PROTOTYPE PATHOGEN APPROACH TO PANDEMIC PREPAREDNESS

HIV → PNEUMOVIRUS → PARAMYXOVIRUS → CORONAVIRUS

ADVAC Alumni
2 April 2020

Barney S. Graham, MD, PhD
Deputy Director
Vaccine Research Center, NIAID, NIH

Recent Zoonotic and Vector-borne Viral Threats

- Hanta virus
- Nipah/Hendra
- West Nile virus
- SARS
- Influenza
- Chikungunya
- Ebola
- MERS
- Zika
- EV-D68
- SARS-CoV-2

NIAID Vaccine Research Center
Public health burden of re-emerging & emerging viruses

Traditional Approaches
- Licensed vaccines/antibiotics
- Passive surveillance
- Contact tracing
- Quarantine

Vaccine Challenges
- Vaccines for animal needs
- Emerging viruses
- Improving licensed vaccines

New Technologies are Transforming Vaccinology
- Structure-based vaccine design
- Single-cell sorting, sequencing, and bioinformatics
  - Rapid isolation of human mAbs
  - Definition of antibody lineages
  - Analysis of immune responses
- Protein engineering of self-assembling nanoparticles
  - Rapid DNA synthesis
  - Recombinant DNA and genetic engineering technology
    - Rapid cell line development
    - Animal model development
- Nucleic acid and vector-based delivery of vaccine antigen

New Technologies Facilitate an Engineering Approach
- Structural biology
- Protein engineering
- Single cell sorting and analysis
- High throughput sequencing
- Rapid isolation of human mAbs
- Antibody lineage analysis
- Rapid diagnostic tools
- Systems biology
Gene Synthesis and Platform Technologies

Historical knowledge about virus biology and structure can help identify antigenic targets and epitopes for immunity.

Surveillance and Discovery → Design and Synthesis → Synthesis of key genes encoding vaccine antigens and other reagents

Graham & Sullivan. Nature Immunology, 2018

Platform Technologies Shorten Manufacturing Timelines

2005 SARS coronavirus 30 days
2006 influenza A/Hong Kong/68 (H3) 31 days
2009 influenza A/California/04/2004 (H1) 4 days
2016 Zika virus 5 - 10 days
100 days → ~50 days

Time from first sequence selection to first Phase 1 clinical trial, too

Graham, Mascola, Fauci. Novel Vaccine Technologies: Essential Components of an Adequate Response to Emerging Viral Diseases JAMA 2018

Coronaviruses: A Phylogenetic Tree

4 endemic coronaviruses (HCoV-229E, NL63, OC43, and HKU1) cause 15-30% of common colds

Severe Human Coronavirus Disease: Past as Prologue

Severe Acute Respiratory Syndrome (SARS) (2002-2003)

Middle East Respiratory Syndrome (MERS) (2012-present)

Cumulative Reported Cases of SARS November 1, 2002 to July 31, 2003

8,096 cases/774 deaths

Confirmed Global MERS Cases, 2012-2020

Number of cases reported:
- 1-5
- 6-29
- 30-99
- 100-999
- 1,000-4,999
- 5,000+

Structure-guided Stabilization of HKU1 CoV Spike

2-P Mutation Stabilizes MERS and SARS CoV S

2P mutations effectively stabilize multiple CoV prefusion S
2P mutations effectively stabilize multiple CoV prefusion S

Endemic Human CoVs
OC43 S-2P
229E S-2P

Porcine CoV
PEDV S-2P

Potentially Emerging CoV
WV1 S-2P

Immunogenicity of MERS S-2P in Mice

Stabilized MERS Spike-2P Protects hDPP4 Knock-in Mice from Lethal Challenge

Survival

Weight Loss

Adam Cockrell, Ralph Baric, Kizzmekia Corbett
MERS S-2P mRNA elicits better neutralizing antibodies than MERS S-WT mRNA

Dr. Kizzmekia Corbett in collaboration with Moderna Therapeutics

Summary

- S from multiple CoV strains can be stabilized in the prefusion conformation using homologous 2P mutations
- Stabilized prefusion S trimers are more immunogenic and protective than WT trimers or monomeric subunits
- May be a general solution for beta-CoV vaccine antigen design

Coronavirus Disease 2019 (COVID-19) (December 2019 – Present)

COVID-19 is the name of the disease caused by the novel coronavirus SARS-CoV-2
CORONAVIRUS BIOLOGY AND NOMENCLATURE

corona = crown or circle of light

Viral membrane

Spike Protein


Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein is on the viral surface and mediates attachment to cells to start the infection process
- Ideal vaccines target coronavirus spikes in order to block viral infection

Human ACE2 Receptor

Cells in Human Body

Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein attaches to ACE2 protein to start infection
Vaccine Target: Coronavirus Spike Protein

• Vaccine-induced antibodies will block the interaction and function of CoV spike protein

COVID-19 Vaccine Development

Previous fastest timelines

ZIKV DNA vaccine
3 days
58 days
24 days

COVID-19 Vaccine Consortium
Structure of Prefusion RSV F Glycoprotein

Generalized Application to Other Fusion Proteins

Summary

- New technologies are transforming vaccinology providing solutions for long-standing problems and emerging viral diseases
- Combining atomic level antigen design with computationally designed nanoparticles and platform manufacturing approaches provides a modular, engineering approach to achieve generalizable solutions for vaccine antigen design
- The advent of precision vaccinology with rapid platform manufacturing makes a prototype pathogen approach for pandemic preparedness feasible
### NIAID Vaccine Research Center

<table>
<thead>
<tr>
<th>VPL</th>
<th>VRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracy Rockwell</td>
<td>Masako Ideyama</td>
</tr>
<tr>
<td>Kathryn Moralez</td>
<td>Michelle Cross</td>
</tr>
<tr>
<td>Giuzella Curti</td>
<td>Soey-Ah Byun-Gil-Raunm</td>
</tr>
<tr>
<td>Emelie Chang</td>
<td>Rebecca Gilleo</td>
</tr>
<tr>
<td>Rachel Zhou</td>
<td>Audrey Cesana</td>
</tr>
<tr>
<td>Deepika Nair</td>
<td>Jared Main</td>
</tr>
<tr>
<td>G缩kadea Abbara</td>
<td>Jia Kunderer</td>
</tr>
<tr>
<td>Aapil Kumar</td>
<td>Geoffrey Hauthkofer</td>
</tr>
<tr>
<td>Alex Dorothy Coleman</td>
<td>Brian Feker</td>
</tr>
<tr>
<td>Anthony Dipalca</td>
<td>Cynthia Zmusa</td>
</tr>
<tr>
<td>Rebecca LaVigne</td>
<td>Devin Rook</td>
</tr>
<tr>
<td>Eric Bar-Neim</td>
<td>Jesse Distefano</td>
</tr>
<tr>
<td>Monique Young</td>
<td>Li-Terai Chapin</td>
</tr>
</tbody>
</table>

### VRC Immunology Cores

- Kathy Foulds
- Amy Noe
- Dillon Flebbe
- Nadesh Nji
- Shing-Fen Kao
- Valerie Ficca
- Madhu Prabhakaran
- Joshua Brand
- David Ambrozak

### Acknowledgements

- UT Austin: Jason McLellan, Morgan Gilman, Nianshuang Wang, Mike Battles, Daniel Wrapp
- UNC: Ralph Baric, Adam Cockrell
- Scripps: Andrew Ward, Jesper Pallesen, Robert Kirchdoerfer, Christopher Cottrell, Hannah Turner
- Vanderbilt: Mark Denison, Jim Chappel

### NIAID VRC Clinical Trials Program

- Nina Berkowitz: Team Lead, Protocol Operations
- Ingelise Gordon: Clinical Operations Manager
- Sarah Plummer: Chief, Clinical Development Unit
- Martin Gaudinski: Medical Director
- Grace Chen: Deputy Chief