Allen Lab Research Profile

The Allen laboratory studies *Helicobacter pylori* and *Francisella tularensis* with a focus on pathogen manipulation of macrophage and neutrophil function and dysregulation of the inflammatory response. Our approach is multi-faceted and addresses fundamental questions in cellular microbiology which lie at the interface of bacterial pathogenesis, phagocyte cell biology and innate immunity.

Helicobacter pylori colonizes the gastric mucosa of 50% of all humans elicits a chronic neutrophil-dominant inflammatory response that can progress to peptic ulceration or gastric cancer. *H. pylori* thrives in this neutrophil-rich environment, but how this is achieved is poorly defined. At the same time, understanding of neutrophil function has been revolutionized in the recent years by the discovery of their phenotypic plasticity and capacity to undergo subtype differentiation in different tissue microenvironments in vivo. We recently discovered that *H. pylori* induces N1-like subtype differentiation of human neutrophils, which is defined by profound nuclear hypersegmentation, changes in surface markers, and a proinflammatory and cytotoxic phenotype. These studies are significant as they are the first evidence that neutrophil subtype differentiation can be induced directly by bacterial infection in vitro. Current projects focus on elucidation of the underlying molecular mechanisms, including identification of new virulence factors and studies of the functional consequences with respect to neutrophil manipulation of NK cell, T-cell and epithelial cell function. Experimental approaches include analysis of intracellular signaling, cytokine production, cell viability, ATAC-Seq and dual RNA-Seq for simultaneous analysis of bacterial and host gene expression during infection.

Francisella tularensis is a facultative intracellular pathogen and the causative agent of the zoonotic disease tularemia. Inhalation of as few as 10 bacteria into the lungs can be fatal. In keeping with this, *F. tularensis* infects several cell types, including macrophages and neutrophils, and escapes the phagosome to replicate in the cytosol. In prior studies we identified receptors used by this organism to infect host cells, discovered multiple mechanisms used to disrupt neutrophil and macrophage defense mechanisms, and characterized novel phenotypes of mutants lacking the pathogenicity island gene *pdpC* or with defects in capsule and O-antigen production. Neutrophils are very short-lived, and current studies are based on our discovery that *F. tularensis* markedly prolongs neutrophil lifespan via inhibition of major apoptosis pathways. On the bacterial side, we have identified *F. tularensis* lipoproteins as important, acting via a mechanism that is influenced by a SNP in human *TLR1* that also influences the outcome of other infectious and inflammatory diseases. Other relevant virulence factors await discovery and characterization. On the host side we are conducting new studies based on the premise that neutrophil longevity is coupled to profound *F. tularensis*-driven metabolic reprogramming that promotes host cell survival while also providing nutrients to enhance bacterial growth.