Title: Development of predictive *in vitro* assays for cardiovascular toxicity using iPSC derived cardiomyocytes

Background: According to Laverty and co-workers (2011), 27% of drugs fail to reach phase I due to cardiovascular liability and up to 45% of drug withdrawals post approval are due to cardiovascular toxicity. Cardiovascular liability may lead to the unnecessary use of toxicology animal models, present a risk to clinical trial subjects, and in the case of post approval withdrawals, can lead to clinical complications in patients. Current in vitro strategies for detecting cardiotoxicity are ineffective in capturing the effects of chronic cardiotoxicity and structural toxicants and rely heavily on the acute electrophysiological effect of compounds in less physiologically relevant platforms, e.g. ion channel assays or on ex vivo animal tissue preparations. The use of human iPSc derived cardiomyocytes as a predictive model for cardiovascular toxicity has been shown by numerous scientific publications and consortiums across multiple sites, including efforts by JICSA, NIH and CiPA.

Aim: To develop predictive assays for cardiovascular toxicity using iPSC derived cardiomyocytes

Methods: iPSc derived cardiomyocytes were obtained from Cellular Dynamics International and grown in accordance with manufacturer's instructions. Cells were exposed to several prototypic compounds and endogenous factors, such as endothelin-1 and Angiotensin II. The effect of these insults was assessed by both functional (Calcium flux and contraction mediated shape change) and structural (sarcomeric organisation, viability, cell morphology) endpoints.

Results: iPSc derived cardiomyocytes formed a spontaneously beating syncytium within 5 days, albeit with an immature phenotype. These cells accurately predicted the effects of the standard chronotropes used as well as accurately predicting the effect of the structural toxicants used. In its current format, the model was unable to capture any inotropic or lusitropic effect.

Conclusions: Multiparametric assays using iPSc derived cardiomyocytes show promise in predicting both structural and chronotropic effects of putative drugs, however further work is needed to predict inotropy. This may be resolved by using alternative detection methods, or maturing the cells, and assessing for indicative properties such as a positive force frequency relationship (Chan *et al*, 2013; Nunes *et al*, 2013).

Further work: Further work will focus on both the maturation of this model to increase its predictivity as well as testing greater numbers of well annotated cardiovascular toxicants.

References:

Laverty *et al*., (2011) How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines? **Br J Pharmacol**, 163, 675-693. 10.1111/j.1476-5381.2011.01255.x

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