Comparison of Predictive Performance for Drug-Induced Proarrhythmia Using hiPSC-Cardiomyocytes, hERG Inhibition, and Action Potential Duration Simulations

hiPSC心筋細胞アッセイ、hERG阻害、活動電位持続時間シミュレーションによる薬剤誘発性不整脈予測性能の比較

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Background

- hiPSC-derived cardiomyocytes (hiPSC-CMs) provide an effective tool for evaluating the integrated effects of drug compounds on cardiomyocyte function.
- To better characterize the features of the hiPSC-CM assay, we compared electrophysiological outcomes from hiPSC-cardiomyocytes with reported results from ion-channel inhibition assays.
- Additionally, we assessed the effects of compounds with distinctive properties on hiPSC-CMs.

1) Ando et al. J. Pharmacol. Toxicol.Methods (2017)
2) O'Hara et al., Plos Comput Biol (2011)
3) https://d-nb.info/1130707415/34

Materials and Methods

<iPSC-CM assay>

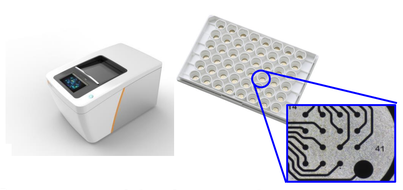
Measuring equipment

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

Reagents

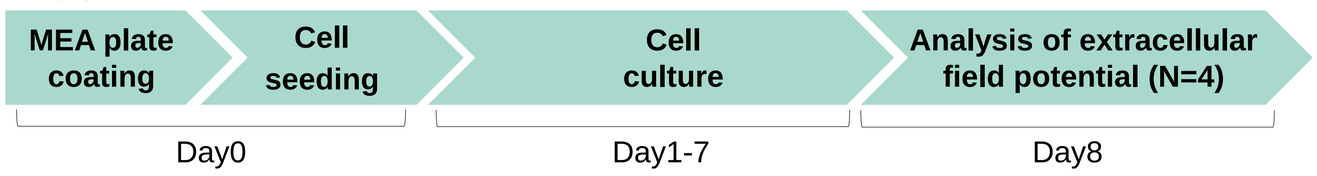
✓Cell：iCell® Cardiomyocytes[2] (FUJIFILM Cellular Dynamics, Inc.)
✓Coating agent：Fibronectin
✓Media：iCell® CM Plating Medium , iCell® CM Maintenance Medium

iCell® Cardiomyocytes[2]



Multi-electrode array

Assay protocol



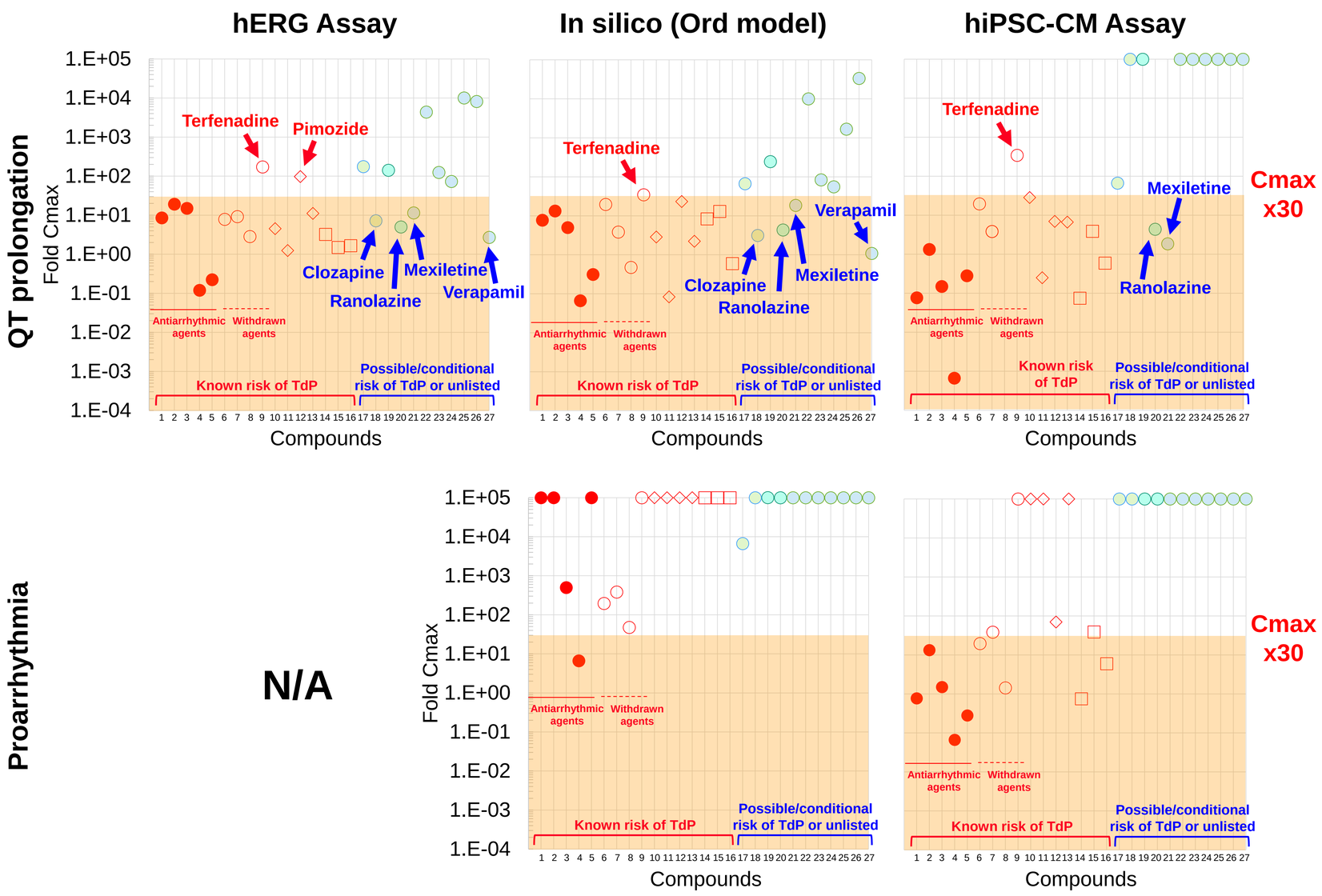
<Data Analysis>

✓FPD and FPDcF were calculated from the recorded extracellular field potentials.
✓Ion-channel inhibition data for the compounds were obtained from a previous report[1].
✓Action potentials of adult cardiomyocytes were simulated based on data from a previous study[2].
✓The risk categories from CredibleMeds[1] were used to assess the clinical proarrhythmic potential of the tested compounds.
✓A threshold of Cmax x 30 was applied to evaluate the proarrhythmic risk of compounds in each assay.

Results

<Evaluation of proarrhythmic potential>

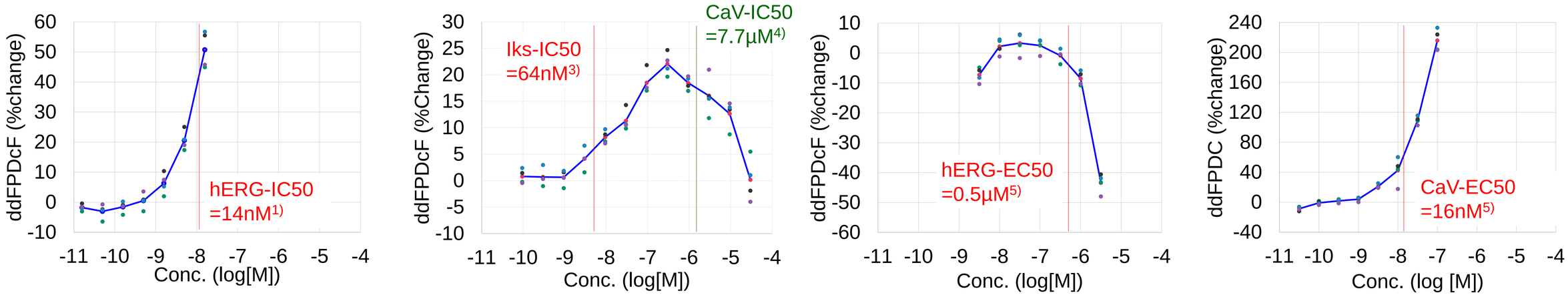
No.	Risk Category (Credible Meds[1])	Compounds	Clinical Cmax [μM][1]
1	Known risk of TdP	D,l – Sotalol	13
2		Disopyramide	0.75
3		Dofetilide	0.002
4		Ibutilide	0.15
5		Qunidine	3.2
6		Astemizole	0.00051
7		Cisapride	0.0026
8		Droperidol	0.021
9		Terfenadine	0.00029
10		Bepridil	0.035
11		Flecainide	1.2
12		Pimozide	0.00043
13		Thioridazine	0.045
14		Erythromycin	12
15		Ondansetron	0.077
16		E-4031	0.0084
17	Possible risk of TdP	Risperidone	0.0015
18		Clozapine	0.32
19	Conditional risk of TdP	Amitriptyline	0.041
20		Ranolazine	2.3
21	Unlisted agent	Mexiletine	5.4
22		Nifedipine	0.01
23		Chlorpromazine	0.012
24		Dilitiazem	0.18
25		Loratadine	0.0006
26		Nitrendipine	0.0030
27		Verapamil	0.092



<Assessment of drugs beyond major ion-channel inhibition (hERG, NaV1.5, and CaV1.2) >

3) https://d-nb.info/1130707415/34
4) ChanTest 2014 ttps://www.onemillionsolutionsinhealth.org/wp-content/uploads/2014/11/ChanTest-Data-Analysis-Summary.pdf
5) https://www.medchemexpress.com

E-4031: hERG inhibitor **JNJ-303: Iks inhibitor** **ICA-105574: hERG activator** **FPL64176: L-type Ca^{2+} agonist**



Discussion

- hiPSC-CMs reduce false-positive rates in the risk prediction of QT prolongation (threshold: Cmax x30) compared to hERG assay and simulation using the Ord model based on hERG, NaV1.5, and CaV1.2 inhibition.
- Many compounds with a known risk of TdP (12 out of 16 tested) induced early after depolarizations (EADs) in hiPSC-CMs.
- Compounds with diverse effects on ion channels induce characteristic extracellular field potential changes in hiPSC-CMs according to their specific properties..

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