**Patient-specific induced pluripotent stem cell-derived cardiomyocytes to model, screen drugs and decipher molecular mechanisms of CPVT1 syndrome**

Yvonne Sleiman1, Marwan M. Refaat2, Valerie Scheuermann1, Melvin Scheinman3, Alain Lacampagne1, Albano C. Meli1.

1 PhyMedExp, Inserm U1046, CNRS UMR9214, University of Montpellier, Montpellier, France.

2 Cardiology Division, Cardiac Electrophysiology Section, American University of Beirut Medical Center, Beirut, Lebanon.

3 University of California, San Francisco Medical Center, San Francisco, California, USA.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a highly lethal inherited arrhythmogenic disorder predominantly caused by mutations in cardiac ryanodine receptor gene (*RYR2*). Human induced pluripotent stem cells (hiPSCs) offer a unique opportunity for disease modeling. We have identified a 25 years-old athletic woman with exercise-induced syncope associated with ventricular tachycardia (VT). Exercise stress electrocardiography revealed no improvement on the β-blocker metoprolol (METO). However, flecainide treatment was able to prevent VT. The patient was found to have a novel single mutation RyR2-D3638A. Our project aimed to derive functional cardiomyocytes (CMs) from the CPVT1 patient via hiPSCs and investigate the response to standard therapy administrated to CPVT patients as well as to a Rycal compound (S107) known to specifically stabilize the RyR2 channel.

When focusing on the intracellular calcium (Ca2+) handling in CPVT hiPSC-CMs under fluorescent confocal microscopy, we observed no preventing effect of METO on the aberrant Ca2+ transients under isoproterenol (ISO), a β-adrenergic receptor agonist, which was consistent with the clinical data. However, both S107 and flecainide applications preceding ISO were able to suppress abnormalities of the Ca2+ transients in CPVT hiPSC-CMs with reduced RyR2 Ca2+ leak and increased Ca2+ release velocity and amplitude. Co-immunoprecipitation of the RyR2 macromolecular complex showed that CPVT hiPSC-CMs exhibited higher basal RyR2 PKA phosphorylation at Ser2809 and less PP1-anchoring protein spinophilin and PP2A bound to RyR2 when compared to healthy control (HC) hiPSC-CMs. Unlike METO, S107 treatment was able to prevent the depletion of calstabin2 (FKBP12.6) a stabilizing partner of RyR2 under stress conditions which is likely associated with its stabilizing effect on the Ca2+ transients.

This work provides new evidence of CPVT modeling, drug screening and molecular mechanism deciphering using patient-specific hiPSC-CMs.