

## **Use of induced pluripotent stem cells for the study of ion channel heart disease**

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**Research Theme/Topic: Precision Medicine - Mechanisms of Cardiac Disease**

The proposed project is part of a transcontinental project funded by the Leducq Foundation entitled: "Towards Precision Medicine with Human iPSCs for Cardiac Channelopathies". The project involves 5 international groups of absolute value, including the group of Prof. Shin'ya Yamanka, Nobel laureate for the discovery of iPSCs, the Stanford group directed by Joe Wu, the newly elected President of the American Heart Association, the group of JS Hulot in Paris, the group of Bjorn Knolmann at Vanderbilt University and Lior Gepstein of the Technion-Israel Institute of Technology, Haifa (Israel). The PhD student will have the opportunity to interact with the researchers of all the labs participating in the network, learning new techniques and dealing with different realities.

The candidate will work at the **Laboratory of Experimental Cardiology**, a space equipped with all the instruments suitable for carrying out cellular and molecular biology experiments. The research group composed by Biotechnologists and PhDs, biotechnology, medical and PhD students. The person in charge is Prof. Gneccchi, Cardiologist and PhD with extensive experience in cardiovascular research. The candidate will also be in contact with numerous Italian and, as mentioned, international research groups with which the Laboratory collaborates. Wide access also to the facility of the IRCCS San Matteo of Pavia where the Laboratory is physically located. Possibility of attending conferences or advanced training courses. During their possible stay abroad, the doctoral student will also participate in the didactic, seminar and training activities of the host laboratories.

**The primary objective of the project** is to use induced pluripotent stem cells (iPSCs) derived from patients with cardiac channelopathies, including long QT syndrome, for the identification of variants of unknown significance (VUS) and modifier genes as well as for the identification of new personalized therapies.

**Rationale:** Recent advances in DNA sequencing have revealed how human genetic variations are associated with differential health risks, disease susceptibility and drug responses. Such information should now help assess individual health risks and design personalized treatments. However, it remains difficult to understand how these genetic variations cause phenotypic alterations in pathogenesis and response to treatment. iPSC technology is emerging as promising strategy for bridging the knowledge gaps between genetic association studies and the underlying molecular mechanisms. Innovations in genome editing technologies and continual improvement of iPSC differentiation techniques are making this research direction more realistic and practical. For example, iPSC-derived cardiomyocytes (iPSC-CM) have been used to study long QT syndrome (LQTS) and other forms of inherited cardiomyopathies.

**Project structure:** The PhD student will initially learn the reprogramming techniques necessary for the generation of iPSC clones. He/she will then learn how to isolate, expand and characterize iPSC clones. In a second step he/she will learn the methodologies for the differentiation into iPSC-CM, their maintenance in culture and their molecular and electrophysiological characterization. Once autonomy in these techniques will be achieved, the student will be assigned a project that will aim to identify factors capable of modifying the clinical penetrance of hereditary cardiomyopathies and identify variants of VUS in LQTS patients. During the project, the candidate will use the latest technologies in genetics, molecular biology and cell biology and will learn how to design experiments independently and interpret their results.

**Research impact:** Patient-derived cell models are essential for studying pathophysiological processes that determine disease and for identifying markers useful for prognostic stratification. More importantly, new pathogenic mechanisms may pave the way towards the identification of personalized treatments, especially in non-responders to standard therapies.