New Approaches for Accessible, Durable and Broadly Protective Coronavirus Vaccines

Corey Casper, MD, MPH
WHO R&D Blueprint Global Consultation on Pan Sarbecovirus Vaccines
28 January 2022
## Approaches to Generate Broad Pan-Sarbecovirus Immune Responses

<table>
<thead>
<tr>
<th><strong>Next Generation RNA Vaccines</strong></th>
<th><strong>Next-Generation hAd5DNA Vaccines</strong></th>
<th><strong>Adjuvanted Protein Vaccines</strong></th>
<th><strong>Heterologous Prime - Boost</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elicit <em>both</em> robust NAbs and polyfunctional T-cell responses</td>
<td>Elicit robust polyfunctional CD4 and CD8 T-cells</td>
<td>Elicit robust NAbs and polyfunctional CD4 T-cell responses</td>
<td>Extraordinary NAb, CD4 and CD8 responses</td>
</tr>
<tr>
<td>Stable at room temperature</td>
<td>Stable under simple refrigeration</td>
<td>Stable at room temperature</td>
<td>Stable at room temperature</td>
</tr>
<tr>
<td>Alternative routes of delivery are feasible (intranasal)</td>
<td>Alternative routes of delivery available (sublingual)</td>
<td>Alternative routes of delivery available (intranasal)</td>
<td>Alternative routes of delivery available</td>
</tr>
<tr>
<td>Inexpensive to produce at scale</td>
<td>More challenging to produce at scale</td>
<td>Cheap to produce at scale</td>
<td>Cheap to produce at scale and diversified supply chain</td>
</tr>
</tbody>
</table>
Next-Generation Nucleic Acid Vaccine Technologies

**saRNA Vaccine**
Self-Amplifying RNA (saRNA)
Nanoparticle Lipid Carrier (NLC) with Spike (S) and Nucleocapsid (N) Proteins

**DNA Vaccine**
Adenovirus (hAd5)
hAd5 S-Fusion + N-ETSD

---

**AAHI-SC2 : S**

**AAHI-SC3 : S+N**

---

Investigational Agent Name:
hAd5-S-Fusion+N-ETSD
AAHI-SC2 Induces Broad Neutralizing Responses Against COVID Variants of Concern

Humoral immunogenicity profiles of optimized engineered SARS-CoV-2 saRNA/NLC vaccine (D614G-2P-3Q) after prime or prime-boost immunization of C57BL/6 mice with 1 µg, 10 µg, or 30 µg of saRNA/NLC vaccine. Panel A: Serum SARS-CoV-2 S protein binding IgG. Panel B,C: Serum SARS-CoV-2 neutralizing antibody titers post prime (B) and post-boost. Data was log transformed and evaluated by Mixed effects analysis with multiple comparisons. *p<0.05, **p<0.01, ***p<0.0001, ****p<0.00001.(C). Panel C: Induction of bone marrow resident memory B cells by ELISPOT
Detailed cellular immunogenicity profiles of optimized engineered SARS-CoV-2 saRNA/NLC vaccine (D614G-2P-3Q) after prime or prime-boost immunization of C57BL/6 mice with 1 µg, 10 µg, or 30 µg of saRNA/NLC vaccine. Panel A: SARS-CoV-2 reactive spleen-resident T cells by ELISPOT. B, C: CD4 (B) and CD8 (C) T cells responding with any TH1 (IFNg, IL-2 and TNFa) or TH2 (IL-5 and IL-10) cytokines post-prime and post-boost were plotted representing the total number of responding cells, for each Th1 or Th2 out of total CD4 or CD8 cells per mouse. D, E: Quality of responding CD4 and CD8 cells. Total TH1 or TH2 responses were subdivided by cells responding with just one cytokine, two, or three cytokines to show magnitude and quality of TH2 and Th2 responses with bar graphs showing the average percentage across each group of mice.
Robust T-Cell Immunity (CD4 and CD8) Induced After AAHI-SC3

Mice primed with AAHI-SC2, boosted with S+N construct. T cells ~1 month post-boost.
Next-Generation hAd5 (Adeno) Generates Cross-Reactive Memory B & T Cells

hAd5 S + N vaccination induces both T cell and cross reactive Memory B cells in healthy subjects

Cross Reactive Memory

T Cells

USA - Phase 1 Cross Reactive T Cell Response

B Cells

Cross Reactive B Cells

November 2021

January 10, 2022

Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts

June 2020

Serologic Cross-Reactivity of SARS-CoV-2 with Endemic and Seasonal Betacoronaviruses

Pre Post Vaccine
Strong Spike-Specific CD4 and CD8 T cell Responses Observed in saRNA Prime Followed by hAd5 S+N Boost

**CD8+ ICS**
IFN-γ, TNF-α

**CD4+ ICS**
IFN-γ, TNF-α, IL-2
3M052-Alum + Ferritin Nanoparticle RBD Protein

SARS-CoV2 RBD Protein + IDRI / 3M adjuvant (3M052-Alum) generated higher nAb titers to mutant COVID strains compared with mRNA vaccine, and also conferred strong protection across coronaviruses.

ANTIGEN: FERRITIN NANO-PARTICLE RBD (NIH VRC)

ADJUVANT: 3M052-ALUM

SYSTEM: NHP

Praised by Dr. Fauci as one of the most promising COVID vaccines in a recent White House press briefing (May 13, 2021).
3M052-Alum With Spike Protein RBD Monomer Antigen

**ANTIGEN:** RBD MONOMER, CODON OPTIMIZED, PRODUCED IN PICHIA

**ADJUVANT:** 3M052-ALUM

**SYSTEM:** NHP

- Robust CD8+ T cell and Th1 biased CD4+ T cell responses in addition to live CoV-2 neutralizing and RBD binding antibody responses in serum, nasal and BAL.
- Superior immunogenicity achieved by alum-3M-052 vs. alum translated to significant reduction of peak (day 2) SARS-CoV-2 virus in upper and lower respiratory tracts compared to unvaccinated controls upon challenge.
- Significantly reduced viral burden in nasal and BAL fluids of several RBD+alum-3M-052 vaccinated animals led to a markedly reduced severity of lung inflammation and total pathology score when compared with controls.
Conclusions

• Four viable approaches for a pan-sarbecovirus vaccine Next-generation saRNA against SARS-CoV-2 S + N protein
  • Next-generation hAd5 DNA vaccine against SARS-CoV-2 S + N protein
  • Next-generation saRNA vaccine against SARS-CoV-2 S + N protein
  • Adjuvanted RBD protein
  • Heterologous prime - boost approaches

• Entering Phase 1 / 2 trials in Q1 2022

• Manufacturing scale up ongoing in USA, RSA and Botswana