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

Title of the Internship: Striated skeletal muscle resistance to cancer metastasis

Laboratory (name, n°, website): PGNM – UMR 5267 – U1315 – https://pgnm.inmg.fr

Research team (name, website): MOUNIER TEAM – https://pgnm.inmg.fr/mounier/

Supervisor to contact (name, email address): Rémi Mounier – remi.mounier@univ-lyon1.fr

Project description including a short introduction, aim/objectives and methods/approach to be used
Cancer is one of the leading causes of mortality in the world, which is mainly due to the development of secondary tumors at distant sites, called metastases. Metastasis formation relies on complex interactions between disseminated tumor cells and their environment. Importantly, **cancer very rarely metastasizes to skeletal muscle**. Interestingly, the muscle has the unique ability to contract, which influences its local metabolic environment. Tumour cell survival is elevated in denervated muscle and diminished in electrically stimulated muscle, highlighting the role of muscle cell **contraction** in conferring the resistance to metastasis. Furthermore, *in vitro* studies have shown that **post-exercise serum, and conditioned medium from cultured myogenic cells inhibit tumour cell proliferation, viability or survival, suggesting that skeletal muscle contraction-induced endocrine and paracrine factors can have anti-tumour and potentially anti-metastatic effects.** We therefore hypothesize that contraction-induced oxygen availability and metabolic changes, including metabolite release or depletion, in the muscle microenvironment, have anti-metastatic effects. The purpose is to comprehend the mechanisms conferring skeletal muscle resistance to metastasis. Due to the rareness of skeletal muscle metastasis, the direct communication between skeletal muscle and metastatic cells cannot be studied *in vivo*. Thus, we use a novel ***ex vivo*** **nerve-induced skeletal muscle contraction setup**, allowing us to study the direct communication between skeletal muscle and metastatic cells.

Our *objectives* are: 1) to assess the impact of *ex vivo* nerve-induced skeletal muscle contraction on the metastatic cascade in human metastatic tumour cell lines; 2) to assess the contraction-induced local metabolic and environmental changes that confer anti-metastatic effects on tumour cells (*i.e.* metabolic muscle characterization, metabolic and hypoxic profiles of the medium)

The *methods* used are 1) cell culture, 2) muscle-nerve dissection and 3) biochemistry (enzymatic assays…).

References:
Hargreaves, M. Skeletal muscle energy metabolism during exercise.
Welch, D. R. & Hurst, D. R. Defining the Hallmarks of Metastasis. *Cancer Res.* **79**, 3011–3027 (2019).
Lasagna, A. *et al.* Skeletal muscle metastases: pitfalls and challenges of a highly inhospitable environment. *Future Oncol.* **18**, 897–901 (2022).
Weiss, L. Biomechanical destruction of cancer cells in skeletal muscle: a rate-regulator for hematogenous metastasis. *Clin. Exp. Metastasis* **7**, 483–491 (1989).
Parlakian, A. *et al.* Skeletal Muscle Phenotypically Converts and Selectively Inhibits Metastatic Cells in Mice. *PLoS ONE* **5**, e9299 (2010).
Crist, S. B. *et al.* Unchecked oxidative stress in skeletal muscle prevents outgrowth of disseminated tumour cells. *Nat. Cell Biol.* **24**, 538–553 (2022).

Skills required: Skeletal muscle physiology, cell biology, cancer biology