Internship offer
M2 Musculo-Skeletal system, Locomotion, Exercise (MuSkLE)

Title of the Internship:

Muscle gene therapy by functionalized lipid nanoparticles: an in vitro and in vivo proof of concept.

Laboratory : PGNM (Pathophysiology and Genetic of Neuron and Muscle) CNRS UMR 5261, INSERM U1315.

Research team : Team Schaeffer, https://pgnm.inmg.fr/schaeffer/

Supervisor to contact : Arnaud JACQUIER (arnaud.jacquier@univ-lyon1.fr)

Project description including a short introduction, aim/objectives and methods/approach to be used

Gene therapy has emerged as a transformative approach for the treatment of neuromuscular disorders, offering the potential to address the underlying genetic causes of diseases such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). Despite significant progress, current delivery strategies largely rely on viral vectors, particularly adeno-associated viruses (AAVs), which present important limitations. These include immunogenicity, limited cargo capacity, production challenges, and restricted possibilities for repeated administration. In this context, lipid nanoparticles (LNPs) have recently gained considerable attention as a promising non-viral delivery system. LNPs offer advantages such as improved safety, scalability, and flexibility for engineering. However, efficient and specific targeting of skeletal muscle remains a major challenge that limits their therapeutic application in neuromuscular diseases.

The aim of this project is to develop and **optimize functionalized LNPs to enhance their targeting and delivery efficiency to skeletal muscle** cells using two complementary strategies. First, LNPs will be decorated with proteins that recognize muscle-specific receptors. Second, LNPs will be functionalized with antibodies targeting receptors involved in transcytosis across endothelial cells.

The project will be conducted in close collaboration with the team of Dr. Giovanna Lollo, with whom we have patented an LNP formulation (patent FR2112931 / PCT/EP2022/084174). The Lollo team will be responsible for producing the LNPs and conjugating antibodies or proteins to their surface using click chemistry. Within the Schaeffer team, the student will work with the Drs. Arnaud Jacquier and Laurent Coudert to establish in vitro models based on myoblast and myotube cultures derived either from primary human muscle cells or from induced pluripotent stem cell (iPSC)-derived models of DMD and SMA. Functionalized LNPs encapsulating mRNA encoding GFP will be used to evaluate uptake efficiency and intracellular delivery. In addition, the student will develop a vascular model using endothelial cells cultured in Boyden chambers to investigate LNP transcytosis across the endothelial barrier. The most promising LNP functionalization strategies will then be evaluated in vivo following systemic administration in Ai9 reporter mice, in order to assess biodistribution and targeting efficiency in skeletal muscle.

By the end of the Master's project, the student will have identified efficient strategies to enhance LNP delivery to skeletal muscle and contributed to a better understanding of nanoparticle transport across vascular barriers.

Skills required:

- background in cell biology, molecular biology, or biomedical sciences
- Experience in cell culture (preferably including iPS cells or primary myoblasts)
- Basic knowledge of gene therapy or nanomedicine
- Experience in animal handling (not mandatory, but appreciated)
- Scientific curiosity and critical thinking
- Ability to work independently and as part of a team