# Silencing C9or72 with rAAV Mediated RNAi

https://www.neurodegenerationresearch.eu/survey/silencing-c9or72-with-raav-mediated-rnai-2/

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**Country**

USA

**Title of project or programme**

Silencing C9or72 with rAAV Mediated RNAi

**Source of funding information**

NIH (NINDS)

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01/07/2014

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2

**The project/programme is most relevant to:**

Motor neurone diseases

**Keywords**

C9orf72, Recombinant adeno-associated virus , RNA Interference, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia

**Research Abstract**

DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a progressive, untreatable, uniformly fatal motor neuron disorder that sometimes develops concurrently with frontotemporal dementia (FTD). ALS is encountered in both sporadic (SALS) and familial (FALS) forms; about 10% of cases are transmitted as autosomal dominant traits. The cause of

sporadic ALS is not known. Recently it was discovered that about 30-50% of FALS cases are caused by expansions of a non-coding hexanucleotide G4C2 expansion in the gene C9ORF72. These expansions are also detected in 10-20% of familial FTD, 10% of sporadic FTD and in ~5% of SALS. These statistics define the C9ORF72 G4C2 expansion as the most common cause of ALS. In the present study, we propose to use rAAV type Rh10 to introduce a microRNA to silence expression of the transcripts of C9ORF72 that harbor the offending G4C2 expansion. In Aim 1, we will screen, identify and optimize potential miRNAs in vitro. In Aim 2, we will further characterize the phenotype of our novel C9ORF72mutant transgenic mouse and investigate use of rAAVRh10-C9miRs to silencing the mutant C9 transgene and thereby mitigate the phenotype in this mouse. In Aim 3 we will investigate delivery and efficacy of the rAAVRh10-C9miRs in a non- human primate model as first step to translating this therapy to clinical application. Relevance: We believe that these studies will be highly relevant for several reasons. (1) There is a compelling unmet need for effective ALS treatments; this project focuses on the most common form of FALS, with applicability as well to some cases of SALS and FTD. (2) This investigation will develop the use of intrathecal rAAVRh10 as a gene therapy vector for the CNS; the intrathecal route is advantageous, permitting widespread delivery within the CNS with doses that are an order-of-magnitude lower than are required via intravenous delivery; and minimizing peripheral exposure to virus. (3) rAAV has not been used in human neurodegenerative disorders. The platform we propose to develop here should have broad applicability across a breadth of neurological disorders.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis and frontotemporal dementia are fatal neurodegenerative disorders for which no effective treatments are available. Recently, a genetic expansion in a gene termed C9ORF72 was found to be the leading genetic cause for these diseases. The mutant C9ORF72 gene causes accumulation of toxic by-products in neuronal cells, leading to neurodegeneration. We have created a mouse model that harbors this same mutation which also results in the accumulation of the mutant C9ORF72 by products. We propose to use this mouse along with patient cell lines to test whether inhibitory small RNA molecules can suppress toxicity of the mutant C9ORF72. To test our hypothesis, we inject mice with viral vectors that express inhibitory small RNA molecules that target C9ORF7. In the mouse model of the disease we can then determine if small RNA molecules are able to suppress the toxicity associated with the mutant C9ORF72. Finally we will test these therapies in a primate model in order to optimize the viral vectors for a future clinical trial.

**Further information available at:**

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Investments > €500k

**Member States:**
United States of America

**Diseases:**
Motor neurone diseases

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