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

DISSERTATION SEMINAR

Kara Eichelberger

"*Yersinia pestis*-host cell interactions during distinct inflammatory phases of primary pneumonic plague."

Friday, November 22, 2019
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1131 Bioinformatics

Dissertation Advisor: Dr. Bill Goldman

Presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy

ABSTRACT

Kara Eichelberger: *Yersinia pestis*-host cell interactions during distinct inflammatory phases of primary pneumonic plague
(Under the direction of Bill Goldman)

Inhalation of *Yersinia pestis* causes primary pneumonic plague, one of the deadliest manifestations of plague. The pneumonic form of plague has played a critical role in the severity of both historical and modern plague outbreaks, yet the host-pathogen interactions that govern the lethality of *Y. pestis* pulmonary infections are incompletely understood. Primary pneumonic plague progresses in two distinct phases as defined by host immune responses and disease pathology. Inhaled *Y. pestis* colonizes the lungs and replicates to high numbers during the initial asymptomatic pre-inflammatory phase. After this time, disease progresses into the pro-inflammatory phase, and *Y. pestis* can be detected in the bloodstream and other organs. This second phase is characterized by the rapid onset of symptoms, high levels of pro-inflammatory cytokines in the lung, and a massive influx of neutrophils into the alveolar spaces. The goal of the research described in this dissertation was to characterize *Y. pestis* interactions with host cells and manipulations of the immune response during the different phases of disease. In Chapter 2, I used transposon sequencing to identify genes involved in *Y. pestis* adherence in the lung early after inoculation. I identified enrichment of genes involved in the regulation and assembly of macromolecules and determined that *YPO3903,* encoding a hypothetical protein, mediates adherence of *Y. pestis* wild-type following intranasal inoculation. In Chapter 3, I investigated bacterial burdens and IL-1 cytokine levels as factors initiating the pro-inflammatory switch. High *Y. pestis* lung burdens, but not bloodstream burdens or the changing ratio of pro- and anti-inflammatory IL-1 cytokines, trigger the onset of inflammation in the lung during primary pneumonic plague. In Chapter 4, I examined the effects of *Y. pestis* infection on neutrophil degranulation during the pro-inflammatory phase. I determined that *Y. pestis* inhibits neutrophil exocytosis of primary granules through direct type III secretion system translocation of effectors YopE and YopH. Taken together, these findings demonstrate the ability of *Y. pestis* to manipulate pulmonary immune defenses and cause severe disease in the lung.