Developing a High-throughput Platform for Drug Toxicity Screening

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Cardiotoxicity accounts for a third of withdrawn pharmaceuticals, hence evaluating drug compounds for cardiotoxicity is essential in drug development. However, primary human cardiomyocytes are not easily obtained and substantial differences between human and animal genomes have resulted in numerous tests failing to correlate drug toxicity when advancing from animal studies to human clinical trials, wasting precious resources. Currently used in vitro systems such as patch clamping and impedance assays are costly or low-throughput. Hence this study aimed to develop a novel high-throughput human model for cardiotoxicity studies using human induced pluripotent stem cell (iPSC)-derived cardiomyocytes. Human iPSCs were differentiated into highly enriched cardiomyocytes which exhibited spontaneous contraction and expressed cardiac marker proteins such as Actinin and cTnT. Functional cardiomyocytes were plated down in 384-well plates and treated with various drugs of known clinical cardiac risk, and their functional endpoints were tracked automatically. The platform developed for toxicity testing yielded results which matched clinical trials, with the cardiomyocytes displaying concentration-dependent response in beating frequency and contraction amplitude for a range of drugs. Several drugs known to cause torsades de pointes arrhythmia, including Cisapride, Dofetilide and Quinidine, resulted in a significant decrease in cardiomyocyte contraction speed and amplitude at low concentrations, suggesting that the assay can accurately predict drug-induced toxicity and detect functional abnormalities. Furthermore, the platform developed was low-cost and allowed for high-throughput screening of multiple compounds, hence making it a sensitive and efficient platform of clinical relevance.

Awards Won:

Fourth Award of $500

National Anti-Vivisection Society: First Award of $5,000

NASA: Second Award of $750