A new antibody/RNAi combination therapy strategy for ALS

https://www.neurodegenerationresearch.eu/survey/a-new-antibody-rnai-combination-therapy-strategy-for-als-2/

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Country

USA

Title of project or programme

A new antibody/RNAi combination therapy strategy for ALS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

422591.7431

Start date of award

20/09/2015

Total duration of award in years

1

Keywords

Amyotrophic Lateral Sclerosis, Familial Amyotrophic Lateral Sclerosis, Combined Modality Therapy, RNA Interference Therapy, RNA Interference

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a neurodegenerative disease that causes progressive motor neuron degeneration, paralysis and death. Currently there is not an effective treatment to slow or stop the disease progression. Mutations in Cu/Zn superoxide dismutase (SOD1) is the first gene identified to cause familial ALS. Although mutations in numerous new genes have been associated with ALS

in recent years, the mechanism whereby the SOD1 mutations cause ALS is the best understood after more than two decades of research. It has been well-established that SOD1 mutants cause the disease by a gain of toxicity, which may originate from the instability and misfolding of the mutants leading to protein oligomerization and aggregation. This protein aggregation process can cause numerous downstream effects that are detrimental to motor neurons, including oxidative stress, mitochondrial damage, defective axonal transport, endoplasmic reticulum stress, Golgi fragmentation, chaperone dysfunction, proteasome deficiency and neuroinflammation involving astrocytes and microglia. In light of this mechanistic understanding, blocking any one of the downstream pathways may be relatively less effective than blocking the origin of the toxicity, the mutant protein aggregation process. Two strategies have been tested in rodent ALS models that express mutant SOD1: one aims at blocking mutant SOD1 expression using RNAi or antisense oligonucleotide and the other is an immunotherapy strategy that aims at reducing the misfolded SOD1 using antibodies. We and others have worked on both strategies and have shown therapeutic efficacy in the animal models. This proposal aims to achieve two main goals: developing a combination therapy strategy that delivers both the anti-SOD1 RNAi and antibody in a single rAAV vector and expanding the antibody repertoire that can be used to deliver the anti-SOD1 immunotherapy. We will accomplish these goals with two specific aims: (1) construct, produce and test rAAV constructs that express anti-SOD1 single-chain fragment variable antibodies, an artificial miRNA (aimR-SOD1) that knocks down SOD1 expression or both in vitro; and (2) test these constructs for their expression, target engagement and therapeutic efficacy in vivo. If successful, we will establish a novel therapeutic strategy for the familial ALS, which may be applicable to other neurodegenerative diseases that are caused by dominant, gain-of-toxicity type of gene mutations. Additionally, we will obtain more therapeutic antibodies that can diversify the therapeutic options for the familial ALS.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A