Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2017-2018

Project Nº 1
Title: Gene therapy with glucocerebrosidase for the treatment of misfolded neurodegenerative proteinopathies
Department/ Laboratory Basal Ganglia Neuroanatomy Laboratory, Center for Applied Medical Research (CIMA)
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Summary: Glucocerebrosidase (GCase) is a lysosomal enzyme encoded by the GBA1 gene. Mutations in the GBA1 gene lead to Gaucher's disease (GD), the most prevalent lysosomal storage disorder. GBA1 mutations reduce GCase activity, therefore promoting the aggregation of alpha-synuclein, a common neuropathological finding underlying Parkinson's disease (PD) and dementia with Lewy bodies (LBD). The presence of a direct link between GBA1 mutations and synucleinopathies like PD and LBD has been recently uncovered by multicenter genetic studies (reviewed in Aflaki et al., 2017). These studies appointed GBA1 mutations as the most common genetic risk factor for developing PD and indeed the association between GBA1 mutations and LBD is even stronger than for PD (Nalls et al., 2013). While the genetic link between GBA1 mutations and synucleinopathies like PD and LBD is the strongest argument linking GCase deficit with the appearance of synucleinopathies, the ultimate basis for this association has remained elusive, with very little experimental evidence to date. This project focuses on the use of gene therapy approaches for increasing GCase activity, thus reducing alpha-synuclein burden and dopaminergic neuronal death. Experiments will be carried out in non-human primates (Macaca fascicularis). Furthermore, data to be generated will be helpful in elucidating a number of crossroads between GCase activity and alpha-synuclein homeostasis. References: - Aflaki E, et al. (2017). The complicated relationship between Gaucher disease and parkinsonism: insights from a rare disease. Neuron, 93(4): 737-746. - Nalls MA, et al. (2013). A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol., 70(6): 727-735.