UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

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

Research Topic ID: XL – 1.22

Project Tutor: Prof. Marcella Rocchetti

Project Title: Stimulation of the sarcoplasmic reticulum-mitochondria coupling as new approach to improve cardiac function in heart failure treatment.

Scientific background and 'open issues'

Heart failure (HF) is one of the principal causes of death in the world and the alteration of intracellular Ca^{2+} homeostasis represents a key marker of pathological cardiac remodeling in HF [1]. In particular, the close cooperation between sarcoplasmic reticulum (SR) and mitochondria, crucial for the efficiency of the excitation-contraction-bioenergetics coupling, is altered in HF [2]. Despite the significant advances in HF treatment, new strategies need to be developed to find druggable targets able to compartimentalize Ca^{2+} and limiting its pro-arrhythmogenic futures when accumulated in the cytosol. Recent studies pointed to SR Ca^{2+} ATPase (SERCA2a) stimulation to limit pathological cytosolic Ca^{2+} accumulation in HF [3,4]. In particular, a new class of compounds able to ameliorate diastolic dysfunction in a model of diabetic cardiomyopathy has been developed [5–7]. In addition, stimulation of the mitochondrial Ca^{2+} uptake through the voltage-dependent anion channel (VDAC) on the outer mitochondrial membrane seems crucial in restoring intracellular Ca^{2+} imbalance in HF [8].

Objectives

To develop an innovative and translational *in vitro* cellular model (i.e. human induced pluripotent stem cell derived cardiomyocytes, hiPSC-CMs) showing the well-known HF markers. To evaluate new pharmacological approaches (druggable targets) stimulating SR-mitochondria coupling to ameliorate HF alterations.

Methodologies

The project needs to be based on a multidisciplinary approach. An adaptable experimental design approach coupled with a high degree of internal and external collaborations will be crucial for the final success of this project. The project can count on the availability of cell culture facilities (included the Biosafety Level 2 laboratory to use human cells and work with viruses), molecular biology techniques (i.e. qRT-PCR and western blot), microscopy platforms (optical and electronic microscopies), electrophysiology setups (i.e. patch clamp and Multi Electrode Array techniques), metabolic flux technologies (i.e. Seahorse technology).

Collaboration / Co-tutoring opportunities

UNIMIB experts in cell metabolism and bioenergetics will be involved; moreover, experts in cardiac stem cell differentiation (i.e. hiPSC) at Istituto Cardiocentro Ticino, Bellinzona, CH) actually collaborating with the Proponent will participate to the project in terms of scientific support, giving the possibility to the PhD student to spend some time in their laboratory.

Project's Sustainability & Mobility

-Given the scientific interest in cardiac cell physiology and pharmacology of the Proponent, the project is completely coherent with the competence of the laboratory (cardiovascular cell physiology lab).

-Some recent pertinent research full articles of the Proponent are the following:

1. Arici M, Hsu SC, Ferrandi M, Barassi P, Ronchi C, Torre E, et al. Selective SERCA2a activator as a candidate for chronic heart failure therapy. J Transl Med. 2024;22:1–13.
2. Arici M, Ferrandi M, Barassi P, Hsu SC, Torre E, Luraghi A, et al. Istaroxime Metabolite PST3093 Selectively Stimulates SERCA2a and Reverses Disease-Induced Changes in Cardiac FunctionS. J Pharmacol Exp Ther. 2023;384:231–44.
3. Altomare C, Bartolucci C, Sala L, Balbi C, Burrello J, Pietrogiovanna N, et al. A dynamic clamping approach using in silico IK1 current for discrimination of chamber-specific hiPSC-derived cardiomyocytes. Commun Biol. 2023; 6: 291.
4. Luraghi A, Ferrandi M, Barassi P, Arici M, Hsu SC, Torre E, et al. Highly Selective SERCA2a Activators: Preclinical Development of a Congeneric Group of First-in-Class Drug Leads against Heart Failure. J Med Chem. 2022;65:7324–33.
5. Lazzarini E, Lodrini AM, Arici M, Bolis S, Vagni S, Panella S, et al. Stress-induced premature senescence is associated with a prolonged QT interval and recapitulates features of cardiac aging. Theranostics. 2022;12:5237–57

-Putative foreign institutions for achieving the required mobility:

- Dr Lucio Barile at Istituto Cardiocentro Ticino, EOC, Bellinzona, CH
- Dr Matteo Mangoni at CNRS, Montpellier, France
- Dr Giancarlo Forte at School of Cardiovascular and Metabolic Medicine and Sciences at King's College London, UK

References

1. Metra M, Teerlink JR. Heart failure. Lancet. 2017;390:1981–95.
2. Lopez-Crisosto C, Pennanen C, Vasquez-Trincado C, Morales PE, Bravo-Sagua R, Quest AFG, et al. Sarcoplasmic reticulum-mitochondria communication in cardiovascular pathophysiology. Nat Rev Cardiol [Internet]. 2017;14:342–60. Available from: http://dx.doi.org/10.1038/nrcardio.2017.23
3. Morales ED, Yue Y, Watkins TB, Han J, Pan X, Gibson AM, et al. Dwarf Open Reading Frame (DWORF) Gene Therapy Ameliorated Duchenne Muscular Dystrophy Cardiomyopathy in Aged mdx Mice. J Am Heart Assoc. 2023;12.
4. Kaneko M, Yamamoto H, Sakai H, Kamada Y, Tanaka T, Fujiwara S, et al. A pyridone derivative activates SERCA2a by attenuating the inhibitory effect of phospholamban. Eur J Pharmacol. 2017;814:1–8.
5. Luraghi A, Ferrandi M, Barassi P, Arici M, Hsu SC, Torre E, et al. Highly Selective SERCA2a Activators: Preclinical Development of a Congeneric Group of First-in-Class Drug Leads against Heart Failure. J Med Chem. 2022;65:7324–33.
6. Arici M, Ferrandi M, Barassi P, Hsu SC, Torre E, Luraghi A, et al. Istaroxime Metabolite PST3093

Selectively Stimulates SERCA2a and Reverses Disease-Induced Changes in Cardiac FunctionS. J Pharmacol Exp Ther. 2023;384:231–44.
7. Arici M, Hsu SC, Ferrandi M, Barassi P, Ronchi C, Torre E, et al. Selective SERCA2a activator as a candidate for chronic heart failure therapy. J Transl Med [Internet]. 2024;22:1–13. Available from: https://doi.org/10.1186/s12967-024-04874-9
8. Rosenberg P. VDAC2 as a novel target for heart failure: Ca2+ at the sarcomere, mitochondria and SR. Cell Calcium. 2022;104.