Report for the ESC First Contact Initiative Grant

Dr. Angelo G. Torrente

Current institute: Institute for Functional Genomics (IGF) - CNRS, Montpellier, France.

Host Institute: Heart Science Centre, Imperial College London, United Kingdom

Initiation of the Collaboration

I would like to thank the ESC Council on Basic Cardiovascular Science (CBCS) for selecting me as a winner of the First Contact Initiative Grant.

Thanks to this scholarship, I was able to visit the laboratory of Prof. Thomas Brand, Chair in Developmental Dynamics at the Heart Science Centre affiliated with Imperial College London. My visit was divided in two parts. Initially, I visited the laboratory of Dr. Brand for three days in September 2015. During this initial stay, Dr. Brand showed me his laboratory and gave me an update on his line of research on the Popeye domain-containing (Popdc) proteins in determining the structure and function of cardiac and skeletal muscle. I also had the opportunity to present my recent data on pacemaker activity of the sinoatrial node in sodium-calcium exchanger knockout mice (1) in a talk organized at the Imperial Centre for Translational and Experimental Medicine (ICTEM). I also met with various researchers of the Section on Cardiovascular Function, which provided me with the opportunity to develop new contacts and to learn about the exciting research environment at this institution. Subsequently, I planned together with Dr. Brand a second longer visit for a whole week that was finally set for October 2016. For this second visit, we planned several experiments, which focused on the role played by Popdc proteins in the control of sinoatrial node (SAN) pacemaking using the mouse Popdc1 null mutant as a model. My results constitute an interesting extension of the initial data obtained by Dr. Brand and will be likely used for a grant application to the Medical Research Council and form the basis for a joint publication. Moreover, thanks to these initial contacts, we are now establishing a long-term collaboration between my current laboratory (Dr. Mangoni, Institute for Functional Genomics in Montpellier) and Dr. Brand’s group, to merge my competence to study cardiac pacemaker activity and the wealth of knowledge of Dr. Brand in his functional studies of Popdc proteins.

Results

Introduction: Popdc genes encode a family of membrane proteins abundantly expressed in cardiac and skeletal muscle (2). Three isoforms, Popdc1 (also known as BVES), Popdc2 and Popdc3 display differential and complementary expression domains in the atrial and ventricular chambers and the cardiac conduction system (3, 4). All three isoforms are present in the SAN and atroventricular node (AVN), with Popdc2 presenting higher level of expression in the nodes compared to the surrounding atrial myocardium. Popdc proteins have three transmembrane domains. In the cytoplasmic part of the proteins, an evolutionary conserved Popeye domain is present, which
functions as a cAMP-binding domain system (4). While the Popeye domain structurally resembles other cAMP-binding domains, the protein sequence is highly divergent in particular in the phosphate-binding cassette (5). Proteomic analysis to identify interaction partners yielded a large list of proteins able to bind to Popdc proteins, including TREK1, CAV3, dystrophin, and dysferlin (6). Some of these proteins have been shown to be important for the pacemaker mechanism of the SAN (7). It has been proposed that Popdc proteins control membrane trafficking of electrogenic proteins in SAN myocytes. In agreement with this hypothesis, Popdc1 and Popdc2 null mutants develop a stress-induced bradycardia in an age-dependent manner (4). This phenotype in mice is similar to the sinus bradycardia and atrioventricular block discovered in patients carrying point mutations in POPDC1 and POPDC2 (7). Furthermore, knockdown of popdc1 and popdc2 genes in zebrafish are causing different degrees of AV-block, sinus exit block, cardiac arrhythmia and heart failure (6,8).

Methods, results and conclusions:

Confidential information

References