Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) to model arrhythmogenic diseases.

Pourrier M, Dou Y, Luerman G, Fedida D.

Cellular models developed to better predict proarrhythmic liability of drug candidates include commercially-available human stem cell-derived cardiomyocytes (hiPSC-CM) obtained from healthy subjects.

Cardiac safety assessment, however, should not be limited to preclinical models using “healthy” cellular systems. It is relevant to test drugs in systems recapitulating various cardiac conditions found in the general population. Similarly, modeling diseases in hiPSC-CM can be used for the discovery of novel therapies. Generating hiPSC-CM from patients is a challenging, costly and lengthy process not suitable for effective drug testing. Thus, alternative approaches are needed. Developing an assay using hiPSC-CM to model mutation-specific arrhythmogenic diseases to screen drug candidates represents a real opportunity at a time where personalized medicine is the focus of many drug safety/ discovery programs.

The objective of this study was to genetically modify hiPSC-CM (Cor.4U™) by transfecting a LQT type 2 dominant negative hERG mutation (G628S) using Xpress.4U. hERG G628S was generated by side-directed mutagenesis and tagged with the green fluorescent protein to identify successfully transfected cells. Ventricular action potentials were recorded from both transfected and non- transfected Cor.4u using the perforated patch clamp method at physiological temperatures and at stimulation frequencies of 0.5 to 1.5Hz. The effects of dofetilide (10 nM), a specific hERG channel inhibitor on AP morphology were compared between control and transfected cells. In non-transfected cells, maximum diastolic potential (MDP)= -75±3 mV, AP amplitude (APA)= 117±2 mV, APD_{90}= 332±36ms and APD_{50}= 263±29 ms (n=5). Superfusion of dofetilide resulted in a depolarized RMP (-63±5 mV), shorter APA (98±8 mV), prolonged APD_{90} (392±60ms, 18% increase) and APD_{50} (284±33ms, 8% increase) (n=5). In G628S transfected cells, RMP and APA were unchanged whereas APD_{50} and APD_{90} were somewhat increased (281±23ms and 382±29 ms, respectively (n=8). G628S cells were more sensitive to dofetilide than control cells. In dofetilide, APD_{90} and APD_{50} were increased by 71% and 23% respectively. In 4 out of 8 cells, Early after depolarizations were recorded. These results suggest that overexpression of mutated ion channels in hiPSC-CM might be used as a model of cellular arrhythmogenic diseases (e.g.LQT syndrome) to evaluate proarrhtyhmic liability or efficacy of test molecules.