# Restoration of excitation/inhibition balance to modulate motoneuron degeneration in Amyotrophic Lateral Sclerosis

**Sujet proposé par**

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SPPIN
Motor Neurons & NeuroMuscular Junctions

## M2 Research project title

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## Keywords

ALS, Motoneuron, Spinal cord, Electrophysiology, In vivo intracellular recordings, Gene therapy, Pharmacology

## Description of the project

Amyotrophic Lateral Sclerosis (ALS) is an invariably fatal motoneuron disease causing the progressive degeneration of motoneurons. Current median survival after diagnosis is only ~3 years and there is no available treatment. We recently showed that vulnerable motoneurons experience a reduced excitation before degeneration, and that restoring excitation reduces some disease markers (Baczyk et al, Journal of Experimental Medecine 2020). Thus, loss of motoneuron excitation is a newly appreciated critical step in the degeneration of motoneurons in ALS. In this project, we propose to alter motoneuron excitability by using pharmacological interventions and viral vectors for gene therapies. The effects of those different strategies on motoneuron degeneration will be evaluated by combining electrophysiology, immunohistochemistry and behavioural testing in SOD1 mice (genetic model for ALS). During this internship, the student will be exposed to all these techniques, with a particular emphasis on in vivo intracellular electrophysiological recording of motoneurons in mice. The goal is for the student to understand how to implement a scientific approach to tackle the pathophysiological changes observed in ALS, and how to gather, analyse and interpret data.

## Methods and techniques

- Usage of a new class of retrograde AAV variants for motoneurons gene therapy with intra muscular delivery - In vivo intracellular recordings of motoneurons in anaesthetised mice - Optogenetics stimulation of motoneurons - Intracellular labeling of recorded motoneurons - Immunocytochemistry of intracellular labeled motoneurons - Imaging with confocal microscopy - Data analysing of electrophysiological recordings and images - Data reporting

## References (at least 3)

Baczyk M, Alami NO, Delestrée N, Martinot C, Tang L, Commisso B, Bayer D, Doisne N, Frankel W, Manuel M, Roselli F, Zytnicki D. Synaptic restoration by cAMP/PKA drives activity-dependent neuroprotection to motoneurons in ALS. J Exp Med. 2020 Aug 3;217(8):e20191734. doi: 10.1084/jem.20191734. Martínez-Silva ML, Imhoff-Manuel RD, Sharma A, Heckman CJ, Shneider NA, Roselli F, Zytnicki D, Manuel M. Hypoexcitability precedes denervation in the large fast-contracting motor units in two unrelated mouse models of ALS. Elife. 2018 Mar 27;7:e30955. doi: 10.7554/eLife.30955. Delestrée N, Manuel M, Iglesias C, Elbasiouny SM, Heckman CJ, Zytnicki D. Adult spinal motoneurones are not hyperexcitable in a mouse model of inherited amyotrophic lateral sclerosis. J Physiol. 2014 Apr 1;592(7):1687-703. doi: 10.1113/jphysiol.2013.265843. Manuel M, Iglesias C, Donnet M, Leroy F, Heckman CJ, Zytnicki D. Fast kinetics, high-frequency oscillations, and subprimaryfiring range in adult mouse spinal motoneurons. J Neurosci. 2009 Sep 9;29(36):11246-56. doi: 10.1523/JNEUROSCI.3260-09.2009.

## Ecole doctorale de rattachement

ED3C (ED158)

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Non