American Diabetes Association.
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Pathway to Stop Diabetes Award

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Project Title: *Harnessing immune privilege mechanisms from stem cells to protect beta-cells from immune attack*

Project Description: Despite notable improvement in treatments with exogenous insulin, they often cannot achieve a tight glucose control and, consequently, over time, many Type 1 Diabetes (T1D) patients develop secondary complications, such as retinopathy and neuropathy. Thus, the ultimate goal to accomplish a definitive cure for T1D is to replace the lost beta-cell mass. This could be done by transplantation of pancreatic islets or stem cell-derived insulin-producing cells, by in situ regeneration or by trans-differentiation. However, any replacement will irrevocably succumb to the same autoimmune attack that killed the original beta-cells. Thus, it is of the utmost importance to develop strategies to preserve newly generated or transplanted pancreatic islets. Unfortunately, many approaches aiming at restoring tolerance by manipulating immune cells have been tested and, although safe, have shown only limited efficacy. Inflammatory processes, infections or major life-style changes can easily alter the balance again towards immune activation.

We recently discovered the existence of immune privileged stem cells in the skin and muscle and found their protection was not dependent on a physical barrier in an immune privileged site. Instead, it is a cell-autonomous process that allows independent cloaking from activated T cells. Here we propose to exploit the molecular circuits controlling this striking phenomenon (that already naturally occurs in our bodies) to provide similar protection to susceptible beta-cells. Since this will be a cell-intrinsic mechanism of immune evasion, changes in overall immune function should not alter their privileged status allowing for long-lasting survival of newly regenerated or transplanted beta-cells.

How will this work help a person with diabetes?
A true cure for type 1 diabetes involves replacement of missing insulin producing beta-cells. However, unfortunately, current approaches for transplantation of beta-cells are limited due to attack by the patients' immune cells and, hence, these patients require long-term strong immune-suppression, which puts them at serious risk of infection and even cancer. The goal of this project is to develop strategies to ensure the survival of transplanted or regenerated beta-cells, by allowing them to effectively and safely cloak from immune cells.

Moreover, these approaches will also benefit type 2 diabetic patients that require exogenous insulin and patients with genetic variants of insulin dependent diabetes, since it will enable transplant of stem cell derived beta-cells, even when there is not a perfect match from the source and the recipient patient.