THE HARTWELL FOUNDATION

2018 Individual Biomedical Research Award

Hiutung "Hiu" Chu, Ph.D.

Assistant Professor
Department of Pathology

University of California, San Diego

Beneficial Bacteria to Induce Regulatory T Cells as a Therapy for Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic immune-mediated condition of the gastrointestinal tract that causes inflammation, pain and digestive problems; characterized by alternating periods of remission and relapse that can lead to severe medical complications. Children affected with IBD live with an incurable condition requiring life-long health care for diarrhea, anxiety, delayed puberty, growth impairment, an increased risk of developing cancer, and early mortality. Approximately 80,000 children in the US endure IBD, with about 25% diagnosed before age 18. The incidence and prevalence of childhood-onset IBD have risen dramatically in recent years, including its principal subtypes, Crohn's disease and ulcerative colitis. The disease pathology of IBD is associated with dysregulation of innate and adaptive immunity, defects in the epithelial barrier that lines the intestine, and dramatic alterations in the composition of gut bacteria (microbiome). The genetic basis of the disease is complex. Current clinical management of IBD includes anti-inflammatories and immunomodulators; biological agents (e.g., antibodies); and surgical intervention. Unfortunately, a significant portion of pediatric IBD patients do not respond to these therapies. Thus, there is a need to develop safe and effective therapies for children with IBD. To address this need, I propose to block the development and progression of IBD by increasing the number or potency of anti-inflammatory intestinal immune cells called T regulatory cells (Tregs). My approach is based upon experimental evidence that suggests gut bacteria play a pivotal role in modulating intestinal immune responses, which is consistent with my recent observations that genetic mutations in many pediatric IBD patients prevent them from responding to beneficial bacteria, leading to a deficiency in Tregs and increased inflammation. Using a high throughput assay to screen bacterial candidates from the microbiome of healthy individuals, I propose to identify bacteria that can induce or potentiate anti-inflammatory Tregs in IBD. I will then determine the anti-inflammatory effects of such beneficial bacteria in germ-free mice subjected to colitis or in a microbiome from a genotyped IBD patients harboring the two most common genetic mutations. The beneficial bacterial candidates will also be used to treat human immune cells in culture, derived from peripheral blood mononuclear cells (PBMC) of IBD patients with and without associated mutations. Beneficial bacteria that successfully induce anti-inflammatory responses in mouse models and in human PBMC will be considered as candidates for a future clinical trial. If I am successful, the clinical management paradigm for pediatric IBD will shift from current modalities to the rational design of probiotic (microbial) therapies that consider any existing genetic mutation(s).