Improving Existing Drugs for Long QT Syndrome type 3 (LQT3) by hiPSC Disease-in-Dish Model

Grant Award Details

Improving Existing Drugs for Long QT Syndrome type 3 (LQT3) by hiPSC Disease-in-Dish Model

Grant Type: Early Translational IV

Grant Number: TR4-06857

Project Objective: The goal is to produce a safer form of mexiletine, a sodium channel blocking antiarrythmic drug. This drug poses an arryhthmia risk in certain LQT3 patients that bear a variant form of the hERG potassium channel. The PI will use patient iPSC-derived cardiomyocytes to screen and optimize analogues of the drug. Analogues will be tested against patient and control hiPSC to confirm activity against the sodium channel and loss of activity against variant hERG. Murine studies will also be performed for preliminary tox and ADME studies.

Investigator:

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

,

Name:	Mark Mercola
Institution:	Sanford Burnham Prebys Medical Discovery Institute
Type:	Co-PI

Disease Focus: Heart Disease

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $6,361,369

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 4 (NCE)

View Report

Grant Application Details

Application Title: Improving Existing Drugs for Long QT Syndrome type 3 (LQT3) by hiPSC Disease-in-Dish Model

Public Abstract: This project uses patient hiPSC-derived cardiomyocytes to develop a safe and effective drug to treat a serious heart health condition. This research and product development will provide a novel method for a human genetic heart disorder characterized by long delay (long Q-T interval) between heart beats caused by mutations in the Na+ channel α subunit. Certain patients are genetically predisposed to a potentially fatal arrhythmogenic response to existing drugs to treat LQT3 since the drugs have off-target effects on other important ion channels in cardiomyocytes. We will use patient-derived hiPSC-cardiomyocytes to develop a safer drug (development candidate, DC) that will retain efficacy against the "leaky" Na+-channel yet minimize off-target effects in particular against the K+ hERG channel that can be responsible for the existing drug's pro-arrhythmic effect. Since this problem is thought to occur severely in patients with the common KCHN2 variant, K897T (~33% of the white population), removing the off-target liability addresses a serious unmet clinical need. Futher, since we propose to modify an existing drug (i.e., do drug rescue), the path from patient-specific hiPSCs to clinic might be easier than for a completely new chemical entity. Lastly, an appealing aspect is that the hiPSCs were derived from a child to test his therapy, & we aim to produce a better drug for his treatment. Our goal is to complete development of the DC and initiate IND-enabling in vivo studies.

Statement of Benefit to California: In the US, an estimated 850,000 adults are hospitalized for arrhythmias each year, making arrhythmias one of the top five causes of healthcare expenditures in the US with a direct cost of more than $40 billion annually for diagnosis, treatment & rehabilitation. The State of California has approximately 12% of the US population which translates to 102,000 individuals hospitalized every year for arrhythmias. Another 30,000 Californians die of sudden arrhythmic death syndrome every year. Arrhythmias are very common in older adults and because the population of California is aging, research to address this issue is important for human health and the State economy. Most serious arrhythmias affect people older than 60. This is because older adults are more likely to have heart disease & other health problems that can lead to arrhythmias. Older adults also tend to be more sensitive to the side effects of medicines, some of which can cause arrhythmias. Some medicines used to treat arrhythmias can even cause arrhythmias as a side effect. In the US, atrial fibrillation (a common type of arrhythmia that can cause problems) affects millions of people & the number is rising. Accordingly, the same problem is present in California. Thus, successful completion of this work will not only provide citizens of California much needed advances in cardiovascular health technology & improvement in health care but an improved heart drug. This will provide high paying jobs & significant tax revenue.