THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Rapid And Flexible Development Of Medical Countermeasures With Computational Structural Biology And Artificial Intelligence

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The rapid emergence of pathogens that threaten human health is apparent. Thus the rapid development of therapeutics against pathogens is imperative. Recent developments in Artificial Intelligence (AI), structural biology (SB), and Molecular Docking (MD) powered by High-Performance Computing allow for rapid evaluation of drug candidates against pathogen protein targets. The team at UNC Charlotte's Center for Computational Intelligence to Predict Environmental and Health Risks (CIPHER) have developed and demonstrated the use of AI, SB, and MD in a scalable, novel, and flexible molecular modeling computational workflow. We have applied these technologies to rapidly assess antibody performance against SARS-CoV-2 variants [1,2,3]. We have shown the variation of efficacy of the small peptide based malaria vaccine against divergent Plasmodium falciparum strains [4]. We have shown immune response variation against different betacoronaviruses [5]. Beyond assessment of existing therapeutics and host factors, we have shown the utility of computational modeling in the design of antibodies and other protein-based therapeutics [6]. We aim to further this research into design and assessment of small molecule drugs against evolving pathogens [7]. Furthermore, recent advancements in protein diffusion and large language models (LLMs) have shown promise for computational drug discovery by enabling the production of realistic antibody sequences that bind to desired antigen targets. We have shown the utility of such models for developing antibody therapeutic candidates in oncology [6] and shall optimize this workflow for pathogens. All of these computational workflows allow us to evaluate drug candidates and pathogen protein targets much faster and at higher volume for less labor that traditional biochemistry. We also can prioritize large libraries of drug candidates for follow on empirical validation with for more effective and rapid development of medical countermeasures in line with the DTRA-JSTO mission.

References

Ford et al. Predictions of the SARS-CoV-2 Omicron Variant (B.1.1.529) Spike Protein Receptor-Binding Domain Structure and Neutralizing Antibody Interactions. Frontiers in Virology, 2022
Ford et al. Predicting changes in neutralizing antibody activity for SARS-CoV-2 XBB.1.5 using in silico protein modeling. Frontiers in Virology, 3, 2023
Yasa et al. Predicting Antibody and ACE2 Affinity for SARS-CoV-2 BA.2.86 with In Silico Protein Modeling and Docking. bioRxiv, 2023
Dieng and Ford et al. Genetic variations of Plasmodium falciparum circumsporozoite protein and the impact on interactions with human immunoproteins and malaria vaccine efficacy. Infection, Genetics and Evolution, 2023
Tomezsko and Ford et al. Human Cytokine and Coronavirus Nucleocapsid Protein Interactivity Using Large-Scale Virtual Screens. Frontiers in Bioinformatics (In Press.), 4, 2024
Colby T. Ford. PD-1 Targeted Antibody Discovery Using AI Protein Diffusion. bioRxiv, 2024
Janies et al. Selection for resistance to oseltamivir in seasonal and pandemic H1N1 influenza and widespread co-circulation of the lineages. International Journal of Health Geographics. 9:13, 2010.

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