Detection of drug-induced toxic effects on cardiac electrophysiology using Pluricyte® Cardiomyocytes and the Maestro™ MEA system

Pluricyte® Cardiomyocytes are fully functional human-induced pluripotent stem cell-derived ventricular cardiomyocytes, obtained without genetic modification or purification/selection procedures. The cells are cultured in a chemically well-defined, serum-free medium (Pluricyte® Cardiomyocyte Medium) and are particularly suitable for electrophysiology-based microelectrode array (MEA) assays that are relevant for predictive preclinical safety pharmacology, toxicology and efficacy testing. The combination of Pluricyte® Cardiomyocytes and the Maestro™ MEA system enables detailed electrophysiological detection of potential cardiotoxic/pro-arrhythmic effects of compounds (e.g. ion-channel blockers) in a non-invasive, label-free throughput up to 96 wells.

Pluricyte® Cardiomyocytes – Strengths and characteristics

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The key advantages of using Pluricyte® Cardiomyocytes in combination with the Maestro™ MEA system

Representative waveform of the field potential of Pluricyte® Cardiomyocytes obtained using the Maestro™ MEA system.

- Pluricyte® Cardiomyocyte field potentials show robust and well-pronounced de- (D) and repolarization (R) peaks, which enable:
  - Easy detection of electrophysiological parameters, such as the field potential duration (FPD).
  - Efficient analysis and interpretation of data generated with the Maestro™ MEA system.
- Due to their relatively low beat rate (~20 – 30 BPM, 0.3 – 0.5 Hz) Pluricyte® Cardiomyocytes can be easily paced for electrophysiological research. Both electrical and optogenetic pacing options are available with the Maestro™ MEA system.
Pluricyte® Cardiomyocytes in combination with the Maestro™ MEA system provide a robust and highly relevant in vitro assay platform to study the cardiac safety profile of compounds during drug development.

A case-study was performed to assess the effects of a set of cardioactive compounds on the electrophysiology of Pluricyte® Cardiomyocytes using the Maestro™ MEA system. Below, the effects of three cardioactive reference compounds on the field potential duration, beat period and sodium spike amplitude of Pluricyte® Cardiomyocytes are shown. Pluricyte® Cardiomyocytes responded as expected when treated with the cardioactive compounds.

**Overview of effects of isoproterenol, flecainide and E4031 on beat period, spike amplitude and field potential duration (FPD) of Pluricyte® Cardiomyocytes using the Maestro™ MEA system.**

- **Isoproterenol**: Exhibits β-adrenergic receptor agonist properties and increases beat rate and sodium spike amplitude. From 10µM arrhythmias were observed.
- **Flecainide**: Exhibits hERG and sodium channel blocking properties over a similar concentration range and, therefore, has effects on both FP and spike amplitude. For 10µM arrhythmias were observed. TdP-like arrhythmias were occasionally observed at high concentrations (≥100 nM, see figure below). Data are expressed as percentage change compared to the baseline. Mean±SD, N=3 wells for each condition.

**Effects of E4031, isoproterenol and mexileine on the field potential signals of Pluricyte® Cardiomyocytes.**

- **A**: E4031, a hERG channel blocker, induced a concentration-dependent increase of the field potential duration, shown here by an overlay of averaged field potential waveforms. Despite flattening of the peak, AxIS software could accurately detect the repolarization peak, even at high concentrations of E4031.
- **B**: TdP-like arrhythmias were observed at ≥100 nM E4031.
- **C**: Addition of 10 nM isoproterenol, a β-adrenergic receptor agonist, induced an increase in beat rate of Pluricyte® Cardiomyocytes, shown here by an increase in the number of beats during a 15 second interval.
- **D**: Mexilene blocks the sodium channels, resulting in a decrease in sodium spike amplitude, shown here by an overlay of the depolarization peaks from field potential signals.

**Pluricyte® Cardiomyocytes** in combination with the Axion Maestro MEA system provide a robust and highly relevant in vitro assay platform to study the cardiac safety profile of compounds during drug development.

**Use of Pluricyte® Cardiomyocytes in combination with the Axion Maestro MEA system is now fully supported by Pluriomics comprehensive application note: available on our websites!**