Human ES cell based therapy of heart failure without allogenic immune rejection

Grant Award Details

Human ES cell based therapy of heart failure without allogenic immune rejection

Grant Type: Early Translational III
Grant Number: TR3-05559

Project Objective: The project objective is to test the ability of CTLA4Ig and PD-L1, two proteins that together prevent T cell co-stimulation, to promote graft acceptance of allogeneic hESC-CM grafts. The PI has considerable experience with and plans to test the hypothesis using humanized mice allogeneic to the grafts. CTLA4Ig and PD-L1 expression will be achieved by knock-in to hESC termed "CP".

Investigator:

<table>
<thead>
<tr>
<th>Name</th>
<th>Yang Xu</th>
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<tbody>
<tr>
<td>Institution</td>
<td>University of California, San Diego</td>
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<tr>
<td>Type</td>
<td>PI</td>
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Disease Focus: Heart Disease
Human Stem Cell Use: Embryonic Stem Cell
Award Value: $1,857,600
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:** Human ES cell based therapy of heart failure without allogenic immune rejection

**Public Abstract:**
Heart failure is a major and ever-growing health problem affecting an estimated 5.8 million Americans with about half a million new cases every year. There are limited therapeutic options for heart failure. Heart transplantation is effective but has limited impact due to scarcity of donor organs and eventual immune rejection even under chronic immune suppression. Therefore, there is a clear unmet medical need to develop new effective therapies to treat heart failure. Human ES cell based cell therapy could provide a cure for heart diseases by providing renewable source of human cardiomyocytes (CMs) to restore lost cardiomyocytes and cardiac functions. In support of this notion, hESC-derived cardiomyocytes (hESC-CMs) can repopulate lost cardiac muscle and improve heart function in preclinical animal models of advanced heart failure. However, one key bottleneck hindering such clinic development is that hESC-CMs will be rejected by allogenic immune system of the recipients, and the typical immunosuppressant regimen is especially toxic for patients with heart diseases and leads to increased risk of cancer and infection. To resolve this bottleneck, I propose to develop a novel approach to protect the hESC-CMs from allogenic immune system. If successful, our approach will not only greatly improve the feasibility of developing hESC-CMs to treat heart failure but also has broad application in other hESC-based cell therapies for which allogenic immune rejection remains a major hurdle.

**Statement of Benefit to California:**
Heart disease is a leading cause of death and disability among Californians with an above average rate of mortality. It costs the State tremendous expenditure for the treatment and loss of productivity. There are limited therapeutic options for advanced heart diseases. In this context, heart transplantation is effective but limited by the shortage of donors. Therefore, there is clearly an urgent unmet medical need for new and effective therapies to treat heart failure. Human ES cell based cell therapy approach offers the unique potential to provide renewable source of cardiomyocytes to treat heart failure by restoring lost cardiomyocytes and cardiac function. However, one key bottleneck is that the allogenic hESC-derived cardiomyocytes will be immune rejected by recipients, and the typical immunosuppression regimen is especially toxic for fragile patients with heart diseases. In addition, chronic immune suppression greatly increases the risk of cancer and infection. Our proposed research is aimed to develop novel strategies to prevent allogenic immune rejection of hESC-derived cardiomyocytes without inducing systemic immune suppression. If successful, our approach will greatly facilitate the development of hESC-derived cardiomyocytes for treating heart disease and also has broad application in other hESC-based therapy for which allogenic immune rejection remains a bottleneck.

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