FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Translating New Science Into Drug Development & Evaluation

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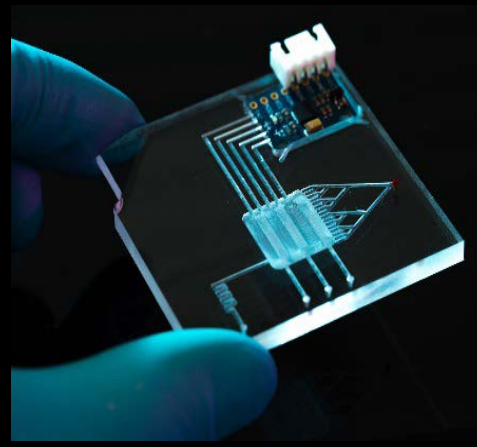
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

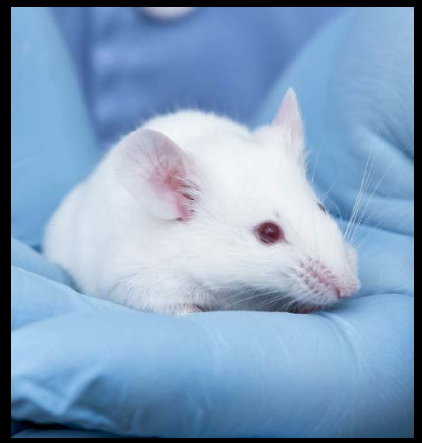
What is Regulatory Science?

1. Modeling & Simulation

2. In Vitro Models



3. In Vivo Models

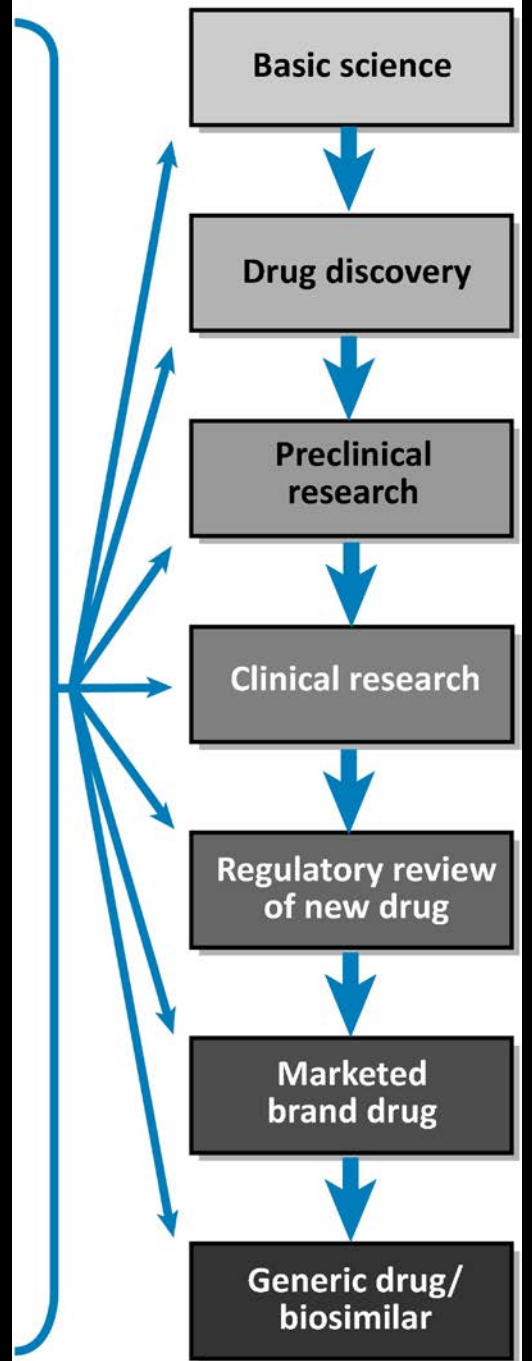


4. Biomarkers

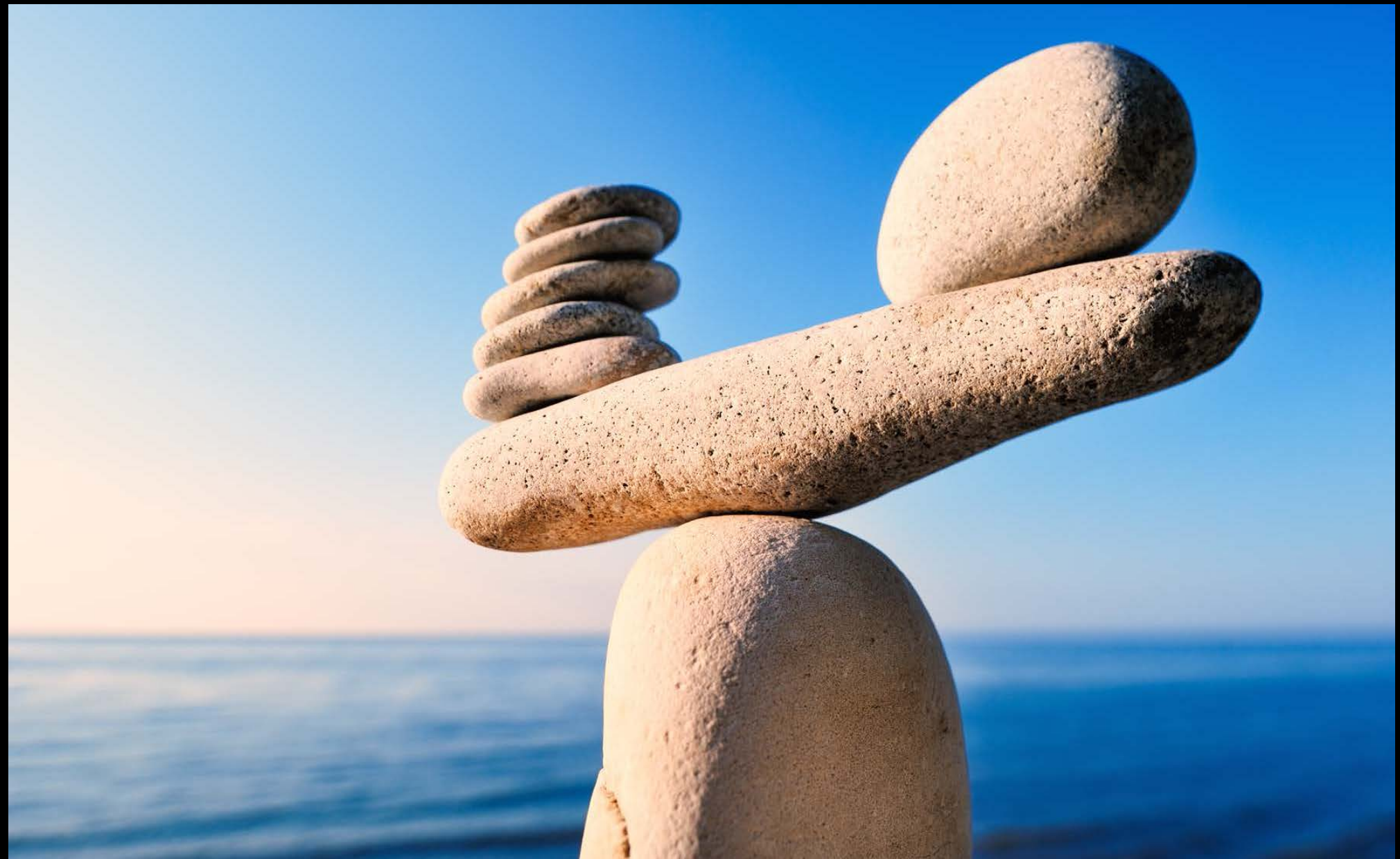
5. Innovative Clinical Trial Designs

6. Real World Data

Rouse, Zineh, Strauss. *Trends in Pharmacological Sciences* 2018;39:225-9.



Why Do We Need Regulatory Science?



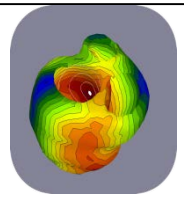
Talk Outline: Regulatory Science at FDA

1. Medical Devices

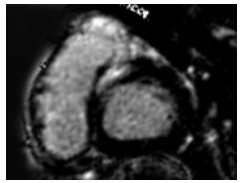
2. Drugs

Translational Regulatory Science Approach

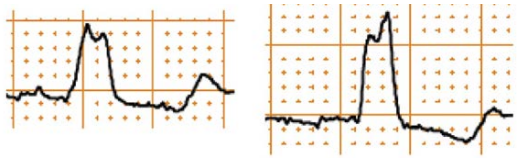
Computational Modeling / Simulation



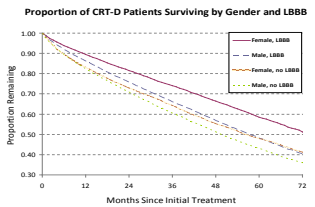
Clinical Physiology (Pharmacology) Studies



Patient-Level Meta-Analysis of Clinical Trials

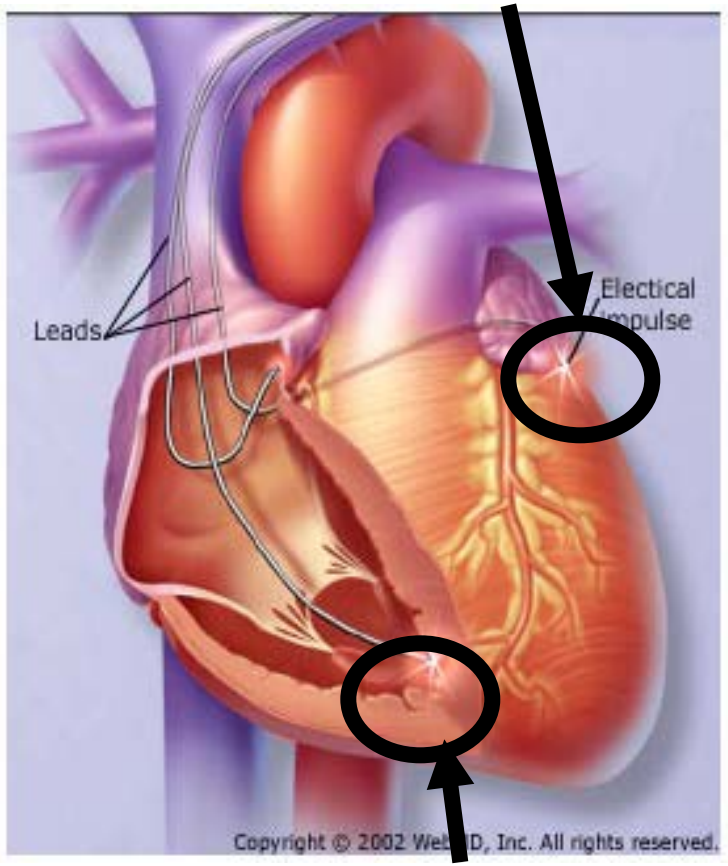


Real World Data



Cardiac Resynchronization Therapy (Biventricular Pacemaker)

Additional lead for cardiac resynchronization therapy



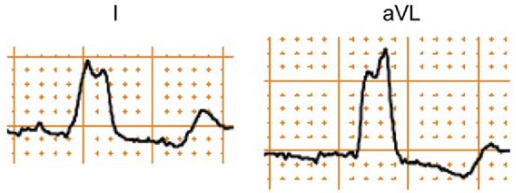
Traditional pacemaker lead

- Shown to improve heart failure symptoms, reduce heart failure hospitalization and reduce mortality
- However, not all patients benefit and significant risks exist
- Thus, there is a need for better risk stratification and patient identification criteria
- ~20% of patients in clinical trials were women, thus overall results primarily reflect effects in men

Improved Biomarkers and Diagnostic Criteria for Patient Selection for Therapy

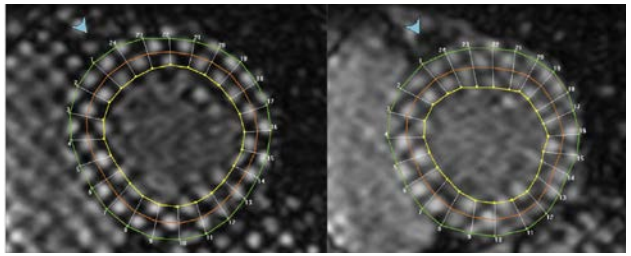
- Patient selection is based on the electrocardiogram (ECG)
- Used modeling & simulation, developed new sex-specific criteria

Defining Left Bundle Branch Block in the Era of Cardiac Resynchronization Therapy



Strauss et al. *American Journal of Cardiology* 2011;15:927-34

- Used cardiac MRI to define the heart pumping characteristics of patients most likely to benefit from therapy



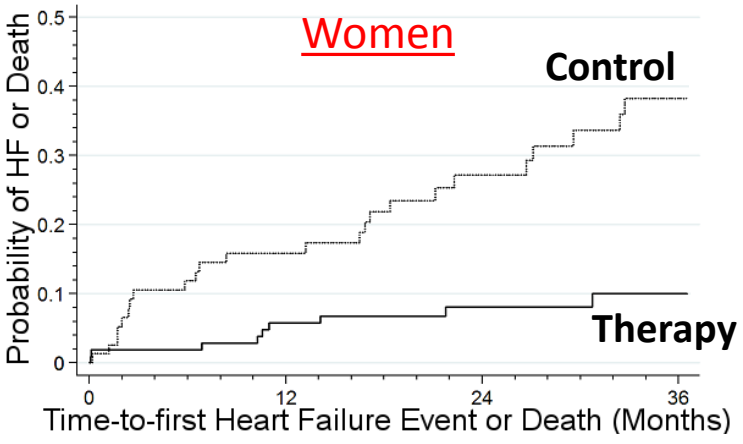
Andersson…Strauss. *American Heart Journal* 2013;165:956-63.

Patient-Level Meta-Analysis of Clinical Trials

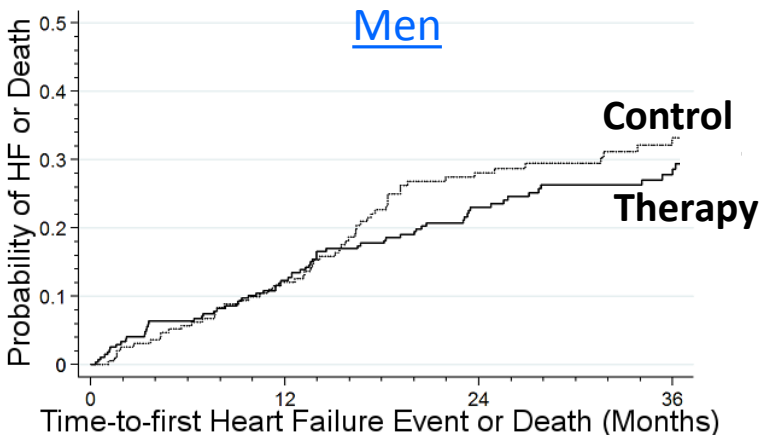
Original Investigation

Cardiac Resynchronization Therapy in Women
US Food and Drug Administration Meta-analysis of Patient-Level Data

Zusterzeel…Strauss. *JAMA: Internal Medicine* 2014;174:1340.



Large benefit in women



No benefit in men

- Both women and men benefited
- However women benefited with different characteristics defined by the ECG
- Women with these characteristics did not receive the highest recommendation for therapy because women only represented ~20% of clinical trial patients and this group of men did not benefit

Patients with QRS duration <150 millisec

Real World Data with National Medical Device Registries & Medicare Patients

Cardiac Resynchronization Therapy in Women Versus Men
Observational Comparative Effectiveness Study From the National Cardiovascular Data Registry

Zusterzeel…Strauss. *Circulation: Cardiovasc Outcomes 2014;8:S4.*

Zusterzeel…Strauss. *J Am Coll Cardiol* 2014;64:887.

Left Bundle Branch Block Predicts Better Survival in Women Than Men Receiving Cardiac Resynchronization Therapy
Long-Term Follow-Up of ~145,000 Patients

Loring…Strauss. *J Am Coll Cardiol: Heart Failure* 2013;1:237.

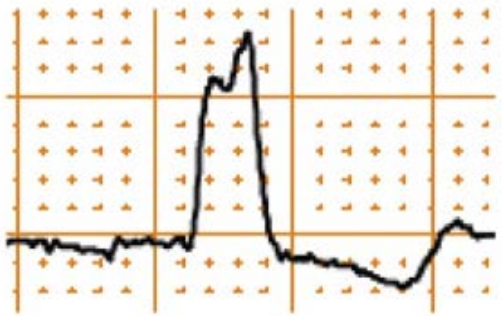
Zusterzeel…Strauss. *Am J Cardiol 2015;116:79-84.*

- Used national implantable defibrillator registry linked to long term mortality outcomes
- Long-term outcomes of all Medicare patients
- Confirmed results of prior FDA meta-analysis that women benefit more than men

Personalized Cardiac Device Therapies Summary

We have worked to:

- Redefine diagnostic criteria to predict individual patient benefit from implantable medical devices
- Personalize treatment to women vs. men



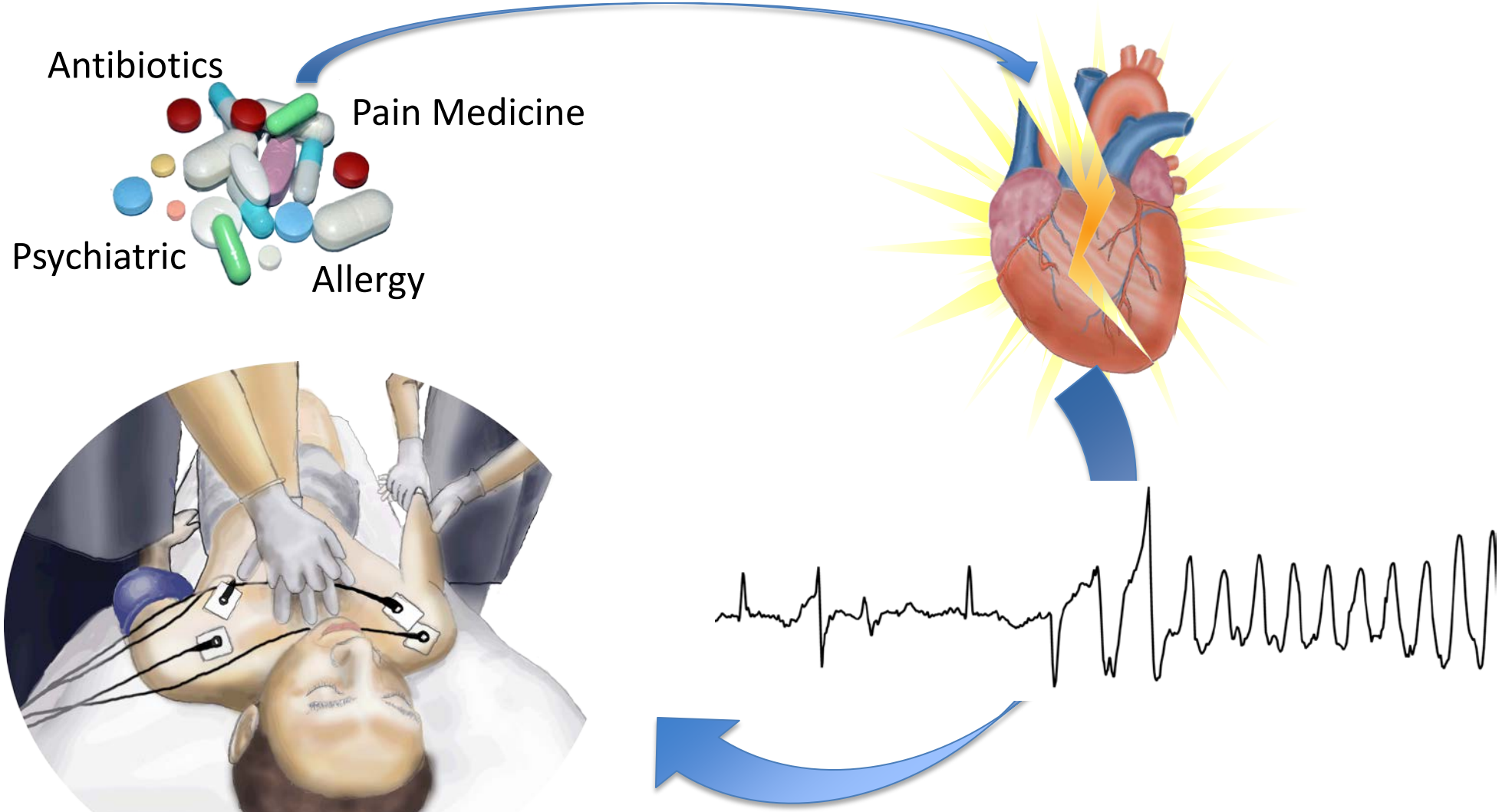
We have accomplished this through:

- Translational regulatory science approach
- Collaboration within FDA, with Universities, professional societies and other government agencies

Translational Research & Review

CDER and Clinical Pharmacology

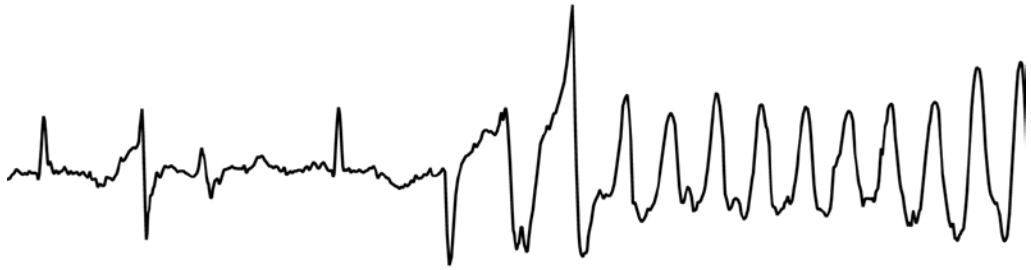
Why Do We Need to Assess Cardiac Safety?



Images by Alan Knapton, FDA

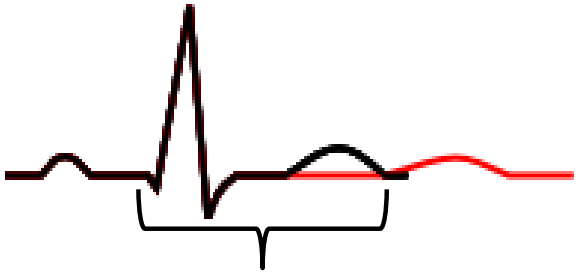
What do the Torsade Drugs Have in Common?

Torsade de pointes …



↓

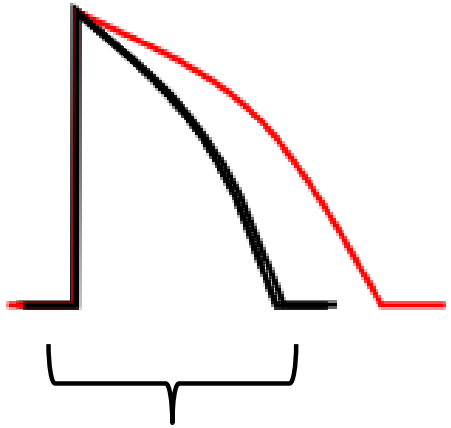
Is associated with QT prolongation …



QT interval

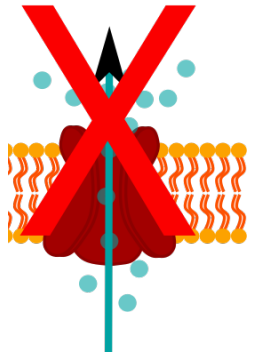
↓

Is associated with action potential prolongation …



Heart cell action potential duration

Is associated with hERG channel block →



Potassium ions

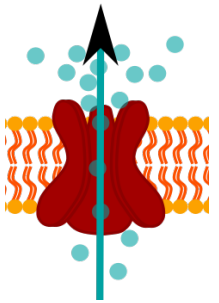
What the Heck Is “hERG”?

Human ***E****ther-à-go-go*-**R**elated **G**ene

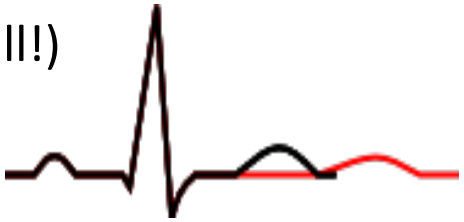
Courtesy of Dr. Barry Ganetzky / Blake Anson, University of Wisconsin

International Council on Harmonization Guidelines in Response to Problem – Established in 2005

- S7B: Non-clinical cardiac safety pharmacology
  - hERG potassium channel block
  - Non-clinical action potential or QT study



- E14: Human Clinical 'Thorough QT' study
  - Threshold of concern is ~2% increase in QT (very small!)
  - Most intensive and expensive clinical pharmacology study in drug development



- **Primary goal of assessing QT is to inform whether ECG monitoring in patients is required in clinical phase 3 trials**
- **<u>Not</u> to inform whether a drug causes torsade de pointes**

<u>As some QT prolonging drugs do not cause torsade de pointes</u>

Why Is This a Problem?

- False positive attribution of proarrhythmic risk can result in
  - Poor lead compound selection
  - Unnecessary complexities in drug development (including drugs being dropped from development)
  - Inaccurate labelling regarding risk
  - Which influences (non-ideal) decisions by healthcare providers and patients

The Scale of the Problem

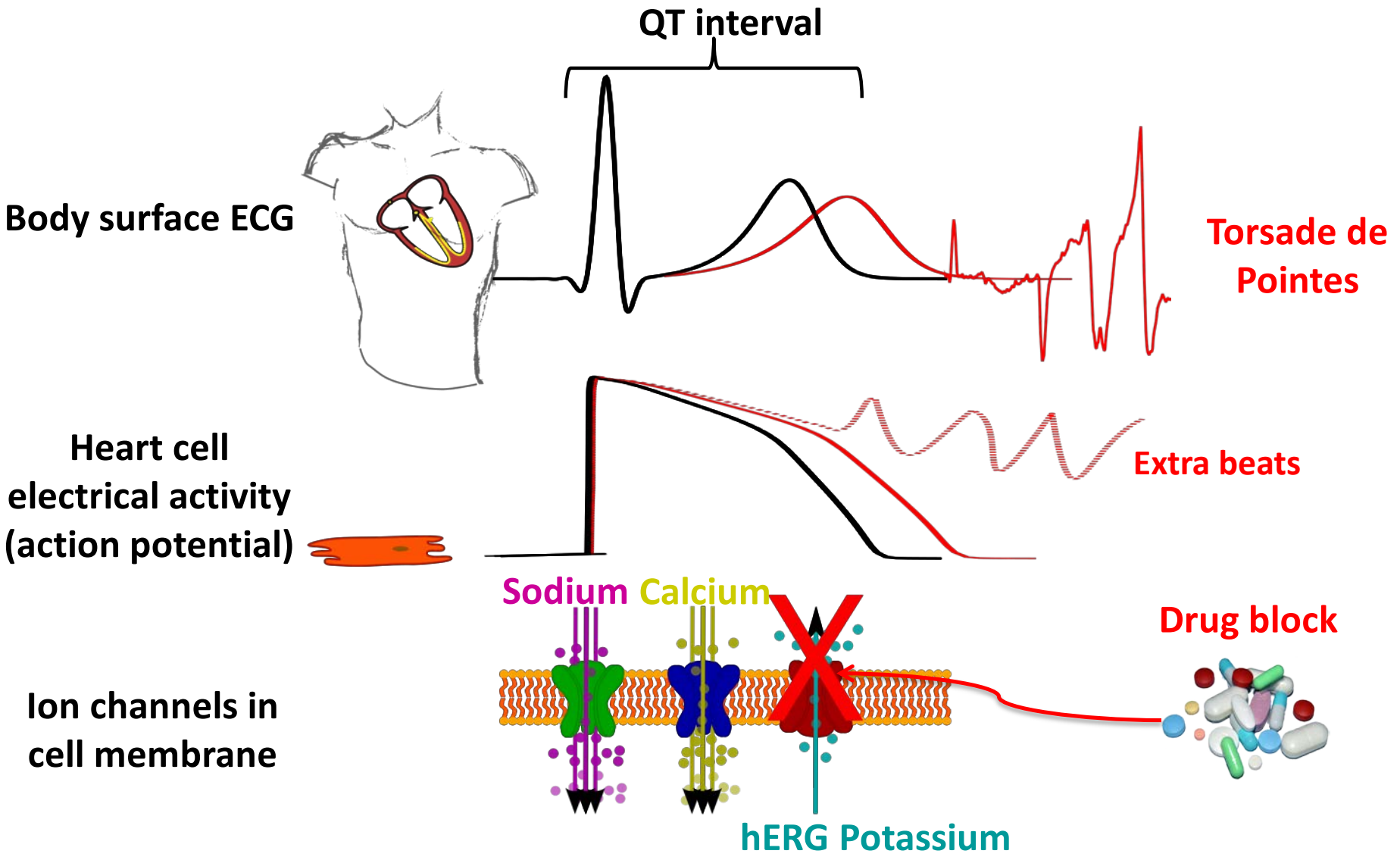
- hERG is “promiscuous”

Up to 70% of compounds block hERG*

- Many of these compounds are dropped from development – which is not always justified!

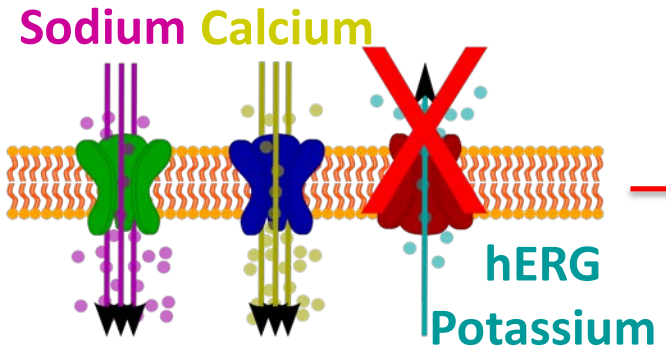
*Fermini et al. 2016 J Biomolecular Screening 2016;21:1-11.

When Does QT Prolongation Cause Torsade?

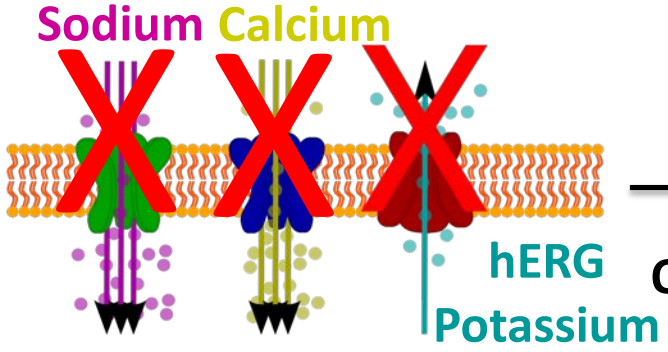


Vicente…Strauss. *Clinical Pharmacology & Therapeutics* 2018;103:54-66.

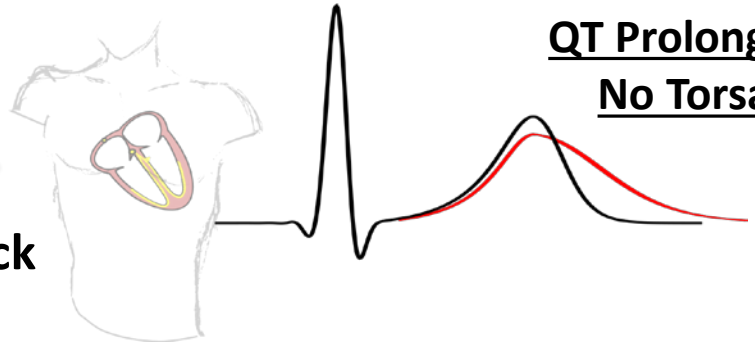
When Does QT Prolongation Not Cause Torsade?



hERG Block Alone → **Torsade**



hERG Block + Sodium Block Or Calcium Block →



QT Prolongation No Torsade

Vicente…Strauss. *Clinical Pharmacology & Therapeutics* 2018;103:54-66.

Translational Regulatory Science

nature publishing group

STATE OF THE ART

Improving the Assessment of Heart Toxicity for All New Drugs Through Translational Regulatory Science

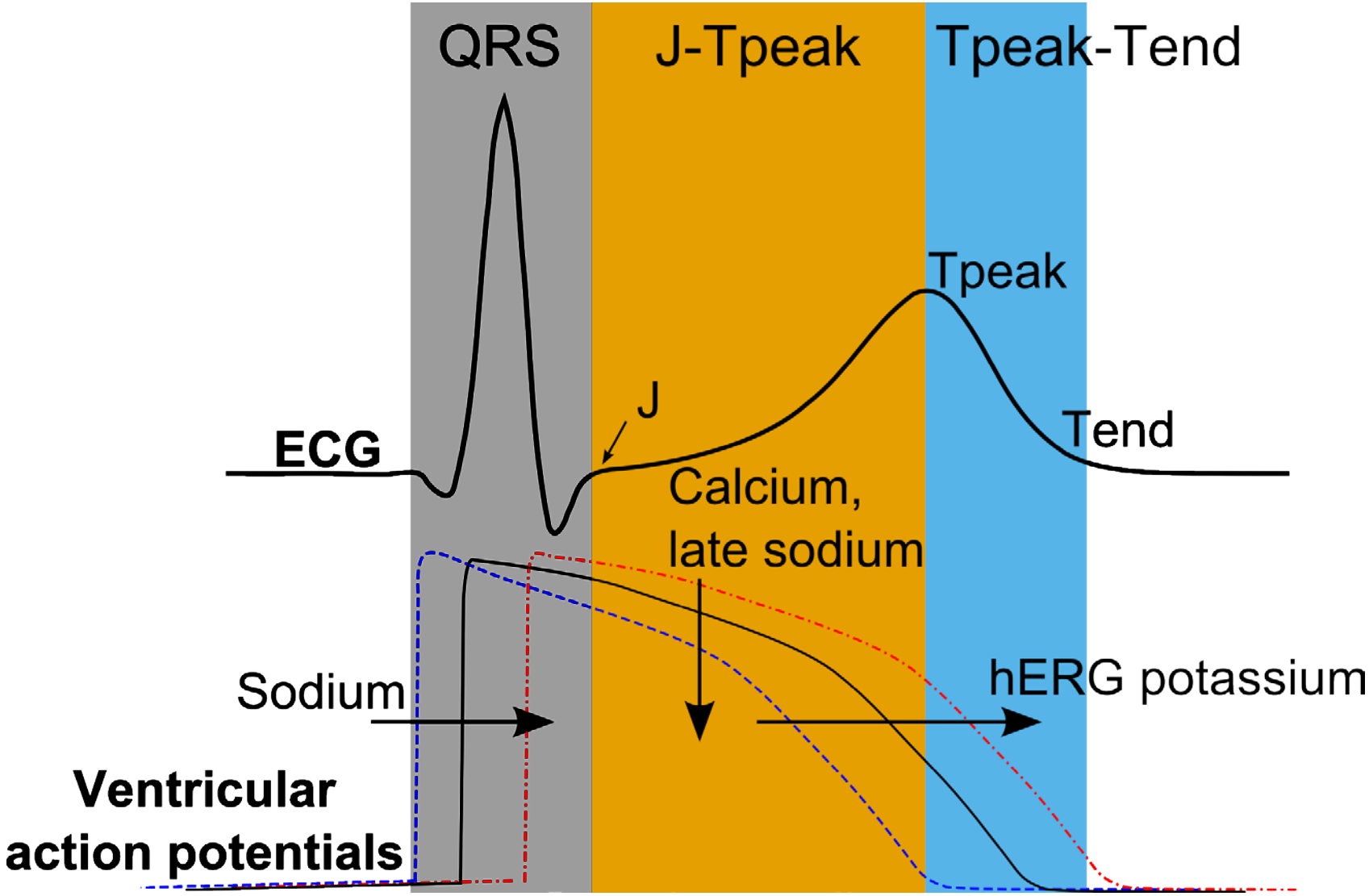
L Johannesen[1,2,3], J Vicente[2,4], RA Gray[2], L Galeotti[2], Z Loring[2], CE Garnett[1,5], J Florian[1], M Ugander[2,3], N Stockbridge[6] and DG Strauss[2]

Clinical Pharmacology & Therapeutics 2014;95:501-8.

- Analysis of 34 'Thorough QT' clinical trials submitted to FDA along with corresponding *in vitro* data

- Identified novel electrocardiographic biomarker to differentiate multi-ion channel block

Going Beyond QT to Differentiate Multi-Channel Effects



Johannesen…Strauss. Clinical Pharmacology & Therapeutics 2014;96:549-58.

Prospective Clinical Trials

nature publishing group

CLINICAL TRIAL

Differentiating Drug-Induced Multichannel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine, and Verapamil

L Johannesen[1,2], J Vicente[1,3], JW Mason[4], C Sanabria[4], K Waite-Labott[4], M Hong[5], P Guo[5], J Lin[5], JS Sørensen[6], L Galeotti[1], J Florian[6], M Ugander[1,2], N Stockbridge[7] and DG Strauss[1,2]

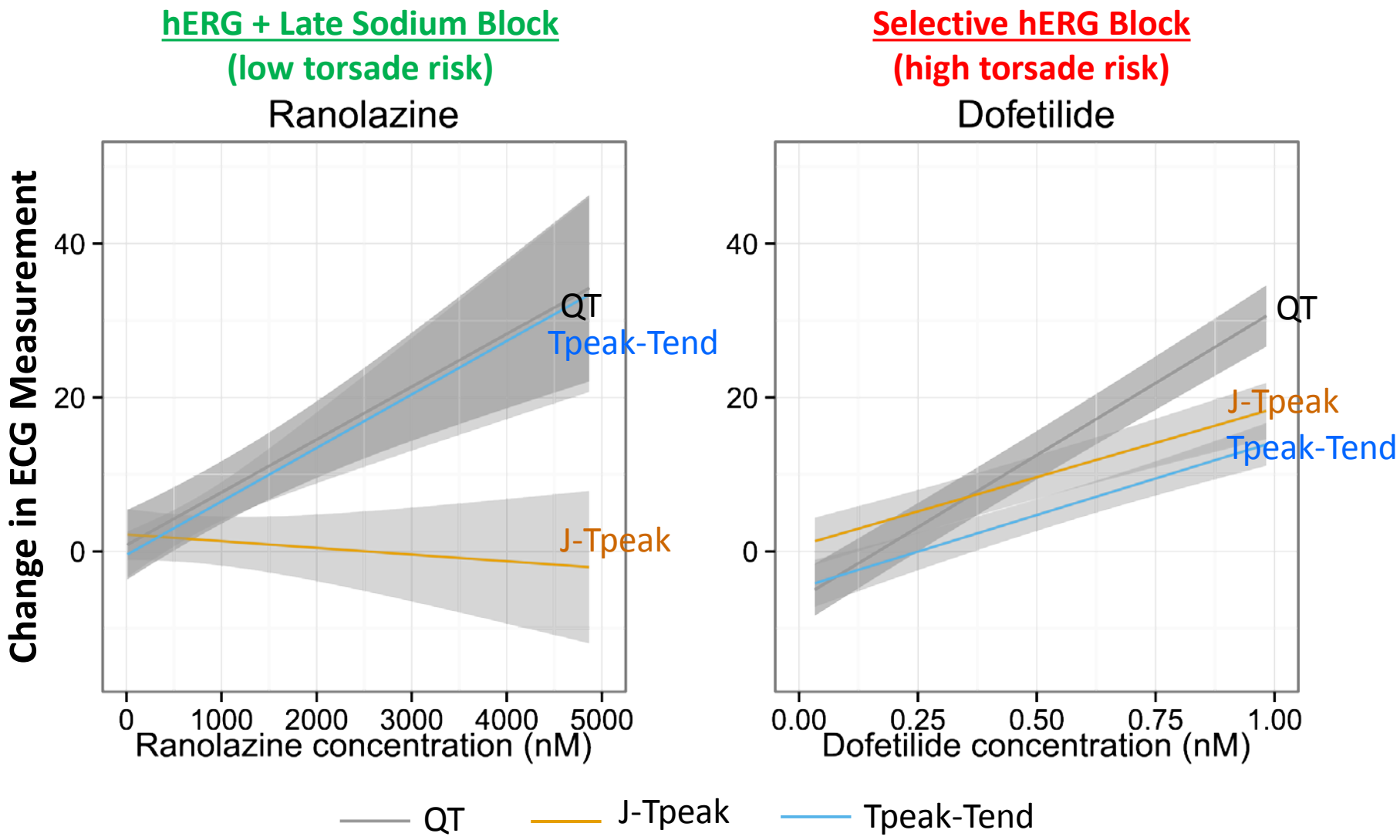
Clinical Pharmacology & Therapeutics 2014;96:549-58.

Late Sodium Current Block for Drug-Induced Long QT Syndrome: Results From a Prospective Clinical Trial

L Johannesen[1,2], J Vicente[1,3,4], JW Mason[5,6], C Erato[5], C Sanabria[5], K Waite-Labott[5], M Hong[7], J Lin[7], P Guo[7], A Mutlib[7], J Wang[7], WJ Crumb[8], K Blinova[1], D Chan[1], J Stohlman[1], J Florian[3], M Ugander[1,2], N Stockbridge[3] and DG Strauss[1,2]

Clinical Pharmacology & Therapeutics 2016;99:214-23.

Clinical Trial 1: Two Example Drugs



Johannesen…Strauss. *Clinical Pharmacology & Therapeutics* 2014;96:549-58.

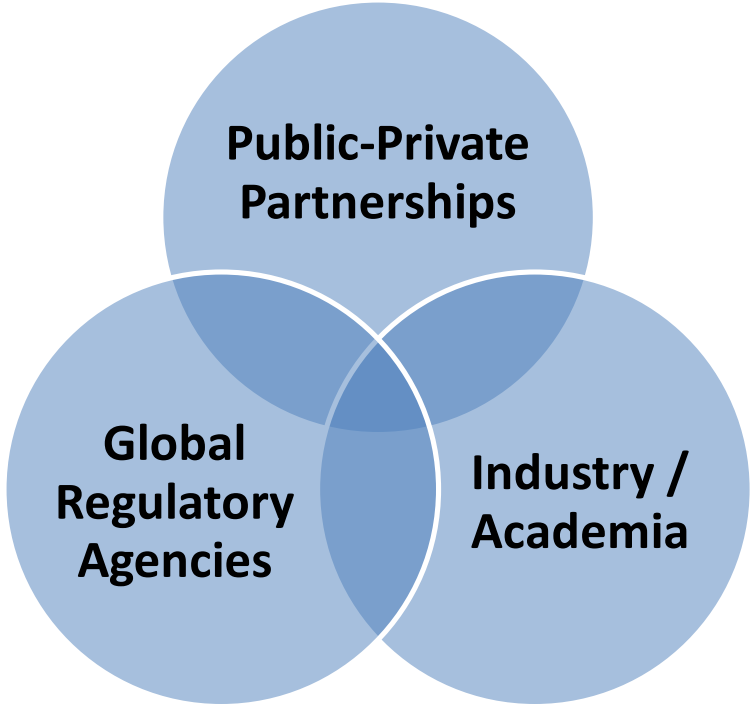
Comprehensive in vitro Proarrhythmia Assay (CiPA) Initiative – A Global Effort

Proposed at public meeting in July 2013

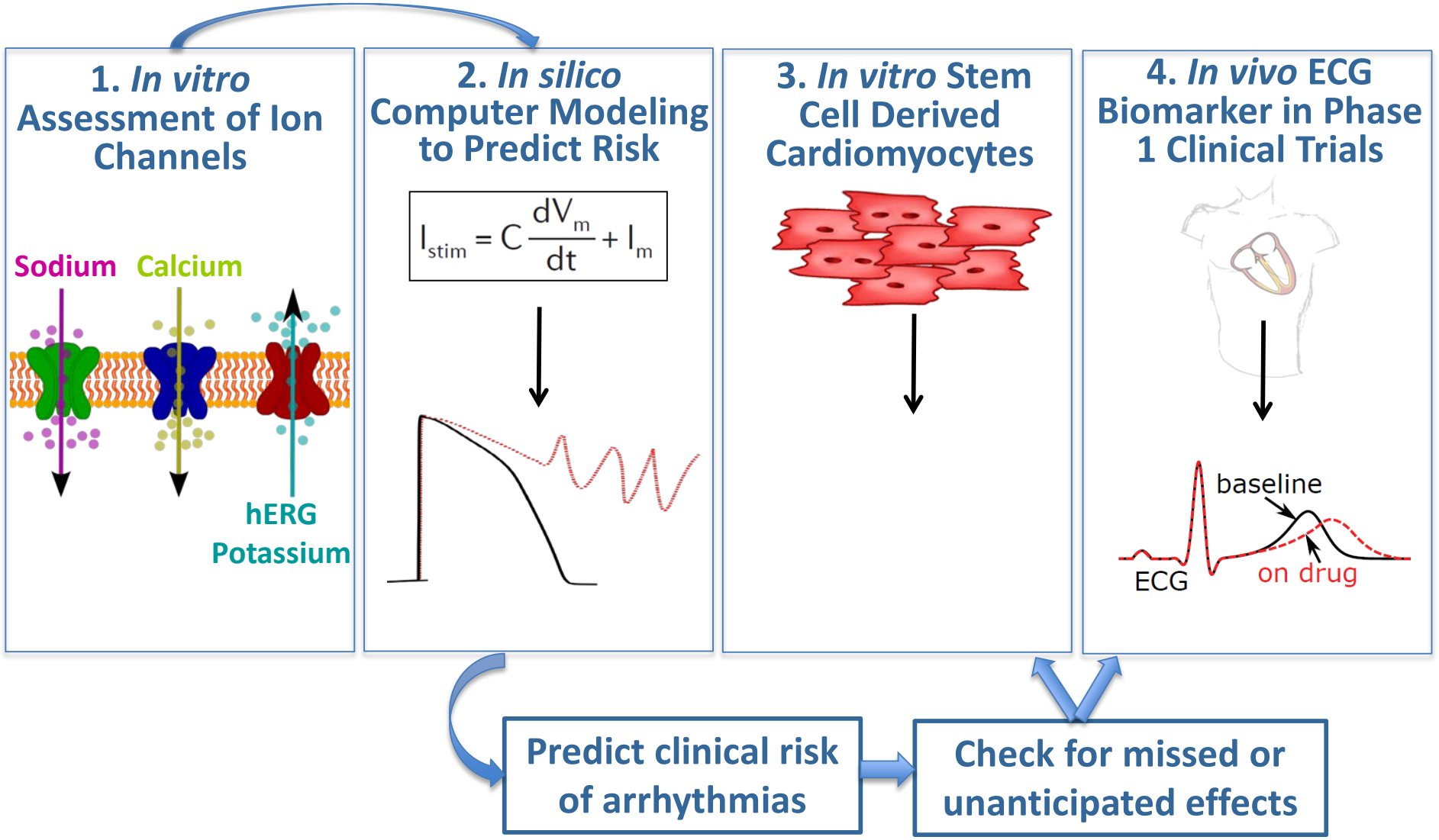
Nonprofits - Public-Private Partnerships
- Health and Environmental Sciences Institute
- Cardiac Safety Research Consortium
- Safety Pharmacology Society

Global Regulatory Agencies
- U.S. Food and Drug Administration
- Japan PMDA / NIHS
- European Medicines Agency
- Health Canada

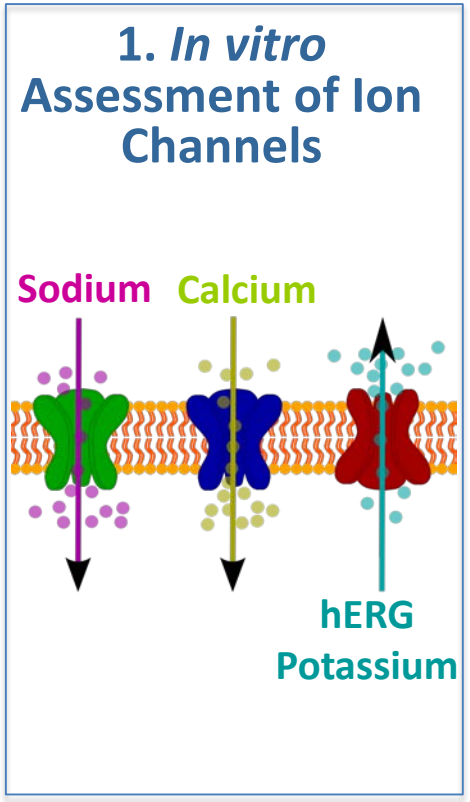
Academia / Industry
- Numerous Pharmaceutical and Device Companies
- Numerous Academic Groups
- Contract Research Organizations



Comprehensive *in vitro* Proarrhythmia Assay (CiPA): 4 Components



1. What Ion Channels Should be Selected?



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

Crumb...Strauss. *J Pharmacol Toxicol Methods* 2016;81:251-62.

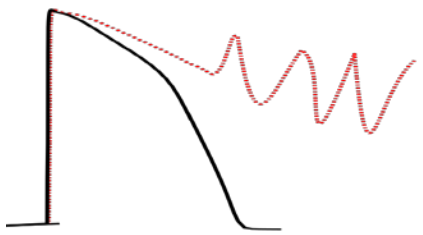
Studied 7 ion channels

- **Most commonly blocked** ion channel currents at clinically relevant concentrations are **hERG, late sodium and calcium**
- **Low risk** drugs had **equal or greater late sodium or calcium** block compared to hERG block

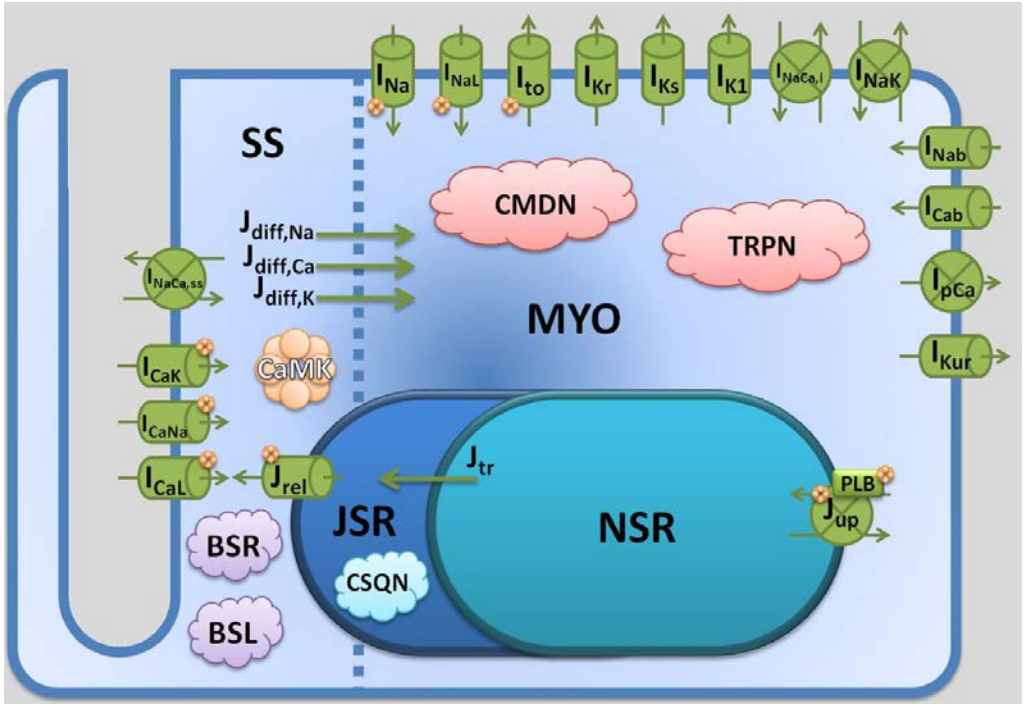
2. *In silico* Working Group

2. *In silico* Computer Modeling to Predict Risk

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

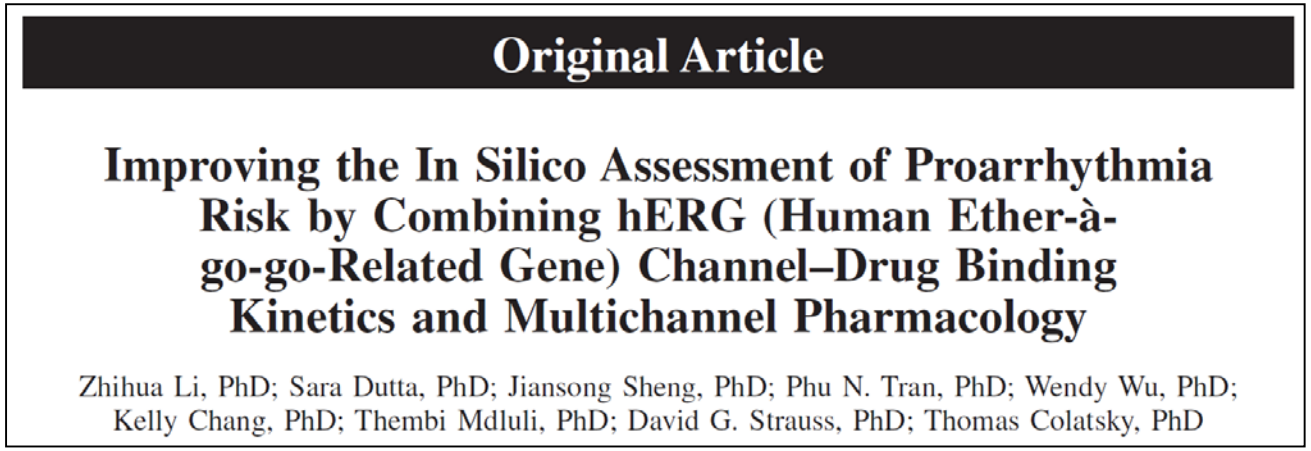


- **Goal**: Use a computer model of the adult human cardiomyocyte to predict the clinical risk of drug-induced arrhythmias



O'Hara … Rudy. *PLOS Comput Biol 2011;7(5):e1002061.*

Optimized Arrhythmia Risk Prediction & Defining Experimental Uncertainty



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

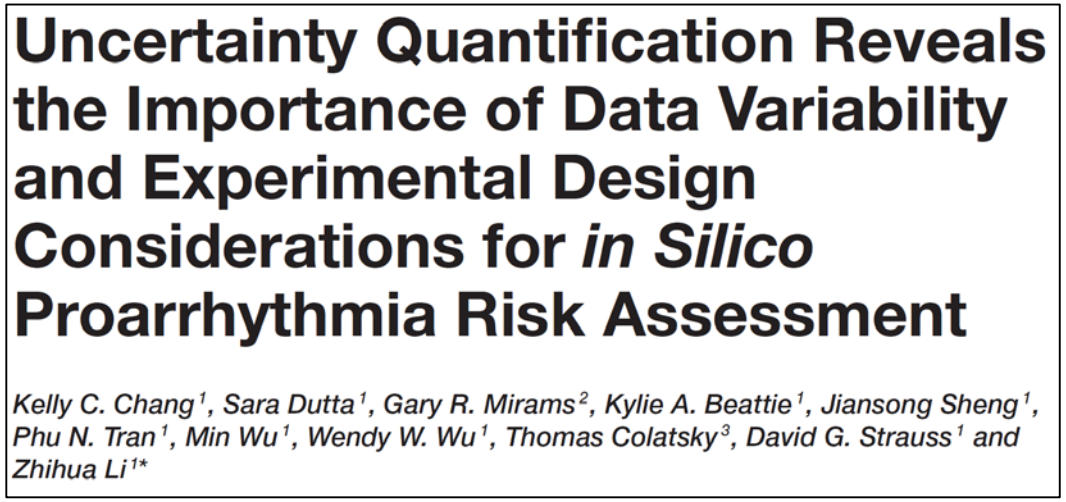
Zhihua Li, PhD; Sara Dutta, PhD; Jiansong Sheng, PhD; Phu N. Tran, PhD; Wendy Wu, PhD; Kelly Chang, PhD; Thembi Mdluli, PhD; David G. Strauss, PhD; Thomas Colatsky, PhD

Circulation: Arrhythmia & Electrophysiology 2017;10:e004628

Optimization of an *In silico* Cardiac Cell Model for Proarrhythmia Risk Assessment

*Sara Dutta, Kelly C. Chang, Kylie A. Beattie, Jiansong Sheng, Phu N. Tran, Wendy W. Wu, Min Wu, David G. Strauss, Thomas Colatsky† and Zhihua Li**

Frontiers in Physiology 2017. doi: 10.3389/fphys.2017.0016



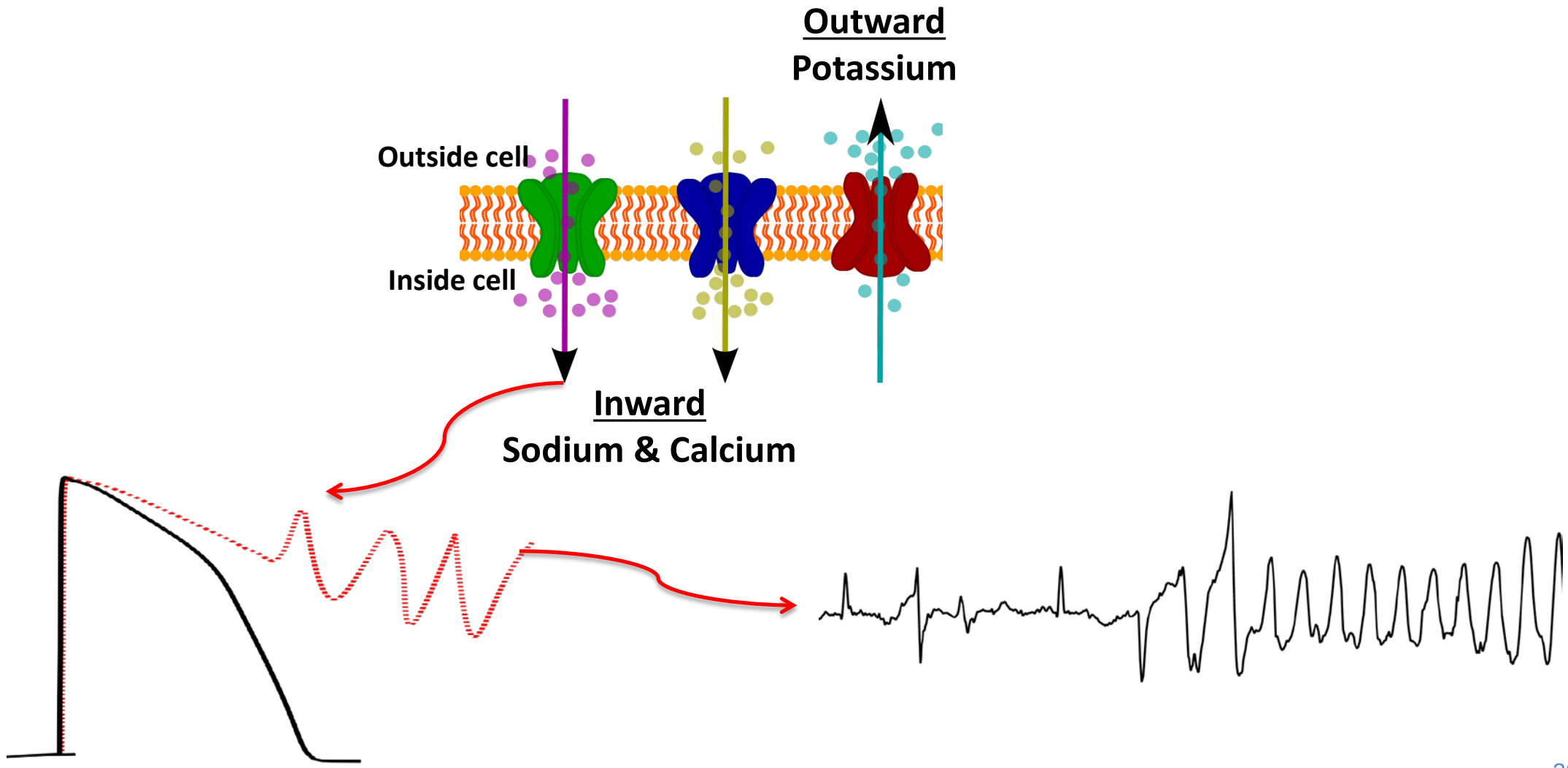
Uncertainty Quantification Reveals the Importance of Data Variability and Experimental Design Considerations for *in Silico* Proarrhythmia Risk Assessment

*Kelly C. Chang[1], Sara Dutta[1], Gary R. Mirams[2], Kylie A. Beattie[1], Jiansong Sheng[1], Phu N. Tran[1], Min Wu[1], Wendy W. Wu[1], Thomas Colatsky[3], David G. Strauss[1] and Zhihua Li[1]**

Frontiers in Physiology 2017.
doi: 10.3389/fphys.2017.00917

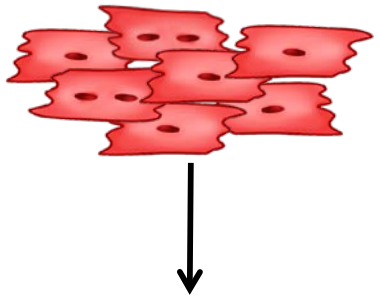
Arrhythmia Metric – Net Current

Balance of Inward and Outward Ion Channel Currents



3. Cardiomyocyte Working Group

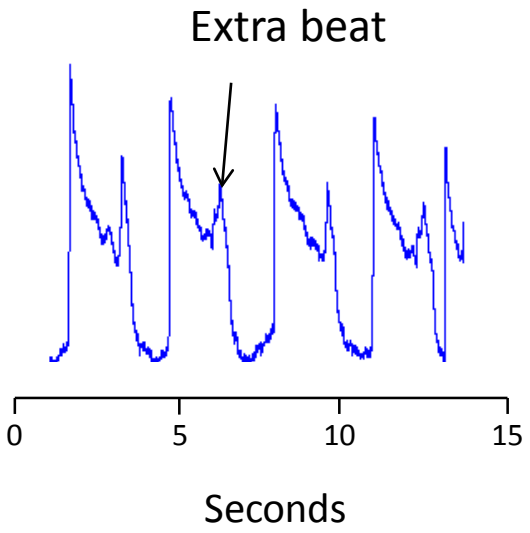
3. *In vitro* Stem Cell Derived Cardiomyocytes



Goal: Identify missed or unanticipated effects not detected from ion channel/*in silico* studies

Action potential duration

Seconds



Induced Pluripotent Stem Cell Derived Cardiomyocytes

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

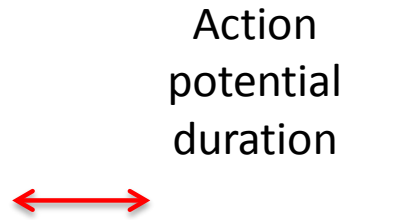
TOXICOLOGICAL SCIENCES, 155(1), 2017, 234–247

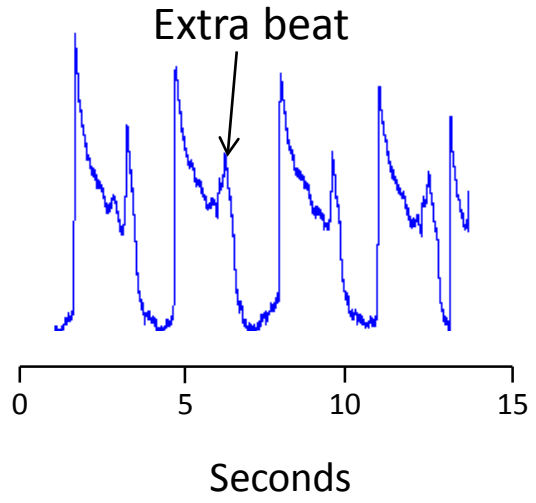
doi: 10.1093/toxsci/kfw200
Advance Access Publication Date: October 3, 2016
Research article

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

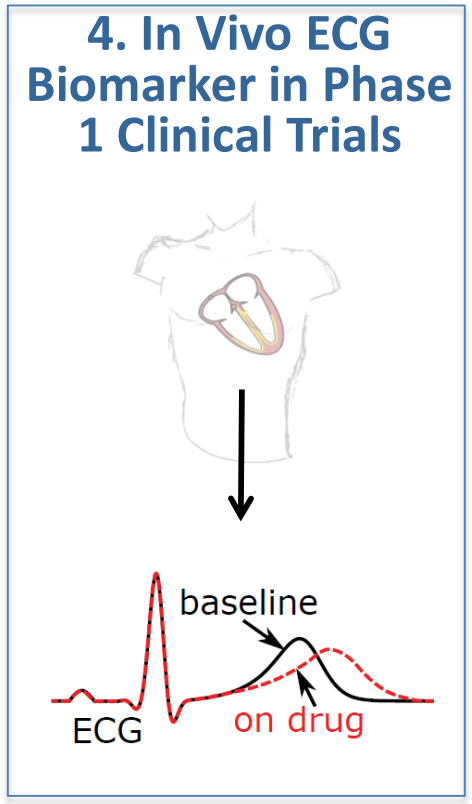
Blinova…Strauss. *Toxicological Sciences* 2017;155:234-47.

- Study included 26 drugs with 2 laboratory devices and 2 commercially available cell lines
- Subsequent validation study with 10 sites from around the world with multiple cell types and device platforms





4. Phase 1 ECG Biomarker Working Group



- **<u>Goal</u>**: Use human ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data

- New ECG biomarker needs to differentiate multi-ion channel effects

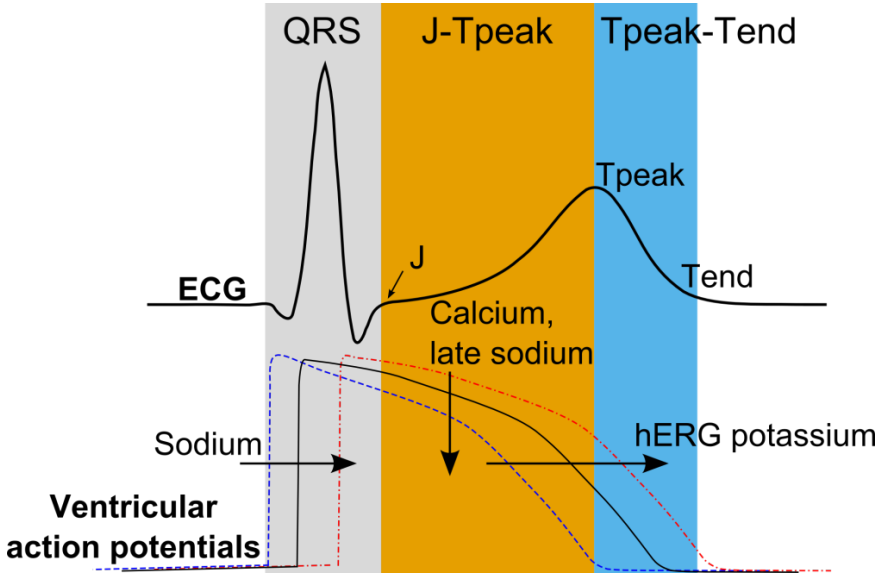
Prospective Clinical Trials, Selecting Biomarker, Releasing Open Access Software

Differentiating Drug-Induced Multichannel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine, and Verapamil

Johannesen…Strauss. *Clin Pharmacol Ther* 2014;96:549-58.

Late Sodium Current Block for Drug-Induced Long QT Syndrome: Results From a Prospective Clinical Trial

Johannesen…Strauss. *Clin Pharmacol Ther* 2016;99:214-23.



All Clinical Trial Data Freely Downloadable Including Open-Source Algorithm

Automated Algorithm for J-T_{peak} and T_{peak}-T_{end} Assessment of Drug-Induced Proarrhythmia Risk

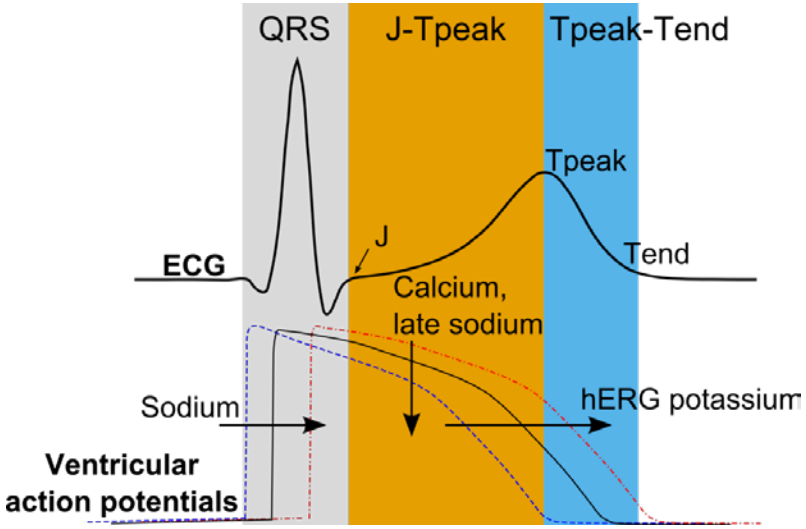
Johannesen…Strauss. *PLOS ONE* 2016;11:e0166925.

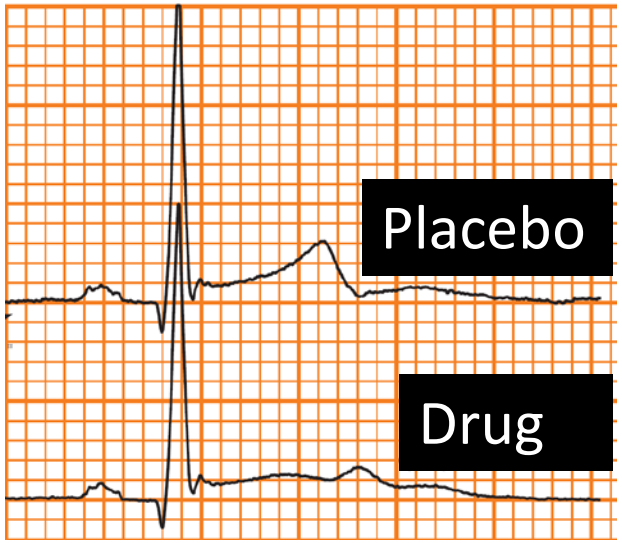
Prospective Clinical Validation Study (Clinical Trial 3)

Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the "CiPA" Initiative and Design of a Prospective Clinical Validation Study

Jose Vicente[1], Robbert Zusterzeel[2], Lars Johannesen[2], Jay Mason[3,4], Philip Sager[5], Vikram Patel[2], Murali K. Matta[2], Zhihua Li[2], Jiang Liu[2], Christine Garnett[1], Norman Stockbridge[1], Issam Zineh[2] and David G. Strauss[2]

Clinical Pharmacology & Therapeutics 2018;103:54-66.





Goal: To verify that combined assessment of QT and J-Tpeak can differentiate between drugs that:

- Are selective hERG blockers

  versus

- Have balanced block of hERG and late sodium and/or calcium

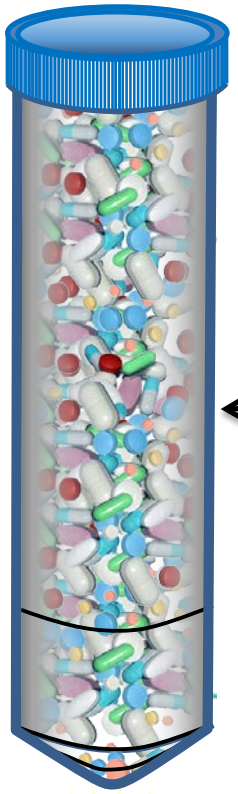
Regulatory Status of the CiPA Initiative

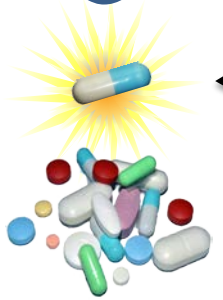
- Discussed at 2017 FDA Advisory Committee on model-informed drug development
- Committee supported proposed regulatory applications and validation approach (pending completion of validation studies)
- We have proposed to update ICH S7B/E14 (Q&A)

ICH
harmonisation for better health

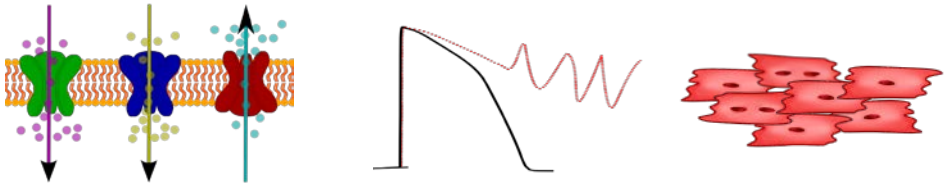
CiPA Summary & Expected Impact

Drug Development

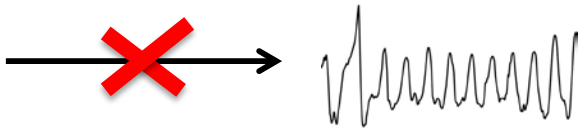




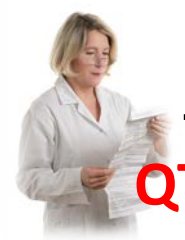
Mechanistic studies early in drug development



QT prolongers with low torsade risk could advance



Update drug labels for marketed drugs



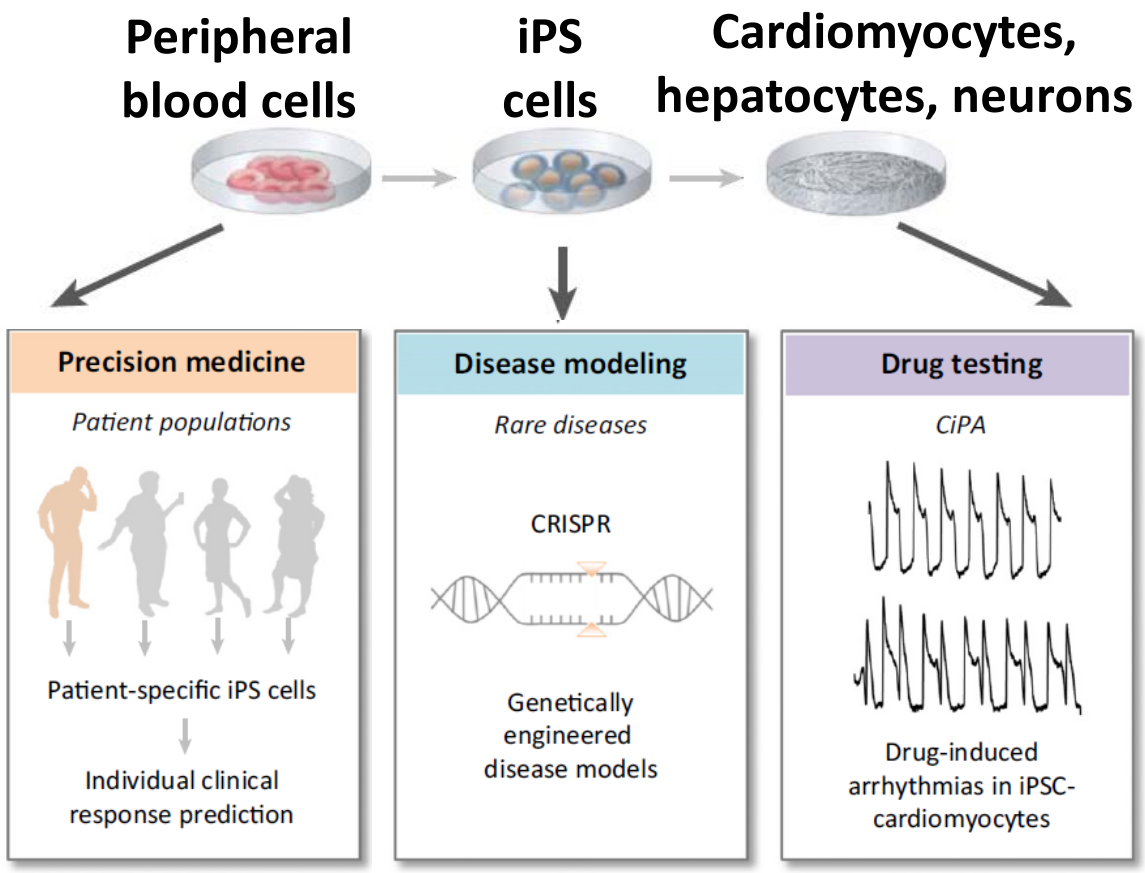
Related Areas of Scientific Focus – Precision Medicine

Common Genetic Variant Risk Score Is Associated With Drug-induced QT Prolongation and Torsade de Pointes Risk.
Strauss et al. *Circulation* 2017;135:1300-1310.

Weighted score of >60 common genetic variant risk score explains

- 23-30% of variability in QT response
- 12% of variability drug-induced torsade de pointes

Clinical Trials in a Dish.
Strauss and Blinova. *Trends Pharmacol Sci* 2017;38:4-7.



We Need Collaboration To Advance Regulatory Science!

"… we focus on the importance of regulatory science to facilitate development of innovative new drugs and optimize use of approved drugs, with a call for community participation."

Trends in Pharmacological Sciences 2018;39:225-9.

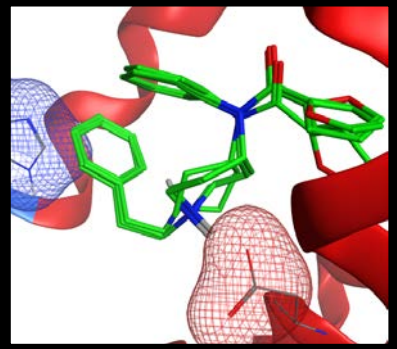
We Do That Through a Translational Regulatory Science Approach in the Division of Applied Regulatory Science

- Multidisciplinary expertise:
  - Physicians, veterinarians, pharmacists
  - Pharmacologists, toxicologists, physiologists, pharmacokineticists
  - Immunologists, molecular biologists, microbiologists
  - Biochemists, inorganic chemists, pharmaceutical scientists
  - Computational biologists, engineers, bio-physicists, mathematicians

Additional Example Focus Areas in the Division of Applied Regulatory Science

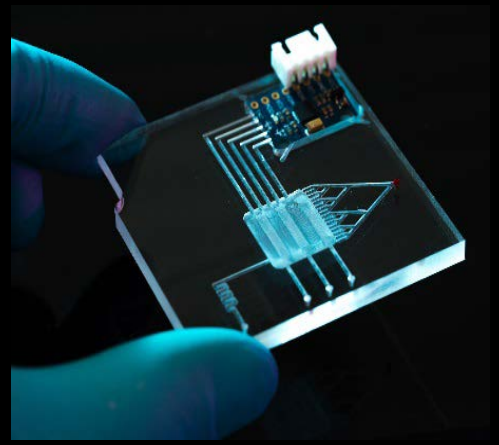
1. Modeling & Simulation

3D Quantitative Structure Activity Relationship Models



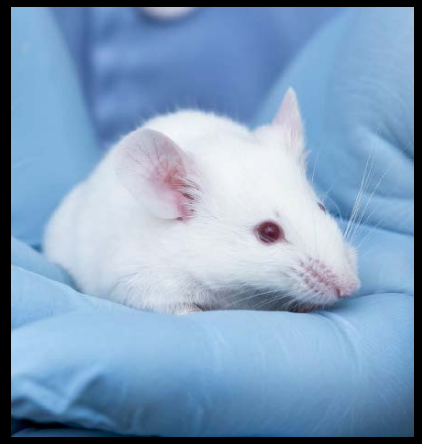
Opioid receptor

2. In Vitro Models



Microphysiological systems ("organ-on-a-chip")

3. In Vivo Models



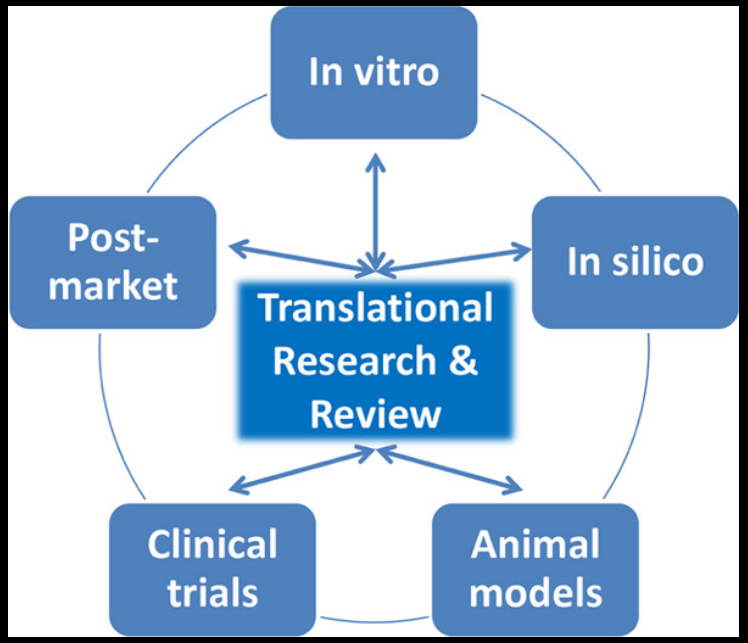
Immune/liver humanized mice

4. Clinical Pharmacology & Biomarker Studies

Want to Learn More?

Translating New Science Into the Drug Review Process: The US FDA's Division of Applied Regulatory Science

Rodney Rouse, DVM, MBA, PhD[1], Naomi Kruhlak, PhD[1], James Weaver, PhD[1], Keith Burkhart, MD[1], Vikram Patel, PhD[1], and David G. Strauss, MD, PhD[1]



Therapeutic Innovation & Regulatory Science 2018;52:244-55.

Thank you!

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

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  - Issam Zineh, FDA/CDER
  - Norman Stockbridge, FDA/CDER
  - Janet Woodcock, FDA/CDER
  - Robert Califf, FDA & Duke
  - Dan Roden, Vanderbilt
- Multiple additional collaborators from numerous teams from FDA, other government agencies, industry and academia
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  - CiPA steering team and working group members; additional major contributors from FDA: Wendy Wu, Zhihua Li, Ksenia Blinova and **many more**
- All staff & colleagues from the Division of Applied Regulatory Science and throughout all of the Office of Clinical Pharmacology