

# CiPA Data Package and Regulatory Approach

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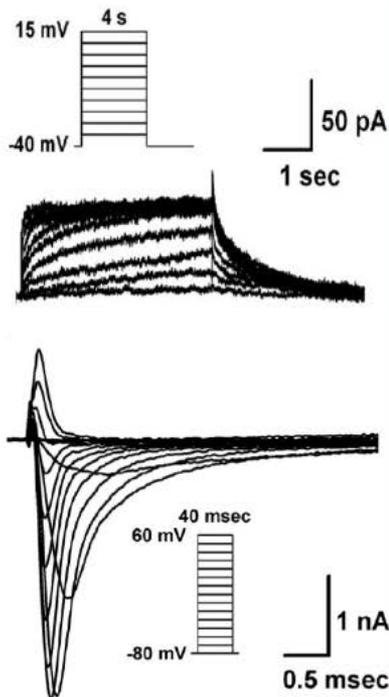
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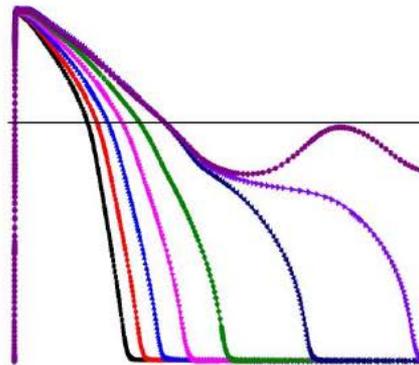
# Four Components of a CiPA Report

## Drug Effects on Multiple Human Cardiac Currents

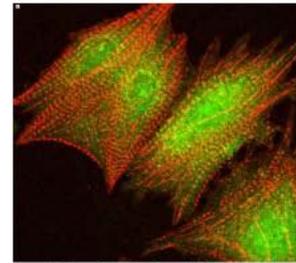


## *In Silico* Reconstruction Cellular Human Ventricular Electrophysiology

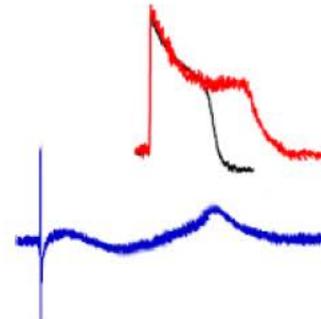
$$I_{stim} = C \frac{dV_m}{dt} + I_m$$



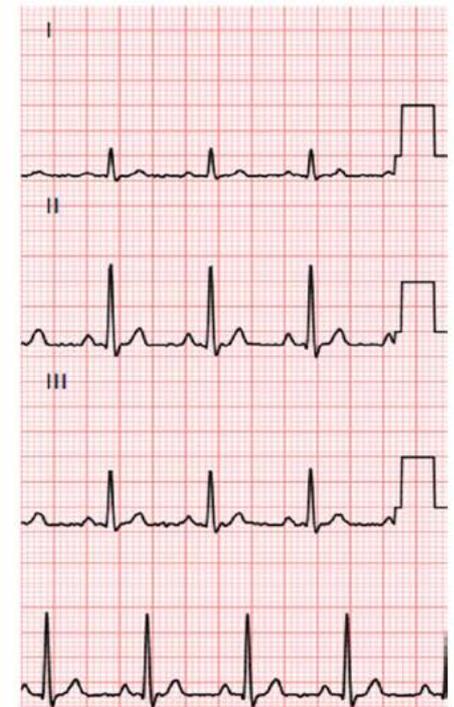
## *In Vitro* Effects Human Stem-Cell Derived Ventricular Myocytes



McEwen Cntr for Regen Med., Toronto



## Clinical Evaluation Unanticipated Electrophysiology



**CHARACTERIZE/CLASSIFY EFFECTS**

**VERIFY EFFECTS**

# CiPA: Comprehensive *In Vitro* Proarrhythmia Assay

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- Define effects on multiple human cardiac currents
- Characterize integrated electrophysiologic response using in silico reconstructions of human ventricular electrophysiology
  - Results in a proarrhythmia risk core
- Verify the observed electrophysiologic effects on
  - On human stem-cell derived myocytes, and
  - ECG data in FIM study(ies)

# Purposes/Outcomes of CiPA

- Regulatory Decision Making
- Internal Decision Making
  - Candidate selection
  - In silico source code to be made available
- Opportunities for Knowledge Advancement
  - Data depository in which composite data can inform on CiPA analytics
    - Potential for data sharing (e.g., like has been done with TQT study ECG's)
  - Iterate and improve on in silico model utilizing new data
  - Increase efficiency of acquiring voltage clamp data
  - Potential for consortia to develop best practices
    - High throughput ion channel approaches
    - Evaluate performance characteristics of different systems
  - **Mechanism to evaluate drugs to test In Silico model**

Data Package to be Supplied to the ICH E14  
Discussion Group by Each Work-Stream

# Ion Channel Work Stream

**Goal:** Provide standardized voltage clamp protocols allowing the generation of data from selected human cardiac ion channels for integration in the in silico model. Protocols focused on high throughput (HT) screening. Should allow determination of IC<sub>50</sub> data for all channels studied, and in the case of hERG, also reliably inform on the dynamic block of the channel. Finally, all protocols should provide data consistent across labs, drugs and studies.

## **CiPA confirmation package data for December 2017:**

- Standardization of voltage clamp protocols for the hERG channel with a test set of 12 drugs using manual patch clamp data obtained at ambient and physiological temperatures to serve as benchmark (work is completed)
- Standardization of voltage clamp protocols for all selected ion channels, including hERG, with an initial test set of 12 drugs in the optimization phase (Phase 1) followed by a set of 18 drugs in the validation phase (Phase 2) using HT automated patch clamp data obtained at ambient and physiological temperatures (Work is ongoing. Proposed timelines for completion: 2Q17)
- Assessment of the intra- and inter-experimental variability and reproducibility of data
- Statistical framework for the analysis of the variability and potential impact on concentration-response determinations and in silico model output
- Establishment of data quality standards
- **First line channels to assess for IC<sub>50</sub> determination:**  
 $I_{Kr} = \text{hERG}$  ;  $I_{Ca}(\text{L-type}) = \text{Cav1.2}$ ;  $I_{Na} = \text{Nav1.5}$  peak and late current – drug modified Nav1.5
- **Second line channels to assess for IC<sub>50</sub> determination:**  
 $I_{TO} = \text{Kv4.3}$ ;  $I_{Ks} = \text{KCNQ1+KCNE1}$ ;  $I_{K1} = \text{Kir2.1}$
- Freely-available methods and voltage clamp protocols for all ion channels, including dynamic block protocol for hERG and other channels, as needed.

# In Silico Proarrhythmia Assessment

**Goal:** Use an in silico model of the adult human ventricular myocyte to integrate multi-ion channel patch clamp data and output a proarrhythmic score ranking drugs as high, intermediate or low risk of torsade de pointes (TdP)

## CiPA confirmation package data for December 2017:

- Calibration of the in silico model and proarrhythmic metric with 12 CiPA training drugs using manual and automated patch clamp data
  - Two proarrhythmic metrics are currently able to separate high, intermediate and low risk drugs:
    - a)  $I_{net}$  (integrated net current) and b) inward current change metric which are mechanistically linked to early after depolarization (EAD) generation, the trigger for TdP. After analysis of automated patch clamp data, the best metric will be proposed
  - Will include methodology and results for assessing the effect of experimental uncertainty and inter-subject variability on the proarrhythmic metric with a recommendation for implementation of uncertainty/variability assessment
  - Minimum data quality criteria for patch clamp recordings to be inputted into the model
- Testing the proarrhythmic metric with patch clamp data from the 16 CiPA test drugs with proarrhythmic risk outputted as a function of drug concentration with uncertainty/variability assessment
  - Leave-one-out classification with all 28 CiPA drugs will be applied to further assess robustness of the metric and establish thresholds and confidence limits
  - Will include comparison among multiple different sites and automated patch clamp systems
- Freely-available, open-source temperature-sensitive dynamic hERG model integrated into a modified O'Hara-Rudy ventricular cell model along with tools for parameterization of the model

# Myocyte Work Stream

**Goal:** Using human IPS cardiomyocytes, provide standardized and robust experimental protocols to

- Assess the acute integrated electrophysiologic effects of drugs on repolarization
- Verify results obtained with human ionic currents/*in silico* reconstructions
- Ensure compatibility with current (and future) high throughput screening approaches (using multielectrode array [MEA] and optically-based voltage-sensitive dyes/proteins [VSO])
- Flexible to account for different characteristics of present and future myocyte preparations.

## **CiPA Supporting Data for Confirmation Package to ICH (December 2017)**

- Standardized experimental protocols across technology platforms to define acute concentration-dependent effects on field potential duration (MEA) or action potential duration (VSO) for present and evolving myocyte preparations.
- Demonstration of consistent, reproducible, concentration-dependent effects for a blinded set of 28 compounds spanning the full range of proarrhythmic risk.
  - This will be accomplished in an ongoing validation study with a core group consisting of 8 sites, 3 MEA / 2 VSO platforms, and 2 commercial cell lines to assess experimental variability.
- Provide a template to enable comparisons of *in vitro* electrophysiologic effects with *in silico* reconstructions
  - Create a statistical framework to define concordant/discordant results.
- Define best practices for and utility of positive control studies in regards to comparisons with *in silico* reconstructions across drugs, experimental platforms, and preparations.

# Clinical Phase 1 ECG Biomarker

**Goal:** Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data

## **CiPA confirmation package data for December 2017:**

- Analysis of 12 ECG biomarkers from multiple prior clinical studies demonstrating J-Tpeakc as the best biomarker to differentiate QT prolonging drugs with selective hERG block from QT prolonging drugs with hERG and late sodium or calcium block
- Statistical framework for combined analysis of QTc and J-Tpeakc for use in small sample size, early phase 1 clinical studies using exposure-response analysis
- Prospective clinical study to verify this approach including drugs with
  - selective/predominant hERG block (dofetilide, chloroquine)
  - hERG + late sodium block (ranolazine)
  - hERG + calcium block (verapamil, dofetilide+diltiazem)
  - hERG + late sodium + calcium block (lopinavir/ritonavir)
- Analysis of QTc and J-Tpeakc in a large number of prior TQT studies with matching hERG, calcium and late sodium ion channel data
- Freely-available open-source software for J-Tpeakc assessment along with comparison to other commercial software

# Discussion

- ICH E14 Discussion Group Members
- CiPA Proposed data package
- Other regulatory issues