DMSO  Aplimod  Remdesivir

Riva et al. Nature (2020)
Clofazimine, LAM-320, Lamprene

- Discovered in the 1950’s
- FDA-Approved (1986); WHO’s list of Essential Medicine
- Treatment of leprosy/ anti-mycobacterial
- $1.43/day

Remdesivir: ~ $3000
Efficacy of Clofazimine in Hamsters

- Administration of Clofazimine results in 10-fold lower virus in the lungs and is comparable to Remdesivir treatment.

- Clofazimine treatment decreases inflammatory responses that lead to severe disease.

(1) bronchiolar and/or peribronchiolar cell death

(2) alveoli destruction and/or alveolar infiltration

(3) blood vessel and perivascular infiltration.
Clofazimine Synergizes with Existing Antivirals

• Combination of low-dose Clofazimine & Remdesivir works better than high-dose Remdesivir alone

• Combo was found to also block virus replication in the nose, which was not seen with high-dose Remdesivir alone
## Current Approved Therapies that Work for Omicron

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Status/ Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir (Veklury)</td>
<td>Approved/ IV</td>
</tr>
<tr>
<td>Molnupiravir (Lagevrio)</td>
<td>EUA/ Oral</td>
</tr>
<tr>
<td>PF-07321332 (Paxlovid)</td>
<td>EUA/ Oral</td>
</tr>
<tr>
<td>Sotrovimab (Xevudy)</td>
<td>Approved/ IV</td>
</tr>
<tr>
<td>LY-CoV1404 (Bebtelovimab)</td>
<td>EUA/ IV</td>
</tr>
<tr>
<td>Evusheld (AZD7442)*</td>
<td>EUA/ IV</td>
</tr>
</tbody>
</table>
The Path Forward for Therapeutics: *Resistance Isn’t Futile*

**HIV:** highly active antiretroviral therapy (HAART)
Consists of 3 or more drug combinations

**HCV:** Curative regimen consists of 2 or more drug combinations

Clinical Trial For Clofazimine:
FAQS: Vaccines & Boosters
mRNA Vaccines

**CENTRAL DOGMA: DNA TO RNA TO PROTEIN**

1. **DNA**
   - Replication
   - Transcription

2. **RNA**
   - Reverse transcription
   - Translation

3. **Protein**
mRNA Vaccines

SARS-CoV-2

mRNA Encapsulated in a Lipid Nanoparticle

From Al Jazeera & NYtimes.com
mRNA Vaccines

Antigen Presentation

Production of Antibodies

Blocking the Virus
Waning Antibodies

Figure 1: Timeline of Detection for COVID-19.
SARS-CoV-2 Variants & Boosting

How Omicron compares

The WHO considers Omicron’s global risk to be ‘very high’. Omicron is a highly divergent variant with a high number of mutations.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Earliest documented samples</th>
<th>Spike protein mutations</th>
<th>Prevalence of analysed sequences*</th>
<th>Countries/territories reported in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omicron</td>
<td>Multiple countries</td>
<td>32*</td>
<td>Unknown</td>
<td>At least 10</td>
</tr>
<tr>
<td>Delta</td>
<td>India</td>
<td>10</td>
<td>99.8%</td>
<td>196</td>
</tr>
<tr>
<td>Gamma</td>
<td>Brazil</td>
<td>12</td>
<td>0.1%</td>
<td>103</td>
</tr>
<tr>
<td>Beta</td>
<td>South Africa</td>
<td>10</td>
<td>&lt;0.1%</td>
<td>146</td>
</tr>
<tr>
<td>Alpha</td>
<td>United Kingdom</td>
<td>11</td>
<td>&lt;0.1%</td>
<td>197</td>
</tr>
</tbody>
</table>

*Known number as of November 28, 2021. Source: WHO, references.com | November 29, 2021

Variant-specific Vaccines?

The structure of SARS-CoV-2 spike protein showing the active site in orange and the residues coloured against different mutational rates.

From Al Jazeera
Safety Data on Vaccines: Benefits Considerably Outweigh Risks

Common

Site of Administration: Pain, Redness, Swelling
Systemic: Tiredness, Headache, Muscle Pain, Chills, Fever, Nausea

Rare

Anaphylaxis- all (~5/ 1 Million)
Thrombosis with thrombocytopenia syndrome (TTS)- J&J & AZ (~3/ 1 Million)
Guillain-Barré Syndrome- J&J & AZ (~16/1 Million)
Myocarditis – Pfizer & Moderna (~10/1 Million)

Boosters

Similar Side Effects to Vaccines

For Perspective

Dying in a Car Accident: 1/ 107
Killed in a Dog Attack: 1/ 86,781
Killed on a Bike: 1/ 3,825
Winning Olympic Gold: 1/ 662,000
Struck by Lightening: 1/ 15,000
Death by Asteroid: 1/ 700,000
FAQ: Potential Trajectories
Where do we go from here? Lessons from 1918
HUMAN INFLUENZA VIRUS PANDEMICS

Estimated deaths in the U.S.

1918

H1N1

1957

H2N2

1968

H3N2

1977

H1N1

2009

SWINE ORIGIN
H1N1

12,000

500,000

Influenza vaccines

1918

1957

1968

1977

2009

500,000

35,000

12,000

Influenza vaccines

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Influenza vaccines

Estimated deaths in the U.S.
Likely Trajectories

“It’s tough to make predictions, especially about the future”

• Omicron is highly transmissible and likely less pathogenic (high level of adaptation to humans)
  > Will become an enduring strain that goes endemic or seasonal (high likelihood)

> Caveats: Emergence of a more transmissible variant with enhanced immune evasion capacity (low likelihood)

> Annual or bi-annual vaccines to strengthen global immunity to variants
FAQ: Understanding Future Pandemic Risks
A Brief History of Pandemics

No longer a 100-year event
Zoonotic Transmission & Pandemic Spread

- Climate Change
- Habitat
  Encroachment/
  Wild Animal Trade
- Global
  Interconnectivity

Hamster
Cat
Tiger
Pangolin
Bat
Human
Threat Matrix

Viruses with Epidemic & Pandemic Potential

- Novel Influenza Virus
- Novel Coronavirus
- Nipah Virus
- Monkeypox
- Enterovirus
- Ebola/ Marburg/ Lassa
- Crimean-Congo hemorrhagic fever
- Rift Valley Fever
- Zika/ Dengue/ West Nile Virus/ Yellow Fever
- Disease X

Transmission:
- Respiratory Droplets
- Bodily Fluids/ Close contact
- Vectors (e.g. mosquitos, ticks)
Mitigation Strategies- Lives & Livelihoods

• **Global Surveillance & Coordinated Response Strategies** (information, treatments/vaccines, travel, and supply chains)

• Prepositioning & Stockpiling of Broad-Spectrum **Antivirals and Vaccines**

• **Increased Scientific Literacy**

• **Pandemic Preparedness Programs** to Minimize Global Health & Economic Impacts
Center for Antiviral Medicines & Pandemic Preparedness

www.CAMPP.org
Our Support....

Governmental and Foundation Funding

Philanthropy

Scripps Research Philanthropy: Meredith Johnston (merejohn@scripps.edu)

Tell Congress You Want Us to Be Better Prepared!
Future Pandemics Are Inevitable, But We Can Be Better Prepared
UPCOMING LECTURES

Taking a new view of vital signs

Wednesday, April 20
1:00 PM PT/4:00 PM ET

Jay Pandit, MD
Director of Digital Medicine
Scripps Research Translational Institute
Assistant Professor
Department of Molecular Medicine
Scripps Research

The hunt for regenerative medicines

Wednesday, June 29
1:00 PM PT/4:00 PM ET

Michael Bollong, PhD
Assistant Professor
Department of Chemistry
Scripps Research

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