Control of cardiomyocyte proliferation in disease and regenerative medicine

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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 (CHD) 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 mutation in *DAND5*. One of them has left-isomerism, atrial septal defect and pulmonary atresia and the other displays Tetralogy of Fallot and pulmonary atresia. Using a Nodal-dependent luciferase assay, we found that this mutation in *DAND5* (and in mouse *Cerl2*) leads to a significant decreased antagonism of NODAL signaling.

With this in mind, in this project we aim to establish *DAND5* mutant patient-derived induced pluripotent stem cells (iPSCs) to differentiate them towards cardiomyocyte lineage and study proliferation and cardiomyocyte function therein. These can then be used has a platform to test drugs that restore cardiomyocyte physiology.

The main aims of the current proposal are:

- Establish the fundamental roles of Cerl2/DAND5 in cardiomyocyte proliferation;
- 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.