Thesis Defense - Thomas C. McCarty, PhD, Bioinformatics and Computational Biology
April 20, 2021 2:00 - 12:00 PM
VIEW EVENT
All are invited to attend the defense. For more information please contact Graduate Coordinator at kharrism@gmu.edu.

Candidate: Thomas C. McCarty

Program: PhD, Bioinformatics and Computational Biology

Date: Tuesday, April 20, 2021

Time: 12:00 PM

Place: https://gmu.zoom.us/j/99872843422?pwd=T2xXUTJmaVRBRGswUFQ1OU1vdGVnZz09

Title: Respiratory Syncytial Virus Vaccine Design Using Structure-based Machine Learning Models

Committee Chair: Dr. Iosif Vaisman

Committee Members: Dr. Saleet Jafri, Dr. Peter Collins, Dr. Dmitri Klimov

ABSTRACT:

When designing live attenuated RSV vaccine candidates, attenuating mutations can be developed through biologic selection or reverse genetic manipulation and may include point mutations, codon and gene deletions, and genome rearrangements. Attenuation typically involves reduction in virus replication, due to direct effects on viral structural and replicative machinery or viral factors that antagonize host defense or cause disease. However, attenuation must be balanced with retention of sufficient replication and antigen expression for immunogenicity. In the present study, we explored a new approach to discover attenuating mutations. Specifically, we used protein structural modeling and computational methods to identify amino acid substitutions in the RSV NS1 protein predicted to cause various levels of structural perturbation. Twelve different mutations predicted to alter the NS1 protein structure were introduced into infectious virus and analyzed in cell culture for effects on viral mRNA and protein expression, interferon and cytokine expression, and caspase activation. We found that: 1) a computer generated three-dimensional (3D) protein model structure appeared to be a suitable surrogate for use with structural stability prediction software and 2) the use of machine learning to predict amino acid substitutions that reduce the structural stability of NS1 resulted in various levels of loss of NS1 function exemplified by effects including reduced multi-cycle viral replication in cells competent for type I interferon, reduced expression of viral mRNAs and proteins and increased interferon and apoptosis responses.