Call for Excellence Doctoral Scholarship – InnovInOnco/ MuSkLE

Unraveling the benefits of adapted physical activity on skeletal muscle homeostasis and treatment efficacy in pediatric cancers

Host Laboratories:
InnovInOnco: Lab#1: CRCL; Cell Death and Childhood Cancers (Team Castets)
MuSkLE: Lab#2: INMG; Stem cell environment and skeletal muscle homeostasis (Team Chazaud)

PhD supervisors: Marie CASTETS (DR INSERM; marie.castets@lyon.unicancer.fr) & Julien GONDIN (DR CNRS; julien.gondin@univ-lyon1.fr)

Project description

Background: Despite considerable research efforts over the past 30 years, nearly 80 000 children and teenagers still die of cancer each year, worldwide. Furthermore, around 66% of the children and adolescents that have been cured, will face long-term sequelae linked to the disease itself but also to the intensive treatments they received (*e.g.*, chemotherapies)[1]. Skeletal muscle, which is the largest organ of the human body, is strongly impacted by pediatric cancer treatment as illustrated by muscle atrophy, muscle weakness, fibrosis and exercise intolerance. Surprisingly, the cellular and molecular mechanisms involved in the side-effects of chemotherapies in pediatric cancer patients are still poorly understood.

Voluntary physical activity is associated with decreased tumor growth[2,3], improved muscle mass and strength[4] and enhanced the efficacy of treatment in adult cancers[5]. Evidence is also emerging on the potential benefits of physical activity in pediatric cancer patients. However, the evaluation of these interventions has been largely limited to qualitative approaches based on questionnaires submitted to patients so far. We also recently demonstrated that contractile activity induced by NeuroMuscular Electrical Stimulation (NMES) plays a key role in skeletal muscle homeostasis in both healthy muscles[6] and mouse models of adult cancer (unpublished data). Overall, the potential biological effects of physical activity and repeated muscle contractions on both muscle and tumor tissues remains to be determined in pediatric cancers together with their impact on treatment efficacy.

Aims: The aims of the PhD program will be i) to characterize the age-dependent skeletal muscle alterations in mouse models of pediatric cancer treated with chemotherapy, ii) to evaluate whether recreational physical activity and NMES could minimize muscle dysfunctions and improve response and tolerance to treatments.

Description of the project methodology: Experiments will be performed in mouse models of orthotopic grafting of paediatric cancers (with a proof-of concept in rhabdomyosarcoma) treated with chemotherapy (Lab#1) and subjected to voluntary physical activity, NMES or control procedures. These experiments will be performed on animals of different ages to mimic pre-pubertal, pubertal and post-pubertal contexts. A variety of methods (immunolabeling, flow cytometry, proteomics…) will be used to characterize muscle changes at tissular, cellular and molecular levels (Lab#2). In parallel, physiological outcomes, including *in vivo* and *in vitro* measurements of hindlimb force production and myofiber size, will be determined (Lab#2). In parallel, tumor aggressiveness will be assessed by measuring tumor size, metastatic spread and histological characteristics (Lab#1). All the mouse models, platforms and resources (FACS, histology room) are already available in the two host labs. We will complete these *in vivo* analyses with *in vitro* modeling, by testing the effects of exercising muscle protein extracts (Lab#2) on the growth and acquisition of invasive properties of an original tumoroid model we have developed (Lab#1).

Consortium: M. Castets has a long experience in *in vivo* and *in vitro* modeling of cancers, including pediatric ones. Her team has notably developed inter-age orthotopic graft models in mice, to define the impact of ontogenic context on tumor phenotype and response to treatment, as well as an original tumoroid model directly derived from patient biopsies, which reproduces as closely as possible the molecular characteristics of the original tumors. J. Gondin is an expert in the field of skeletal muscle physiology. The unifying theme of his research concerns the skeletal muscle plasticity associated with physiological (hypertrophy, regeneration) or pathophysiological conditions (*e.g.*, cancer cachexia). This pluridisciplinary project will combine unique expertise in muscle physiology, exercise, cell biology and oncology. By working close together and sharing resources, we aim at deciphering how chemotherapy and physical activity affect skeletal muscle and tumor homeostasis and at unraveling the underlying mechanisms.

Planned Schedule (Lab#1 *vs.* Lab#2)

Year 1				Year 2				Year 3			
WP1 – Characterization of the age-dependent skeletal muscle alterations in mice treated with chemotherapy											
WP2 – Impact of physical activity on muscle homeostasis and tumor growth											

References: [1]Geenen *et al. JAMA* 297, 2705–2715 (2007); [2]Pedersen *et al. Cell Metab.* 23, 554–562 (2016); [3]Rundqvist *et al. Elife* 9, e59996 (2020); [4]Ballarò *et al. FASEB J* 33, 5482–5494 (2019); [5]Kurz *et al. Cancer Cell* 40, 720-737.e5 (2022); [6]Fessard *et al. Skelet Muscle* 15, 3 (2025).

Skills required: Immunostaining, histology, microscopy, cell culture, animal experiments