Major challenges with the Development of Pan-coronavirus Vaccines

Immunologic Targets:
Spike et al.

Collaborations: Gilead, Ridgeback Bio., Adagio, Pfizer, Takeda, BioNet, Eli Lily, VaxArt, Moderna, Pardes Bio
Pan CoV Vaccine Challenges

Virologic
- Phylogenetic and Antigenic Breadth
- SARS-CoV2/HCoV Antigenic Drift
- Broad, Divergent Live Virus Panels
- Pan-CoV Immunologic Assays/Conserved Epitopes
- Vaccine Design Considerations

Animal Models
- Small and Large Animals
- Acute ARDS
- Models of Vaccine-associated enhanced respiratory (VAERD) disease
- Human Challenge Models
  - SARS-CoV2, Contemporary HCoV

Lots of CoV Live Here

ssRNA+ ~30,000
Pan CoV Vaccine Challenges

Virologic
- Phylogenetic and Antigenic Breadth
- SARS-CoV2/HCoV Antigenic Drift
- Broadly Divergent Live Virus Panels
- Pan-CoV Immunologic Assays/Conserved Epitopes
- Vaccine Design Considerations

Animal Models
- Small and Large Animals
- Acute ARDS
- Models of Vaccine-associated enhanced respiratory (VAERD) disease
- Human Challenge Models
  - SARS-CoV2, Contemporary HCoV

Immune Considerations
- PreImmune Status on Pan-CoV Vaccine Performance
- Vaccine Performance in Naïve/Vulnerable Populations
  - Children/Infants
- Immune Kinetics, Breadth, Durability, Memory
- Defined Correlates of Protection
  - T cell, B cell and Antibody and cross protective immunity, cross neutralizing antibodies, AB Fc-mediated protective immunity

Product Development Plan (PDP)

ssRNA+ ~30,000
### Vaccine PDP

#### Pan CoV

<table>
<thead>
<tr>
<th>Species</th>
<th>Genus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miniopterus bat coronavirus 1</td>
<td>Alphacoronavirus</td>
</tr>
<tr>
<td>Miniopterus bat coronavirus HKU8</td>
<td></td>
</tr>
<tr>
<td>Porcine epidemic diarrhea virus</td>
<td></td>
</tr>
<tr>
<td>Scotophilus bat coronavirus S12</td>
<td></td>
</tr>
<tr>
<td>Human coronavirus 229E</td>
<td></td>
</tr>
<tr>
<td>Human coronavirus NL63</td>
<td></td>
</tr>
<tr>
<td>Rhinolophus bat coronavirus HKU2</td>
<td></td>
</tr>
<tr>
<td>Alphacoronavirus 1</td>
<td></td>
</tr>
<tr>
<td>Betacoronavirus 1</td>
<td></td>
</tr>
<tr>
<td>Murine coronavirus</td>
<td>Betacoronavirus</td>
</tr>
<tr>
<td>Human coronavirus HKU1</td>
<td></td>
</tr>
<tr>
<td>SARS-related coronavirus</td>
<td></td>
</tr>
<tr>
<td>Rousettus bat coronavirus HKU9</td>
<td></td>
</tr>
<tr>
<td>Tylonycteris bat coronavirus HKU4</td>
<td></td>
</tr>
<tr>
<td>Pipistrellus bat coronavirus HKU5</td>
<td></td>
</tr>
<tr>
<td>To be established</td>
<td></td>
</tr>
<tr>
<td>Avian coronavirus</td>
<td>Gammacoronavirus</td>
</tr>
<tr>
<td>Beluga whale coronavirus SW1</td>
<td></td>
</tr>
<tr>
<td>Munia coronavirus</td>
<td></td>
</tr>
<tr>
<td>Bulbul coronavirus</td>
<td></td>
</tr>
<tr>
<td>Thrush coronavirus</td>
<td></td>
</tr>
<tr>
<td>Deltacoronavirus</td>
<td></td>
</tr>
</tbody>
</table>

#### Basic Virology Campaigns

- CoV Virome Discovery
- Receptor Identification
- Animal Model Development
- Conserved Epitope Discovery
- Vaccine Design Strategies

#### Multiplex Strategies:
- Immunodominance?
- or Balanced Immunity

#### Strain Selection

- Immunologic Targets
- Available Animal Models
- Gaps in the Phylogeny
PanSarbecovirus Vaccines

The goal is likely achievable

- **Focus Immune Response on Conserved Sarbecovirus Neutralizing Epitopes**

- **Multiplexed Chimeric Sarbecovirus Spikes Delivered from mRNA Vaccines**

- **Focus the Immune Response on multiplexed Sarbecovirus RBD’s delivered by nanoparticle vaccines**

---

**Vaccine PDP**

**Pan CoV**

**Species**

- *Miniopterus bat coronavirus 1*
- *Miniopterus bat coronavirus HKU8*
- *Porcine epidemic diarrhea virus*
- *Scotophilus bat coronavirus SI2*
- *Human coronavirus 229E*
- *Human coronavirus NL63*
- *Rhinolophus bat coronavirus HKU2*
- *Alphacoronavirus 1*
- *Betaocoronavirus 1*
- *Murine coronavirus*
- *Human coronavirus HKU1*
- *SARS-related coronavirus*
- *Roussettus bat coronavirus HKU9*
- *Tylocoine bat coronavirus HKU4*
- *Pipistrellus bat coronavirus HKU5*
- *To be established*
- *Avian coronavirus*
- *Beluga whale coronavirus SW1*
- *Munia coronavirus*
- *Bulbul coronavirus*
- *Thrush coronavirus*

**Pan-Genus Specific**

- Alphacoronavirus
- Betacoronavirus
- Gammacoronavirus
- Deltacoronavirus

**Pan-Subgroup Specific (Sarbecoviruses)**

**Multiplex Strategies:** Immunodominance? or Balanced Immunity
Sarbecoviruses (Model)

High Throughput Immune Assays

Human BEI Reference Panel

K18-hACE2 % starting weight

Mouse adapted Strains
SARS-CoV MA15
SHC014, WIV1, WIV16
SARS-CoV2 MA10
SARS-CoV2 Beta MA10
SARS-CoV2 Omicron MA10
HKU3-SRBD MA
Sarbecoviruses

Mouse adapted Strains
SARS-CoV MA15
SHC014, WIV1, WIV16
SARS-CoV2 MA10
SARS-CoV2 Beta MA10
SARS-CoV2 Omicron MA10

Human BEI Reference Panel

Vaccinated Infant Primates: Neut Titers

W8 grouped by Vaccine Group ID80

SARS-CoV mRNA S2P in mice
Chimeric Pan Sarbecovirus Spike Vaccines

Focus Response on Specific Domains Expand Response Breadth to RBD and NTD Domains

Structural Domains in Spike are Interchangeable: Live Virus

Martinez et al., Science 2021
Chimeric Sarbecovirus Spike Vaccines

SARS-CoV RBD

SCH014 RBD

SARS-CoV2 RBD

SARS-CoV2

HKU3 NTD

SARS-CoV2

SARS-CoV2

Focus Response on Specific Domains Expand Response Breadth to RBD and NTD Domains

Focus Immune Responses on Conserved Epitopes

Clade 1, 2, 3 Vaccine, focus Homologous Clade 3 S2

Clade 1, 2, 3 Vaccine, heterotypic Clade 1 + 2 boost
SARS-CoV Clade I

SARS-CoV2 Clade III

Days

Days

Days

PFU/Lobe

PFU/Turbinate

% Starting Weight

Titer: Nasal Turbinates (d4)

SARS-CoV Lung Titer (d4)

Titer: Nasal Turbinates (d4)

LoD

LoD

n.s.

n.s.

n.s.
Spike Vaccine Considerations

Full length vs RBD
Quaternary Epitopes
Domain Specific Targeting Differ/Clades
Multiplexing Strategies
Heterologous Prime Boost Immunogens
Heterologous Prime-Boost Vector Platforms
Adjuvant Considerations
T cell Immunity

- Critical role in Virus Clearance
- VRP-N Vaccines Provide Some Protection from Lethal Infection
  - Airway Memory CD4(+) T Cells Mediate Protective Immunity against Emerging Respiratory Coronaviruses (Zhao J et al., Immunity 2016)

**VRP N Vaccines**

- Cross Reactive, Pan Betacoronavirus Epitopes Have Been Defined
- Best in combination with Spike driven neutralization assays
Common Obstacles

• Sarbecoviruses
  – Group II and Group III strains and assays
  – More High Risk Strains

• Other Betacoronaviruses-
  – MERS-CoV (group 2c)
    • heterologous group 2c high-risk strains/models
  – Group 2d strains (to be identified and developed)
  – Group 2a (HCoV OC43/HKU1)
    • limited reagents/animal models
    • lots of animal strains (surrogates)

• Other Alphacoronaviruses
  – NL63 and HCoV229E animal models (weak/nonexistent)
  – High Priority Zoonotic Strains (to be identified and developed)
    – Several animal strains/models available

• Deltacoronaviruses
  – Porcine epidemic diarrhea virus
  – Other high priority strains (to be identified and developed)
Acknowledgements

UNC School of Medicine
Dr. William Fischer
Dr. Mark Heise

Richard Boucher
Kenichi Okuda
Scott Randell

UNC Epidemiology
Gralinski Lab
Sheahan Lab

Vanderbilt University
Mark Denison
James E. Crowe

Baric Laboratory
David Martinez
Rachel Graham
Lisa Gralinski
Lisa Lindesmith
Ande West
Ethan Fritch
Alexandra Schaefer
Michael Mallory
Trevor Scobey
Tommy Baric
Lilly Adams
Victor Tse
Deana Zhu
Sarah Leist
Jesica Swanstrom
Paul Brewer-Jensen
Boyd Yount
Ellen Young
Caitlin Edwards
Jenny Munt
Kenny Dinnon
John Powers
Fernando Moreira
Rita Maganck