Máster en Investigación Biomédica

Facultad de Ciencias

# Research Project Proposal
Academic year 2015-2016

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| **Project Nº 18 * ASIGNADO** |
| **Title:** Alpha synuclein-dependent mechanisms of neurodegeneration. |
| **Department/ Laboratory** *Cellular Neurobiology laboratory (2.05), Neurosciences Department-CIMA* |
| **Director 1.** *Montserrat Arrasate Iragui* <br> **Contact:** *email: marrasatei@unav.es Phone Number: 948194700 Ext:2008* |

**Summary**

Abnormal accumulation of alpha-synuclein into Lewy Bodies (LBs) is a hallmark of neurodegenerative disorders like Parkinson's disease, dementia with Lewy Bodies and others, commonly known as synucleopathies. Point mutations and duplications/triplications of the alpha-synuclein gene cause autosomal dominant Parkinson's disease, pointing towards alpha-synuclein cellular levels as a causative factor of neuronal death. Yet, how alpha-synuclein is causally tied to the death of selected neuronal populations affected on these disorders is unknown.

Aim: We seek to identify alpha-synuclein dependent mechanisms of neurodegeneration. Specifically; we want to determine how the expression of wild-type and mutant versions of alpha-synuclein as well as post-translational modifications affecting the protein (phosphorylation and N-terminal acetylation) influence particular cellular pathways and neuronal survival.

Methodology: We will use a microscopy based-system that we have established to follow individual neurons over long periods of time and simultaneously monitoring events of interest (i.e. expression levels, protein turnover) and survival. Using this approach -named longitudinal survival analysis- and observing the same neuron repeatedly we link the appearance of a particular feature with its ultimate fate. By using longitudinal survival analysis we will determine if/how transient expression of wild-type and mutant versions of alpha-synuclein and activation of a particular cellular pathway affects neuronal survival. The project requires molecular biology techniques, protein techniques (western blot, immunofluorescence) preparation and transfection of primary neurons, microscopy and statistics.

**References**

1. Tsvetkov AS., **Arrasate M.**, Barmada S., Ando M.D., Sharma P., Shaby B.A., and Finkbeiner S. **(2013)** Proteostasis of polyglutamine varies among neurons and predicts neurodegeneration. *Nature Chemical Biology,* Sep;9(9):586-92.
2. Miller* J., **Arrasate* M.,** Brooks E., Peters-Libeu C., Legleiter J., Hatters D., Curtis J., Cheung K., Krishnan P., Mitra S., Widjaja K., Shaby B.A., Lotz G.P.Newhouse Y., Mitcell E., Osmand A., Gray M., Thulasiramin V., Saudou F, Muchowski P.J., Segal M., Yang W.X., Masliah E., Thompson L.M., Muchowski P.J., Weisgraber K. H., and Finkbeiner S. **(2011)** Identifying polyglutamine protein species *in situ* that best predict neurodegeneration. *Nature Chemical Biology*. 7(12):925-34. **(*equal contribution)**

3. **Arrasate M**. and Finkbeiner S**. (2005)**. Automated microscope system for determining factors that predict neuronal fate. *Proc. Natl. Acad. Sci. USA*, 102 (10) 3840-5.

**POSSIBILITY OF PhD**

I would like the project to be continued with a Ph.D. It will depend on the performance of the fellow and the available financial support at the moment.