Validation study for the possible usage of human iPS-derived cardiomyocytes for the safety pharmacology led by Japan iPS cardiac safety assessment (JiCSA)

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A major problem in drug development is whether toxicity and safety tests using experimental animals can successfully predict human responses to drugs. Species differences between animals and humans in several aspects sometimes result in drug developments to fail in the clinical trials. Limitations in using animal models are encouraging researchers to develop new methodologies that focus on humans. The ICH S7B guideline describes how to evaluate the ability to block the human ether-a-go-go-related gene (hERG) channel in vitro for predicting drug-induced QT prolongation which is a surrogate marker for Torsades de Pointes (TdP). However, many drugs with effects on hERG and QT prolongation but have little actual TdP risk are excluded from drug developments. Human inducible pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) have tremendous potential to improve upon the predictive power of a safety assay. We have standardized an experimental protocol to measure drug-induced changes in extracellular field potentials of spontaneously active hiPS-CMS with a multielectrode array (MEA) platform. Japan iPS Cardiac Safety Assessment (JiCSA) was organized for a large-scale validation study. The results of MEA assay for 60 compounds have shown good concordance with TdP risks which were reported in CredibleMed clinical reports. We are now collaborating with Comprehensive in vitro Proarrhythmia Assay (CiPA) in the US and will collect results from 32 blinded compounds. Significant scientific progress has been established in the usage of hiPS-CMS for safety pharmacology.