ISOLATION OF PAN-SARBECOVIRUS MABs THAT NEUTRALIZE SARS-CoV-1 AND SARS-CoV-2 VARIANTS

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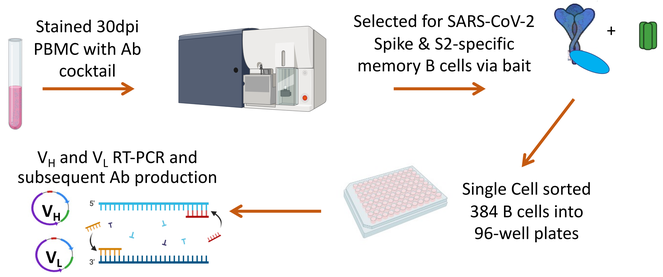
Background

- Two SARS-related coronaviruses (sarbecoviruses), SARS-1 and SARS-CoV-2, have spilled over to humans and caused outbreaks
- A large diversity of sarbecoviruses have been detected in various animal reservoirs, some of which bind the same entry receptor as SARS-1 and SARS-CoV-2
- Antibodies that can bind across sarbecoviruses and target more conserved regions in Spike may contribute to therapeutic efforts against future sarbecovirus outbreaks
- We have isolated broad and potent NAbs that retain robust neutralization activity despite viral evolution and are cross-reactive

We have identified novel antibodies that show **breadth in binding and neutralization against SARS-CoV-2 Variants of Concern and SARS-1**. Two NAbs potently bind **highly divergent SARS-related coronaviruses**. Given their breadth, these SARS-CoV-2 cross-reactive NAbs may be robust to viral evolution and thus could contribute to therapeutic efforts against future spillover events.

Methods

Isolated SARS-CoV-2 specific memory B cells from a Delta breakthrough infection case using Spike antigen



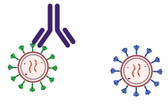
Donor C68 experienced a Delta breakthrough infection ~2 months post second dose vaccination. Here, we isolated memory B cells from a 30 dpi PBMC sample.

Functional characterization of isolated mAbs

Assess binding to a panel of SARS-CoV-2 Spike trimers

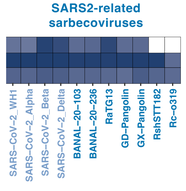
Assess neutralization activity against a panel of Spike-pseudotyped lentiviral particles





Assess binding breadth with a Pan-sarbecovirus RBD panel expressed on the surface of yeast

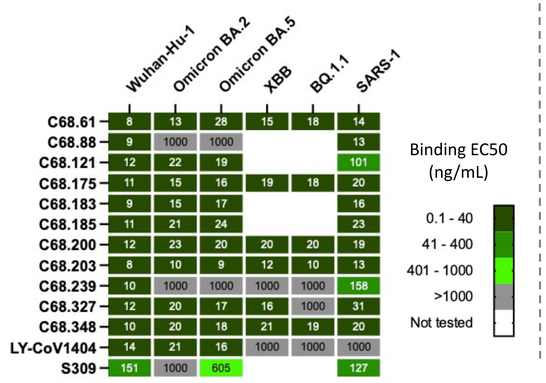
Epitope profile with yeast-display deep mutational scanning system of SARS-CoV-2 RBD



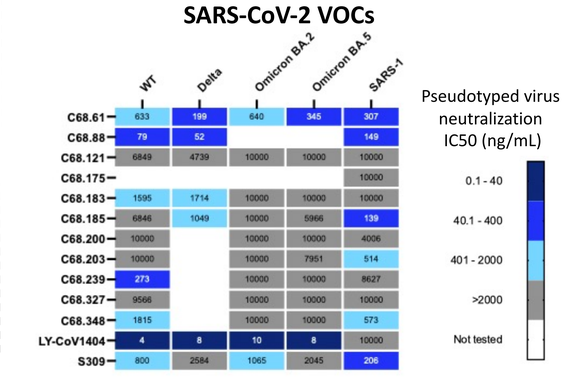


Results

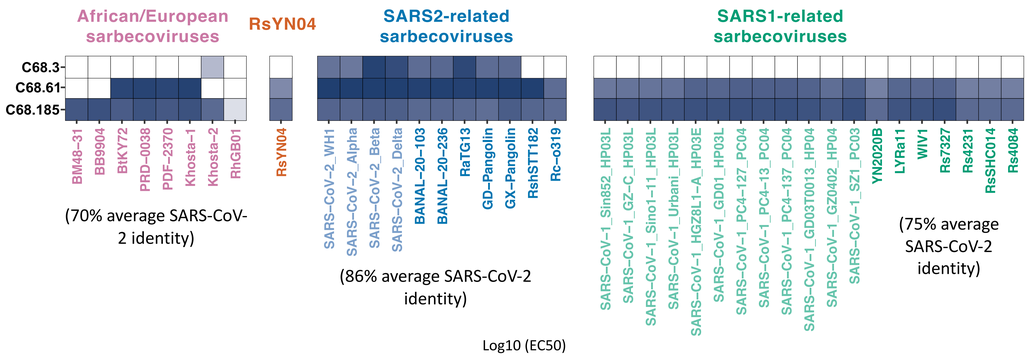
Identification of C68 mAbs with SARS-CoV-2 binding breadth and SARS-1 cross-reactivity

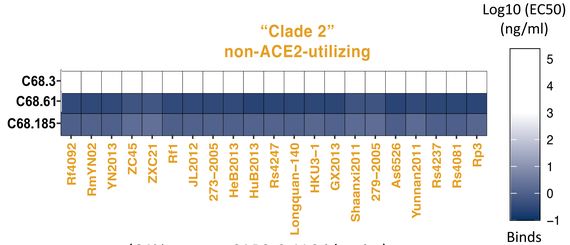


C68 NAbs can potently neutralize SARS-1 and some NAbs display neutralization breadth across SARS-CoV-2 VOCs



C68 mAbs bind highly divergent sarbecovirus RBDs

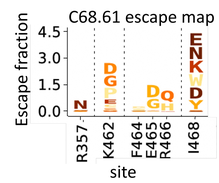


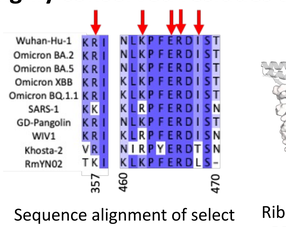


- C68.61 and C68.185 exhibited broad cross-reactive binding to RBDs from SARS-1 and related ACE2-dependent sarbecoviruses, and sarbecoviruses isolated in Europe and Africa
- C68 mAbs also potently bind RBDs of the highly divergent non-Ace2-utilizing sarbecoviruses

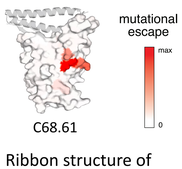
Results continued

C68 mAbs target highly conserved residues across VOCs

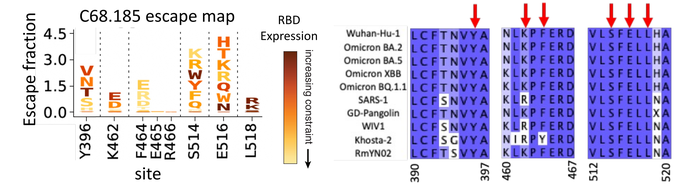




Sequence alignment of select SARS-CoV-2 VOCs and sarbecoviruses



Ribbon structure of RBD with sites of escape





C68.185

C68.61 and C68.185 target residues that constrain RBD expression and are highly conserved across VOCs and select sarbecoviruses

Conclusions

- We identified mAbs from a SARS-CoV-2-infected individual that bound and neutralized across SARS-CoV-2 VOCs and SARS-1
  - One of these, C68.61, displays broad and potent neutralizing activity
- C68.61 and C68.185 displayed robust binding activity across highly divergent sarbecovirus RBDs including sarbecoviruses that do not utilize ACE-2 for host entry. This binding breadth has only been observed in 1 other mAb
- Epitope profiling revealed that these NAbs target residues that constrain RBD expression and are functionally conserved across VOCs

Future Directions

Utilizing single-cell sequencing approaches:

- We plan to interrogate the longitudinal antibody response of C68
- We will assess the affinity maturation of antibodies clonally related to C68 mAbs

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