Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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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

prerequisite for drug-design efforts. Longer simulations of the inhibitor-bound states were also performed using structurally optimal protonation states, and the stability of different inhibitor classes was investigated.

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Vitamin D and Its Derivatives as Promising Drugs Against COVID-19 - A Computational Study

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COVID-19 pandemic caused by SARS-CoV-2 presents a great threat to public health. Epidemiologic correlation of SARS-CoV-2 infection with vitamin D deficiency patients with critical symptoms was observed worldwide. Vitamin D has a central role in regulating body calcium homeostasis and musculoskeletal system. Vitamin D derivative $1,25(OH)_2D3$ alsohas important pleiotropic effects affecting almost all body functions and organs including neuroendocrine and immune systems. SARS-CoV-2 entry involves interaction between receptor binding domain (RBD) of spike protein in SARS-CoV-2 and human angiotensin-converting enzyme 2 (hACE2) receptor. Molecules with potential to inhibit the interaction of SARS-CoV-2 RBD and hACE2 could prevent SARS-CoV-2 cellular entry. In this study, we aim to determine the potential of vitamin D and its derivatives to inhibit hACE2 and SARS-CoV-2 RBD interaction and its underlying structural basis using combined molecular docking and molecular dynamics (MD) simulations. Available electron microscopy structure of hACE2 and SARS-CoV-2-RBD and the known binding sites between hACE2 and SARS-CoV-2-RBD provide structural basis for this study. Results showed that vitamin D3 and its derivatives are all favorable to bind either ACE2 or SARS-CoV-2-RBD at ACE2-RBD binding site. These results indicated that vitamin D3 and its derivatives have the potential to inhibit or block SARS-CoV-2-RBD binding hACE2. Electrostatic analysis results of $1,25(OH)_2D3$ with hACE2 and SARS-CoV-2-RBD showed that charged residues in the binding sites between ACE2 and SARS-CoV-2-RBD steadily hold $1,25(OH)_2D3$ polar groups through electrostatic interaction. Our MD simulations results showed that $1,25(OH)_2D3$ interaction with ACE2 and SARS-CoV-2-RBD resulted in their conformation and dynamical motion changes, particularly for its binding site(s), which further support the potential of vitamin D3 and its derivatives inhibition of SARS-CoV-2 binding hACE2 for entry. The results could propose vitamin D and its derivatives as promising drugs against COVID-19.

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Investigating Bacterial Malonyl-COA:Acyl Transferase as a Potential Secondary Target of 3-Hydroxy-3-Methyl-Glutaryl-COA Reductase Inhibitors

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Antibiotic-resistant gram positive bacteria are a serious global health hazard, causing severe infections as well as significant healthcare associated costs. Among these pathogens, *Staphylococcus aureus, Streptococcus pneumoniae*, and *Enterococcus faecalis* rely on the conserved mevalonate pathway to produce the peptidoglycan precursor isopentenyl diphosphate (IPP). Inhibitors developed against bacterial HMG-CoA reductase (HMGR), which converts HMG-CoA to mevalonate, appear to have a secondary bactericidal effect that is not yet understood. Evidence exists that HMG-CoA causes toxicity at accumulated levels, possibly due to inhibition of Malonyl-CoA:acyl transferase (FabD). FabD is therefore being investigated for inhibition both by HMG-CoA and our bacterial HMGR inhibitors. FabD is an initiating enzyme of the type II fatty acid cycle (FAS II) that transfers the malonyl moiety of malonyl-CoA to Acyl Carrier Protein(ACP), producing malonyl-ACP. Cross-linking and computational studies show that the interaction of ACP with each Fab enzyme in the elongation cycle, while apparently highly conserved, is transient and likely influenced by the size of the growing acyl chain. This study seeks to examine FabD-ACP binding in gram positive pathogens and identify HMGR inhibitors with secondary activity against FabD using structural and biophysical techniques. The native structure of *E. faecalis* FabD has been solved to1.74Å using Xray crystallography. Ligand co-crystallization and kinetics studies are ongoing with HMGR inhibitors that show thermal shift activity against FabD. The FabD-ACP interface will be examined by ITC using interface residue mutants, which have been identified through computational FabD-ACP docking simulations performed with LZERD (Local 3D Zernike descriptor-based Docking algorithm) and comparison to existing structures. Information gained will determine whether established mevalonate pathway inhibitors have dual activity against the fatty acid cycle, and will contribute a better understanding of FabD-ACP binding in gram positive pathogens.

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Discovery of Small Molecule Inhibitors and Activators of Death Receptor 5 Signaling using High Throughput Screening

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Apoptosis is essential for the proper function of the immune system. The tumor necrosis factor related apoptosis-inducing ligand (TRAIL) and its cognate death receptors (DR5 and DR4) regulate apoptotic responses in the immune system. TRAIL specifically induces apoptosis in tumor cells while showing very little or no toxicity in normal cells. Because of its high tumor specificity, recombinant soluble TRAIL and agonistic antibodies against its receptors are actively being developed for cancer therapy. In the current study, we developed a DR5 biosensor (DR5-GFP-RFP) to screen for compounds that specifically bind to DR5. Using live-cell high-throughput fluorescence lifetime screening platform, we have identified two compounds that increased the TRAIL-induced apoptosis and three compounds that decreased the TRAIL-induced apoptosis in Jurkat cancer cells. We will determine mode of action of these DR5 hit compounds using biophysical (SPR, FACS and TR-FRET) and biochemical (Co-IP, Immunoblotting and electrophoresis) assays. Inhibition and activation of DR5 signaling have important therapeutic applications in diseases such as nonalcoholic fatty liver disease and lymphomas, respectively.

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Investigating the Binding Interaction between β-Lactoglobulin and Vitamin B12: A Spectroscopic and Computational Approach

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Binding interaction of the major whey protein β-Lactoglobulin (βLG) with vitamin B12 is crucial for understanding the potency of βLG as a transporter for vitamin B12. Hence, the binding interaction of the βLG with vitamin B12 was studied using spectroscopic (UV-Visible absorption spectroscopy, steady-state & time-resolved fluorescence spectroscopy, synchronous fluorescence spectroscopy (SFS), circular dichroism (CD), and fluorescence correlation spectroscopy (FCS)) and computational (molecular docking and molecular dynamics (MD) simulation) tools. The quenching of the intrinsic fluorescence of βLG by vitamin B12 confirms the binding of vitamin B12 with βLG. The nature of the quenching is found to be static due to ground state complex formation. The calculated thermodynamic parameters suggest the binding process is hydrophobic. Synchronous fluorescence spectroscopy revealed that vitamin B12 affects the tryptophan residue microenvironment of the protein. Vitamin B12 does not alter the secondary and tertiary structure of βLG, as concluded from the CD and FCS experiments. From the molecular docking results, vitamin B12 is found to bind at the β- barrel site of βLG. The MD simulation results suggest that vitamin B12 bound βLG complex is stable. The secondary structural element analysis of MD simulation results show no alteration in protein secondary structure after binding with vitamin B12, which is matched with the experimental findings. This biophysical binding interaction study of βLG with vitamin B12 might have promising applications in the pharmaceutical and food industries.

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Mapping the Interactions of PKNB with Small Molecule Inhibitors using Plasma Induced Modifications of Biomolecules (PLIMB)

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Newly advanced PLIMB (Plasma Induced Modifications of Biomolecules) technology provides a uniquely powerful method for mapping protein-protein and protein-ligand interactions. PLIMB is a mass spectrometry