THE HARTWELL FOUNDATION

2008 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **David J. Hackam, MD, Ph.D.**
Associate Professor
Department of Surgery, Cell Biology and Physiology

Institution: **University of Pittsburgh**

Proposal: **Discovering Novel Immune Modulatory Agents Using High Content Screening in the Treatment of Neonatal Necrotizing Entercolitis**

Based upon his pioneering research, Dr. Hackam proposes target drugs to prevent and cure necrotizing enterocolitis (NEC), an often-devastating bacterial infection of the intestine seen in premature infants, where portions of the bowel undergo tissue necrosis (death). NEC affects approximately 25,000 babies per year, by causing profound impairment of multiple organ systems. With a mortality rate of nearly 50%, NEC is the leading cause of death from gastrointestinal disease in children. There does not appear to be a specific cause of the disease, but lack of adequate blood flow to the intestine in the presence of bacterial infection appears critical to its development, especially in a vulnerable, immune-compromised low birth-weight or preterm babies. Although NEC presents initially as a gastrointestinal disease, patients may rapidly develop systemic infection, sepsis, and multi-system organ failure. There are currently no effective means to counteract NEC, as clinicians can only offer antibiotics and remove surgically the necrotic intestine, which are both often ineffective. New strategies to prevent and cure this devastating disorder are required. Toward this end, Dr. Hackam recently discovered that the expression and signaling activity of a molecular "switch" called toll-like receptor 4 (TLR4) was elevated in the intestine of human infants with NEC. By contrast, he was able to demonstrate that knockout mice lacking TLR4 received protection from the development of NEC. Administration of a specific product known to activate the immune system of mice by blocking TLR4-mediated immunity and inflammation in their intestine also reduced the severity of experimental NEC. To avoid the non-selective inhibition of signaling in all cells and avoid systemic toxicity, Dr. Hackam proposes a bold and innovative strategy that will reduce the risk of NEC by inhibiting selectively TLR4 signaling in certain types of cells. To exploit his discoveries, he will seek to identify specific inhibitors of TLR4 signaling in the human intestine utilizing a strategy of high content screening of molecular chemical libraries. If successful, such target drugs will improve the management and long-term prognosis of this devastating bacterial infection in neonates.