Engineered immune tolerance by Stem Cell-derived thymic regeneration

Grant Award Details

Engineered immune tolerance by Stem Cell-derived thymic regeneration

Grant Type: Transplantation Immunology

Grant Number: RM1-01739

Project Objective: Overall purpose of this project is to use stem cell derived thymic epithelial stem cells (TECs) to induce tolerance in an experimental model of multiple sclerosis (MS).

Investigator:

Name:	Kenneth Weinberg
Institution:	Stanford University
Type:	PI

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Name:	Claude Bernard
Institution:	Monash University
Type:	Partner-PI

Disease Focus: Immune Disease, Pediatrics

Collaborative Funder: Victoria, Australia

Human Stem Cell Use: Adult Stem Cell

Award Value: $1,271,729

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: "Engineered immune tolerance by Stem Cell-derived thymic regeneration"

Public Abstract:

Stem cell therapies have the potential to transform medicine by allowing the regeneration of tissues or organs damaged by disease or trauma. In order for stem cell therapies to proceed, it will be essential that the regulation of immune responses to the stem cell derived tissues be achieved. While the function of the immune system in protection from infections is essential throughout life, some immune reactions are undesirable. Illnesses due to autoimmunity, in which the immune system attacks one's own body, instead of only germs that cause infection, are common. Examples of autoimmune diseases that are amenable to stem cell based therapies include Type I diabetes caused by abnormal immune responses directed against the insulin producing cells and multiple sclerosis (MS) caused by immune responses that attack the nervous system. Another type of undesirable immune response is the attack on transplanted tissues, leading to rejection. Control of immune reactions is the major impediment to successful organ transplantation, and is highly likely to be an obstacle to therapeutic uses of stem cells.

T lymphocytes are white blood cells that choreograph the multiple responses that the body uses to control infection. T lymphocytes are produced in the thymus, a specialized organ located in the chest in front of the heart. A function of the thymus is to "edit" the immune response by selecting desirable T cells that are allowed to grow up, and removing young T cells that would cause autoimmunity if they were released into the body. Abnormal selection in the thymus, due to genetic variation, disease or errors in editing leads to autoimmune disease. On the other hand, replacement of the immune system by bone marrow transplantation can be used to engineer the immune system so that the body will accept organ transplants if they came from the same donor as the bone marrow.

We are evaluating a stem cell based strategy to control the editing of the immune response to both treat autoimmunity and permit stem cell-derived tissues to be transplanted. Members of the international collaborative team have developed techniques for directing embryonic stem cells (ESC) into specialized thymic epithelial cells (TEC), which can be transplanted into recipient mice to support the development of new T cells. We have also developed mouse models for MS and for stem cell rejection which can be controlled by modification or suppression of the immune system. We will evaluate the ability of TEC made from ESC to 1) edit the immune system to prevent or treat MS, or 2) allow ESC to be transplanted without rejection. The studies will test TEC to support the production of new T cells that can respond normally to germs, but will not attack either nervous system cells or transplanted ESC. Success of the studies will advance our understanding of how to regulate the immune system for the goal of using stem cells therapies to treat disease and regenerate tissues.

Statement of Benefit to California:

The research is aimed at understanding the how ESC can be used to re-engineer immune responses so that autoimmune diseases can be controlled and other stem cell derived tissues can be transplanted. The studies are based on our team's demonstration that functional TEC can be generated from ESC. Since TEC are very important for selection in the thymus of which T cells will be allowed to mature and become part of the immune system. The studies will explore two models for the use of such ESC-derived TEC – 1) an autoimmune disease of mice that mimics many aspects of human multiple sclerosis; and 2) transplantation of ESC from between genetically non-identical donors and recipients.

Autoimmunity is a major cause of disease in California. A recent study of the Kaiser Northern California patient population estimated an overall incidence for 11 autoimmune diseases of 160 new cases per 100,000 person years (PY)(Klein NP et al, Vaccine [2009] 28:1062-68). With an estimated California population of 37 million, this translates to nearly 60,000 new cases of autoimmune disease yearly. Furthermore, many of these diseases are disproportionately found in younger individuals, thereby amplifying the potential effects of disability on the population. The autoimmune disease that is being approached in this grant, multiple sclerosis (MS), has the fourth highest incidence in the Kaiser study at 14.2 cases/100,000 PY overall, and 22.9 cases/100,000 PY for women 25-62 years of age. The proposed studies include a novel use of ESC to control autoimmune responses in mouse models of MS as well as a novel approach to immune suppression, which could have a significant impact on MS and autoimmune diseases in general.

The second proposed application of ESC-derived TEC is the control of rejection of transplanted ESC. Since one of the limitations of all ESC-based therapies is likely to be immune responses leading to rejection of the transplanted tissues, a strategy to make recipients tolerant to the ESC has the potential to benefit all Californians who might benefit from stem cell based therapies. Examples would include patients who could benefit from regenerated nervous system, heart, liver or kidney tissue, as well islet cells for treating diabetes. The proposed studies include the innovative use of ESC-derived TEC to re-engineer the immune system to allow it to accept (become tolerant of) cells derived from the same ESC, an approach that could significantly advance the development of treatments for all Californians likely to benefit from stem cell therapies.
