

A regulatory perspective on assessment of cardiotoxicity

Beyond QTc
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Cardiotoxicity

- Plumbing
- Mechanical
- Electrical

Cardiotoxicity—plumbing

- Macroscopic structural issues related to organogenesis
- Other structural—valvulopathy
- Vessel obstruction—thromboembolic, atherosclerotic, inflammatory

Cardiotoxicity—plumbing

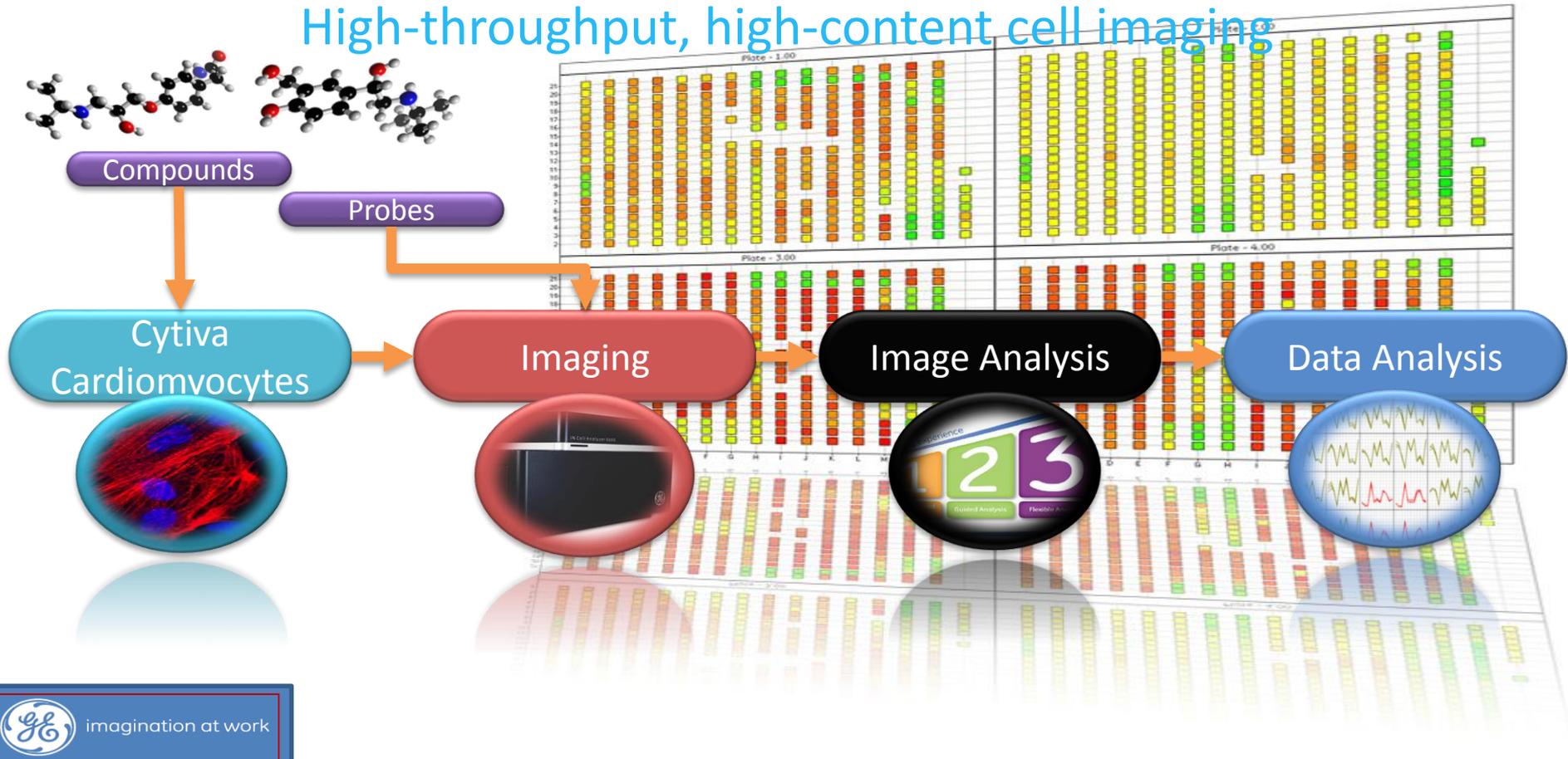
- Adequately addressed through chronic and reproductive toxicity studies, in animals
- These studies may give no deep mechanistic insight, but false negative/positive rate low enough that typical workup suffices
- Probably no unmet need

Cardiotoxicity—mechanical

- Indirect—pressors,
- Direct—positive/negative inotropes, cytotoxicity
 - Useful to understand failure modes at drug screening time
 - ...based on HUMAN biology, to minimize false negatives/positives

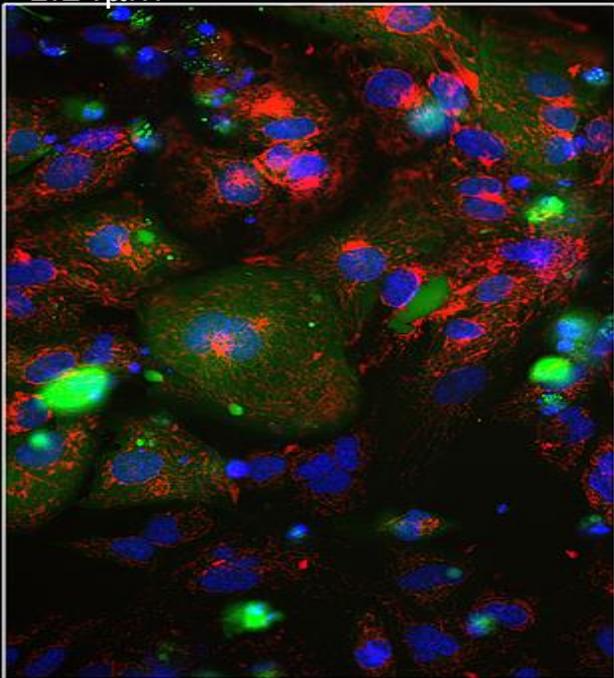
Cardiotoxicity Assay Workflow

High-throughput, high-content cell imaging

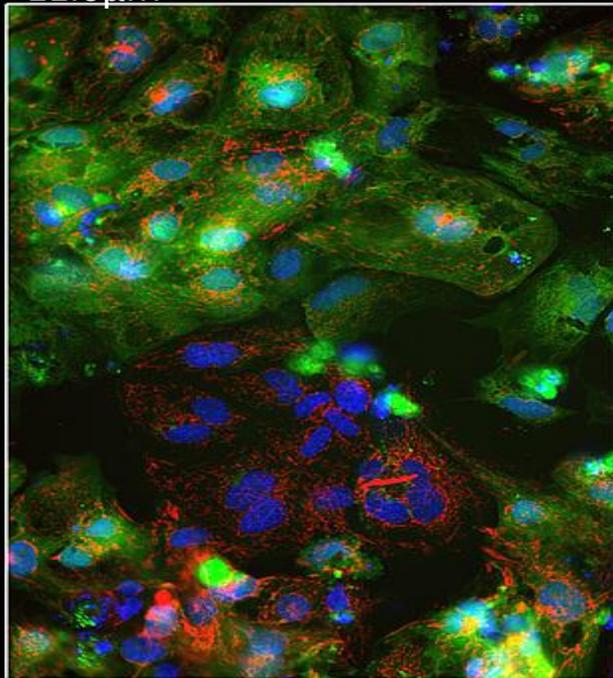


Vatalanib

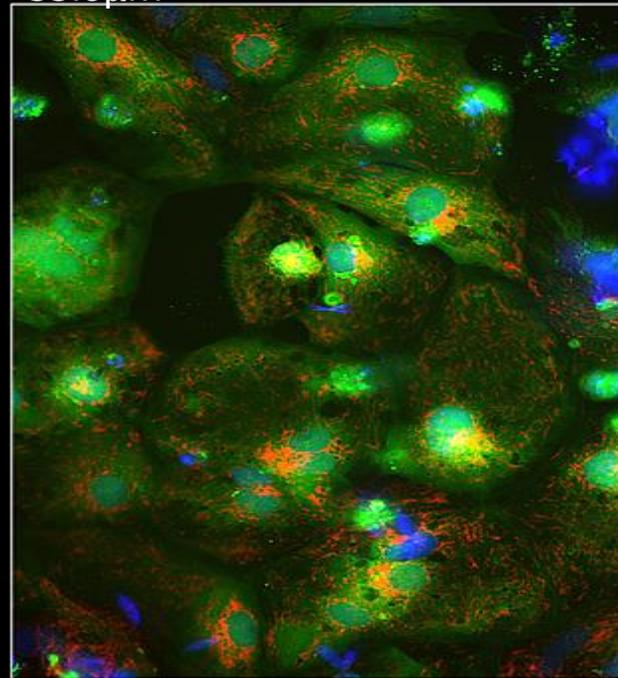
1.24 μ M



11.0 μ M



33.0 μ M



72 hours DNA Mitochondria Ca²⁺



imagination at work

Cardiotoxicity—mechanical

- Direct cardiotoxicity can be approached with understanding of failure modes, but you need to select component assays that add information
- Even so, analysis of multidimensional data is treacherous. Fortunately, in the limited chemical space explored, there are patterns of response that facilitate classification of risk.

Cardiotoxicity—electrical

- Arrhythmias
 - Conduction abnormalities—heart block
 - Small effects do not matter
 - Safe enough with ECGs in dogs, monkeys, and early phase clinical studies
 - Automaticity—ventricular arrhythmias
 - Small effects matter
 - Compensation for outliers
 - Compensation for rarity of events (required substrate)

Cardiotoxicity—electrical

- Interest in small effects predictive of rare ventricular arrhythmias led to
 - ICH S7B – focus on hERG/IKr
 - Myth that IKr is more vulnerable to drugs than other cardiac ion channels
 - ICH E14 – focus on QTc in man
 - Turning continuous metric of risk into dichotomous one—
“positive” vs. “negative”
 - Inappropriately adverse labeling
 - Inappropriate decisions about compounds to develop

Fix—stage 1

- Can we at least do the TQT study cheaper?

Use exposure-response data

- From early-phase clinical study
- TQT-like attention to collecting ECGs and PK data
- Minimal interference with other aspects of phase I study
- Fully pre-specified methods to model exposure-QTc relationship
- Predict QTc at some dose's Cmax

- FDA agreed...but wanted a prospective study to demonstrate validity

ORIGINAL ARTICLE

The IQ-CSRC Prospective Clinical Phase 1 Study: “Can Early QT Assessment Using Exposure Response Analysis Replace the Thorough QT Study?”

Borje Darpo, M.D., Ph.D.,^{1,*} Nenad Sarapa, M.D.,^{2,†} Christine Garnett, Pharm.D.,^{3,*}
Charles Benson, M.D., Ph.D.,^{4,†} Corina Dota, M.D.,^{5,*} Georg Ferber, Ph.D.,^{6,‡}
Venkateswar Jarugula, Ph.D.,^{7,†} Lars Johannesen, M.Sc.,^{8,9} James Keirns, Ph.D.,^{10,†}
Kevin Krudys, Ph.D.,¹¹ Catherine Ortemann-Renon, Pharm.D., Ph.D.,^{12,*}
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and Norman Stockbridge, M.D., Ph.D.¹⁴

Design

- 20 healthy subjects underwent 3 treatments
 - Incomplete block design: 9 on each drug, 6 on placebo
- Drugs:
 - Positive: Ondansetron, quinine, dolasetron, moxifloxacin and dofetilide
 - Negative: levocetirizine
- Each period consisted of 2 days
 - Day 1: Low dose intended to give ~ 10 to 12 ms QTc
 - Day 2: High dose intended to give ~ 15 to 20 ms QTc

Criteria for QT Assessment

Positive QT assessment :

1. The QT effect is detected:

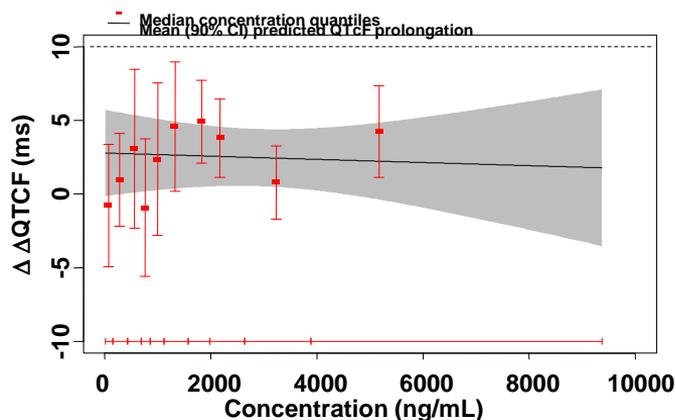
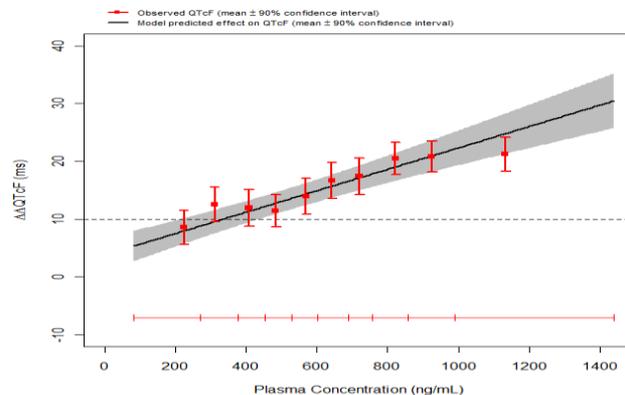
The upper bound of the 2-sided 90% confidence interval (CI) of the projected placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean C_{max} of the drug.

2. The slope of the ER relationship is statistically significant:

The lower bound of the 90% confidence interval for the slope of $\Delta\Delta\text{QTcF}$ vs. concentration is above zero.

Negative QT assessment :

- The upper bound of the confidence interval of the predicted placebo-corrected ΔQTcF at the observed geometric mean C_{max} of the drug is below 10 ms.



Results



Cardiac Safety Research Consortium
www.cardiac-safety.org



INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Sharing Results from Novel Research Symposium

10903 New Hampshire Avenue, Silver Spring, Maryland 20993

White Oak Facility, FDA Headquarters • Silver Spring, MD • December 12, 2014

The results from the **IQ-CSRC prospective study 'CAN EARLY ECG ASSESSMENT USING EXPOSURE RESPONSE ANALYSIS REPLACE THE THOROUGH QT STUDY?'** will be presented at a meeting on FDA's White Oak campus. The study evaluates whether the QT effect of 5 marketed, mild QT-prolonging drugs can be identified in a study design typical for a phase 1 First-in-Man trial in healthy volunteers. The choice of the drugs and the design and the analysis plan of the study have been done in close collaboration with the FDA and the clinical phase of the study is now completed. The results of the study analyzed by the IQ-CSRC group and by FDA separately will be presented with comments from different stakeholders. The clinical and regulatory implications of the study will be discussed at the meeting with participation from FDA and other regulators, as well as from the ICH E14 Discussion group.

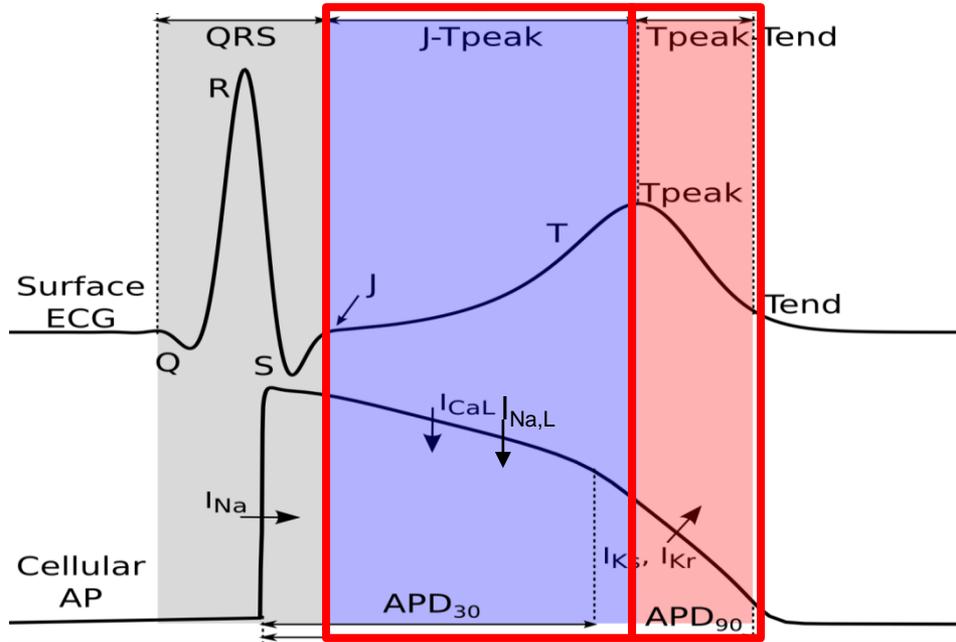
What's wrong with that?

ICH S7B and E14 were well-intentioned responses to a public health issue, but they had costs that were wildly out of proportion to the problem we were trying to solve, most importantly in the form of fewer safe and effective drugs entering development.

Fix—stage 2a

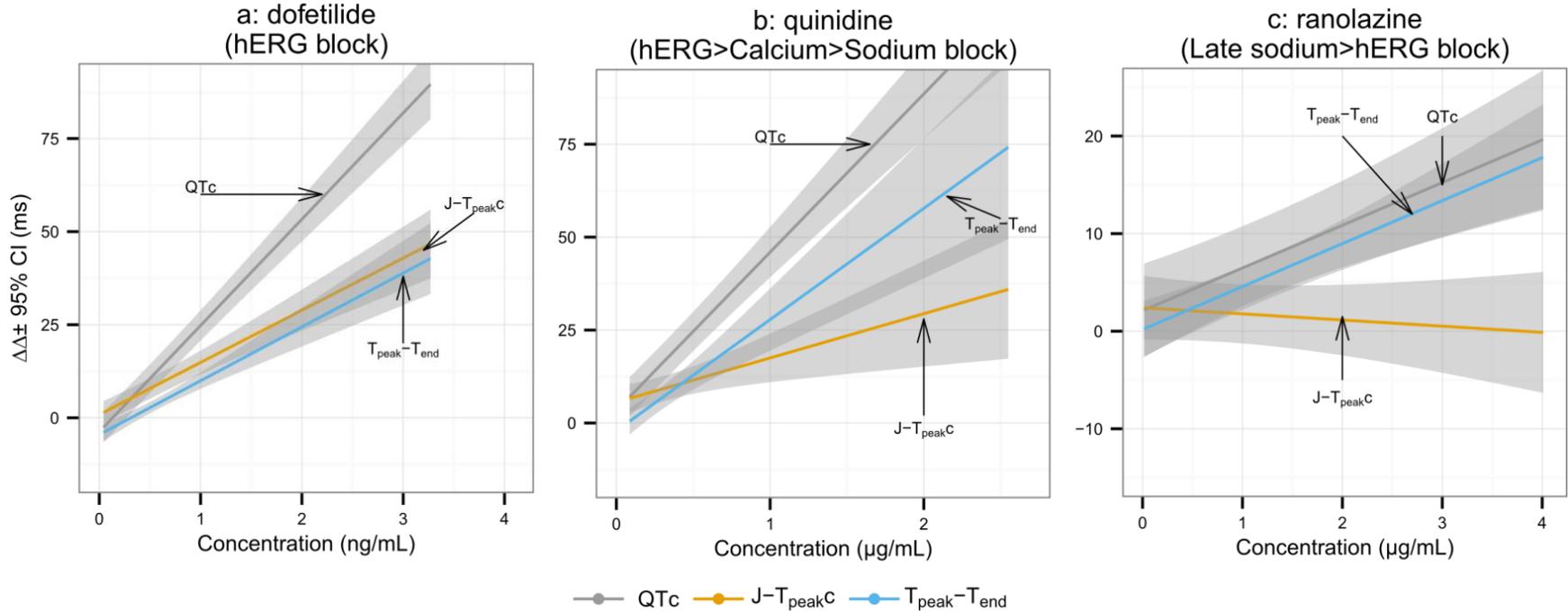
- Can you get at mechanism—channel effects—through the ECG?

ECG reflects channel effects



- David G. Strauss
- Lars Johannesen
- Jay Mason
- Jose Vicente
- Martin Ugander
- Jeffrey Florian
- Kristin Waite-Labott
- Staff at Spaulding Clinical Research and Frontage Laboratories

Signatures for channel block



Fix—stage 2b

- Getting at mechanism through study of drug effects on human cardiac ion channel types

CiPA

- Changing approach to assessment of arrhythmia risk relating to automaticity
 - Deep understanding of how such arrhythmias arise
 - Available cells manifesting all individual HUMAN ion channel types
 - High throughput voltage clamp systems
 - Reconstruct drug effects on the action potential to measure vulnerability during repolarization
- Translation to clinic is so compelling that it is difficult to specify a validation program

Aside

- How do you bring about change efficiently?

Evolution of TQT

- Regulatory
 - ICH S7B, E14 guidances
 - FDA QT interdisciplinary review team
- Technical
 - HL7 ECG data standard
 - ECG Warehouse
- Community & Research
 - Specialized QT study vendors
 - ECG Metrics Consortium
 - Cardiac Safety Research Consortium

Engineering of CiPA

- Societies and individuals leading work groups appropriate to expertise, and an oversight group
 - ILSI-HESI, SPS, CSRC
- Community engagement
- Direct involvement of ICH and regional regulators on validation plans
- Attention to technical infrastructure
 - Equipment mfrs, service providers, computation resource

Summary

- Especially where small effects matter, as they do with automaticity and direct cytotoxicity
 - Probably better off with assays that provide mechanistic information
 - Based on the only relevant species—mine.