Variant-proof versus pan-sarbecovirus vaccines

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What do we mean by pan-sarbecovirus?
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SARS-CoV-1

SARS-CoV-2

Wells et al., 2021, Virus Evolution
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What type of protection do we aim at?

• Protection from infection
  • Neutralizing antibody is needed
  • Target: likely RBD

• Protection from disease
  • Neutralizing antibody is needed
  • Other immune mechanisms (antibody effector functions, cellular immunity) may contribute
  • Target: likely RBD, spike

• Protection from severe disease
  • Binding antibody e.g. through effector functions
  • Anamnestic response through T-cells, memory B-cells
  • Target: spike including S2, potentially NP etc.
What should these vaccines cover?

**Variant-proof SARS-CoV-2 vaccine**
- Wild type SARS-CoV-2
- All current VOCs and VOIs
- All future VOCs and VOIs
- Artificial escape mutants
  - E.g. PMS20 (Schmidt et al., NEJM, 2021)
  - Mutants from yeast libraries (Jesse Bloom lab)
  - Etc.

**Pan-sarbecovirus vaccine**
- Wild type SARS-CoV-2
- All current VOCs and VOIs
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- Artificial escape mutants
  - E.g. PMS20 (Schmidt et al., NEJM, 2021)
  - Mutants from yeast libraries (Jesse Bloom lab)
  - Etc.
- All ACE2 binding sarbecoviruses
- All non-ACE2 binding sarbecoviruses
Sequential exposure to SARS-CoV-1 followed by SARS-CoV-2 vaccination leads to broadly neutralizing antibodies.

Tan et al., 2021, NEJM
Crossneutralization of non-ACE2 using sarbecoviruses is rare

Starr et al., 2021, Nature
Strategies and challenges

• Low hanging fruit
  • Exposure to SARS-CoV-1 and SARS-CoV-2 already induces broad immunity
  • Exposure to wild type SARS-CoV-2 and Omicron may also induce broader immunity already
  • Multivalent vaccines containing several variants may provide broader protection

• Vaccines that cover all ACE2 binding sarbecoviruses have the highest chance of success

• Despite broad binding across ACE2 binding sarbecoviruses, antigenic drift within SARS-CoV-2 may still be problematic
  • Antibody pressure may change conserved epitopes

• Mucosal immunity?
• Waning immunity?
What is needed moving forward

• A better understanding of crossprotection and protective mechanisms across sarbecoviruses

• Reagents and animal models to test crossneutralization and crossprotection

• A better understanding what type of cross-reactive immunity different exposures in humans induce (e.g. wt SARS-CoV-2 followed by Omicron)

• More research into non-ACE2 binding sarbecoviruses is needed to identify receptors, suitable cell lines for neutralization assays, animal models etc.

• What would the regulatory pathway for such vaccines be?