International PhD School in Molecular Medicine
Curriculum: NEN

DoS: Angela Gritti

Unit: Gene/neural stem cell therapy for lysosomal storage diseases
SR-Tiget

http://research.hsr.it/en/institutes/san-raffaele-telethon-institute-for-gene-therapy/gene-and-neural-stem-cell-therapy-for-lysosomal-storage-diseases.html

Project title

Defining mechanisms of neurodegeneration caused by lysosomal dysfunction in relevant murine and human models

Project description

Perturbation of the lysosomal-autophagic-exocytic network is a common feature underlying rare early-onset lysosomal storage diseases (LSDs) and late-onset neurodegenerative diseases (i.e. Alzheimer and Parkinson's disease - PD), and largely accounts for the presence of similar neurodegenerative hallmarks in these apparently disparate conditions (1). Mutations in the *GBA* gene, which encodes the lysosomal enzyme glucocerebrosidase that is deficient in Gaucher's disease, are important and common risk factors for PD and related disorders. More recent data identify the *GALC* gene, which encodes the lysosomal enzyme galactosylcerebrosidase that is deficient in Globoid cell Leukodystrophy (GLD), as an additional risk locus for PD (2).

We have a long-standing interest in understanding GLD pathogenesis and developing novel gene/cell therapy strategies to treat this fatal LSD (3). Interestingly, our pre-clinical data show α-synuclein aggregation and autophagy dysfunction in the brain of gene/cell therapy-treated aged GLD mice, despite restoration of therapeutic GALC levels. Indeed, growing pre-clinical and clinical evidences suggest that preventing the early death typical of these severe LSDs by innovative treatments may uncover a prominent late-onset neurodegenerative phenotype that has been overlooked so far.

In this project, we will investigate the mechanisms of age-related α-synuclein accumulation and neurodegeneration in the context of lysosomal dysfunction (in basal conditions and upon gene/cell therapy treatment) using relevant murine models and human iPSC-derived neurons (generated from patient's somatic cells or obtained in an isogenic context by state-of-the art gene-editing technologies). On these models, we will test the safety and efficacy of genetic and/or pharmacological approaches to reduce the flux of substrates, promote the clearance of storage, and counteract neurodegeneration. This project will enhance our understanding of the link between lysosomal dysfunction, storage and neurodegeneration. Also, it will pave the way to the development of disease-modifying therapeutic approach for GLD, to be eventually combined with tailored gene/cell therapy approaches.

Skills to be acquired by the student: murine and human cell cultures, immunocytochemistry, molecular biology, gene editing, biochemistry, live imaging, animal handling and treatment.

References

1. Boland, B. & Platt, F. M. Bridging the age spectrum of neurodegenerative storage diseases. *Best Practice and Research: Clinical Endocrinology and Metabolism* **29,** 127–143 (2015).
2. Chang, D. *et al.* A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat. Genet.* (2017). doi:10.1038/ng.3955
3. Ricca, A. *et al.* Combined gene/cell therapies provide long-term and pervasive rescue of multiple pathological symptoms in a murine model of globoid cell leukodystrophy. *Hum. Mol. Genet.* **24,** 3372–3389 (2015).