

Understanding SOD1 Kinetics in Amyotrophic Lateral Sclerosis

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Country

USA

Title of project or programme

Understanding SOD1 Kinetics in Amyotrophic Lateral Sclerosis

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NIH (NINDS)

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01/06/2016

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3

The project/programme is most relevant to:

Motor neurone diseases

Keywords

superoxide dismutase 1, Amyotrophic Lateral Sclerosis, Kinetics, Half-Life, Cerebrospinal Fluid

Research Abstract

Project Summary Amyotrophic lateral sclerosis is an adult onset neurodegenerative disease characterized by loss of motor neurons resulting in stiffness, weakness, muscle atrophy and death from failure of respiratory muscle 3-5 years after diagnosis. The only FDA approved drug

for ALS, Riluzole, is only marginally effective. With disappointing therapeutic options, we have developed targeted therapeutic strategies for genetic subsets of ALS, such as those caused by dominantly inherited mutations in the superoxide dismutase 1 gene (SOD1). Our previous data suggest that SOD1 in the cerebral spinal fluid (CSF) will be an excellent pharmacodynamics marker for an SOD1-focused therapeutic approach. One of the main missing pieces in understanding SOD1 as a marker is SOD1 CSF half-life data. The half-life of the protein will aid in clinical trial planning since half-life influences the amount of SOD1 protein reduction and will dictate the best timing of CSF collection for pharmacodynamics measures. We have recently made huge strides in understanding the protein kinetics of SOD1 by establishing a stable isotope amino acid labeling method using mass spectrometry to measure SOD1 half-life in rat models and normal, healthy human controls. While important first of its kind human data, the CSF SOD1 half-life we have established needs to be extended from normal controls to participants with ALS-causing SOD1 mutations. We will determine SOD1 half-life in CSF of 12 participants with SOD1 mutations by analyzing the kinetics of wild type, mutant, and total SOD1 protein. We hypothesize that the mutant half-life will be decreased in participants with SOD1 mutations. Additionally, some pathological studies suggest that SOD1 becomes misfolded in sporadic ALS and is therefore more broadly implicated in ALS. It is imperative to determine whether this is true as the need to develop SOD1-targeted therapeutics would be greatly increased. However, what's needed is an assay to determine SOD1 involvement in living patients. We hypothesize that protein half-life of SOD1 will be such a measure. We will determine SOD1 half-life in CSF of 19 controls and 19 sporadic ALS participants without SOD1 mutations using our kinetic method. If SOD1 half-life is decreased in sporadic ALS compared to controls, this would suggest that these participants may benefit from the SOD1 targeted strategy and we will consider a therapeutic trial in this population as well. With successful completion of this grant, we will have defined SOD1 kinetics in the most important patient population for SOD1 focused clinical trials and tested whether SOD1 half-life is decreased in sporadic ALS.

Lay Summary

Project Narrative Novel therapies are being developed for Amyotrophic Lateral Sclerosis (ALS) caused by changes in the gene superoxide dismutase 1 (SOD1). Our study will assess how quickly SOD1 protein is cleared from the cerebrospinal fluid (CSF) that bathes the brain and spinal cord. These data will be used to determine the optimal time to administer the drug and measure how well the drug works, and may also help us understand whether changes in SOD1 are involved in ALS patients who do not have genetic mutations.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Motor neurone diseases

Years:

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Database Tags:

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