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Development of an *in vitro* platform using the human primary cardiomyocyte work loop assay to screen for drug-induced effects on cardiac contractility

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Drug-induced changes in cardiac function is a common cause of compound attrition. A decrease in cardiac contractility reduces perfusion to vital organs, while drug-induced increases may lead to increased workload and oxygen demand, both of which can lead to increased mortality. The significance of adverse drug effects on cardiac contractility is often dependent on the safety margin. Available *in vitro* assays are poorly predictive of the concentrations that may affect contractility in humans and furthermore, current *in vivo* contractility measurements are often invasive, resource/time consuming, low throughput and indirect. Therefore, there is a need for more predictive *in vitro* assays that have a higher throughput than available assays. We have demonstrated that the Work Loop cardiac contractility assay is more predictive of human findings than existing assays. We have also recently demonstrated that the Work Loop cardiac contractility assay is highly predictive of inotropy risk to man. Recently we have expanded this investigation to determine whether the cardiomyocyte Work Loop assay had the potential to provide a predictive, higher throughput model of heart muscle dynamics to assess inotropic effects. Development of a human heart primary cardiomyocyte contractility assay could greatly improve the understanding of the human relevance of non-clinical findings. We have developed novel isolation protocols for adult human cardiomyocytes. The myocytes retain rod-shaped striated morphology, contracting in response to field electrical stimulation. We have developed stable cardiomyocyte work loop assay protocols which remain stable and enable cumulative concentration drug responses to be applied. To characterize adult human cardiomyocyte contractility, we are assessing a range of reference inotropic agents and effective concentrations compared with those tested in the clinic. The Work Loop assay has the potential to be a new approach to the detection of inotropic drug effects on cardiac contractility. Assays that provide greater concordance with man are crucial in the assessment of cardiac safety in drug development.

Biography

Mayel Gharanei has completed his PhD on the investigation of the cardiotoxicity of doxorubicin and strategies for adjunctive cardio protection. During his PhD, he worked on the optimization of the cardiac work loop technique for the safety assessment of pharmaceutical compounds. During his Postdoctoral research, he undertook dedicated studies on the development and validation of the cardiac rat papillary muscle and human trabeculae muscle work loop technique. He is working as the Lead Research Scientist at InoCardia where he supervises research staff and projects associated with testing pharmaceutical compounds on rat papillary and human trabeculae muscle mechanics. As a Research Fellow at Coventry University, he is supervising PhD and Masters by Research students in the field of Cardiotoxicity, myocardial ischemia-reperfusion injury, cardio protection, obesity, aging and development and validation of novel clinically relevant cardiovascular non-clinical assays.

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