Thymus based tolerance to stem cell therapies

Grant Award Details

Thymus based tolerance to stem cell therapies

Grant Type: Transplantation Immunology

Grant Number: RM1-01717

Project Objective: Induce graft tolerance via thymic chimerism.

Investigator:

Name: Jeanne Loring

Institution: Scripps Research Institute

Type: PI

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Name: Ann Chidgey

Institution: Monash University

Type: Partner-PI

Disease Focus: Immune Disease

Collaborative Funder: Victoria, Australia

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,108,921

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: Thymus based tolerance to stem cell therapies

Public Abstract: This proposal focuses on the role of the immune system in transplantation of derivatives of human pluripotent stem cells (hPSCs). A critical roadblock to successful cell replacement therapies, no matter what the disease or injury, is the fact that the immune system's main function is to prevent the introduction of foreign substances into our bodies. Unfortunately, this means that transplantation of organs or cells will inevitably lead to rejection unless the immune system is repressed or "tricked" into accepting the transplants as non-foreign. Long term immune suppression is harmful, because of the toxicity of the drugs used and because the repressed immune system is unable to protect against infections and monitor for cancerous cells. Our strategy is to "trick" the immune system into recognizing the cells used for replacement therapy as "self" rather than as foreign. We have had early success with these methods, and now propose to test them in a realistic situation that may lead directly to human applications. Each human being has a particular complement of proteins that are exposed on the surfaces of cells and serve to distinguish "self" from "non-self". During our development, our immune system is trained to recognize our own molecules (called HLA or MHC) and not reject cells carrying them. However, as we age, our bodies lose this ability to "teach" the immune system what to reject and what to protect. Our scientific strategy is to use specific hPSCs (with specific HLA types) to regenerate the body's ability to instruct the immune system. We will do this by regenerating the thymus, an organ that is active in childhood but atrophies in adulthood. The thymus is integral to determining what is self, removing the immune system cells that would attack one's own cells. For this pre-clinical study, we will regenerate the thymus in experimental animals by transplanting thymus cells derived from specific hPSC lines. If successful, this will cause the immune system to recognize the new cells as "self" and not reject cells from this particular cell line when they are later used to repair degenerated tissues. This method, called "inducing tolerance", will be tested using three diverse PSC lines, derived from Caucasians and Africans, which have very different HLA types. The research team includes three well-established researchers: 1. An expert in deriving and characterizing hPSC lines, who has already made the cell lines to be used; 2. A leader in the field of immune tolerance, who has developed methods for transplantation of thymus cells; and 3. An expert in a widespread human degenerative disease, multiple sclerosis (MS), who will transplant hPSC-derived neural stem cells to a mouse model of MS that has been tolerized to accept these cells. This method will be applicable to any disease that can benefit from cell therapy, and this team has all of the expertise and knowledge necessary to develop a successful strategy.

Statement of Benefit to California:	One in seven Americans lives in California, and these people make up the single largest health care market in the United States. The diseases and injuries that affect Californians affect the rest of the US and the world. Many of these diseases involve degeneration of healthy cells and tissues, including neuronal tissue in multiple sclerosis, Parkinson disease, Alzheimer disease, stroke, and ALS, connective tissue in arthritis, pancreatic islet cells in diabetes, heart muscle in cardiovascular disease, the immune system in HIV/AIDs, and other cell types in a host of other diseases, genetic disorders and injuries. There is a great deal of optimism about the use of stem cell-derived cells for replacement therapy for these disorders, and a great deal of progress has been made toward developing the appropriate cell types from human pluripotent and multipotent (adult) stem cells. However, a huge roadblock to the success of these potential therapies remains: how can transplanted cells be successfully engrafted without rejection? The immune system has evolved to protect individuals from infection and the result is that it specifically eliminates “non-self” organ, tissues, cells or molecules. A long history of research on the immune system predicts that all cells that are recognized as being non-self will ultimately be rejected by the host. The goal of this project is to develop a general method that can be used for any cell replacement therapy, to allow the transplanted cells to survive and function, while retaining the immune system’s ability to guard against infection and destroy cancerous cells. Our strategy is based on the idea of immune “tolerance”, which is a procedure that is designed to allow transplanted cells to be recognized as "self" and not be rejected. If our research efforts are successful, this method will enable the whole range of cell replacement therapies that will provide cures to previously incurable degenerative disease and injury.