

A new paradigm of lineage-specific reprogramming

Grant Award Details

A new paradigm of lineage-specific reprogramming

Grant Type: Basic Biology IV

Grant Number: RB4-06035

Project Objective: The PI is attempting to use non-integrating methods (e.g., mRNA, miRNA, episomal vectors and/or small molecule-based) to improve direct reprogramming efficiencies for converting fibroblasts into expandable cardiovascular precursor cells.

Investigator:

Name:	Sheng Ding
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Heart Disease

Human Stem Cell Use: Directly Reprogrammed Cell

Cell Line Generation: iPS Cell

Award Value: \$1,568,395

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Grant Application Details

Application Title: A new paradigm of lineage-specific reprogramming

Public Abstract: Recently, we devised and reported a new regenerative medicine paradigm that entails temporal/transient overexpression of induced pluripotent stem cell based reprogramming factors in skin cells, leading to the rapid generation of "activated" cells, which can then be directed by specific growth factors and small molecules to "relax" back into various defined and homogenous tissue-specific precursor cell types (including nervous cells, heart cells, blood vessel cells, and pancreas and liver progenitor cells), which can be expanded and further differentiated into mature cells entirely distinct from fibroblasts.

In this proposal, combined with small molecules that can functionally replace reprogramming transcription factors as well as substantially improve reprogramming efficiency and kinetics, we aim to further develop and mechanistically characterize chemically defined, non-integrating approaches (e.g., mRNA, miRNA, episomal plasmids and/or small molecule-based) to robustly and efficiently reprogram skin fibroblast cells into expandable heart precursor cells. Specifically, we will: determine if we can use non-integrating methods to destabilize human fibroblasts and facilitate their direct reprogramming into the heart precursor cells; characterize of heart cells generated by the direct programming methods, both in the tissue culture dish and in a mouse model of heart attack; and characterize newly identified reprogramming enhancing small molecules mechanistically.

Statement of Benefit to California: This study will develop and mechanistically characterize a new method of generating safe patient specific heart cells that could be useful in treating heart failure which afflicts millions of Californians and accounts for billions of dollars in healthcare spending annually. Additionally, the small molecules discovered in this study could be good candidates for future drug development as well as being broadly useful for other regenerative medicine applications. These advances could also be a platform for new personalized medicine/ cell banking businesses which could bring economic growth in addition to improving the health of Californians.

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