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?

Organizer
the MHLW Grant for National Institute of Health Sciences

Collaborator
CSAHi (Consortium of Pharmaceutical Companies, CROs, Supporting Companies)

Grant Members
CIRA (Kyoto), Univ Tokyo TMDU, Gunma Univ, PEIJJ Ezai, Ono, Nippon Shinyaku Teijin Pharma ShinNihonKagaku Kyowa hakko-Kirin Inovecs Sci. Yokokawa

MHLW Research Project
Validation study for proarrhythmia risk prediction (J-iCSA)

Japanese Safety Pharmacology Society (JSPS)

Advisors from Venders, Makers

J-iCSA: Japan iPS Cardiac Safety Assessment
MHLW: Ministry of Health, Labour and Welfare

CiPA Initiative (US)
HESI / FDA / CSRC / PHARMA / Academia /EMA/Health Canada/Japan NIHS & PMDA
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)
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
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.

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

Modified from the data presented at the meeting (Sawada, et al.)
Recent results (unpublished)

E-4031

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 grops) & Axiobio Mastro (1 CRO)

**Simultaneous recording using MEA and VSD**
2 groups