Title: Internship in muscle pathophysiology: Role of TGF-β family members in muscle wasting

Supervisor: Laetitia Mazelin

Duration: 3 months

Project Context:
Skeletal muscle wasting is a major comorbidity factor of many chronic diseases (cardiac failure, diabetes, myopathies, chronic obstructive pulmonary disorder, renal failure, Cushing syndrome, cancer...) and is also associated with aging. It is associated with poor prognosis, reduced quality of life, reducing tolerance and response to treatments and ultimately leading to increased mortality. Skeletal muscle atrophy results from 3 different mechanisms: (i) excessive catabolism in muscle fiber, (ii) muscle fiber regeneration defect (impaired regeneration from resident muscle stem cells) and (iii) muscle dysfunction (weakness, neuromuscular junction dysfunction). Skeletal muscle atrophy can result from disorders directly affecting either muscle or motoneurons. These disorders can be mediated by systemic perturbations via secreted “atrophy” factors. Among the cytokines involved in cachexia, members of the Transforming Growth Factor β (TGFβ) family, such as TGFβs, myostatin, activin are major negative regulators of muscle mass.

Project Objectives:
The main objective of this project is to define the consequences in skeletal muscle of chronic TGFβ activation. Our strategy stands out from previous studies as we have developed a new muscle-specific and inducible genetically engineered mouse model with constitutive activation of TGFβ signaling in muscle. Our mice model develops a severe muscle atrophy and functional muscle alterations thus recapitulating muscle alterations observed in chronic disorders.

The internship project aims to characterize mice phenotype through in vivo and in vitro investigations of (i) molecular mechanisms involved in myofiber atrophy (protein degradation (ubiquitin-proteasome pathway and autophagy/lysosomal pathway) and protein synthesis (crosstalk with AKT/mTOR pathway, analysis of polysome profiles)), (ii)
characterization of metabolic changes (glycolytic and oxidative properties, generation of oxidative stress) and (iii) characterization of molecular signatures involved in TGFβ-mediated muscle atrophy (analysis of deregulated signaling pathways and deregulated gene expression). A broad range of experimental techniques will be used: histology, immunofluorescence, Western-blot analyses, quantitative PCR, RNAseq analysis, development of primary muscle cell cultures using our mice model.

Contact Information:
Laetitia Mazelin (Researcher, INSERM)
Phone: 04 72 72 89 05 / 06 15 42 59 86
laetitia.mazelin@ens-lyon.fr; laetitia.mazelin@univ-lyon1.fr

Location:
INMG - Rockefeller medical university
4, Avenue Rockefeller
69373 Lyon
France

Institute
The Institut NeuroMyoGène (INMG) is a novel institute dedicated to the study of the nervous and muscular systems. It was created in 2016 in Lyon at the heart of a dense hospital network and of one of the biggest medical universities in France. One of its priorities is to develop relevant strategies to decipher multiple forms of neuromuscular diseases, identify new therapeutic targets and foster novel strategies for innovative treatments. The INMG is a consortium of three research organizations: the CNRS, the INSERM and the University Claude Bernard in Lyon. The Institute also gets strong support from the French Association against Myopathies (AFM). It gathers 14 individual research teams and about 160 people. Within the next few years the Institute will be able to host up to 250 people.

Lab:
Nerve-Muscle Interactions Team
Director: Laurent Schaeffer, Institut NeuroMyoGène (INMG)
http://www.inmg.fr/fr/eq_schaeffer.php

Our lab is part of the NeuroMyoGen Institute (INMG), dedicated to the study of the nervous and muscular systems. The team develops a series of research topics to understand the functioning of the neuromuscular junction and the role of signaling pathways involved in muscle growth and metabolism.

Bibliography