Modeling mutations in SARS-CoV-2 Spike protein

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SARS-CoV2 virus caused a pandemic with more than a million people deaths and the number grows. The studies on virus receptor binding domain (RBD) revealed its increased affinity to angiotensin converting enzyme 2 (ACE2) compared to SARS-CoV that caused 2002-2004 SARS outbreak. Thus, we attempted to simulate further evolution of RBD in this direction and suggest the class of drugs that could inhibit mutant RBD (RBD-mut).

We analysed RBD-ACE2 interface in the PyMOL and identified key amino acid residues of their interaction. Using the FoldX based pipeline we went through all possible missense mutations in these codons and selected combinations of them that: a) preserve the stability of RBD; b) increase the stability of the RBD/ACE2 complex. Two RBD-muts with high affinity were chosen for molecular docking - RBD-mut-1 (Y489F;Q498L) and RBD-mut-2 (Y453F;N487K;Y489F;Q498L). Our results show that one of the ways of the virus evolution can possibly be associated with an increase of RBD hydrophobicity.

Using AutoDock Vina based pipeline, FDA-approved molecules were docked against the selected RBD-muts, and the resulting complexes were ranked by interaction energy. Possible intermolecular interactions in the first 100 RBD-mut/ligand complexes for each RBD-mut were manually analyzed in PyMOL. The molecules that could reliably bind the interface region by the formation of polar contacts and hydrophobic interactions were suggested as potentially effective competitive inhibitors of each RBD-mut. For RBD-mut-1 molecules with heterocyclic core and polar groups on the sides were chosen as possible inhibitors. For RBD-mut-2 molecules with aromatic parts instead of heterocycles were suggested.