THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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Development of Live Attenuated Vaccines Against Chlamydial Eye and Genital Tract Disease

Chlamydia trachomatis is the leading cause of bacterial sexually transmitted infections in the United States, with an estimated annual incidence of at least 3 million cases and the impact of related healthcare costs exceeding $2 billion per year. Sadly, young girls 15 to 19 years old represent 46% of infections, with as many as 1 in 10 adolescent girls testing positive for chlamydial infection! Worse, most infected individuals are asymptomatic, remaining undiagnosed and untreated. Antibiotic therapy will eliminate the infection, but it does not eliminate the silent complications of established pathology, including chronic pelvic pain, ectopic pregnancy, infertility, spontaneous abortion, premature births, and postnatal pneumonia and eye infections. Clearly, there is a compelling need to combat this disease with more than aftercare. Using genetically defined mouse strains that exhibited differential susceptibilities to Chlamydia disease, Darville has determined that certain immune responses are protective, whereas others lead to disease. She has observed that while an essential immune signaling pathway (Tolllike receptor-2) drives the tissue-damaging processes in chlamydial disease, the pathway is not required for development of a protective response. In this regard, toll-like receptors are a family of surveillance proteins that recognize characteristic molecules produced by bacteria, fungi and viruses; and are important components of the innate immune response that typically occurs with infection. Based on these insights, Darville and her collaborator made the exciting discovery that removal from Chlamydia of the resident plasmid, a piece of extra-chromosomal DNA that replicates independently from the rest of the genome will, in a female mouse model, result in a bacterial strain attenuated in its ability to cause disease but capable of eliciting a protective immune response. Darville proposes that if she can demonstrate this approach is as effective in guinea pigs as it is in mice, then plasmid-deficient strains of Chlamydia should be useful as candidate antichlamydial vaccines in humans (the FDA requirement for a vaccine to enter into pre-clinical studies is effectiveness in two independent animal models of disease).