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## Stem cell based small molecule therapy for Alzheimer's disease

### Grant Award Details

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Stem cell based small molecule therapy for Alzheimer's disease

**Grant Type:** Early Translational III

**Grant Number:** TR3-05669

**Project Objective:** There are no drugs that prevent the death of nerve cells in Alzheimer's disease (AD), nor has any drug been identified that can stimulate nerve cell replacement in aged human brains. Unless a neurogenic drug is also neuroprotective, the replacement of lost neurons will not be sufficient to stop disease progression because cells are born into a toxic environment. The Objective of this award is to optimize a recently synthesized an exceptionally potent neuroprotective compound that also stimulates the division of hESC-derived neuronal precursor cells (NPCs) for human cells as a new approach to find small molecules that wuccesfully treat Alzheimer's disease (AD). This compound also stimulates neurogenesis in very old AD and wild type mice, something no other drug that we are aware of is able to do. They plan to use hESCs for a new approach to AD therapeutics. There are three Milestones: The first describes the SAR-driven iterative chemistry approach and screening assays designed to tailor the structure of the J147 lead compound for enhanced efficacy on hNPCs, better metabolic stability, and maintain its neuroprotective activity. The second is a PK analysis to verify that the new compounds are stable and get into the brain, followed by limited toxicology to assure that the compounds are probably safe. The third involves animal models to determine dosing and efficacy in transgenic AD mice.

**Investigator:**

<b>Name:</b>	David Schubert
<b>Institution:</b>	Salk Institute for Biological Studies
<b>Type:</b>	PI

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**Disease Focus:** Alzheimer's Disease, Neurological Disorders

**Human Stem Cell Use:** Embryonic Stem Cell

**Cell Line Generation:** Embryonic Stem Cell

**Award Value:** \$1,673,757

**Status:** Closed

### Progress Reports

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**Reporting Period:** Year 1

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**Reporting Period:** Year 2

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**Reporting Period:** Year 3

**View Report**

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## Grant Application Details

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**Application Title:** Stem cell based small molecule therapy for Alzheimer's disease

**Public Abstract:** Over 6 million people in the US suffer from AD. There are no drugs that prevent the death of nerve cells in AD, nor has any drug been identified that can stimulate their replacement. Even if nerve cells could be replaced, the toxic environment of the brain will kill them unless they are protected by a drug. Therefore, drugs that stimulate the generation of new neurons (neurogenesis) alone will not be effective; a drug with both neurogenic and neuroprotective properties is required. With the ability to use cells derived from human embryonic stem cells (hESCs) as a screen for neurogenic compounds, it should now be possible to identify and tailor drugs for therapeutic use in AD. Our laboratory has developed a drug discovery scheme based upon using hESCs to screen drug candidates. We have recently identified a very potent drug that is exceptionally effective in rodent models of AD. However, this molecule needs to be optimized for human use. In this proposal, we will harness the power of hESCs to develop derivatives of J147 specifically tailored to stimulate neurogenesis and be neuroprotective in human cells. This work will optimize the chances for its true therapeutic potential in AD, and presents a unique opportunity to expand the use of hESCs for the development of a therapeutic for a disease for which there is no cure. This work could lead to a paradigm shift in the treatment of neurodegenerative disease.

**Statement of Benefit to California:** Over 6 million people in the US suffer from Alzheimer's disease (AD). Unless a viable therapeutic is identified it is estimated that this number will increase to 16 million by 2050, with a cost of well over \$1 trillion per year, overwhelming California and national health care systems. Among the top 10 causes of death, AD (6th) is the only one with no treatment available to prevent, cure or slow down the condition. An enormous additional burden to families is the emotional and physical stress of having to deal with a family member with a disease which is going to become much more frequent with our aging population. In this application we use new human stem cell technologies to develop an AD drug candidate based upon a strong lead compound that we have already made that stimulates the multiplication of nerve precursor cells derived from human embryonic stem cells.

This approach presents a unique opportunity to expand the use of human embryonic stem cells for the development of a therapeutic for a disease for which there is no cure, and could lead to a paradigm shift in the treatment of neurodegenerative disease. Since our AD drug discovery approach is fundamentally different from the unsuccessful approaches used by the pharmaceutical industry, it could also stimulate new biotech. The work in this proposal addresses one of the most important medical problems of California as well as the rest of the world, and if successful would benefit all.