Japanese Stem Cell Efforts

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CARDIAC SAFETY RESEARCH CONSORTIUM

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Today's Talk

1. Japan iPS Cardiac Safety Assessment (JiCSA) Activity
   - ➢ Results
     - Clinical relevance of hiPSC-CMs to human ECG study

       The paper accepted by PLoS ONE.
     - Validation study using 60 compounds for TdP risk categorization

       The paper accepted by J.Pharmal.Toxicol.Method
2. Proposal for scoring method to predict high and low proarrhythmic risk

JiCSA activity

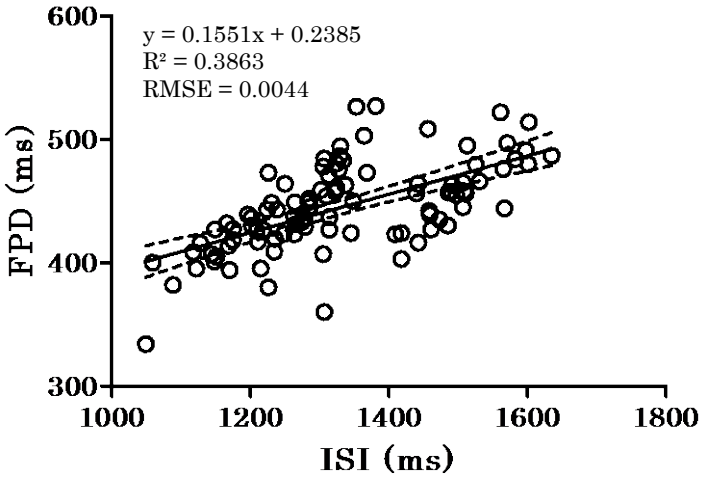
Is now supported by the Grant from Japan Agency for Medical Research and Development (AMED).

- **Aims to validate the utility of human iPS-derived cardiomyocytes for safety pharmacology testing.**
- **Aims validate the ability of hiPSC cardiomyocytes to predict TdP occurrence.**

JiCSA 60 compound study :MEA platform

- 4 sites; Esai, Nippon-shinyaku, Ono, Teijin
- iCell cardiomyocytes
- Compounds selection & collection of clinical information for 60 compounds
- Data collection
- Data analysis for inter-laboratory variation of 4 sites
- Analysis for baseline data
- Free concentrations of compounds and clinical Cmax.
- Scoring by biomarkers; change in FPDc & EAD incidence
- Proposal for a method of the TdP risk prediction

The rate correction method applied for hiPSC-derived CMs



Spontaneously betating iCell cardiomyocytes showed linear ISI-FPD relationship with positive slope (similar to Framingham study).

QT_C= QT + 0.154 (1-RR)

N=5,018 (2,239 men;2,779 women). 44 yrs (range 28-62)

(Sagie A., et al. *Am J Cardiol*. 70; 797-801,1992)

1. Reverse use-dependent FPD prolongation by hERG inhibition is detected as reverse use-dependent QT prolongation by E-4031 or dofetilide in clinical studies.
2. Because our in vitro results with human stem cell cardiomyocytes are similar to clinical electrophysiological data, hiPSC-CMs will provide useful data for assessing the torsadogenic potential of drug candidates.

A proposed scoring system

- **Scoring based on extent of FPDc prolongation and EAD incidence**

Score	-1	0	1	2	3
FPDc change	<-10%	No change	≧ 10%, <30%*	≧ 30%*	-
EAD	-	-	-	-	+

- **Example scores with drugs from different proarrhythmia risk categories**

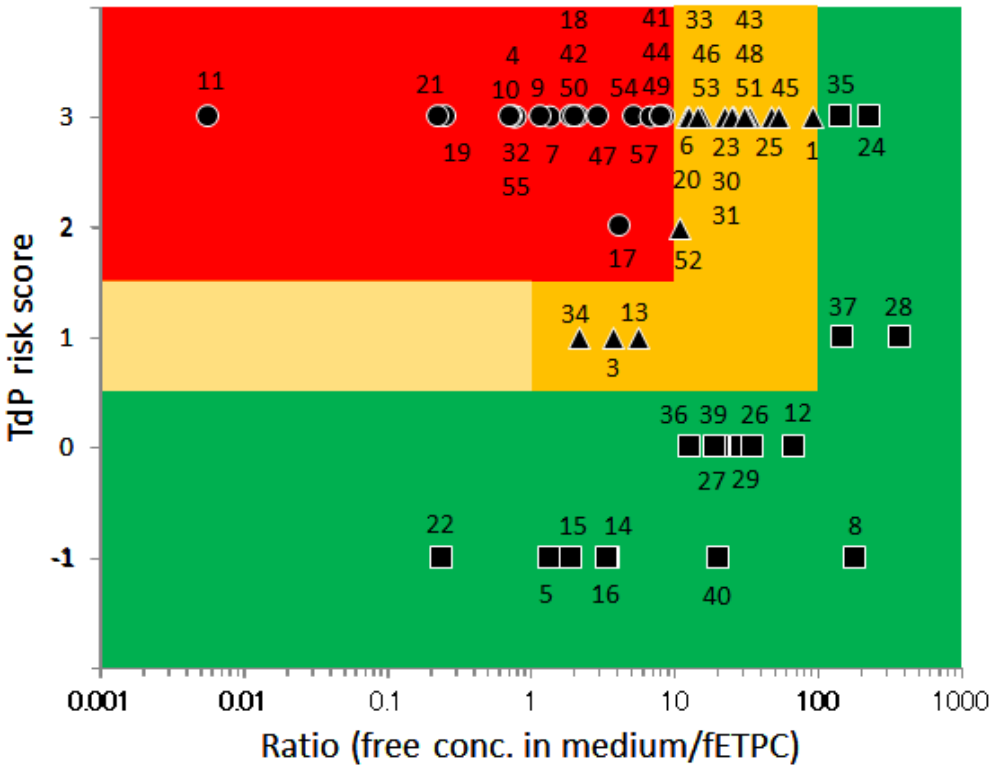
Compound	Concentration（μM）						Score
Astemizole	0.0001	0.0003	0.001	0.003 (14%)	0.01 (26%)	0.03 [EAD 5/6]	3
Cisapride	0.003	0.01	0.03 (13%)	0.1 [EAD 6/6]	-	-	3
Diphenhydramine	0.1	0.3	1 (12%)	3 (21%)	10 (109%)	-	1
Moxifloxacin	3	10	30 (16%)	100 (46%)	300 (2nd peak flat)	-	2
Nifedipine	0.001	0.003	0.01	0.03	0.1 (-33%)	-	-1

Risk categorization byJiCSA method

High risk
17TP & 2 FP

- Clarithromycin(49)
- Dofetilide (7)
- Domperidone (32)
- Droperidol (41)
- E-4031 (9)
- Erythromycin (50)
- Flecainide (10)
- Haloperidol (42)
- Ibutilide (11)
- Nilotinib (55)
- Pimozide (44)
- Prenylamine (17)
- Procainamide (18)
- Quinidine (19)
- Quinine sulfate(54)
- Sematilide (21)
- D,L-sotalol (4)
- Thioridazine (47)
- Vandetanib (57)

17TP/17+4 FN
Sensitivity **0.81**



Ajmaline (1)
Astemizol(23)
Bepridil(3)
Cisapride(30)
Disopyramide(6)
Diphenhydramine(25)
Dolasetrone(31)
Gatifloxacin(51)
Mexiletine(13)
Moxifloxacin(52)
Ondansetrone(33)
Paliperidone(43)
Risperidone(45)
Sertindole(46)
Sparfloxacin(53)
Terodiline(34)
Ziprasidone(48)

Intermediate risk (17 comps)

Low risk
13TN & 4 FN

- Aspirin (36)
- Chlorpheniramine (24)
- Chlorpromazine (39)
- Cilostazole (37)
- Clozapine (40)
- Diltiazem (5)
- Dronedarone (8)
- Famotidine (29)
- Levocetirizine (26)
- Loratadine (27)
- Metoprolol (12)
- Mibefradil (14)
- Nifedipine (15)
- Nitrendipine (16)
- Terfenadine (28)
- Tolterodine (35)
- Verapamil (22)

13TN/13+2FP
Specificity **0.87**

Arrest
Amiodarone(2)
Amitriptylin(38)
Flecainide(10)
Ranolazine(20)
Tamoxifen(56)

Conclusion of JiCSA 60 Compound Study

- JiCSA evaluated the effects of 60 compounds on FPD of hiPSC-CMs using MEA platform.
- The rate correction shows that the ISI-FPD relation of the hiPSC-CMS is similar to the result of the Framingham study.
- Two dimensional maps (plotting risk scores vs. exposure margins normalized to ETPC) used to classify the compounds.
- TdP risk ranking showed good concordance with CredibleMeds information.

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