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Characterization of a mature human 3D cardiac cell system

Background: Cardiovascular disease is currently the leading cause of mortality in high- and middle-income countries, and it is predicted that by 2020 it will be the leading cause of death worldwide. Not only are cardiovascular complications prevalent due to disease but also as both on and off-target effects of a multitude of prescribed drugs. At present, animals that harbour species variability and human embryonic stem cell-derived cardiomyocytes, which tend to be immature cells and not fully representative of an adult phenotype, are used to model cardiac disease and toxicity in humans.

Results: To overcome the use of animal models and immature cells we have developed a 3D cardiac spheroid system comprising of human cardiomyocytes, endothelial cells and fibroblasts that recapitulates the beating rate and displays signs of structural maturation when visualized by immunofluorescence and electron microscopy, more demonstrative of an adult human heart. Mass spectrometry analysis showed an increase in structural proteins such as □-actinin and MYL2 as well as an increase in RyR2, SERCA and PLN, proteins involved in contraction upon maturation. Fluo-4 analysis showed a response to stimulation by caffeine and inhibition to thapsigargin indicating a functioning sarcoplasmic reticulum comparative to mature cells. Doxorubicin dosing displayed a concentration dependent decrease in cell viability and structure.

Conclusion: This highly reproducible system aims to provide a more relevant human adult-like cardiovascular system that can be used for the study of disease and cardiotoxicity. It will allow us to overcome species variability and reduce the number of animals used in cardiovascular research and toxicity studies. We are now able to use this system, which is viable for ten weeks, to study structural and functional changes in mature human cardiac cells and carry out repeat dose studies to investigate both acute and chronic incidences of cardiac disease and toxicity.