Engineering Thymic Regeneration to Induce Tolerance

Grant Award Details

Engineering Thymic Regeneration to Induce Tolerance

Grant Type: Transplantation Immunology

Grant Number: RM1-01707

Project Objective: To develop Thymic Epithelial Cell/engineered thymic mesenchyme aggregates to induce central tolerance.

Investigator:

Name:	Gay Crooks
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Immune Disease

Award Value: $1,235,445

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Engineering Thymic Regeneration to Induce Tolerance

Public Abstract:

A healthy immune system produces T cells that can recognize and react against foreign molecules (antigens) to protect against infection, while leaving normal host cells with "self antigens" undamaged. All T cells are produced in the thymus from blood stem cells that migrate from the bone marrow. "Tolerant" T cells are those that have been "educated" to not react against self antigen on host cells. The key cells in the thymic microenvironment that control T cell production and tolerance are the thymic epithelial cells (TECs). When TECs are lost or become dysfunctional, T cell production is poor and patients are at risk for a wide range of infections. When tolerance is lost, T cells react to host tissues as if they were foreign, producing inflammation and damage and causing autoimmune diseases such as Type I Diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus. The ability of a patient to accept cells or an organ transplant from another person also requires tolerance to occur, or the graft will be rejected. The goal of our studies is to develop a method for engineering and transplanting new, healthy thymus tissue into patients, thus creating a way to generate healthy, tolerant T cells.

We have developed a method to engineer one component of the thymic microenvironment (thymic mesenchyme aka Tmes) to produce specific growth factors in a regulated fashion to help TECs grow, and are able to combine TECs and Tmes to form a functional thymus which can then be implanted into mice. This method can be applied to either mouse thymus or human thymus, and in each case the thymic implants allow T cells to develop. We now propose to engineer the thymic implants to produce specific growth factors that we have identified as critical for the rapid thymic growth seen in the fetal and neonatal periods. The ability of engineered thymic aggregates to support the production of mouse and human T cells in cell culture and after transplants in mice will be determined. Importantly, the ability of the thymic implants to educate T cells to become immune tolerant will be assessed.

The success of this proposal will have wide-ranging applications for stem cell and regenerative medicine. Re-generation of new thymic tissue for transplantation will be useful for patients who have poor thymic function e.g. during aging, after chemotherapy and bone marrow transplantation and in certain conditions such as AIDS. Induction of immune tolerance with regenerated thymus will be a critical component of the treatment of autoimmune diseases and graft versus host disease of bone marrow transplantation and to prevent rejection of organs and stem cells from mis-matched donors.

Statement of Benefit to California:

The ability to regenerate and control the immune system is of critical importance in the treatment of a wide-range of life-threatening diseases. A healthy immune system is required to control infections and prevent autoimmune diseases. The thymus gland, which is central in the regulation of the immune system, is damaged by infections such as HIV-1, by chemotherapy and by aging. Each year, tens of thousands of new patients are diagnosed with autoimmune diseases such as Type I Diabetes, Multiple Sclerosis, Systemic Lupus Erythematosus and rheumatoid arthritis. Over 21,000 Californians and 100,000 Americans are estimated to be in need of organ donation for life threatening diseases [Donate Life, California, Organ and Tissue Donor Registry]. Heavy suppression of the immune system is required to prevent rejection of transplanted organs resulting in many serious side effects for patients. Each year, thousands of patients undergo bone marrow transplantation for leukemia and genetic diseases. The main problem for patients after bone marrow transplantation is immune-mediated graft versus host disease and infection from poor thymic function. Thus, understanding how to regenerate and control the function of the thymus would have an enormous potential impact on the treatment of many common and debilitating diseases that affect Californians.