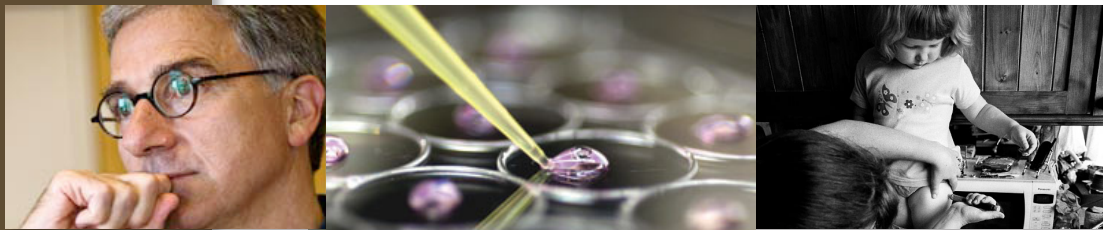


HSCI Fighting Disease

Type 1 Diabetes

With us, it's personal.



Seventeen years ago, Doug Melton was a biologist studying the development of frogs. And then his infant son, Sam, was diagnosed with type 1 diabetes, and Melton began the quest that has ever since been the focus of his professional life—finding a cure for the disease that plagues not only Sam, and Melton's daughter, Emma, but one in every 400–600 children and adolescents in the US.

So when we say that our fight to cure diabetes is personal, you know we mean it.

Diabetes results from the body's failure to produce insulin, a hormone that signals the body to allow glucose to enter cells and fuel them. The cause of type 1 diabetes is the absence of a single kind of cell, the pancreatic beta islet cell (beta cell). For unknown reasons, the immune system sometimes launches an attack against the body's own insulin-producing beta cells and destroys them. So to find a cure, scientists need to identify a source for new beta cells, and they need to convince the immune system not to attack them.

Harvard Stem Cell Institute

- 225 Faculty
- 20 Institutions
- 1 Promising Scientific Field

Collaborative stem cell science speeding the development of safer, more effective treatments for disease

Replenishing beta cells

HSCI laboratories are exploring three strategies for replacing the lost beta cells.

The first involves the generation of the cell *de novo* by guiding either embryonic stem (ES) cells or induced pluripotent stem (iPS) cells to become beta cells. Advances in ES cell differentiation are encouraging, but significant hurdles still remain. We are working on increasing the efficiency of the process as well as figuring out the signals, either biological or chemical, that can drive differentiation of the last few steps of the maturation process. Then we have to make sure that these cells are fully functional beta cells and can properly regulate insulin secretion as well as maintain the ability to create new cells.

The second strategy involves reprogramming other mature cells in the body into beta cells. HSCI laboratories have reprogrammed cells from the exocrine pancreas, normally devoted to the production and secretion of digestive enzymes, into endocrine, insulin-producing beta cells. This has been done in mice but, in theory, the crucial advantage of this strategy is that it can be tailored specifically to each patient. One important hurdle to overcome is that the delivery of the reprogramming factors must be replaced by safer reagents such as small molecules. Also, currently, the newly formed beta cells stay either as single cell or small clusters and do not form structured islets which may be important for function.

The third approach is to promote the replication of existing beta cells either *in vivo* or *in vitro*. Beta cells do replicate but at a very low rate. Recent studies suggest that when not hindered by a persistent autoimmune attack or the toxicity of high blood glucose levels, beta cells may have capacity to regenerate through enhanced

proliferation of remaining beta cells. Increasing this rate is the goal of a project that screens for small molecules that could act as chemical inducers of beta cell proliferation.

Stopping the destruction of beta cells

Generating more beta cells will address type 2 diabetes but does not solve the immune system attack in type 1. How and why the immune system attacks the beta cells is not known. We are approaching this problem by creating a mouse model that has features of the human immune system. This system will allow us to see how and why the immune system attacks the beta cells and thus help us find mechanisms to prevent or minimize the damage from such an attack.

We expect that the combination of these approaches will progressively lead us to solutions for a disease that affects 24 million Americans today and costs the US healthcare system \$174 billion annually.

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