Resumen de la propuesta a la convocatoria TRIP

Proposal title:

Novel therapies in pediatric neurodegeneration with energy metabolism dysfunction: MENCIA LAB

Project Leaders:

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ABSTRACT

The growing incidence of neurodegenerative diseases represents a huge challenge, and their understanding requires multidisciplinary approaches. Neurodegenerative disorders are heterogeneous and characterised by a progressive loss of neurons leading to the loss of previously acquired motor, sensory and cognitive functions. The mechanisms by which neurodegeneration develops are not well understood, and increasing evidence implicates mitochondrial dysfunction in its development and progression. Unlike the case of neurodegenerative pathologies in adulthood, in pediatric neurology neurodegeneration, the defects are mostly monogenic, and this situation offers a unique opportunity to identify novel neurodegeneration pathways and therapeutic targets.

We propose to create an IRB Clinics Laboratory initially oriented to study the mechanisms that control the synthesis of mitochondrial proteins, and to search for therapies in one neurodegenerative disorder, referred to as COXPD1. This disease is caused by mutations in the nuclear gene GFM1, which encodes the mitochondrial translation elongation factor G1 (EFG1), and it manifests very early after birth with a hepatoencephalopathic clinical picture. There is no treatment for this disease and patients often die during the first months of life.

The approach will involved two distinct strategies:

a) Search for therapies through the screening in human fibroblasts and in bacteria with a library of compounds to rescue the alterations driven by EFG1 mutations, followed by delineation of a preclinical path, and a clinical trial.

b) Search of processes downstream of EFG1 by analysis of mitochondrial and cytosolic translation by ribosome profiling in control or mutant fibroblasts, and identification of RNA-binding proteins and mRNAs in the vicinity of control and diseased fibroblasts.

We propose a transformative research that will change our understanding on the mechanisms that drive neurodegeneration, and will permit the identification of compounds with beneficial activity in cells and mice carrying GFM1 mutations.