

COMBATting FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Understanding Natural Variation Of LPS To Promote Attenuation In *Francisella Tularensis*

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Emerging biological threats are difficult to predict and can arise from a multitude of scenarios, the most probable of which being from the formation of a novel variant of an already known pathogen. *Francisella tularensis* is a formidable pathogen that can infect a broad range of host cells and also is able to survive or persist in the environment. As a human pathogen, a unique lipopolysaccharide (LPS) on the cell surface of *F. tularensis* is crucial for virulence. Curiously, *F. tularensis* is known to vary this structure, but all variant forms identified to date are attenuated to some degree. In the literature, this phenomenon has been referred to as blue/gray phase variation with the “wild-type” considered the blue form and variants being the gray form. Phase variation also has been identified with the production of live attenuated vaccine strains as the presence of gray variants decreases the vaccine efficacy due to a loss of antigenicity. Little is known about the factors that promote phase variation in *F. tularensis*; however, understanding how this variation occurs genetically could allow for the development of a future live vaccine or a background strain for a vaccine to be derived. Furthermore, this transition from blue to gray variation could be exploited to identify small molecules that promote this event and attenuate *F. tularensis* as a post-exposure medical countermeasure. To understand the genetic root cause of this variation, whole genome sequencing was performed on a number of gray *F. tularensis* variants. It was found that single nucleotide polymorphisms in LPS biosynthesis genes appeared to be the root cause of this variation. One variant, a *wbtJ* mutant, was investigated further, and we found that this gene has a role in not only LPS synthesis, but phase variation, biofilm formation and virulence in *F. tularensis*.

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Disclaimers:

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