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**microRNA Regulation of Cardiomyocyte Differentiation from Human Embryonic Stem Cells**

**Grant Award Details**

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microRNA Regulation of Cardiomyocyte Differentiation from Human Embryonic Stem Cells

**Grant Type:** Comprehensive Grant

**Grant Number:** RC1-00142

**Investigator:**

<b>Name:</b>	Deepak Srivastava
<b>Institution:</b>	Gladstone Institutes, J. David
<b>Type:</b>	PI

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**Disease Focus:** Heart Disease

**Human Stem Cell Use:** Embryonic Stem Cell

**Award Value:** \$2,994,719

**Status:** Closed

**Progress Reports**

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

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**Reporting Period:** Year 4

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**Grant Application Details**

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**Application Title:** microRNA Regulation of Cardiomyocyte Differentiation from Human Embryonic Stem Cells

**Public Abstract:**

Regenerative therapies could be particularly beneficial for heart disease, which is the leading killer of adults in the U.S, and is responsible for the 5 million Americans with insufficient cardiac function. At the other end of the age spectrum, malformations of the heart involving abnormal cell lineage or morphogenetic decisions are the leading noninfectious cause of death in children. Unfortunately, since adult heart cells cannot multiply after birth, the heart has almost no regenerative capacity after injury or in response to malformations. Deciphering the secrets of heart formation might lead to novel approaches to repair or regenerate damaged heart muscle using embryonic stem cells (ESCs) and progenitor cells. Our research is focused on determining what causes ESCs to specialize into cells that belong to the mesodermal, or middle, layer of an embryo, which develops into blood, muscle, and bone, among other cells, with a specific focus on cues that stimulate cardiac and skeletal muscle formation. Small RNA molecules called microRNAs have emerged as an elegant and novel mechanism nature uses to titrate dosage of critical proteins by regulating the flow of genetic information as it is translated into proteins. microRNAs are active dynamically and specifically in developing cardiac and skeletal muscle during muscle formation. In mice and flies, microRNAs regulate the balance of muscle formation vs. expansion of progenitor cells. We have evidence that microRNAs can control mouse embryonic stem cells (mESCs) and can promote formation of mesoderm and inhibit formation of other cell types such as brain or gut cells. This may be true in human ESCs also. However, NIH-approved human ESC (hESC) lines are contaminated with mouse feeder cells, are difficult to disperse into single cells and do not grow robustly enough to generate homogeneous pools of genetically altered cells. This has made it difficult to generate homogenous population of cells that could be used for discovery and future potential therapeutic applications. The aims of this grant will use non-NIH approved lines to meet these objectives and are not fundable by the NIH. We hypothesize that specific microRNAs influence early mesoderm commitment and later steps of myogenic expansion or formation from hESCs by controlling other key regulatory events. To test this hypothesis, we propose three specific aims: 1) Determine if microRNAs can promote mesoderm formation and subsequent decisions of cardiac muscle proliferation or differentiation in hESCs; 2) Determine if specific microRNAs repress other lineages in hESCs; 3) Determine the mechanisms by which microRNAs regulate mesoderm commitment, muscle differentiation and proliferation. The tools and understanding developed here will ultimately be used to generate myocytes either directly or through subsequent screens for drugs targeted at the pathways discovered by the proposed work.

**Statement of Benefit to California:**

The work proposed here will reveal novel mechanisms to induce human embryonic stem cells (hESCs) to differentiate into cardiac and possibly skeletal muscle. The major focus of the aims is to more efficiently derive cardiac cells from hESCs and to understand the mechanisms by which this occurs. Novel pathways will lead to pharmacologic targets that are amenable to high throughput screening. This knowledge will lead to protocols that will allow efficient generation of cardiac muscle cells that could eventually be used for therapeutic purposes in individuals with heart disease. In the short-term, California will benefit from being at the forefront of technology and discovery in hESC biology and by remaining the epicenter of the most progressive basic and translational science. If we are successful in the long-term, California residents will benefit from novel therapies and potential commercialization of discoveries for heart disease, the number one cause of death in the U.S.

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