# Discovering Potent Molecules with Human ESCs to Treat Heart Disease

## Grant Award Details

Discovering Potent Molecules with Human ESCs to Treat Heart Disease

**Grant Type:** SEED Grant

**Grant Number:** RS1-00169

**Investigator:**

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| **Name:** | John Cashman |
| **Institution:** | Human BioMolecular Research Institute |
| **Type:** | PI |

**Disease Focus:** Heart Disease

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

**Award Value:** $688,274

**Status:** Closed

## Progress Reports

**Reporting Period:** Year 2

**View Report**

**Reporting Period:** NCE

**View Report**

## Grant Application Details

**Application Title:** Discovering Potent Molecules with Human ESCs to Treat Heart Disease

**Public Abstract:**

This work is directly relevant to human embryonic stem cell (hESC) research because it brings new ideas about novel compounds to affect cardiomyogenesis. The work addresses an urgent need to develop new agents to treat cardiovascular disease. We will develop potent and selective drug-like molecules as cardiomyocyte differentiation agents.

Heart disease is the leading cause of mortality and decline in the quality of life in the developed world. The ability of hESCs to form cardiomyocytes has spawned hope that these cells may be used to replace damaged myocardium. Despite their ability to form cardiomyocytes, efficient and controlled cardiomyogenesis in ESC cultures has not been achieved due to the unavailability of differentiation agents and an incomplete understanding of the pathways that regulate cardiac development.

Success has been achieved in developing a robust and dependable high-throughput assay to study the effects of small molecules on cardiomyocyte differentiation. Powerful cell-based assays were developed and provided readouts that led to high-content results because multiple signals were probed. The assay is capable of capturing fast or long-acting biology because of the time-course readouts. Cell-based assays are superior to molecular screens because the cell-based assay delivers active compounds or “hits” that are permeable and non-cytotoxic. Moreover, refined “hits” can be used as probes to reveal novel signaling pathways and proteins that control differentiation, in a process termed chemical biology. By taking advantage of knowledge of the current “hits” we will rapidly synthesize novel drug-like compounds in a low-risk approach to. The “hits” will be refined and improved through an efficient synthetic process we use in our lab called “Dynamic Medicinal Chemistry”.

Even after miniaturization and automation, screening is still expensive. A key to improve the screening process is to use pharmacologically active, drug-like compounds to provide rich target-relevant information. Intelligently designing libraries for screening by incorporating drug-like features into “lead” library design will improve the attrition rate and lead to more pharmacologically relevant compounds for future studies.

This proposal is directly responsive to the California Institute for Regenerative Medicine SEED Grant Program because it provides for developing and testing new agents of use in cardiomyoenesis of hESCs. Importantly, it brings new investigators and a collaborative approach to the stem cell field. The agents discovered and developed may hold great promise as the groundwork for future medications development for a new class of damaged myocardium replacement agents. The theoretical rationale for the work is the use of high-content screening coupled with drug-like new agent discovery approaches. The work will also be of use in the elucidation of key biochemical targets and novel signaling pathways important in hESC cardiomyogenesis.

**Statement of Benefit to California:**

In 2002, in the State of California, approximately 697,000 adult Californians died from heart disease. The cost as measured by loss of lifelong earnings was more than $79 billion. Setting aside the pain and suffering, the economic impact of cardiovascular disease to the State of California is staggering. Despite recent advances in cardiovascular medications development, new approaches and novel drug-like compounds are urgently needed to treat cardiovascular disease in California and elsewhere. The poor prognosis for heart disease for Californians underscores the critical need to develop alternative therapeutic strategies. The demonstrated ability of human embryonic stem cells (hESCs) to form cardiomyocytes has spawned widespread hope that these cells may be used as a source to replace damaged myocardium in humans. Despite their ability to form cardiomyocytes, efficient and controlled cardiomyogenesis in hESC culture has not been achieved due to the unavailability of differentiation agents and also because of an incomplete understanding of the pathways that regulate cardiac cell development.

Using a high-throughput whole cell assay with image analysis, we have identified four small molecules that promote cardiomyogenesis in human ESCs. This proposal is directly responsive to the California Institute for Regenerative Medicine SEED Grant Program because it provides for developing and testing new agents of use in cardiomyogenesis of hESCs. It also brings new investigators and new collaborative approaches to the field. The promising agents discovered already constitute an excellent starting point and further refinement and development of these compounds may hold great promise as the groundwork for future medications development for a new class of damaged myocardium differentiation agents. The theoretical rationale for the work is the use of high-content screening coupled with drug-like new agent discovery approaches. The work will be of use in the elucidation of key biochemical targets and novel signaling pathways important in hESC cardiomyogenesis.

The compounds discovered in our whole hESC-based assays thus far are not potent enough to be developed as drug candidates. But these compounds hold great promise as agents that could be refined further into drug leads. If the leads become drugs, promise of a new class of medication to treat cardiovascular disease may become a reality. Such drugs would decrease cardiovascular disease and decrease health care costs in California. This will likely have a significant economic impact to the State of California. The proposed work represents essential translational research required for new drug development.

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