POST-DOCTORAL POSITION IN CARDIAC PHYSIOLOGY: **S-nitrosylation of cardiac myofilaments: Consequence on (mal)-adaptive response to mechanical stress**

Laboratory of Cardiovascular Physiology, NO-Stress Group, LaPEC UPR4278, Avignon, France

Partner Laboratories of the project:

Laboratory Physiologie et Médecine Expérimentale du Coeur et des muscles, UMR INSERM CNRS, Montpellier, France

Laboratory Médicaments et Technologies pour la Santé (DMTS), UMR CEA Paris Saclay Université, Bagnols sur Cèze, France

Research project:

Pressure overload stretches the myocardium leading to functional and eventually structural adaptations if the mechanical stress persists. Repetitive ventricular stretch can result in physiological remodeling of the heart as is observed in response to exercise training. However, when this stress is chronic, it leads to unfavorable cardiac remodeling that is associated with dysfunction. To date, the main effective treatment to limit myocardial remodeling is by reducing the pressure overload. Hence, there is a dire need for better understanding of the signaling pathways that underlie the cardiac load-dependent (mal)adaptations to provide pathways for the development of novel therapeutics.

In response to stretch, the myocardium produces increased amounts of nitric oxide (NO). Until recently, NO signaling was considered to mainly involve activation of the cyclic guanosine monophosphate (cGMP) dependent protein kinase (cGMP-PKG) pathways. However, NO can also directly attach covalently to cysteine thiol residues, a process called S-nitrosylation (SNO). This second mechanism has been less investigated and is the focus of the present project. SNO is a major reversible post-translational modification involved in the regulation of protein activity; it is also proposed to protect proteins from irreversible oxidation of thiol moieties. This process has been well described in mitochondria where it is associated with reduced ROS production. Cardiac myofilaments are also redox sensitive and, thus, potentially impacted by NO signaling. Whether SNO is involved in the regulation of cardiac contractile machinery remains to be deciphered.

The NitrosoCard proposal aims to test the hypothesis that **in response to stretch, eNOS translocates to the myofilaments to activate a SNO signaling pathway that regulates contractile properties. This pathway is lost under chronic stretch, resulting in a maladaptive response of the heart and the subsequent development of cardiac pathology.**

Objectives:

1- To demonstrate the role of myocardial stretch in the translocation of eNOS/NO/SNO signaling to myofilaments.
2- To evaluate the direct or indirect impact of protein SNO on myofilament function following stretch.
3- To evaluate the impact of Repetitive *vs* chronic stretch on myofilament S-nitrosoproteome.

Requirements:

- A PhD degree in biology or relevant field
- Experience with animal models and animal experimentation

Optional requirements:

- A strong background in cardiac physiology
- Cardiac and cellular physiology

- Primary cell isolation (cardiomyocytes)
- Protein biology (western blot, immunofluorescence)
- Microscopy and image analyses

Associated activities:

- Trainee supervision (M1, M2)

Host structure:

Laboratory CardioVascular Physiology of Avignon, NO-Stress Group, Centre INRAE PACA, Site Agroparc. A part of the experiments will be carried out in the Montpellier laboratory (Laboratory Physiologie et Médecine Expérimentale du Coeur et des muscles, UMR INSERM CNRS) and will require temporary accommodation in Montpellier.

Contract: The position is planned to start in the 1st semester of 2022. Post-doctoral position 24-36 months (ANR funding).

To apply: send your application (CV, cover letter, list of publication and the contact details of two referees) as a single PDF-file to Cyril.reboul@univ-avignon.fr

Recent lab publications related to the project:

- Exercise-induced cardioprotection: a role for eNOS uncoupling and NO metabolites. Farah C, Kleindienst A, Bolea G, Meyer G, Gayrard S, Geny B, Obert P, Cazorla O, Tanguy S, Reboul C. Basic Res Cardiol (2013) 108:389
- Exercise does not activate the β3 adrenergic receptor-eNOS pathway, but reduces inducible NOS expression to protect the heart of obese diabetic mice. A. Kleindienst, S. Battault, … Reboul C. 2016, Basic Res Cardiol 2016 Jul;111(4):40. doi: 10.1007/s00395-016-0559-0
- Subendocardial increase in reactive oxygen species production affects regional contractile function in ischemic heart failure. Andre L*, Fauconnier J*, Reboul C*, Feillet-Coudray C, Meschin P, Farah C, Fouret G, Richard S, Lacampagne A, Cazorla O. Antioxid Redox Signal. 2013 Mar 20;18(9):1009-20. doi: 10.1089/ars.2012.4534.
- Stress-induced protein S-glutathionylation and phosphorylation crosstalk in cardiac sarcomeric proteins - Impact on heart function. Chakouri N*, Reboul C*, Boulghobra D, Kleindienst A, Nottin S, Gayrard S, Roubille F, Matecki S, Lacampagne A, Cazorla O.Int J Cardiol. 2018 May 1;258:207-216. doi: 10.1016/j.ijcard.2017.12.004