Human Induced Pluripotent Stem Cell-Derived Cardiovascular Progenitor Cells for Cardiac Cell Therapy.

**Reporting Period:** Year 1

Cardiovascular disease remains to be a major cause of morbidity and mortality in California and the United States. Despite the best medical therapies, none address the issue of irreversible myocardial tissue loss after a heart attack and thus there has been a great interest to develop approaches to induce regeneration. Our lab has focused on harvesting the full potential of patient specific induced pluripotent stem cells (iPSCs) to use to attempt to regenerate the damaged tissue. We believe that these iPSCs can be potentially used in the future to generate sufficient number of cells to be implanted in the damaged heart to regenerate the lost tissue post heart attack. Our lab has studied how these cardiac progenitors evolve in the developing heart and applied our finding to iPSCs to recapitulate the cardiac progenitors to ultimately use in clinical therapies. We have successfully derived these cardiac progenitors from patient derived iPSCs in a clinical grade fashion to ensure that we can apply same protocols in the future to clinical use if we are successful in demonstrating the efficacy of this therapy in our translational large animal studies that we will be conducting.

**Reporting Period:** Year 2

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**Reporting Period:** Year 3

We have completed the first phase of in vivo studies demonstrating that human cardiac progenitor cells were effective is restoring the function of the hearts in a heart attack model in a rat. We have shown that once injected, these human cardiac progenitor cells into the rat heart, the heart function was restored back close to normal. We plan next to test the human cardiac progenitor cells in a pig heart attack models as a preclinical model prior to human studies.

**Grant Type:** New Faculty Physician Scientist

**Grant Number:** RN3-06455
Project Objective: The PI is developing hiPSC derived cardiac progenitor cells (trilineage potential) to replace lost cardiomyocytes post MI (acute). PI anticipates these cells will differentiate to myocytes, endothelial cells and smooth muscle cells post transplant. The PI ultimately plans to achieve preclinical POC in nude rats and SCID pigs. Manufacturing challenges include characterizing the population and achieving adequate expansion and yields of hiPSC CPC. Preclinical challenges include potential ectopic tissue and arrhythmia from immature cardiomyocytes. Mechanism of action for these cardiac progenitors remains unknown. Dr Marban’s work with primary cardiac progenitors has not resulted in long term engraftment or in vivo differentiation to cardiomyocytes. Despite the in vitro potential these primary cells their in vivo mechanism appears paracrine. However, the in vivo potential of Dr Nsair’s iPSC derived population may differ. SO suggested PI prioritize initial transplantation studies to address cell persistence and potential activity in nude rats early in the award to address.

Investigator:

<table>
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<tr>
<th>Name</th>
<th>Ali Nsair</th>
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<tr>
<td>Institution</td>
<td>University of California, Los Angeles</td>
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<tr>
<td>Type</td>
<td>PI</td>
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Disease Focus: Heart Disease

Human Stem Cell Use: iPS Cell

Award Value: $2,316,894

Status: Closed

Application Title: Human Induced Pluripotent Stem Cell-Derived Cardiovascular Progenitor Cells for Cardiac Cell Therapy.

Public Abstract: Despite therapeutic advances, cardiovascular disease remains a leading cause of mortality and morbidity in California. Regenerative therapies that restore normal function after a heart attack would have an enormous societal and financial impact. Although very promising, regenerative cardiac cell therapy faces a number of challenges and technological hurdles. Human induced pluripotent stem cells (hiPSC) allow the potential to deliver patient specific, well-defined cardiac progenitor cells (CPC) for regenerative clinical therapies. We propose to translate recent advances in our lab into the development of a novel, well-defined hiPSC-derived CPC therapy. All protocols will be based on clinical-grade, FDA-approvable, animal product-free methods to facilitate preclinical testing in a large animal model. This application will attempt to translate these findings by:
- Developing techniques and protocols utilizing human induced pluripotent stem cell-derived cardiac progenitor cells at yields adequate to conduct preclinical large animal studies.
- Validation of therapeutic activity will be in small and large animal models of ischemic heart disease by demonstrating effectiveness of hiPSC-derived CPCs in regenerating damaged myocardium post myocardial infarction in small and large animal models. This developmental candidate and techniques described here, if shown to be a feasible alternative to current approaches, would offer a novel approach to the treatment of ischemic heart disease.
Cardiovascular disease remains the leading cause of morbidity and mortality in California and the US costing the healthcare system greater than 300 billion dollars a year. Although current therapies slow progression of heart disease, there are few options to reverse or repair the damaged heart. The limited ability of the heart to regenerate following a heart attack results in loss of function and heart failure. Human clinical trials testing the efficacy of adult stem cell therapy to restore mechanical function after a heart attack, although promising, have had variable results with modest improvements.

The discovery of human induced pluripotent stem cells offers a potentially unlimited renewable source for patient specific cardiac progenitor cells. However, practical application of pluripotent stem cells or their derivatives face a number of challenges and technological hurdles. We have demonstrated that cardiac progenitor cells, which are capable of differentiating into all cardiovascular cell types, are present during normal fetal development and can be isolated from human induced pluripotent stem cells. We propose to translate these findings into a large animal pre-clinical model and eventually to human clinical trials. This could lead to new therapies that would restore heart function after a heart attack preventing heart failure and death. This will have tremendous societal and financial benefits to patients in California and the US in treating heart failure.