CiPA Phase 2 Study: A case study in development and validation of an automated microelectrode array (MEA) assay of hiPSC-derived cardiomyocyte electrophysiology for cardiac safety evaluation

Axion BioSystems, Atlanta, GA

Maestro™ multwell MEA

Abstract
The need for simple, reliable and predictive pre-clinical assays for cardiac safety has motivated initiatives worldwide including the Comprehensive in vitro Proarrhythmia Assay (CiPA) and Japan’s Cardiac Safety Assessment (JCSA). Towards this end, the Maestro MEA platform enables assessment of function in vitro at a cardiomyocyte activity with an easy to use bench top system. The Maestro MEA platform records electrical signals from cells cultured directly onto an MEA, allowing for high throughput data collection across the cardiomyocyte synapse. With plate capacity up to 48 wells, the Maestro offers high throughput for safety screening needs.

Why use microelectrode arrays?
Microelectrode array technology offers a platform for directly connecting key biological variables, such as gene expression or ion channels, to measure of cellular and network function.

A planar grid of nanowires (a) interface with electro-active cultured cells (b), to model complex, human excitation in a dish. Functional changes in current-voltage (c) caused by the electrical activity of cardiomyocytes, analogous to the ECG in vivo.

Raw voltage signals are processed in real-time to obtain extracellular action potentials from the network, providing a valuable electrophysiological principle for applications in drug discovery, toxicology and safety screening, disease models, and stem cell characterization.

- Lab-friendly and non-invasive recording of extracellular voltage from cultured cells on Axion MEA plates
- Environmental control provides a stable benchtop environment for short- and long-term toxicity studies
- Fast data collection rate (12.5 KHz) accurately quantifies the magnitude of depolarization events
- Sensitive voltage resolution detects subtle extracellular action potential waveforms
- Industry-leading array density provides high quality data through high-integrity information from multiple locations in the culture
- Scalable format (12-, 48-, and 96-well plates) meets all throughput needs on a single system

Why incorporate automation?
• Automated cell culture improves consistency and reliability of cultures.
• Significant walk-away time frees the user for other tasks, increasing efficiency.
• Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
• Redesigned environmental control provides continuous delivery of CO2 at all times.
• Incorporated incubator with 44 plate capacity supports many simultaneous studies.
• Integrated HEPA filter and UV illumination ensures sterile operation.

Maestro APEX™

Why use the Maestro?
Maestro APEX offers significant efficiency gains, as user time is minimal for completing important tasks. As an example, to prepare a 768 well plate, the Maestro APEX platform supplies the compounds at a stock concentration and arranges experimental information. APEX then completes compound plate preparation, MEA plate dosing, and data acquisition, freeing the user to engage in other activities.

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.

Efficiency and Throughput
Maestro APEX features a 4-channel robotic liquid handler, automated gas mixer, dedicated Maestro deck handler, on-board gas mixer that provides CO2 respiration, and dedicated Maestro deck atmosphere control. A custom APEX user interface provides access to preconfigured routines for cell spotting, media change, and compound plate preparation, MEA plate dosing, and data acquisition, freeing the user to engage in other activities.

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.

Biological Stability
It is commonly known that small perturbations to cardiomyocyte cultures can result in unstable assay performance. APEX minimizes changes to the local MEA environment:
1) a sterile plate deck that enables dosing directly on the Maestro, and
2) an on-board gas mixer that provides CO2 concentration compensation during dosing to facilitate a rapid return to stable breathing patterns (left).

CiPA Phase II

The CiPA Phase II study was completed in 12 calendar days using the APEX for all spotting, maintenance, and dosing of the eight 384-well plates. The study required less than 6 hours of human interaction with APEX and 54 hours of unattended, automated routine. Data analysis was performed in parallel with APEX execution.

Why use the Maestro?
Axion makes high-throughput cardiac safety screening simple from start to finish.

- Automated cell plating contributed to highly reproducible endpoints across all eight plates, significantly exceeding CiPA protocol requirements. The stable dosing environment enabled consistent baseline activity and provided high assay sensitivity to minimal positive control (dobutamine 0.5 µM).
- Maestro APEX, the first automated MEA workstation, provides significant advancements in throughput cardiac safety screening simple from start to finish.
- Why use the Maestro?
Axion software provides a comprehensive suite of tools to guide a user through all phases of experimentation and analysis. A custom Axion user interface provides access to pre-written protocols and configuration options (Hi-Vol software). Analysis Tool complements the cardiac analysis performed within Axiv by providing semi-automated algorithms for fast and accurate data processing (right).

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.

- Automated cell culture improves consistency and reliability of cultures.
- Significant walk-away time frees the user for other tasks, increasing efficiency.
- Precustomized routines for cell spotting, media change, and dosing carry the user through the entire experiment.
- Redesigned environmental control provides continuous delivery of CO2 at all times.
- Incorporated incubator with 44 plate capacity supports many simultaneous studies.
- Integrated HEPA filter and UV illumination ensures sterile operation.