

# Modulating the Nucleopathy caused by FUS Mutants of ALS

<https://www.neurodegenerationresearch.eu/survey/modulating-the-nucleopathy-caused-by-fus-mutants-of-als/>

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### Country

USA

## Title of project or programme

Modulating the Nucleopathy caused by FUS Mutants of ALS

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2

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Acute Promyelocytic Leukemia, Amyotrophic Lateral Sclerosis, Nuclear, Motor Neurons, multicatalytic endopeptidase complex

## Research Abstract

Abstract Dominant mutations in the gene encoding the nucleic acid binding protein FUS cause ~5% of familial amyotrophic lateral sclerosis (ALS). Our long-term objectives are to discern the mechanism(s) by which FUS mutants injure aging motor neurons and to develop novel therapeutic approaches to increase the defenses against these insults. Our laboratory has identified a novel and robust nuclear phenotype caused by ALS- linked FUS mutants: impaired

stress-responsive processing of sub-nuclear assemblies known as promyelocytic leukemia (PML) nuclear bodies. PML nuclear bodies are induced by a variety of cellular stresses and regulate nuclear protein homeostasis, transcription, DNA-damage pathways, and cellular senescence, yet their potential role in ALS has not been explored. We observed that PML bodies were abnormally enlarged both in cell lines and in primary ALS human fibroblasts expressing mutant FUS. Furthermore, proteasome activities were decreased, and exposure to mild oxidative stress or proteasome inhibition in FUS mutant but not control cells stalled the turnover of expanded PML bodies. We hypothesize that the observed abnormality of PML nuclear bodies may report upon altered nuclear homeostasis resulting from FUS mutant expression. In Aim 1 of this project, we will develop an imaging-based phenotypic screening assay to identify small molecule compounds that modulate the observed PML nuclear body enlargement in cells expressing FUS mutants. We will test compound libraries that include FDA-approved drugs and diverse CNS-active agents predicted to cross the blood-brain barrier. We will prioritize initial hits using dose-response studies and will determine whether proteins known to be targeted to the proteasome following stress are more effectively eliminated upon treatment with hit compounds. We have established transgenic mice harboring ALS-linked FUS variants and have observed a phenotype of age-dependent loss of the connection between motor nerves and muscle in mice that express the R495X mutant. In Aim 2 of this project, we will validate hit compounds and analyze pathways related to PML nuclear body function in CNS cells and tissues from our mutant FUS transgenic mice. We will test whether a subset of the prioritized hit compounds from Aim 1 ameliorate defects of nuclear protein homeostasis or proteasome activity in transgenic primary cortical neurons, glial cells, or motor neurons. In further experiments, which do not depend upon the success of obtaining modulator compounds in Aim 1, we will define more precisely which pathways related to PML nuclear body function are most relevant to FUS-mediated ALS. We will purify proteasomes from the CNS of our FUS mice at pre-symptomatic and symptomatic ages and will quantify subunit expression, assembly, and activities in collaboration with Dr. Fred Goldberg's group. We will also use a high-resolution tissue monolayer preparation to identify nuclear insults related to altered PML body function in aging neurons from our FUS transgenic mice.

**Further information available at:**

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Investments < €500k

**Member States:**

United States of America

**Diseases:**

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**Years:**

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**Database Categories:**

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**Database Tags:**

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