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Parallel Cytotoxicity and Safety Assessment Monitoring Using Human iPSC Cardiomyocytes and Cancer Cells

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The validation of human induced pluripotent stem cells (hiPSCs) models for predictive cardiac safety testing has recently been demonstrated in publications derived from the comprehensive in vitro proarrhythmia assay (CiPA) studies. Here we combined automated patch clamp (APC), impedance and extracellular field potential (EFP) measurements to study cardiac ion channels in hiPSC-CMs. We also used impedance measurements to monitor in vitro cancer cell proliferation and cardiotoxicity effects in hiPSC-CMs following chemotherapy treatment. We will present long-term effects of compounds cyclophosphamide, adriamycin (doxorubicin) and 5-fluorouracil (CAF) aiming at understanding cardio-toxicity of oncological drugs.

Dynamic clamp is an electrophysiology technique that digitally adds real-time simulated membrane currents into patch clamped cells. This approach has been successfully used in conventional patch clamp electrophysiology to introduce an inward rectifier potassium current (IK1) into hiPSC-CMs. Increasing the amount IK1 expressed in hiPSC-CMs hyperpolarizes their membrane potential to values comparable to adult cardiomyocytes. In doing so, dynamic clamp may simulate a more "mature" hiPSC-CM phenotype model that provides a viable alternative to using scarcely available dissociated adult human cardiomyocytes. Reference compounds including nifedipine, E4031 and Bay K8644 were examined in hiPSC-CMs and their pharmacological impact on the cardiac action potential with and without IK1 dynamic clamp application will be presented. In parallel to the patch clamp experiments, the arrhythmogenicity of these three compounds and others were investigated via high throughput contractility and extracellular field potential recordings in 2D monolayers of the same iPSC-CM cell types.