Molecular Characterization of ALS/FTD in a novel C9orf72 BAC mouse model.

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5

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Motor neurone diseases

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Research Abstract
Project Summary The expansion of a microsatellite GGGGCC repeat in the C9orf72 gene has

been linked to both familial and sporadic forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). While the molecular basis of this disease (C9-ALS/FTD) remains largely unknown, proposed disease mechanisms include C9orf72 loss of function due to haploinsufficiency, RNA gain of function (GOF) leading to protein sequestration and repeat-associated non-ATG (RAN) translation resulting in the production of toxic C9-RAN dipeptide repeat proteins. Based on our prior studies on other microsatellite expansion diseases, this proposal is designed to test our sequestration failure hypothesis, which integrates RNA and RAN gain of function mechanisms. According to this hypothesis, bidirectional sense and antisense C9orf72 transcription results in the recruitment of cellular factors to repeat expansion RNAs to produce sense and antisense RNA foci that sequester these toxic RNAs in the nucleus. Somatic repeat expansion and/or age-related cellular stress results in titration of GGGGCC and GGCCCC RNA binding proteins followed by nucleocytoplasmic export of these RNAs and translation of highly toxic C9-RAN proteins in the cytoplasm that lead to neurodegeneration. We have generated a BAC transgenic model of C9-ALS/FTD that will allow us to test this hypothesis. This mouse develops both the molecular (RNA foci, C9-RAN proteins) and pathophysiological (neuronal loss, paralysis, decreased survival) features of C9-ALS/FTD. In this proposal, we will initially test the hypothesis that RNA GOF effects precede RAN protein accumulation by performing RNA-FISH, transcriptome analysis and immunological assays at various developmental periods and in different brain and spinal cord regions on asymptomatic, pre-symptomatic and symptomatic C9-BAC mice. This information will be used in conjunction with histopathological and electrophysiological assays test the hypothesis that C9-RAN protein accumulation triggers neurodegeneration and the acute disease phase. The possibility that stress pathways modulate RAN translation will also be tested. Finally, we will test whether antisense oligonucleotide (ASO) gapmer-mediated knockdowns of sense, antisense or both sense and antisense C9orf72 transcripts blocks the development of RNA and RNA toxicity in our C9-BAC transgenic mice. Overall, the objective of this study is to define pathogenic mechanisms underlying C9-ALS/FTD disease development and progression and provide an accessible and well-characterized mouse model for therapeutic development.

Lay Summary

Project Narrative A microsatellite repeat expansion mutation in the C9orf72 gene is the most common reported cause of familial forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). This proposal is designed to determine the molecular basis of this disorder using a novel transgenic mouse model that we have recently generated that develops both the molecular hallmarks of this disease and motor neuron degeneration, paralysis and reduced lifespan. In addition, a therapeutic strategy designed to reduce the toxicity burden of sense and antisense mutant C9orf72 transcripts will be tested to determine if this approach reverses both the molecular and pathophysiological manifestations of this devastating disease.

Further information available at:

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Investments > €500k

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United States of America

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