### Development of human ES cell lines as a model system for Alzheimer disease drug discovery

#### Grant Award Details

- **Grant Type:** SEED Grant
- **Grant Number:** RS1-00247
- **Investigator:**
  - **Name:** Frank LaFerla
  - **Institution:** University of California, Irvine
  - **Type:** PI

- **Disease Focus:** Alzheimer's Disease, Neurological Disorders
- **Human Stem Cell Use:** Embryonic Stem Cell
- **Cell Line Generation:** Embryonic Stem Cell
- **Award Value:** $473,963
- **Status:** Closed

#### Progress Reports

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#### Grant Application Details

- **Application Title:** Development of human ES cell lines as a model system for Alzheimer disease drug discovery
Alzheimer disease (AD) is a progressive neurodegenerative disorder that currently affects over 5 million Americans. By the middle of the century, the prevalence of AD in the USA is projected to almost quadruple. As current therapies do not abate the underlying disease process, it is very likely that AD will continue to be a clinical, social, and economic burden. Progress has been made in our understanding of AD pathogenesis by studying transgenic mouse models of the disease and by utilizing primary neuronal cell cultures derived from rodents. However, key proteins that are critical to the pathogenesis of this disease exhibit many species-specific differences at both a biophysical and functional level. Additional species differences in other as yet unidentified AD-related proteins are likely to also exist. Thus, there is an urgent need to develop novel models of AD that recapitulate the complex array of human proteins involved in this disease. Cell culture-based models that allow for rapid high-throughput screening and the identification of novel compounds and drug targets are also critically needed. To that end we propose to model both sporadic and familial forms of AD by generating two novel human embryonic stem cell lines (hES cells). Differentiation of these lines along a neuronal lineage will provide researchers with an easily accessible and reproducible neuronal cell culture model of AD. These cells will also allow high-throughput screening and experimentation in neuronal cells with a species-relevant complement of human proteins. In Aim 1 we will develop and characterize hES cell lines designed to model both sporadic and familial forms of AD. To model sporadic AD we will stably transfect HUES7 hES cells (developed by Douglas Melton) with lentiviral constructs coding for human wild type amyloid precursor protein (APP-695) under control of the human APP promoter. APP is well expressed within hES cells and upregulated upon neuronal differentiation. To model familial AD and generate cells that exhibit a more aggressive formation of oligomeric Aβ species we will also develop a second hES cell line stably transfected with human APP that includes the Arctic (E693G) mutation. In Aim 2 we will utilize our wild-type APP hES cells to perform a high-throughput siRNA screen. We will utilize AMAXA reverse-nucleofection in conjunction with a human druggable genome siRNA array (Dharmacon) that targets 7309 genes considered to be potential therapeutic targets. Following transfection conditioned media will be examined by a sensitive ELISA to identify novel targets that modulate Aβ levels. In addition a Thioflavin S assay will determine any effects on Aβ aggregation. Follow-up experiments will confirm promising candidates identified in the high-throughput screen. Taken together these studies aim to establish novel AD-specific hES cell lines and identify promising new therapeutic targets for this devastating disease.
discovery