UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

DOTTORATO DI RICERCA IN Tecnologie Convergenti per i Sistemi Biomolecolari – XLII CICLO

Research Topic ID: XLII – 1.5

Project Tutor: Marcella Rocchetti

Project Supervisor/s: Annarita Di Mise (unimib), Luca Sala (Istituto Auxologico Italiano IRCCS)

Project Title: The sympathetic regulation in cardiac congenital arrhythmias.

Scientific background & Objectives

Inherited cardiac arrhythmias are rare genetic disorders and a major cause of sudden cardiac death in young individuals. Many are ion channelopathies, including Long QT Syndrome (LQTS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). LQTS is mainly linked to *KCNQ1*, *KCNH2*, and *SCN5A* variants, while CPVT commonly involves *RYR2* and *CALM* genes. Although genetic mechanisms are well characterized, the influence of sympathetic regulation on arrhythmic risk remains unclear.

This project aims to generate patient-specific neurocardiac models using sympathetic neurons (hSNs) and cardiomyocytes (hCMs) derived from patients' iPSCs. In addition, hSNs will be isolated from patients' ganglia collected during cardiac sympathetic denervation procedures. By integrating molecular and functional analyses, this study will assess how the sympathetic nervous system modulates arrhythmias and will characterize the molecular machinery involved in neurotransmitter synthesis and regulation. Co-culture models of hSNs and hCMs will recapitulate cardiac innervation and provide a platform to develop novel therapeutic strategies.

Project's Networks, Sustainability & Mobility

a) the coherence of the suggested project with competences/tools of the hosting lab
b) intradepartmental or external collaborations
c) at least one pertinent research article published by the proposer/s
d) 1 (or more) putative foreign institutions for achieving the required ordinary mobility (6 months)

a) The hosting laboratory is based at the Istituto Auxologico Italiano (Cusano Milanino, MI) and is directed by Prof. Peter Schwartz, internationally recognized as a leading expert in genetic disorders causing sudden cardiac death in infants and young individuals, particularly LQTS and CPVT. The lab has extensive expertise in advanced single-cell live imaging techniques to study second messengers dynamics (calcium and cAMP) and intracellular signaling pathways (Dr. Di Mise), as well as in cellular and cardiac electrophysiological investigations (Dr. Sala).

b) The laboratory has established a wide network of national and international collaborations:
- Policlinico San Matteo, Pavia, Italy (where cardiac sympathetic denervation procedures are performed in LQTS and CPVT patients);
- Prof. M. J. Ackerman - Mayo Clinic, Rochester, MN, USA;
- Prof. C. A. Remme, Amsterdam University Medical Center, The Netherlands;
- Prof. C. Mummery, Leiden University Medical Center, The Netherlands.

c) Pertinent research articles:
1. Schwartz PJ, Crotti L. Long QT Syndrome. N Engl J Med. 2025 Nov 20;393(20):2023-2034. doi: 10.1056/NEJMra2400853. PMID: 41259757;
2. Schwartz PJ, Ackerman MJ. Cardiac sympathetic denervation in the prevention of genetically mediated life-threatening ventricular arrhythmias. Eur Heart J. 2022 Jun 6;43(22):2096-2102. doi: 10.1093/eurheartj/ehac134. PMID: 35301528;
3. Di Mise A et al. Activation of Calcium-Sensing Receptor increases intracellular calcium and decreases cAMP and mTOR in PKD1 deficient cells. Sci Rep. 2018 Apr 9;8(1):5704. doi: 10.1038/s41598-018-23732-5. PMID: 29632324;
4. Lee YK, Sala L et al. MTMR4 SNVs modulate ion channel degradation and clinical severity in congenital long QT syndrome: insights in the mechanism of action of protective modifier genes. Cardiovasc Res. 2021 Feb 22;117(3):767-779. doi: 10.1093/cvr/cvaa019. PMID: 32173736.

d) Prof. D. J. Paterson, Department of Physiology, Anatomy and Genetics, University of Oxford, UK.
David Paterson leads a research team in cardiac neurobiology. Their research focuses on the neural control of the cardiovascular system using isolated cardiac tissues and human induced pluripotent stem cell (hiPSC)-based co-culture systems.