

Summary

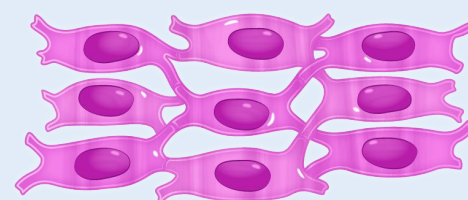
Our vision is the establishment of a comprehensive *in vitro* platform that helps drug hunters to make confident, early decisions about cardiac risk.

We have established a multi-tiered platform that enables a mechanistic and functional assessment of cardiovascular toxicity across a spectrum of key biological processes with varying levels of translational value.

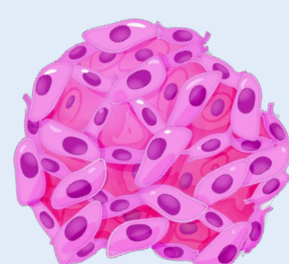
- Cell Line Models (Box 1 and 2)**
- Simple, fast, high-throughput*
- Manual/automated patch clamp (box 1), fluorescence assays, radioligand binding, and trafficking readouts (box 2).
- Suitable for early identification of ion-channel block or trafficking interference.
- Useful for defining mechanistic electrophysiology risk and guiding chemistry.



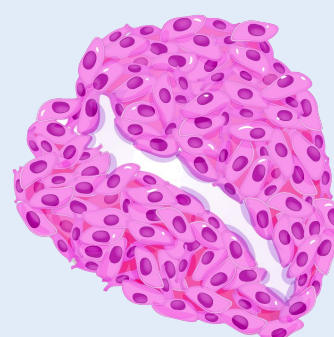
- 2D hiPSC-Cardiomyocyte Models (Box 3)**
- Moderate complexity, scalable, functional*
- Action and field potential recordings, calcium transients, contractility, and viability.
- Suitable for assessing functional cardiac effects like repolarization delays or beat instability.
- Useful for linking ion-channel effects to whole-cell human physiology.



- 3D hiPSC-Cardiomyocyte Spheroids (Box 4)**
- Higher complexity, mid-throughput*
- Measures field potential profiles, viability, mitochondrial function, and calcium dynamics in 3D tissue-like structures.
- Suitable for detecting structural and meta-bolic cardiotoxicity.
- Useful for distinguishing functional vs structural injury mechanisms.



- Human Heart Organoids: Cardioids (Box 5)**
- Most complex, organ-like, high biological relevance*
- Self-organized 3D cardiac microtissues with multicellular organization and emerging chamber-like features.
- Suitable for studies requiring tissue-level context and multicellular interaction.
- Useful to identify complex cardiotoxicity phenotypes.

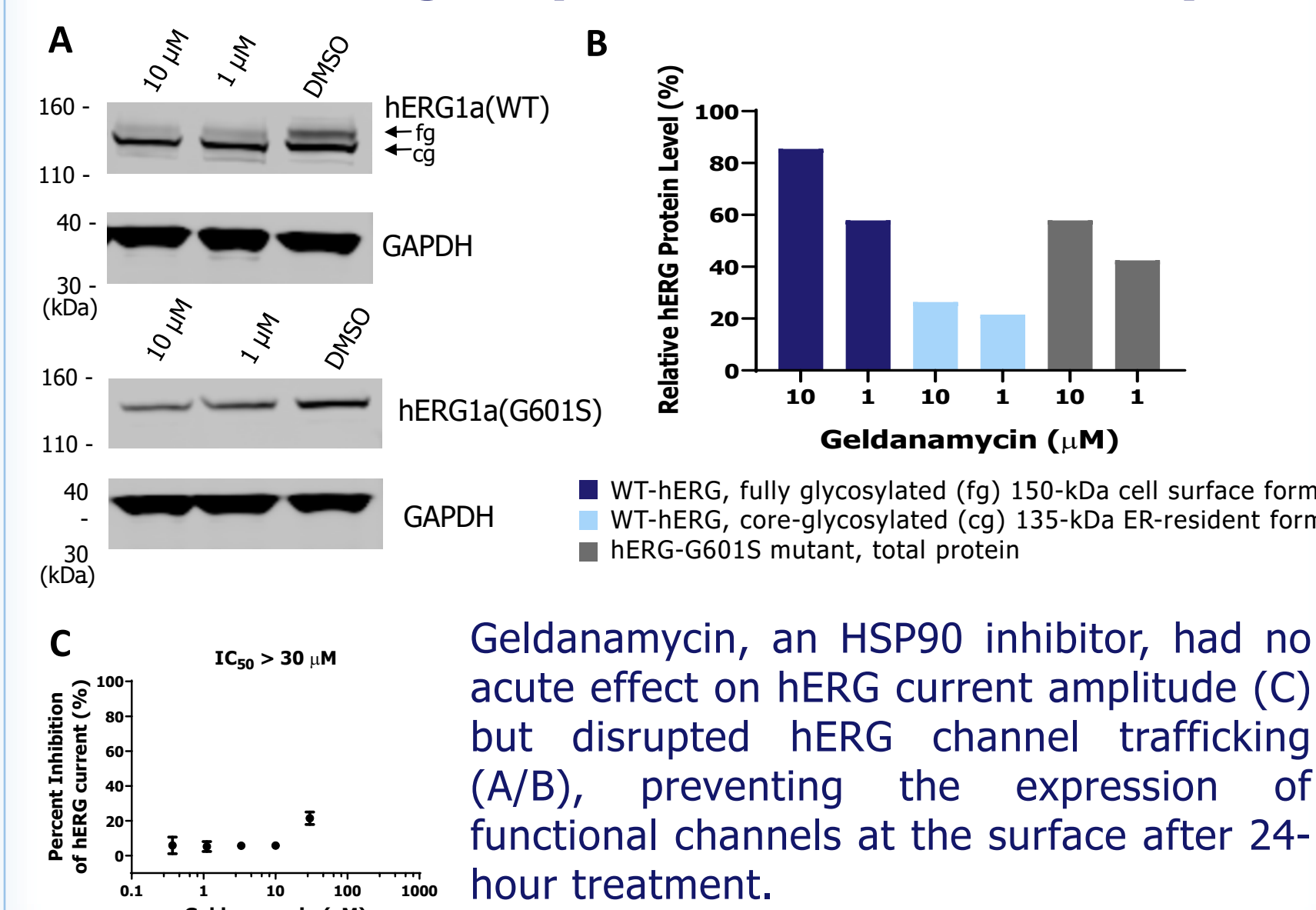


Our approach holds significant promise for reducing late-stage attrition and enhancing the cardiac safety profile of new therapeutic agents.

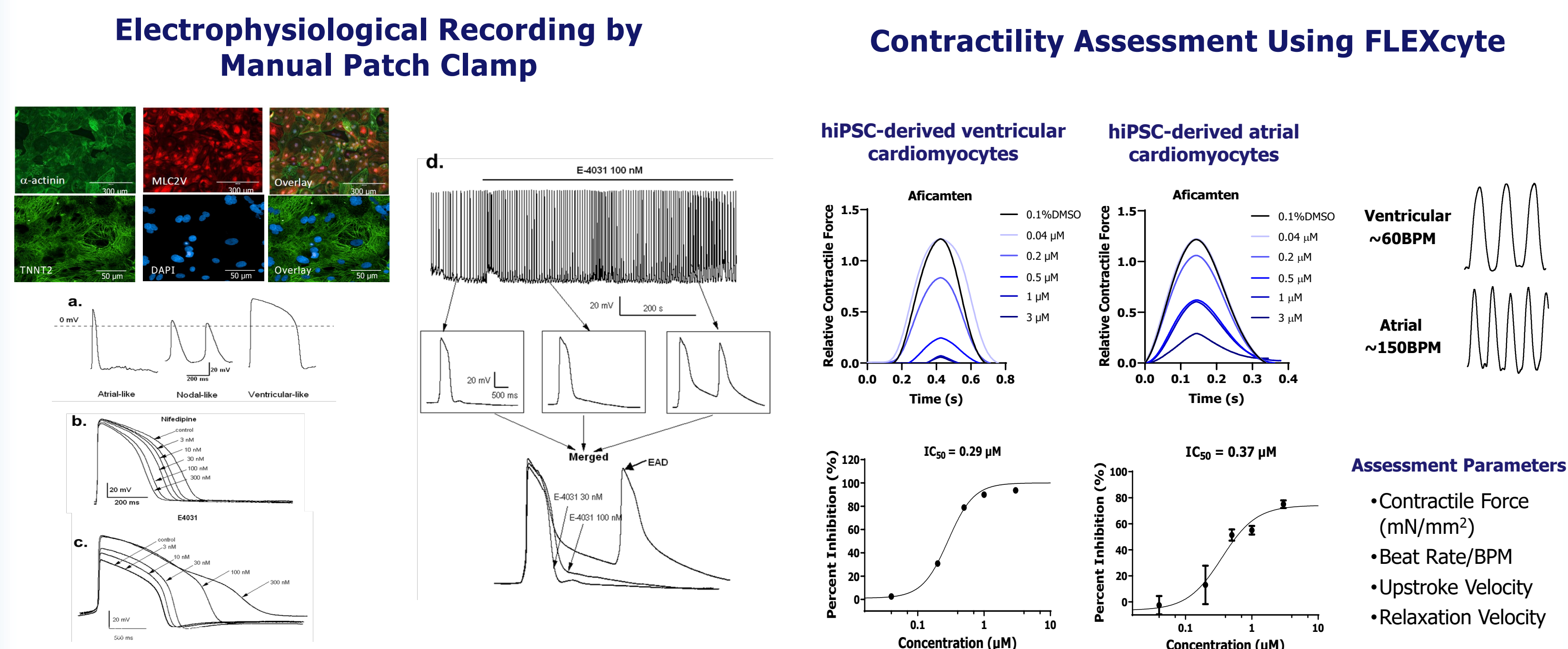
1 Multi-Ion Channel Profile

	ICH guideline	NMPA guideline	Pharmaron
I _{Kr} (hERG)	+	+	+
I _{Na,Late} (Nav1.5 late)	+	+	+
I _{Na,peak} (Nav1.5 peak)	+	+	+
I _{Ca,L} (L-type; Cav1.2)	+	+	+
I _{to} (Kv4.3)		+	+
I _{Ks} (KCNQ1+KCNE1)		+	+
I _{K1} (Kir2.1)		+	+
I _{Kur} (Kv1.5)		+	+

2 Trafficking-Dependent Cardiotoxicity

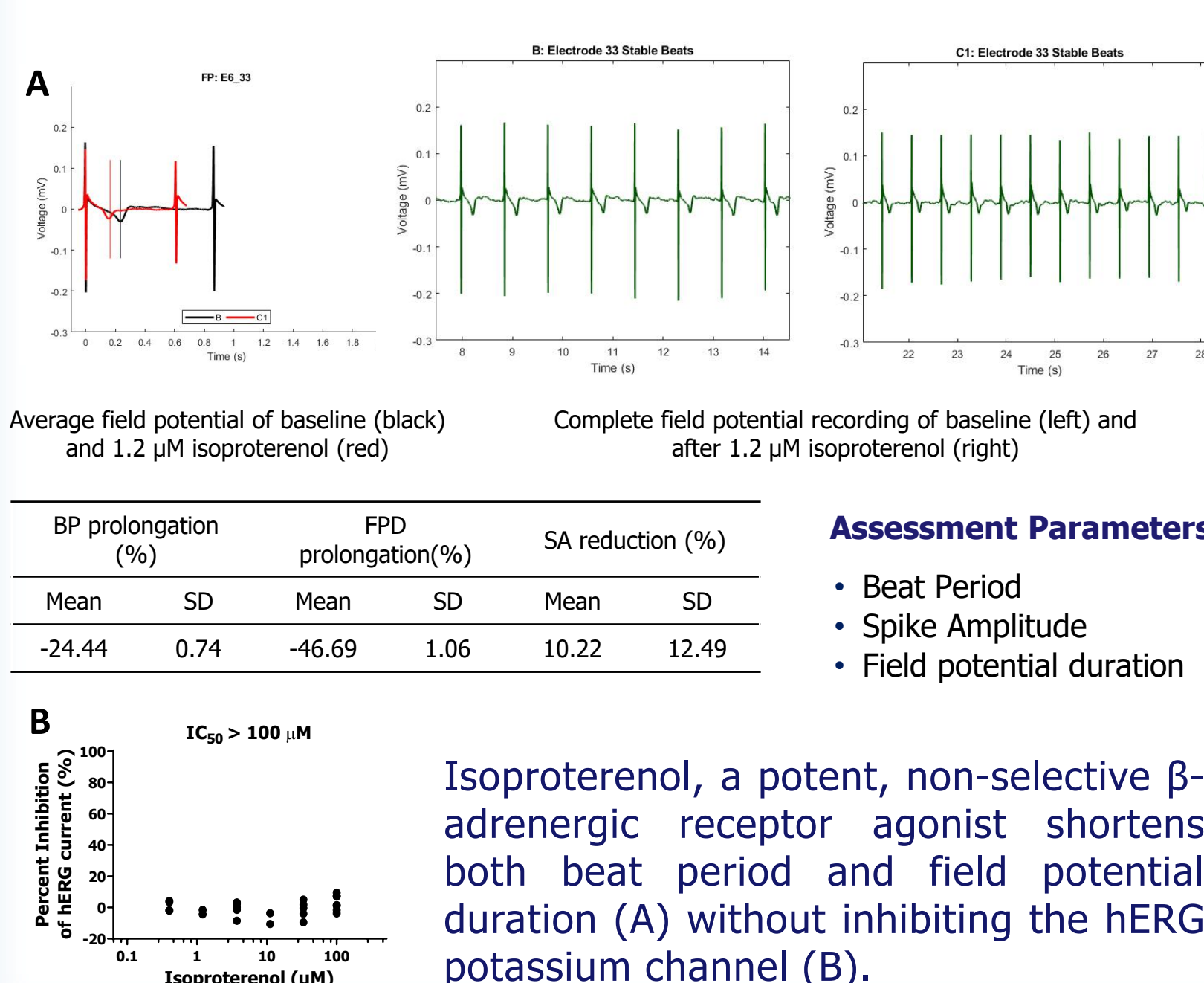


3 Integrated Cardiac Function in 2D hiPSC-Cardiomyocyte Models

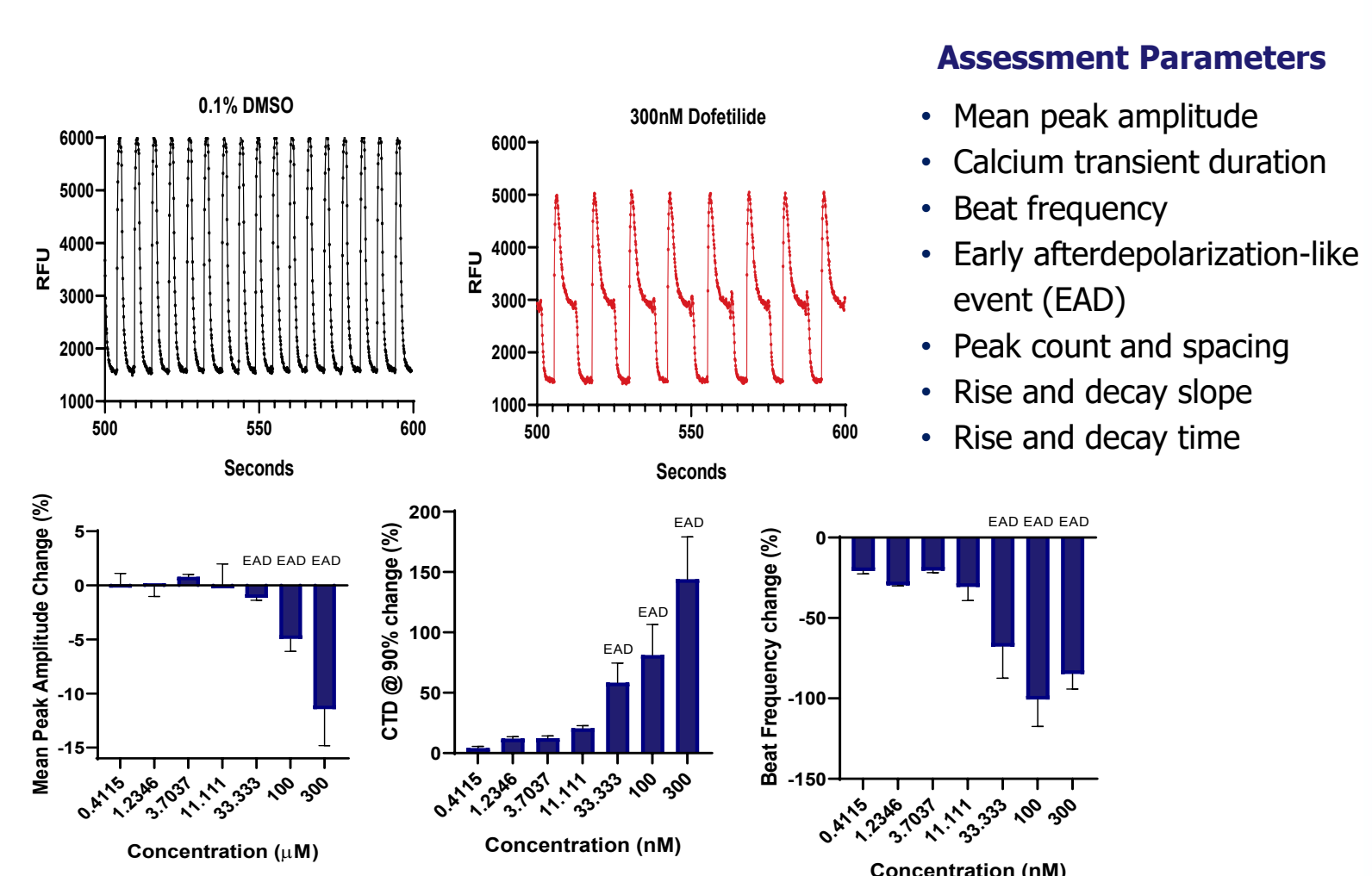


Human iPSC-derived cardiomyocytes exhibited distinct action potential morphologies corresponding to atrial-like, nodal-like, and ventricular-like subtypes (a). Nifedipine shortened action potential duration (APD) in a concentration-dependent manner, while E-4031 prolonged APD and induced early afterdepolarization (EAD) events at 100 nM (b-e).

Field Potential Recording Using Multi-Electrode Array (MEA)

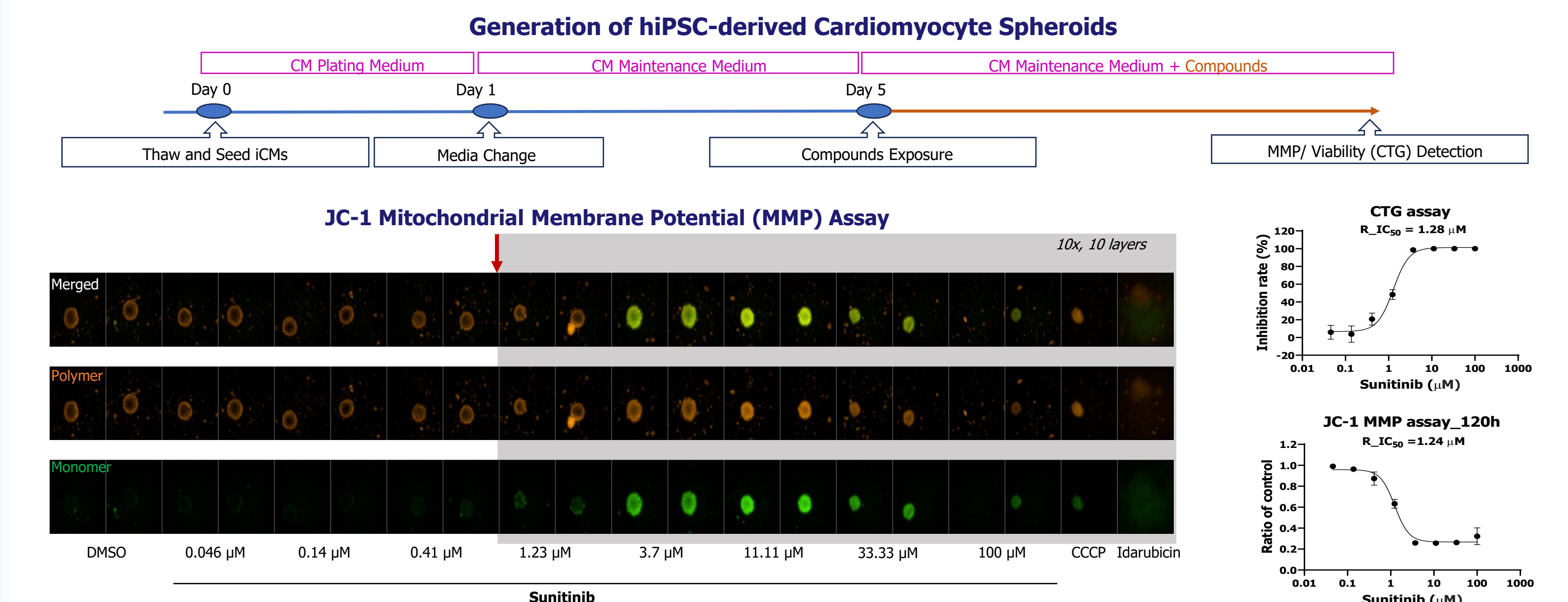


Calcium Transient Assay Using FLIPR

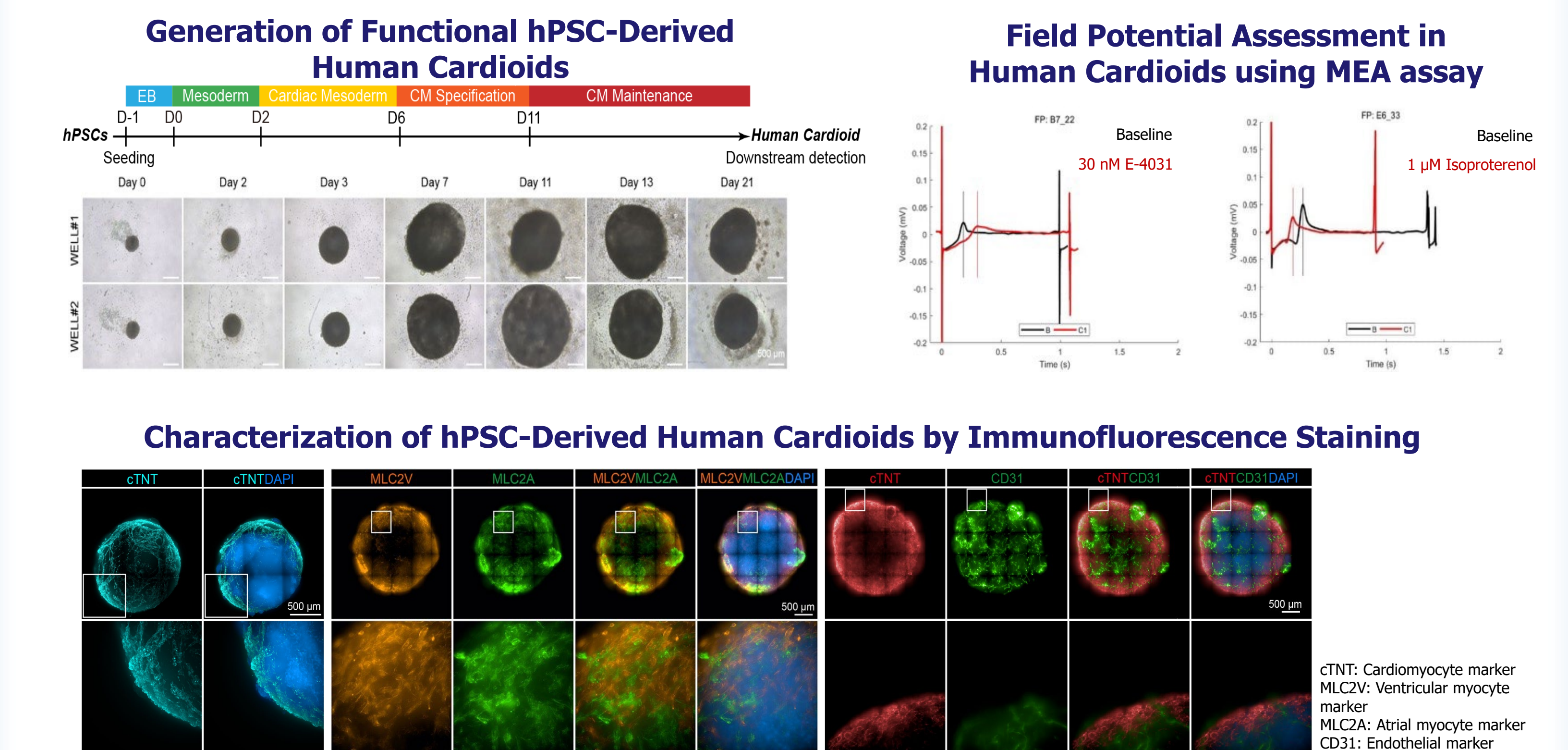


The hERG blocker dofetilide dose-dependently prolongs calcium transient duration. Early afterdepolarization (EAD) events - a hallmark of proarrhythmic risk - appeared at higher concentrations.

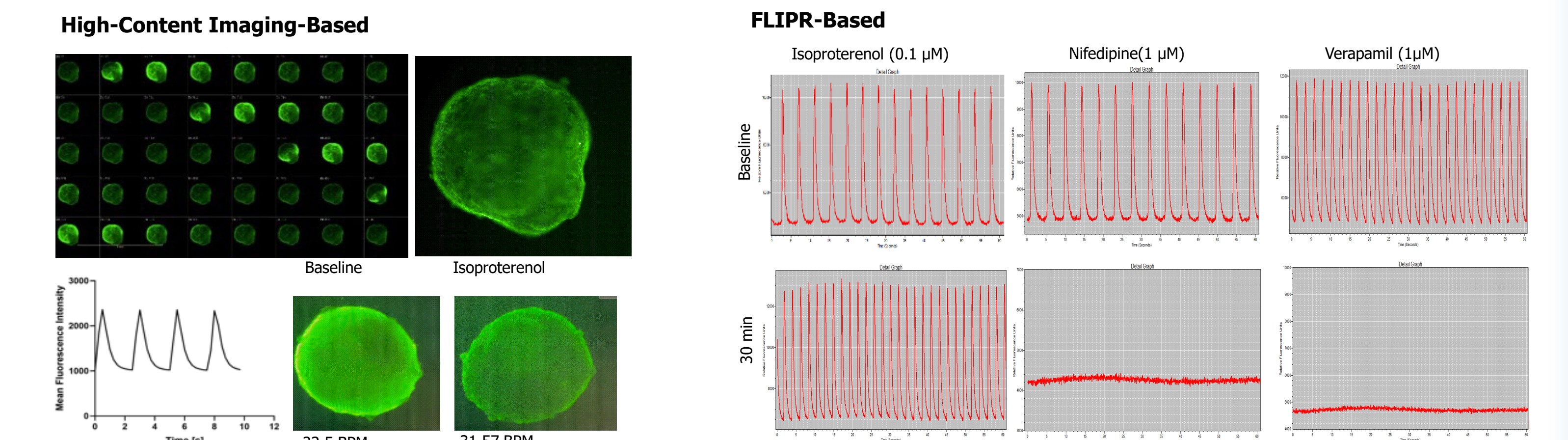
4 3D hiPSC-derived Cardiomyocyte Spheroid Model for Structural Cardiotoxicity Evaluation



5 Integrated Cardiac Function in 3D hiPSC-derived Human Cardioids Model



Calcium Transient Assay in Human Cardioids



We demonstrate that hPSC-derived Human Cardioids recapitulate key structural, electrophysiological, and pharmacological properties of human cardiac tissue. They provide a predictive 3D model for assessing compound-induced cardiovascular toxicity, bridging the gap between conventional 2D assays and *in vivo* studies.