THE HARTWELL FOUNDATION

2011 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Christopher Deppmann, Ph.D.**
Assistant Professor
Departments of Biology and Biomedical Engineering

Institution: **The University of Virginia**

Proposal: **Childhood Metabolic Disorders: Targeting the Peripheral Nervous System to Reverse Obesity**

The question of how the body detects and responds to energy requirements and nutritional status is a long-standing and fundamental issue in medicine. With CDC estimates suggesting over 15% of pre-school children in the U.S. are afflicted with childhood obesity/metabolic disorder, there is a looming health and economic crisis driving an acute public health concern. More than 12 million children age 2-19 are overweight and clinically obese. Disorders strongly linked to obesity variously include fatty liver, hypertension, coronary heart disease, stroke, sleep apnea, and a high propensity for mental health disorders. About 25% of obese children have impaired glucose tolerance and 4% go on to develop type II diabetes, which 20 years ago was restricted almost exclusively to individuals over 40. How crucial metabolic processes are disrupted in childhood, leading to metabolic syndrome (*diabesity spectrum disorder*) is an unsolved and urgent problem, with most attention focused on insulin regulation and not what regulates energy utilization to-and-from fat stores. The autonomic peripheral nervous system (outside the brain and spinal cord) acts to regulate body functions both below the level of consciousness (heart rate, digestion, respiratory rate, salivation, perspiration, diameter of the pupils, etc.) and in parallel with the conscious mind (respiration, etc.). Through the release of norepinephrine, it also regulates fat breakdown for energy liberation. It is unknown whether modulating peripheral nervous system activity by targeted drug therapy could be a viable option to treat diabesity spectrum disorder. In this regard, Chris proposes a paradigm shift: the peripheral nervous system may be as important as insulin for regulating fat storage and may represent a better target for anti-obesity and diabetes prevention therapies. Using a unique mouse model to study developmental competition between sympathetic neurons for survival, he discovered a significant change in the diameter of the cell bodies of peripheral neurons that regulate the ability to respond to changing diet and weight loss. The mouse was resistant to normal diet-induced changes in neuron cell body diameter and lost at least double the weight of normal mice. Based upon these observations, Chris proposes that the sympathetic nervous system may represent a novel independent sensor for the nutritional state of the animal and he now seeks to identify a class of chemical compounds that when safely administered in combination with diet would reverse obesity. If he is successful, clinical trials aimed at treating childhood metabolic syndrome will follow.