NIH Award from the National Institute of Allergy and Infectious Diseases

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- **Project:** ExoU and the Pathogenesis of Pseudomonas Pneumonia
- **Start Date:** August 13, 2009
- **Total Award Amount:** $376,391

**How the results of this project will benefit society:**
The bacterium *Pseudomonas aeruginosa* is one of the most frequent causes of pneumonia acquired in the hospital, a disease that has a mortality rate of 30 to 60 percent. Our overall objective has been to understand how this bacterium causes severe pneumonia. This information will lay the foundation for therapeutic interventions useful in the treatment of pneumonia.

**The problem the project is trying to solve:**
*Pseudomonas aeruginosa* (PA) is one of the two most frequent causes of hospital-acquired pneumonia (HAP), a disease that afflicts 10 percent of all patients admitted to intensive care units. Studies in humans and animal models have shown that the type III secretion system of PA plays an important role in the pathogenesis of infections caused by this bacterium. This system injects four effector proteins into mammalian cells during infection: ExoU, ExoS, ExoT, and ExoY. Our overall objective has been to define the contribution of this system and the individual effector proteins secreted by it to the pathogenesis of acute pneumonia. Our prior studies have demonstrated that secretion of ExoU has the most marked impact on morbidity and mortality in acute pneumonia, both in humans and animal models. It remains unclear how PA wields this potent weapon to cause overwhelming infection and death during pneumonia.

**How this project will work:**
This proposal will continue our studies utilizing a mouse model to clarify the role of ExoU in the pathogenesis of acute pneumonia and how ExoU secretion results in especially severe pneumonia. Our preliminary data show that whereas ExoU- *pseudomonas aeruginosa* (PA) bacteria are rapidly cleared from the lungs over the first 24 hours of infection, ExoU+ bacteria persist in high numbers. We therefore hypothesize that ExoU is targeted to specific cell types during the first 24 hours of infection, which in turn compromises pulmonary defenses and allows PA to persist in the lungs rather than be cleared. Our studies will broadly examine which pulmonary cells are targeted for injection of ExoU but will pay special attention to ExoU interactions with phagocytic cells, since these cells are rapidly recruited to the lungs during this time period and constitute a defensive barrier that must be overcome by any pathogen if it is to persist in the lungs. Such persistence lays the foundation for subsequent tissue injury and the pathophysiological manifestations of pneumonia. The completion of these aims will define the cellular targets of ExoU and the consequences of this targeting to the pathogenesis of early acute pneumonia. This information will in turn lay the foundation for future studies designed to block ExoU intoxication, which may lead to therapeutic interventions useful in the treatment or prevention of pneumonia.

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