

Focus on the CiPA paradigm

Update from the front lines

BRC June 2016



WORLDWIDE RESEARCH & DEVELOPMENT
Drug Safety R&D



Revolution dawning in cardiotoxicity testing

Stem cell technology and computational modeling offer the promise of reducing the current burden of cardiotoxicity assessment.

Current status of cardiac safety assessment

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved or removed from the market
- However, at a significant cost
- Negative impact on drug development
 - hERG assay has assumed role as gatekeeper in screening approach
 - Premature discontinuation due to hERG or QT “signal”
 - (Inaccurate) perception of risk leading to drug discontinuation
 - Estimates of up to 60%
- Concerns regarding development burden, costs, labeling
- Many potentially good compounds never get evaluated in humans due to a hERG effect
 - Drug development in specific areas- CNS
 - Many drugs with QT labeling are unlikely to be proarrhythmic
 - Engineering-out hERG- applicability/other effects

Current status of cardiac safety assessment

- Does not directly address endpoint of clinical concern: proarrhythmia (TdP)
- Focus on block of one repolarization current: HERG
- Not all QT prolongation represents effects on HERG
- Block of HERG alone is not always sufficient to predict delayed repolarization or proarrhythmic risks
- Some true HERG blockers are anti-arrhythmic, because of effects on inward currents
- Increases in QTc: sensitive but not specific to predict proarrhythmia

Linking Arrhythmias and Ion Channels

- We have a solid mechanistic understanding of the ionic factors that confer proarrhythmic risk to candidate drugs
- Such insights is directly amenable to ion channel studies
- Ion channel data has been used previously to help support in silico reconstruction of ventricular AP to understand arrhythmias however;
 - The majority of the data has been obtained under various, unconstrained, experimental conditions often leading to conflicting results
 - Historically, the majority of the work has been performed on models or expression systems that are not of human origin
- CiPA is focussed on assessing the effects of candidate drugs on ion channels present in human ventricle
- CiPA is structured to ensure robustness, reliability and reproducibility of the ion channel dataset generated by providing rigorously standardized patch clamp protocols and defined experimental conditions in order to minimize bias and variability

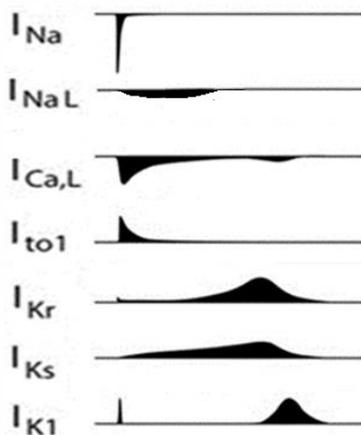


Focuses on the real issue: Proarrhythmia

- Reduce the premature termination of drugs with favourable benefit/risk profiles
- Makes drug development more efficient
 - Move the bulk of proarrhythmic assessment to the discovery phase; simplify clinical development
 - Earlier removal of regulatory uncertainty
 - Pre-clinical approach can potentially guide candidate selection
 - Obviate the TQT study
- Enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks

Comprehensive *In Vitro* Proarrhythmia Assay: Four Components

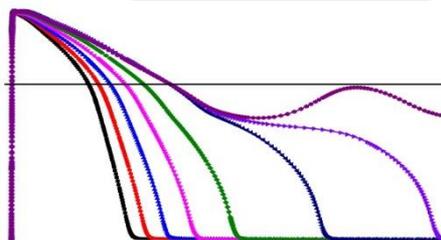
Drug Effects on Multiple Human Cardiac Currents



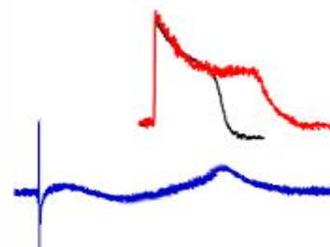
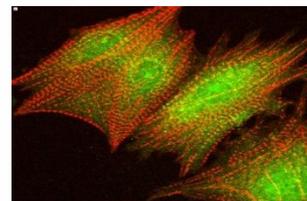
modified from Hoekstra et al., 2012

In Silico Reconstruction Human Ventricular Cellular Electrophysiology

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



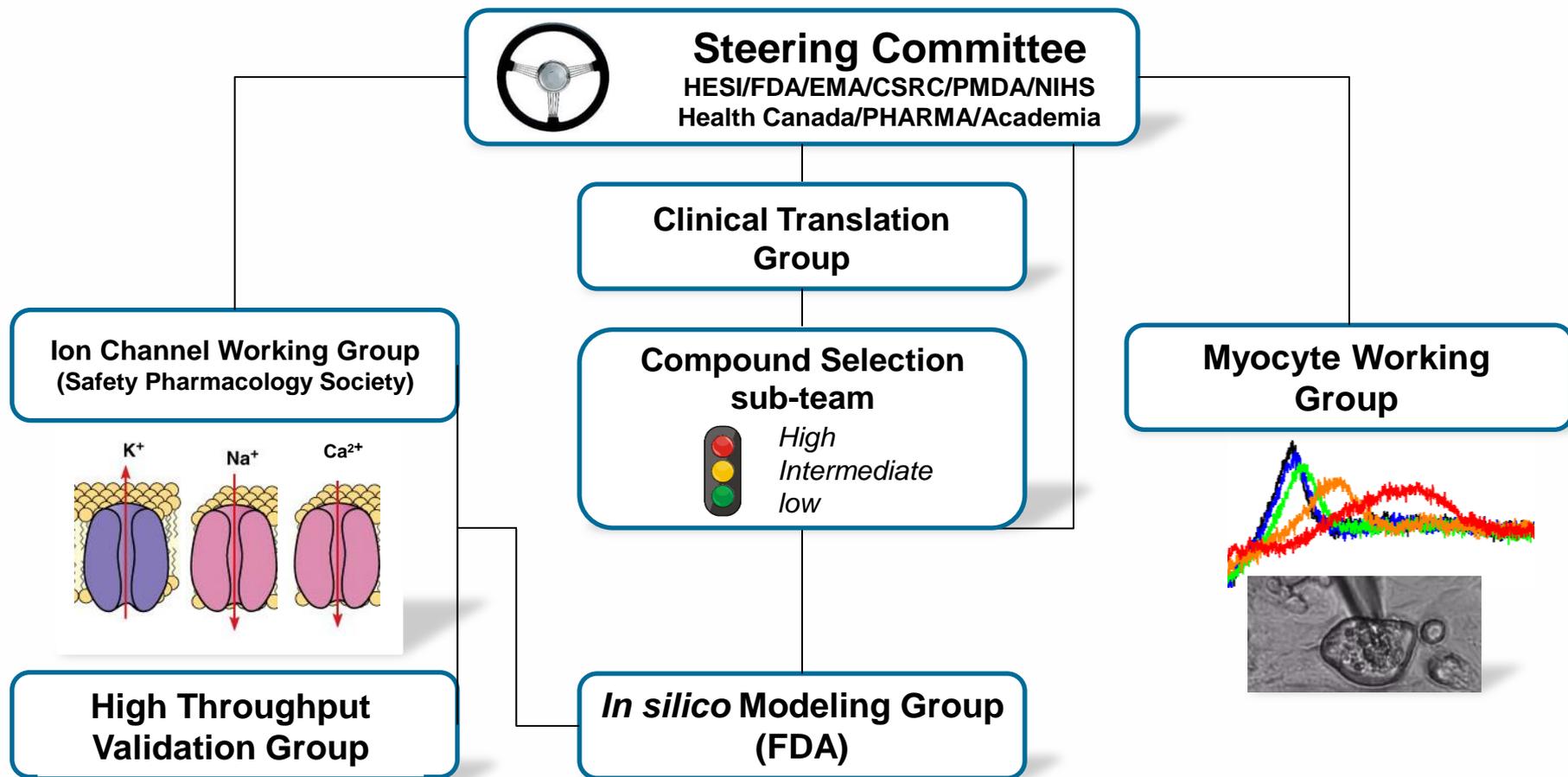
In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes



Clinical Evaluation Unanticipated EP Effects



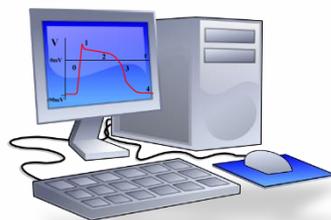
CiPA Organization



Derived from Sager et al. 2014



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Slide provided by Jim Kramer, CRL

Ion Channel Working Group (ICWG)

Deliverables

- Established in Dec 2013
 - sponsored by Safety Pharmacology Society
- Assemble a group of expert electrophysiologists to help guide the project
- Deliver robust, reliable and reproducible ion channel protocols to support *in silico* working group (ISWG) reconstruction of human ventricular AP
 - Which ion channels should be selected to support ISWG efforts
 - What properties should be studied
 - IC₅₀ determination, kinetics, rate/use/voltage dependence, etc...?
- What requirements are needed to deliver robust, reliable and reproducible ion channel data in a high throughput screening (HTS) environment

CiPA Ion Channel Selection

Selection based on:

- Fundamental role in defining human action potential duration
- Information obtained from the Safety Pharmacology Society survey
- Literature

Selected as initial working material for the CiPA assays

- Recombinant Human channels expressed in replicating cell lines
 - $I_{Kr} = hERG$
 - $I_{Ca}(L\text{-type}) = Cav1.2$
 - $I_{Na} = Nav1.5$ peak and late current – drug modified Nav1.5
 - $I_{TO} = Kv4.3$
 - $I_{Ks} = KCNQ1+KCNE1$
 - $I_{K1} = Kir2.1$



Recommendations for Ion Channel Testing

- Test article of interest to be investigated for effects on multiple ion channels using manual or automated planar patch clamp technology
- For each channel: use of a single voltage clamp protocol to generate 2 key data elements:
 - Potency (IC_{50} value)
 - Time constant of block development (fractional block)
- Protocol should be simple, easy to run, cost effective, robust and reproducible
- Each protocol developed and validated to optimize data capture from each individual channel (not one size fits all)
- Ascending concentrations tested will allow determination of a concentration-response relationship, or until physicochemical properties of test article become concentration-limiting
- Duration of exposure will be sufficient to obtain steady-state effects, unless precluded by viability of cells.
- Approach will establish best practices for ion channel studies by providing rigorously standardized patch clamp protocols and defined experimental conditions in order to minimize bias and variability



CiPA Training Set

Risk group based on Torsadogenic potential

HIGH

Azimilide

Bepiridil

Dofetilide

Sotalol

INTERMEDIATE

Astemizole

Cisapride

Terfenadine

Risperidone

LOW

Loratadine

Mexiletine

Ranolazine

Verapamil

Determination of Proarrhythmic risk challenged by several factors

- TdP risk is highly correlated with drug-independent properties such as patient CV/TdP risk:
 - LV function, heart failure, proclivity to have electrolyte abnormalities
 - Factors that may increase exposure
 - Risks conferred by concomitant medications to treat the disease state

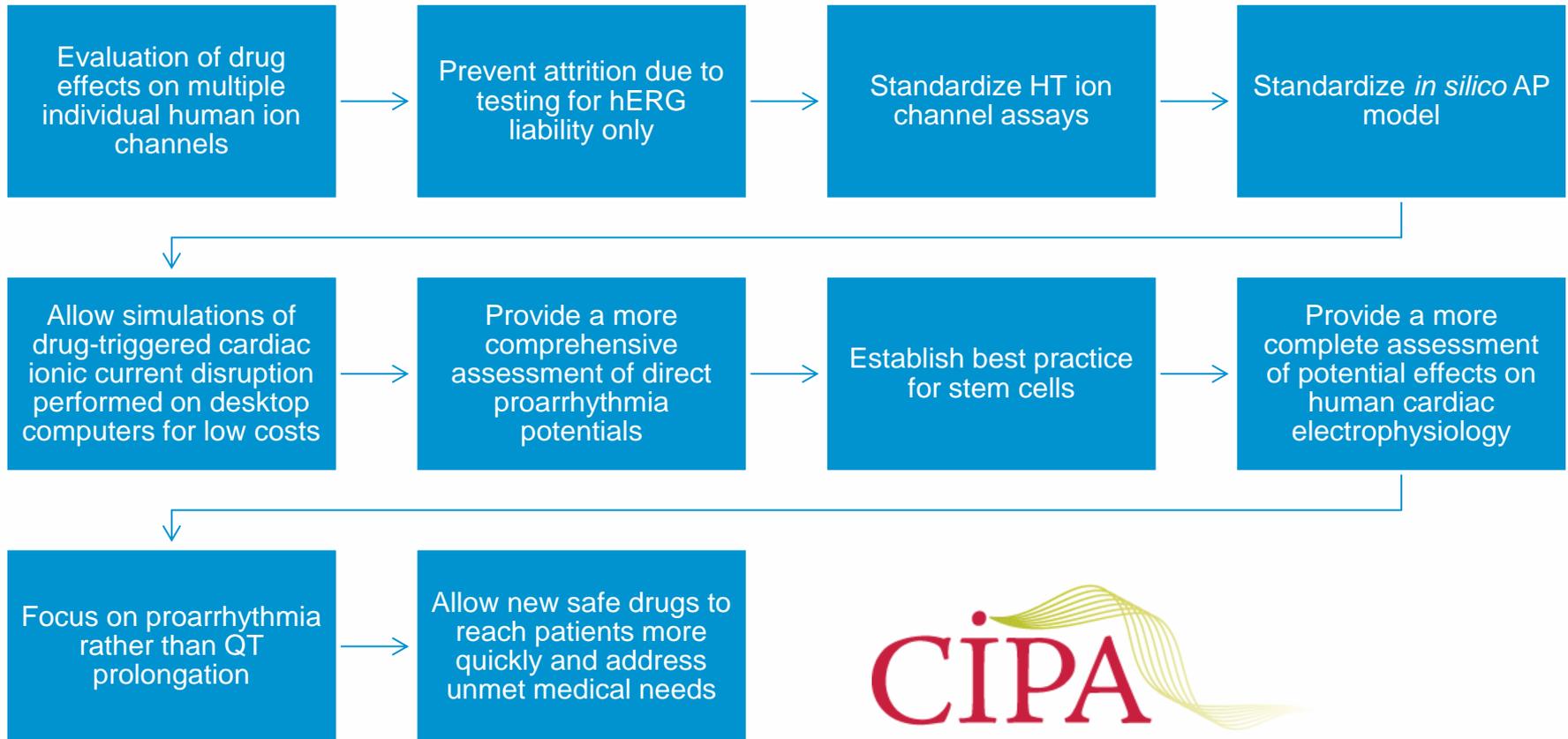


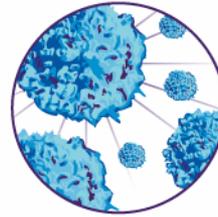
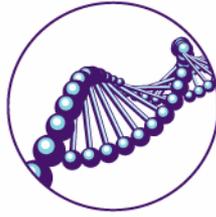
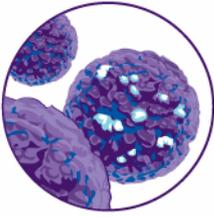
ICWG Status

- All manual hERG work (Physiologic & RT) completed
- Data currently used by in silico group
- Pilot studies ongoing looking at protocols on HT system
- Large, multi-center, multi-HT platform work to kick-off by 2Q16
- All remaining non-hERG ion channel work to be performed by HT work stream
- Future CiPA meeting scheduled for Dec 2016



What will success look like...





Thank you!