THE HARTWELL FOUNDATION

2019 Individual Biomedical Research Award

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Bacteria-Derived Therapy to Cure Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD), which include ulcerative colitis and Crohn's disease, are life-long chronic illnesses that result from a combination of genetic susceptibility, immune system disturbances, and certain environmental triggers. The incidence of pediatric IBD in the United States is about 1 per 10,000 children and is increasing by nearly 7% each year. Nearly 80,000 American children currently endure IBD. Many different therapies exist for IBD, but no single approach works for all patients. The current standard of care largely involves suppressing the immune system with relatively non-specific drugs, all of which leave the patient more susceptible to infections. Unfortunately, because current IBD medications do not work as well as desired, many children need to undergo surgery to remove parts of their intestine: 60% of children with severe Crohn's disease and 30% of patients with ulcerative colitis will require surgery within 5-10 years of diagnosis. Even those children whose disease is controlled by medicine often suffer from other co-existing chronic diseases, including growth failure, depression, anxiety, and reduction in bone density. Clearly, better treatment options are urgently needed for children living with or at risk for IBD. Given that IBD is known to involve an abnormal immune response against bacteria that reside within the intestine and that the bacteria in the intestines of children with IBD are different from healthy children, one possibility is to "fix" the discrepancy and rebalance the underlying abnormal immune response. The main challenge has been identifying specific bacteria that would prove clinically useful. Based upon his recently developed methodology that applies classical genetic principles to the inheritance of microbial traits, Neil discovered a novel bacterial species, Clostridium immunis (C. immunis), that protects a mouse model of IBD from colitis. The bacteria appear to regulate the number and function of colonic group 3 innate lymphoid cells, immune cells that reside in the intestine and are required for immunity to intestinal bacterial infections. To evaluate whether the same immunomodulatory effect occurs in humans, he proposes to examine how C. immunis impacts the human intestinal immune system in tissue samples from children with and without IBD, and to characterize the gut microbiome of each child to determine if variation is correlated to differences in the observed tissue response. Using an in vitro screening platform that in cell culture combines patient-derived intestinal cells, patient-derived innate lymphoid immune cells, and C. immunis bacteria, Neil will determine the specific bioactive principle released from C. immunis that mediates protection against colitis. If he is successful, medicinal chemistry can then be applied to improve upon potency and selectivity of this bacterium-derived therapy that has the potential to improve the lives of tens of thousands of children suffering from the debilitating effects of IBD.