
New Cell Lines for Huntington's Disease

Grant Award Details

New Cell Lines for Huntington's Disease

Grant Type: New Cell Lines

Grant Number: RL1-00678

Investigator:

Name:	Leslie Thompson
Institution:	University of California, Irvine
Type:	PI

Disease Focus: Huntington's Disease, Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: Embryonic Stem Cell, iPS Cell

Award Value: \$1,302,526

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Grant Application Details

Application Title: New Cell Lines for Huntington's Disease

Public Abstract:

Huntington's disease (HD) is a devastating neurodegenerative disease with a 1/10,000 disease risk that always leads to death. These numbers do not fully reflect the large societal and familial cost of HD, which requires extensive caregiving and has a 50% chance of passing the mutation to the next generation. Current treatments treat some symptoms but do not change the course of disease. Symptoms of the disease include movement abnormalities, inability to perform daily tasks and and psychiatric problems. A loss os specific regions of the brain are observed. The mutation for HD is an expansion of a region of repeated DNA in the HD gene and the longer the repeat, in general the earlier the onset of disease. While the length of this polyglutamine repeat largely determines the age-of-onset, there is variance in onset age that is not accounted for by repeat length but is determined by genetic and environmental factors. In addition, the symptoms can vary significantly among patients in a non-repeat dependent manner. To assist in preventing onset of HD, there is a great need to identify genes that are involved in why one individual with 45 repeats will manifest symptoms at age 40 while another manifests symptoms at age 70. Further, there is a lack of early readouts to determine when to begin HD treatments. Because the disease mutation is known, preimplantation genetic diagnosis (PGD) is possible and mutant Htt embryos are available. Stem cell lines can be derived from PGD embryos with varying repeat lengths and genetic backgrounds to provide new methods to identify genetic modifiers and readouts of disease progression. The development of pluripotent stem cells, termed induced pluripotent stem cells (iPS) cells, derived directly from HD patient fibroblasts, would also provide new methods for these analyses. Chemical compound screens to identify drugs that protect against the effect of mutant Htt protein expression in patient derived hESCs cells would allow evaluation of drug responses in on cells having different genetic backgrounds Ultimately, the iPS cells can provide a way to transplant neurons or neuronal support cells from affected individuals or from unaffected family members having a normal range repeat. Such cells would help reduce immune rejection effects likely to occur with transplantation, however, while patient-derived cells overcome the problems of immune rejection, the mutant protein is still expressed. To overcome this problem we will genetically modify these stem cells to reduce the mutant protein and produce a normal gene. Beyond the immediate application to HD, the development of these models is applicable to a range of neurodegenerative diseases including Alzheimer's and Parkinson's diseases.

Statement of Benefit to California:

The disability and loss of earning power and personal freedom resulting from Huntington's disease (HD) is devastating and creates a financial burden for California. Individuals are struck in the prime of life, at a point when they are their most productive and have their highest earning potential. Further, as the disease progresses, individuals require institutional care facilities at great financial cost. Therapies using human embryonic stem cells (hESCs) have the potential to change the lives of hundreds of individuals and their families, which brings the human cost into the thousands. Further, hESCs from HD patients will help us understand the factors that dictate the course of the disease and provide a resource for drug development. For the potential of hESCs in HD to be realized, a very forward approach such as that proposed will allow experienced investigators in HD and stem cell research and clinical trials to come together and create cell lines to more fully mimic the diseases neurons and allow for future treatment options. The federal constraints on hESCs create a critical need for the development of treatments using hESCs supported and staffed with non-federal funds. We have proposed goals and strategies for generating new stem cells derived from patient preimplantation diagnosis embryos and patient fibroblasts. We have put in place critical milestones to be met We will build on existing regional stem cell resources . Anticipated benefits to the citizens of California include: 1) development of new stem cell lines that will allow us to more closely model the disease for mechanistic studies and drug screening, 2) improved methods for following the course of the disease in order to treat HD as early as possible before symptoms are manifest; 3) development of new cell-based treatments for Huntington's disease with application to other neurodegenerative diseases such as Alzheimer's and Parkinson's diseases that affect thousands of individuals in California; 4) development of intellectual property that could form the basis of new biotech startup companies; and 5) improved methods for drug development that could directly benefit citizens of the state.

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