THE HARTWELL FOUNDATION

2009 Individual Biomedical Research Award

Review of Proposed Research

.Investigator: **Ruth Ley, Ph.D.**
Assistant Professor
Department of Microbiology

Institution: **Cornell University**

Proposal: **Host-Microbial Interactions Underlying Metabolic Syndrome**

Today, health problems associated with childhood obesity are some of the most daunting in the United States. At the cutting edge of a paradigm shift within medical science, Ruth Ley proposes that gut microbiota (microorganisms that live in the digestive tract) are one of the triggers of metabolic syndrome (insulin resistance, hypertension, elevated cholesterol, increased risk for blood clotting, and obesity), and thus offer a promising target for therapeutic intervention. While we are born germ-free from a sterile womb, our intestinal tract is rapidly colonized by microbes like bacteria, fungi, and even protozoan parasites, which collectively become our microbiome. From birth until we reach adulthood, our intestine carries about ten times as many microorganisms as all the cells in the rest of our body. A new view of human biology is emerging: we are a composite of many species and our genome is an amalgam of H. sapiens plus those contributed by the genomes of our personal microbiome. For example, based on observations made by Dr. Ley in controlled experiments, when the gut microbiotas from obese Ob/Ob-deficient (knockout) mice were transplanted into germ-free animals, the latter remarkably experienced a significant weight gain. She has also demonstrated that non-obese diabetic mice, deficient in the gene Myd88, were unexpectedly protected from developing type-1 diabetes by their gut microbiota. Surprisingly, others have shown in TLR5 knockout mice that develop metabolic syndrome that simply transferring the gut microbiota alone was sufficient to transfer the syndrome to germ-free mice. Similarly, in T-bet knockout mice that develop intestinal colitis, the syndrome can be transmitted just by cohabitation with unaffected wild type littermates. Given the applicability of animal models to the human condition, a thorough understanding of our biology and our health will, no doubt, require taking into account the composition of our gut microbiota and its interaction with our body. In this regard, Dr. Ley seeks to understand in metabolic syndrome how the TLR5-deficient mice alter the relative abundance of bacterial species in the gut and to what extent a high-fat diet contributes to altering the microbiota. If Dr. Ley is successful, she anticipates it will be possible to “reshape” a microbiome out of balance; to “educate” the immune system of children in order that they will maintain a healthy microbiome throughout their life. In this way, children at risk for metabolic syndrome can be protected from developing the chronic disease. Successful manipulation of the microbiome towards a healthy state could have widespread applicability in alleviating disorders associated with other disease states, as well.