Evaluation of Human iPS Cell-Derived Cardiomyocytes in High-Throughput Toxicity Screening Applications

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Failure to correctly predict adverse cardiotoxic effects of new pharmaceuticals is the major cause of compound attrition during drug development as well as for withdrawal of drugs already on the market. This is partly due to lack of relevant human models for pre-clinical testing. With recent advances in the stem cell field it is now possible to generate human iPS cell-derived cardiomyocytes (hiPSC-CM) that recapitulate the native behavior and accurately assess the pro-arrhythmic potentials of candidate drugs. At present, these cells are being actively investigated with high-throughput technology, especially through the CiPA initiative, for their potential use as a model system for complete cardiac safety screening ("beyond hERG"). In this study, hiPSC-CM (Cellartis® Cardiomyocytes) were validated in high-throughput automated patch clamp platforms; the Patchliner, SyncroPatch 96 and SyncroPatch 384PE. In addition, combined impedance and MEA-like recordings were performed using the hybrid system CardioExcyte 96 to provide complementary data for patch clamp. Cellartis Cardiomyocytes, reproducibly generated without genetic engineering or selection in a monolayer containing >80% cardiomyocytes (measured by cardiac troponin T positive cells), displayed spontaneous beating and expressed the major cardiac markers and ion channels. Voltage-gated Na+ and Ca2+ currents could be reliably recorded in these hiPSC-CM, and a large proportion of the cells expressed Na and Ca currents. NaV could be blocked by tetracaine, and CaV could be blocked by nifedipine with an IC50 in good agreement with the literature. Upon exposure to increasing concentrations of 12 CiPA Phase II Validation Study Compounds identified as High, Medium or Low risk for manifesting human TdP, the cells showed an expected ability to predict cardiotoxic effects. These data illustrate that the expected drug responses were reproduced with Cellartis Cardiomyocytes, suggesting high physiological relevance of the cells. The study confirms that the cells are suitable for use on high-throughput automated patch clamp devices and impedance/EFP platforms, providing an excellent assay for accurate drug safety testing in the light of the CiPA initiative.