

1. *Toxicol Sci.* 2013 Dec;136(2):581-94. doi: 10.1093/toxsci/kft205. Epub 2013 Sep 19.

Refining the human iPSC-cardiomyocyte arrhythmic risk assessment model.

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Human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) are capable of detecting drug-induced clinical arrhythmia, Torsade de Pointes (TdP), and QT prolongation. Efforts herein employ a broad set of structurally diverse drugs to optimize the predictive algorithm for applications in discovery toxicology and cardiac safety screening. The changes in the beat rhythm and rate of a confluent monolayer of hiPS-CMs by 88 marketed and 30 internal discovery compounds were detected with real-time cellular impedance measurement and quantified by measures of arrhythmic beating (IB20, lowest concentration inducing = 20% arrhythmic [irregular, atypical] beats in 3 consecutive 20-s sweeps, and predicted proarrhythmic score [PPS]-IB20) or changes in beat rate (BR20, the lowest concentration inducing a reduction in beat rate of = 20% at 3 consecutive sweeps compared with the time-matched vehicle control group, and PPS-BR20). Drug-induced arrhythmic beats and reductions in beat rates are predictive of clinical arrhythmia and QT prolongation, respectively. A threshold of = 10 μ M for class determination results in 82% in vitro-in vivo concordance for TdP prediction and 91% sensitivity for non-TdP arrhythmia detection, or 83% and 91% if clinically efficacious plasma (effective serum therapeutic concentration [C_{eff}]) values are incorporated. This human cardiomyocyte arrhythmic risk (hCAR) model provides greater predictivity for torsadogenicity in humans compared with either human ether-a-go-go-related gene (hERG) inhibition (75%) or QT prolongation (81%). The concordance of beat rate reductions to predict clinical QT prolongation is 86%, or 87% when C_{eff} is considered, which is greater than a hERG signal (80%). Further, arrhythmic beats resulting from cytotoxicity were identified by a distinct arrhythmic beating pattern, which occurred after the onset of cytolethality. This hCAR assay showed increased performance over existing preclinical tools in predicting clinical QT prolongation, arrhythmia, and TdP. Thus, hiPS-CMs are a relevant cell system to improve evaluating cardiac safety liabilities of drug candidates.

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