M & I
Microbiology
and Immunology
University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

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"The opal termination codon regulates disease outcomes during alphavirus infection"

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1131 Bioinformatics

Dissertation Advisor: Dr. Mark Heise

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Doctor of Philosophy

ABSTRACT

Jenny Jones: The opal termination codon regulates disease outcomes during alphavirus infection
(Under the direction of Dr. Mark Heise)

Alphaviruses are members of the Togaviridae family of viruses. These viruses are arboviruses, most often transmitted by a mosquito host. Serious outbreaks of alphavirus infection occur worldwide and affect millions of people. Currently, the greatest risk to human health among the alphaviruses is chikungunya virus (CHIKV). CHIKV infection causes a range of symptoms, including fever, rash, and pain and swelling of the muscles and joints that can persist for months or years. The latest outbreak of CHIKV originated in the Caribbean islands in 2013 and spread throughout the North and South American continents, afflicting nearly 2 million patients. There are no effective therapies or vaccines against alphavirus infection, yet serious outbreaks of alphavirus infection continue to occur. Therefore, the study of factors that
contribute to severe alphavirus-induced disease is essential. The study of viral determinants of severe disease in particular is paramount to vaccine design. Here, we present an investigation of a single viral determinant of alphavirus pathogenesis: the opal termination codon. The opal termination codon is a conserved element within alphavirus genomes that regulates several
aspects of alphavirus replication. However, mutations to the opal termination codon have been identified in several alphaviruses. This work describes the consequences of such mutations on alphavirus disease severity. We report that mutation of the opal termination codon in CHIKV restricts severe disease in a mouse model. We further investigate how the opal termination codon
contributes to severe disease using a related alphavirus, Sindbis virus (SINV). We tested the possibility that the opal termination codon restricts the host stress response to SINV. However, we report no correlation between mutation of the opal termination codon and evasion of the stress response during SINV infection. Lastly, we instead provide evidence that mutation of the
opal termination codon specifically alters NF-kB signaling in response to CHIKV infection. This work identifies the opal termination codon as a key determinant of CHIKV disease outcomes. These findings aid our understanding of factors that restrict severe alphavirus-induced disease, and could contribute to the design of effective therapies against alphavirus infection.