EPIC-STI PROJECT 1 (STARNBACH): Stimulating Protective CD4+ T Cell Immunity to *Chlamydia trachomatis*

PROJECT SUMMARY

Infection with *Chlamydia trachomatis* is responsible for significant morbidity throughout the world. Women infected in the upper genital tract with *Chlamydia* can develop severe disease pathologies leading to conditions such as infertility and ectopic pregnancy. Human infection with *C. trachomatis* stimulates a $CD4^+$ T cell response that can protect against reinfection with the pathogen. However, T cell immunity in humans appears to be short-lived and may also influence the development of immunopathology. The prevention of *C. trachomatis* infections and their complications, derived from a better understanding of the host-parasite interaction and the development of a vaccine, could have substantial worldwide effects on both morbidity and health care costs.

We will work within the EPIC-STI to dissect the function of $CD4^+$ T cells responding to infection at the genital mucosa. We will address three major questions regarding *Chlamydia*-specific $CD4^+$ T cell function; how $CD4^+$ T cells are activated and home to the site of infection, how the IFNγ derived from these cells mediates protection, and how the genital tract environment alters protective $CD4^+$ T cell immunity. First, we will study the initial activation steps required to imprint antigen-specific $CD4^+$ T cells to home to the genital mucosa in response to infection. These studies will identify critical antigen presenting cell populations as well as homing molecules that are required for $CD4^+$ T cells to home to the site of *C. trachomatis* infection and provide protection (and determine whether those responses can be differentiated from those causing pathology). We will next investigate which IFNγ-stimulated pathways are required for immunity once activated pathogen-specific $CD4^+$ T cells traffic to the genital mucosa. These studies will be conducted in mice lacking the murine IRG response (and correlated with data from human sera obtained in EPIC-STI), allowing the discovery of IFNγ–dependent pathways that may play a protective role during human infection. We will combine these studies with *in vivo* imaging techniques so that we can describe $CD4^+$ T cell behavior and cell-cell interactions at the clinically relevant site of infection in real-time. Finally, we will determine whether the infected genital environment negatively impacts $CD4^+$ T cell-mediated protection or memory development. Previous work has suggested that IFNγ-induced expression of indole-2,3-dioxygenase (IDO) can directly induce a quiescent form of *C. trachomatis*. What remains unexplored is whether IDO or its catabolites suppress $CD4^+$ T cell immunity in the genital mucosa. Since IDO is not strongly induced in the murine genital tract we will use newly generated humanized mice that express human IDO at the higher levels observed in people (and again confirmed with human secretion samples). In developing candidate vaccines against *C. trachomatis*, a key objective will be to determine if protective immunity can be driven without resulting pathology. It is towards this goal of a safe, effective *C. trachomatis* vaccine that these experiments are ultimately directed.