

1. *Toxicol Sci.* 2011 Sep;123(1):281-9. doi: 10.1093/toxsci/kfr158. Epub 2011 Jun 20.

Estimating the risk of drug-induced proarrhythmia using human induced pluripotent stem cell-derived cardiomyocytes.

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Improved in vitro systems for predicting drug-induced toxicity are needed in the pharmaceutical and biotechnology industries to decrease late-stage drug attrition. One unmet need is an early screen for cardiotoxicity, which accounts for about one third of safety-based withdrawn pharmaceuticals. Herein, the first published report of a high-throughput functional assay employing a monolayer of beating human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) is described, detailing a model that accurately detects drug-induced cardiac abnormalities. Using 96-well plates with interdigitated electrode arrays that assess impedance, the rhythmic, synchronous contractions of the iPSC-CMs were detected. Treatment of the iPSC-CMs with 28 different compounds with known cardiac effects resulted in compound-specific changes in the beat rate and/or the amplitude of the impedance measurement. Changes in impedance for the compounds tested were comparable with the results from a related technology, electric field potential assessment obtained from microelectrode arrays. Using the results from the set of compounds, an index of drug-induced arrhythmias was calculated, enabling the determination of a drug's proarrhythmic potential. This system of interrogating human cardiac function in vitro opens new opportunities for predicting cardiac toxicity and studying cardiac biology.

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