THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Neal M. Alto, Ph.D.**
Assistant Professor
Department of Microbiology

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

Proposal: **Discovery of Cancer Inhibition Pathways by Novel Bacterial Toxins and Effector Proteins**

Over the course of evolution, microbes have performed life and death "experiments" on their hosts to develop ways of benefitting themselves without killing their hosts. They have developed such limited virulence with great success. Bacterial virulence is based upon retaining the most efficient mechanisms that benefit bacterial growth, while preserving host tissue integrity. Evolutionary pressure has produced bacterial toxins with amazing specificity and potent activity toward essential host cellular processes. By mimicking regulatory factors that control the physiological wellbeing of human cells, these toxins have evolved in order to gain control of human cell-to-cell communication systems. Based upon his discovery that many toxins encoded by pathogenic Gram-negative bacteria inhibit genes that are commonly mutated in cancer, Neal proposes that such toxins might be useful to selectively inhibit growth and proliferation of cancer cells. In the United States, approximately 10,000 new cases of pediatric cancer are diagnosed each year of which many are incurable. Standard of care includes often dangerous drugs (chemotherapy), hazardous radiation, and problematic surgery. Unfortunately, developing children are particularly susceptible to the devastating side effects caused by these treatments, including fatigue, flu-like symptoms, severe pain, cognitive impairment, physical limitations and susceptibility to other diseases. Moreover, the causes of cancer, especially relapse and metastasis, are diverse and often poorly defined, making selection of treatments a particularly challenging aspect of therapy. Developing new therapeutic strategies that selectively eradicate tumors while sparing normal tissues from damage would vastly improve children's survival rates and their future quality of life. To address this unmet need, Neal proposes a novel hypothesis with the potential to be paradigm changing: cancer growth and proliferation can be selectively inhibited through cellular expression of bacterial toxins. Indeed, Neal has identified a unique relationship between the actions of bacterial toxins and the genes involved in abnormal cellular growth (oncogenes) and those that naturally protect cells from the path to cancer (tumor-suppressor genes). He has engineered a library of over 205 such toxins, which will be used in a high-throughput assay designed to eliminate two particularly aggressive and deadly childhood cancers, rhabdomyosarcoma and neuroblastoma. After the targets of the toxins have been identified, therapy will be evaluated in an animal model and drug development will begin. If he is successful, treatment of childhood cancer will be more effective, with the potential to eliminate the devastating side effects observed in current therapies.