Strategies to Broaden Immune Responses Induce by PanSarbecovirus Vaccines

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Outline

• Strategies for PanSarbecovirus vaccines

• Status on the first generation Duke PanSarbecovirus vaccine
Strategies for Development of PanSarbecovirus Vaccines

**Goal** is to develop vaccines to be prepared for the next betaCoV zoonotic spillover to humans, and, as well, for the current SARS-CoV-2 virus as variants emerge to current vaccines.
Strategies for Development of PanSarbecovirus Vaccines

• Variant specific RBD or Spike on a iterative platform- mRNA-LNPs, sortase conjugated nanoparticles.

• Add several RBD or Spike on one nanoparticle for cross-reactive responses.

• Identify cross-reactive epitopes on RBD and/or S2 and design immunogens that focus antibody responses on them.

• ? Vaccine that induces non-neutralizing antibodies and T cell responses.
Outline

• Strategies for PanSarbecovirus vaccines

• Status on the first generation Duke PanSarbecovirus vaccine
Generation of a SARS-CoV-2 receptor-binding domain nanoparticle vaccine

The RBD-sortase conjugated (sc)-ferritin nanoparticle (NP) induced antibodies to Sarbecoviruses (Group 2b) and to Pre-emergent animal CoVs

- Induced neutralizing antibodies for SARS-CoV-2 (WA-1), SARS-CoV-1 but not MERS (Group 2c).
- Induced neutralizing antibodies for Bat CoV SHC014, WIV-1, Pangolin CoV
- Protected against SARS-CoV-2 WA-1 strain in monkeys
The RBD-sortase conjugated (sc)-ferritin nanoparticle (NP) induced antibodies variants of SARS-CoV-2 including Delta and Omicron

- Induced antibodies that neutralized WA-1, Alpha, Beta, Gamma, Epsilon, Iota, Kappa, Delta and Omicron variants
- Protected in monkeys WA-1, Beta and Delta variant challenges
- Protected monkeys as a boost of mRNA-S2P-LNP

Breadth of SARS-CoV-2 Neutralization and Protection Induced by A Nanoparticle Vaccine

BioRxiv, 2022
The RBD-sortase conjugated (sc)-ferritin nanoparticle (NP) induced antibodies variants of SARS-CoV-2 including Delta and Omicron

Mark Lewis, Hanne Andersen, BioQual
1. In mice, RBD-sortase conjugated-ferritin nanoparticles protected from transmission and disease of SARS-CoV-2 WA-1 Beta variants

2. In mice, RBD-sortase NPs reduced lung viral loads and protected from disease from SARS-CoV-1 and Bat RSCH014 CoVs.
Key for design of PanSarbecovirus vaccines is to define those RBD regions that induce cross-reactive neutralizing antibodies and design immunogens that focus the response on them.

DH1284, Similar to S2K146

DH1193, Similar to S309
Ongoing work- Year 1 P01 AI158571, NIH, NIAID, DMID

• Group 2b (Sarbecovirus) + Group 2c (Merbecovirus) vaccine as modified mRNAs-LNPs

• Quadravalent cold virus vaccine for the two Group 2a (OC43, HKU1) and 2 Alphaviruses (NL63, 229E) as modified mRNAs-LNPs

• Experiments to determine the protective effect of non-neutralizing antibodies or T cell responses to protect.
Summary

• SARS-CoV-2 and other Sabecovirus RBDs have epitopes that broadly neutralize current VOCs and other Sarbecoviruses.

• Goal is to evaluate current vaccines and to design improved future immunogens to these epitopes.

• Future work will design RBDs that focus the immune response on conserved epitopes, as well as define epitopes on spike S2 that induce protective responses and are conserved across many CoV groups.

• Durability of responses is key for current and future vaccines.
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