

# NAD metabolism and mitochondrial dysfunction in ALS models

<https://www.neurodegenerationresearch.eu/survey/nad-metabolism-and-mitochondrial-dysfunction-in-als-models/>

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### Country

USA

## Title of project or programme

NAD metabolism and mitochondrial dysfunction in ALS models

## Source of funding information

NIH (NINDS)

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01/08/2015

## Total duration of award in years

4

## The project/programme is most relevant to:

Motor neurone diseases

## Keywords

Nicotinamide adenine dinucleotide, Amyotrophic Lateral Sclerosis, mitochondrial dysfunction, superoxide dismutase 1, Motor Neurons

## Research Abstract

? DESCRIPTION (provided by applicant): The long-term goal of the proposal is to develop new therapeutic strategies using mechanistic insights drawn from understanding astrocyte-motor

neuron interaction in amyotrophic lateral sclerosis (ALS). In particular, the primary objective of this proposal is to establish whether increased nicotinamide adenine dinucleotide (NAD) availability ameliorates motor neuron degeneration in ALS models. ALS or Lou Gehrig's disease accounts for about 1 in 500 to 1 in 1,000 adult deaths in the United States and is caused by the progressive degeneration of motor neurons in the spinal cord, brain stem, and motor cortex. Motor neuron death leads to muscle weakness and paralysis causing death in one to five years from the time of symptoms onset. Most ALS cases are sporadic (SALS) and exposure to yet unidentified environmental toxicants might be responsible for SALS. About 5-10% of the cases are inherited (familial ALS, FALS) but FALS and SALS are phenotypically indistinguishable, and a significant share of our understanding come from the study of rodent models over-expressing ALS-linked mutant human superoxide dismutase 1 (hSOD1). Primary astrocytes isolated from mutant hSOD1 over-expressing mice induce motor neuron death in co-culture, and it has been demonstrated that astrocytes differentiated from spinal cord autopsy-derived neuronal progenitor cells from FALS and SALS patients are also toxic for motor neurons in co-culture. Sirtuins are a family of enzymes capable of catalyzing NAD-dependent deacetylation and mono(ADPribosyl)ation reactions. Remarkably, NAD- dependent sirtuin-mediated deacetylation has been shown to modulate all major mitochondrial processes. Since mitochondrial dysfunction has been linked to ALS and the toxicity of ALS-astrocytes, we seek to better define the role of NAD-dependent signaling in motor neuron degeneration and determine if the modulation of NAD levels may be a potential therapeutic strategy for ALS. Our ongoing experiments demonstrate that increasing NAD content in ALS-astrocytes reverts its toxicity towards co-cultured motor neurons, while NAD synthesis and NAD-dependent signaling may be compromised in mutant hSOD1 mice. Thus, the specific aims of the proposal are: Aim 1-To determine the role of NAD content in the toxicity of astrocytes expressing ALS- linked mutant hSOD1s toward co-cultured motor neurons. Aim 2-To evaluate the effect of transgenic models with altered NAD synthesis and degradation on the onset and progression of the disease in ALS mouse models. Aim 3-To evaluate the effect of treatment with a key NAD precursor on the onset and progression of the disease in ALS mouse models. The outcome of the proposal will contribute to the current understanding of NAD metabolism and mitochondrial dysfunction in neurodegeneration. More important, since we have shown that therapeutic targets identified in our astrocyte-motor neuron co-culture system have a beneficial effect when translated into animal models of ALS, the proposal is likely to provide in vivo proof of the value of modulating NAD metabolism as a therapeutic target in ALS.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease is characterized by the specific death of nerve cells that control muscle movement, leading to paralysis and eventual death. Malfunction of the mitochondria, the powerhouse of the cell, may be responsible for the observed neurodegeneration. This proposal will investigate the role of nicotinamide adenine dinucleotide, a redox molecule found in the cells, as a key player for mitochondrial function in the context of ALS and its potential therapeutic applications.

**Further information available at:**

### **Types:**

Investments > €500k

### **Member States:**

United States of America

**Diseases:**

Motor neurone diseases

**Years:**

2016

**Database Categories:**

N/A

**Database Tags:**

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