Outline

• Our Target: SARS-CoV-2
• The Complexity of Vaccine Development
• Vaccines for SARS-CoV-2
  • Vaccine platforms and attributes
  • Candidates in development
  • Upcoming trials
What do we know about the pathogen and immunity?

Single stranded, positive RNA with 4 major structural proteins:
- Spike Protein (S) → Contains receptor binding domain
- M Protein
- Envelope (E) Protein
- Nucleocapsid (N) Protein
Vaccine Development Lessons from Other Coronaviruses

- Sequence comparison Spike S protein
  - MERS spike S protein 30% homologous
  - SARS Spike S protein is 80% homologous
- Good vaccine responses to several vaccine constructs in animals for SARS, MERS
- Phase 1 human trials in SARS, MERS
  - Broadly neutralizing antibodies
  - MERS development continues
  - SARS investments re-allocated
SARS-CoV-2 Spike Protein: Viral Entry

corona = crown or circle of light

Spike Protein

Viral membrane

SARS-CoV-2 Spike Protein: Viral Entry

- Trimeric fusion protein
- Metastable prefusion conformation
- Undergoes substantial structural rearrangement to fuse the viral membrane with the host cell membrane
- Process triggered when S1 subunit binds to host cell receptor – S2 engages cell with fusion peptide
- Shedding of S1 subunit and transition of S2 subunit to stable postfusion conformation

Receptor-binding domain of S1 undergoes hinge-like conformational movements that transiently hide or expose determinants of receptor binding. Two stabilizing proline mutations effective for other betacoronaviruses applied to SARS-CoV-2.
What Do We Know About Immunity in Humans?

• Immune response post-infection to spike protein
• Neutralizing responses

*SARS-CoV-2 NAb Titer (ID50)*

- Healthy
- COVID-19

*Plasma*

*p<0.0001*

[medRxiv preprint doi: https://doi.org/10.1101/2020.03.30.20047365](https://doi.org/10.1101/2020.03.30.20047365)
What Do We Know About Immunity in Humans?

- Immune response post-infection to spike protein
- Neutralizing responses
  - Don’t cross-react with SARS virus
- Level of antibody needed to prevent re-infection?
- Duration of protection from natural immunity?
- Importance of T cell immunity?

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Does Infection with SARS-CoV-2 Protect Upon Re-Exposure?

SARS-CoV-2 infection protects against rechallenge in rhesus macaques

Abishek Chandrashekar¹*, Jinyan Liu¹*, Amanda J. Martinot¹,²*, Katherine McMahan¹*

bioRxiv preprint doi: https://doi.org/10.1101/2020.03.13.990226. This version posted May 1, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

1 Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2

2

3 Linlin Bao¹, Wei Deng¹, Hong Gao¹, Chong Xiao¹, Jiayi Liu², Jing Xue¹, Qi
Vaccine Development: A Lengthy, Risky and Expensive Process

Traditional Paradigm — Multiple Years

- Target ID, development partner selection, and preclinical trial
- Small-scale clinical trial material
- Manufacturing scale-up, commercial scale, validation of process
- Large-scale manufacturing
- Go or no-go decision to invest in candidate
- Phase 1: First trial in humans
- Phase 2a: Efficacy trial in humans
- Phase 3: Evaluation trial in humans
- Licensure
- 15-20 years

Outbreak Paradigm — Overlapping Phases, Shorten Development Time

- Target ID, development partner selection, and preclinical trial
- Clinical development
  - Safety/dose selection
  - Safety/efficacy
- Go or no-go decision to invest in candidate
- First in humans (safety)
- Efficacy trial
- Regulatory pathway for emergency authorization
- Manufacturing development, scale-up, clinical trial material, commercial scale, validation of process
- Large-scale manufacturing
- Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure
- 12-18 months

## Vaccine Platforms and Attributes

<table>
<thead>
<tr>
<th>Platform</th>
<th>Single Dose</th>
<th>Licensed Platform</th>
<th>Speed</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>Medium</td>
</tr>
<tr>
<td>RNA</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>Low to medium</td>
</tr>
<tr>
<td>Nonreplicating vector</td>
<td>Possibly</td>
<td>No</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Replicating viral vector</td>
<td>Possibly</td>
<td>Yes</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Protein subunit</td>
<td>No</td>
<td>Yes</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Inactivated</td>
<td>No</td>
<td>Yes</td>
<td>Medium</td>
<td>Medium to high</td>
</tr>
<tr>
<td>Live attenuated</td>
<td>Yes</td>
<td>Yes</td>
<td>Slow</td>
<td>High</td>
</tr>
</tbody>
</table>
Vaccine Approach: Strategies

* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.
### COVID-19 Vaccine Candidates in Clinical Evaluation

<table>
<thead>
<tr>
<th>Platform</th>
<th>Type</th>
<th>Developer</th>
<th>Phase</th>
<th>Same Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-replicating viral vector</td>
<td>ChAdOx1-S</td>
<td>Oxford/AZ</td>
<td>1/2</td>
<td>MERS, influenza, TB, Chik, Zika</td>
</tr>
<tr>
<td>Non-replicating viral vector</td>
<td>Ad Type 5</td>
<td>CanSino Biol Inc</td>
<td>2</td>
<td>Ebola</td>
</tr>
<tr>
<td>RNA</td>
<td>LNP-mRNA</td>
<td>Moderna/NIAID</td>
<td>2</td>
<td>Influenza, Zika, Chik</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Inactivated +/- alum</td>
<td>Multiple Chinese developers</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>Protein subunit</td>
<td>Recombinant GP nanoparticle/matrix M</td>
<td>Novavax</td>
<td>1/2</td>
<td>RSV; CCHF, HPV, VZV, Ebola</td>
</tr>
<tr>
<td>RNA</td>
<td>3 LNP-mRNAs</td>
<td>Pfizer/BioNTech</td>
<td>1/2</td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>DNA plasmid/electroporation</td>
<td>Inovio Pharm.</td>
<td>1</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
Vaccine Approach: Nucleic Acid – DNA and RNA

- **DNA vaccine**
  - Electroporation
  - Coronavirus spike gene
  - A process called electroporation creates pores in membranes to increase uptake of DNA into a cell
  - DNA

- **RNA vaccine**
  - RNA is often encased in a lipid coat so it can enter cells
  - RNA
  - Coronavirus spike peptide

RNA- and DNA-based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.

Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus

May 18, 2020

After two doses all participants evaluated to date across the 25 µg and 100 µg dose cohorts seroconverted with binding antibody levels at or above levels seen in convalescent sera

mRNA-1273 elicited neutralizing antibody titer levels in all eight initial participants across the 25 µg and 100 µg dose cohorts, reaching or exceeding neutralizing antibody titers generally seen in convalescent sera

mRNA-1273 was generally safe and well tolerated

mRNA-1273 provided full protection against viral replication in the lungs in a mouse challenge model

Anticipated dose for Phase 3 study between 25 µg and 100 µg; expected to start in July
Vaccine Approach: Viral Vectored Vaccine

Replicating viral vector – weakened measles

Non-replicating viral vector – adenovirus

Coronavirus spike gene
Viral genes

Coronavirus spike gene
Viral genes (some inactive)

Coronavirus spike peptide

Immune response

Virus replicates

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

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

www.thelancet.com  Published online May 22, 2020  https://doi.org/10.1016/S0140-6736(20)31208-3
Adverse Reactions to Ad5 Vectored COVID-19 Vaccine

<table>
<thead>
<tr>
<th>All adverse reactions within 0-7 days</th>
<th>Low dose group (n=36)</th>
<th>Middle dose group (n=36)</th>
<th>High dose group (n=36)</th>
<th>Total (N=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>30 (83%)</td>
<td>30 (83%)</td>
<td>27 (75%)</td>
<td>87 (81%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
<td>6 (17%)</td>
<td>10 (9%)</td>
</tr>
<tr>
<td><strong>Injection site adverse reactions within 0-7 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>17 (47%)</td>
<td>20 (56%)</td>
<td>21 (58%)</td>
<td>58 (54%)</td>
</tr>
<tr>
<td>Induration</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Redness</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>4 (11%)</td>
<td>4 (11%)</td>
<td>0</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Itch</td>
<td>2 (6%)</td>
<td>3 (8%)</td>
<td>0</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Systemic adverse reactions within 0-7 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>15 (42%)</td>
<td>15 (42%)</td>
<td>20 (56%)</td>
<td>50 (46%)</td>
</tr>
<tr>
<td>Grade 3 fever</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
<td>5 (14%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (39%)</td>
<td>11 (31%)</td>
<td>17 (47%)</td>
<td>42 (39%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (47%)</td>
<td>14 (39%)</td>
<td>16 (44%)</td>
<td>47 (44%)</td>
</tr>
</tbody>
</table>
ELISA Antibody Responses to the RBD and Neutralizing Antibodies

- Dose-dependent antibody response
- High pre-existing Ad5 neutralizing antibody responses compromised neutralizing antibody post-vaccination, regardless of vaccine dose
Rapid COVID-19 vaccine development

By Barney S. Graham

Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. Email: bgraham@niaid.nih.gov

Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls

Potential risks associated with vaccine development for COVID-19

Antibodies that bind virus without neutralizing infectivity can cause disease through increased viral replication or formation of immune complexes that deposit in tissue and activate complement pathways associated with inflammation. Th2-biased responses have also been associated with ineffective vaccines that lead to enhanced disease after subsequent infection. Antibody-dependent enhancement (ADE) of viral replication has occurred in viruses with innate macrophage tropism. Virus-antibody immune complexes and Th2-biased responses can both occur in vaccine-associated enhanced respiratory disease (VAERD).

<table>
<thead>
<tr>
<th>Antibody-mediated</th>
<th>T cell–mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADE</strong></td>
<td><strong>VAERD</strong></td>
</tr>
<tr>
<td>Mechanism</td>
<td>Immune complex formation and complement deposition</td>
</tr>
<tr>
<td>Fc-mediated increase in viral entry</td>
<td></td>
</tr>
<tr>
<td>Effectors</td>
<td>Complement activation and inflammatory cytokines</td>
</tr>
<tr>
<td>Macrophage activation and inflammatory cytokines</td>
<td></td>
</tr>
<tr>
<td>Mitigation</td>
<td>T(_2)-biased immune response</td>
</tr>
<tr>
<td>Conformationally correct antigens and high-quality neutralizing antibody</td>
<td>Allergic inflammation and Th2 cytokines</td>
</tr>
<tr>
<td></td>
<td>T(_1)-biasing immunization and CD8(^+) T cells</td>
</tr>
</tbody>
</table>

Cite as: B. S. Graham et al., Science 10.1126/science.abb6923 (2020).
Summary

• Safe and effective **vaccines** that is accessible, affordable and globally available is needed for COVID-19

• Robust pipeline of promising candidates in clinical development
  • We need multiple wins
  • Many challenges – New disease, poorly understood immunity, uncertain trajectory of outbreak
  • Vaccine safety will be meticulously assessed
  • If enhanced disease occurs it will be carefully assessed and immune mechanisms investigated
Thank You

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