THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

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Engineering Commensal Bacteria to Treat Juvenile (Type-1) Diabetes

In individuals with type-1 diabetes, the immune system attacks the islet cells of the pancreas, which provide the body's primary source of insulin. Once the islet cells are gone, the body effectively loses its ability to regulate sugar (glucose) metabolism and the affected individuals require several injections of insulin per day. In the US, type-1 diabetes affects nearly 1 out of 400 children under the age of 20 each year; with prevalence at 7% of the total population, it is a growing problem. There is no way to prevent the disease and there does not need to be a family history for it to appear. The complications from the disease are extensive, including severe blindness, kidney failure, nerve damage, dental disease, and coronary vascular disease. The American Diabetes Association estimates the impact on US healthcare well in excess of $92 billion per year. Current alternative methods for insulin secretion replacement include implantation of pancreatic cells, which are not only of limited availability and very expensive, but are complicated by a requirement for life-long suppression of the immune system. Clearly, a safe, cost-effective, and permanent surrogate source for insulin secretion is highly desirable. In a remarkably innovative approach, John March proposes to engineer ordinary, consumer-grade commensal (probiotic) bacteria that live in the human gastrointestinal tract, to produce a protein that would stimulate the epithelial cells that line the intestine to secrete insulin into the blood circulation, effectively "hiding" the insulin production site from the autoimmune response that destroys β-cells in type 1 diabetes. Normally, commensal bacteria are indispensable for maintaining intestinal physiology, development, and function. As proof of concept, March has demonstrated the ability to bioengineer commensal bacteria to dampen the virulence of cholera. Here, he proposes to use a unique 3-dimensional "gut-tube reactor" model system that will enable high throughput characterization of interactions in a potentially more "human-like" system than a mouse model. If March is successful, ultimate implementation would move the center of glucose response from the pancreas to the gut, which could result in a treatment for type-1 diabetes that might cost as little as $100 per year.