ImmunoTools *special* Award 2017

Oriol Iborra-Egea, PhD-student

Supervisor: Dr. Antoni Bayés Genís

Germans Trias i Pujol Health Research Institute,
Ctra. de Can Ruti s/n, Edifici Escoles

08916 Badalona (Barcelona), SPAIN

iPSC modeling for cardiac regeneration and heart failure

In short, cardiovascular disease remains the lead cause of mortality worldwide, accounting for almost 30% of all deaths. Not only that, but it is also tightly connected to many other serious diseases such as diabetes mellitus and obesity, constituting a spreading pandemic that needs to be tackled and a heavy burden on health budgets all over the world.

In this context, myocardial infarction prompts a massive cardiomyocyte cell death, which in turn hampers contractility and leads to a maladaptive ventricle remodeling (heart failure). The emerging field of regenerative medicine holds promise to cater new therapies that could drastically improve patients' outcomes across many different disciplines, and induced pluripotent stem cells (iPSC) stand as one of the most encouraging tool to achieve this aim. iPSC come directly from reprogrammed adult cells, which acquire an undifferentiated state that allows them to divide indefinitely, together with unrestricted differentiating competence towards any other cell type.

Theoretically, the administration of iPSC could reverse this condition. iPSC would repopulate the affected region(s) of the heart, differentiate *in situ* into new functional cardiomyocytes and/or other cardiac cell types, and recover lost functions. Moreover, if the cells come from the treated patient, it would also avoid potential graft rejection.

However, this technology exists not without constraints. Current iPSC-related techniques, from taking a given patient's cells to further reprogramming and differentiation, remain unfortunately so much expensive, inefficient and time-consuming. Furthermore, iPSC ability to divide indefinitely raises many concerns as they can develop uncontrolled tumorigenesis once implanted, leading to undesired teratoma formation. This situation hinders its viability as an established therapy.

To that end, additional research is needed to polish and refine iPSC technology, as well as many dedicated studies to assess new approaches to fully exploit its capacity, avoiding current caveats.

Specifically, my PhD project look at how to combine iPSC technology with innovative cardiac tissue engineering. Engaging our group's expertise in the development of different types of scaffolds *in vitro* with iPSC technology, our goal is to achieve a scaffold embedded with iPSC -or derivatives- that could potentially help regeneration of failing hearts.

To do so, we branch out our experiments: First, we study different potential mechanisms for maturation of the cardiomyocytes derived from iPSC (iPSC-CM), mainly via mechanical and electrical stimulation that mimics their original niche within the heart. In this regard, we assess the use of mesenchymal stem cells as a potential therapeutic source, and would need several antibodies (CD14, CD29, CD44, CD45…) to analyse them and validate our experiments.

Secondly, we perform *in vivo* experiments using the swine model due to its close resemble to the human circulatory system. Thus, we can pre-clinically validate our *in vitro* results and translate them with much more confidence to the clinical scenario. Therefore, we would use HLA-ABC, HLA-II, HLA-DP, HLA-DR to validate the suitability of our treatments, as well as to perform tracking and viability experiments.

Finally, we use iPSC technology to model specific cardiovascular conditions. For instance, we use genetic engineering to induce genetic mutations to replicate certain disease phenotypes, such as hypertrophic cardiomyopathy, and compare them to a control group as they further develop and differentiate.