Identification and characterization of human ES-derived DA neuronal subtypes

Grant Award Details

Identification and characterization of human ES-derived DA neuronal subtypes

Grant Type: Basic Biology I

Grant Number: RB1-01358

Project Objective: To develop markers and approaches for the identification of different classes of dopaminergic neurons.

Investigator:

Name:	Susan McConnell
Institution:	Stanford University
Type:	PI

Disease Focus: Neurological Disorders, Parkinson's Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,404,853

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3 & NCE

View Report

Grant Application Details

Application Title: Identification and characterization of human ES-derived DA neuronal subtypes

Public Abstract: Parkinson's disease (PD) is a neurodegenerative movement disorder that affects 1 in 100 people over the age of 60, one million people in the US and six million worldwide. Patients show a resting tremor, slowness of movement (bradykinesia), postural instability and rigidity. Parkinson's disease results primarily from the loss of neurons deep in the middle part of the brain (the midbrain), in particular neurons that produce dopamine (referred to as "dopaminergic"). There are actually two groups of midbrain dopaminergic (DA) neurons, and only one, those in the substantia nigra (SN) are highly susceptible to degeneration in Parkinson's patients. There is a relative sparing of the second group and these are called ventral tegmental area (VTA) dopaminergic neurons. These two groups of neurons reside in different regions of the adult ventral midbrain and importantly, they deliver dopamine to their downstream neuronal targets in different ways. SN neurons deliver dopamine in small rapid squirts, like a sprinkler, whereas VTA neurons have a tap that provides a continuous stream of dopamine.

A major therapeutic strategy for Parkinsons' patients is to produce DA neurons from human embryonic stem cells for use in transplantation therapy. However early human trials were disappointing, since a number of patients with grafts of human fetal neurons developed additional, highly undesirable motor dyskinesias. Why this occurred is not known, but one possibility is that the transplant mixture, which contained both SN and VTA DA neurons, provided too much or unregulated amounts of DA (from the VTA neurons), overloading or confusing the target region in the brain that usually receives dopamine from SN neurons in small, regular quantities. Future human trials will likely utilize DA neurons that have been made from human embryonic stem cells (hES). Since stem cells have the potential to develop into any type of cell in the body, these considerations suggest that we should devise a way to specifically produce SN neurons and not VTA neurons from stem cells for use in transplantation. However, although we can produce dopaminergic neurons from hES cells, to date the scientific community cannot distinguish SN from VTA neurons outside of their normal brain environment and therefore has no ability to produce one selectively and not the other. We do know, however, that these two populations of neurons normally form connections with different regions in the brain, and we propose to use this fact to identify molecular markers that distinguish SN from VTA neurons and to determine optimal conditions for the differentiation of hES to SN DA neurons, at the expense of VTA DA neurons. Our studies have the potential to significantly impact transplantation therapy by enabling the production of SN over VTA neurons from hES cells, and to generate hypotheses about molecules that might be useful for coaxing SN DA neurons to form appropriate connections within the transplanted brain.

Statement of Benefit to California: The goal of our work is to further optimize our ability to turn undifferentiated human stem cells into differentiated neurons that the brain can use as replacement for neurons damaged by disease. We focus on Parkinson's disease, a neurodegenerative disease that afflicts 4-6 million people worldwide in all geographical locations, but which is more common in rural farm communities compared to urban areas, a criteria important for California's large farming population. In Parkinson's patients, a small, well-defined subset of neurons, the midbrain dopaminergic neurons have died, and one therapeutic strategy is to transplant healthy replacement neurons to the patient. Our work will further our understanding of the biology of these neurons in normal animals. This will allow us to refine the process of turning human embryonic stem cells onto biologically active dopaminergic neurons that can be used in transplantation therapy. Our work will be of benefit to all Parkinson's patients including afflicted Californians. Further, this project will utilize California goods and services whenever possible.
