Developing ASO Therapy for Repeat Expanded C9orf72 ALS-FTD

https://neurodegenerationresearch.eu/survey/developing-aso-therapy-for-repeat-expanded-c9orf72-als-ftd/

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Country

USA

Title of project or programme

Developing ASO Therapy for Repeat Expanded C9orf72 ALS-FTD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,964,558.72

Start date of award

01/07/2014

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease and other dementias|Motor neurone diseases

Keywords

Antisense Oligonucleotide Therapy, C9orf72, Antisense Oligonucleotides, Amyotrophic Lateral Sclerosis, Dipeptides

Research Abstract
DESCRIPTION (provided by applicant): Expanded hexanucleotide repeats in a non-coding region of C9orf72 are the most common genetic cause of both amyotrophic lateral sclerosis

(ALS) and frontal temporal degeneration (FTD) (C9-ALS/FTD). Many recent lines of evidence strongly suggest that pathogenesis is related to RNA toxicity, similar to a subset of other repeat expansion diseases. There are two, non-mutually exclusive mechanisms by which RNA-mediated toxicity is thought to occur: one is sequestration of nuclear RNA binding proteins, the hallmarks of which are RNA nuclear foci; and the other is translation of unconventional, repeat-associated non-ATG translation (“”RAN translation””), the hallmarks of which are dipeptide repeat proteins (DPRs). With either of these mechanisms, antisense oligonucleotides (ASOs) that cause sequence-selective transcript degradation in the nucleus can be engineered to target the transcripts that are toxic and thus potentially provide therapy that is fundamental in pathogenesis. ASOs have already proven to be safe in humans in a clinical trial for SOD1 mutation-mediated ALS, are now in trial for spinal muscular atrophy, and are expected to enter trials next year for myotonic muscular dystrophy and Huntington’s disease. Our ultimate long-term goal is ASO therapy development for C9-ALS/FTD patients. Recently, we and others have shown that expanded repeats in C9orf72 are bidirectionally transcribed in C9-ALS/FTD: the signature features of RNA nuclear foci and DPRs are generated from both sense and antisense strands. Thus, the critical next steps and the primary objectives for this proposal are to determine the relative contributions of each strand to pathogenesis and, in turn, to establish which targets and ASOs are the most critical for testing in patients. The research team and collaborators have in hand the preliminary data, the patient derived materials, the cellular and animal models, and the critical tools to determine this. In Aim 1, we will calibrate ASOs targeting sense and antisense transcripts measuring transcript levels, foci and RAN-translated products in cell culture models and transgenic mice expressing human C9orf72 with ~450 hexanucleotide repeats. In Aim 2, we will define the RNA signature in the transgenic mice using RNA-seq of the disease-relevant cell type, spinal motor neurons, which will be isolated by laser capture microdissection. In Aim 3, we will quantitatively compare efficacy of ASOs targeting each strand to correct the RNA signature in the transgenic mice. In Aim 4, we will define dose and duration effects of ASOs in transgenic mice. Upon completion of the projects, we will have determined whether one or both strands carrying the expansion are most critical for patient therapy and define a strategy for clinical trials.

Lay Summary

Project Narrative: The most frequent genetic cause of two devastating neurodegenerative diseases, amyotrophic lateral sclerosis (also called Lou Gehrig’s disease) and frontotemporal degeneration, has recently been identified in the C9orf72 gene. Strong evidence supports that the mechanism by which the mutation causes the diseases is by toxicity of RNAs that are generated from them. New gene therapies can be brought to bear to target RNAs in highly selective manner. This grant seeks to identify how and where in the gene we should do this to treat patients. If successful, they will be brought forward to treat humans in clinical trials.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias, Motor neurone diseases

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