Use of Human iPSC-derived Endothelial Cells for Calcific Aortic Valve Disease Therapeutics

Grant Award Details

Use of Human iPSC-derived Endothelial Cells for Calcific Aortic Valve Disease Therapeutics

Grant Type: Quest - Discovery Stage Research Projects

Grant Number: DISC2-09098

Project Objective: A small molecule therapeutic candidate(s) that arrests or delays calcific aortic valve disease and a genetic profile of potential responders.

Investigator:

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

Disease Focus: Heart Disease, Vascular Disease

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $2,400,048

Status: Active

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Use of Human iPSC-derived Endothelial Cells for Calcific Aortic Valve Disease Therapeutics

Public Abstract:

Research Objective

To develop drugs to treat Calcific Aortic Valve Disease (CAVD), the third leading cause of adult heart disease, by screening a stem cell-based platform based on CAVD patient-derived stem cells.

Impact

CAVD represents a major unmet medical need, with no treatments other than valve replacement. We will identify drugs, already proven to be safe, that normalize gene dysregulation and prevent CAVD.

Major Proposed Activities

- Generate iPSCs from 100 subjects with early onset CAVD and BAV.
- Perform genetic analyses of the 100 subjects for enrichment of variants in N1-related gene networks and osteogenic networks.
- Derive endothelial cells from CAVD iPSC lines, and study their gene expression under biophysical conditions related to valve calcification.
- Screen nine drugs validated in N1+/– iPSC-ECs for their effects on correcting gene network dysfunction in sporadic CAVD patient-derived iPSC-ECs.
- Determine efficacy of nine drugs validated in N1+/– iPSC-ECs in preventing CAVD in a mouse model.
- Initiate studies of optimal dosing and timing of potential therapeutic compound, which will be determined by best efficacy in Activity 5.

Statement of Benefit to California:

This research will benefit California by developing drugs to treat Calcific Aortic Valve Disease (CAVD), a major unmet medical need that imposes a serious economic burden. The only clinical option is valve replacement, with 100,000 patients receiving transplants per year in the US. To address this, we will use a stem cell-based platform based on CAVD patient-derived stem cells to test drugs, already proven to be safe, that normalize gene dysregulation and prevent CAVD.

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