M & I
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University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

Ashley Bone

"Understanding the Regulatory Dynamic of the Two-Component Systems, PlrSR and BvgAS, During *Bordetella* Colonization of the Mammalian Respiratory Tract."

Friday, June 28, 2019
2:30 p.m.
6004 Marsico Hall

Dissertation Advisor: Dr. Peggy Cotter

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

ABSTRACT

Ashley Bone: Understanding the Regulatory Dynamic of the Two-Component Systems, PlrSR and BvgAS, During *Bordetella* Colonization of the Mammalian Respiratory Tract
(Under the direction of Peggy Cotter)

Pertussis is a severe respiratory disease caused by the bacterium *Bordetella pertussis*. Despite high vaccination coverage, the number of pertussis cases has rebounded in recent years. To combat this disease, more efficacious vaccines and improved knowledge of *Bordetella* pathogenesis is critical. Bacteria often use two-component systems (TCSs) to coordinate essential cellular processes in response to the diverse environments they encounter. In *B. pertussis* and the closely related subspecies *B. bronchiseptica,* the essential TCS, BvgAS, controls the expression of almost all known virulence factor-encoding genes and is considered the main virulence regulatory system. Recently, another TCS, PlrSR, was identified that is also required for *Bordetella* infection within the lower respiratory tract (LRT). However, why PlrSR is important for colonization is unknown. Using engineered strains of *B. bronchiseptica* and genetic reporters, we demonstrated that PlrS is required for the maintenance of BvgAS activity in the lungs of mice, indicating that PlrSR, and not BvgAS, coordinates virulence specifically in the LRT. Moreover, our data indicate that PlrSR may regulate genes that are required for persistence in the LRT independent of BvgAS. Importantly, these genes and their corresponding proteins may serve as new vaccine components or therapeutic targets. We have also shown that the Per-Arnt-Sim (PAS) domain of BvgS is required for BvgS inactivation in the absence of PlrS, indicating that the PAS domain is important for the PlrSR-BvgAS connection and functions as an independent signaling domain. Based on published data and our findings, we hypothesize that PlrSR controls the expression of high-affinity cytochrome oxidases (HACOs) that are required for bacterial respiration and maintenance of BvgAS activity in the LRT. We have demonstrated that two of four HACOs contribute to LRT colonization. However, BvgAS activity is unaffected by the loss of these HACOs and it is unknown if PlrSR regulates the expression of any HACO encoding genes. Together, this work provides a more detailed understanding of the coordinated regulation imposed by PlrSR and BvgAS to promote *Bordetella* survival within the mammalian host.