Translating New Science Into Drug Development & Evaluation

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
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

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

Proportion of CRT-D Patients Surviving by Gender and LBBB
Cardiac Resynchronization Therapy
(Biventricular Pacemaker)

Additional lead for cardiac resynchronization therapy

- 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


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

Patient-Level Meta-Analysis of Clinical Trials

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

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

- 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

Large benefit in women
No benefit in men
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

- 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

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

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
Why Do We Need to Assess Cardiac Safety?

Antibiotics
Pain Medicine
Psychiatric
Allergy
What do the Torsade Drugs Have in Common?

- Torsade de pointes ...
- Is associated with QT prolongation ...
- Is associated with action potential prolongation ...
- Is associated with hERG channel block
- Potassium ions
What the Heck Is “hERG”? 

Human *Ether-à-go-go*-Related Gene

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
  • Not to inform whether a drug causes torsade de pointes

As some QT prolonging drugs do not cause torsade de pointes
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!

When Does QT Prolongation Cause Torsade?

Body surface ECG

Heart cell electrical activity (action potential)

Ion channels in cell membrane

Sodium Calcium hERG Potassium

Drug block

Torsade de Pointes

Extra beats

Vicente...Strauss. Clinical Pharmacology & Therapeutics 2018;103:54-66.
When Does QT Prolongation Not Cause Torsade?

Vicente...Strauss. *Clinical Pharmacology & Therapeutics* 2018;103:54-66.
Improving the Assessment of Heart Toxicity for All New Drugs Through Translational Regulatory Science

L Johanesen1,2,3, J Vicente2,4, RA Gray2, L Galeotti2, Z Loring2, CE Garnett1,5, J Florian1, M Ugander2,3, N Stockbridge6 and DG Strauss2


• 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

Prospective Clinical Trials

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

I. Johannesen¹,², J. Vicente¹,³, J.W. Mason⁴, C. Sanabria⁴, K. Waite-Labott⁴, M. Hong⁵, P. Guo⁵, J. Lin⁵, J.S. Sørensen⁶, L. Galeotti¹, J. Florian⁶, M. Ugander¹,², N. Stockbridge⁷ and D.G. Strauss¹,²


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

I. Johannesen¹,², J. Vicente¹,³,⁴, J.W. Mason⁵,⁶, C. Erato⁵, C. Sanabria⁵, K. Waite-Labott⁵, M. Hong⁷, J. Lin⁷, P. Guo⁷, A. Mutlib⁷, J. Wang⁷, W.J. Crumb⁸, K. Blinova¹, D. Chan¹, J. Stohlman¹, J. Florian³, M. Ugander¹,², N. Stockbridge³ and D.G. Strauss¹,²

Clinical Trial 1: Two Example Drugs

hERG + Late Sodium Block
(low torsade risk)

Ranolazine

Selective hERG Block
(high torsade risk)

Dofetilide

Change in ECG Measurement

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. *In vitro* Assessment of Ion Channels
   - Sodium
   - Calcium
   - hERG
   - Potassium

2. *In silico* Computer Modeling to Predict Risk
   - \( I_{\text{stim}} = C \frac{dV_m}{dt} + I_m \)

3. *In vitro* Stem Cell Derived Cardiomyocytes

4. *In vivo* ECG Biomarker in Phase 1 Clinical Trials

**Predict clinical risk of arrhythmias**

**Check for missed or unanticipated effects**
1. What Ion Channels Should be Selected?

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


**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

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

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

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

Kelly C. Chang¹; Sara Dutta¹, Gary R. Mirams², Kylie A. Beattie¹, Jiansong Sheng¹, Phu N. Tran¹, Min Wu¹, Wendy W. Wu¹, Thomas Colatsky¹, David G. Strauss¹ and Zhihua Li*²


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 Colatsky¹ and Zhihua Li*

3. Cardiomyocyte Working Group

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

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**3. *In vitro* Stem Cell Derived Cardiomyocytes**

- Action potential duration
- Extra beat

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Seconds | 0 | 5 | 10 | 15
---|---|---|---|---

Induced Pluripotent Stem Cell Derived Cardiomyocytes

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


- 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

- **Goal**: 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


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


All Clinical Trial Data Freely Downloadable Including Open-Source Algorithm

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

Prospective Clinical Validation Study (Clinical Trial 3)

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

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

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

Jose Vicente¹, Robbert Zusterzeel², Lars Johannesen², Jay Mason³,⁴, Philip Sager⁵, Vikram Patel⁵, Murali K. Matta⁵, Zhihua Li⁵, Jiang Liu⁵, Christine Garnett¹, Norman Stockbridge¹, Issam Zinch² and David G. Strauss²

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

Mechanistic studies early in drug development

QT prolongers with low torsade risk could advance

Update drug labels for marketed drugs

CiPA Summary & Expected Impact
Related Areas of Scientific Focus – Precision Medicine

Common Genetic Variant Risk Score Is Associated With Drug-induced QT Prolongation and Torsade de Pointes Risk.

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.

Peripheral blood cells  
iPS cells  
Cardiomyocytes, hepatocytes, neurons

Precision medicine  
Patient populations  
Rare diseases

Disease modeling  
Patient-specific IPS cells  
Genetically engineered disease models

Drug testing  
CRISPR  
Drug-induced arrhythmias in iPSC-cardiomyocytes
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.”

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

Rodney Rouse, DVM, MBA, PhD\textsuperscript{1}, Naomi Kruhlak, PhD\textsuperscript{1}, James Weaver, PhD\textsuperscript{1}, Keith Burkhart, MD\textsuperscript{1}, Vikram Patel, PhD\textsuperscript{1}, and David G. Strauss, MD, PhD\textsuperscript{1}

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  – 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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