Deciphering transcriptional control of pancreatic beta-cell maturation in vitro

Grant Award Details

Deciphering transcriptional control of pancreatic beta-cell maturation in vitro

Grant Type: Basic Biology IV

Grant Number: RB4-06144

Project Objective: The overall goal is to identify inducers of beta cell genes so that glucose-responsive mature beta cells can be produced from hESC in vitro. Key factors will be temporally manipulated to overcome current deficiencies in differentiation protocols.

Investigator:

Name:	Maike Sander
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Diabetes, Metabolic Disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,258,560

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Deciphering transcriptional control of pancreatic beta-cell maturation in vitro
Public Abstract:	The loss of pancreatic beta-cells in type 1 diabetes results in absence of insulin secreted by the pancreas, and consequently elevated blood sugar which leads to various long-term complications. Diabetic patients would benefit tremendously from availability of transplantable replacement beta-cells. Much of current research focuses on producing beta-cells from stem cells. Despite some progress, it is at present still not possible to generate functional beta-cells in culture. The beta-like cells generated with current protocols in vitro lack key features of normal beta-cells, most notably the ability to secrete insulin a regulated manner. However, when stem cell-derived beta-cell precursors are transplanted into mice, they acquire properties of functional beta-cells, indicating that the precursors have the potential to transition into a mature beta-cell state. By comprehensively comparing the molecular profiles of mature, functional beta-cells and malfunctioning insulin-producing cells generated in vitro, we have identified molecular cues that are not appropriately induced under current culture conditions. These studies have led to short list of candidate regulators of beta-cell maturation. We propose to manipulate these candidate factors in stem cell-derived beta-cell precursors in culture, with the goal of forcing them to adopt a mature phenotype. We will first characterize these cells in vitro and then test functionality in diabetic animal models.
Statement of Benefit to California:	Diabetes is a metabolic disorder that affects 8.3% of the U.S. population. Average medical expenditures among people with diabetes are 2.3 times higher than those of people without diabetes. The disease is characterized by either absolute insulin deficiency due to the autoimmune destruction of pancreatic insulin-producing beta-cells [Type 1 diabetes], or relative insulin deficiency due to defective insulin secretion or insulin sensitivity [Type 2 diabetes]. The resulting elevated blood glucose levels eventually lead to damage of the blood vessels followed by kidney failure, blindness, neuropathy, heart disease, and stroke. Despite current treatment regimens of several insulin injections per day, blood glucose levels still fluctuate significantly in diabetic patients, making diabetes the seventh leading cause of death in the United States. Alternative approaches to insulin injections include attempts to develop a cell therapy by producing transplantable beta-cells from stem cells. A cell therapy would lead to better blood glucose control and therefore ameliorate long-term complications. This proposal seeks to identify factors that force stem cell-derived beta-cells to functionally mature in culture with the goal to produce an unlimited source of transplantable beta-cells. Given the high prevalence of diabetes in California, we believe that the proposed research will have tremendous benefit to the State of California and its citizens.

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