UNIVERSITÀ DEGLI STUDI DI MILANO

DIPARTIMENTO DI BIOSCIENZE

The Cell Physiology MiLab.

December21ts, 2023

One 18 months positions is available at the cell Physiology MiLab (https://sites.unimi.it/cellphysiomilab/), immediately for enthusiastic postdoctoral fellow with a keen interest in using patch clamp electrophysiology and imaging techniques; some knowledge on trascriptomic will be considered as a plus. Loss of function (LoF) variants in GNB5 cause IDDCA syndrome whose main features include cognitive disability, epilepsy, retinopathy, and bradycardia. The latter being the primary cause of premature and sudden death in IDDCA patients. Genotype-phenotype correlation showed that carriers of truncating GNB5 variants present with the most severe form of this syndrome, while missense alleles are associated with milder phenotypic manifestations. GNB5 encodes the Gβ5 subunit, a member of the G-protein coupled receptor cascade (GPCR) that plays a pivotal role in regulating neuronal, cardiac, and retinal ion channels activity and thus cellular excitability. Gβ5 forms complexes with R7-RGS that serves as negative regulators of GPCR signalling, affecting processes such as learning, motor control, heart rate and vision. Of note, most of the pathological manifestations of IDDCA have been linked to alterations of ion channels/cellular excitability. Pathological bradycardia arises from a dysfunction in the sinoatrial node (SAN), the tissue that generates and transmits action potentials to the rest of the heart. Notably, accumulating data show that the pathological mechanism behind this syndrome implies the control of ion channels in all three main affected tissues: brain, retina, and heart. In zebrafish and in human iPSC-derived cardiomyocytes loss of GNB5 causes membrane hyperpolarization through an over-activation of GIRK channels. However, developmental defects and pathogenic mechanisms behind the plethora of phenotypes of IDDCA are largely unknown and not only attributable to GIRK channels overactivation. Here, respectful of both the budget limitation and number of Centres being involved, we will focus on the cardiac phenotype, that is the main known cause of death in IDDCA patients. Our preliminary data support the hypothesis that GNB5 controls the expression of essential genes involved in SAN development and in the modulation of ion channels activity; therefore, we hypothesize that GNB5 contributes to the IDDCA-linked bradycardia by an impairment in the development and function of pacemaker SAN cells. However, analysing human SAN cells is not a trivial task because they cannot be retrieved directly from the human heart of neither patients nor healthy people. Thus, here we propose to carry out specific molecular and functional analyses using SAN-like cardiomyocytes (SAN-like CM) differentiated from induced pluripotent stem cells (hiPSCs), which have been shown to recapitulate native SAN cells. We will compare data obtained through electrophysiology, single cells RNASeq, in SAN-like CM obtained from IDDCA patients, and healthy individuals in order to dissect molecular pathogenic mechanisms at the basis of IDDCA heart dysfunctions.

1.3 Durata del progetto: (espressa in anni, minimo 1, indicare la decorrenza ipotizzata dell'assegno, compatibilmente coi tempi della selezione) • SCADENZA PROGETTO (inserire data nel formato 27/09/2025 • 01/03/2024 1.4 Composizione del gruppo di ricerca ed eventuali collaborazioni nazionali o internazionali in atto: (unità operative e risorse umane a disposizione, distinti per qualifica e sede di servizio) Prof Andrea Barbuti, Professore associato Università degli Studi di Milano Prof Giuseppe Merla, Professore ordinario Università degli Studi di Napoli Federico II Dr Patrizia Benzoni, Ricercatore Università degli Studi di Milano.

Sincerely,
Andrea Barbuti, PhD
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