THE HARTWELL FOUNDATION

2010 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Gurol M. Suel, Ph.D.**
Assistant Professor
Department of Pharmacology

Institution: **University of Texas Southwestern Medical Center**

Proposal: **Treatment of Inflammatory Bowel Disease with Engineered Microbial Nano-Devices**

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, are incurable chronic disorders that affect at least 50,000 children in the United States; in total about 1.5 million Americans suffer from the disease. While IBD can develop at any age, it commonly affects children and young adults between the ages of 10 and 30. It usually involves the small intestine, but may affect the entire digestive tract, including the mouth, esophagus, stomach, duodenum, appendix or anus. About 25% of patients are less than 18 years old and suffer painful GI symptoms, including the debilitating effects of an intestinal fistula (connection between the bowel and other organs or the skin), increased risk for malnutrition, growth deficits, delayed pubertal onset, and colorectal cancer. Treatment often involves systemic administration of high doses of steroids and immunosuppressants, therapies inadequate for long term management of IBD. Extended use of these drugs can lead to numerous adverse side effects, including Cushing's disease, osteoporosis and associated bone fractures, type II diabetes, cataracts, and increased risk of infection and cancer. When drug treatment is unsuccessful, removal of the colon is often the only alternative. To address these issues, Dr. Suel proposes to design and create a nano-sized drug delivery device (engineered bacterium) that autonomously recognizes diseased tissue in the bowel and delivers anti-inflammatory drugs directly to affected areas. To engineer the device, he will build upon his previous efforts (2009, 2010) that demonstrated how genes and proteins in biology are analogous to resistor and capacitor elements in electronic circuits. In effect, cellular processes are regulated in large part by genetic circuits, with particular architectures of interactions among genes and proteins identifiably responsible for distinct properties of the cell. For example, gene replication generates DNA, which leads through the processes of transcription and translation to the formation of protein. Circuits for transcription (a small set of recurring regulation patterns or network motifs) control the regulation of genes. By these means, genetic circuit architectures are able to control biologically important cell behavior such as signaling, periodicity, and susceptibility to noise from the environment; dynamic behavior that in part represents the cellular response to maintaining an environment critical for normal cell function. By engineering the interaction between genes and proteins in new combinations Gurol will create synthetic genetic circuits in a bacterium that can direct it to perform specific tasks. If successful, his engineered microbial nano-device will provide children a more effective treatment for IBD that is local to the gut and without the currently employed and often devastating side effects of off-target, systemic drug therapy.