Characterization and Engineering of the Cardiac Stem Cell Niche

Grant Award Details

Characterization and Engineering of the Cardiac Stem Cell Niche

Grant Type: Basic Biology III

Grant Number: RB3-05086

Project Objective: Overall objective is to identify the best conditions for expansion of human PSC derived cardiac progenitor cells and to push them towards a ventricular cardiomyocyte lineage for transplantation studies.
The work will be carried out by first characterizing the endogenous niche and CPC clusters in human fetal heart and then exploiting the ECM findings to generate a synthetic niche. Efforts are also under way to identify better niches through a screen of various ECM components and growth factors. These materials will be presented to cells in 2D and 3D to determine their impact upon CPC maintenance, proliferation and differentiation to the ventricular cardiac myocyte lineage.

Investigator:

Name:	Ali Nsair
Institution:	University of California, Los Angeles
Type:	PI

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Name:	Heike Walles
Institution:	Fraunhofer-Institut für Grenzflächen- und Bioverfahrenstechnik
Type:	Partner-PI

Disease Focus: Heart Disease

Collaborative Funder: Germany

Human Stem Cell Use: iPS Cell

Award Value: $1,127,741

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: Characterization and Engineering of the Cardiac Stem Cell Niche

Public Abstract: Despite therapeutic advances, cardiovascular disease remains a leading cause of mortality and morbidity in both California and Europe. New insights into disease pathology, models to expedite in vitro testing and regenerative therapies would have an enormous societal and financial impact. Although very promising, practical application of pluripotent stem cells or their derivatives face a number of challenges and technological hurdles. For instance, recent reports have demonstrated that cardiac progenitor cells (CPCs), which are capable of differentiating into all three cardiovascular cell types, are present during normal fetal development and can be isolated from pluripotent stem cells. induced pluripotent stem cell (iPSC)-derived CPC therapy after a myocardial infarction would balance the need for an autologous, multipotent stem cell myocardial regeneration with the concerns of tumorigenicity using a more primitive stem cell. However, translating this discovery into a clinically useful therapy will require additional advances in our understanding of CPC biology and the factors that regulate their fate to develop optimized cell culture technology for CPC application in regenerative medicine.

Cardiac cell therapy with hiPSC-derived cells, will require reproducible production of large numbers of well-characterized cells under defined conditions in vitro. This is particularly true for the rare and difficult to culture intermediates, such as CPCs. Our preliminary data demonstrated that a CPC niche exists during cardiac development and that CPC expansion is regulated by factors found within the niche microenvironment including specific soluble factors and ECM signals. However, our current understanding of the cardiac niche and how this unique microenvironment influences CPC fate is quite limited. We believe that if large scale production of hiPSC-derived CPCs is ever to be successful, new 3D cell culture technologies to replicate the endogenous cardiac niche will be required. The goals of this proposal are to address current deficiencies in our understanding of the cardiac niche and its effects on CPC expansion and differentiation as well as utilize novel bioengineering approaches to fabricate synthetic niche environments in vitro. The development of advanced fully automated in vitro culture systems that reproduce key features of natural niche microenvironments and control proliferation and/or differentiation, are critically needed both for studying the role of the niche in CPC biology but also the advancement of the field of regenerative medicine.

Statement of Benefit to California:	Heart disease, stroke and other cardiovascular diseases are the #1 killer in California. Despite medical advances, heart disease remains a leading cause of disability and death. Recent estimates of its cost to the U.S. healthcare system amounts to almost $300 billion dollars. Although current therapies slow the progression of heart disease, there are few, if any options, to reverse or repair damage. Thus, regenerative therapies that restore normal heart function would have an enormous societal and financial impact not only on Californians, but the U.S. more generally. The research that is proposed in this application could lead to new therapies that would restore heart function after and heart attack and prevent the development of heart failure and death. We will develop the techniques to expand and transplant human cardiac progenitor cells. Combining tissue engineering with human pluripotent stem cells will facilitate the creation of new cardiovascular therapies.