Generation of a functional thymus to induce immune tolerance to stem cell derivatives

Grant Award Details

Generation of a functional thymus to induce immune tolerance to stem cell derivatives

Grant Type: Basic Biology V

Grant Number: RB5-07262

Project Objective: To generate TEPs from human pluripotent stem cells and demonstrate their potential to establish and maintain specific immune tolerance to other stem-cell-derived tissue in a humanized mouse model. They will also identify the cellular mechanisms involved in the induction of tolerance, using a model antigen system to assess antigen-specific immune responses.

Investigator:

Name:	Mark Anderson
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Diabetes, HIV/AIDS, Immune Disease, Infectious Disease, Metabolic Disorders

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,191,000

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 4 (NCE)

View Report

Grant Application Details

Application Title: Generation of a functional thymus to induce immune tolerance to stem cell derivatives

Public Abstract: Stem cell research offers the promise of replacing missing or damaged tissues in the treatment of disease. Stem-cell-derived transplants still face problems with rejection as in traditional organ transplants. Several drugs can prevent rejection but also suppress the immune system, leaving patients vulnerable to infections and cancer. To avoid rejection without using drugs requires re-educating the immune system to "tolerate" the transplant and not see it as foreign. Because of its role in educating developing immune cells, the thymus is a critical organ in establishing what the immune system recognizes as "self" and not foreign, in a process known as immune tolerance. By growing a new thymus from stem cells matched to transplanted tissues, we can condition the immune system to be tolerant to the transplant and avoid chronic immunosuppression. We have developed a method to grow stem cells into thymic cells that become normal thymus tissue when grafted into mouse models. Notably, the new thymus can promote normal development of immune cells, indicating the potential for generating new, tolerant immune cells. We propose to induce immune tolerance to other stem-cell derived tissues using stem-cell-derived thymus tissue to engineer tolerance. We will optimize our methods of growing thymus tissue, which will be used to condition mice to accept stem-cell-derived pancreas grafts, testing their ability both to prevent rejection and to cure diabetes in a transplant model.

Statement of Benefit to California: The proposed work aims to improve the effectiveness of stem cell treatments by preventing immunological rejection of transplanted tissue derived from stem cells. An important barrier to the clinical use of stem-cell-derived organs and tissues is the potential of the immune system to reject or damage this regenerated tissue. Improved approaches to address immune rejection are needed since stem cell therapies are underway in treating diseases that have a wide impact on the health of Californians, including diabetes, Parkinson's disease, Alzheimer's disease, retinal eye diseases, and musculoskeletal diseases.

The proposed studies will improve treatment for these diseases by providing a novel method to halt immunologic rejection or destruction of tissues that are derived from stem cells. We have successfully developed methods to grow thymus tissue, which controls the ability of the immune system to be "tolerant" of transplanted tissue. Here we will improve methods to generate thymus from stem cells and show that it can promote survival of transplanted tissue derived from the same cells. By using the thymus to condition the immune system towards tolerance, we hope to avoid immune rejection without the use of immunosuppressive drugs. Induction of a tolerant immune system in this way would represent a significant advance in improving stem cell therapies. Thus, this work could have a broad impact on a large number of the disease treatments that involve stem cells.