Discovery of COVID-19 N-Protein Active Sites for Efficient Antiviral Drug Target Treatment: An Innovative Approach using Torsion Angle Changes in Relation to Functional Activity of Viral N-Proteins

under the direction of

Dr. M. Saleet Jafri, M.D. Ph.D.

School of Systems Biology, George Mason University

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Abstract

COVID-19, a SARS-CoV-2 coronavirus originating from Southeast Asia, has resulted in 13.4 million cases and 580,000 deaths worldwide. The COVID-19 N-protein is responsible for viral replication by assisting in viral RNA synthesis and attaching the viral genome to the replicase-transcriptase complex (RTC). Novel vaccine systems, such as live-attenuated and inactive vaccines, are aimed at suppressing the N-protein by blocking its active sites involved in phosphorylation, oligomerization, and RNA binding. The purpose of this study was to determine active sites of the COVID-19 N-protein for drug targets by identifying torsion angle classifiers for N-protein structural change that correlated with the respective angle's residue inactivation of the N-protein.

In the study, classifiers with a minimum accuracy of 80% determined from NAMD molecular simulation data were analyzed by Principal Component Analysis and cross-validated by Logistic Regression, Support Vector Machine, and Random Forest Classification. Active sites were found at residue 189 for phosphorylation deactivation, residues 252 and 375 for preventing N-protein oligomerization, and residues 252 and 375 for blocking RNA binding. These residues not only were crucial for the aforementioned functions, but they also correlated with torsion angles psi 252 and phi 375 to 100% accuracy. The correlation for the residue matching angles phi/psi 189 was 90.7% accurate. Future applications include virtual drug screening to test the accuracy of drug targets and determining active sites for COVID-19 S-Protein and ACE2 protein, which are proteins used to bind to and invade host cells.