Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure

**Reporting Period: Year 1**

Patients with end-stage heart failure (ESHF), which can result from heart attacks, have a 2-year survival rate of 50% with conventional medical therapy. Unlike cells of other organs, the billions of cardiomyocytes lost due to damage or disease do not regenerate. Recently, implantable mechanical pumps that take over the function of the failing left ventricle (left ventricular assist devices; LVADs) have been used to prolong the lives of heart failure patients. However, these devices carry an increased risk of stroke. The only current bona fide cure for ESHF is heart transplantation, but the shortage of donor organs and the risks associated with life-long use of powerful immunosuppressive drugs limit the number of patients that can be helped. Human embryonic stem cells (hESCs) have the unique properties of being able to grow without limit and to be converted into all the cell types of the body, including cardiomyocytes. Our project seeks to find ways to treat patients by replacing their lost cardiomyocytes with healthy ones derived from hESC. The ultimate goal of this 4 year project is to evaluate the feasibility, safety, and efficacy of this approach in both small and large animal models of heart disease and to use this data to initiate a clinical trial to test the therapy in patients. In our first year, we developed methods for producing essentially unlimited quantities of cardiomyocytes from hESCs using a process that is compatible both with clinical needs and large-scale industrial cell production. We have also developed models of heart disease in both rats and pigs, and have begun transplanting the stem cell-derived cardiomyocytes into the rat model. We have demonstrated that stem cell-derived cardiomyocytes can engraft in this animal model and we are testing their effects on the pumping function of the heart, the growth of replacement blood vessels lost during a heart attack, and the size of the scar that typically forms after injury. In the next several years, we will continue to evaluate the safety and function of these cells and will start to transplant in our large animal model of heart disease, which will enable us to test these cells in a heart with very similar characteristics to humans, delivered in a minimally invasive way that would be ideal for clinical use.

**Reporting Period: Year 2**

Patients with end-stage heart failure (ESHF), which can result from heart attacks, have a 2-year survival rate of 50% with conventional medical therapy. Unlike cells of other organs, the billions of cardiomyocytes lost due to damage or disease do not regenerate. Recently, implantable mechanical pumps that take over the function of the failing left ventricle (left ventricular assist devices; LVADs) have been used to prolong the lives of heart failure patients. However, these devices carry an increased risk of stroke. The only current bona fide cure for ESHF is heart transplantation, but the shortage of donor organs and the risks associated with life-long use of powerful immunosuppressive drugs limit the number of patients that can be helped. Human embryonic stem cells (hESCs) have the unique properties of being able to grow without limit and to be converted into all the cell types of the body, including cardiomyocytes. Our project seeks to find ways to treat patients by replacing their lost cardiomyocytes with healthy ones derived from hESC. The ultimate goal of this 4 year project is to evaluate the feasibility, safety, and efficacy of this approach in both small and large animal models of heart disease and to use this data to initiate a clinical trial to test the therapy in patients. In our first year, we developed methods for producing essentially unlimited quantities of cardiomyocytes from hESCs using a process that is compatible both with clinical needs and large-scale industrial cell production. We also developed models of heart disease in both rats and pigs, and began transplanting the stem cell-derived cardiomyocytes into the rat model. We demonstrated that stem cell-derived cardiomyocytes could engraft in this animal model for at least 1 month, and we observed their effect on the damaged tissue— we saw engraftment of healthy human cardiomyocytes, and noted that the graft induced the formation of new blood vessels. In the second year, we a) discussed our strategy with FDA to get their advice and input (a “pre-PreIND call”); b) transplanted larger numbers of rats with 2 different doses of hESC-derived cardiomyocytes and will monitor them for longer periods (up to 9 months) to verify that no tumors form and there are no unexpected effects on the animals; c) developed in vitro assays to characterize the cardiomyocytes and to rule out the presence of any significant residual undifferentiated stem cells in the final product that will be used for cell therapy; and d) began designing and evaluating different immunosuppression strategies for the pig model, in order to allow the transplanted human cells to survive.
Patients with end-stage heart failure (ESHF) have a 2-year survival rate of 50% with conventional medical therapy. We propose to evaluate a new cell therapy approach (human embryonic stem cell-derived cardiomyocytes; hESC-CMs) to improve survival and cardiac function in these patients. The proposed cell product is generated from the federally approved human embryonic stem cell (hESC) line WA07; the hESC-CMs are then produced in a good manufacturing practice (GMP)-compliant process at City of Hope. The hESC-CMs are cryopreserved at harvest and thawed for subsequent immediate use. The overall dose of hESC-CMs in our phase 1 safety clinical trial is expected to be between 100 million and 300 million cells; the percentage of cardiomyocytes in the cell product is ≥ 80%, as assessed by flow cytometry for cardiomyocyte-specific protein expression. The population for this study will be a subgroup of ESHF patients: those undergoing left ventricular assist device (LVAD) implantation, either as a bridge toward orthotopic heart transplantation (OHT) for refractory heart failure or as destination therapy when patients are not eligible for transplant or appropriate donor hearts are unavailable.

Clinical assessment of improved function will be assessed by temporary “LVAD weaning”, in which the pump speed of the device is turned down to minimal levels and the patient’s cardiac function is assessed by both echocardiography and the 6 minute walk test. Accordingly, it is possible to assess the effects of therapies without putting the patient at serious risk. Due to the allogeneic nature of the H7 hESC-CMs, patients will undergo low-dose temporary immunosuppression (starting on the day of LVAD implantation/hESC-CM injection; 2 weeks in duration). We do not anticipate long-term survival of transplanted cells, which is the current norm in the cardiac stem cell field. We do anticipate that the injected cells will release angiogenic factors that act upon the native myocardium, resulting in improved function. This biological mechanism has been well described in numerous other pre-clinical studies as well as clinical trials, whereby the injected stem cells do not persist long-term in the heart but still provide functional benefits. In order to demonstrate the feasibility and safety of this approach, we have performed studies over the past year showing that a) animals that received transplants of the hESC-CMs show no evidence of any tumors after more than 6 months; b) the hESC-CMs improve heart function in a rodent model of heart disease; and c) delivery of the full human dose of hESC-CMs into a large animal model of heart failure (immunosuppressed pigs) shows no evidence of increased risk of dangerous arrhythmias or other adverse effects. We are in the process of evaluating any improvements in cardiac function in this large animal model of heart disease as well; due to the extreme difficulty of preventing rapid rejection of human cells in these animals, we do not necessarily anticipate seeing the same changes in function we expect to see in patients, where the cells should survive longer. We have met with FDA to help us design our crucial preclinical studies, if results show the hESC-CMs are safe and efficacious, we will use this data to gain approval to go forward with a proposed clinical trial.

Patients with end-stage heart failure (ESHF) have a 2-year survival rate of 50% with conventional medical therapy. This dismal survival rate (largely unknown to the medical community and lay public) is actually significantly worse than patients with AIDS, liver cirrhosis, stroke, and other debilitating diseases. Stem cell therapy may be a promising strategy for inducing myocardial regeneration via paracrine activation, prevention of cardiac apoptosis, and other mechanisms. The proposed cell product is generated from the federally approved human embryonic stem cell (hESC) line WA07. The hESC-CMs are then produced in a good manufacturing practice (GMP)-compliant process using a combination of small molecules and suspension culture at City of Hope. The hESC-CMs are cryopreserved at harvest and thawed for subsequent immediate use. The overall dose of hESC-CMs in our phase 1 safety clinical trial is expected to be between 100 million and 300 million cells; the percentage of cardiomyocytes in the cell product is ≥ 80%, as assessed by flow cytometry for cardiomyocyte-specific protein expression. Over the last six months, we were engaged in conversations with FDA reviewers regarding our revised pre-IND enabling studies package. Based on their recommendations and internal discussions, we reached an agreement regarding our preclinical studies being proposed in our final Pre-IND package. Over the last 3 months, our partner COH has procured most of the required cells and have them ready to be transferred to the CRO upon initiation of our small animal studies (efficacy and tumorigenicity) and for the large animal studies (safety & feasibility).

Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure

Grant Type: Disease Team Therapy Development - Research
Grant Number: DR2A-05394
Project Objective: To submit a well supported IND for a FIH trial of human embryonic stem cell derived cardiomyocytes (hESC-CM).

Investigator:

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Disease Focus: Heart Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $19,060,330

Status: Active

Application Title: Human Embryonic Stem Cell-Derived Cardiomyocytes for Patients with End Stage Heart Failure

Public Abstract:
Patients with end-stage heart failure have a 2-year survival rate of only 50% with conventional medical therapy. This dismal survival rate is actually significantly worse than patients with AIDS, liver cirrhosis, stroke, and other comparable debilitating diseases. Currently available therapies for end stage heart failure include drug and device therapies, as well as heart transplantation. While drug and device therapies have proven effective at reducing symptoms, hospitalizations and deaths due to heart failure, new approaches are clearly required to improve this low survival rate. Organ transplantation is highly effective at increasing patient survival, but is severely limited in its potential for broad-based application by the very low number of hearts that are available for transplantation each year. Stem cell therapy may be a promising strategy for improving heart failure patient outcomes by transplanting cells rather than a whole heart. Several studies have convincingly shown that human embryonic stem cells can be differentiated into heart muscle cells (cardiomyocytes) and that these cells can be used to improve cardiac function following a heart attack. The key objective of this CIRM Disease Team Therapy proposal is to perform the series of activities necessary to obtain FDA approval to initiate clinical testing of human embryonic stem cell-derived cardiomyocytes in end stage heart failure patients.
Coronary artery disease (CAD) is the number one cause of mortality and morbidity in the US. The American Heart Association has estimated that 5.7 million Americans currently suffer from heart failure, and that another 670,000 patients develop this disease annually. Cardiovascular disease has been estimated to result in an estimated $286 billion in direct and indirect costs in the US annually (NHLBI, 2010). As the most populous state in the nation, California bears a substantial fraction of the social and economic costs of this devastating disease. In recent years, stem cell therapy has emerged as a promising candidate for treating ischemic heart disease. Research by our group and others has demonstrated that human embryonic stem cells (hESCs) can be differentiated to cardiomyocytes using robust, scalable, and cGMP-compliant manufacturing processes, and that hESC-derived cardiomyocytes (hESC-CMs) can improve cardiac function in relevant preclinical animal models. In this proposal, we seek to perform the series of manufacturing, product characterization, nonclinical testing, clinical protocol development, and regulatory activities necessary to enable filing of an IND for hESC-CMs within four years. These IND development activities will be in support of a Phase 1 clinical trial to test hESC-CMs in heart failure patients for the first time. If successful, this program will both pave the way for a promising new therapy to treat Californians with heart failure numbering in the hundreds of thousands, and will further enhance California’s continuing prominence as a leader in the promising field of stem cell research and therapeutics.

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