Research Project Proposal
Academic year 2018-2019

Project Nº 21

Title: *Alpha-synuclein mechanisms of neurodegeneration*

Department/ Laboratory

Cellular Neurobiology laboratory (2.05), Neurosciences Department-CIMA

Director 1 *Montserrat Arrasate Iragui*
Contact: *email: marrasatei@unav.es Phone Number: 948194700 Ext:2008*

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

Mutations in the gene that encodes for the protein alpha-synuclein (aSyn) cause familial cases of Parkinson's disease and other neurodegenerative diseases grouped together as synucleinopathies. Moreover, aSyn abnormal accumulation forming intraneuronal inclusions known as Lewy Bodies constitutes a pathological hallmark of both sporadic and familial cases of synucleinopathies. Therefore, aSyn has a key role in neurodegeneration but yet the mechanisms by which this protein leads to neuronal death are not well understood. We have developed a primary neuronal model in which a longitudinal survival analysis can be performed by following the overexpression of fluorescently tagged wild-type or pathologically mutant aSyn constructs. Most aSyn mutations linked to neurodegenerative disease hindered neuronal survival in this model, of which the E46K mutation proved to be the most toxic. Using this model we have studied the effect of E46K mutation to aSyn phosphorylation, stability and aggregation and evaluated their contribution to neuronal death. Moreover, we have developed an assay to assess whether neurons expressing E46K aSyn affect the survival of neighbouring control neurons. Although we identified a minor cell non-autonomous component spatially restricted to proximal neurons, most E46K aSyn toxicity was cell autonomous *(Iñigo-Marco I., et al. PNAS, 2017)*. Our goal is to identify cell autonomous components of toxicity underlying E46K aSyn-dependent toxicity.

METHODOLOGY: Molecular biology techniques, generation of lentivirus, primary neuronal cultures and longitudinal survival analysis with automated microscopy.

yes	**X**
no	

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