The New Paradigm for Proarrhythmia Assessment Without the TQT Study

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Collaborators

- Drs. Stockbridge, Gintant, Pettit
- FDA
- EMA
- PMDA
- Health Canada
- CSRC
- HESI
- SPS
- In Silico Modelers
- Pharmaceutical and Device Companies
- CRO’s
- Numerous Academic Groups
QT Prolonged/Drug-Induced Torsade

- QT prolongation/TdP – single most common cause of withdrawal or restriction on marketed drugs
- This has resulted in the need for regulatory guidance

- TdP rarely observed during clinical development

- Focus on surrogates- HERG and QTc testing
  - QTc- sensitive but not very specific
S7B: Nonclinical Testing Strategy

Chemical/Pharmacological Class

In vitro \( I_{Kr} \) assay*

In vivo QT assay

Other nonclinical and clinical information

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
Consequences: Compound with QT effect

ICH E14- increase in QTc~5m is “positive

Consequences of developing a compound with QT effect

- Significant development burden
- Increased perceived risk = increased burden to demonstrate benefit
- Increased costs
- Delays in filing and/or approval
- Label warnings and competitive implications
- Licensing/partnering issues
- Often leads to termination of development
Torsadogenic Drugs

- ICH E14/S&B have resulted in no drugs with unrecognized risk being approved

- **Success!**

- Negative impact on drug development
  - Premature discontinuation due to hERG or QT “signal”
    - (Inaccurate) perception of risk, development burden, costs, labeling
    - Some potentially good compounds never get evaluated in humans
  - Drug development in specific areas- CNS
  - Many drugs with QT labeling are unlikely proarrhythmic
Ventricular Repolarization

- P wave
- QRS complex
- T wave

- Na⁺ current
- Ca²⁺ current (L-type, T-type)
- Transient outward current (I_TO1, I_TO2)
- Delayed rectifiers (I_Ks, I_Kr)
- Inward rectifier (I_K1)
- Pacemaker current (I_f)
- Na⁺-Ca²⁺ exchange
- Na⁺, K⁺-ATPase
QT Prolongation: Dissociation from TdP

- Sodium Pentobarbital
  - Prolongs QT but no TdP
  - Inhibits $I_{kr}$, $I_{ks}$, and late $I_{Na}$

- Amiodarone
  - TdP very rare
  - Inhibits $I_{kr}$, $I_{ks}$, late $I_{Na}$, and $I_{Ca}$

- Verapamil
  - Inhibits $I_{Kr}$ but also Ca influx

- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late $I_{Na}$, $I_{kr}$, and $I_{NaCa}$
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- Verapamil
  - Inhibits $I_{Kr}$ but also Ca influx
  - No QT prolongation or TdP

- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late $I_{Na}$, $I_{kr}$, and $I_{NaCa}$
  - No EAD’s, reduces dispersion;
  - Suppresses E4031 induced TdP

Thus QTc Prolongation need not cause TdP
Issues

- QT prolongation ≠ Proarrhythmia
- HERG block ≠ Proarrhythmia
- Negative impact on drug development
- New paradigm- based on our deep mechanistic understanding of TdP
New Paradigm

Might a new cardiac safety paradigm focused on non-clinical measurement of proarrhythmia proclivity:

Focus on the real issue: Proarrhythmia

- Reduce the premature termination of drugs with favourable benefit:risk profiles
- Make drug development more efficient
  - Move the bulk of proarrhythmic assessment to the discovery phase
  - Use the assays to 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
Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium

Philip T. Sager, MD, FACC, FAHA, a Gary Gintant, PhD, b J. Rick Turner, PhD, c Syril Pettit, MEM, d and Norman Stockbridge, MD, PhD e Palo Alto, CA; North Chicago, IL; Durham, NC; Washington, DC; and White Oak, MD

- Proarrhythmic risk can be determined by pre-clinical assessments

- Proclivity to develop EAD’s
  - Ionic Currents
    - in silico modeling
  - Cell-Based Approach

- Focus on high throughput approaches

- ECG Phase 1 Assessment
Background: Proarrhythmic Vulnerability and Early Afterdepolarizations (EAD’s)

We understand the mechanism!

Proarrhythmic vulnerability linked to impairment of repolarization and repolarization instability culminating in early afterdepolarizations (EAD’s)

- EAD’s are triggers for Torsades de Pointes arrhythmia
- Ease of EAD induction reflects proarrhythmic vulnerability
- Provide means of ranking proarrhythmic potential
## Assays and Approaches Considered for Comprehensive Assay (In Order of Complexity, Integration)

<table>
<thead>
<tr>
<th>Approach</th>
<th>Description</th>
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<tr>
<td><strong>QSAR</strong></td>
<td>Models describing relationship between molecular structural features and properties or activities at given pharmacological/toxicological endpoint</td>
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<tr>
<td><strong>Receptor Affinity Assays</strong></td>
<td>Typically competitive binding studies to ion channels</td>
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<tr>
<td><strong>Single Channel Recording</strong></td>
<td>Highly detailed measure of current through a single ionic channel</td>
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<tr>
<td><strong>Macroscopic Ionic Currents</strong></td>
<td>Detailed analysis of drug effects on functional cardiac currents; widely accepted</td>
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<td><strong>Isolated Cardiac Myocytes</strong></td>
<td>Cardiocytes of human origin more likely to reflect native physiology; availability of stem-cell cardiocytes vs. tissues</td>
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<tr>
<td><strong>In vitro/in vivo proarrhythmia</strong></td>
<td>Tissues/organs or whole animal models mimicking enhanced proarrhythmia risk</td>
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<tr>
<td><strong>Computer Models of Cardiac Myocytes</strong></td>
<td>Reconstruction of electrical activity of ventricular myocytes from channel effects (delayed repolarization and EAD's)</td>
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<tr>
<td><strong>Whole Heart Computer Models</strong></td>
<td>Reconstruction of ECG and drug effects (incorporates individual channels and action potential studies)</td>
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CiPA: Two Component Proposal

Ionic Currents / In Silico Based Approach

- Effects on Multiple Cardiac Currents (Voltage Clamp Studies)
- + Reconstruction of Cellular Electrophysiology (In Silico Studies)

Myocyte-Based Approach

- Effects on Human Ventricular Myocytes (In Vitro Studies)

- Complementary approaches
- Not designed to reproduce arrhythmia

Define a gradation of risk instead of a binary approach
Core *In Vitro* Strategy. **Voltage Clamp Studies**

**Ionic Currents**

- **Voltage clamp studies**
  - Effects on cardiac currents
  - **Human channels** in heterologous expression systems
  - Establish best practices, *standardization across assays, laboratories*
  - Inhibition of current, ? Use dependency

- **Higher throughput automated patch platforms**
  - Efficiently determine *basic characteristics* of drug effects on currents for *in silico* reconstruction
**Likely Candidate Currents**

- **iKr** (hERG) – delayed ventricular repolarization

- **INafast** (Nav1.5) – excitability, conduction

- **INalate** (Nav1.5) – repolarization, mitigate hERG block

- **ICaL** (Cav1.2) – A-V conduction, mitigate hERG block

- **IKs** (KvLQT1-minK) – delayed ventricular repolarization

[Diagram of ionic currents showing depolarizing and repolarizing currents]
Core *in silico* Strategy: Reconstruction of the Cardiac Action Potential

*Silico* Reconstruction of Action Potentials

- Global effects on repolarization based on multiple ion channel effects
- Approach based on link between delayed repolarization supporting early afterdepolarizations (EAD’s) and TdP

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![Diagram](image)

O’Hara et al, PLOS, 2011
Core *In vitro* Strategy: Human Cardiomyocytes

Electrophysiologic studies:
- Human stem-cell derived ventricular cardiomyocytes; well characterized, physiologic recording conditions
  - Action potential studies, **focus on repolarization** (duration, early afterdepolarizations, cellular integration)
  - Reproducibility essential, robust validation
  - Confirm drug effects from voltage clamp/*in silico* reconstructions
Stem-Cell Derived Myocytes: Possible Experimental Approach

Field Potential Measures (Microelectrode Array Techniques)

E-4031: Concentration-dependent Block of iKr Delays Repolarization, Provokes EAD’s

Nifedipine: Concentration-dependent Block of IcaL Speeds Repolarization
Stem-Cell Derived Myocytes: Possible Experimental Approach

Perforated patch method

? Determine excitability during Phase 3

Human IPS-Derived Stem Cells

- New technology that is evolving
- Desire to have as homogenous a population of adult cardiomyocytes as possible
- Evolving maturation and changes in EP properties over time
- “Standardization” across laboratories and stem cell sourcing
- Determination of appropriate drug-induced metrics indicating proarrhythmia proclivity
Summary and Paths Forward: CiPA Proposal

Approach based on

a) mechanistic understanding, integrating effects on multiple ion currents with *in silico* reconstruction

b) confirmation in human ventricular myocyte-based assay

- Not typical preclinical assay based on binary discrimination in complex, integrated (poorly understood) biological system

- Need input from safety pharmacologists, electrophysiologists, computational modelers, cell biologists, regulators

**First Steps:** Seek Input, Establish Workstreams (ongoing)
Comprehensive *In Vitro* ProArrhythmia Assay (*CiPA*)

**What It Will Do:**
- Standardize *in vitro* assays (used to characterize drug effects) and *in silico* modeling of drug effects
- Define role of human cardiomyocytes to inform on proarrhythmic potential of drugs
- Provide proarrhythmic **ranking** based on calibration efforts with agreed-upon standards
  - Not a binary approach

**What It Will Not Do:**
- Maintain status-quo for an imperfect surrogate marker of proarrhythmia
CIPA PROCESS

- Work streams
  - In Silico, Ion Channel, Myocyte, Regulatory, Steering Team

- Topical area leads

- Coordination and cross-stream interaction
Work Streams

**In Silico** – model design, execution, feedback and vetting
Tom Colatsky (Thomas.Colatsky@fda.hhs.gov)

**Ion Channel** – channel selection, protocol development, novel data generation to test model; Syril Petit (Spettit@hesiglobal.org)

**Stem Cell Myocyte** – protocols, platforms and validation; (Gary.Gintant@abbvie.com)

**Regulatory** – model design and validation compound selection, arrhythmia metrics, ECG assessment (Psager@Stanford.edu)

**Steering Team** – Coordination and integration

Norman Stockbridge, FDA: Norman.Stockbridge@fda.hhs.gov
Jennifer Pierson (HESI): Jennifer.Pierson@hesiglobal.org
# CIPA Steering Team

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Summary

• Exciting potential evolution in CV Arrhythmia assessment

• Potential to change current approaches with positive impact on drug development

• Can concepts be extended to other areas?

• Many opportunities for those interested in contributing to become involved
Thank you

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