Stem Cell and biotherapy Team, IBPS
Pierre Joanne (PhD) & Onnik Agbulut (PhD, HDR)
pierre.joanne@sorbonne-universite.fr
onnik.agbulut@sorbonne-universite.fr

Biophysics Team, ILM
Mme Hélène Delanoë-Ayari (PhD, HDR)
helene.ayari@univ-lyon1.fr

PHD Proposal

Desmin-related cardiomyopathy is a debilitating genetic disorder characterized by the occurrence of cardiac defects evolving to dilated cardiomyopathy and heart failure. The underlying cause of this disease lies in mutations within the *DES* gene, which encodes for desmin, a crucial muscle intermediate filament protein essential for maintaining cellular structure, integrity and communication through the stabilization of several sub-cellular components such as sarcomeres, desmosomes and mitochondria. Among the classic symptoms of patients with desmin-related cardiomyopathy, cardiac conduction defects have been poorly studied. The development of induced pluripotent stem cells (iPSCs), together with genome editing and three-dimensional (3D) tissue engineering, offer new promising approaches for cardiac disease modeling and mechanistic investigation.

The thesis will involve two laboratories (thesis in co-direction) with different expertise that will be both crucial to better understand cardiac rhythms disorders linked to desmin mutation. To investigate this question, a 3D model of cardiac tissue (spheroid) will be developed through the use of cardiomyocytes derived from iPSCs of patients carrying desmin mutations and their CRISPR-Cas9 corrected counterparts. Then, the candidate will develop new software tools for the automatic, robust and fast analysis of contractility, calcium transients and conduction of the action potential in this model to characterize the impact of desmin mutations on these parameters. The candidate will also explore the relationship between force generated by spheroids measured using the deformation of an embedding substrate, the mechanical properties of these spheroids and their behavior in terms of motion kinetics and amplitude to build an automated analysis tools fully compatible with high throughput screening. Using these software tools, the candidate will then assay the role of external mechanical constraints on the tissue organization of spheroids through constrictions in microfluidic channels that induce large cell deformations. This approach will be used to question the role of desmin in the maintenance of tissue organization under mechanical stress.

Then, the candidate will build an integrative model of the disease based on all the different data types gathered by the partners of the project and especially to try to link structural defaults (sarcomere, desmosomes organization), to their consequences in force transmission, and in particular to study the coupling with rhythms disorders.

Areas of expertise of the candidate: Good programming skills in any language is required and a background in biology would be highly appreciated.