Research Project Proposal
Academic year 2020-2021

Máster en Investigación Biomédica

Project Nº 50 ASIGNADO

Title: *Molecular and cellular mechanisms underlying Amyotrophic Lateral Sclerosis*

Department/ Laboratory *Laboratory where the project will be carried out indicating Department, Area, Faculty, CUN, CIMA etc.*

Neurosciences Department, CIMA, Laboratory 2.05

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Summary *Short summary of the project with a **maximum extension of 250 words**, including the goals and the methodology that will be used.*

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 Unfolded Protein Response (UPR) and the Integrated Stress Response (ISR) -cellular pathways activated when misfolded proteins accumulate or when the cell is under stress- 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 monitored UPR activation in vivo in this model showing that closely correlates with neuronal death (*Bugallo et al, 2020, Cell Death and Disease*).

The goals of this project are to identify targets of the UPR and ISR pathways involved in the death of motoneurons. Additionally, we will evaluate pharmacological inhibitors of the UPR/ISR as potential modulators of toxicity in neuronal and animal models of ALS.

Methodology: Automated microscopy and survival analysis, CRISPR/Cas9, transgenic ALS animal models, electrophysiological analysis (electromyographies), immunohistochemistry.

yes	**X**	**Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator?**
no		