Molecular determinants of accurate differentiation from human pluripotent stem cells

Grant Award Details

Molecular determinants of accurate differentiation from human pluripotent stem cells

Grant Type: Basic Biology III

Grant Number: RB3-05207

Project Objective: This award's goal is to define the molecular mechanisms underlying the developmental maturity in the progeny of hPSCs. There is focus on NPCs and gliogenic cells which become astrocytes or oligodendrocytes cells

Investigator:

Name:	William Lowry
Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $677,115

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Molecular determinants of accurate differentiation from human pluripotent stem cells

Public Abstract: The use of human pluripotent stem cells for cell-based therapeutics is predicated on the ability to convert these cells into functional equivalents of those lost in disease or injury. However, there is only scant evidence that either human embryonic stem cells or human induced pluripotent stem cells make differentiated progeny that are functionally equivalent to those found in tissues. Our preliminary results, gathered over several years suggest that in fact human pluripotent stem cells may make authentic tissue derived cells, but they appear to be most similar to cells found only during very early fetal development. As a result, it is unclear if these cells will suitably replace tissue derived cells in postnatal therapies. We have also uncovered several genes whose expression appears to distinguish mature tissue derived cells and those generated from human pluripotent stem cells. We have designed this project to determine whether manipulating expression of those genes in pluripotent derivatives can bring them closer to postnatal tissue derived cells. We also propose to discover small molecule compounds that can have the same effect. Upon successful completion of these aims, we will bring to the community compounds that allow for appropriate maturation of all types of pluripotent derivatives. Therefore, these reagents will facilitate cell based therapeutics enormously and perhaps allow for successful transplantation of pluripotent derivatives for the treatment of a wide variety of diseases and injuries.

Statement of Benefit to California: For human pluripotent stem cells to reach their full potential in cell based therapeutics it is absolutely essential that their differentiation to particular cell types produces a product with the functional capacity to replace lost tissue. As California is a leader in the adoption of pluripotent stem cell therapies, it is vital that it also be a leader in the generation of derivatives from pluripotent stem cells that accurately mimic cells found in tissue. Our data suggests that instead of generating cells that would normally be found in adult tissue, human pluripotent stem cells instead produce cells found during very early fetal development. Not only does this suggest that cell based therapies with such cells might be hampered, but in fact the proliferative nature of these cells could even make them dangerous. We propose a series of experiments that will test the idea that manipulating the gene expression of pluripotent derivatives during differentiation will make cells that more accurately reflect those found in tissues that would typically require stem cell based treatments. We will develop tools that will be easily applicable for a wide range of cell types and yield mature, functional cells that not only mimic tissue derived cells, but can also functionally replace cells that are lost in disease or injury. This work will be particularly beneficial to ongoing efforts in California to apply pluripotent stem cells in therapeutic settings, and will therefore greatly benefit Californians requiring such treatment.