Evaluating neutralizing immune responses to potential pan-sarbecovirus vaccines

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WHO Global Consultation - Why do we need a pan-sarbecovirus vaccine?
January 28th, 2022
What do we mean by pan-sarbecovirus?
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Wells et al., 2021, Virus Evolution
What do we mean by pan-sarbecovirus?
Building a panel for measuring virus neutralization

Variant-proof SARS-CoV-2 vaccine

- Wild type SARS-CoV-2
- A selection of VoCs and VoIs
- BA.1 and BA.2 (Omicron)
- To probe the extremes
  - SARS-CoV-1
  - RaTG13
  - WIV
- Artificial escape mutants
  - E.g. PMS20 (Schmidt et al., NEJM, 2021)
  - Mutants from yeast libraries (Jesse Bloom lab)
  - Etc.

Pan-sarbecovirus vaccine

- A selection of sarbecoviruses from all clades (ACE2 and non-ACE2 binding)
- Wild type SARS-CoV-2
- A selection of VoCs and VoIs
- BA.1 and BA.2 (Omicron)
- To probe the extremes
  - SARS-CoV-1
  - RaTG13
  - WIV
- Artificial escape mutants
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  - Mutants from yeast libraries (Jesse Bloom lab)
  - Etc.
Example of panels (here for RBD binding assays)

SARS-CoV-2 clade (1b)
- SARS-CoV-2 GD-pangolin
- RaTG13
- GX-pangolin

SARS-CoV-1 2002/2003 human
- Sin852
- GZ-C
- Sino1-11
- Urbani
- HGZ8L1-A
- GD01
- PC4-127
- PC4-13
- PC4-137
- GD03T0013
- GZ0402
- SZ1
- LYRa1
- WIV
- Rs7327
- Rs4231
- RsSHC014
- Rs4084

SARS-CoV-1 clade (1a)

RBM

Starr et al., 2021, Nature
Available neutralization assays

• Live virus neutralization assays
  • Plaque reduction neutralization test (PRNT)
  • Focus reduction neutralization test (FRNT)
  • Microneutralization assay (MN)

• Pseudotyped particle assays
  • Lentiviral systems
  • VSV-based systems
    • Single cycle
    • Multi-cycle (replication competent)

• ACE2-RBD interaction inhibition assay (ARIIA)
Assessing neutralization

(b)

Degrace et al., submitted – courtesy of NIAID SAVE group
Assessing neutralization

• For SARS-CoV-2, VoC and Vol authentic virus could be used in PRNT/FRNT/MN
• For SARS-CoV and related viruses authentic virus could be used as well but may fall under e.g. Select Agent regulations or similar
• For many sarbecoviruses, only sequences are known but viruses have not be isolated
  • Could be used in pseudotyped particles (VSV, lentiviral systems etc.)
  • Could be rescued in e.g. SARS-CoV-2 backbones → likely GoF and therefore not recommended
• Artificial escape mutants can also safely be used in pseudotyped particle assays
• RBD-ACE2 interaction inhibition assays are likely less helpful (especially for non-ACE2 using sarbecoviruses)
Conclusions/needs

• A carefully curated panel of diverse sarbecovirus constructs for pseudotyped entry inhibition assays would be very helpful

• The panel could be distributed as plasmids e.g. by NIBSC for global use

• Reagents for assay standardization would be helpful
  • We would likely need to rely on mAbs like S2H97 are needed for this

• More research into non-ACE2 binding sarbecoviruses is needed to identify receptors and suitable cell lines for neutralization assays