Graduate MuSkLE - Excellence Doctoral Scholarships 2026

PhD project: Disease mechanisms involved in the muscular comorbidities of rare genetic diseases

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Defective skeletal muscle function such as generalized hypotonia or muscle weakness is among the first clinical manifestations seen in patients diagnosed with rare genetic disease, but this aspect remains largely overlooked. Indeed, very few studies attempted to understand how the underlying genetic mutations affect multiple tissues, particularly those in which symptoms first become visible in skeletal muscle. It is the ambition of the present PhD project to use a multidisciplinary approach to reveal the underlying myopathic mechanisms through a combination of cellular physiology, live imaging and high-resolution episcopic microscopy (HREM). Addressing this gap has the potential to uncover shared disease mechanisms and offer therapeutic advantages across a wide range of rare genetic disorders.

More specifically, this PhD project will focus on the muscle defects associated with two genes coding for the intermembrane lipid transfer protein VPS13B and the Major Vault Protein (MVP), respectively, responsible for rare diseases associated with muscle function defects in patients at neonatal stages (Montillot et al., 2023; Kretz et al., 2023). Experiments will be achieved using genetically modified mouse models of the two diseases that recapitulate the muscle symptomatology of the patients at the whole organism level. Experiments will aim 1- at characterizing the properties of membrane excitability, Ca^{2+} signaling and excitation-contraction coupling using a combination of electrophysiology and Ca^{2+} imaging on isolated muscle fibers (see Schreiber et al., 2025), 2- at complementing these functional data by molecular approaches and by a detailed characterization of the muscle fibers sub-compartments using confocal and super-resolution imaging, 3- at achieving a differential anatomical analysis at the cellular level of the control and diseased muscles using HREM technology (see Amelan et al., 2026). This technique which allows deep-phenotyping using 3D reconstruction of a tissue, down to the cellular level, is in routine use in the co-supervising laboratory on brain preparations, where it is combined with artificial-intelligence tools to segment the investigated structures. The technique will be adapted for the first time to skeletal muscle tissue to identify and quantify pathological abnormalities and to establish genotype-phenotype correlations. This innovative technological development will ultimately offer the perspective to use it to understand a wide variety of other muscle diseases. Overall, this project will contribute to understand the molecular and cellular mechanisms involved in the muscle defects associated with ultra-rare diseases. Ultimately, it could help improve the diagnosis and the stratification and follow-up of patients and open therapeutic perspectives. In addition, the project will allow the development and validation of a novel technology of investigation of muscle properties, based on HREM imaging.

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