cyprotex AN EVOTEC COMPANY

In vitro **Toxicology**

eCiphr®Cardio: Cardiac Assessment Using Microelectrode Array

Background Information

'The recent applications of pluripotent stem cells and their derivatives in toxicology and drug research provide new alternatives to the standard routine tests performed by the industry and offer new strategies for chemical safety assessment.'

[1]Wobus AM and Löser P (2011) *Arch Toxicol* **85(2)**; 79-117

- A highly purified population of cardiomyocytes, differentiated from human induced pluripotent stem (iPS) cells (Cellular Dynamics iCell® Cardiomyocytes), are used.
- The cells are a mixture of spontaneously electrically-active atrial, nodal and ventricular-like myocytes. They possess typical human heart cell characteristics forming electrically connected syncytial layers that beat in synchrony, and exhibit expected electrophysiological and biochemical responses upon reference drug exposure.
- Viability is maintained for an extended culture periods (up to 2 weeks) allowing for acute and chronic studies.
- Microelectrode array (MEA) is one of the most sophisticated and efficacious technologies for measuring changes in spontaneously-active cells, such as cardiomyocytes and neurons.
- Cyprotex's eCiphr®Cardio uses microelectrode array recording to monitor electrophysiological activity by measuring beat rate, field duration potential, amplitude and conduction velocity.
- Unlike the patch-clamp hERG assay, eCiphr®Cardio assesses changes in all major ion channels implicated in an action potential.
- This cardiac assay provides a unique *in vitro* system for preclinical drug discovery, cardiotoxicity assessment, disease modelling and high throughput phenotypic screening of drug candidates.

Protocol

Instrument
Maestro 48-well MEA System
(Axion BioSystems)

Cell Type
Human iPS cell-derived iCell® cardiomyocytes
(Cellular Dynamics International) plated and allowed to fully mature and beat synchronously

Assay Details
Five concentrations in duplicate
(dependent on customer requirements)
Single time point
Additional time points and washout (optional)

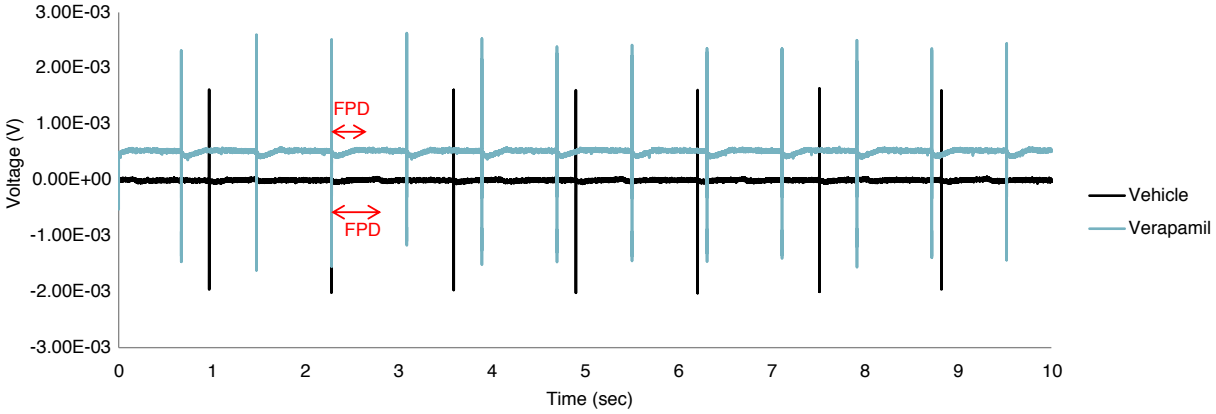
Data Delivery
Beat rate and number
Field potential duration
Amplitude
Conduction velocity (optional)

To find out more contact **enquiries@cyprotex.com**

eCiphr®Cardio assesses electrophysiological changes for all major ion channels implicated in an action potential and shows strong concordance with the *in vivo* and *ex vivo* cardiac effects of multiple compound classes.

Figure 1

Raw traces for vehicle control (0.1 % DMSO) and test compound (verapamil).



Red arrows point to the field potential duration (FPD, indicative of the QT interval duration). Verapamil clearly shortens FPD as compared to 0.1% DMSO (vehicle control). Note: In order to distinguish between the two traces, the voltage for verapamil is purposely shifted upward.

Table 1

Comparison of eCiphr®Cardio, hERG channel[2,3,5,6] and *ex vivo/in vivo*[2,4,7,8,9,10] results for compounds known for their effects on cardiac function.

Compound	Family	Number of Beats	Number of Beats (AC_{50}; µM)	Fast Na+ Slope (V/s)	Fast Na+ Slope (AC_{50}; µM)	Fast Na+ Amplitude (mV)	Fast Na+ Amplitude (AC_{50}; µM)	Field Potential Duration (ms)	Field Potential Duration (AC_{50}; µM)	*In vivo* or *ex vivo* Indication	Canine Purkinje Fibre Preparation (µM)	hERG Block (IC_{50}; µM)
Aspirin	Irreversible cyclooxygenase inhibitor	no change	>100	no change	>100	no change	>100	no change	>100	no prolongation	not reported	not reported
Cisapride	Serotonin $5HT_4$ agonist	↓	0.083	↓	0.16	↓	0.16	↑	0.15	prolongation	0.1	0.03-0.1
FPL64176	L-type Ca^{2+} channels activator	↓	0.039	↓	0.052	↓	0.053	↑	0.044	prolongation	not reported	not reported
Isoproterenol	ß-adrenergic receptor agonist	↑	0.18	no change	no change	no change	no change	↓	0.17	shortening	not reported	not reported
Nifedipine	L-type Ca^{2+} channel blocker	↑	0.34	no change	no change	no change	no change	↓	0.12	no prolongation	>10	not reported
Quinidine	hERG K^+ channel blocker/class I antiarrhythmic	↓	5.8	↓	5.0	↓	5.0	↑	2.7	prolongation	8.5	1
Sotalol	ß-adrenergic receptor blocker	↓	44	↓	41	↓	42	↑	53	prolongation	100	>30
Verapamil	L-type Ca^{2+} channel blocker	↑	0.34	↓	1.0	↓	1.0	↓	0.11	shortening	1	0.125

eCiphr®Cardio is highly reproducible and shows strong concordance with the *in vivo* or *ex vivo* cardiac effects of multiple classes of compounds. eCiphr®Cardio is a powerful system for assessing preclinical cardiac safety and is more informative than the traditional hERG assay and conventional animal models.

References

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