Comprehensive *In Vitro* Proarrhythmia Assay Initiative (CiPA): Evolving Efforts

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for the CiPA Steering Committee & volunteers (CSRC/HESI/FDA/Japan Nat'nl Inst. of Health Sciences, Health Canada, EMA, PDMA (Japan), Japan IPS Cardiac Safety Assessment, Safety Pharmacology Society, NCI, CRO's Stem Cell providers, Platform providers, Academicians, Modelers, others)

CSRC Annual Meeting

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CiPA: Comprehensive *In Vitro* Proarrhythmia Assay

- ***Goal:***

  - Develop a **new *in vitro* paradigm** for cardiac **safety evaluation** of new drugs

  - Provide a more accurate and **comprehensive, non-binary mechanistic-based assessment** of **proarrhythmic potential**

  - Focus on **proarrhythmia (not QT prolongation) to improve specificity** (versus preclinical hERG current & clinical TQT studies)

CiPA:
Comprehensive *In Vitro* Proarrhythmia Assay

- ***How?***

- Define effects on multiple human cardiac currents

- Characterize integrated electrophysiologic response using in silico reconstructions of human ventricular electrophysiology

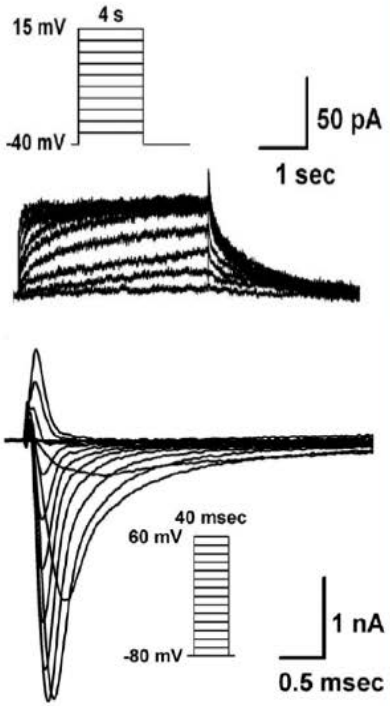
- Categorize proarrhythmic risk based on clinically-ranked TdP risk

Verify effects on

a) on human stem-cell derived myocytes, and
b) early clinical QT (exposure response) studies

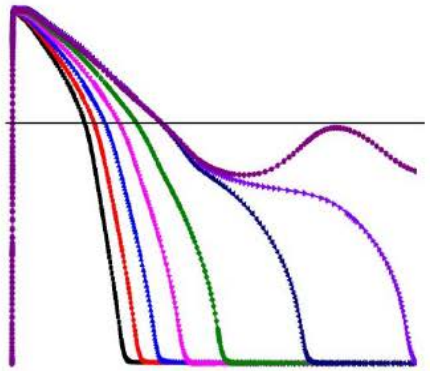
Components of CiPA

Drug Effects on Multiple Human Cardiac Currents

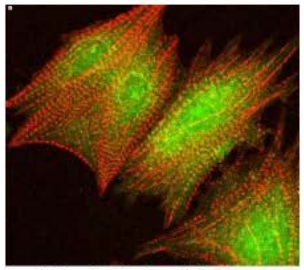


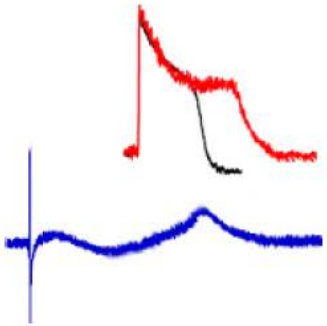
In Silico Reconstruction Cellular Human Ventricular Electrophysiology

$$I_{stim} = C\frac{dV_m}{dt} + I_m$$

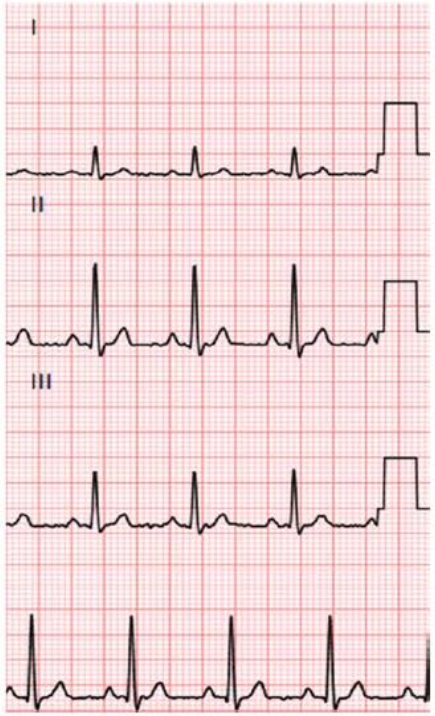


In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes





Clinical Evaluation Unanticipated Electrophysiology



CHARACTERIZE/CLASSIFY EFFECTS

VERIFY EFFECTS

Define Effects on Multiple Human Cardiac Currents. *Ion Channel Group*

Goal:

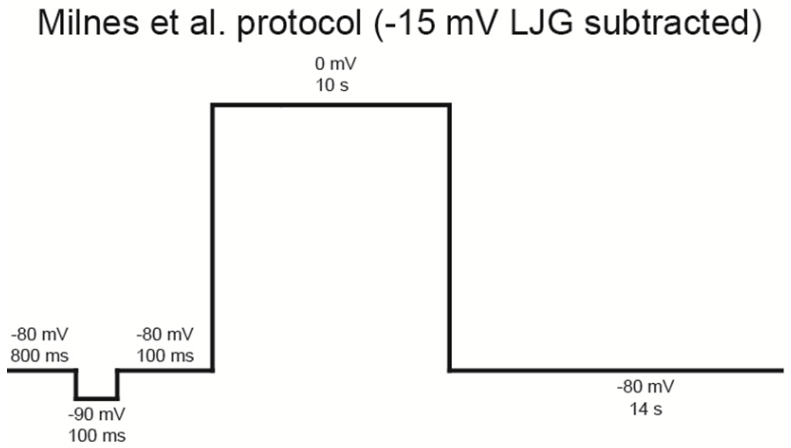
- Provide robust ionic current data (human channels in heterologous expression systems) for in silico reconstructions of drug effects

How:

- Define requirements for reliable and reproducible ion channel data in high throughput screening (HTS) environment
- Produce consensus protocols for predominant channels
  - Seven currents proposed: INa, INaLate, Ito, ICaL, IKr, IKs, IK1

Challenges:

- Variability in data across platforms
- Static vs. kinetic data descriptions for hERG block



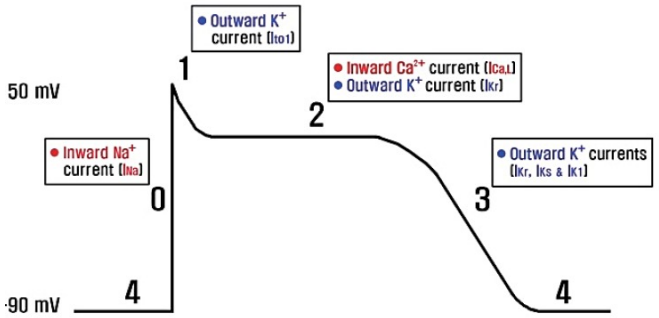
Characterize Integrated Electrophysiologic Response Using In Silico Reconstructions of Human Ventricular Electrophysiology. *In Silico Group*

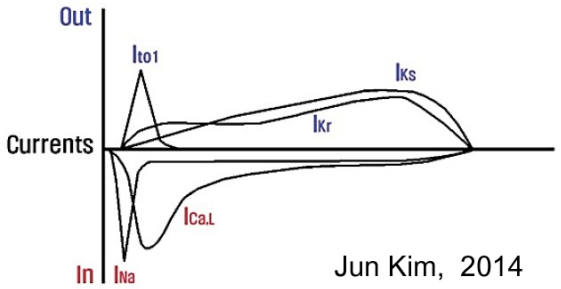
Goal:

- To develop an in silico model of adult human ventricular myocyte that predicts clinical risk of TdP for use in regulatory decision making
- O'Hara Rudy model (human based) identified as "Gold Standard"
- hERG channel kinetics modified to better describe repolarization effects

Challenges:

- Risk metric best suited for proarrhythmia : quantitative, continuous, conc.-dependent, mechanistically relevant
- Ability to distinguish 3 levels of clinical TdP risk (Low/no, Intermediate, High):ongoing
- Education/familiarity with in silico approaches
- Model availability for novel users/end users





Categorize Proarrhythmic Risk Based on Three-Tier Clinical Ranking of TdP Risk (CiPA 28 Drugs)

High TdP Risk	Intermediate TdP Risk	Low TdP Risk
Calibration:	**Calibration:**	**Calibration:**
Bepridil	Chlorpromazine	Diltiazem
Dofetilide	Cisapride	Mexiletine
Quinidine	Terfenadine	Ranolazine
D,l Sotalol	Ondansetron	Verapamil
Validation:	**Validation:**	**Validation:**
Azimilide	Astemizole	Loratadine
Ibutilide	Clarithromycin	Metoprolol
Vandetanib	Clozapine	Nifedipine
Methadone	Domperidone	Nitrendipine
	Droperidol	Tamoxifen
	Pimozide	
	Risperidone	

Clinical Translational Working Group

Verify Electrophysiologic Effects Using Human Stem-Cell Derived Cardiomyocytes and Early Clinical QT (ER) Studies.

Myocyte Group

Goal:

- Establish human stem cell derived cardiomyocytes as an integrating model system to identify potential gaps in electrophysiologic effects (not detected previously) that may impact TdP risk classification

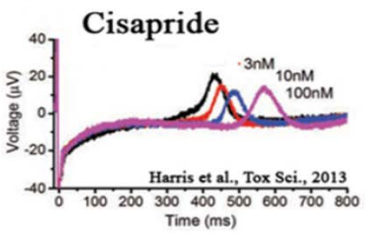
How:

- Report on drug-induced repolarization abnormalities using multielectrode array (MEA) or voltage-sensing optical (VSO) technologies (focus on repolarization (FPD-APD), beat frequency, proarrhythmia events (EAD activity)

Progress:

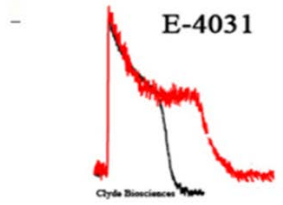
HESI sponsored validation studies ongoing (“CiPA 28”)

Micro-Electrode Array (MEA)



Extracellular Field Potential Recordings

Voltage-Sensitive Dye (VSO)



Transmembrane Action Potential Waveforms

Verify Electrophysiologic Effects Using Human Stem-Cell Derived Cardiomyocytes and Early Clinical QT(ER) Studies. *Clinical Translations*

Goal:

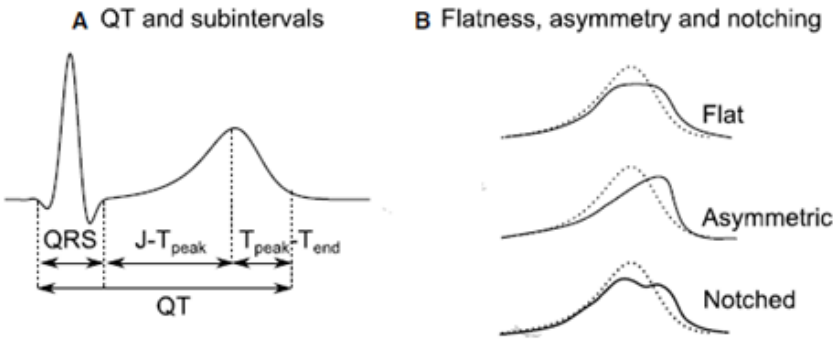
- Detect unexpected electrophysiologic effects compared to preclinical ion channel data/in silico reconstructions (e.g. human specific metabolite, protein binding, channel modulation)

How:

- Early human phase 1 ECG evaluation
  - a) QT prolongation (Exposure-response)
  - b) QT morphological changes (J-Tpeak, Tpeak-Tend) to identify multi-ion channel effects on repolarization

Challenges:

- New ECG biomarker(s) would add additional information beyond PR/QRS/QTc



Summation

A new cardiac safety paradigm focused on nonclinical measurement of proarrhythmic proclivity

Focus on the real issue: ***Proarrhythmia***

- Reduce the premature termination of drugs with favorable benefit:risk profiles
- Make drug development more efficient
- Provide a more comprehensive assessment of risk to earlier discovery phase, using assays to guide candidate selection and reducing later stage attrition
- Obviate the TQT study
- Enhance the accuracy with which existing and/or new drugs are labeled relative to actual proarrhythmic risks