



Japan iPS Cardiac Safety Assessment (JiCSA) Study Data Review

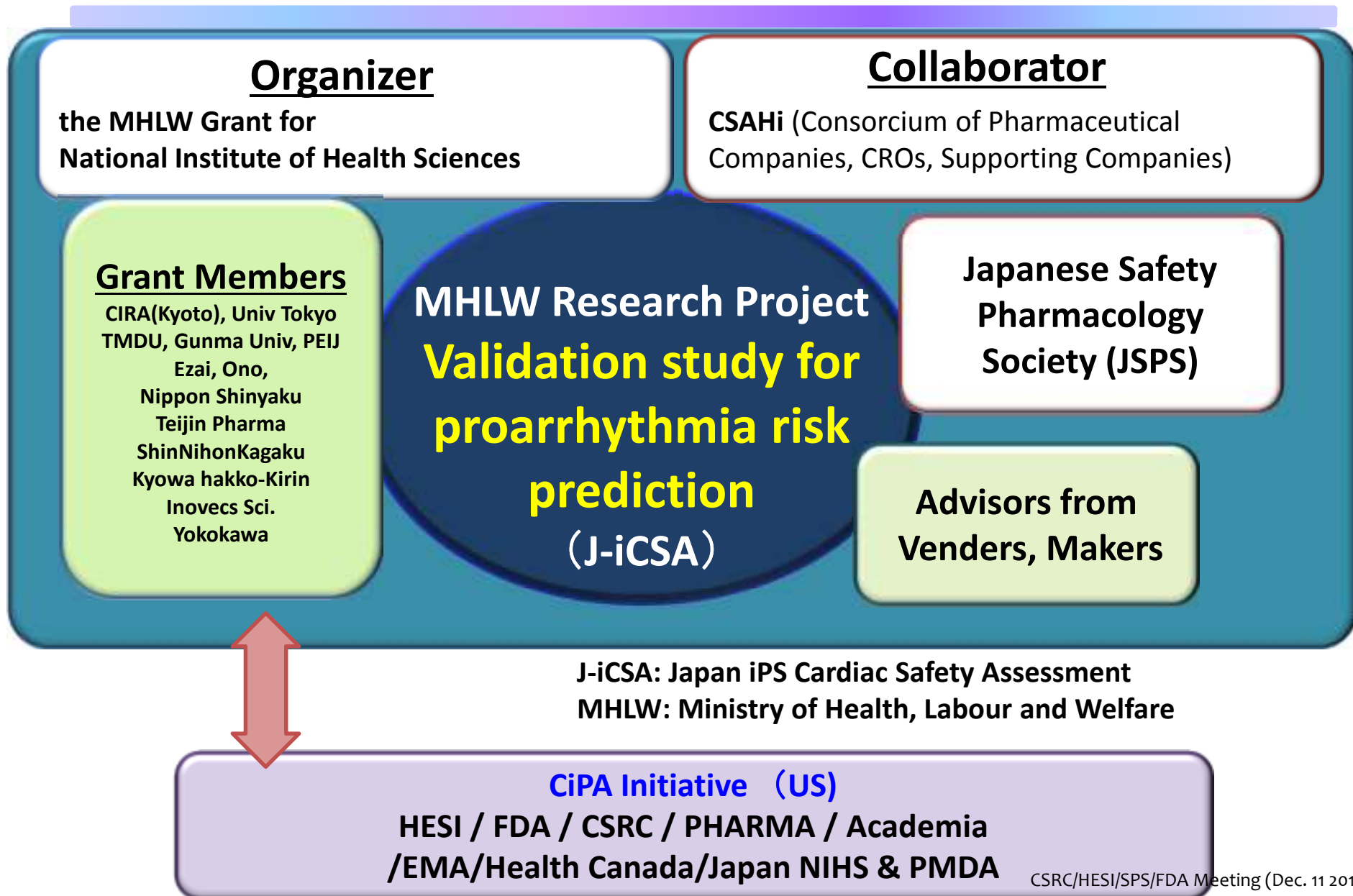
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Today's Presentation:

- What is JiCSA
- What we have done
- What we are doing
- What we will do

What is JiCSA?



What we have done

- 2010-2011: Literature studies
No standardized protocol for experiments
- 2012: Proposal of a standardized protocol
 - ✓ We have chosen a high density sheet preparation with iCell
Cardiomyocytes from CDI
 - ✓ MEA system (MED64 systems from Alpha MED Scientific
Inc.)
 - ✓ Prolongation of repolarization time (Field potential duration)
EAD/triggered activity

What we have done



The validation of the protocol

A Tripartite Research : Industry-Government-Academia

Proposal of a standardized protocol at HESI Workshop on "Pluripotent Stem Cells: Applications for Cardiovascular Risk Assessment. (March 18-19, 2013)

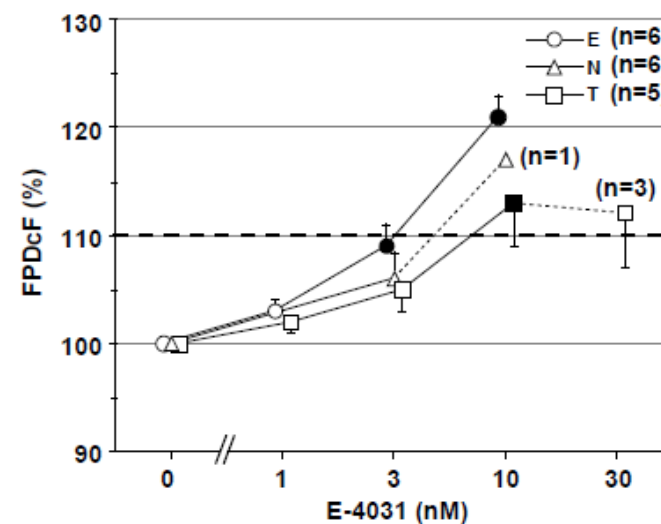
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Full Paper

Assessment of Testing Methods for Drug-Induced Repolarization Delay and Arrhythmias in an iPS Cell-Derived Cardiomyocyte Sheet: Multi-site Validation Study

Yuji Nakamura¹, Junko Matsuo^{1,2,3}, Norimasa Miyamoto⁴, Atsuko Ojima⁴, Kentaro Ando¹, Yasunari Kanda¹, Kohei Sawada⁴, Atsushi Sugiyama^{1,4*}, and Yuko Sekino^{3,5,6*}



What we are doing



Semi-large Scale Validation for Proarrhythmia with MEA devices

- **MED64(4 groups) : Inter facility variation and compound evaluation**
 - **1st stage: Inter facility variation with E4031, cisapride, chromanol293B**
 - 2nd stage: 60 test compounds (two or three facilities for one comp)
 - 3rd stage: several blinded compounds
- MCS (2 groups) & Axiobio Mastro (1 group): Inter-MEA device difference
- VSD (2 groups) team: Translation from MEA to VSD, Simultaneous recording
- Cell production (3 groups) : CiRA, University of Tokyo, Takara

What we are doing



To achieve a high degree of reproducibility through a common protocol

1. use a protocol in which details are evaluated in more depth for:

Culture density

Culture period

Temperature calibration

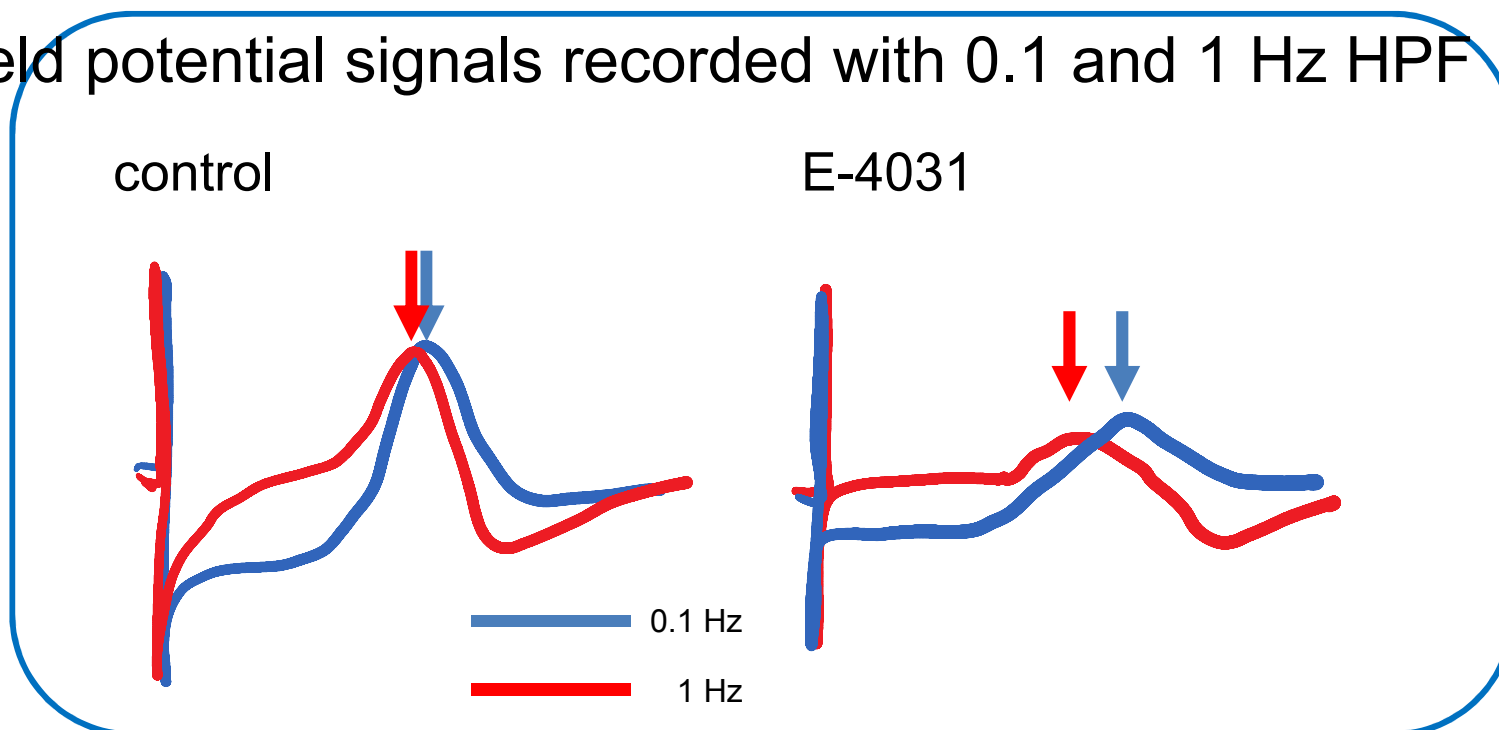
Recording filter frequency

2. Technical levels : people need to be trained.

(J.S.P.S. held training courses three times in 2014)

Using 0.1 Hz of High Pass Filter (HPF) for MEA recording improved the accuracy

Field potential signals recorded with 0.1 and 1 Hz HPF



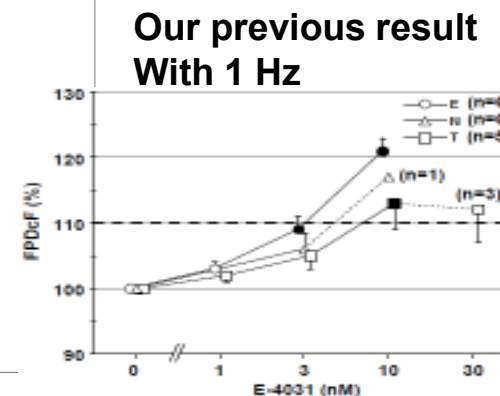
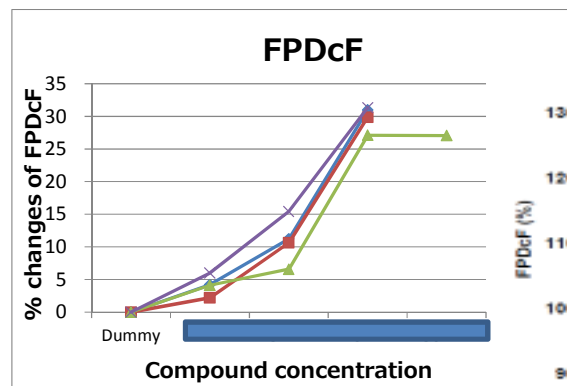
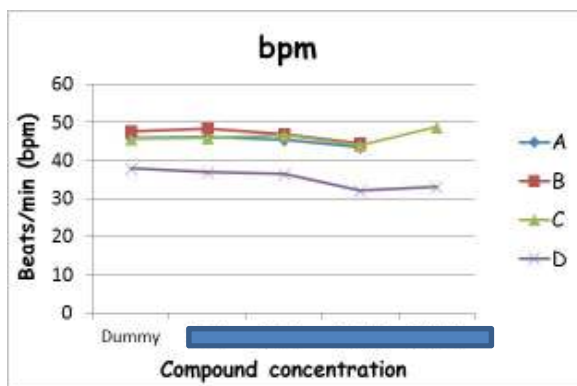
Modified from the data presented at the meeting (Sawada, et al)

Recording with 1Hz results in underestimation of QT prolongation in many cases

Recent results (unpublished)

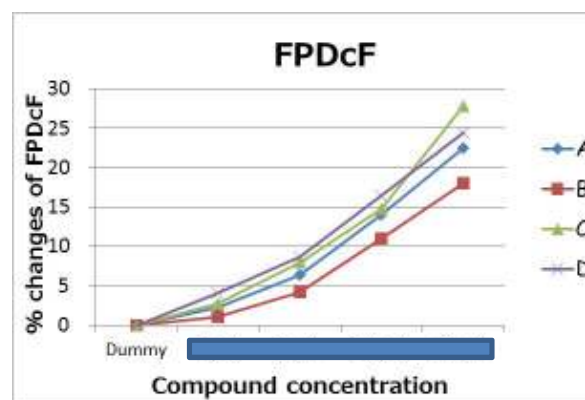
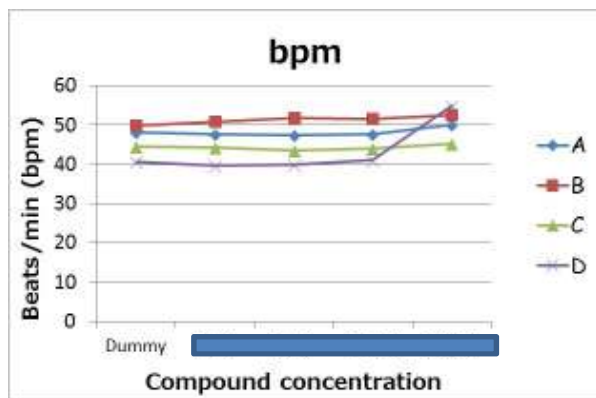


E-4031



Nakamura et al. (2014)

Chromanol 293B



Variation was smaller and % changes were bigger than our previous result.

What we plan to do



Semi-large Scale Validation for Proarrhythmia with MEA devices

- **MED64(5 groups) : Inter facility variation and compound evaluation**
 - **1st stage: Inter facility variation with E4031, cisapride, chromanol293B**
 - **2nd stage: over 30 test compounds (two or three facilities for one comp)**
 - **3rd stage: several blinded compounds**
- **Lot-to-lot difference**
- **Cell line differences**
- **Inter-MEA device difference: MCS (2 groups) & Axiobio Mastro (1 group): VSD (2 groups) team: Translation from MEA to VSD, Simultaneous recording**
- **Cell production (3 groups) : CiRA, University of Tokyo, Takara**

Until March in 2015

Over 30 test compound using one lot of one cell line

Lot-to-lot difference as possible we can do.

Cell line differences if possible

Inter-platform difference

MCS (2 groups) & Axiobio Mastro (1 CRO)

Simultaneous recording using MEA and VSD

2 groups