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Ph.D. THESIS DEFENSE

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MENTOR: Daniel Bolon, PhD
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"ADAPTING THE EMPIRIC APPROACH TO INVESTIGATE EVOLUTIONARY CONSTRAINTS IN INFLUENZA A VIRUS SURFACE PROTEINS"

Controlling influenza A virus (IAV) infections remains a challenge largely due to the high replication and mutation rates of the virus. IAV is a negative-sense RNA virus with two main surface proteins — hemagglutinin (HA) and neuraminidase (NA). HA and NA interact with sialic acid molecules on host cell receptors leading to virus entry and the release of progeny virus, respectively. Because HA and NA bind the same molecule on host cells with opposing effects, HA-NA functional balance is essential for optimal viral infectivity. However, the evolutionary constraints maintaining this balance, despite the high mutation rate of IAV, are not fully understood.

To systematically investigate the constraints shaping HA evolution, and to study how the HA-NA balance influences virus function and evolution, I adapted the Exceedingly Meticulous and Parallel Investigation of Randomized Individual Codons (EMPIRIC) approach to study the effects of varying NA activity on the HA fitness landscape. Analyzing effects of mutations in the HA signal sequence revealed that, despite structural constraints on viral RNA, this region was evolving faster than another region of HA used for comparison. Additionally, we identified HA mutations with adaptive potential under selection by the NA inhibitor oseltamivir. These results highlight the importance of the HA-NA functional balance in virus replication, and in the development of resistance to neuraminidase inhibitors.

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