

CiPA validated iPSC-derived cardiomyocytes: A power tool in Drug Safety and Discovery

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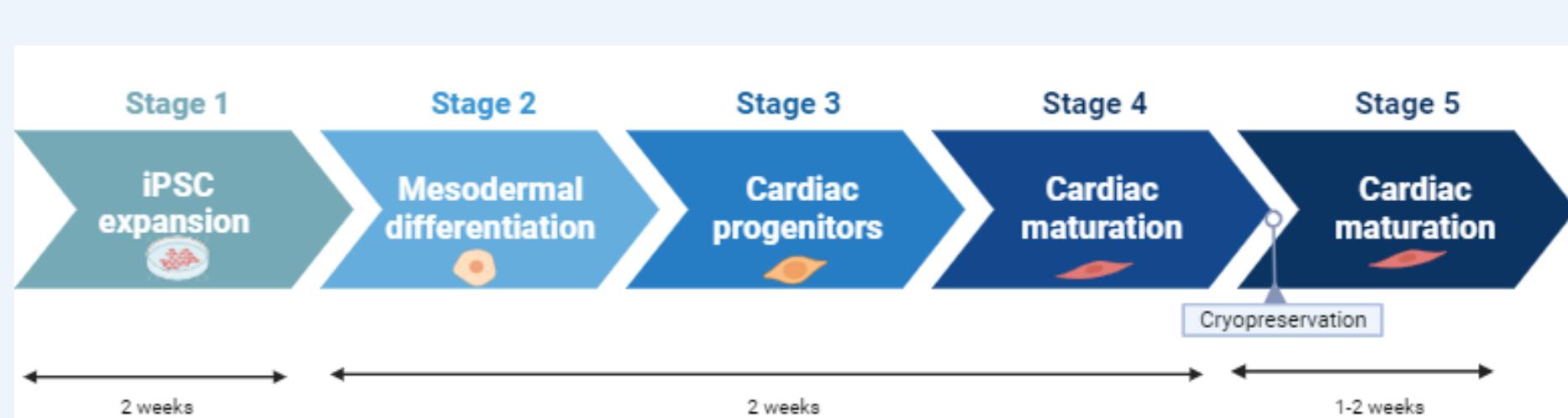
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Introduction

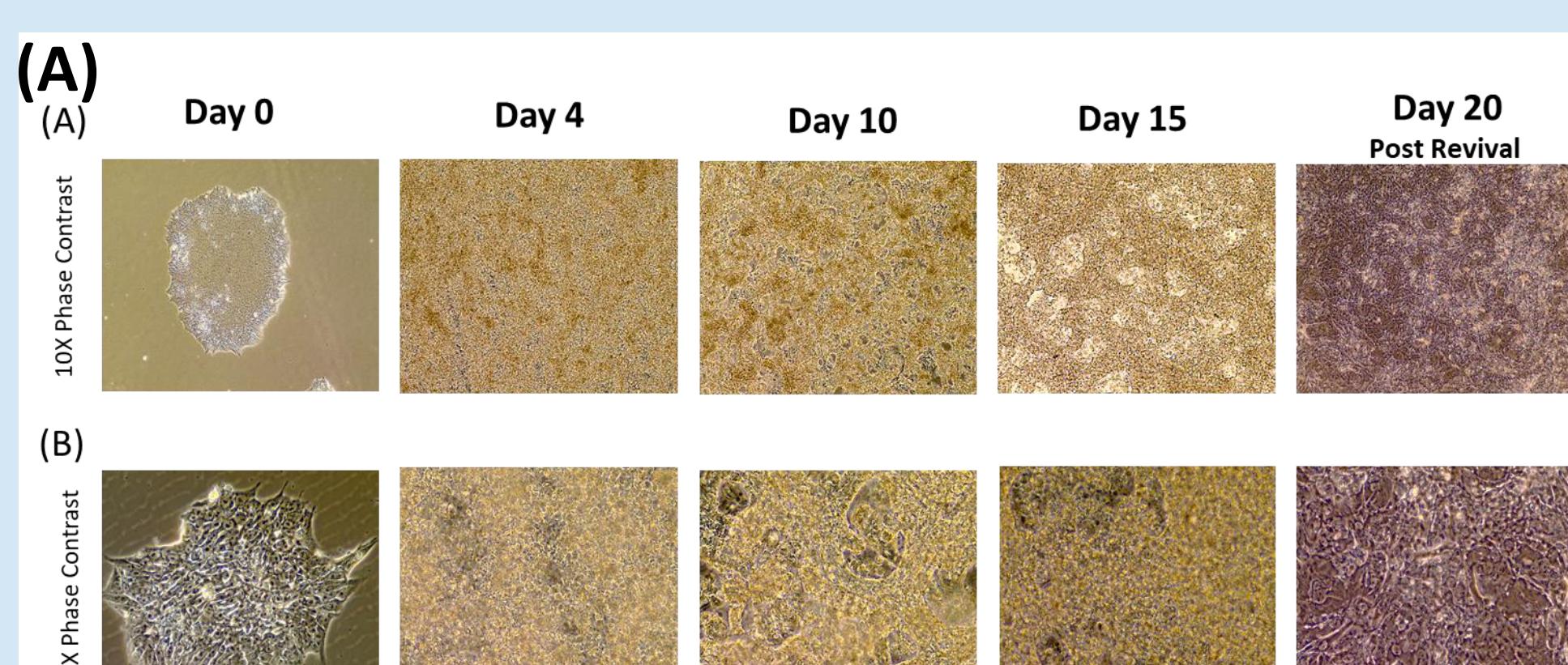
- Cardiotoxicity manifests as electrophysiological, contractile, and structural disturbances, leading to severe clinical outcomes such as proarrhythmia, heart failure, and cardiomyocyte damage and loss.
- Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) present a promising in vitro model for predicting cardiotoxicity across different toxicity profiles.
- YBLiCardio was validated for both acute and chronic toxicity assessments, including the Comprehensive in vitro Proarrhythmia Assay (CiPA), which provides an alternate proarrhythmic risk assessment rather than relying solely on clinical QT interval measurements.
- Our cells responded to all compounds as expected based on HESI CiPA reference data, confirming their suitability for in vitro cardiac safety testing and in vitro proarrhythmic risk assessment for new drug candidates.

Methodology

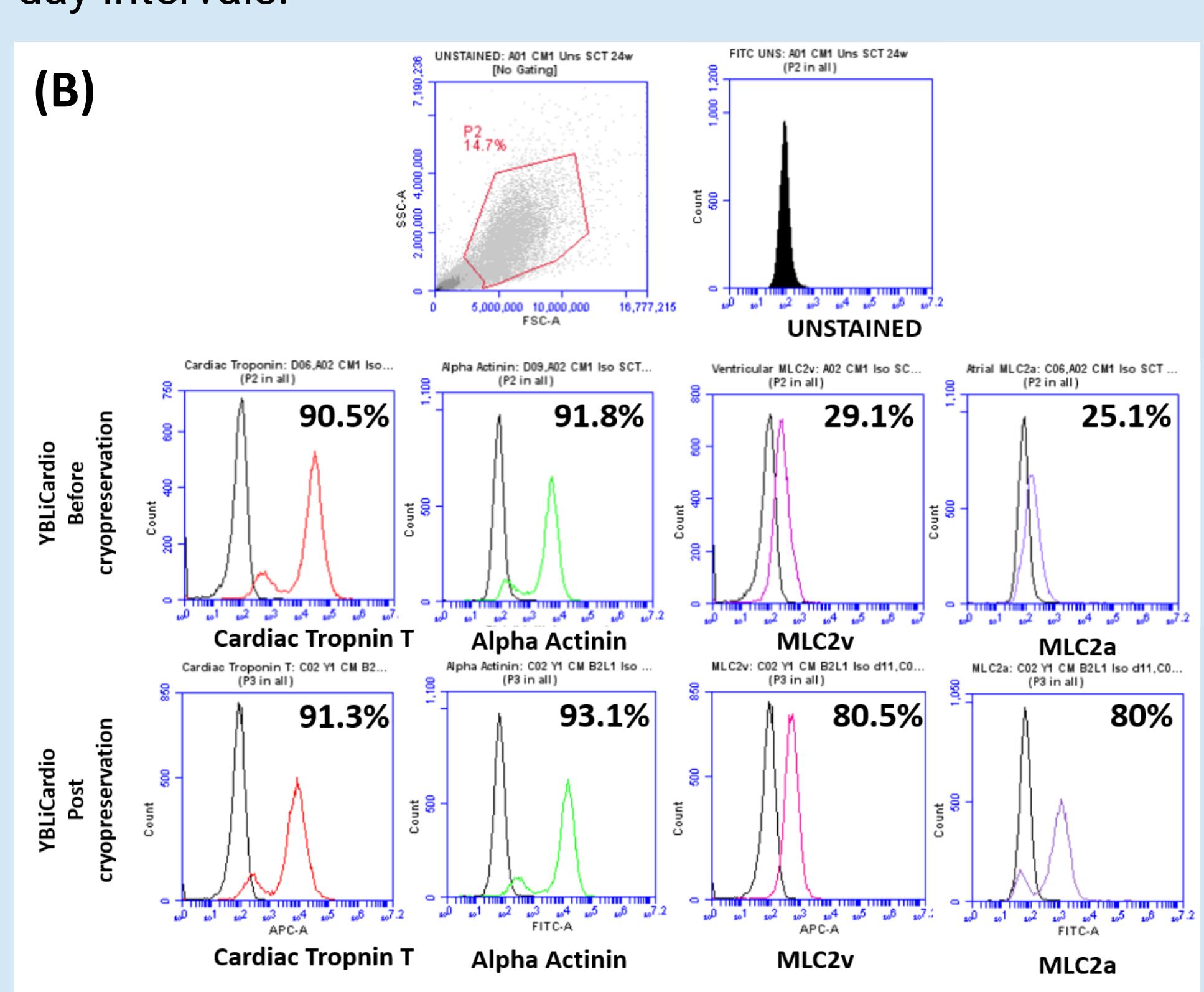
We cultured and expanded YBLi001 hiPSCs in STEMCELL technologies' mTeSR Plus medium and seeded 8×10^5 cells per well to generate ventricular cardiomyocytes using carefully curated in-house media. Cryopreserved cardiomyocytes were revived in a curated media that aids the maturation of cardiomyocytes showing a spike in the cardiac troponin T2 expression with prolonged culture.



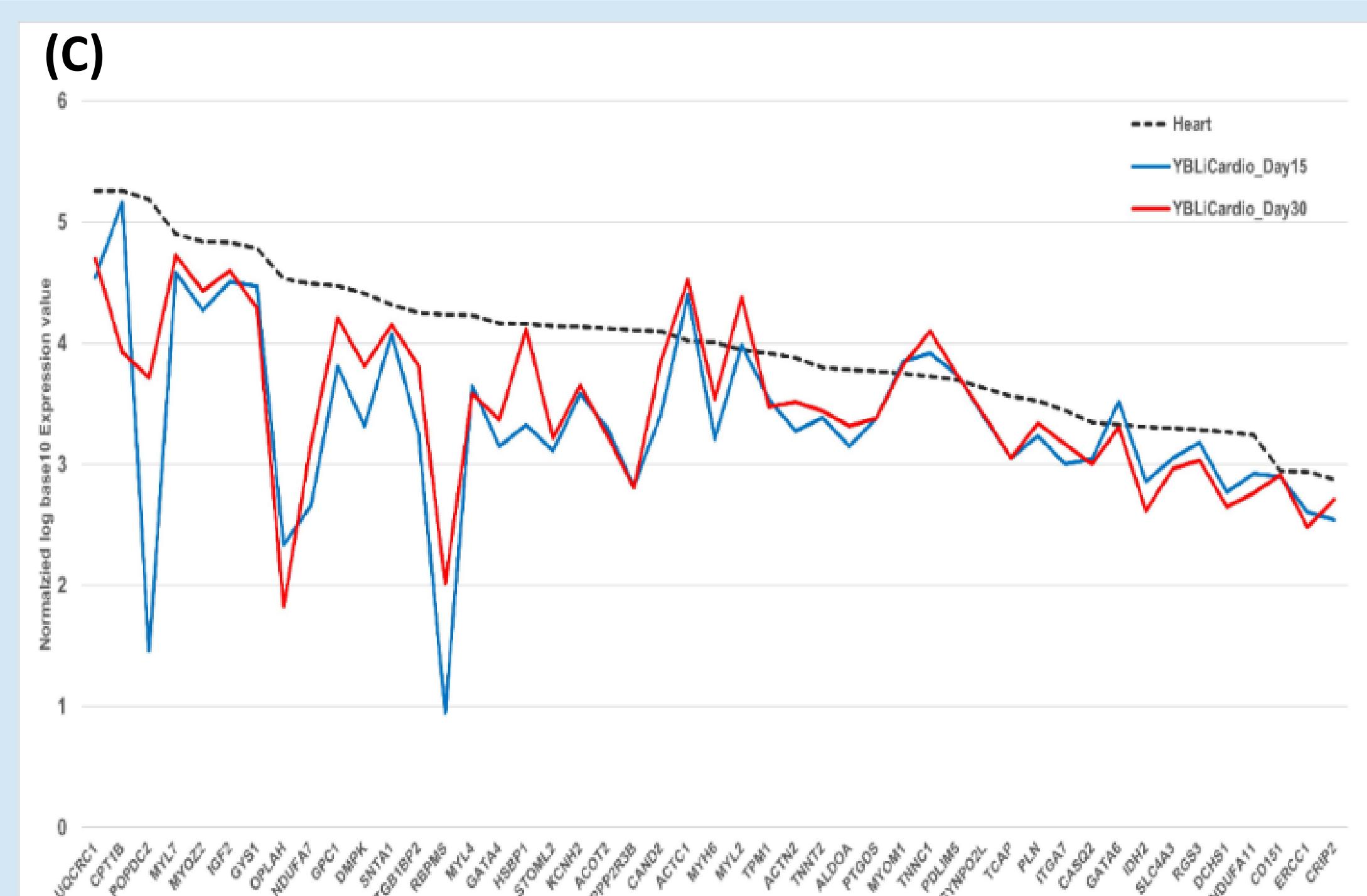
Results



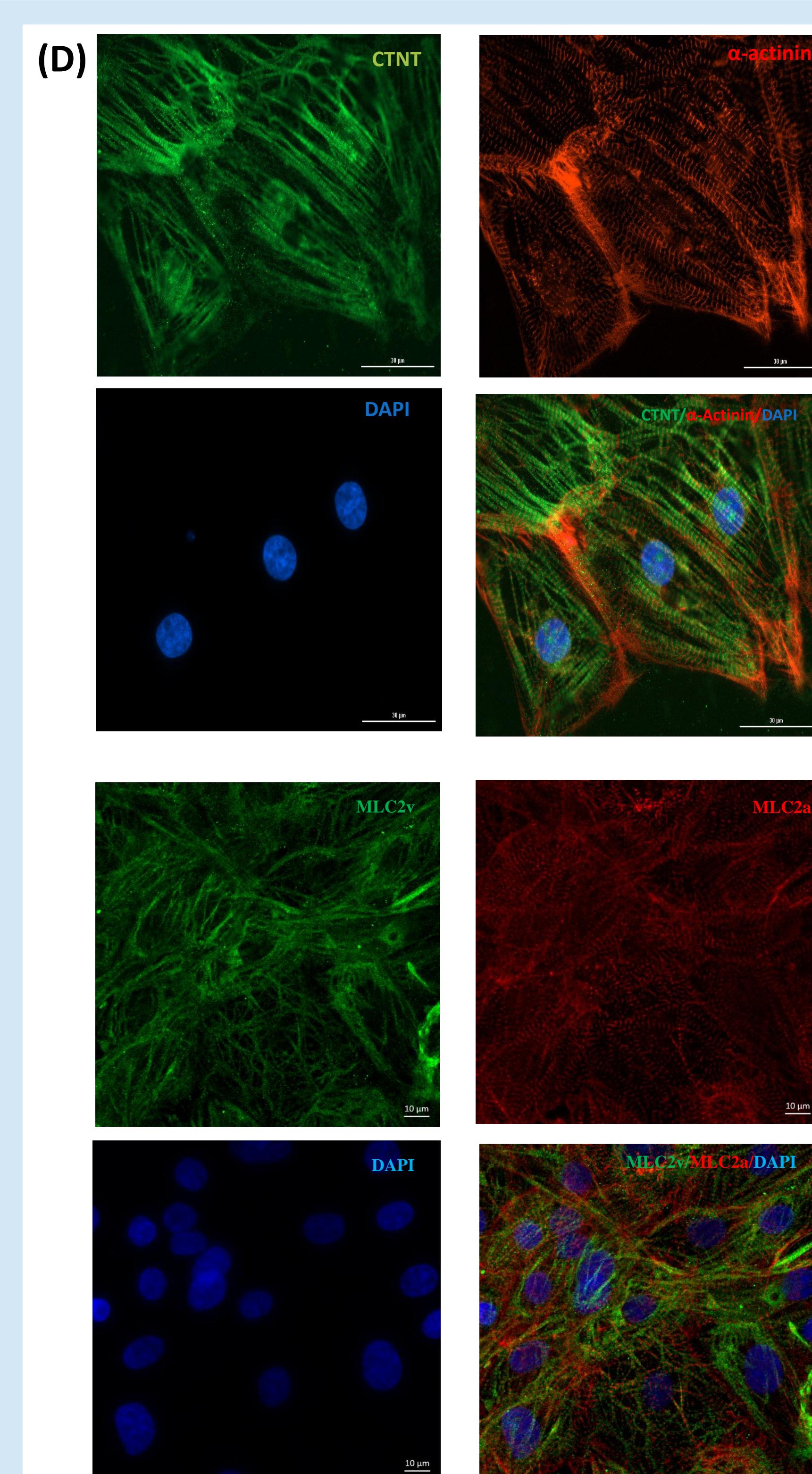
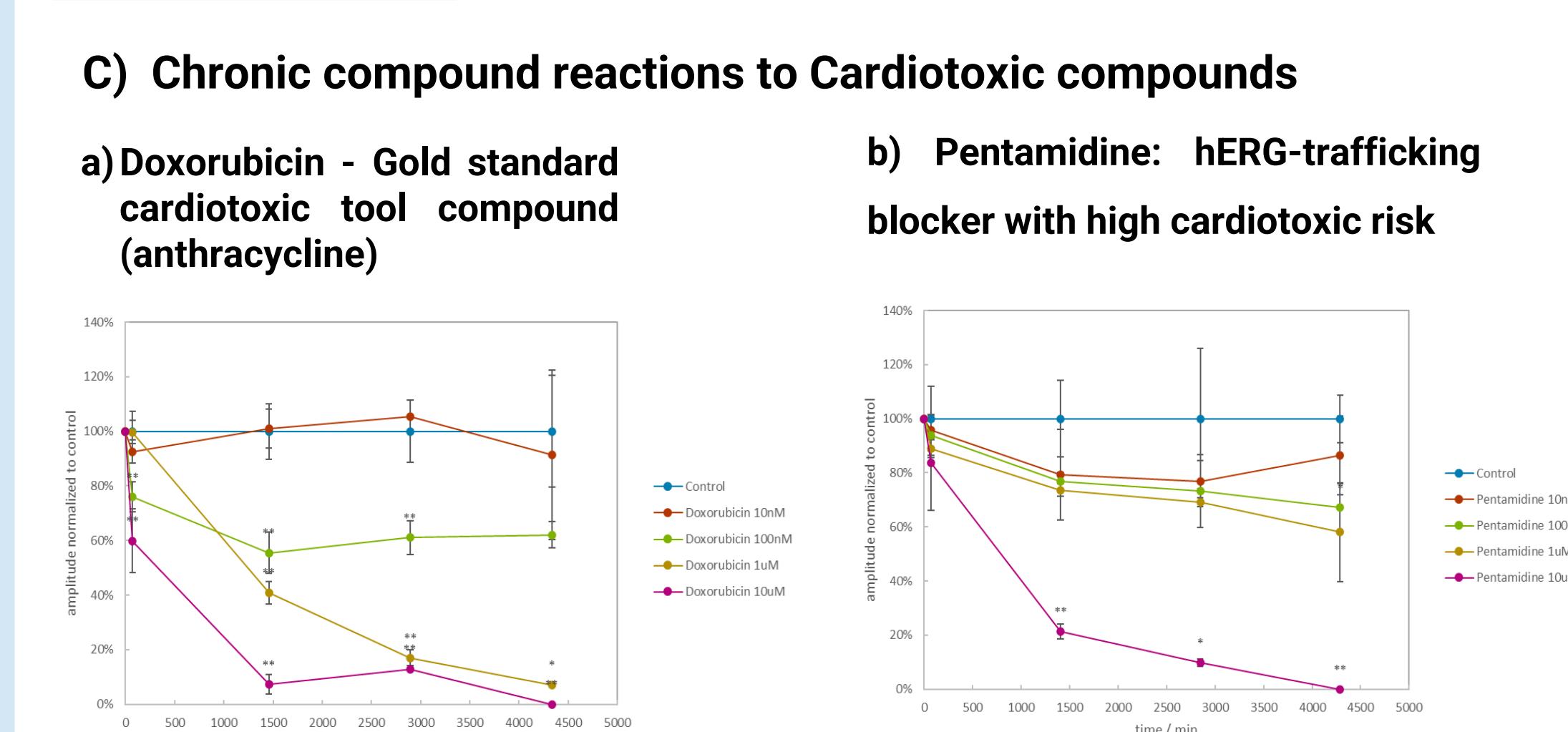
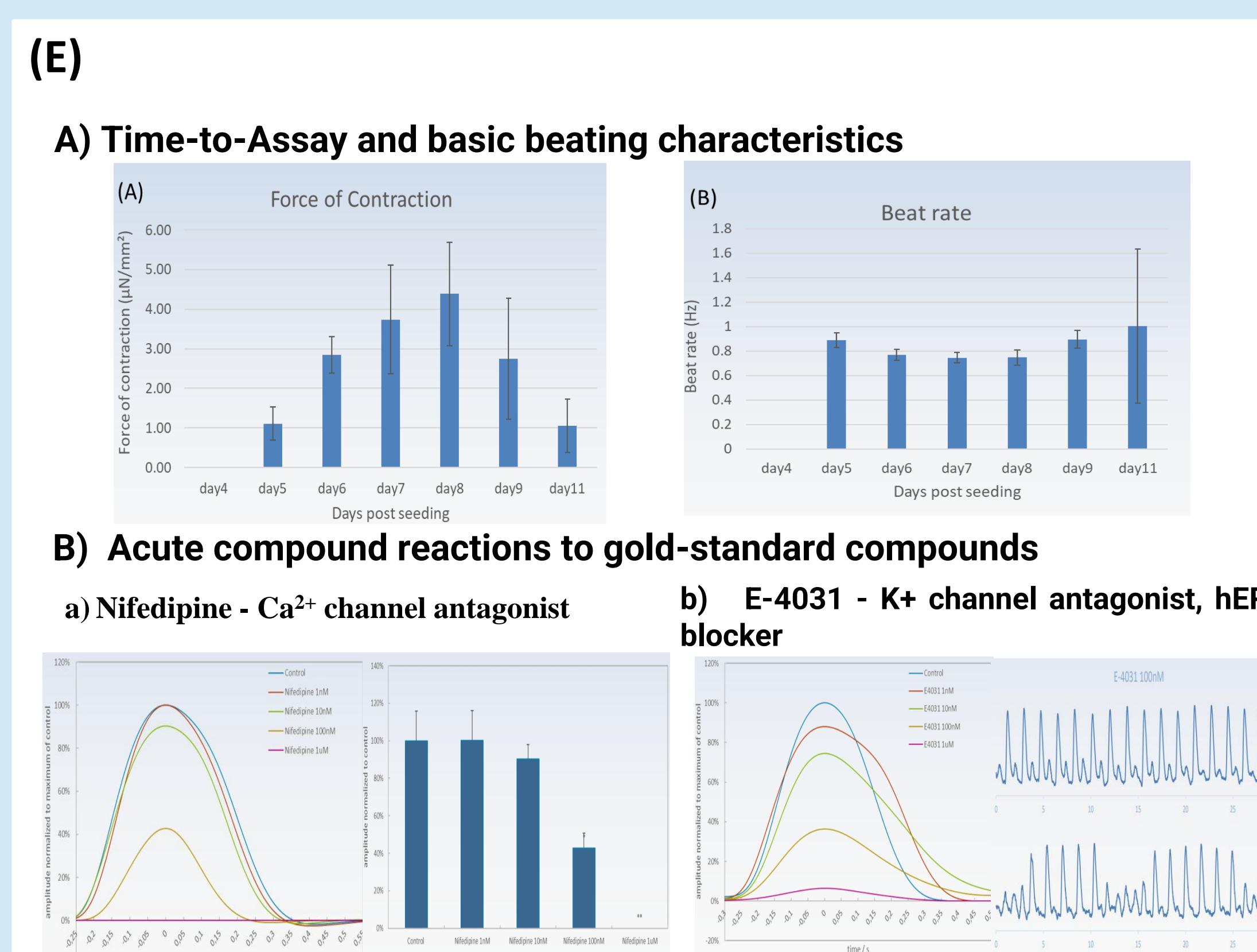
Panel A: Representative images of cardiomyocyte differentiation from hiPSCs (A)10X; (B) 40X at different day intervals.



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

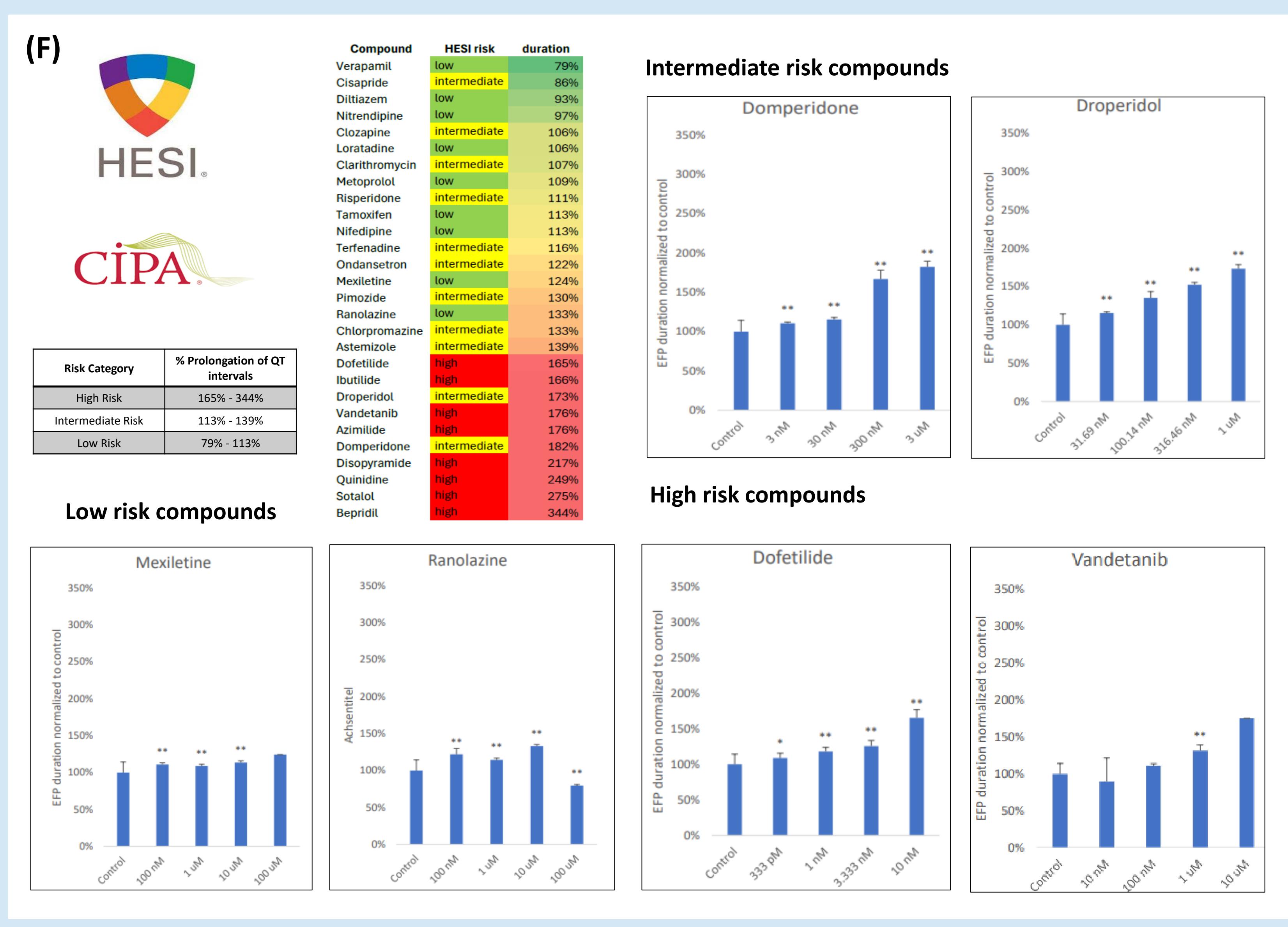


Panel C: Genomic expression profile for YBLiCardio compared with that of adult human cardiac tissue.



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

Panel E: Electrophysiological assessment of YBLiCardio:
A) Contraction analysis recorded force of contraction and beating rate.
B) Acute compound reactions to gold-standard compounds
C) Chronic reactions to cardiotoxic compounds The y-axis denotes the normalized beating amplitude, while the x-axis represents the logarithmic scale of drug concentrations applied.



Panel F: CiPA Study:
To assess the predictive power of YBLiCardio, we conducted CiPA testing with all 28 compounds from the CiPA panel across four concentrations. Representative data denotes that YBLiCardio cells responded to all compounds in full accordance with the effects expected from the results from the HESI CiPA study

Conclusion

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.