

The Effect of Doxorubicin on Cardiomyocytes derived from Human iPS Cells

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Background and aim: Specific tissue lineage differentiation of embryonic stem (ES) cells as well as induced pluripotent stem (iPS) cells can serve as an *in vitro* organ toxicity testing tool other than application in cell transplantation and disease modelling outcomes. Besides giving options for effectively checking large amounts of toxicants and chemicals, *in vitro* toxicity using pluripotent stem cells gives an added advantage for refinement, reduction and replacement of use of animals. Our efforts, in EU project- DETECTIVE (Detection of endpoints and biomarkers for repeated dose Toxicity using *in vitro* systems) aims to respond to the urgent need for development of repeated dose *in vitro* toxicity test methods to ultimately investigate and validate human biomarkers.

Demand: The general long term use of cosmetics and chronic disease treatments, from past experience, have led to drop out several commonly used chemicals after human usage, in this context, *in vitro* models for assessment of long-term effects (Repeated-dose) can be helpful by prevalidation procedures.

Methods: To access the repeat dose toxicity of doxorubicin using pluripotent stem cells, we use (>98%) pure population of hiPS derived cardiomyocytes and subject them to 1) functional readout using xCELLigence impedance scoring, to achieve the action potential and return characterize chemical by variation caused in amplitude and beating frequencies. 2) by generating a toxicogenomic signatures and look for effective marker genes that can optimally act as predictive biomarker.

Results and conclusion: In our report, we studied the effect sub lethal repeat doses of doxorubicin. We observed that the repeated dose of doxorubicin resulted in a long term arrhythmicity within the beat rate and/or the amplitude of the impedance measurement. Notably, Several genes from cardiac specific ion channels were found to be dysregulated at significant levels. This approach of *in vitro* repeat dose toxicity offers high predictability and accuracy with reduced duration of testing and can provide an alternative to the classical animal testing schemes.

