Down-Regulation of Alloreactive Immune Responses to hES Cell-Derived Graft Tissues

Grant Award Details

Down-Regulation of Alloreactive Immune Responses to hES Cell-Derived Graft Tissues

Grant Type: SEED Grant

Grant Number: RS1-00402

Investigator:

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Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

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Progress Reports

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View Report

Grant Application Details

Application Title: Down-Regulation of Alloreactive Immune Responses to hES Cell-Derived Graft Tissues

Public Abstract: Human Leukocyte Antigens (HLA) are proteins that are expressed on the surface of almost all cells in the body. Because HLA sequences are highly variable and each person generally has a different set of HLA gene sequences, these cell surface markers serve as the identifiers of “self” vs. “non-self”. If immune cells in the body encounter foreign cells transplanted from a different individual, in most cases these foreign cells are recognized due to their display of a different “non-self” HLA on their cell surfaces, and attacked by the immune system. However, because it is difficult to obtain donors with precise matches, many patients succumb to their disease while on a waiting list for matched bone marrow or organs. Even one mismatch in HLA can result in immune responses against the transplant graft, making it necessary to administer immunosuppressive drugs for the lifetime of the patient.Initially it was thought that human embryonic stem cell (hESC)-derived cells and tissues might not be attacked by the immune system because these cells do not have much HLA on their surfaces in their primitive state. However, it is now known that once hESC start to develop into mature adult-type cells, they also start to increase their display of HLA, marking them as foreign “non-self” transplants. Thus, for hESC-derived cell and tissue transplants face the same problem of immune rejection as adult organ transplants.Gene therapy is a promising new treatment approach that involves the delivery of genetic material such as DNA or RNA directly into cells, thus altering their genetic configuration and “re-programming” them to change the pattern of cellular protein expression. Long-term genetic re-programming can be efficiently achieved with the use of certain types of virus, chiefly retroviruses, which insert themselves directly into the chromosomes of the infected cell, becoming a permanent part of that cell’s genome. Lentiviruses are a type of retrovirus which includes pathogens such as HIV, but as gene delivery vehicles (“vectors”), they have been completely disabled by removal of the viral genes, and replacing them with the therapeutic sequences we want them to deliver, thus turning viral foes into friends. We propose to use this approach to deliver a newly discovered class of “small interfering RNA” (siRNA) that can be designed to target and down-regulate specific sequences in the cell, thereby silencing expression of specific genes such as HLA, without affecting other cellular proteins. Since the genetically re-programmed hESC-derived transplants will no longer display their own HLA due to siRNA-mediated silencing, this gene therapy approach may make it possible to create “universal” donor cells by erasing the HLA identifiers completely, or at least may expand the usefulness of existing hESC-derived donor cells and tissues by nullifying certain subsets of HLA sequences and thus making it easier to find matches with the remaining HLA sequences.

Statement of Benefit to California:	This project proposes to develop novel strategies and technologies that will reduce the likelihood that human embryonic stem cell (hESC)-derived cell and tissue transplants might be rejected by the patient's immune system, by eliminating the cell surface identifiers (Human Leukocyte Antigens (HLA)) that allow the immune system to discriminate between "self" vs. "non-self". By allowing the hESC-derived transplants to survive without rejection for longer periods of time, these strategies will improve the effectiveness of regenerative medicine. In fact, immune rejection due to recognition of "non-self" HLA is the same problem that is encountered in the field of adult tissue and organ transplantation of bone marrow, kidneys, etc., and so if the proposed strategies prove successful, there is potential to benefit not only patients who need hESC-derived cells and tissues, but patients waiting to be HLA-matched for conventional adult organ transplants as well. The need suitable HLA-matches between the donor and recipient greatly limits the availability of transplantable organs and tissues, therefore our proposed strategy has the potential to greatly increase the accessibility of transplantation-based treatments, thereby improving healthcare for the Californian population.Since even one mismatch in HLA can result in immune responses against the transplant graft, making it necessary to administer immunosuppressive drugs for the lifetime of the patient, the development of strategies to nullify HLA altogether would greatly reduce morbidity and mortality due to the side effects of post-transplant immunosuppression. These side effects include increased susceptibility to infections and malignancies, therefore reducing the incidence of these adverse events would also improve the health and productivity of Californians, and reduce health care costs. Furthermore, for certain transplant patients on the waiting list, currently it is often difficult to obtain donors with precise HLA matches due to ethnic differences in HLA types. Therefore, development of these novel methods for nullifying HLA identifiers on transplanted cells would eliminate otherwise unavoidable racial or ethnic differences in availability of life-saving treatments, and thus has the potential to improve the health of underserved populations in California.