An All-Human Model for the Evaluation of Cardiotoxicity in hiPSC-Derived Cardiomyocytes

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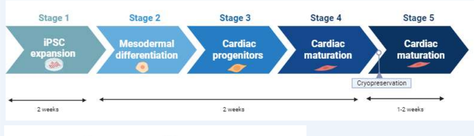
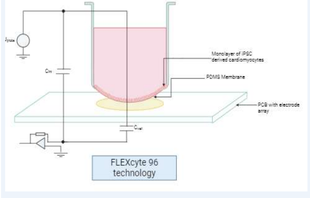
Introduction

- Cardiac contractility evaluation using human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) has recently attracted much attention as a preclinical cardiotoxicity predictive model.
- We present a xeno-free human pluripotent stem cell-derived cardiomyocyte model that allows for the prediction of both acute and chronic adverse effects on human cardiomyocyte function.
- The resulting cardiomyocytes exhibit the expression of cardiac-specific markers such as Troponin, MLC and Alpha actin and display electrophysiological properties that validate their status as functional and mature cardiomyocyte.
- We investigated the relationship between contraction parameters and beating rates of YBLiCardio by directly measuring the contraction force and compared the effects of ion channel drugs (Nifedipine, Lidocaine, E-4031 and Isoproterenol) on contraction parameters.
- Our findings reveal that YBLiCardio cells provide a valuable model for studying cardiotoxicity and drug responses, particularly in the context of contractility and arrhythmias, thus contributing to the advancement of drug safety evaluation.

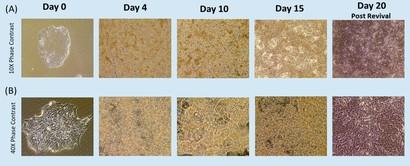
Methodology



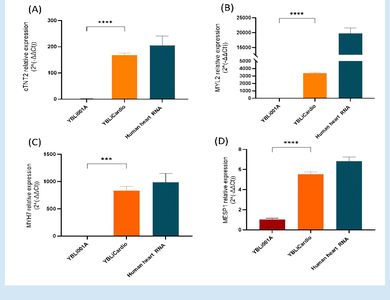


Deflected by the weight of the cell culture medium on top of the cell-membrane composite material, rhythmic contraction of the cells leads to a dynamic decrease of deflection, which is monitored by means of capacitive distance sensing.

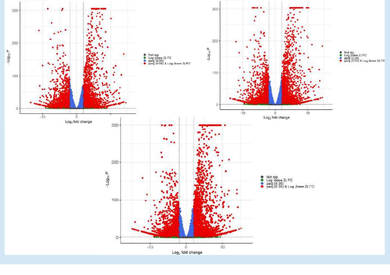
Results

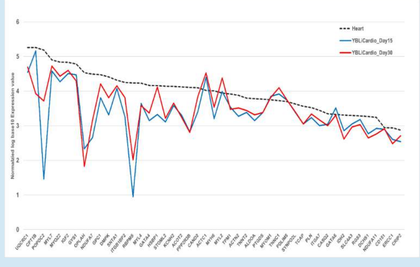


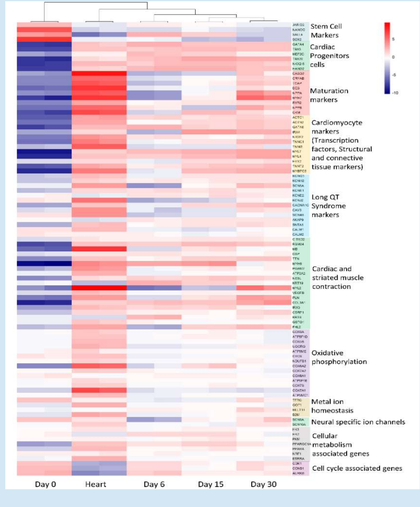
Panel A: Representative images of cardiomyocyte differentiation from hiPSCs (A)10X; (B) 40X at different day intervals.



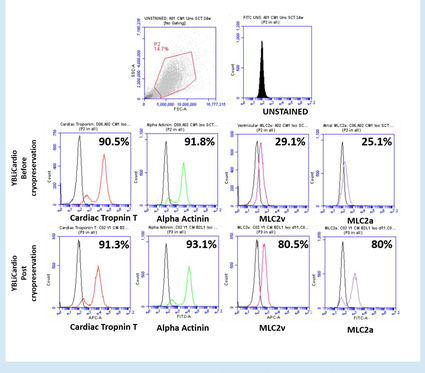
Panel B: Gene expression of Cardiomyocytes genes. Graph showing the expression of cardiac related genes A) CTNT2, B) MYL2, C) MYH7, D) MESP1.



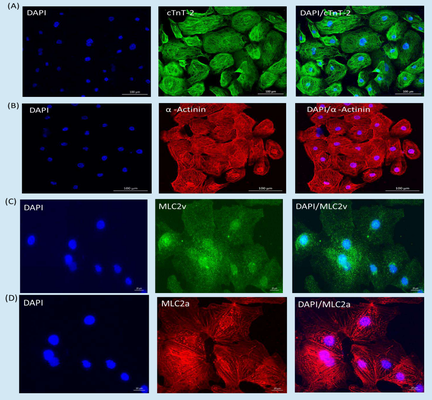




Panel C: Data from RNA Sequencing: A) Volcano plot of expressed RNA at different time points B) Heat map illustrating up-and down-regulated genes from each pairwise cluster comparison. C) Genomic expression profile for YBLiCardio compared with that of adult human cardiac tissue.

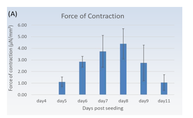


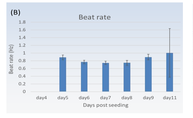
Panel D: Flow cytometric analysis of YBLiCardio demonstrates the expression of cardiac markers such as Cardiac Troponin, Alpha-Actinin, MLC2v, and MLC2a before and after cryopreservation



Panel E: Confocal images of YBLiCardio showing expression of cardiac-specific markers

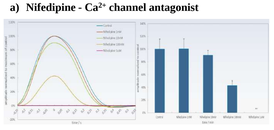
A) Time-to-Assay and basic beating characteristics



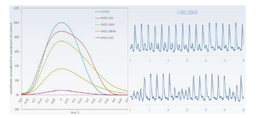


B) Acute compound reactions to gold-standard compounds

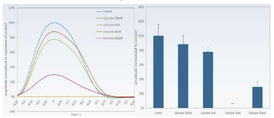
a) Nifedipine - Ca^{2+} channel antagonist



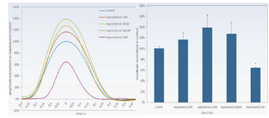
c) E-4031 - K+ channel antagonist, hERG blocker



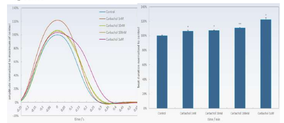
b) Lidocaine (Na^{+} antagonist)



d) Isoproterenol - β-adrenergic agonist

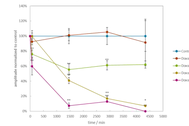


e) Carbachol (muscarinic ACh receptor agonist) Atrial-specific

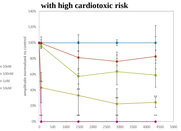


C) Chronic compound reactions to Cardiotoxic compounds

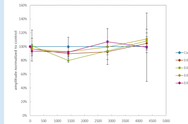
a) Doxorubicin - Gold standard cardiotoxic tool compound (anthracycline)



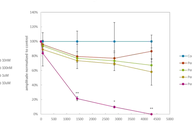
b) Sunitinib: Tyrosine Kinase Inhibitor (TKI) with high cardiotoxic risk

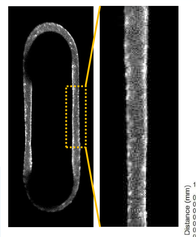


c) Erlotinib: Tyrosine Kinase Inhibitor (TKI) with low cardiotoxic risk

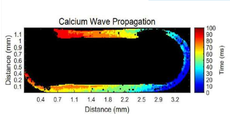


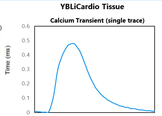
d) Pentamidine: hERG-trafficking blocker with high cardiotoxic risk

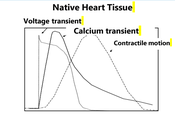


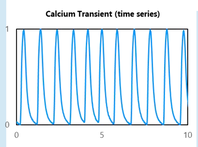


YBLiCardio tissues display synchronous contractions, indicative of well-assembled and highly aligned cardiac structure









Conclusion

1. The expression of cardiac-specific markers and gene expression profile of YBLiCardio validate their status as functional and mature cardiomyocytes.
2. YBLiCardio cells serve as a robust tool for safety assessment, especially in the context of contractility and arrhythmias.