Research Project Proposal
Academic year 2019-2020

Project Nº 39

Title: Study of molecular mechanisms underlying neurodegenerative diseases like Parkinson's disease to identify effective therapeutic targets

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

Neurosciences Department, CIMA

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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. Specifically, we are interested in 1) alpha-synuclein mechanisms of toxicity and 2) the role of the Unfolded Protein Response (UPR) -a cellular pathway activated when misfolded proteins accumulate- in neurodegeneration.

Alpha-synuclein constitutes a key protein in neurodegenerative diseases like Parkinson´s disease (PD). Mutations in alpha-synuclein cause familial forms of the disease and its abnormal accumulation into structures named Lewy Bodies constitutes the pathological hallmark of the disease. We have developed a neuronal model of Parkinson´s disease based on the expression of mutant alpha-synuclein proteins in primary neurons and longitudinal survival analysis with automated microscopy. This approach enables us to score the toxicity of different mutant versions of alpha-synuclein and to study molecular mechanisms underlying its toxicity (Iñigo-Marco I., PNAS). Since protein misfolding and aggregation is a pathological hallmark not only in PD but in other neurodegenerative diseases, we have developed tools for in vivo monitoring the UPR activation in this model.

The goals of this project are to identify differential protein interactors of alpha-synuclein mutant versions and to evaluate its effect in neuronal toxicity. Additionally, we will evaluate pharmacological inhibitors of the UPR as potential modulators of toxicity in different models of neurodegeneration.

Methodology: Automated microscopy and survival analysis, identification of protein interactomes by proximity-dependent labeling by BioID2, CRISPR/Cas9

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