Induced Pluripotent Stem Cells for Cardiovascular Diagnostics

Grant Award Details

Induced Pluripotent Stem Cells for Cardiovascular Diagnostics

Grant Type: New Cell Lines

Grant Number: RL1-00639

Investigator:

Name:	Bruce Conklin
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Heart Disease, Toxicity

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,708,560

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Induced Pluripotent Stem Cells for Cardiovascular Diagnostics

Public Abstract:

Our objective is to use induced pluripotent stem (iPS) cell technology to produce a cell-based test for long QT syndrome (LQTS), a major form of sudden cardiac death. Nearly 500,000 people in the US die of sudden cardiac death each year. LQTS can be triggered by drug exposure or stresses. Drug-induced LQTS is the single most common reason for drugs to be withdrawn from clinical trials, causing major setbacks to drug discovery efforts and exposing people to dangerous drugs. In most cases, the mechanism of drug-induced LQTS is unknown. However, there are genetic forms of LQTS that should allow us to make iPS cell–derived heart cells that have the key features of LQTS. Despite the critical need, current tests for drug-induced LQTS are far from perfect. As a result, potentially unsafe drugs enter clinical trials, endangering people and wasting millions of dollars in research funds. When drugs causing LQTS such as terfenadine (Seldane) enter the market, millions of people are put at serious risk. Unfortunately it is very difficult to know when a drug will cause LQTS, since most people who develop LQTS have no known genetic risk factors. The standard tests for LQTS use animal models or hamster cells that express human heart genes at high levels. Unfortunately, cardiac physiology in animal models (rabbits and dogs) differs from that in humans, and hamster cells lack many key features of human heart cells. Human embryonic stem cells (hESCs) can be differentiated into heart cells, but we do not know the culture conditions that would make the assay most similar to LQTS in a living person. These problems could be solved if we had a method to grow human heart cells from people with genetic LQTS mutations, so that we know the exact test conditions that would reflect the human disease. This test would be much more accurate than currently available tests and would help enable the development of safer human pharmaceuticals. Our long-term goal is to develop a panel of iPS cell lines that better represent the genetic diversity of the human population. Susceptibility to LQTS varies, and most people who have life-threatening LQTS have no known genetic risk factors. We will characterize iPS cells that have well-defined mutations that have clinically proven responses to drugs that cause LQTS. These iPS cell lines will be used to refine testing conditions. To validate the iPS cell–based test, the results will be directly compared to the responses in people. These studies will provide the foundation for an expanded panel of iPS cell lines from people with other genetic mutations and from people who have no genetically defined risk factor but still have potentially fatal drug-induced LQTS. This growing panel of iPS cell lines should allow for testing drugs for LQTS more effectively and accurately than any current test.

Statement of Benefit to California:

Heart disease is the leading killer of adults in the Western world. Nearly 500,000 people in the US die of sudden cardiac death each year. Our goal is to develop a cell-based test to screen for drugs that can cause sudden cardiac death. Drug-induced cardiac side effects are the most common reason for withdrawal of drugs from clinical trials, causing major setbacks to drug discovery efforts. Therefore our test we will improve the safety of pharmaceuticals. Our test will also reduce the change that a drug in development will fail during clinical trials, thereby decreasing the financial risk for pharmaceutical companies. The results of our studies will help develop new technology that is likely to contribute to the California biotechnology industry. Our studies will develop multiple lines of iPS cells with unique genetic characteristics. These cell lines could be valuable for biotechnology companies and researchers who are screening for drug compounds. We are working closely with California companies to develop new microscopes, assay devices, and analytical software that could be the basis for new product lines or new businesses. If therapies do come to fruition, we anticipate that California medical centers will be leading the way. The most important contribution of this study will be to improve the health of Californians. Heart disease is a major cause of mortality and morbidity, resulting in billions of dollars in health care costs and lost days at work. Our goal is to contribute research that would ultimately improve the quality of life and increase productivity for millions of people who suffer from heart disease.