Excellence Doctoral Scholarship
Musculo-Skeletal system, Locomotion, Exercise (MuSkLE)

Title of the Internship: Role of TRPV1 channels in exertional heat stroke

Laboratory : CarMeN Laboratory https://carmen.univ-lyon1.fr/en/

Research team: Ischemia-Reperfusion Injury Syndrome Team https://carmen.univ-lyon1.fr/en/teams/team-iris/

Supervisor to contact : DUCREUX, Sylvie, sylvie.ducreux@univ-lyon1.fr

Co-supervisor : FAURE Julien, julien.faure@univ-grenoble-alpes.fr

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

Climate change is expected to cause a significant increase in heatwaves in the coming decades, leading to a rise in heat-related illnesses. Among them, exertional heat stroke (EHS) affects young and healthy individuals, such as athletes, military personnel, and outdoor workers, during intense physical activity. EHS primarily targets skeletal muscle and can result in multi-organ failure, which may be fatal without rapid medical intervention. While the clinical presentation of EHS is well documented (core body temperature > 40°C, severe muscular, inflammatory, metabolic, and neurological disturbances), the molecular mechanisms and individual susceptibility factors remain poorly understood. We recently identified human variants in the TRPV1 gene in military personnel with EHS (1–3). TRPV1 is a non-selective cation channel with high calcium permeability and widespread tissue distribution; however, its specific role in skeletal muscle remains unclear. This PhD project aims to fill this critical knowledge gap and to contribute to long-term strategies for preventing and adapting to heat stress.

The main aims of this PhD project are to (a) unravel the role of TRPV1 in skeletal muscle function; (b) characterize the molecular and pathophysiological mechanisms underlying EHS, and (c) explore translational strategies, including biomarker discovery and pharmacological modulation of TRPV1 for personalized prevention.

To achieve these goals, we developed a knock-in mouse model carrying a TRPV1 mutation (R7772C) identified in a patient who experienced an EHS episode using a CRISPR-Cas9 strategy. The project will combine cellular and molecular studies, such as calcium imaging, electrophysiology, and advanced microscopy, with in vivo analyses of muscle performance, thermoregulation, and metabolic profiling under normal and heat-stress conditions. The findings will contribute to the development of predictive models for personalized prevention strategies and to the development of new approaches to reduce vulnerability to heat stress.

This project offers an opportunity to engage in cutting-edge research at the intersection of physiology, genetics, and climate adaptation, while acquiring expertise in advanced experimental techniques and contributing to public health and climate resilience.

References:

1. Lotteau, S.; Ducreux, S.; Romestaing, C.; Legrand, C.; Coppenolle, F. V. Characterization of Functional TRPV1 Channels in the Sarcoplasmic Reticulum of Mouse Skeletal Muscle. *PLOS ONE* **2013**, *8* (3), e58673. https://doi.org/10.1371/journal.pone.0058673
2. Lafoux, A.; Lotteau, S.; Huchet, C.; Ducreux, S. The Contractile Phenotype of Skeletal Muscle in TRPV1 Knockout Mice Is Gender-Specific and Exercise-Dependent. *Life* **2020**, *10* (10), 233. https://doi.org/10.3390/life10100233
3. Bosson, C.; Rendu, J.; Pelletier, L.; Abriat, A.; Chatagnon, A.; Brocard, J.; Brocard, J.; Figarella-Branger, D.; Ducreux, S.; van Coppenolle, F.; Sagui, E.; Marty, I.; Roux-Buisson, N.; Faure, J. Variations in the TRPV1 Gene Are Associated to Exertional Heat Stroke. *J. Sci. Med. Sport* **2020**. https://doi.org/10.1016/j.jsams.2020.04.018.

Skills required: We are seeking a motivated student with a background in physiology or cell biology. Skills in biochemistry, statistics, calcium imaging, and animal experimentation are also highly valued.