
Enhancing Survival of Embryonic Stem Cell-Derived Grafts by Induction of Immunological Tolerance

Grant Award Details

Enhancing Survival of Embryonic Stem Cell-Derived Grafts by Induction of Immunological Tolerance

Grant Type: New Faculty I

Grant Number: RN1-00554

Project Objective: Overall objective of the project is to evaluate the use of ESC derived HSC in inducing tolerance to allogeneic cells in an animal model diabetes

Investigator:

Name:	Jennifer Manilay
Institution:	University of California, Merced
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$1,576,389

Status: Closed

Progress Reports

Reporting Period: Year 2

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Reporting Period: Year 4

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Reporting Period: Year 5

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Grant Application Details

Application Title: Enhancing Survival of Embryonic Stem Cell-Derived Grafts by Induction of Immunological Tolerance

Public Abstract: Although ESC-based therapies hold great promise for the cure of a wide diversity of degenerative diseases, rapid progress to actual human clinical trials is hindered by the lack of preclinical data for specific ESC-based therapies. I aim to move the process forward by establishing a protocol in which immune system cells are reproducibly produced from ESC and tested in vivo for the induction of and maintenance of immunological tolerance to therapeutic ES-derived cells. I will use the mouse as a model system to test this protocol, as the mouse is the model system of choice for study of the immune system due to the availability of genetically identical strains and well-studied models of human disease. Moreover, my protocol design will reflect strategies already used for successful organ transplantation, making the protocol suitable for clinical use.

The immune system is the primary barrier to the acceptance of any embryonic stem cell (ESC)-based therapy. Immune system cells are derived from a stem cell in the blood which has the potential to differentiate into a number of mature cell types, such as red blood cells, macrophages, granulocytes, B lymphocytes (B cells) and T lymphocytes (T cells). During development, B and T cells are educated to recognize what is "self" versus what is "foreign." This precise education regulates the activation of the immune response during viral or bacterial infection. For example, T cells can distinguish between healthy and infected cells, and selectively destroy the infected ones while leaving the healthy ones intact. Breakdown of this recognition, or self-tolerance, occurs in autoimmune diseases such as Type I Diabetes and multiple sclerosis, resulting in the destruction of pancreatic and neural cells by the body's own immune system. In clinical organ transplantation, overcoming "self-tolerance" and re-education of the patient's immune system to recognize the donated organ as "self" is necessary for acceptance of the transplanted organ. I hypothesize that this will also be the case for ESC-based therapies, in which the ESC and its derivatives can be thought of as a "transplant" to which the patient's immune system must learn to recognize as "self". Regardless of the disease one is attempting to treat with ESC-based therapies, if immune tolerance is not achieved, all ESC-derived grafts will be destroyed, and disease will persist.

The last goal of the project is to validate whether my protocol can be used as a real ESC-based therapy for Type I Diabetes. Although diabetes is my initial focus, induction of immune tolerance to therapeutic ESCs is a general but necessary requirement for the success of any ESC-based therapy. Therefore, if successful, this research could be applied to a wide variety of degenerative diseases, such as muscular dystrophy, Alzheimer's, Parkinson's, multiple sclerosis, cancer and immune deficiencies.

Statement of Benefit to California: Results from my proposed research project will benefit the State of California and its citizens at several levels.

Direct Impacts: My research project aims to target an obvious barrier to ESC-therapy for any disease: the avoidance of immune rejection in the patient. If immunological tolerance to ESC-derived grafts is not achieved, the therapeutic ESC is destroyed and disease persists. The immune system is formed from hematopoietic (blood) stem cells, and my research goals are to establish reproducible protocols to derive blood stem cells from ESC and promote engraftment of these ES-derived blood stem cells in a recipient to induce immunological tolerance to the ESC-graft, and then test them in a well-studied mouse model of diabetes. If successful, this would be the first preclinical data to demonstrate that ESC-based therapies can cure diabetes. As immunological tolerance is important for all potential ESC-therapies, my work can have broad applications to a wide diversity of diseases. The work will also have indirect impacts outside of the research, such as notoriety to CIRM as the funding agency for this groundbreaking research, and be the springboard for improvements in health care, increase in tax revenues, and improvements in education for California residents.

Health Care: I will test my protocols in a well-studied model of human diabetes. The California Diabetes Program reported that two million Californians are diabetic and there are many more that are pre-diabetic. If successful, my research could provide stem cell therapies for these patients, alleviating the need for insulin therapies and extensive medical care. As this research is funded by CIRM, it is highly likely that Californians would be the primary recipients of therapies designed using my research. Furthermore, my research plan is designed to have broad applicability, so ESC-therapies for other illnesses such as cancer, Alzheimer's, Parkinson's, multiple sclerosis, and cardiovascular disease can next be evaluated.

Biotechnology: My research already relies on a number of products and tools manufactured and sold in the state of California. If successful, research will require a scaled-up version of protocols designed in my studies. This could attract new biotechnology companies in the state, boosting the tax revenue in the state. This in turn, will provide new jobs for California state residents.

Education: Establishment of successful ESC-therapeutics in California will encourage institutions of higher education to promote science education to fill the jobs created by stem cell research. This will retain California students in the state that are interested in biomedical research and medical careers. Furthermore, it could attract out-of-state students seeking degrees that will allow them access to careers in stem cell research. It is envisioned that this will trickle down to the K-12 levels and provide funding to promote science education at all levels.

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