Utilizing hiPSC-Derived Cardiomyocytes for Comprehensive Electrophysiological and Inotropic Evaluation of Cardiovascular Safety in Early Drug Discovery

ヒトiPSC由来心筋細胞を用いた電気生理と変力作用評価による創薬初期段階における化合物の心血管系への影響の包括的評価

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Background

- Side effects on the cardiovascular system are a primary reason for the termination of drug development. Therefore, it is crucial to accurately understand the effects of compounds on the cardiovascular system at an early stage.
- Human iPSC-derived cardiomyocytes have gained importance for evaluating the potential effects of compounds on the cardiovascular system, including impacts on the QT interval, proarrhythmic events, and contractility dysfunction.
- We have established assays to evaluate the potential effects of compounds on the electrophysiology and inotropy of cardiomyocytes. The predictivity and reproducibility of these assays are summarized in this poster.

Materials and Methods

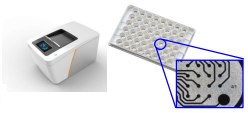
Measuring equipment

✓MEA：Maestro Pro (Axion BioSystems)
✓MEA plate: Cytoview (Axion BioSystems)

Reagents

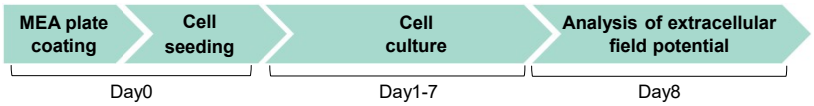
✓Cell：iCell® Cardiomyocytes[2] (FUJIFILM Cellular Dynamics, Inc.)
✓Coating agent：Fibronectin
✓Media：iCell® CM Plating Medium , iCell® CM Maintenance Medium

iCell Cardiomyocytes[2]

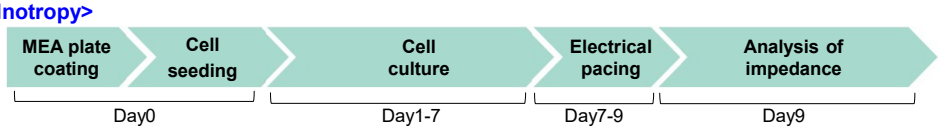

Multi-electrode array

Protocol

<QT interval and proarrhythmic event>

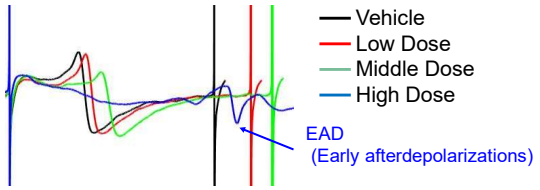


<Inotropy>

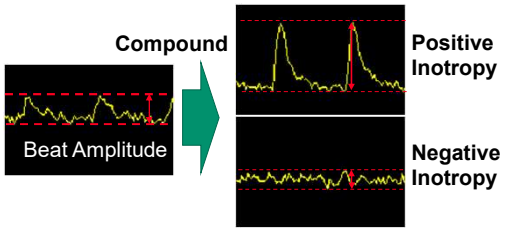


Data analysis

Extracellular Field Potential

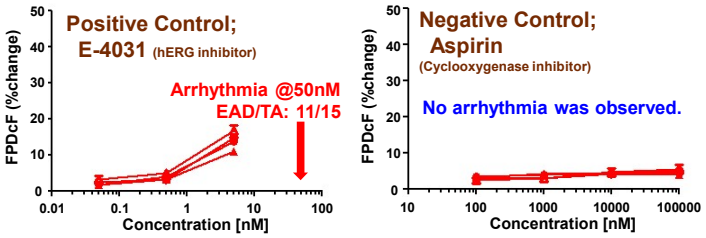


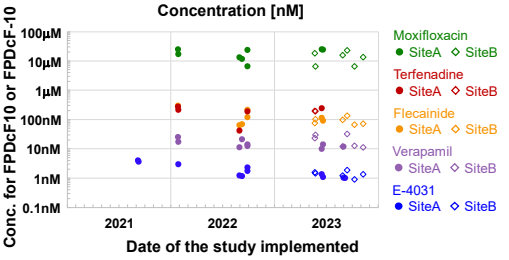
Impedance (Beat Amplitude)



Result

<QT interval and proarrhythmic event>





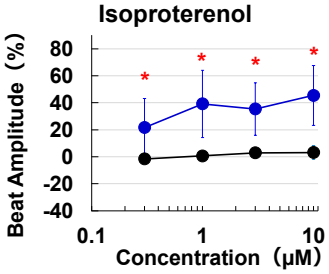
The concentrations to increase FPDcF by 10% (FPDcF10) for E-4031, flecainide, terfenadine and moxifloxacin or to decrease FPDcF by 10% (FPDcF-10) for verapamil are consistent over years These data were generated using 6 product lots of iCell® cardiomyocyte[2].

Consistent results within and between experiments over 2 years.

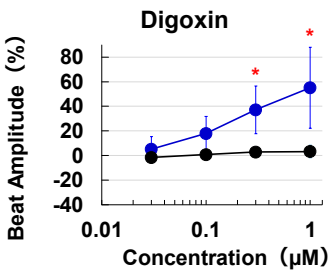
Risk Category	Compounds	Concentration Range [mM]	Ratio	FPDc Prolongation [μM]*	EAD/TA [μM]
High	Ibutilide	0.0001-0.1	Log10	0.0001	0.01
	D,l Sotalol	0.1-100	Log10	1	10
	Azimilide	0.003-3	Log10	0.03	0.3
	Dofetilide	0.0003-0.01	1/2 Log10	0.0003	0.003
	Quinidine	0.9-30	1/2 Log10	0.9	0.9
	Disopyramide	0.1-100	Log10	1	10
	Vandetanib	0.01-10	Log10	1	10
	Bepridil	0.01-10	Log10	1	N.D.
Intermediate	Domperidone	0.003-3	Log10	0.03	0.3
	Droperidol	0.03-1	1/2 Log10	(not detected)	0.03
	Ondansetron	0.03-30	Log10	0.3	3
	Astemizole	0.0001-0.1	Log10	0.01	0.01
	Cisapride	0.003-0.1	1/2 Log10	0.01	0.1
	Pimozide	0.0009-0.03	1/2 Log10	0.003	0.03
	Clarithromycin	0.1-100	Log10	10	100
	Risperidone	0.003-0.1	1/2 Log10	0.1	N.D.
	Terfenadine	0.001-1	Log10	0.1	N.D.
	Chlorpromazine	0.09-3	1/2 Log10	(shortening)	N.D.
	Clozapine	0.09-3	1/2 Log10	(shortening)	N.D.
Low	Ranolazine	0.1-100	Log10	10	N.D.
	Metoprolol	3-100	1/2 Log10	N.D.	N.D.
	Mexiletine	0.1-100	Log10	10	N.D.
	Loratadine	0.0009-0.03	1/2 Log10	N.D.	N.D.
	Tamoxifen	0.09-3	1/2 Log10	N.D.	N.D.
	Nitrendipine	0.009-0.3	1/2 Log10	(shortening)	N.D.
	Nifedipine	0.001-1	Log10	(shortening)	N.D.
	Diltiazem	0.01-10	Log10	(shortening)	N.D.
	Verapamil	0.001-1	Log10	(shortening)	N.D.

<Inotropy>

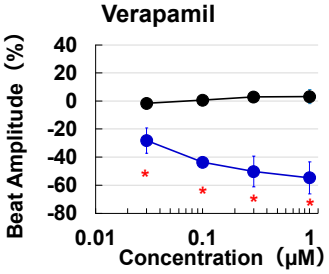
β adrenergic receptor agonist



N^+/K^+ ATPase inhibitor



L-type Ca^{2+} channel blocker



Compounds with known effect on cardiac contractility

DMSO (Vehicle)

* Significant differences between compound and vehicle (DMSO) (Dunnet's test, p<0.05)

Discussion

- Extracellular field potential of hiPSC-derived cardiomyocytes is a useful indicator for evaluating the potential of drug compounds to prolong the QT interval or induce proarrhythmic events. We have established a robust protocol in a 96-well plate format that generates consistent outcomes over the years.
- This assay system is also effective for evaluating the inotropic effects of compounds after electrical pacing for two days.
- It has been demonstrated that hiPSC-derived cardiomyocytes are a powerful tool for comprehensively evaluating drug effects on cardiomyocytes at an early stage of drug discovery.

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