# Role of MMP-9 in selective motor neuron degeneration in ALS

https://neurodegenerationresearch.eu/survey/role-of-mmp-9-in-selective-motor-neuron-degeneration-in-als/

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**Country**

USA

**Title of project or programme**

Role of MMP-9 in selective motor neuron degeneration in ALS

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NIH (NINDS)

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2

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

Motor neurone diseases

**Keywords**

motor neuron degeneration, Gelatinase B, Amyotrophic Lateral Sclerosis, Motor Neurons, Muscle denervation procedure

**Research Abstract**

DESCRIPTION (provided by applicant): Despite multiple clinical trials, there is still no effective therapy for the adult-onset neurodegenerative disease ALS (amyotrophic lateral sclerosis). One

major reason for this is that, aside from the genes that are causal in familial ALS, no therapeutic targets have been validated. Examples of targets would be enzymes that play a critical role in disease progression and whose inhibition retards disease onset or slows progression. Strikingly, even in late-stage patients with amyotrophic lateral sclerosis (ALS), eye movement and continence are preserved, reflecting the near-complete resistance of motor neurons in oculomotor and Onuf's nuclei to the disease process. If it were possible to confer even a fraction of this resistance upon the normally vulnerable spinal motor neurons, there would be significant therapeutic benefit. Understanding the mechanisms of resistance therefore provides a method for defining new targets. In preliminary studies, we identified novel genes expressed in ALS-susceptible but not in ALS-resistant motor neurons, or vice versa, using laser-capture microdissection and microarray analysis. One of these is MMP-9 (matrix metalloproteinase-9), an extracellular enzyme which is absent from resistant oculomotor and Onuf's nuclei. We showed that its expression in different motor neuron subsets is tightly correlated with their vulnerability. Strikingly, we find that inactivation of the mmp9 gene in ALS model mice – whose normal lifespan is ~6 months – leads to a >3-month delay in muscle denervation and a 24% increase in survival. Significant benefit was observed even in mice that were heterozygotes for mmp9. MMP-9 is therefore a strong candidate as a potential therapeutic target in ALS. The overall goal of the proposed project is to understand the cellular and molecular mechanisms through which MMP-9 triggers motor neuron degeneration and to provide initial evaluation of potential therapeutic strategies to block this. The proposal is structured around three main questions. First, we will determine the molecular mechanism(s) through which MMP-9 triggers motor neuron degeneration, focusing on candidate pathways involving the Fas receptor and glutamate excitotoxicity. Second, we will investigate the cellular site of action of MMP-9, using different routes of administration of viral vectors expressing mmp9 shRNA. Third, we will ask whether inhibition of the enzymatic activity of MMP-9 is sufficient to confer benefit, or whether is known non-enzymatic modes of action are also implicated. Overall, the results should provide novel insights into the mechanisms of motor neuron degeneration in ALS and important preclinical indications as to the potential of MMP-9 as a therapeutic target for future development.

**Lay Summary**
PUBLIC HEALTH RELEVANCE: In patients with ALS (amyotrophic lateral sclerosis, also known as Lou Gehrig's disease), many nerve cells in the spinal cord degenerate, leading to fatal paralysis. However, the motor neurons that move the eyes survive, allowing patients to communicate through eye-tracking software. We have identified a toxic gene that is present in the nerve cells that die but not in the eye motor neurons, and will ask whether by inhibiting this gene in different ways we can confer resistance on the motor neurons that are normally lost.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Motor neurone diseases

**Years:**

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**Database Categories:**
N/A

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