

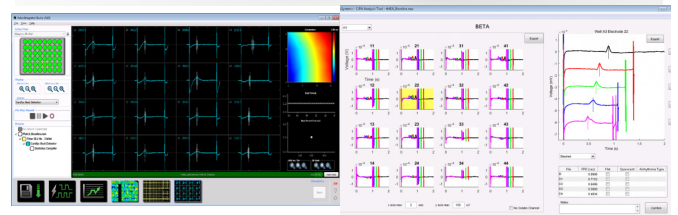
# CiPA ON THE MAESTRO

## SUPERIOR CARDIAC SAFETY STUDIES

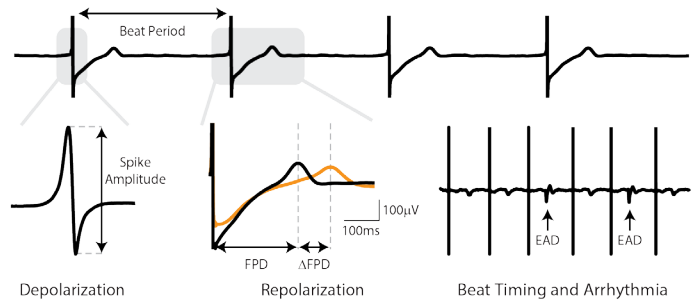
### ***In vitro* cardiac safety assays with the Maestro™**

The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative seeks to redefine preclinical cardiac safety assessment for new drugs. Previous regulations focused on the blockade of the human Ether-à-go-go related gene (hERG) potassium channel, resulting in QT prolongation and *Torsades de Pointes*. While highly sensitive, this approach lacks specificity, leading to a high drug attrition rate. CiPA aims to increase predictivity of drug safety assessments, with *in vitro* evaluation of whole cell drug effects on human stem cell-derived cardiomyocytes (hSC-CM) playing a critical role. Specifically, hSC-CMs provide an integrated assessment of multiple ion channel effects which may compensate for hERG block.

Axion BioSystems' Maestro™ multiwell MEA platforms are well-positioned to evaluate complex hSC-CM electrophysiology with accessible high-throughput tools. The Maestro platforms offer an industry-leading 768 electrodes for precise and efficient evaluation of key cardiac electrophysiology endpoints at scale. The Maestro Pro and Edge integrate seamlessly with AxIS software and offline tools to make analysis and standardized reporting quick and intuitive. These automated analysis tools extract measures of repolarization and arrhythmia, while also allowing for user visual inspection and verification.



Axion's Maestro MEA systems (top) integrate seamlessly with AxIS software (bottom left) to provide cardiac beat, FPD, and conduction tracking. The CiPA Analysis Tool (bottom right) enables semi-automated FPD detection and arrhythmia classification across files.



Sample cardiomyocyte field potentials with dosed data showing FPD prolongation and early after depolarizations (EADs).

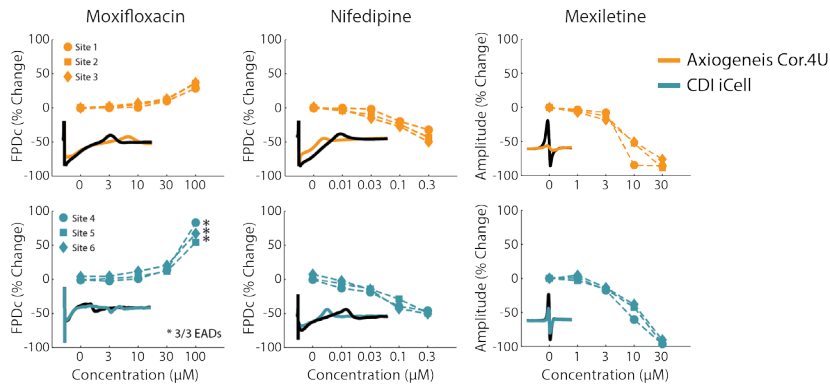
## THE MAESTRO ADVANTAGE

- Label-free, non-invasive voltage recording enables long-term monitoring of cardiomyocytes
- Industry-leading number of electrodes (768) provides high quality spatiotemporal resolution
- Environmental controls provide a stable environment for both acute and chronic studies
- Fast data collection rate (12.5 kHz) accurately captures depolarization spike amplitude
- Scalable format (12-, 48-, and 96-well plates) allows throughput flexibility all on one system



## HIGHLY REPRODUCIBLE ACROSS SITES AND CELL TYPES

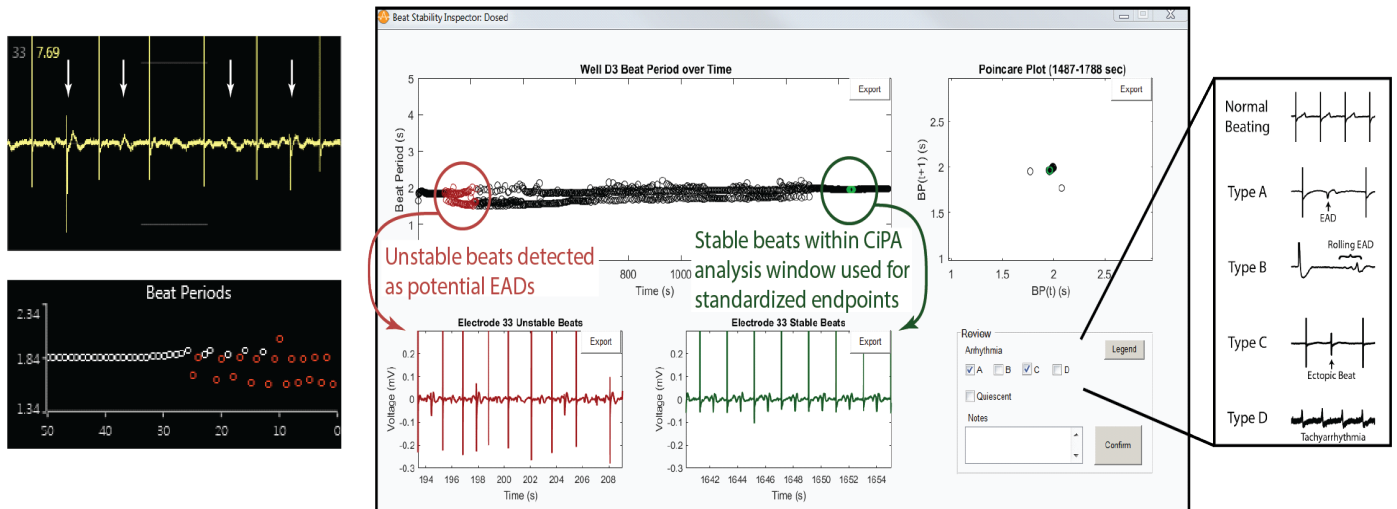
In the CiPA pilot study, six core sites used the Maestro for their MEA studies with two different cell types and eight compounds with known mechanism. The Maestro and accompanying software tools demonstrated high reliability across replicates, sites, and cell types, while accurately detecting phenotypic changes in depolarization (spike amplitude), repolarization (field potential duration), and arrhythmias.



CiPA pilot study results for three representative compounds across six Maestro sites using Axiogenesis Cor.4U (orange) or CDI iCell (blue) cardiomyocytes. The Maestro reliably detected field potential duration (FPD) prolongation for HERG blockers, FPD reduction for Ca<sup>2+</sup> blockers, and spike amplitude reduction for Na<sup>+</sup> blockers across sites and cell types.

## AUTOMATED CiPA PROTOCOL WITH ARRHYTHMIA DETECTION

Axion's AxIS software enables real-time visualization of EADs, while the CiPA Analysis Tool provides automated detection of potential arrhythmias with a user interface for inspection and classification. The completed analysis can be readily exported as "publication-ready" dose response figures or in the official CiPA reporting format.



Sample raw data trace in AxIS showing ectopic beats and EADs (left top, arrows) and corresponding unstable beating (left bottom). In the CiPA Analysis Tool (middle), unstable beating was automatically flagged as a potential arrhythmia. In the inspection window, arrhythmias can then be further classified as EADs, rolling EADs, ectopic beats, and/or tachyarrhythmia (right).

