Defining links between chromatin state and developmental competence

Grant Award Details

Defining links between chromatin state and developmental competence

Grant Type: Basic Biology V

Grant Number: RB5-07236

Project Objective: To define a link between the “primed/poised” state of enhancers and the acquired ability of cells to respond to lineage-inductive cues. The role of pioneer factors in establishing such a link will be investigated in the context of hESC differentiation to pancreas, liver and lung.

Investigator:

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

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,050,300

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:	Defining links between chromatin state and developmental competence
Public Abstract:	This proposal aims to define fundamental mechanisms that underlie the production of human pancreas and liver cells. The proposed research seeks to advance the development of stem cell-based therapies for diabetes and chronic liver disease. Diabetes is characterized by insulin deficiency due to destruction and/or malfunction of insulin-producing beta cells in the pancreas. Diabetic patients would benefit tremendously from the availability of transplantable replacement beta cells produced from stem cells. Similarly, stem cell-derived replacement liver cells could help improve liver function in patients with chronic liver disease and/or help identify drugs that protect the liver form damage. Despite some progress, it is at present not possible to produce functional beta or liver cells from stem cells. During embryonic development, the pancreas and liver arise from a common precursor cell. To produce functional beta or liver cells from stem cells in culture, cells have to transition through this pancreas/liver precursor step. We propose to identify mechanisms by which stem cell-derived precursors acquire the ability to develop into beta or liver cells. Knowledge gained from this proposal will have several important applications. First, it will help devise strategies to produce functional replacement beta and liver cells from stem cells. Second, it will inform approaches aimed at directly converting other tissues, such as skin, into insulin-producing or liver cells.
Statement of Benefit to California:	This proposal will have relevance to finding cures for two major diseases: diabetes and liver disease. 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 insulin deficiency due to destruction and/or malfunction of insulin-producing beta cells in the pancreas. An ultimate treatment for diabetes would be to replace lost beta cells with transplantable insulin-producing cells. Similarly, replacing damaged liver cells could have major impact on alleviating the consequences of chronic liver disease. One in ten people in the U.S. have liver disease and chronic liver diseases such as hepatitis, non-alcoholic fatty liver disease and liver cancer are on the rise. Thus, deriving pancreatic beta cells or liver cells from stem cells could have major impact on improving the life of people with diabetes or liver disease. Stem cell-derived beta or liver cells could also be used in drug discovery screens with the hope of identifying drugs that can improve cell function. This proposal seeks to identify strategies for deriving functional pancreatic and liver cells from stem cells; a goal that remains to be been achieved. Given the high prevalence of diabetes and liver disease in California, we believe that the proposed research will have tremendous benefit to the State of California and its citizens.