Structure, Volume *29*

Supplemental Information

A monoclonal antibody against staphylococcal enterotoxin B superantigen inhibits SARS-CoV-2 entry *in vitro*

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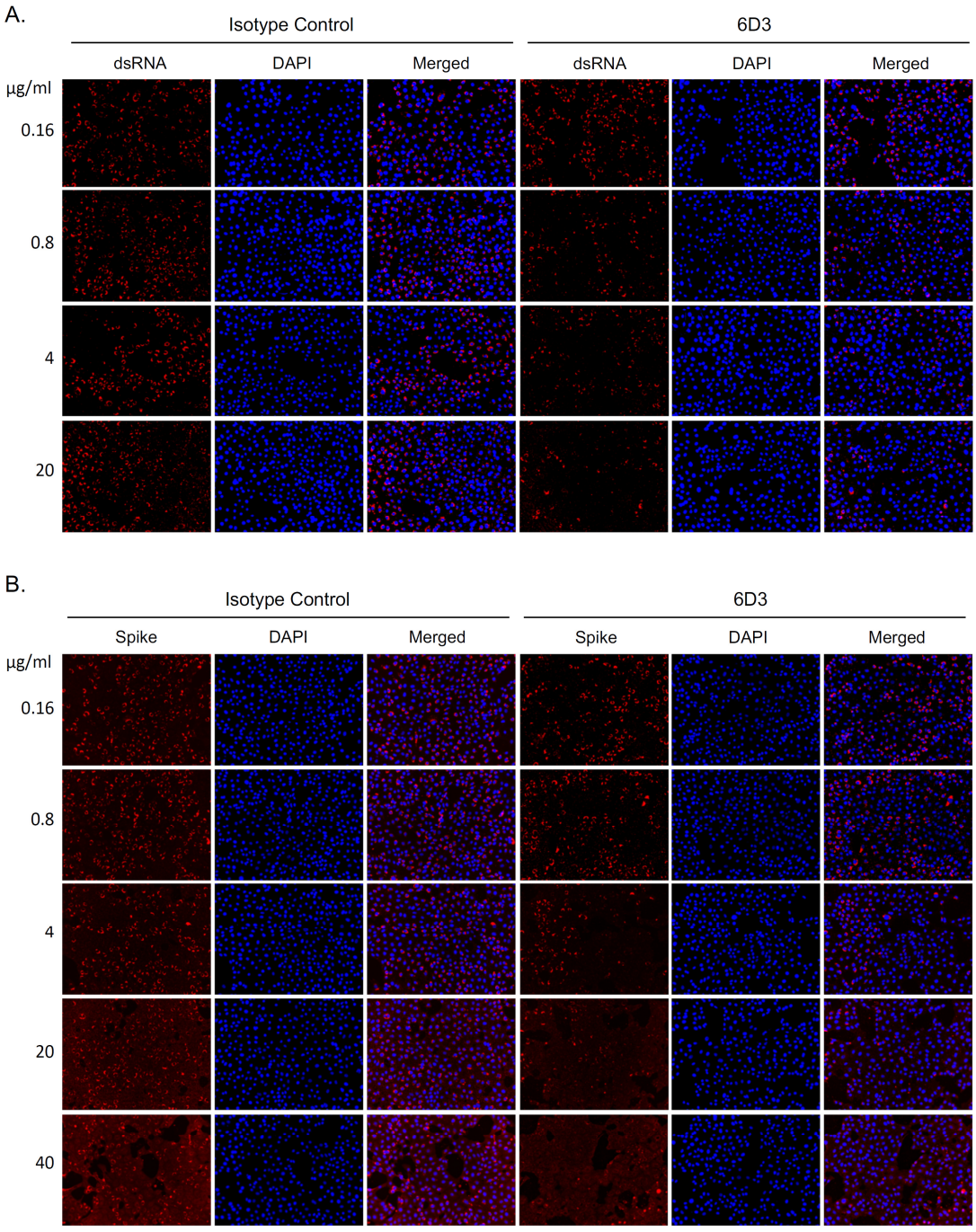

Figure S1: Monoclonal antibody 6D3 prevents SARS-CoV-2 infection, Related to Figure 4.

6D3 or isotype control antibodies (at indicated concentrations) were incubated with virus (100 PFU/well) for 1 hour at room temperature before addition to Vero-E6 cells ($5x10^3$ cells/well). 48 hours post infection cells were fixed and stained for dsRNA or SARS-CoV-2 spike protein. **(A)** Representative fluorescence images of 6D3 mediated inhibition of virus infection as measured by dsRNA staining. **(B)** Representative fluorescence images of 6D3 mediated inhibition of virus infection as measured by SARS-CoV-2 spike staining.

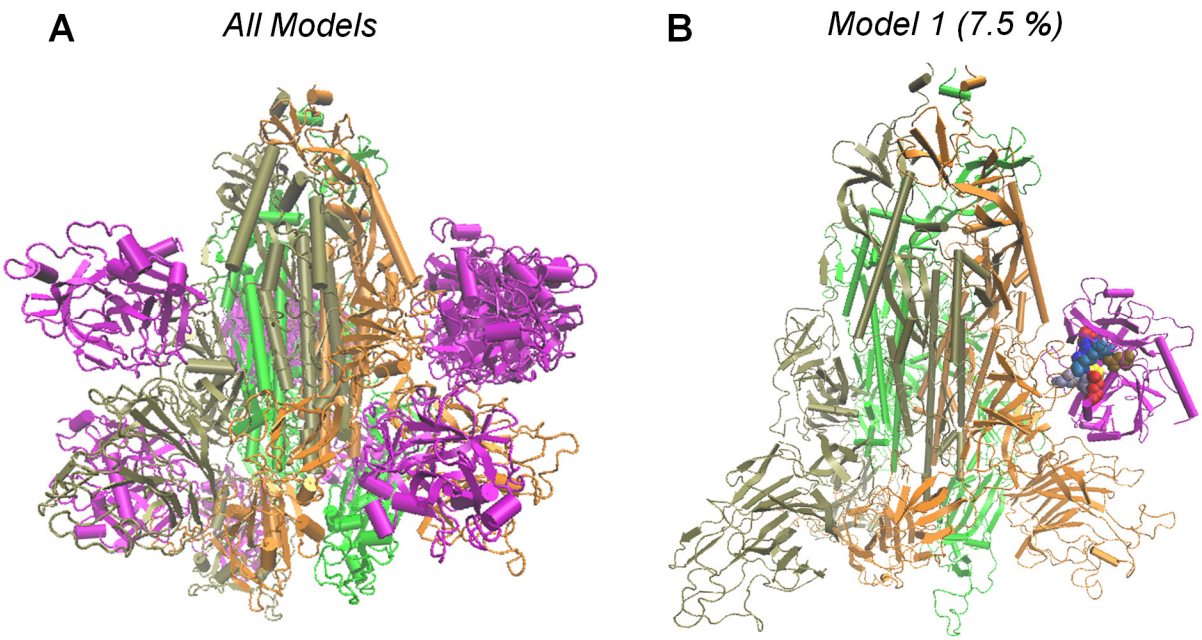

Figure S2: **Binding of TMPRSS2 to the SARS-CoV-2 Spike (S) protein yields an ensemble of conformers including one where the protease binds to the PRRA insert**, **Related to Figure 5A.**

(**A**) Overlay of models generated by the protein docking software ClusPro(Kozakov et al., 2017). The three subunits of the S protein are colored *tan*, *orange* and *green*; alternative poses of TMPRSS2 are shown in *magenta*. (**B**) Model 1 where TMPRSS2 catalytic residues are positioned in close proximity of the S1/S2 cleavage site. Three basic residues, R682, R683, and R685 from the S protein, are shown as van der Waals (vdW) balls in different shades of *blue*; the acidic residues of TMPRSS2 which form salt bridges with these three basic residues are displayed in *red* vdW balls with catalytic residue D345 in a *darker red* and catalytic serine residue S441 is shown as *yellow* vDW balls. *Model 1*, found to be most favorable energetically, is shown in **Figure 5A**.

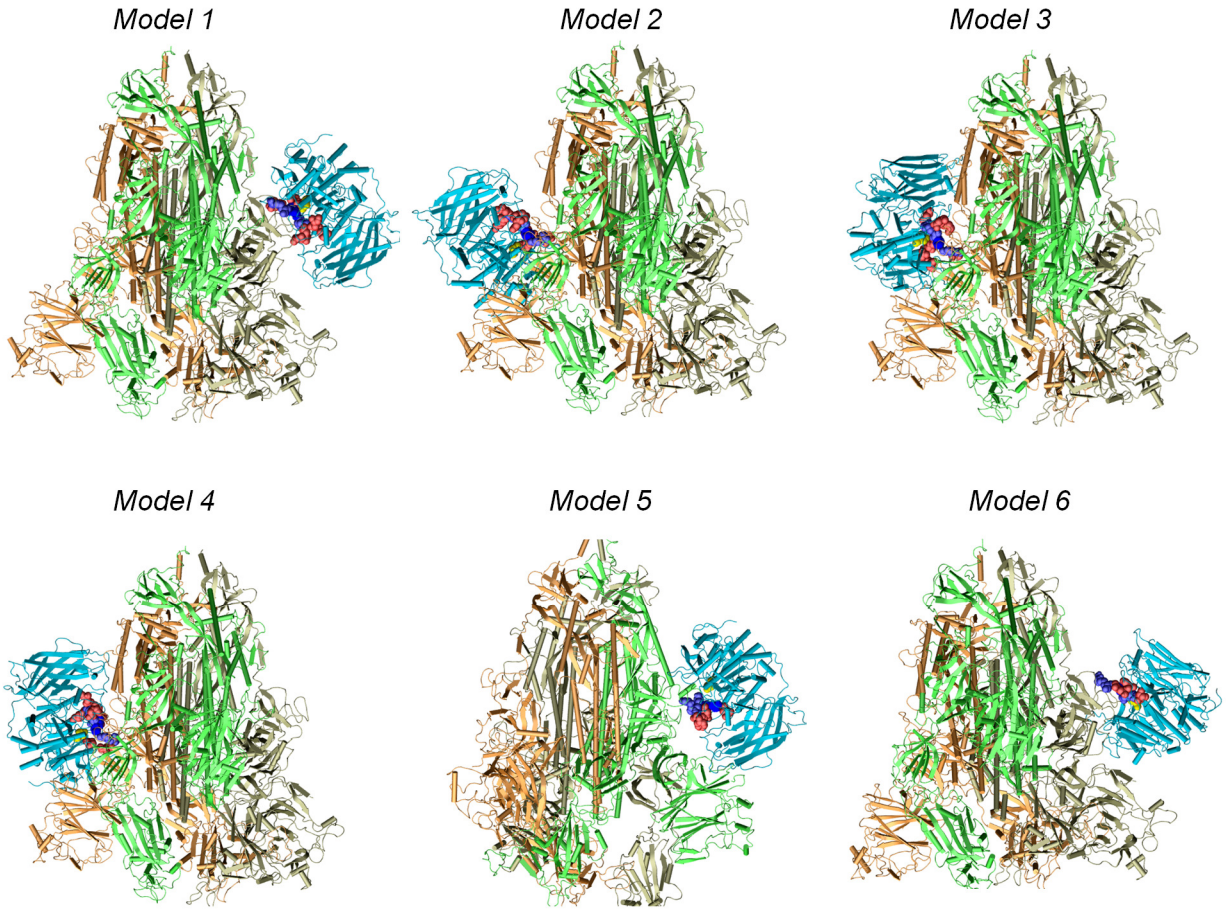

Figure S3: Structural models generated for SARS-CoV-2 S protein complexed with furin, Related to Figure 5B.

Six models, labeled *Model 1* to *Model 6,* representative of clusters formed by top-ranking conformers are displayed. In all models, the catalytic residues (D153, H194 and S368) of furin are in close proximity to the cleavage site $_{685}$RS$_{686}$ of spike. The subunits from the S protein are colored *tan*, *orange* and *green*; and furin is in *cyan* cartoons. Three basic residues R682, R683, and R685 from spike are shown in *blue* vdW representation; the acidic residues which form salt bridges with these three basic residues from spike are displayed in *red* vdW balls. Note that furin has multiple acidic residues that form intermolecular salt bridges in multiple poses: D153, D154, E236, D258, D264, D306, and E331, and the close proximity of the S1/S2 site is highly favorable, both energetically and entropically. *Model 5*, found to be most favorable energetically, is shown in **Figure 5B**.

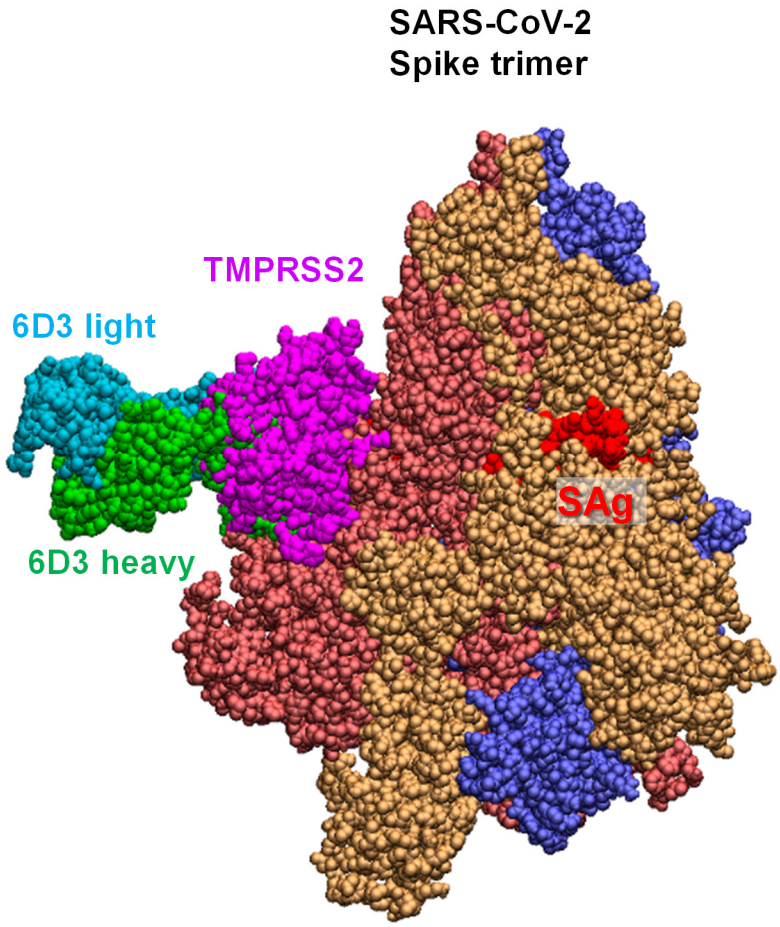

Figure S4: **Antibody 6D3 and TMPRSS2 compete for the same binding site on SARS-CoV-2 spike protein, Related to Figure 2 and Figure 5.**

The figure shows the overlay of the structural models generated for spike-TMPRSS2 and spike-6D3 complexes, which illustrates how TMPRSS2 spatially overlaps with the variable domains (not seen, eclipsed by TMPRSS2) of 6D3. The diagram is generated by superposing the S protein of the complexes predicted *in silico*. Similar results were found for the spike-furin complex (not shown). The three S subunits are colored *blue/violet*, *brick* and *dark orange*, with the SAg region colored *red* (visible for the *orange* monomer only).

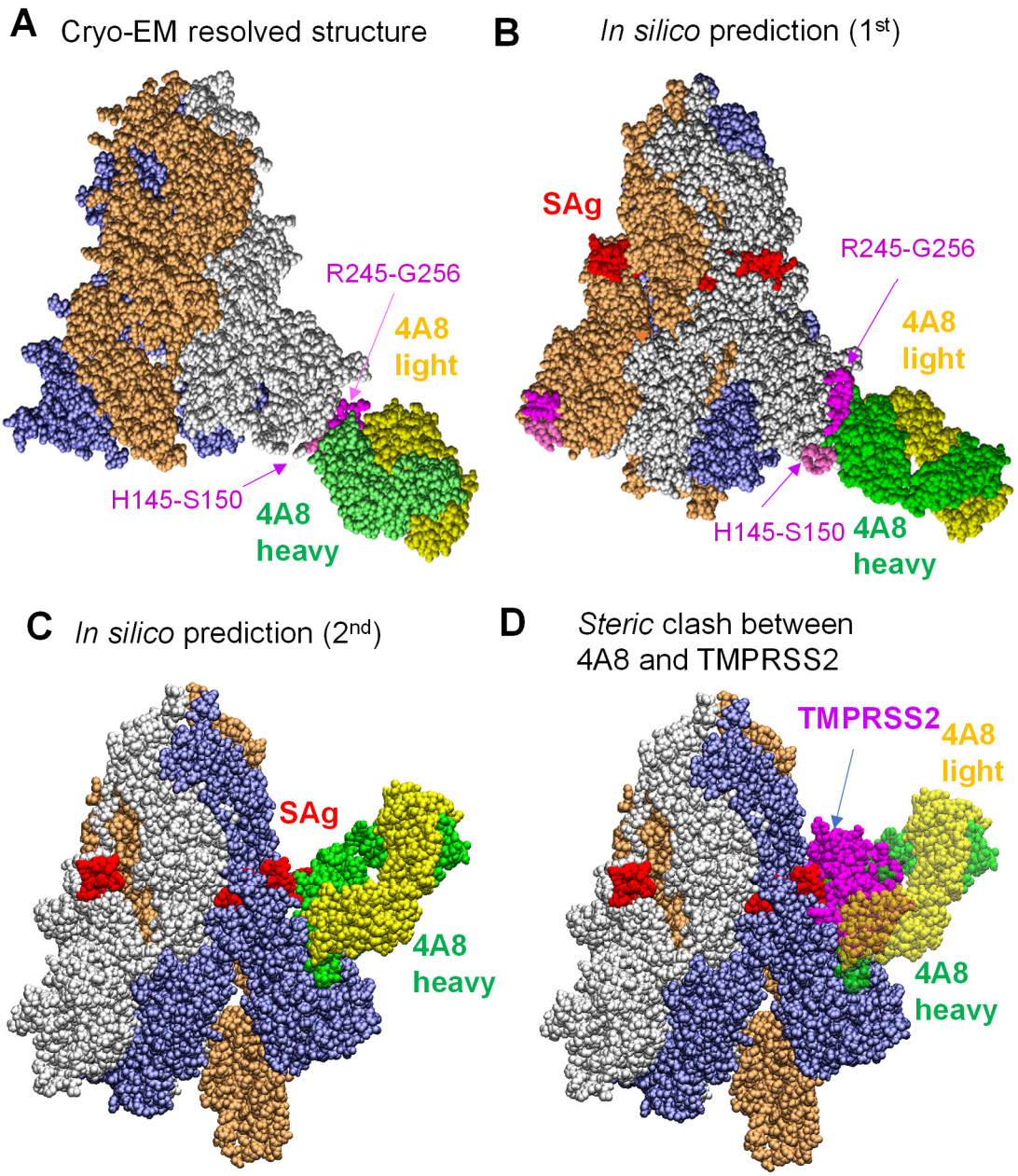

Figure S5: Examination of binding characteristics of SARS-CoV-2-neutralizing mAbs 4A8, Related to Figure 5 and Figure 6.

(A) Cryo-EM structure (PDB: 7C2L) (Chi et al., 2020); (**B-C**) Energetically most favorable conformers predicted for the S protein-4A8 complex. The former resembles the cryo-EM structure, involving the same segment, R245-G256, at the binding epitope of S. In the latter case, the viral SAg-like region which also overlaps with the S1/S2 cleavage site, serves as the 4A8-binding epitope. (**D**) Competition between 4A8 and TMRPSS2 for binding to the S1/S2 cleavage site, based on the overlap between the binding poses of these two substrates. The diagram is generated by superposing the S protein of the two complexes predicted *in silico*.