Studying Arrhythmogenic Right Ventricular Dysplasia with patient-specific iPS cells

Grant Award Details

Studying Arrhythmogenic Right Ventricular Dysplasia with patient-specific iPS cells

Grant Type: Basic Biology IV

Grant Number: RB4-06276

Project Objective: The goal is to explore the molecular basis underlying metabolic derangement of PPAR pathways in ARVD hearts through the study of patient cells with different ARVD inducing mutations to those already characterized by the PI. There is also an effort to treat the phenotype with PPAR gamma inhibitors.
In background work, ARVD iPSC-CMs from a single patient and pathogenic induction, the team found that activation of PPARα for normal fatty acid oxidation and abnormal PPARγ activation resulted in exaggerated lipogenesis, CM apoptosis and defective intracellular calcium ([Ca2+]i) handling, recapitulating the pathological signatures of ARVD in vitro. PPARγ antagonists rescued ARVD pathological phenotypes and reactive oxygen radical (ROS) scavengers, e.g. N-acetyl-cysteine, could curtail CM apoptosis in our ARVD in-vitro model.

Investigator:

Name:	Huei-sheng Chen
Institution:	Sanford Burnham Prebys Medical Discovery Institute
Type:	PI

Disease Focus: Heart Disease, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,579,250

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4/NCE

View Report

Grant Application Details

Application Title: Studying Arrhythmogenic Right Ventricular Dysplasia with patient-specific iPS cells

Public Abstract: Most heart conditions leading to sudden death or impaired pumping heart functions in the young people (<35 years old) are the results of genetic mutations inherited from parents. It is very difficult to find curative therapy for these inherited heart diseases due to late diagnosis and lack of understanding in how genetic mutations cause these diseases. Using versatile stem cells derived from patients' skin cells with genetic mutations in cell-cell junctional proteins, we have made a significant breakthrough and successfully modeled one of these inherited heart diseases within a few months in cell cultures. These disease-specific stem cells can give rise to heart cells, which allow us to discover novel abnormalities in heart energy consumption that causes dysfunction and death of these diseased heart cells. Currently, there is no disease-slowing therapy to these inherited heart diseases except implanting a shocking device to prevent sudden death. We propose here to generate more patient-specific stem cell lines in a dish from skin cells of patients with similar clinical presentations but with different mutations. With these new patient-specific stem cell lines, we will be able to understand more about the malfunctioned networks and elucidate common disease-causing mechanisms as well as to develop better and safer therapies for treating these diseases. We will also test our new therapeutic agents in a mouse model for their efficacy and safety before applying to human patients.

Statement of Benefit to California: Heart conditions leading to sudden death or impaired pumping functions in the young people (<35 years old) frequently are the results of genetic mutations inherited from parents. Currently, there is no disease-slowing therapy to these diseases. It is difficult to find curative therapy for these diseases due to late diagnosis. Many cell culture and animal models of human inherited heart diseases have been established but with significant limitation in their application to invent novel therapy for human patients. Recent progress in cellular reprogramming of skin cells to patient-specific induced pluripotent stem cells (iPSCs) enables modeling human genetic disorders in cell cultures. We have successfully modeled one of the inherited heart diseases within a few months in cell cultures using iPSCs derived from patients' skin cells with genetic mutations in cell-cell junctional proteins. Heart cells derived from these disease-specific iPSCs enable us to discover novel disease-causing abnormalities and develop new therapeutic strategies. We plan to generate more iPSCs with the same disease to find common pathogenic pathways, identify new therapeutic strategies and conduct preclinical testing in a mouse model of this disease. Successful accomplishment of proposed research will make California the epicenter of heart disease modeling in vitro, which very likely will lead to human clinical trials and benefit its young citizens who have inherited heart diseases.