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

Master 2 Internship proposal (2024-2025)

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

Lab: L'institut du thorax, Inserm UMR1087, CNRS UMR6291

Team: II - Ion channels and cardiopathies

Name and position of the supervisor: Aurélia Leroux

Email of the supervisor: Aurelia.Leroux@univ-nantes.fr

Candidate (if known):

Title of the internship: O-GlcNAcylation as a Therapeutic Strategy in Equine Neonatal Sepsis, an Innovative Model for Studying Acute Cardiac Dysfunction in Pediatric Sepsis.

Summary of the internship proposal:

Sepsis is a systemic inflammatory response syndrome, described as a dysregulated host response to an infection, leading to acute cardiovascular shock, acute cardiac dysfunction and other fatal consequences. In 2017, 48.9 million cases of sepsis were recorded globally in humans, resulting in 11 million deaths. Among these cases, 20.3 million were children, ranking it as an important cause of pediatric death worldwide, with a mortality rate ranging from 4% to 50%. Horses, like humans, are prone to sepsis and foals are more affected than adults, with a prevalence of 8 to 12% and mortality rates of 19 to 55%. Clinical picture including acute cardiovascular shock and cardiac dyfunction are similar in horses and humans during sepsis.
O-GlcNAcylation is a ubiquitous, dynamic, and reversible post-translational modification involved in most biological processes, particularly in cell survival and stress response. Preliminary studies have shown that O-GlcNAc levels decrease during sepsis in many species, including horses and humans. Moreover, stimulation of O-GlcNAcylation by an O-GlcNAcase inhibitor in a murine model of endotoxemia is associated with reduced mortality, confirming the interest in O-GlcNAc levels as a therapeutic target. Although O-GlcNAc levels are physiologically higher in young rats and children compared to adults, our team has recently confirmed the benefit of increasing O-GlcNAc levels in young subjects with sepsis.
The objectives of this study are therefore: 1) to characterize cardiovascular shock in equine neonatal sepsis cases and confirm its similarity to pediatric sepsis cases; 2) to confirm that the kinetics of O-GlcNAc levels in foals are similar to those in young rats and children; 3) to evaluate O-GlcNAc stimulation as a potential treatment against sepsis-induced acute cardiovascular dysfunction in equids and humans. To achieve these objectives, quantitative PCR to quantify the levels of specific genes associated with sepsis (TNF-α, IL-6, IL-10...) in children and foals, western blots to quantify their O-GlcNAc levels; and cell cultures (with endothelial cells and/or cardiomyocytes) to study cellular responses to conditions simulating sepsis, with or without stimulation of O-GlcNAcylation will be performed.