Control of cardiomyocyte differentiation and proliferation in disease and regenerative medicine

Supervisor: José António Belo, PhD
Institution: CEDOC / NMS
Webpage: http://cedoc.unl.pt/stem-cells-and-development/
Contact: email/phone: jose.belo@nms.unl.pt / +351 218803102

Location of research lab/research center:
Centro de Estudos de Doenças Crónicas (CEDOC/NMS/UNL)
Edifício CEDOC II, Rua Câmara Pestana n.º 6
1150-082 Lisboa. PORTUGAL

Summary:

Cardiovascular disease is the leading cause of death in developed countries arising mostly from dysfunction or loss of cardiomyocytes. Cardiovascular diseases, including congenital heart defects and acute heart failure, have fueled a huge market for drugs designed to prevent or limit disease symptoms and restore some life quality. Restoring function in a patient diseased heart remains however a formidable challenge, largely attributable to the limited regeneration capability of adult cardiomyocytes.

We have reported that loss-of-function of *Cerl2* in mice leads to massive increase of the heart ventricular walls caused by increased mitotic index of the cardiomyocytes at the compact myocardium. The increased numbers of cardiomyocytes in the KOs is associated with prolonged TGF-β/Nodal signaling in the heart. In humans, the *Cerl2* homolog – *DAND5* – is also associated with such defects. Indeed, we have recently identified two patients with a missense alteration in *DAND5*. We found that this mutation in h*DAND5* (and in mouse *Cerl2*) leads to a significant decreased antagonism of NODAL signaling. Recently, we have derived and characterized a *Cerl2* KO mouse embryonic stem cell (mESC) line using the available *Cerl2* KO mice in the laboratory, as well as, induced pluripotent stem cells (iPSCs) from two patients with the alteration in *DAND5*.

Using these generated Cellular tools along with other powerful State-of-the-Art technologies like CRISPR/Cas9 genome editing, organoid cultures and animal genetic manipulation tools, we aim to characterize the *in vitro/in vivo* differentiation and proliferation properties of *Cerl2/DAND5* pluripotent stem

cells-derived cardiac progenitor cells and cardiomyocytes.

Therefore, the candidate will be integrated into the research team's work to:

- Establish the fundamental roles of Cerl2/DAND5 in cardiomyocyte proliferation/differentiation;
- Investigate how these roles reflect in Cerl2/DAND5-associated heart diseases;
- Evaluate if targeting Cerl2/DAND5 function can be translated in to production of high number of high quality cardiomyocytes that can be used for regenerative medicine and drug discovery purposes.