Molecular and Cellular Transitions from ES Cells to Mature Functioning Human Neurons

Grant Award Details

Molecular and Cellular Transitions from ES Cells to Mature Functioning Human Neurons

Grant Type: Comprehensive Grant

Grant Number: RC1-00115

Investigator:

Name:	Fred Gage
Institution:	Salk Institute for Biological Studies
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Genetic Disorder, Neurological Disorders, Parkinson's Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,749,293

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Grant Application Details

Application Title: Molecular and Cellular Transitions from ES Cells to Mature Functioning Human Neurons

Public Abstract: Human embryonic stem cells (hESCs) are pluripotent entities, capable of generating a whole-body spectrum of distinct cell types. We have developmental procedures for inducing hESCs to develop into pure populations of human neural stem cells (hNS), a step required for generating authentic mature human neurons. Several protocols have currently been developed to differentiate hESCs to what appear to be differentiated dopaminergic neurons (important in Parkinson's disease (PD) and cholinergic motor neurons (important in Amyolateral Sclerosis (ALS) in culture dishes. We have developed methods to stably insert new genes in hESC and we have demonstrated that these transgenic cells can become mature neurons in culture dishes. We plan to over express alpha synuclein and other genes associated with PD and superoxide dismutase (a gene mutated in ALS) into hESCs and then differentiate these cells to neurons, and more specifically to dopaminergic neurons and cholinergic neurons using existing protocols. These transgenic cells can be used not only for the discovery of cellular and molecular causes for dopaminergic or cholinergic cell damage and death in these devastating diseases, but also can be used as assays to screen chemical libraries to find novels drugs that may protect against the degenerative process. Until recently the investigation of the differentiation of these human cells has only been observed in culture dishes or during tumor formation. Our recent results show that hESC implanted in the brains of mice can survive and become active functional human neurons that successfully integrate into the adult mouse forebrain. This method of transplantation to generate models of human disease will permit the study of human neural development in a living environment, paving the way for the generation of new models of human neurodegenerative and psychiatric diseases. It also has the potential to speed up the screening process for therapeutic drugs.

Statement of Benefit to California: We plan to develop procedures to induce human ES cells into mature functioning neurons that carry genes that cause the debilitating human neurological diseases, Parkinson's disease and Amyolateral Sclerosis (ALS). We will use the cells to reveal the genes and molecular pathways inside the cells that are responsible for how the mutant genes cause damage to specific types of brain cells. We also will make the cells available to other researchers as well as biotech companies so that other investigators can use these cells to screen small molecule and chemical libraries to discover new drugs that can interfere with the pathology caused by these mutant cells that mimic human disease, in hopes of accelerating the pace of discovery.

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