



MÁSTER EN INVESTIGACIÓN BIOMÉDICA

Research Project Proposal

Academic year 2022-2023

Project Nº47 ASIGNADO

Title: New ways to modulate the ISR as potential therapies for ALS

Department/ Laboratory

Gene therapy and Regulation of Expression, CIMA, Laboratory 4.03.

Director1: *Tomás Aragón Amonarriz*

Contact: *taragon@unav.es*

Codirector: *Montse Arrasate Iragui*

Contact: *marrasatei@unav.es*

Summary

The development of effective treatments that delay or stop neurodegenerative diseases requires the identification of new therapeutic targets. To pursue that goal, our laboratory seeks to understand the specific molecular mechanisms underlying neuronal death. In this project we will focus in 1) mechanisms of toxicity underlying neuronal death in Amyotrophic Lateral Sclerosis (ALS) and 2) the role of the Integrated Stress Response (ISR), a cellular pathways activated when misfolded proteins accumulate or when the cell is under stress such as in ALS. ALS is a neurodegenerative disease that affects motoneurons in the central nervous system. Although mostly sporadic, familial cases account for 5-10% of the cases. Mutations in SOD1 account for at least 20% of familial ALS. To score the toxicity of different SOD1 mutant versions, we have developed a neuronal model of ALS based on the expression of mutant SOD1 versions in primary neurons and longitudinal survival analysis with automated microscopy. We have found that modulation of the ISR improves neuronal survival (Bugallo et al, 2020, Cell Death and Disease). Moreover, we have confirmed that in a transgenic mouse model of ALS, modulation of the ISR determines the onset of the disease (Marlin E. In preparation). In this project we want to identify main ISR targets that determine neuronal death and the progression of the disease in neuronal and transgenic models of ALS.

Methodology: Cloning with molecular biology, cell and primary neuronal cultures, automated microscopy and survival analysis, CRISPR/Cas9, immunofluorescence, transgenic ALS animal models, electrophysiological analysis (electromyographies), immunohistochemistry.

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?

yes	X
no	

Yes, the project includes the possibility of supervised animal manipulation training.