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: UMR-S 1180, Signalisation and cardiovascular physiopathology, Faculté de Pharmacie, Université Paris-Saclay.

Team: Team 1, Cardiac energetic signalisation

Name and position of the supervisor: Pauline GAIGNARD, teacher researcher

Email of the supervisor: pauline.gaignard@universite-paris-saclay.fr

Candidate (if known):

Title of the internship: **Role of poly-ADP-ribose polymerases in mitochondrial energy signaling pathways in heart failure and sexual dimorphism**

Summary of the internship proposal:
Background: Heart failure (HF) remains a major cause of morbidity and mortality, and finding more targeted treatments is prioritised. The deregulation of mitochondrial functions plays an increasingly recognized central role in the pathophysiology of HF. Our team has helped to show that deregulation of the PGC-1α axis, the main regulator of mitochondrial biogenesis, is involved in HF in both animals and humans, making this axis a potential therapeutic target. We then demonstrated that activation of AMP kinase (AMPK) or Sirtuin 1 (SIRT1, NAD deacetylase), both of which modulate PGC-1α activity and hence mitochondrial function, had cardioprotective properties in models of HF.
Biological sex has a major influence on cardiovascular disease. Younger women are generally protected, but this cardioprotection is lost at the menopause. Interestingly, the PGC-1α axis cascade is more deregulated in men than in women, consistent with the presence of an estrogen recognition site in the PGC-1α promoter. We extended this notion by showing that AMPK activation was also subject to sexual dimorphism.
Poly-ADP-Ribose Polymerases (PARP) are enzymes that repair DNA after oxidative damage by PARylation from NAD ADP-ribose. PARP1 thus competes directly with SIRT1 for the use of NAD. PARP1 is also one of the targets of AMPK phosphorylation. Studies on male mice have shown that inhibiting PARP1 protects mitochondrial function during cardiac damage. Furthermore, in models of cerebral ischaemia and nephritis, PARP1 activation differs between males and females, probably due to the binding of PARP1 to the oestrogen receptor. However, this aspect has never been studied in cardiac tissue.

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Objective: The aim of our study is to determine whether PARP1 activation and its consequences on energy signaling pathways (AMPK and SIRT1) and mitochondrial function differ according to sex in the context of HF. The study will be carried out first *in vitro* on primary cultured cardiomyocytes and then *in vivo* on male and female mice with induction of HF.

The Master 2 project will focus on cardiomyocytes and will aim to analyse :

- PARP activation and cytosolic and nuclear NAD levels ;
- the regulation of SIRT1, AMPK and PGC-1α following PARP activation;
- the activity of respiratory chain complexes.

These measurements will be made first after induction of DNA damage by an alkylating agent and then in the presence of estradiol and an estrogen receptor antagonist.

The student will acquire techniques for isolating and culturing neonatal rat cardiomyocytes, western-blot techniques, spectrophotometric enzymatic assays and quantitative RT-PCR. All these techniques have already been developed in the lab.

Perspectives: This work could be followed up by a PhD thesis on both models (cardiomyocytes and murine model), leading to a complete characterization of PARP/SIRT1/AMPK interactions in HF and a possible sexual dimorphism.