Strategies For A Pancoronavirus Vaccine

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Duke University School of Medicine
March 25, 2022
Hypothesis: Activation of multiple arms of the immune system will lead to the broadest protective immunity.

- **Protective T cell responses**
  - Collaborators: Bette Korber, Drew Weissman

- **Protective non-neutralizing antibody responses**
  - Collaborators: Guido Ferrari

- **Neutralizing antibodies to conserved sites**
  - Collaborators: Priyamvada Acharya, Kevin Wiehe, Mihai Azoitei, Barton Haynes
Activation of multiple arms of the immune will lead to the broadest protective immunity

Protective T cell responses
Collaborators: Bette Korber, Drew Weissman

Protective non-neutralizing antibody responses
Collaborators: Guido Ferrari

Neutralizing antibodies to conserved sites
Collaborators: Priyamvada Acharya, Barton Haynes, Kevin Wiehe, Mihai Azoitei
Multimerization of antigen to induce potent humoral immunity

Multimerization of SARS-CoV-2 S ectodomain to make virus-like particles

Li D et al Biorxiv 2022
Structures of cross-neutralizing antibodies define multiple broadly neutralizing epitopes on RBD
Multimerization of SARS-CoV-2 RBD to focus antibodies on the RBD

Can nanoparticle vaccines protect against SARS-CoV-2 Beta variant of concern?

Study week

Immunizations

0 2 4 6 8

Mouse-adapted B.1.351 SARS-CoV-2

Immunizations

Aged BALB/c

WA-1 or B.1.351

WA-1 or B.1.351

HIV-1 Env trimers (CH848, CH505, BG505, others)

SIV Env trimers (CAM13, MT145, EK505, others)

Other pathogen fusion proteins (SARS2, Flu, others)

Universal nanoparticle vaccine platform

Sortase A + Ferritin NP

Receptor binding domain nanoparticle ACE2 binding site

Protein nanoparticle

Nanoparticle assembly

Receptor binding domain

Negative Stain EM RBD Ferritin

WA-1 or B.1.351

or

WA-1 or B.1.351

Aged BALB/c
Nanoparticle vaccines protect against lethal challenge with the Beta variant of SARS-CoV-2

RBD Nanoparticles

SARS-CoV-2 B.1.351 MA10 weight loss

% of initial weight

0 1 2 3 4

Days post challenge

50% mortality

Wuhan-Hu-1 RBD scNP
B.1.351 RBD scNP
Sham

David Martinez, Ralph Baric, Barton Haynes
Nanoparticle vaccines protect against lethal challenge with the Beta variant of SARS-CoV-2

**RBD Nanoparticles**

SARS-CoV-2 B.1.351 MA10 weight loss

% of initial weight

- Wuhan-Hu-1 RBD scNP
- B.1.351 RBD scNP
- Sham

† 50% mortality

**Ectodomain Nanoparticles**

SARS-CoV-2 B.1.351 MA10 weight loss

% of initial weight

- Wuhan-Hu-1 S-2P scNP
- B.1.351 S HexaPro scNP
- Sham

† 50% mortality

David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes
## Approaches for broadening potent antibody responses

<table>
<thead>
<tr>
<th>Mosaic nanoparticle immunogens</th>
<th>Epitope focusing immunogens based on antibody structures</th>
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<tbody>
<tr>
<td>Chimeric envelope designs</td>
<td>Heterologous Prime boost regimens</td>
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Approaches for broadening potent antibody responses

- Mosaic nanoparticle immunogens
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Mosaic conjugate nanoparticle immunogens

Monovalent RBD nanoparticle

SARS-CoV-2 WT RBD 24-mer

Trivalent Mosaic RBD nanoparticle

Groups 2b + 2c MERS SHC014 SARS-CoV-2 RBD 24-mer
Can mosaic nanoparticle vaccines protect against a heterologous betacoronavirus?

Immunogen: 10mcg
Adjuvant: 5mcg GLA-SE (IDRI-EM082)
Route: 2 sites IM (50mcl)

Haiyan Chen, Esther Lee, Amanda Newman, Cynthia Bowman, David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes
Mosaic NP immunization generates Group 2B+2C reactive antibodies and protects against heterologous betacoronavirus infection.

**Serum IgG reactivity**

- Binding titer (Log AUC)

**Weight loss**

- Percent initial body weight

**Coronavirus antigen**

- SARS-CoV-2 RBD scNP
- SARS CoV-2_MERS_RsSHC014 RBD scNP
- Adjuvant only

David Martinez, Alexandra Schaefer, Ralph Baric, Barton Haynes
Approaches for broadening potent antibody responses

- Mosaic nanoparticle immunogens
- Epitope focusing immunogens based on antibody structures
- Heterologous Prime boost regimens
- Chimeric envelope designs
Optimization of heterologous prime boost regimens to increase neutralization breadth

SARS-CoV-1 NP prime
SARS-CoV-2 NP boost

Study week
0 1 2 3 4

SARS-CoV-1 RBD NP
SARS-CoV-2 RBD NP

Bivalent 2B /2C RBD NP
Bivalent 2B /2C RBD NP

Heterologous Group 2B+2C

Study week
0 1 2 3 4

Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors

Tan, CW, Wang, L et al NEJM, 2021

Defining the rules for which spikes work best as primes versus which spikes work best as boosts
Approaches for broadening potent antibody responses

- Mosaic nanoparticle immunogens

- Epitope focusing immunogens based on antibody structures

- Heterologous Prime boost regimens

- Chimeric envelope designs
Broadly neutralizing antibodies can serve as immunogen targets

<table>
<thead>
<tr>
<th>Ab</th>
<th>WA-1</th>
<th>Alpha B.1.1.7</th>
<th>Beta 1.351</th>
<th>Gamma P1</th>
<th>Epsilon 1.429</th>
<th>Iota 1.526</th>
<th>Kappa 1.617.1</th>
<th>Delta 1.617.2</th>
<th>Omicron BA.1</th>
<th>BA.3</th>
<th>BA.3</th>
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<tr>
<td>DH1284</td>
<td>0.0034</td>
<td>0.0042</td>
<td>0.0249</td>
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<td>DH1047</td>
<td>0.1214</td>
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<td>0.1238</td>
<td>0.1631</td>
<td>0.1475</td>
<td>0.1585</td>
<td>0.1328</td>
<td>0.1609</td>
<td>&gt;25</td>
<td>NT</td>
<td>NT</td>
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Neutralization titers against betacoronaviruses (IC50 mcg/ml)

<table>
<thead>
<tr>
<th>Ab</th>
<th>SARS-CoV-2 D614G peudovirus</th>
<th>SARS-CoV-2 WT MN titer (IC99 mcg/ml)</th>
<th>SARS-CoV-2 2AA MA</th>
<th>SARS-CoV-1 MA</th>
<th>WIV-1</th>
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<tr>
<td>DH1047</td>
<td>0.09</td>
<td>0.12</td>
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<td>DH1073</td>
<td>6.79</td>
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<td>0.81</td>
<td>0.008</td>
<td>0.27</td>
<td>&gt;10</td>
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David Montefiori, Surender Khurana, Ralph Baric, Barton Haynes
Structure-guided, epitope focused immunogens

Collaborator: Mihai Azoitei

Priyamvada Acharya unpublished, 2021
S2 region includes highly conserved neutralizing epitopes

**Broad betacoronavirus neutralization by a stem helix-specific human antibody**

Dora Pinto\(^1\), Maximilian M. Sauer\(^2\), Nadine Czudnochowski\(^3\), Jun Siong Low\(^4\), M. Alejandra Tortorici\(^2\), Michael P. Housley\(^5\), Julia Noack\(^6\), Alexandra C. Walls\(^7\), John E. Bowen\(^8\), Barbara Guarino\(^9\), Laura E. Rosen\(^3\), Julia di Iulio\(^8\), Josipa Jerak\(^4\), Hannah Kaiser\(^9\), Saiful Islam\(^9\), Stefano Jaconi\(^8\), Nicole Sprugasci\(^1\), Katja Culap\(^1\), Rana Abdelnabi\(^5\), Caroline Foo\(^9\), Lotte Coelmont\(^5\), Istvan Bartha\(^5\), Siro Bianchi\(^9\), Chiara Silacci-Fregni\(^1\), Jessica Bassi\(^9\), Roberta Marzi\(^1\), Eneida Vetti\(^1\), Antonino Cassotta\(^9\), Alessandro Ceschi\(^6\), Paolo Ferrari\(^9\), Pietro E. Cippà\(^9\), Olivier Giannini\(^9\), Samuele Ceruti\(^1\), Christian Garzon\(^1\), Agostino Riva\(^1\), Fabio Benigni\(^3\), Elisabetta Camerioni\(^1\), Luca Piccoli\(^1\), Matteo S. Pizzuto\(^1\), Megan Smithey\(^1\), David Hong\(^9\), Amalio Telenti\(^9\), Florian A. Lempp\(^3\), Johan Neyts\(^5\), Colin Havenar-Daughton\(^1\), Antonio Lanzavecchia\(^3\), Federica Sallusto\(^4\), Gyorgy Snell\(^3\), Herbert W. Virgin\(^3\), Martina Beltramello\(^1\), Davide Corti\(^9\), David Veesler\(^2\)

PDB: 7NRJ
Stem helix region represents a conserved site for epitope-focusing immunogens

S2 of coronavirus spike amino acid alignment

<table>
<thead>
<tr>
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<th>1134</th>
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<th>1156</th>
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<tbody>
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<td>SARS-CoV-2</td>
<td>NNT VYDPL - - - QPELDSFKEELDKYFKHNHTS</td>
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<tr>
<td>SARS-CoV</td>
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<td>PANG/GD</td>
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<td>OC43</td>
<td>- TKAPYVMLNTSIPNLPDFKEELDQWFKNQTS</td>
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<td>HKU5</td>
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</table>

Epitope-focused immunogens

Collaborator: Mihai Azoitei
Approaches for broadening potent antibody responses

- Mosaic nanoparticle immunogens
- Epitope focusing immunogens based on antibody structures
- Heterologous Prime boost regimens
- Chimeric envelope designs
• Developed chimeric spike designs of RBD, NTD and S2 components.

• Induced panSarbecovirus cross-reactive responses.

• Current work has expanded to including other betacoronaviruses to make chimeras.

Drew Weissman, David Martinez, Ralph Baric

SARS-CoV-2 Coronavirus Spike PDB: 6VXX
Combining chimeric Spike ectodomains with multimerization to induce broad and potent antibody responses

SARS-CoV-2 Coronavirus Spike PDB: 6VXX

David Martinez, Ralph Baric, Kevin Saunders
Implications for Pancoronavirus vaccine design

Our design goals include integrating each of the aforementioned concepts. In brief:

• Combining T cell immunogens with antibody immunogens to activate multiple arms of the immune system.

• Designing antibody-based immunogens that focus antibodies to conserved epitopes.

• Broaden the reactivity by increasing epitope diversity present during vaccination with heterologous prime-boost regimens.
# Collaborators

<table>
<thead>
<tr>
<th>Duke Human Vaccine Institute</th>
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<tr>
<td><strong>Barton Haynes</strong></td>
<td><strong>Kevin Saunders</strong></td>
<td><strong>Mihai Azoitei</strong></td>
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<tr>
<td>• Dapeng Li</td>
<td>• Esther Lee</td>
<td>• Aria Arus-Altuz</td>
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<tr>
<td>• Robert Parks</td>
<td>• Haiyan Chen</td>
<td>• Steve Slater</td>
</tr>
<tr>
<td>• Maggie Barr</td>
<td>• Alecia Brown</td>
<td><strong>Derek Cain (Flow Cytometry)</strong></td>
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<tr>
<td>• Laura Sutherland</td>
<td>• Xiaozhi Lu</td>
<td>• Aria Arus-Altuz</td>
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<tr>
<td>• Cynthia Bowman</td>
<td>• Dylshan Malewana</td>
<td>• Steve Slater</td>
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<tr>
<td>• Grace Stevens</td>
<td>• James Counts</td>
<td><strong>Wes Rountree</strong></td>
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<tr>
<td>• Charlie Mu</td>
<td>• Beth Bryan</td>
<td><strong>Tony Moody</strong></td>
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<tr>
<td>• Richard Scearce</td>
<td>• Nolan Jamieson</td>
<td>• Yousef Abuhamad</td>
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<tr>
<td>• Victoria Lee</td>
<td>• Lena Smith</td>
<td><strong>Munir Alam</strong></td>
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<tr>
<td>• Meg Deyton</td>
<td>• Jingjing Li</td>
<td>• Kara Anasti</td>
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<tr>
<td>• Amanda Newman</td>
<td>• Aja Sanzone</td>
<td>• Advaiti Khanore</td>
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<tr>
<td>• Whitney Edwards</td>
<td>• Andrew Foulger</td>
<td><strong>Wilton Williams</strong></td>
</tr>
<tr>
<td>• Priyamvada Acharya (Structural Biology)</td>
<td>• Chuancang Jiang</td>
<td><strong>Upenn (mRNA vaccines)</strong></td>
</tr>
<tr>
<td>• Kartik Manne</td>
<td>• Elizabeth Donahue</td>
<td>• Drew Weissman</td>
</tr>
<tr>
<td>• Rory Henderson (Molecular Dynamics)</td>
<td>• Christine Daniels</td>
<td>• Norbert Pardi</td>
</tr>
<tr>
<td>• Kevin Wiehe (Bioinformatics)</td>
<td>• Fangping Cai</td>
<td><strong>UNC Chapel Hill (CoV mouse</strong></td>
</tr>
<tr>
<td>• Sravani Venkatayogi</td>
<td>• Shi-Mao Xia</td>
<td>and neutralization)</td>
</tr>
<tr>
<td>• Madison Berry</td>
<td>• RJ Edwards (Negative Stain EM)</td>
<td>• Ralph Baric</td>
</tr>
<tr>
<td>• David Montefiori (Neutralization)</td>
<td>• Katayoun Mansouri</td>
<td>• David Martinez</td>
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**DMID Program and Product Development teams**

P01 AI158571