**Roles of phospholipids and regulating enzymes in skeletal muscle under physiological and pathological (myopathy) conditions**

Phosphoinositides (PIs) are key phospholipids that differently tag specific membrane sites and thus regulate intracellular trafficking and signal transduction. Mutations in their regulating enzymes, as PI 3-kinases (PI3K) or phosphatases, cause human diseases like cancer, obesity or neuromuscular defects. Among these, centronuclear myopathies (CNM) are due to mutations in the phosphoinositides phosphatase myotubularin (MTM1) or in the phosphoinositides binding proteins amphiphysin 2 and dynamin 2. Importantly, while these genes are ubiquitously expressed, different mutations in myotubularins or dynamin 2 can cause either CNM myopathies or peripheral neuropathies, supporting tissue-specific functions. However, the regulation and cellular role of this pathway in muscle is not known and the pathological mechanisms leading to the myopathies not understood.
The aim of the PhD project is to decipher the relationship between phosphoinositides and related proteins mutated in myopathies, their roles in muscle, and to validate therapeutic proof-of-concept to balance this pathway in myopathies.
-Role of PIs substrate/product of MTM1 in muscle. Impact of this pathway on the formation, maintenance, dynamic and function of muscle-specific membrane structures will be investigated in an in vitro muscle differentiation system and in vivo in mice with biochemistry, immunolabeling and confocal and live imaging.
-Implication of phosphoinositides in CNM myopathies. Mice models reproducing the CNM pathology are already available in the lab and will be used to assess the importance of phosphoinositides in the pathology through cell culture, histology, imaging and animal phenotyping.
-Modulation of this pathway to treat CNM myopathy in mice. Using our mice models and the knowledge obtained from the other tasks, therapeutic proof-of-principle will be conceived and validated, through gene modulation and pharmacology.
This project will decipher the role of phosphoinositides in the pathophysiology of these diseases, and their therapeutic potential.

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Wished skills :
-basic knowledge in molecular and cellular biology
-previous training period in a research lab
-interest for cellular mechanisms, genetic disease, and physiology
-scientific ethic
-ability to acquire independence
-highly motivated to learn and to work in a team

Expertises which will be acquired during the training :
Technical:
-cell culture
-intravital and confocal imaging
-pathophysiology in mouse models
-viral gene transfer
-drug therapy
General:

-management of a research project (choice of strategies, experiments, analysis and validation)
-oral (meetings, congress) and written (publications, posters) communications
-participation to the writing of grant applications and publications

References:
Ketel K, Krauss M, Nicot AS, Puchkov D, Wieffer M, Müller R, Subramanian D, Schultz C, Laporte J, Haucke V. A phosphoinositide conversion mechanism for exit from endosomes. Nature. 2016 Jan 21;529(7586):408-12.
Cowling BS, Toussaint A, Muller J, Laporte J. Defective membrane remodeling in neuromuscular diseases: insights from animal models. PLoS Genet. 2012 Apr;8(4):e1002595.

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