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Prediction and Analysis of Multiple Sites and Inhibitors of SARS-CoV-2 Proteins

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In the current COVID-19 pandemic, it is critical to understand, as swiftly as possible, how the viral proteins function and how their function might be modulated. The machine learning method Partial Order Optimum Likelihood (POOL) is used to predict binding sites in protein structures from SARS-CoV-2, the virus that causes COVID-19. Using the 3D structure of each protein as input, POOL uses computed electrostatic and chemical properties to predict the amino acids that are biochemically active, including residues in catalytic sites, allosteric sites, and other secondary sites. Docking studies are then performed to predict ligands that bind to each of these predicted sites. For instance, for the x-ray crystal structures of the main protease, POOL predicts two sites: the known catalytic site containing the catalytic dyad His41 and Cys145 and a second nearby site on an adjacent face of the protein surface. The x-ray crystal structure of the SARS-CoV-2 2’-O-ribose RNA methyltransferase (NSP16) protein has been reported in complex with its activating partner NSP10 and with two bound ligands, S-adenosylmethionine (SAM) and β-D-fructopyranose (BDF). POOL predicts three binding sites, including the catalytic SAM-binding site, the BDF binding site on the opposite side, and a third site adjacent to the catalytic / SAM-binding site. Predicted binding ligands (including selected compounds from the ZINC and Enamine databases, Chemical Abstract Service database compounds, and COVID-specific libraries from Enamine and Life Chemicals) are reported for several SARS-CoV-2 proteins. Kinetics assays to test for catalytic activity of the main protease and of 2’-O-ribose RNA methyltransferase in the presence of predicted binding ligands with high scores are underway. Theoretical and experimental methods are aimed at identifying molecules having inhibitory effects on the function of viral proteins. Supported by NSF CHE-2030180.

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The Design of a Destabilizer Peptide to Disrupt SARS-CoV-2 Fusion with Its Targeted Cell Membrane

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Cell entry of the SARS-CoV-2 has been suggested to involve binding of the head domain from spike protein on the virus with hACE2 protein on the human cells. The spike protein is composed of the S1 head, S2 domain which carries two heptad repeats (HR1 and HR2) and other domains; some of which are located between the HR1 and HR2. It is believed that the S1 head is cleaved upon binding to the hACE2 receptor, which liberates a fusion peptide in the spike protein that fuses with the cell membrane of the human cell. The HR1 and HR2 then interact with each other causing a structural change in the spike protein which leads to membrane fusion. Several studies have suggested to target the HR1-HR2 interaction to prevent viral passage into the cell. To block infection, a “destabilizer” peptide is designed against the coiled coil HR2 domain that may likely disrupt its structure. Since HR2 is more conserved than HR1, the peptide has the potential to cover more mutated “versions” of the virus. The destabilizer design was based on HR2 sequence with few amino acids substitutions to induce stronger binding to the HR2. This peptide may also compete with HR2 on HR1, albeit less potentially. In conclusion, a peptide was designed by computational chemistry to disrupt the HR1-HR2 binding thus possibly interrupting the transit of the virus inside the cell. (Supported in part by NIH/NHLBI R01HL149164.)

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Mechanism and Pathways of Inhibitor Binding to the Human ACE2 Receptor for SARS-CoV1/2

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Angiotensin converting enzyme 2 (ACE2) plays a key role in renin-angiotensin system regulation and amino acid homeostasis. Human ACE2 acts as the receptor for severe acute respiratory syndrome coronaviruses SARS-CoV and SARS-CoV2. ACE2 is widely expressed in epithelial cells of lungs, heart, kidney, and pancreas. It is an important drug target for treating pulmonary diseases, heart failure, hypertension, renal diseases and diabetes. It is also considered one of the primary targets for developing the treatment of SARS-CoV2. Despite its importance, the mechanism and pathways of ligand dissociation and binding in ACE2 remain unknown. Here, we have applied all-atom ligand Gaussian accelerated molecular dynamics (LiGaMD) simulations to investigate binding of the MLN-4760 inhibitor and associated protein conformational changes in the ACE2. The LiGaMD simulations successfully captured inhibitor binding and unbinding and provided important mechanistic insights into ligand binding to the receptor. In summary, this study allowed us to understand the mechanism of drug recognition by ACE2 receptor in order to design effective drugs against this therapeutically important target.

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Identification of FDA Approved Antiviral Drugs for COVID-19 Treatment using Unbiased Virtual Screening

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COVID-19 has led to a worldwide pandemic and treatments are limited and only used in severe cases. This study aims to identify FDA-approved antiviral drugs for the inhibition of host proteins of ACE2 and TMPRSS2 and key SARS-CoV-2 proteins of Mpro, NSP15, RBD of S protein, and RdRp domain of NSP12 for potential COVID-19 treatment through unbiased virtual screening. To reduce the bias of using a single molecular docking program for virtual screening, we used three docking programs, AutoDock Vina, AutoDock4, and RosettaLigand, and adopted unbiased rank-by-rank scoring method to identify top FDA-approved antiviral drug candidates for each receptor protein, which could be repurposed for potential COVID-19 treatment. A series of positive and negative controls of ligand-receptor binding were used to validate the unbiased virtual screening methods and set binding free energy threshold values as positive ligand-receptor binding for each docking program. With the validated unbiased virtual screening method, top 20 FDA-approved antiviral drugs for each of the studied host and SARS-CoV-2 proteins were identified. The FDA-approved antiviral drugs that could inhibit multiple studied receptors are also identified. The top drug candidates targeting multiple receptors are FDA-approved anticancer drug, HIV-1 antiretroviral drug, and hepatitis C (HCV) antiviral drugs. Interactions of the top drug candidate with target receptors are investigated. Results from this study presented the potential of repurposing FDA-approved drugs to target the host proteins and key SARS-CoV-2 proteins to inhibit SARS-CoV-2 from binding to host proteins and stop viral replications. The identified FDA-approved drugs with the reposition potential for COVID-19 treatments could inspire clinical trials, further accelerating the translation efforts to treat COVID-19. Clinical data from UAB showed that one of the identified drugs is correlated with a lower mortality rate among COVID19+ patients.

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Inhibitor Binding Influences the Protonation State of Histidines in SARS-CoV-2 Main Protease

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The main protease (M^{pro}) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plays a central role in the viral life cycle by cleaving the two SARS-CoV-2 polyproteins, and is an attractive target for antiviral therapeutics. Several promising lead compounds have already been identified, and structure-based drug design efforts targeting M^{pro} have been facilitated by the release of many apo and inhibitor-bound structures. Multiple histidines are present in the M^{pro} binding site, including His41 that is a part of the His41-Cys145 catalytic dyad. The protonation states of these histidines and the catalytic nucleophile Cys145 have been debated in earlier studies of SARS-CoV M^{pro}, but they have not been investigated for SARS-CoV-2. Here, molecular dynamics simulations were used to determine the structural stability of SARS-CoV-2 M^{pro} as a function of the protonation assignments for these residues in both the apo and inhibitor-bound enzyme. We found that the conformational stability of the binding site, bound inhibitors, and the hydrogen bond networks of M^{pro} are highly sensitive to these protonation assignments. Furthermore, distinct protonation state stabilities were observed for the two studied inhibitors: the peptidomimetic N3 and a ketoamide. Our results illustrate the importance of using accurate histidine protonation states to model the structure and dynamics of SARS-CoV-2 M^{pro} in both the apo and inhibitor-bound states, a necessary