CIPA - Replacing the TQT with Non-clinical Proarrhythmia Testing: A New Paradigm

Current status, opportunities, and challenges

Hugo M. Vargas, PhD, DSP
Scientific Director
Safety & Exploratory Pharmacology
Amgen, Inc

19-Feb-2015
Outline

• Introduction to CIPA
  - Background

• Core Pillars and Supporting Foundation
  - Human Ionic Currents
  - In Silico Computer Reconstruction (Human)
  - Human Stem-Cell Derived Cardiomyocytes

• Challenges and Expectations

• Summary
Comprehensive *In Vitro* Proarrhythmia Assay: Three Scientific Core Pillars

**Drug Effects on Multiple Human Cardiac Currents**

- $I_{Na}$
- $I_{Na L}$
- $I_{Ca,L}$
- $I_{to1}$
- $I_{Kr}$
- $I_{Ks}$
- $I_{K1}$

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**

Preclinical ECG & Phase 1 ECG Studies: Complementary Data
S7B: Nonclinical Testing Strategy (2005)

Chemical/Pharmacological Class

- *In vitro* $I_{Kr}$ assay*
- *In vivo* QT assay

Other nonclinical and clinical info

Integrated Risk Assessment

Follow-up studies

Evidence of Risk

- None
- Weak
- Strong

*The hERG (gene for $K_v 11.1$ alpha subunit of $I_{Kr}$) related current is used*
ICH S7B/E14 Guidelines: Intended & Unintended Consequences

- **Successful**: no drugs with unrecognized risk being approved or removed from the market

- **Negative impact** on drug development
  - Premature discontinuation due to hERG or QT “signal”
    - (Inaccurate) perception of risk leading to drug discontinuation
      - Estimates of up to 60%
  - Development burden: increased costs; labeling
  - Many potentially good compounds never get evaluated in humans due to a hERG effect
Comprehensive *In Vitro* Proarrhythmia Assay

**Goal:** A new paradigm for cardiac safety evaluation of new drugs

- Provide a more accurate and comprehensive mechanism-based assessment of proarrhythmic potential
- Improve specificity (vs. preclinical hERG/clinical TQT)
- **focus** on ventricular proarrhythmia (torsade de pointes) rather than QT interval prolongation
Comprehensive *In Vitro* Proarrhythmia Assay

**How?**

- Characterize drug effects on multiple human cardiac currents
  - beyond hERG channel blockade alone
- Utilize *in silico* reconstructions that provide integrated cellular electrophysiologic responses of human ventricular myocytes
- Verify drug effects using human stem-cell derived myocytes
Repolarization: *Multiple Currents Involved*

**Repolarization:**
*integrated response of many currents*

**DELAYED** Repolarization:
*reduced NET OUTWARD CURRENT*
  - block outward current (hERG)
  - enhanced inward current (Na^+\, Ca^{++})
    during plateau (phases 2, 3)

Balance of inward and outward human currents that define drug effects on ventricular repolarization.

Present focus on IKr (hERG) results in premature and unwarranted drug attrition, misclassification of risk
Cellular Proarrrhythmia: Abnormal Emergent Responses affect Repolarization

Focus on proarrrhythmic vulnerability:

- impaired cellular repolarization & electrical instability
- not simply ↑APD and ↑QTc

- In extreme form, instability manifest as early after-depolarizations (EAD’s) associated with initiation of proarrrhythmia

- Impaired repolarization: rank proarrrhythmia based on comparisons with known TdP drugs

Evaluating human proarrrhythmic risk (an integrated, emergent effect) at cellular level
Comprehensive *In Vitro* Proarrhythmia Assay: Four Components

- **Drug Effects on Multiple Human Cardiac Currents**
- **In Silico** Reconstruction Human Ventricular Cellular Electrophysiology
- **In Vitro** Effects Human Stem-Cell Derived Ventricular Myocytes
- Evaluation of Clinical Drugs for Proarrhythmic TdP Liability
Lack of selectivity of drugs on cardiac currents affecting (depolarization and repolarization) necessitates consideration of multiple currents
Example: Delayed Repolarization with Dofetilide (hERG Block) Mitigated by Other Currents

- Calcium current block (Nifedipine) mitigates delayed repolarization with Dofetilide (hERG block)

- Sodium current block (Lidocaine) mitigates delayed repolarization with Dofetilide (hERG block)
Core Component I: Voltage Clamp Studies, Human Currents, Heterologous Expression Systems

Ion Channel Working Group (SPS):
- Develop hERG & non-hERG protocols; testing
- Standardize voltage clamp protocols to establish best practices, reduce bias and variability, enable comparisons of automated platforms across laboratories
- Information on kinetics-, voltage-, and use-dependence to parameterize models (hERG essential)

Robust characterization of drug effects on human currents enables *in silico* reconstructions of integrated responses
Core Component II: Computer Reconstructions of Drug Effects on Human Cellular Electrophysiology

**In Silico Group (FDA):**
- Multiple currents integrated to describe cellular electrophysiologic effects
- Ability to elicit changes in repolarization instability, early afterdepolarizations, reduced upstroke velocity using select model (modified O’Hara-Rudy model: model)
- Ranking of integrated responses compared with clinical examples of different TdP liabilities
Core Component III: *In vitro* Effects, Human Stem Cell-Derived Cardiomyocytes

Myocyte Group (HESI):
Verification of *in silico* reconstructions with well characterized human stem-cell cardiomyocytes

13 Site Pilot Study Ongoing
- Microelectrode array (MEA, field potential duration, 4 platforms)
- Voltage-sensing optical (VSO, 4 platforms)
- 3 myocyte types

8 Blinded Compounds
- 4 to calibrate sensitivity (IKr, IKs, INa, ICa)
- 4 as pilot test set
Clinical Foundation:
Compound Selection & Clinical Regulatory Group

**TdP Risk**

- **High Risk**
- **Intermediate Risk**
- **Low Risk**

**Compound Selection/Regulatory (CSRC):**
Categorize available drugs for proarrhythmic risk:
- High, Intermediate, Low risk categories
- Evaluate clinical data for proarrhythmia
- Overall experience, history, patient population, pharmacokinetics
- 31 drugs nominated for model development and verification

- Input from clinical developers & regulators
  - Validation/acceptance of CiPA paradigm

- Define Phase 1 ECG Verification
Challenges:

- **Ion Channels:** optimal number of currents, standardization and reproducibility (e.g. hERG), adequate characterization (time-, voltage-, and use-dependent block) for input for *in silico* reconstruction

- **In Silico:** selection and characterization of model, variability of input data, assessment of emergent responses

- **Stem Cell-Derived Myocytes:** maturity of cells (adult phenotype), fit for purpose use of preparations, stability, sensitivity, signal strength/granularity, electrophysiologic heterogeneity

- **Compound Selection/Regulatory:** identification/rank-ordering for TdP risk from clinical experience; Phase 1 ECG Metrics
Identifying Different Phenotypes

CIPA Assays Must Differentiate:

1. hERG blockers with QTc Prolongation & associated with TdP (1)

2. hERG blockers with QTc Prolongation BUT NOT associated with TdP (2)

3. Drugs with no-direct ion channel effects with modest QTc Prolongation (3)

Slide courtesy of D. Leishman (Lilly; modified with permission)
Summary

- **CIPA**
  - proarrhythmic risk based on mechanistic understanding of integrated electrophysiologic drug effects
    - Focus: multiple human cardiac currents on cellular level

- **Expectations**
  - reduce unwarranted attrition early candidates
  - enable efficient progression of more drugs
  - improve efficiency of drug development by replacing strict dependence on preclinical hERG and binary clinical QT prolongation & TQT studies
  - revise current warning language for some drugs
Acknowledgments

- Philip Sager, MD (Stanford Uni)
- Gary Gintant, PhD (Abbvie)
- Derek Leishman, PhD (Lilly)

CIPA Working Groups
- Ion Channel WG (Safety Pharmacology Society)
- In Silico WG (Food & Drug Admin)
- Myocyte WG (Health & Environmental Science Ins)

CIPA Steering Team
- Regulatory/Government Reps (6)
- Pharma Reps (4)
- Academia (2)
- Private Industry Reps (2)
- HESI (2)