THE HARTWELL FOUNDATION

2010 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **Stacey Schultz-Cherry, Ph.D.**
Associate Member
Department of Infectious Diseases

Institution: **St. Jude Children's Research Hospital**

Proposal: **Regulation of Intestinal Epithelial Tight Junctions by a Novel Viral Enterotoxin**

Gastroenteritis and the sequelae that produce diarrhea are the most common causes of morbidity and mortality in young children. In the United States alone, approximately 9% of all hospitalizations in children under the age of 5 are due to diarrhea; more than 200,000 children under the age of 5 are hospitalized annually with an even higher incidence for children less than 3 years of age. Of great concern in children, repeated episodes of acute diarrhea increase its persistence and significantly impair the child's growth rate. Immunocompromised children are even more susceptible to diarrhea and develop chronic systemic infections, often leading to wasting and fatal encephalitis. Children who suffer from viral gastroenteritis are infected with enteric viruses that are often linked to local outbreaks, where transmission occurs through contaminated food or water, direct contact or contact with infected animals. Using the turkey as a small animal model (2007), Stacey found that in baby turkeys, astrovirus induces diarrhea by a novel, previously unknown mechanism. The virus disrupts the junctions between the cells that line the intestine by means of liberating a toxin, independent of cellular damage or an inflammatory response. In fact, she recently found that oral administration of only the astrovirus coat protein (i.e. the putative enterotoxin) is sufficient to induce acute diarrhea in baby turkeys (manuscript in preparation). This appears to be the first evidence that any viral coat protein is an enterotoxin. Intriguingly, and most importantly, astroviruses have been found in 3-20 % of children with diarrhea, with up to 50% of astrovirus infections occurring as a co-infection with other enteric pathogens. Her proposal is to examine the prevalence and diversity of viruses in children at St. Jude who suffer from gastroenteritis and compare their clinical course of infection and the presence of diarrhea with non-virally infected children. She intends to initially define the mechanism of action of novel viral enterotoxins with regard to disrupting the tight junctions of intestinal cells and subsequently, with regard to long-term changes induced by viral enterotoxins to the gut microbiome. Translation of research results to children will lead to improved management of the disease, better tools for rapid diagnosis, and potentially to the development of new therapies for treating these infections. If successful, she will contribute new information about the prevalence, diversity, and adverse effects of enteric viruses in all children suffering from diarrhea. She suggests that while it is likely that the regulation of intestinal cellular tight junctions will have broad implications for many gastrointestinal diseases like intestinal cancer and Crohn's disease, there may also be other implications for drug discovery in controlling the tight junctions of the blood brain barrier, as well.