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

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for the CiPA Steering Committee & volunteers
(CSRC/HESI/FDA/Japan Nat’n’l 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)

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CiPA: Comprehensive

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**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

**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)

<table>
<thead>
<tr>
<th>High TdP Risk</th>
<th>Intermediate TdP Risk</th>
<th>Low TdP Risk</th>
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<tbody>
<tr>
<td><strong>Calibration:</strong></td>
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<tr>
<td>Bepridil</td>
<td>Chlorpromazine</td>
<td>Diltiazem</td>
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<td>Dofetilide</td>
<td>Cisapride</td>
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<td>Astemizole</td>
<td>Loratadine</td>
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<td>Ibutilide</td>
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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”)
Goal:
- Detect unexpected electrophysiological 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