

**UNIVERSITY GRADUATE SCHOOL BULLETIN
ANNOUNCEMENT**

Florida International University
University Graduate School

Doctoral Dissertation Defense

Abstract

Insights to Protein Pathogenicity from the Lens of Protein Evolution

by

Janelle Nunez-Castilla

As protein sequences evolve, differences in selective constraints may lead to outcomes ranging from sequence conservation to structural and functional divergence. Evolutionary protein family analysis can illuminate which protein regions are likely to diverge or remain conserved in sequence, structure, and function. Moreover, nonsynonymous mutations in pathogens may result in the emergence of protein regions that affect the behavior of pathogenic proteins within a host and host response. I aimed to gain insight on pathogenic proteins from cancer and viruses using an evolutionary perspective. First, I examined p53, a conformationally flexible, multifunctional protein mutated in ~50% of human cancers. Multifunctional proteins may experience rapid sequence divergence given trade-offs between functions, while proteins with important functions may be more constrained. How, then, does a protein like p53 evolve? I assessed the evolutionary dynamics of structural and regulatory properties in the p53 family, revealing paralog-specific patterns of functional divergence. I also studied flaviviruses, like Dengue and Zika virus, whose conformational flexibility contributes to antibody-dependent enhancement (ADE). ADE has long complicated vaccine development for these viruses, making antiviral drug development an attractive alternative. I identified fitness-critical sites conserved in sequence and structure in the proteome of flaviviruses with the potential to act as broadly neutralizing antiviral drug target sites. I later developed Epitopedia, a computational method for epitope-based prediction of molecular mimicry. Molecular mimicry occurs when regions of antigenic proteins resemble protein regions from the host or other pathogens, leading to antibody cross-reactivity at these sites which can result in autoimmunity or have a protective effect. I applied Epitopedia to the antigenic Spike protein from SARS-CoV-2, the causative agent of COVID-19. Molecular mimicry may explain the varied symptoms and outcomes seen in COVID-19 patients. I found instances of molecular mimicry in Spike associated with COVID-19-related blood-clotting disorders and cardiac disease, with implications on disease treatment and vaccine design.

Date: June 29, 2022

Time: 10:00AM

Place: ZEB 150

Zoom: <https://fiu.zoom.us/j/95419526174?pwd=aDNseE5qNDZVRzdHZ3JMalkrbW5uZz09>

Department: Biological Sciences

Major professor: Dr. Jessica Siltberg-Liberles