

An Update on CiPA Activities from an FDA Perspective

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Outline of the Talk

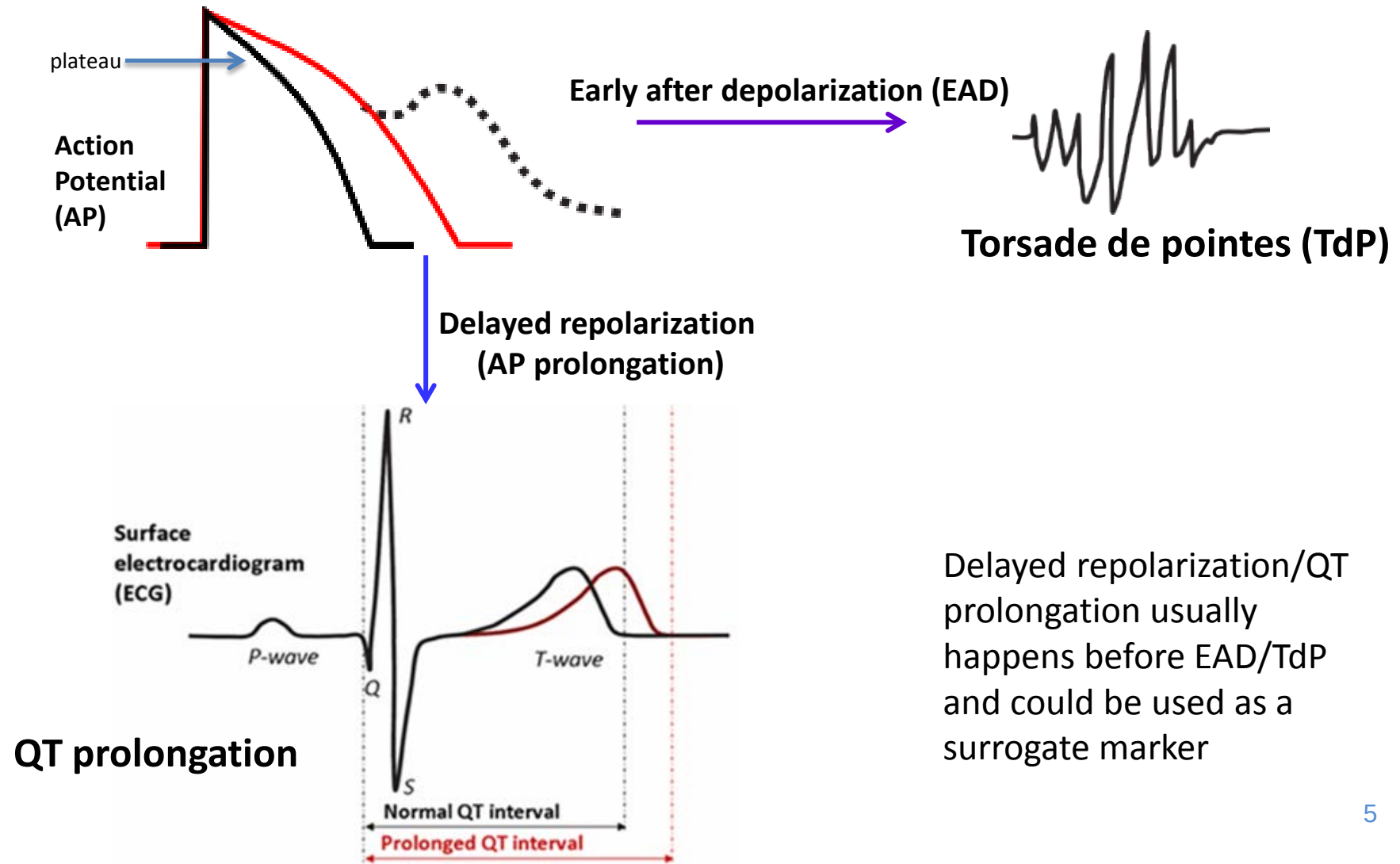
- A brief description of the regulatory issue, the mechanistic background, and the current international guideline
- Overall picture of CiPA, and a brief introduction of the goals and progresses of the four components
- Detailed explanation of the In Silico work and current TdP risk assessment metric
- Expected outcomes of CiPA as a new regulatory paradigm

Drugs Withdrawn from Market Due to QTc Prolongation or Torsade de Pointes

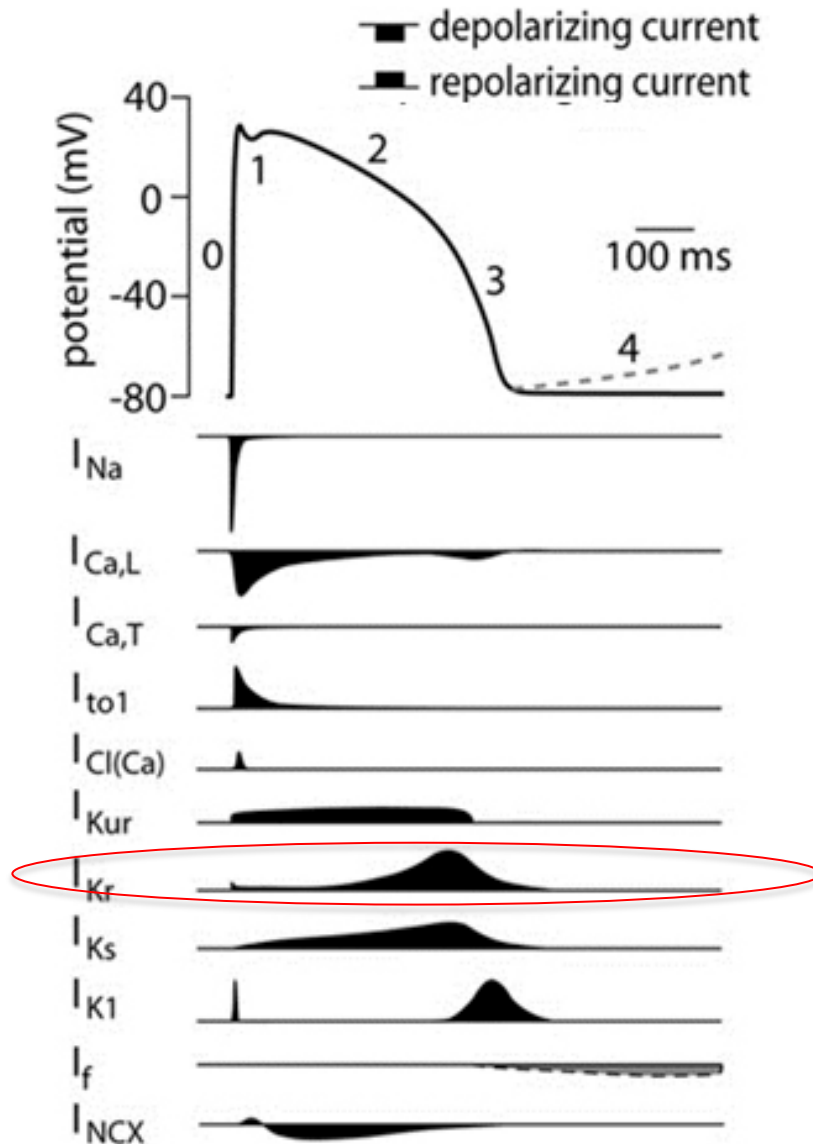


Drug	Therapeutic Class	Year of Withdrawal
Prenylamine	Antianginal	1988 (EU, not marketed in US)
Terodiline	Antianginal/urinary incontinence	1991 (EU, not marketed in US)
Terfenadine	Antihistamine	1998
Sertindole	Antipsychotic	1998 (not marketed in US, EU reintroduction in 2002)
Astemizole	Antihistamine	1999
Sparfloxacin	Antibiotic	2001
Cisapride	Gastric prokinetic	2000
Droperidol	Tranquilizer/analgesic	2001
Levacetylmethadol	Methadone substitution	2003
Thioridazine	Antipsychotic	2005 (ex-US)
Propoxyphene	Opioid analgesic	2010

Cellular Mechanism of Torsade de Pointes : Early After Depolarization



Ionic Currents Underlying Repolarization



- Balance between depolarizing (inward) currents and repolarizing (outward) currents determines the rate of repolarization (AP duration/QT interval)
- I_{Kr} (hERG channel) is the most prominent repolarizing current

Regulatory Guidelines

- ICH S7B: The nonclinical evaluation of the potential for **delayed ventricular repolarization** (QT interval prolongation) by human pharmaceuticals, with the focus on IKr/hERG
- ICH E14: The clinical evaluation of **QT/QTc interval prolongation** and proarrhythmic potential for non-antiarrhythmic drugs
 - Revisions made through Questions and Answers

Consequences of ICH S7B and E14

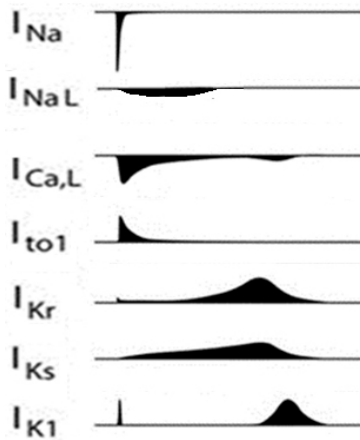
- Successful: No drugs that went through the ICH S7B and E14 assessment removed from market due to TdP
- However:
 - Both guidelines assess the surrogate marker (delayed repolarization/QT prolongation), not the clinical end point TdP (cellular mechanism = early afterdepolarization [EAD])
 - S7B focuses on IKr/hERG, sensitive but not specific
 - Triggers additional costly synthetic efforts to remove hERG liability
 - Some drugs that came to market before S7B/E14 may not be available today

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Comprehensive *in vitro* Proarrhythmia Assay (CiPA)

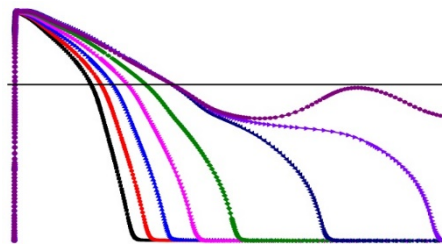
1. In Vitro Assessment of Effects on Multiple Ionic Currents



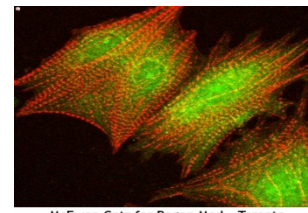
modified from Hoekstra et al., 2012

2. *In silico* Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology

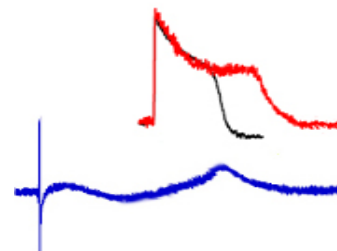
$$I_{stim} = C \frac{dV_m}{dt} + I_m$$



3. *In vitro* Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes



McEwen Cntr for Regen Med., Toronto



4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies



Characterize and assess relative TdP risk levels

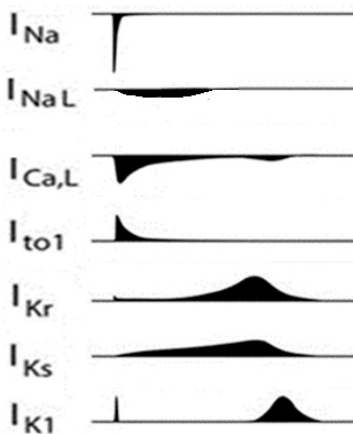
Check for missed or unanticipated effects

1. Ion Channel Working Group

Goals: characterize effects of drugs on prominent ionic currents that define ventricular repolarization

- Reliably characterize block of human cardiac ionic currents in heterologous expression systems
- Design standard protocols and quality metrics to ensure reproducibility of in vitro drug block experiments
- Explore the impact of different experimental conditions (temperature, platform, etc.) on the quality and variability of in vitro data
- Seven cardiac currents initially selected to be measured in CiPA assays (IKr, IKs, IK1, Ito, INa, INaL, ICaL)
 - IKr, ICaL, INa/INaL found to be most critical

Drug Effects on Multiple Human Cardiac Currents



modified from Hoekstra et al., 2012

Ion Channel Progress

- Decided on the dynamic protocol to be used for studying drug-hERG dynamic interactions (Milnes *et al.*, 2010)
- hERG data has been generated using manual voltage clamp technique at physiologic temperature (Wendy Wu lab, FDA) and room temperature (Adam Hill, Victor Chang Research Institute)
- Percent block (IC50) data are being generated using manual system for all remaining, non-hERG, channels
- Automated High Throughput Patch Clamp Systems (HTS) are being used to generate data for all channels

Manual Patch Clamp Assessment of 7 Ion Channel Currents



Contents lists available at [ScienceDirect](#)

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox



An evaluation of 30 clinical drugs against the comprehensive *in vitro* proarrhythmia assay (CiPA) proposed ion channel panel

William J. Crumb Jr. ^{a,*}, Jose Vicente ^b, Lars Johannesen ^b, David G. Strauss ^b

Key findings:

- Most commonly blocked ion channel currents at clinically relevant concentrations are hERG, late sodium and calcium
- Drugs with low torsade risk had equal or greater late sodium or L-type calcium block compared to hERG block

Ongoing High Throughput System Study



Goals: assess variability and reproducibility of automated high throughput patch clamp systems (HTS) for defining drug effects on cardiac ionic currents across different platforms & sites using standardized protocols

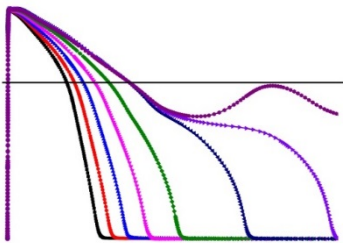
- Generate steady state drug block data (IC50s) for all CiPA compounds
- Generate drug binding kinetic data for hERG (selected platforms/sites)
- Data across platforms/sites are being analyzed by In Silico Working Group (ISWG) to assess variability and compatibility with the model
- Phase 1 (12 drugs) completed; Phase 2 (16 drugs) to be started

2. In Silico Working Group

Goals: Integrate in vitro data into a computational model of human ventricular myocyte and identify a mechanistic metric that can quantify the relative risk of inducing EAD/TdP

In silico Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology

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



- O'Hara-Rudy (ORd) human ventricular cardiomyote model was chosen as the consensus base model for CiPA
- The base model to be further optimized based on new and published data of drug effects on selected human cardiac currents
- A set of 12 training drugs classified into 3 torsade de pointes (TdP) risk categories (high, intermediate and low) is used to calibrate the model; Another set of 16 drugs for independent validation

CiPA Drugs Selected for Model Development

High TdP Risk

Training:

Bepiridil
Dofetilide
Quinidine
D,l Sotalol

Validation:

Azimilide
Ibutilide
Vandetanib
Disopyramide

Intermediate TdP Risk

Training:

Chlorpromazine
Cisapride
Terfenadine
Ondansetron

Validation:

Astemizole
Clarithromycin
Clozapine
Domperidone
Droperidol
Pimozide
Risperidone

Low TdP Risk

Training:

Diltiazem
Mexiletine
Ranolazine
Verapamil

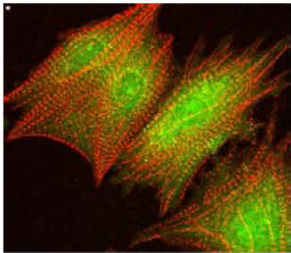
Validation:

Loratadine
Metoprolol
Nifedipine
Nitrendipine
Tamoxifen

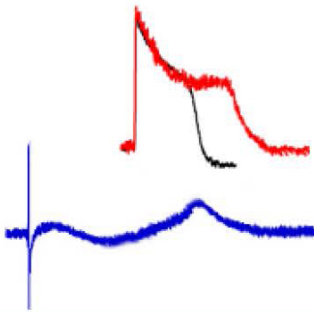
Clinical Translational Working Group

3. Cardiomyocyte Working Group

In Vitro Effects Human Stem- Cell Derived Ventricular Myocytes



McEwen Cntr for Regen Med., Toronto



Goals: To identify potential gaps in cellular electrophysiological effects (not detected from in vitro/in silico studies) that may impact TdP risk assessment

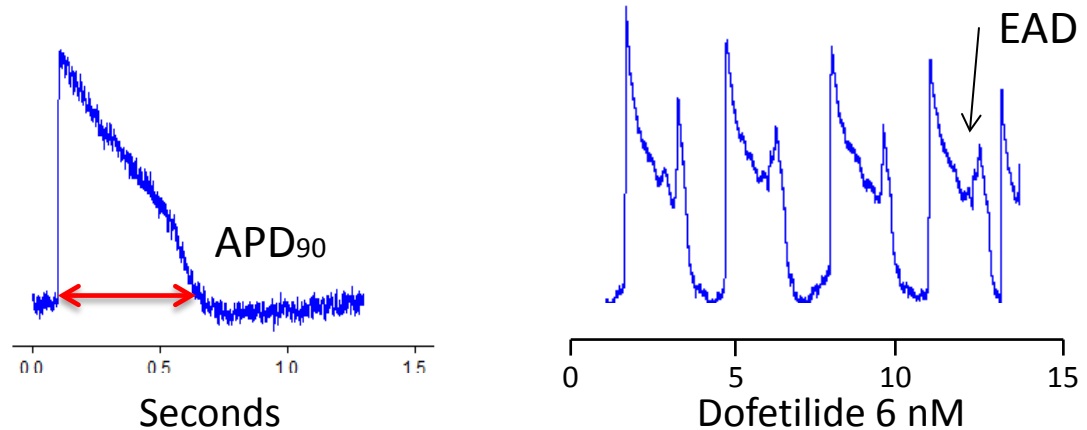
- Relies on ability of myocytes to recapitulate integrated effects of critical systems that influence electrophysiology found in human myocytes
- Report drug-induced repolarization abnormalities using induced pluripotent stem cell derived cardiomyocytes
- Approaches: microelectrode arrays and voltage-sensing dyes

Cardiomyocyte Measurements

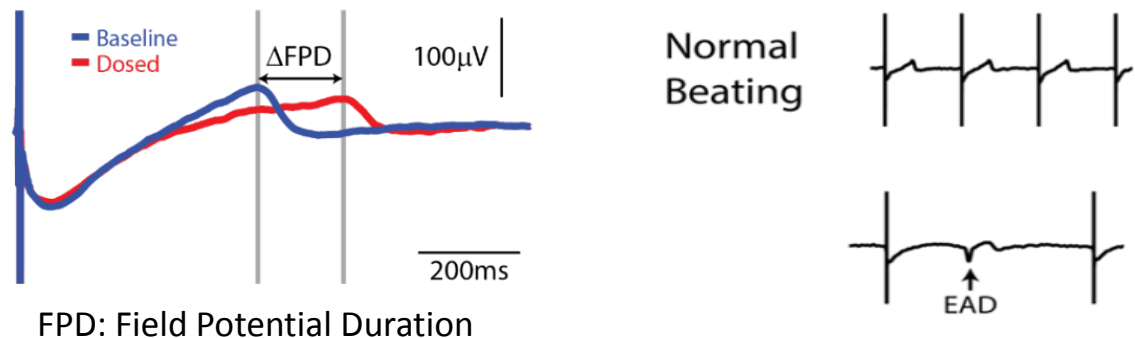
Key measurements:

- Action potential duration (APD)
- Early after depolarizations (EAD) and other arrhythmias

Optical Imaging – Voltage Sensitive Dyes



Microelectrode Arrays



FPD: Field Potential Duration

Cardiomyocyte Progress

- Pilot study evaluated reproducibility and variability of electrophysiologic responses across multiple cells, platforms and volunteer study sites for 8 compounds
 - Additional published FDA study (next slide) with voltage sensitive dye and microelectrode arrays with multiple cell vendors
- Phase II validation study with all 28 CiPA drugs – study completed, data analysis ongoing
- Results will be compared with prospective *in silico* reconstructions and categories of high-, intermediate- and low-risk of torsade de pointes

FDA iPSC-cardiomyocyte Study



SOT | Society of
Toxicology
www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 155(1), 2017, 234–247

doi: 10.1093/toxsci/kfw200

Advance Access Publication Date: October 3, 2016

Research article

Comprehensive Translational Assessment of Human-Induced Pluripotent Stem Cell Derived Cardiomyocytes for Evaluating Drug-Induced Arrhythmias

Ksenia Blinova,^{*,1} Jayna Stohlman,^{*} Jose Vicente,^{*,†,‡} Dulciana Chan,^{*} Lars Johannesen,^{*} Maria P. Hortigon-Vinagre,^{§,¶} Victor Zamora,^{§,¶} Godfrey Smith,^{§,¶} William J. Crumb,^{||} Li Pang,^{|||} Beverly Lyn-Cook,^{|||} James Ross,^{|||} Mathew Brock,^{|||} Stacie Chvatal,^{|||} Daniel Millard,^{|||} Lorian Galeotti,^{*} Norman Stockbridge,[†] and David G. Strauss^{*,#}

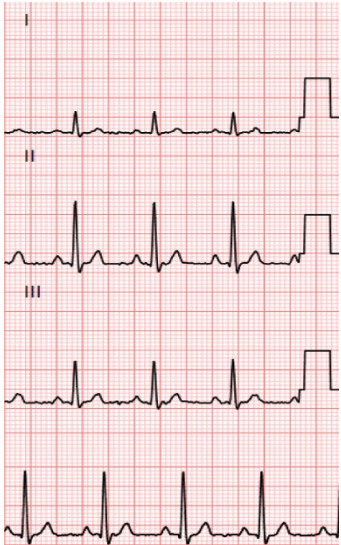
Methods:

- Voltage sensitive dyes (VSD) and microelectrode arrays (MEA)
- 2 different commercially available cell lines
- 26 drugs + 3 drug combinations

4. Phase 1 ECG Biomarker Working Group



Evaluation of Unanticipated Effects in Clinical Phase 1 Studies



- **Goal**: Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data
 - Human specific metabolite, protein binding
- New ECG biomarker(s) would need to add additional information beyond QTc
 - Differentiate multi-ion channel effects during repolarization
 - Can be corrected for heart rate (if needed)
 - Sufficient power to detect changes in small sample sizes with exposure-response analysis
 - Available for wide-spread use

ECG Biomarker Analysis Summary

- Examined 12 potential ECG biomarkers and compared to ion channel data
 - 2 prospective FDA-sponsored clinical trials including 8 drugs and 3 drug combinations, some additional drugs
- Multiple ECG biomarkers can be applied in exposure-response analysis
- Receiver operating characteristic – area under the curve analysis showed that J-Tpeakc is the strongest predictor of late sodium block in the presence of hERG block
- J-Tpeak has similar inter/intra-subject variability and heart rate relationship as QT; other ECG biomarkers have variable heart rate relationship
- J-Tpeak & Tpeak-Tend FDA algorithms released as open-source software

Johannesen et al. *Clin Pharmacol Ther* 2014;96:534; *Clin Pharmacol Ther* 2016;96:549 and *Clin Pharmacol Ther* 2016;99:214.

Vicente et al. *J Am Heart Assoc* 2015 pii: e001615;

Vicente et al. *PLOS ONE* 2016;11(12):e0163619; Johannesen et al. *PLOS ONE* 2016;11(12):e0166925.

Ongoing Prospective Clinical Validation Study

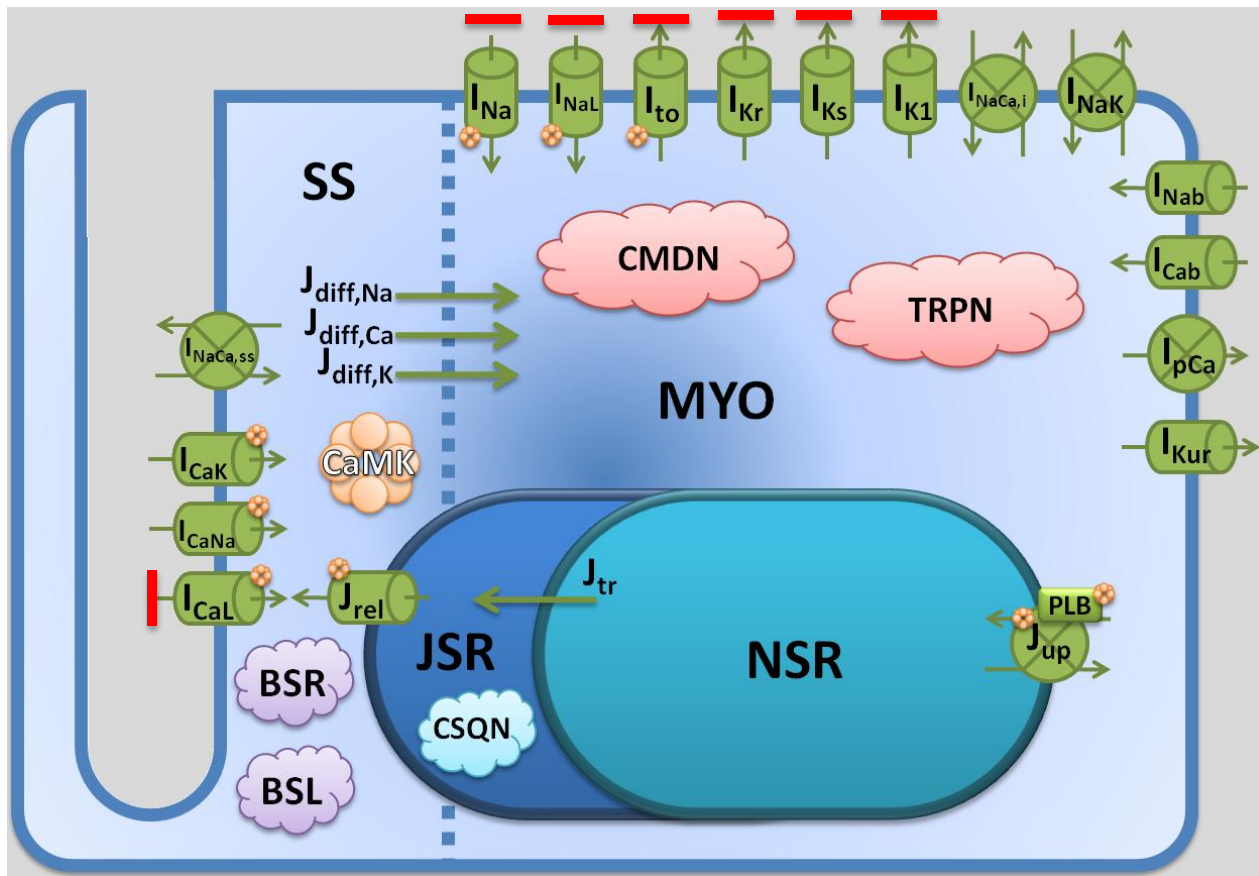


- Prospective small sample size early Phase 1-type clinical study to verify that a combined assessment of QTc and J-Tpeakc can differentiate between drugs that
 - Are selective hERG blockers versus
 - Have balanced block of hERG and late sodium and/or calcium
- Will include 6 drugs
 - selective hERG block (dofetilide, chloroquine)
 - hERG + late sodium block (ranolazine)
 - hERG + calcium block (verapamil, dofetilide + diltiazem)
 - hERG + late sodium + calcium block (lopinavir/ritonavir)
- To be completed in 2017
 - See details at: <https://clinicaltrials.gov/ct2/show/NCT03070470>

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O'Hara-Rudy (ORd) Cardiomyocyte Model



Improving the ORd Model for CiPA

- Making the IKr/hERG component temperature dependent
- Modeling dynamic drug-hERG interactions rather than using simple IC50s
- Optimizing model parameters based on experimentally recorded drug effects on human ventricular myocytes

Development of a Temperature Sensitive hERG Model



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox



A temperature-dependent *in silico* model of the human ether-à-go-go-related (hERG) gene channel

Zhihua Li *, Sara Dutta, Jiansong Sheng, Phu N. Tran, Wendy Wu, Thomas Colatsky

Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, United States

- Because O'Hara-Rudy model operates at physiological temperature, while industry-generated hERG data are often obtained at room temperature, a dynamic, temperature-sensitive hERG model is required
- We developed a modified hERG model that can reproduce temperature-induced changes in major channel gating processes

Original Article

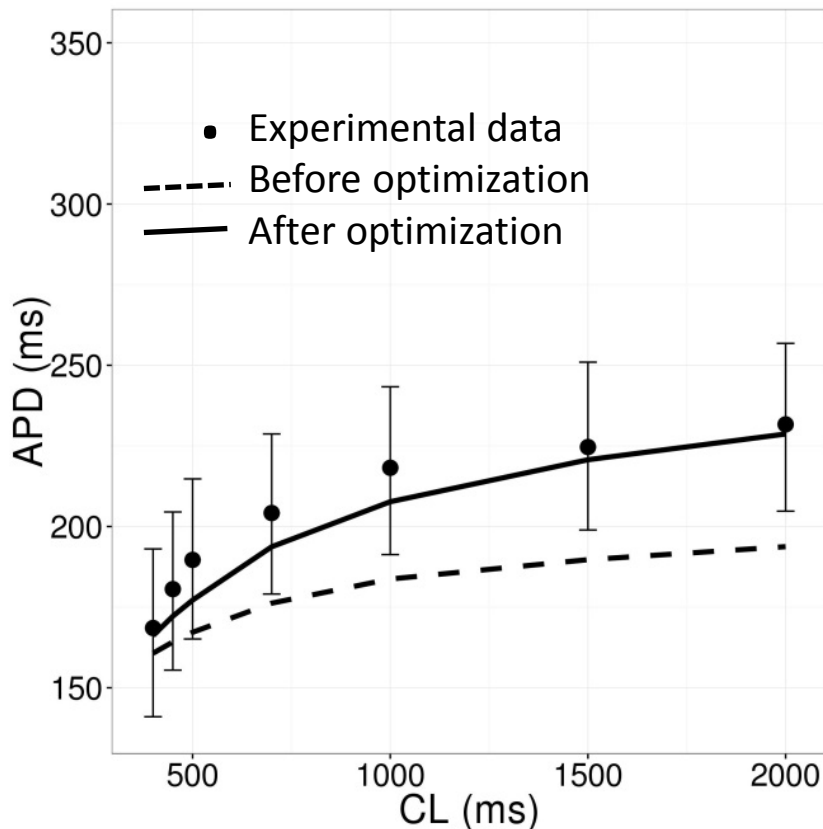
Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-à-go-go-Related Gene) Channel–Drug Binding Kinetics and Multichannel Pharmacology

Zhihua Li, PhD; Sara Dutta, PhD; Jiansong Sheng, PhD; Phu N. Tran, PhD; Wendy Wu, PhD; Kelly Chang, PhD; Thembi Mdluli, PhD; David G. Strauss, PhD; Thomas Colatsky, PhD

Li Z et al. Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG-Drug Binding Kinetics and Multichannel Pharmacology. *Circulation: Arrhythmia & Electrophysiology*. 2017;10:e004628

- Because the same drug may show different block potency under different conditions (i.e. heart rate), a novel model was developed to capture this dynamic drug-hERG interaction
- This model can distinguish between hERG blockers with similar IC₅₀s but different TdP liabilities because of some drugs' ability to induce reverse use-dependent AP prolongation

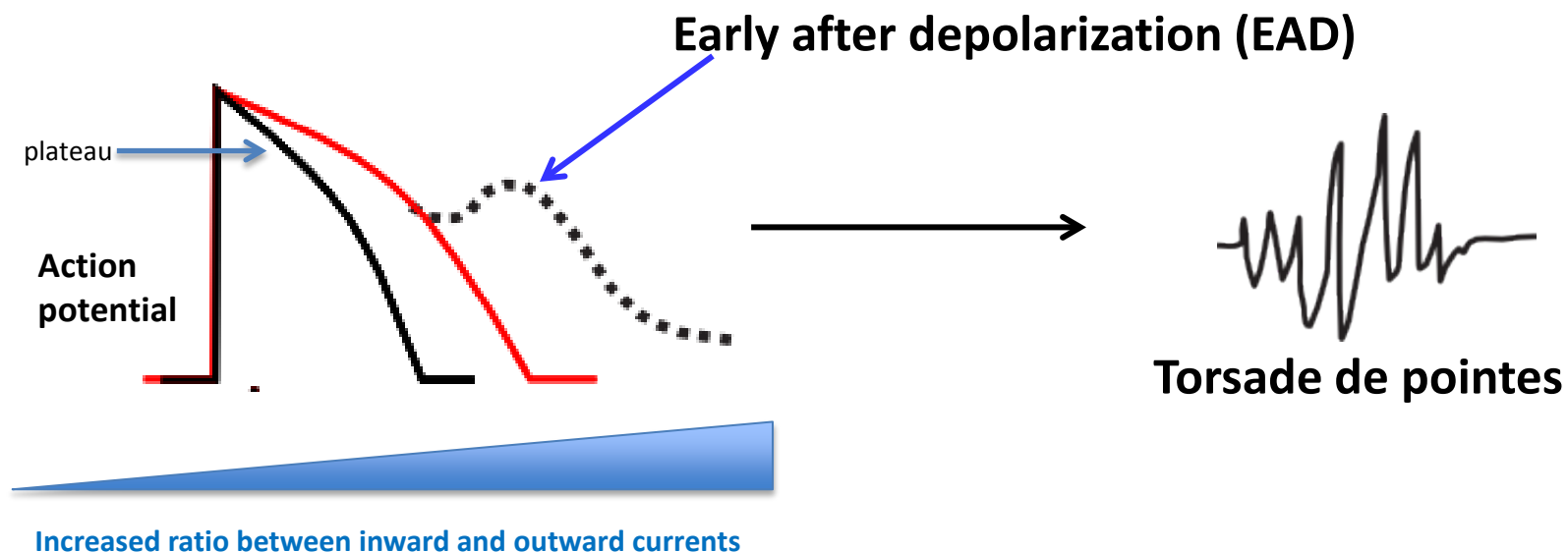
Optimizing Model Parameters Based on Human Cardiomyocyte Data



- Human cardiomyocyte action potential duration (APD) was recorded under L-type calcium current (ICaL) blocker (1 μ M nisoldipine)
- The optimized model was able to reproduce the experimental data better than the original model
- Similar improvement seen for other major potassium currents (IKr/hERG, IKs, IK1) and also late sodium current INaL.

Dutta S et al. Optimization of an In Silico Cardiac Cell Model for Proarrhythmia Risk. (In revision)
Experimental data were taken from O'Hara et al. PloS Computational Biology. 2011

Key Mechanism of TdP: imbalance of Inward and Outward Currents



Major currents modulating repolarization

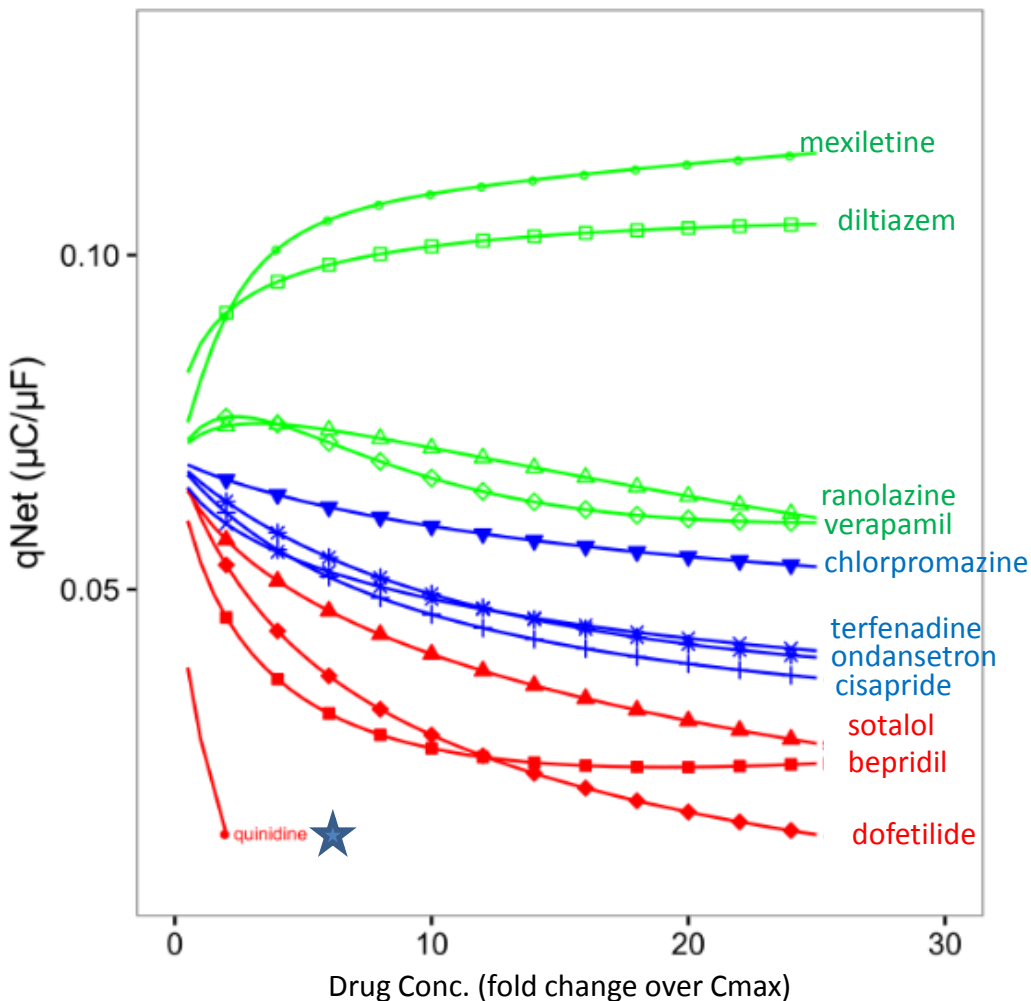
Inward	Outward
ICaL (L type calcium)	IKr (potassium)
INaL (late sodium)	IKs (potassium)
	IK1 (potassium)
	Ito (potassium)

The net current between inward and outward currents reflect their balance.

$$I_{net} = I_{CaL} + I_{NaL} + I_{Kr} + I_{Ks} + I_{K1} + I_{to}$$

qNet: Amount of electronic charge carried by I_{net}

Performance of qNet on 12 CiPA Training Compounds



- **Red:** CiPA TdP High Risk
- **Blue:** CiPA TdP Intermediate Risk
- **Green:** CiPA TdP Low/No Risk

★: EAD induced

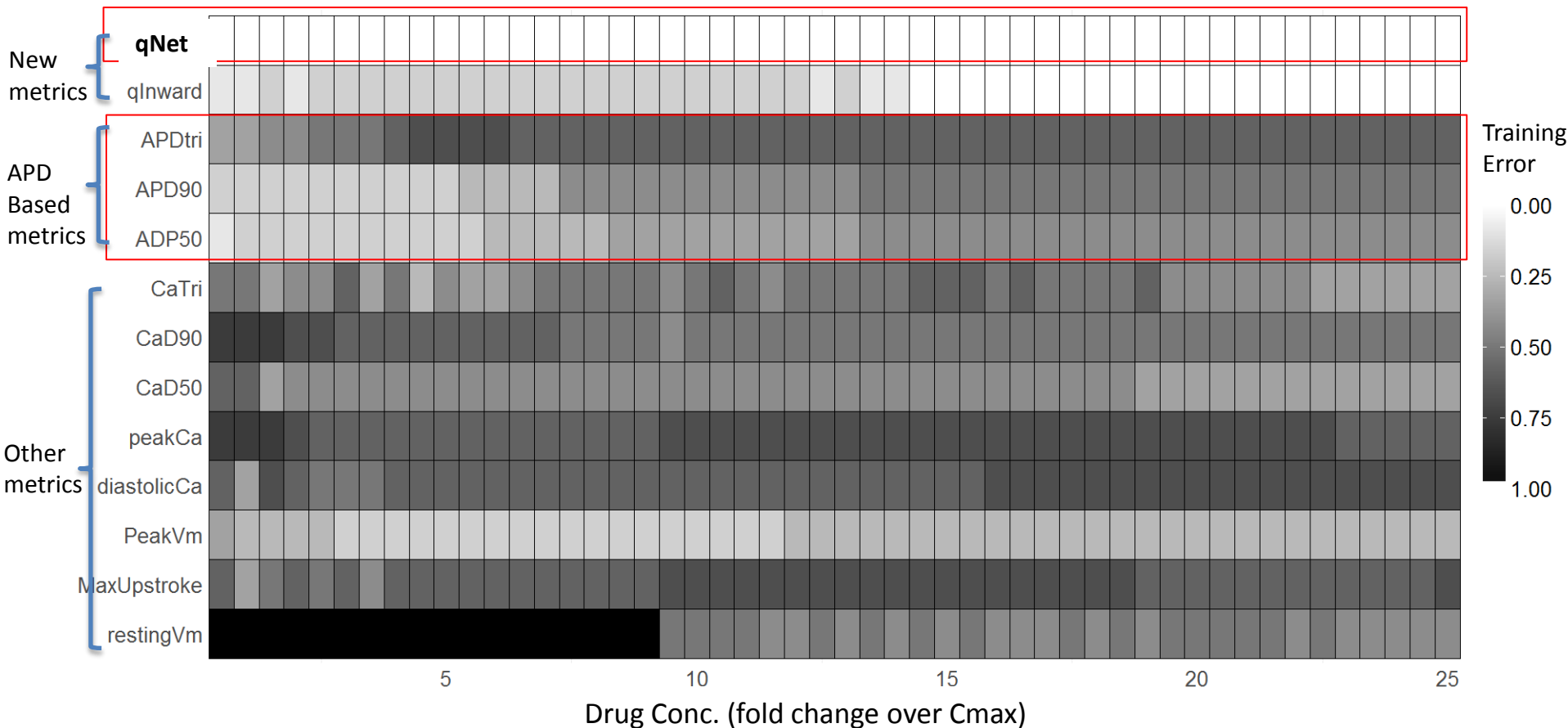
qNet:

Net amount of electronic charges passing through the membrane carried by selected currents

Simulation with 2000 ms cycle length

- Drug separation is good along all concentrations from 1x to 25x Cmax

Comparison of the New Metric(s) with All Other Tested Markers

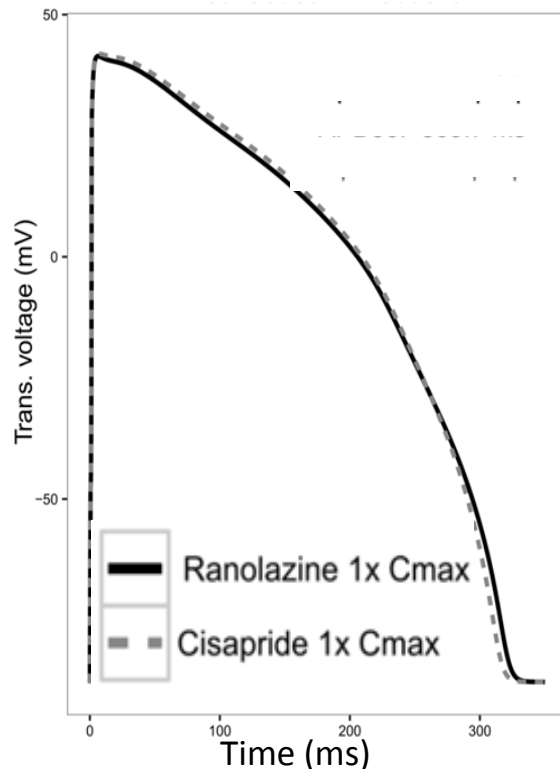


- qNet is the only metric with 0 training error across all concentrations
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs

qNet vs APD : A Case Study

Q: Which cell is in a more dangerous status (closer to EAD generation)?

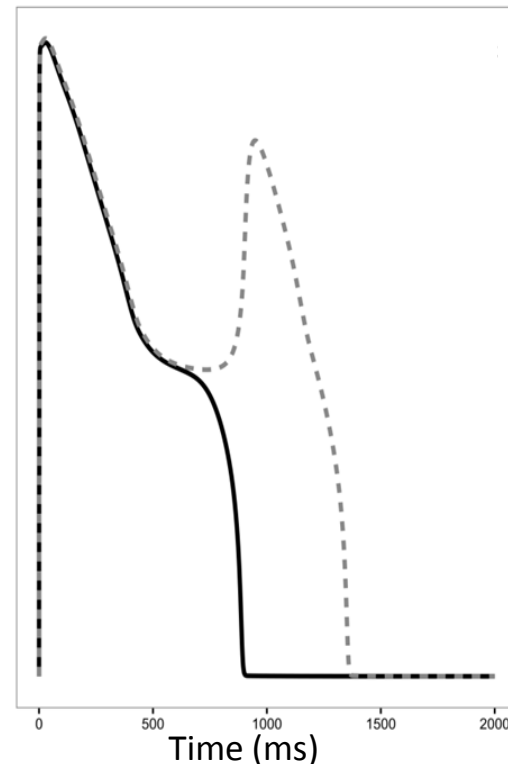
- APD: The cell with ranolazine (black)
- qNet: The cell with cisapride (grey)



Applying the same
pro-EAD “push”



Added 91.6% IKr
conductance
reduction



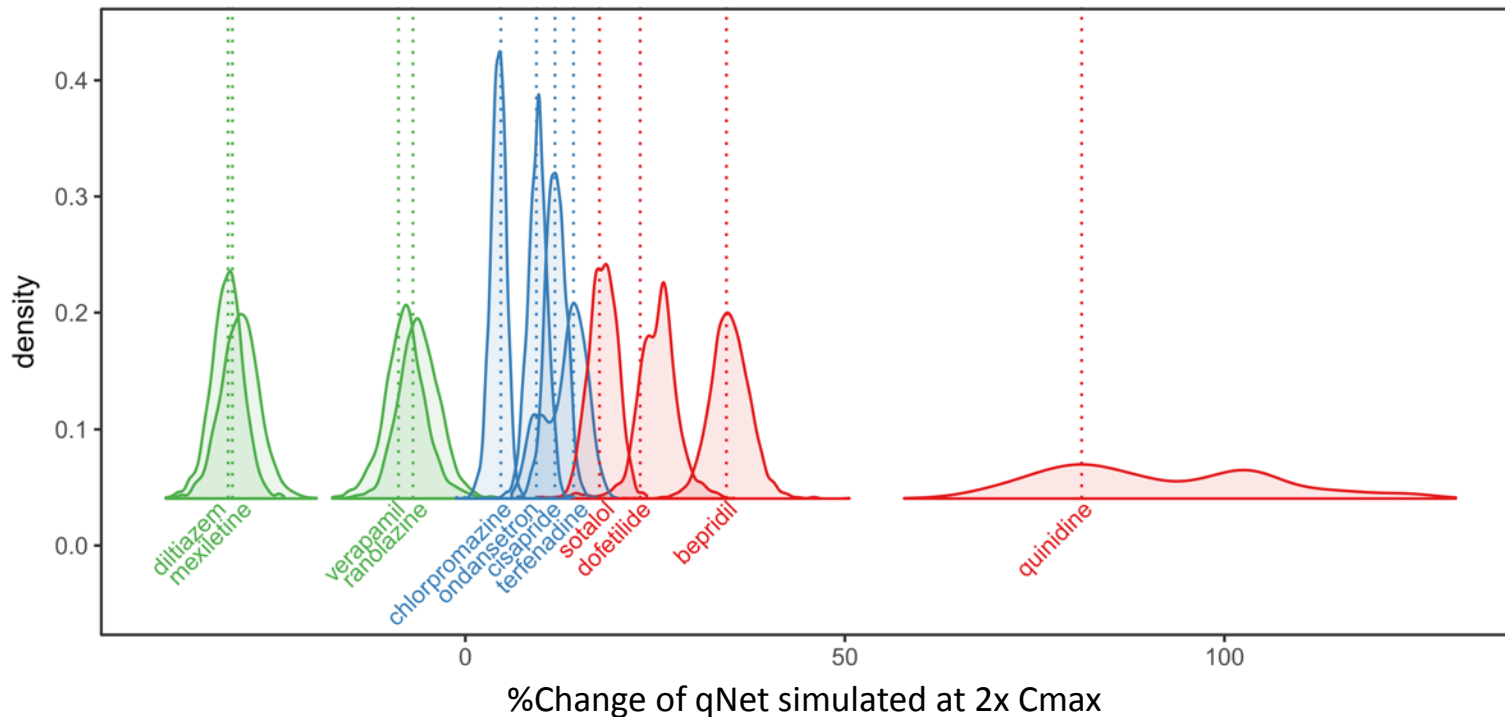
- qNet, but not APD, correctly predicts the distance from EAD
- qNet, but not APD, independently supports the rank order of the two drugs in CiPA categories

What About Experimental Uncertainty?



- Experimental data have intrinsic (i.e. inherent randomness) and extrinsic (i.e. cell-to-cell variability) uncertainty
- This will lead to uncertainty in metric calculation and TdP risk assessment
- Thus each drug at a specific concentration should have a range of possible metric values

Metric Calculation with Experimental Uncertainty



- A method was developed to translate experimental uncertainty (i.e. variability of IC50s) to uncertainty in metric calculation
- Each drug has a distribution of possible metric (change of qNet) values due to experimental uncertainty
- The distribution peaks (most probable metric values for each drug) are completely separated for the three categories

Summary of In Silico Work



- The consensus cardiac model (ORd) is further enhanced with temperature-dependent dynamic drug-hERG interaction, and optimized model parameters based on human cardiomyocyte data
- A promising metric identified using training drugs; its performance to be assessed using independent validation drugs
- Method to incorporate experimental uncertainty established; Method to capture inter-subject variability also being considered
- The experimental quality criteria, data format standard, and efficient route for sponsor data submission are being developed in collaboration with industry collaborators.

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CiPA Summary

- CiPA is a fit-for-purpose assay
- Will utilize an in silico mechanistic model to serve as the prediction of proarrhythmic risk of a drug in comparison to known clinical comparators
- An additional preclinical check with iPSC-cardiomyocytes to ensure that drug effects on repolarization are not missed
- ECGs will still be assessed in Phase 1 clinical studies with exposure-response modeling

CiPA Expected Outcomes

- Standardized, nonclinical mechanistic-based studies to determine proarrhythmic risk that can be applied early in drug development to aid in compound selection
- Proarrhythmic risk calibrated against consensus clinical comparators ranked according to clinical experience
- Compounds with hERG block/QTc prolongation that might be dropped from development under current paradigm could have a clearer path to advance if they are shown to not be proarrhythmic
- QTc prolonging drugs on the market that are not proarrhythmic could have labeling updated to reflect this
- Model for comprehensive, model-informed, mechanistic-based approaches to be applied to other drug safety areas

2017 FDA Advisory Committee Meeting



- On March 15th 2017, FDA held a Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting on the topic of “Model Informed Drug Development”, where CiPA was presented as a potential new regulatory paradigm to seek external expert opinions
- The Committee was asked to vote on three questions:
 1. For a QT prolonging drug, does the committee think that this mechanistic, model-based approach will be fit for determining whether ECGs need to be collected in Phase 3, and informing proarrhythmic risk language in drug labeling?
 2. Does the committee agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate and high risk by an expert panel?
 3. As this new mechanistic, model-based approach is implemented, should FDA collect the world’s experience (i.e. digital waveform data from *in vitro* experiments) to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?
- The Committee voted in favor of all these three questions

CiPA Progress from the Steering Committee



- CiPA teams have presented multiple times to the ICH S7B/E14 Discussion Group the rationale and approach being taken in the CiPA project
- CiPA Steering Committee is optimistic that this interaction will speed acceptance of this alternative pathway for assessment of proarrhythmic potential for regulatory purposes
- After the planned implementation, we are interested in carefully evaluating approved drugs that show evidence of being QTc prolongers without TdP risk, with the expectation that application of CiPA will result in drugs having their current labeling changed to more benign language if appropriate

The Comprehensive in vitro Proarrhythmia Assay Initiative – Update on Progress.

Colatsky, Fermini, Gintant, Pierson, Sager, Sekino, Strauss, Stockbridge.

J Pharmacol Toxicol Methods (2016) <http://dx.doi.org/10.1016/j.vascn.2016.06.002>.

Acknowledgements

CiPA Steering Committee

Ayako Takei, Bernard Fermini, Colette Strnadova, David Strauss, Derek Leishman, Gary Gintant, Jean-Pierre Valentin, Jennifer Pierson, Kaori Shinagawa, Krishna Prasad, Kyle Kolaja, Natalia Trayanova, Norman Stockbridge, Philip Sager, Tom Colatsky, Yuko Sekino, Zhihua Li, Gary Mirams

All CiPA Working groups

- Ion Channel working group
- In silico working group
- Cardiomyocyte working group
- Phase 1 ECG working group

ALL contributors to CiPA (there are a lot!)

- Public-private partnerships: HESI, SPS, CSRC
- Regulatory Agencies: FDA, EMA, PMDA/NIHS, Health Canada
- Many pharmaceutical, CRO, and laboratory device companies
- Academic collaborators

FDA Contributors

- Norman Stockbridge
- Christine Garnett
- John Koerner

In silico / ion channel

- Zhihua Li
- Wendy Wu
- Sara Dutta
- Phu Tran
- Jiangsong Sheng
- Kelly Chang
- Kylie Beattie
- Min Wu
- Richard Gray

Cardiomyocyte

- Ksenia Blinova
- Derek Schocken
- Li Pang

Phase 1 ECG biomarker

- Jose Vicente
- Lars Johannesen
- Meisam Hosseini
- Alexander Wong
- Dustin McAfee
- Robbert Zusterzeel
- Krystal Lansdowne

