From Computational Analysis to Immune Evasion: Understanding the Interaction between SARS-COV-2 Spike Protein and Antibodies

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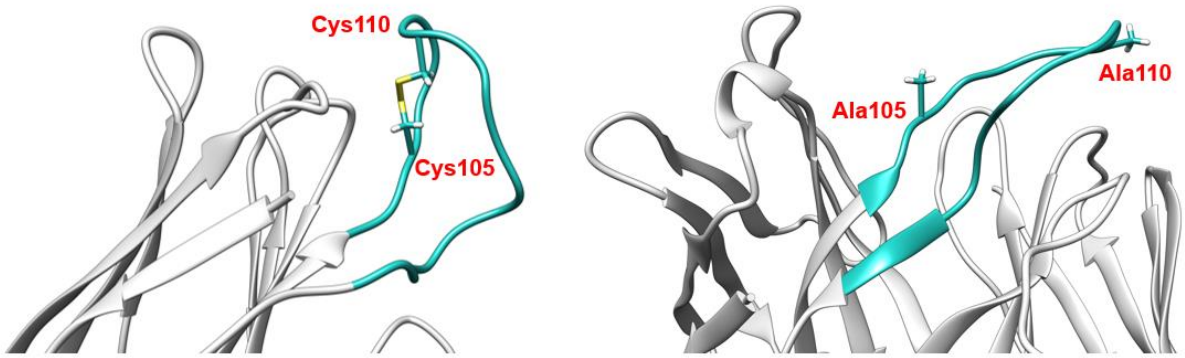
In this study, we employed free energy interaction analysis to identify key interaction sites between SARS-COV-2 spike protein and antibody structures. We generated a pipeline for mapping these interactions via in-silico alanine scans. Our results reveal the major interaction sites between the SARS-COV-2 spike protein and an early monoclonal neutralizing antibody. Noteworthy were the strong influence of the complementary determining loop structures CDR2 and CDR3 especially a tandem Arg motif in CDR2 and a disulfide inside the CDR3 that stabilises a kinked loop.

The neutralizing capabilities of this monoclonal antibody was strongly diminished against the beta virus variant. Structural analysis revealed that the E484K mutation of the beta variant causes electrostatic repulsion with the tandem Arg motif inside the CDR2. In an attempt to tackle the beta variant's escape mutations and to understand mechanisms of immune evasion, we utilized free energy interaction analysis to exchange all 20 amino acids and find potential antibody variants that restore binding capabilities. Potential AA exchanges produced only minor optimization potential. Experimental tests of these variants showed no restored neutralization against beta suggesting an evolutionary dead end for this type of antibody.

Variants without the intra CDR3 disulfide showed reduced binding against the WT variant and complete loss of binding against beta. MD simulation showed a more flexible CDR3 loop in the variant thus highlighting the role of cysteines for structural stabilization of CDRs.



MD simulation of free mab1-9 (left) and mab1-9 with intraloop Cys substituted by Ala (right) shows the CDR3 (cyan) and disulphide (yellow) to form a finger-like structure similar to the HIV PGT121 antibodies in the Ala mutant.