

Development of Novel Autophagy Inducers to Block the Progression of and Treat Amyotrophic Lateral Sclerosis (ALS) and Other Neurodegenerative Diseases

Grant Award Details

Development of Novel Autophagy Inducers to Block the Progression of and Treat Amyotrophic Lateral Sclerosis (ALS) and Other Neurodegenerative Diseases

Grant Type: Early Translational IV

Grant Number: TR4-06693

Project Objective: The objective of this award to show proof-of-concept for a small molecule neuronal autophagy inducer (NAI) in ALS patient iPSC-derived motor neurons (i-MNs) and an animal model of ALS. NAIs will be tested in vitro in i-MNs from both familial and sporadic ALS patients, then tested in familial ALS patient derived i-astrocytes, then in vivo in three mouse models (one that allows visualization of autophagy and two separate familial ALS models).

Investigator:

Name:	Steven Finkbeiner
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders

Human Stem Cell Use: iPS Cell

Award Value: \$2,049,053

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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Reporting Period: Year 3 FINAL

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Grant Application Details

Application Title: Development of Novel Autophagy Inducers to Block the Progression of and Treat Amyotrophic Lateral Sclerosis (ALS) and Other Neurodegenerative Diseases

Public Abstract: ALS is a progressive neurodegenerative disease that primarily affects motor neurons (MNs). It results in paralysis and loss of control of vital functions, such as breathing, leading to premature death. Life expectancy of ALS patients averages 2–5 years from diagnosis. About 5,600 people in the U.S. are diagnosed with ALS each year, and about 30,000 Americans have the disease. There is a clear unmet need for novel ALS therapeutics because no drug blocks the progression of ALS. This may be due to the fact that multiple proteins work together to cause the disease and therapies targeting individual toxic proteins will not prevent neurodegeneration due to other factors involved in the ALS disease process. We propose to develop a novel ALS therapy involving small molecule drugs that stimulate a natural defense system in MNs, autophagy, which will remove all of the disease-causing proteins in MNs to reduce neurodegeneration. We previously reported on a class of neuronal autophagy inducers (NAIs) and in this grant will prioritize those drugs for blocking neurodegeneration of human iPSC derived MNs from patients with familial and sporadic ALS to identify leads that will then be tested for efficacy *in vivo* in animal models of ALS to select a clinical candidate. Since all of our NAIs are FDA approved for treating indications other than ALS, our clinical candidate could be rapidly transitioned to testing for efficacy and safety in treating ALS patients near the end of this grant.

Statement of Benefit to California: Neurodegenerative diseases such as ALS as well as Alzheimer's (AD), Parkinson's (PD) and Huntington's Disease (HD) are devastating to the patient and family and create a major financial burden to California (CA). These diseases are due to the buildup of toxic misfolded proteins in key neuronal populations that leads to neurodegeneration. This suggests that common mechanisms may be operating in these diseases. The drugs we are developing to treat ALS target this common mechanism, which we believe is an impairment of autophagy that prevents clearance of disease-causing proteins. Effective autophagy inducers we identify to treat ALS may turn out to be effective in treating other neurodegenerative diseases. This could have a major impact on the health care in CA. Most important in our studies is the translational impact of the use of patient iPSC-derived neurons and astrocytes to identify a new class of therapeutics to block neurodegeneration that can be quickly transitioned to testing in clinical trials for treating ALS and other CNS diseases. Future benefits to CA citizens include: 1) development of new treatments for ALS with application to other diseases such as AD, HD and PD that affect thousands of individuals in CA; 2) transfer of new technologies to the public realm with resulting IP revenues coming into the state with possible creation of new biotechnology spin-off companies and resulting job creation; and 3) reductions in extensive care-giving and medical costs.

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