Engineering Defined and Scaleable Systems for Dopaminergic Neuron Differentiation of hPSCs

Grant Award Details

Engineering Defined and Scaleable Systems for Dopaminergic Neuron Differentiation of hPSCs

Grant Type: Tools and Technologies II

Grant Number: RT2-02022

Project Objective: This project is to develop engineered and chemically defined surfaces for cultured and differentiation of dopaminergic neurons from human ESCs for cell therapy to treat Parkinsons Disease

Investigator:

Name:	David Schaffer
Institution:	University of California, Berkeley
Type:	PI

Disease Focus: Neurological Disorders, Parkinson's Disease

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $1,340,816

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: Engineering Defined and Scaleable Systems for Dopaminergic Neuron Differentiation of hPSCs

Public Abstract: Human pluripotent stem cells (hPSC) have the capacity to differentiate into every cell in the adult body, and they are thus a highly promising source of differentiated cells for the investigation and treatment of numerous human diseases. For example, neurodegenerative disorders are an increasing healthcare problem that affect the lives of millions of Americans, and Parkinson's Disease (PD) in particular exacts enormous personal and economic tolls. Expanding hPSCs and directing their differentiation into dopaminergic neurons, the cell type predominantly lost in PD, promises to yield cells that can be used in cell replacement therapies. However, developing technologies to create the enormous numbers of safe and healthy dopaminergic neurons required for clinical development and implementation represents a bottleneck in the field, because the current systems for expanding and differentiating hPSCs face numerous challenges including difficulty in scaling up cell production, concerns with the safety of some materials used in the current cell culture systems, and limited reproducibility of such systems.

An emerging principle in stem cell engineering is that basic advances in stem cell biology can be translated towards the creation of “synthetic stem cell niches” that emulate the properties of natural microenvironments and tissues. We have made considerable progress in engineering bioactive materials to support hESC expansion and dopaminergic differentiation. For example, basic knowledge of how hESCs interact with the matrix that surrounds them has led to progress in synthetic, biomimetic hydrogels that have biochemical and mechanical properties to support hESC expansion. Furthermore, biology often presents biochemical signals that are patterned or structured at the nanometer scale, and our application of materials chemistry has yielded synthetic materials that imitate the nanostructured properties of endogenous ligands and thereby promise to enhance the potency of growth factors and morphogens for cell differentiation.

We propose to build upon this progress to create general platforms for hPSC expansion and differentiation through two specific aims: 1) To determine whether a fully defined, three dimensional (3D) synthetic matrix for expanding immature hPSCs can rapidly and scaleably generate large cell numbers for subsequent differentiation into potentially any cell , and 2) To investigate whether a 3D, synthetic matrix can support differentiation into healthy, implantable human DA neurons in high quantities and yields. This blend of stem cell biology, neurobiology, materials science, and bioengineering to create “synthetic stem cell niche” technologies with broad applicability therefore addresses critical challenges in regenerative medicine.

Statement of Benefit to California:	This proposal will develop novel tools and capabilities that will strongly enhance the scientific, technological, and economic development of stem cell therapeutics in California. The most important net benefit will be for the treatment of human diseases. Efficiently expanding immature hPSCs in a scaleable, safe, and economical manner is a greatly enabling capability that would impact many downstream medical applications. The development of platforms for scaleable and safe cell differentiation will benefit therapeutic efforts for Parkinson's Disease. Furthermore, the technologies developed in this proposal are designed to be tunable, such that they can be readily adapted to numerous downstream applications. The resulting technologies have strong potential to benefit human health. Furthermore, this proposal directly addresses several research targets of this RFA – the development and validation of stem cell scale-up technologies including novel cell expansion methods and bioreactors for both human pluripotent cells and differentiated cell types – indicating that CIRM believes that the proposed capabilities are a priority for California's stem cell effort. While the potential applications of the proposed technology are broad, we will apply it to a specific and urgent biomedical problem: developing systems for generating clinically relevant quantities of dopaminergic neurons from hPSCs, part of a critical path towards developing therapies for Parkinson's disease. This proposal would therefore work towards developing capabilities that are critical for hPSC-based regenerative medicine applications in the nervous system to clinically succeed. The principal investigator and co-investigator have a strong record of translating basic science and engineering into practice through interactions with industry, particularly within California. Finally, this collaborative project will focus diverse research groups with many students on an important interdisciplinary project at the interface of science and engineering, thereby training future employees and contributing to the technological and economic development of California.
