

96-well Cardiac MEA assay with Simplified Arrhythmia Detection

iCell Lab Note

Introduction.

Human iPSC-derived cardiomyocytes (iCell® Cardiomyocytes²) are spontaneously beating cells produced in high quantities with excellent lot-to-lot reproducibility. As a result, iCell Cardiomyocytes² have been used extensively since 2015 to evaluate cardiac activity from cell monolayers and are the only commercial model still available from the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) validation study (Colatsky et. al). Microelectrode array (MEA) is now the preferred method of choice for assessing potential adverse drug effects on cardiomyocytes. The Maestro Pro MEA system from Axion BioSystems features 96-well assay format and Local Extracellular Action Potential (LEAP) technology (Hayes et. al.) that bring unique advancements in arrhythmia detection to support rapid, reliable, and simplified next-generation cardiac MEA assays for high-throughput assessment of cardiotoxicity.

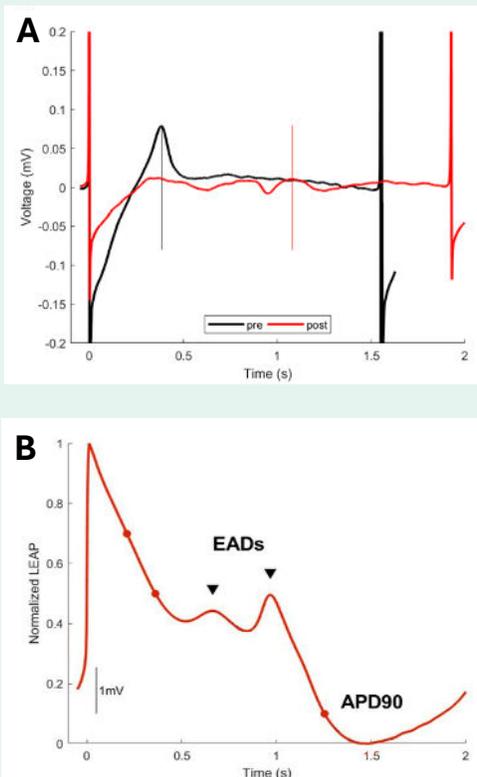


Figure 1. Comparison of FPD vs. APD for Detection of hERG Block. iCell Cardiomyocytes² were cultured on a 96-well BioCircuit MEA plate and dosed on Day 7 with 30 nM E-4031. (A) Overlay of pre-dose (black) and post-dose (red) traces with FPD markings indicated. (B) LEAP trace showing the cardiac action potential recorded from the same well, with quantitation of APD90 and automatic detection of early after depolarization (EAD). LEAP induction transforms the field potential into an action potentials, and the resulting signal amplitude is much larger (~0.1 mV vs. ≥5 mV).

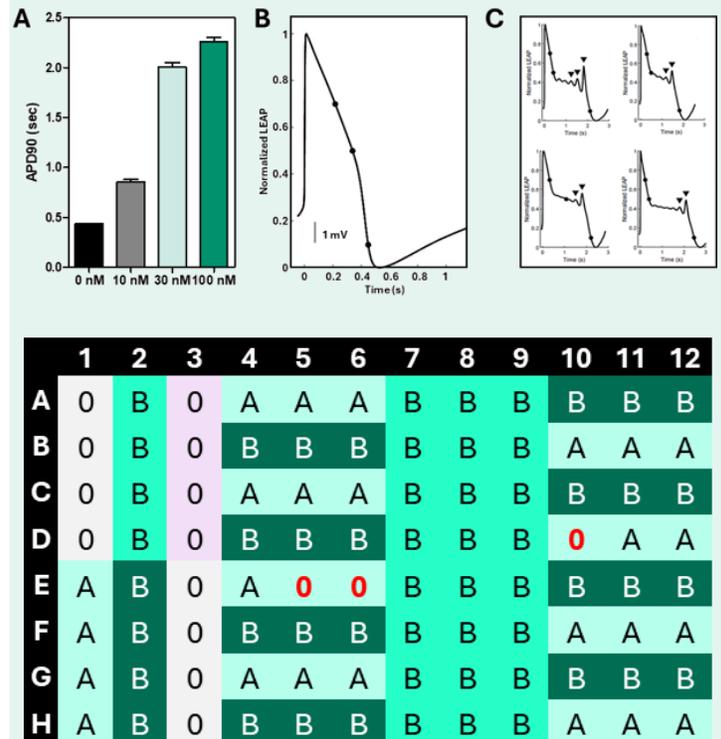
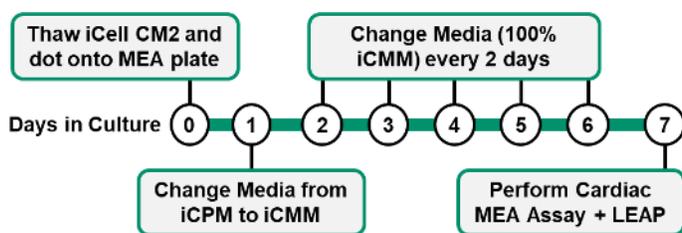


Figure 2. Robust Cardiac Arrhythmia Detection. iCell Cardiomyocytes² were dosed with (A) E-4031 according to the plate map above (□10 nM, ■30 nM, and ■100 nM). (B) Controls wells received media only (A3-D3; pink) or 0.1% DMSO (A1-D1, E3-H3; gray). Cells exposed to hERG blocker were flagged for automatic arrhythmia detection (marked A or B) in 81/84 wells. Zero (0) indicates that no irregularities were detected – see 12 control wells and 3 wells of 10 nM compound. (C) Example LEAP traces show that 100 nM E-4031 significantly prolongs the APD90 and illustrate how consistently EADs are identified with a ▼.

Assay Workflow.



Change Media	Place cells back in incubator for 2-4 hours	
Equilibrate cells on MEA (10 min)	Record baseline FPD "pre-dose" (5 min)	
Dose Cells	Incubate cells on MEA (30 min)	Perform "post-dose" FPD recording (5 min)
LEAP Induction	Incubate cells (10-15 min on MEA)	Perform "post-LEAP" recording (10 min)

Methods.

- Day 0: Coat MEA with Fibronectin (50 µg/ml for 1 h at 37°C).
- Thaw cells according to the User's Guide / Quick Guide.
 - Use viable number of cells/vial on CoA for cell counts.
 - Recommended plating density is ~50K cells/well in 8 µl droplet.
 - Flood the wells with 200 µl of iCPM after 60 min.
- Day 1: Perform 100% media change (iCPM → iCMM).
- Days 2-6: Change 100% media every 2 days until assay.
 - It is recommended to work row-by-row (or column-by-column) when aspirating and replacing media.
- Day 7: Day of assay, perform 100% media change (200 µl); incubate cells for 4 h before dosing.
 - Equilibrate MEA plate on system for ≥10 min prior to taking 5 min baseline recording using Field Potential configuration.
- Prepare 5X compounds (e.g., E-4031) and dose with 50 µl.
- Incubate MEA plate for 30 min and then acquire post-dose FPD recording for 5 min.
- Start LEAP induction (10-15 min) and immediately record cardiac activity (post-LEAP) for 10 min.
- Process files with AxIS Navigator and analyze data with the Cardiac Analysis Tool software.

Table 1. Materials Needed

Product	Vendor	Cat. #
iCell Cardiomyocytes ² , 01434 kit	FCDI	R1017
▪ iCell Cardiomyocytes Plating Medium (iCPM)	(incl. in kit)	M1001
▪ iCell Cardiomyocytes Maintenance Medium (iCMM)	(incl. in kit)	M1003
Fibronectin, human plasma †	Sigma	F0895
BioCircuit MEA 96 ‡	Axion	M768-BIO-96
E-4031 (hERG blocker) ◇	Tocris	F10488
Maestro Pro MEA System	Axion	N/A
AxIS Navigator Software	Axion	Latest version
Cardiac Analysis Tool	Axion	Latest version

† Alternate ECM and different sources of fibronectin have been tested and can be used. Please contact Technical Support for more information.
 ‡ CytoView MEA plates are not recommended for the LEAP assay.
 ◇ See the Colatsky paper for a list of the 28 compounds used for CiPA.



Scan here to download the iCell Cardiomyocytes² Application Protocol.

Summary.

This iCell Lab Note provides a general outline for running a cardiac MEA assay with iCell Cardiomyocytes² for safety and toxicity testing. The large signal amplitude and high resolution of LEAP allow for easy identification of EADs and enhanced quantification of associated metrics that come from recording an action potential instead of a field potential. The 96-well format workflow provides a simpler and more high-throughput assay solution for automated detection of cardiac arrhythmias using human cells.

References.

- Colatsky, T. et al. *J. Pharmacol. Toxicol. Methods*. **2016** 81:15. <doi: 10.1016/j.vascn.2016.06.002>
 Hayes, H.B. et al. *Sci Rep*. **2019** 9(1):11893. <doi: 10.1038/s41598-019-48174-5>
 Geiger, R.M. et al. *JACC Clin Electrophysiol*. **2020** 6(14):1860. <doi: 10.1016/j.jacep.2020.08.034>

iCell Cardiomyocytes² exhibit spontaneous beating that is both stable and reproducible, ideal for robust electrophysiological readouts of cardiotoxicity.

LEAP offers simple and reliable arrhythmia detection in iCell Cardiomyocytes², streamlining the traditional approach to running and analyzing cardiac MEA assay data.

High-throughput 96-well assay format enables you to perform the entire CiPA study using only four (4) vials of cells and four (4) MEA plates!!



Scan here to download the iCell Cardiomyocytes² Quick Guide.

Contact **Technical Support** for more protocol details and supportive data.

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