CMD InnoCARE (Innovation pour les maladies CArdiovasculaires, métaboliques et REspiratoires)

Master 2 Internship proposal (2025-2026)

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Profile(s) linked to the project:
☒ Experimental Biology *(Recherche expérimentale)*
☐ Research and Omics Data Analysis *(Recherche et analyse de données omiques)*
☐ Clinical Research *(Recherche clinique)*

Lab: l'institut du thorax

Team: Equipe II

Name and position of the supervisor: Céline Marionneau, PhD, DR CNRS

Email of the supervisor: celine.marionneau@univ-nantes.fr

Candidate (if known):

Title of the internship: Post-translational regulation of cardiac Nav1.5 channels

Summary of the internship proposal:

The voltage-gated Na^+ channel Nav1.5 is essential for normal cardiac excitability, as evidenced by the strong link between channel dysfunction and life-threatening arrhythmias. Yet, many molecular aspects of this channel regulation remain poorly understood. In particular, Nav1.5 is tightly regulated within macromolecular protein complexes and local signaling domains that control channel expression, function and post-translational modifications (PTMs). However, while previous studies have suggested roles for numerous interacting proteins in regulating Nav1.5, the native interactome of cardiac Nav1.5 channels, the detailed sites of interaction of these proteins with the channel, and how this interactome is altered in response to the various physiological and pathophysiological circumstances remain largely unknown. The research developed in this team is aimed at delineating the molecular dynamics of cardiac $Na_V1.5$ channel protein complexes in physiological and pathophysiological excitability. The proposed project of the internship will contribute to one of the following work packages (WP). WP1 will identify by proteomics the native cardiac Nav1.5 channel interactome. WP2 will delineate the binding domains and functional roles of newly-identified Nav1.5 interacting proteins. Finally, WP3 will investigate the dynamics of channel complex composition in two pathophysiological conditions associated with an increased arrhythmogenic late Na^+ current: (1) acute *versus* sustained β-adrenergic stimulations, and (2) Phosphoinositide 3-Kinase (PI3K)-associated anti-cancer drug-induced long QT syndrome. In addition to providing new insights into the comprehension of cardiac Nav1.5 channel physiology, the proposed research will provide an exhaustive framework for interpreting channelopathies that remained mechanistically unexplained and will give a clearer view on how PTMs dynamically influence channel interactome and function.