Mechanisms of Direct Cardiac Reprogramming

Grant Award Details

Mechanisms of Direct Cardiac Reprogramming

Grant Type: Basic Biology III

Grant Number: RB3-05174

Project Objective: Goal is to understand the molecular mechanisms (targets and epigenetic changes) throuhgh which GMT induces direct cardiac reprogragmming.

Investigator:

Name:	Deepak Srivastava
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Heart Disease

Award Value: $1,572,380

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: Mechanisms of Direct Cardiac Reprogramming

Public Abstract:

Heart disease is a leading cause of adult and childhood mortality. The underlying pathology is typically loss of heart muscle cells that leads to heart failure, or improper development of specialized cardiac muscle cells called cardiomyocytes during embryonic development that leads to congenital heart malformations. Because cardiomyocytes have little or no regenerative capacity after birth, current therapeutic approaches are limited for the over 5 million Americans who suffer from heart failure. Embryonic stem cells possess clear potential for regenerating heart tissue, but efficiency of cardiac differentiation, risk of tumor formation, and issues of cellular rejection must be overcome.

Our recent findings regarding direct reprogramming of a type of structural cell of the heart or skin called fibroblasts into cardiomyocyte-like cells using just three genes offer a potential alternative approach to achieving cardiac regeneration. The human heart is composed of muscle cells, blood vessel cells, and fibroblasts, with the fibroblasts comprising over 50% of all cardiac cells. The large population of cardiac fibroblasts that exists within the heart is a potential source of new heart muscle cells for regenerative therapy if it were possible to directly reprogram the resident fibroblasts into muscle cells. We simulated a heart attack in mice by blocking the coronary artery, and have been able to reprogram existing mouse cardiac fibroblasts after this simulated heart attack by delivering three genes into the heart. We found a significant reduction in scar size and an improvement in cardiac function that persists after injury. The reprogramming process starts quickly but is progressive over several weeks; however, how this actually occurs is unknown. Because this finding represents a new approach that could have clinical benefit, we propose to reveal the mechanism by which fibroblast cells become reprogrammed into heart muscle cells, which will be critical to refine the process for therapeutic use. We will do this by analyzing the changes in how the genome is interpreted and expressed at a genome-wide level at different time points during the process of fibroblast to muscle conversion, which represents the fundamental process that leads to reprogramming. The findings from this proposal will reveal approaches to refine and improve human cardiac reprogramming and will aid in translation of this technology for human cardiac regenerative purposes.

Statement of Benefit to California:

This research will benefit the state of California and its citizens by helping develop a new approach to cardiac regeneration that would have a lower risk of tumor formation and cellular rejection. In addition, the approach could remove some of the hurdles of cell-based therapy including delivery challenges and incorporation challenges. The mechanisms revealed by this research will enable refinement of the method that could potentially then be used to treat the hundreds of thousands of Californians with heart failure.
