Beyond QT—
The Comprehensive in Vitro Proarrhythmia Assay

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ICH E14/ S7B: Current FDA Policy

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS

E14

Current *Step 4* version
dated 12 May 2005

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

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THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS

S7B

Current *Step 4* version
dated 12 May 2005

Success of E14/S7B

- No QT-related withdrawals
- Reduction in post-marketing reports of TdP for non-anti-arrhythmic drugs
- Continued to approve some drugs with QT liability where benefits clearly outweigh apparent risks

False positives

- TQT assay limitations
- Small effects from blocking minor outward currents (not hERG)
- Real hERG blockers, but still not proarrhythmic

Cost

- $B in TQT studies (OK)
- Cautionary labeling when QT effect not from hERG (not good)
- Perversion of lead candidate selection (really bad)
  - Some true hERG blockers are not proarrhythmic
  - Selection against hERG forces other compromises

We can do better…

- TdP class of arrhythmias
  - Susceptibility in the form of derangement of the balance of inward and outward currents during repolarization
    - Very well understood
    - We know how to assay for this USING HUMAN CHANNELS, how to reconstruct the action potential, and how to probe for vulnerability during repolarization
  - Regional heterogeneity in electrical state across the ventricle
    - Role is well understood
    - Rare conditions (why you go hours to decades in susceptible state)

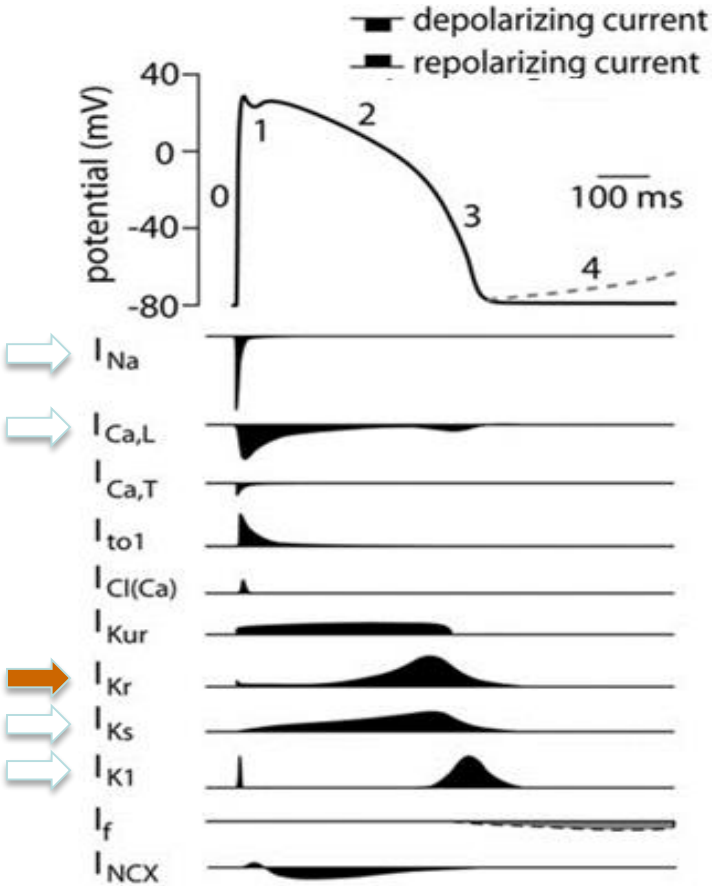
…and some firms already are

- AbbVie
- Astra-Zeneca
- GSK
- Lilly
- Others?

The assay

- Characterization of drug effects on human ion channels
- Reconstruction of the action potential from the summed effects of the drug
- Comparison of modeled effects with responses of cultured stem-cell-derived human cardiac myocytes

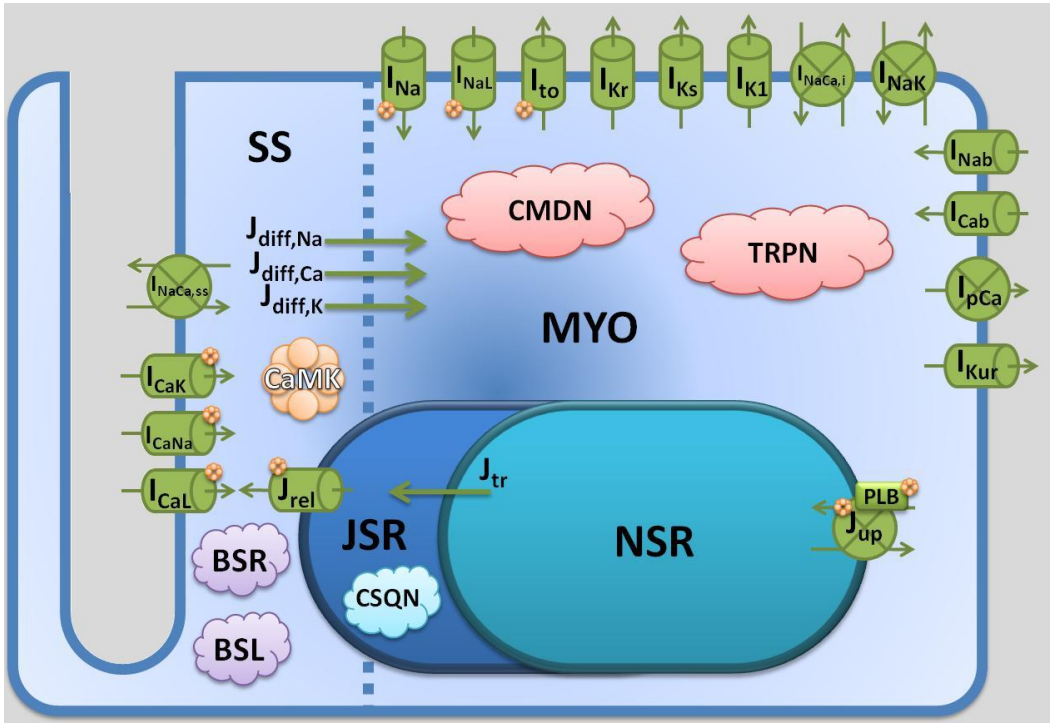
Cardiac action potential



Hoekstra et al., 2012

- Human channels
- Cells overexpressing single channel types
- Amenable to high-throughput electrophysiology

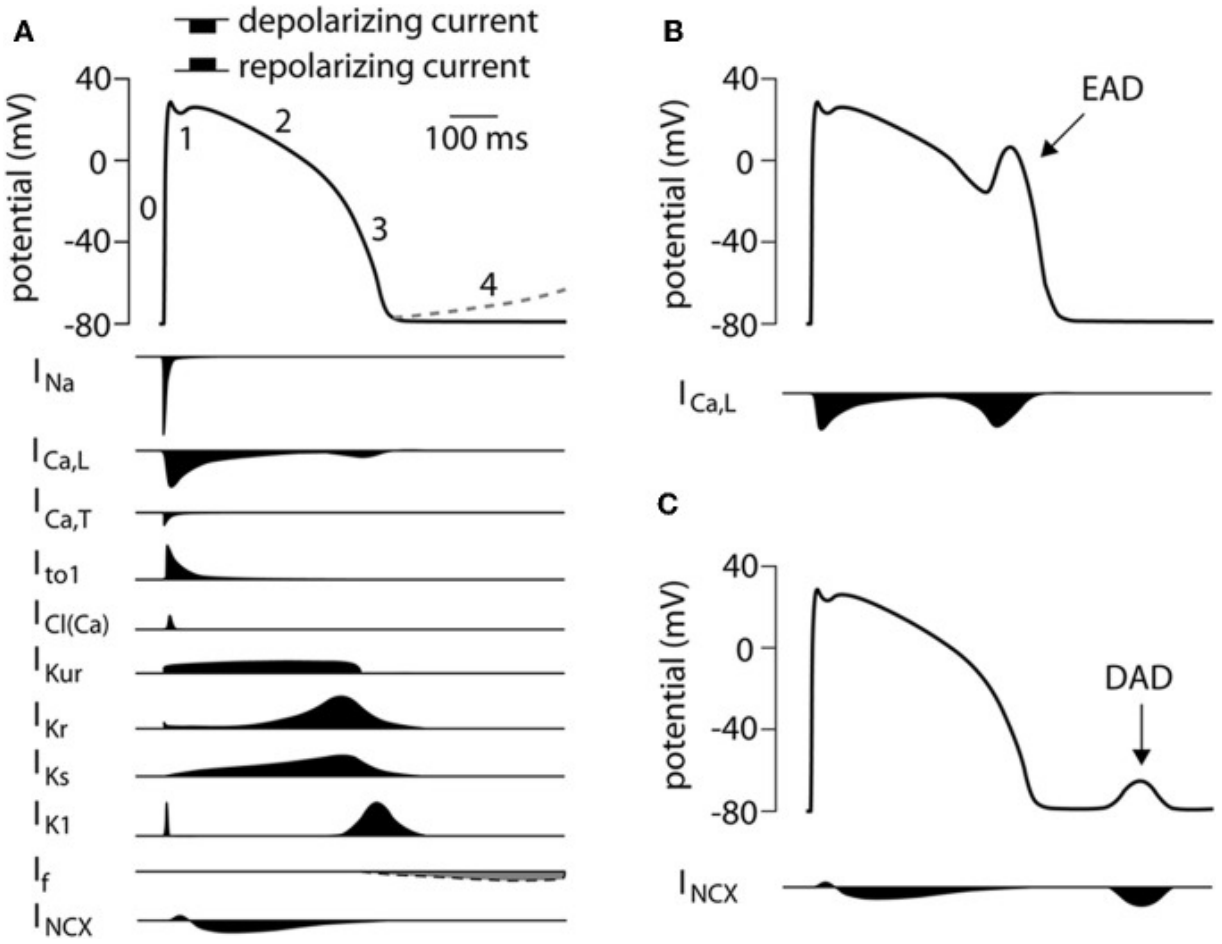
O'Hara-Rudy model



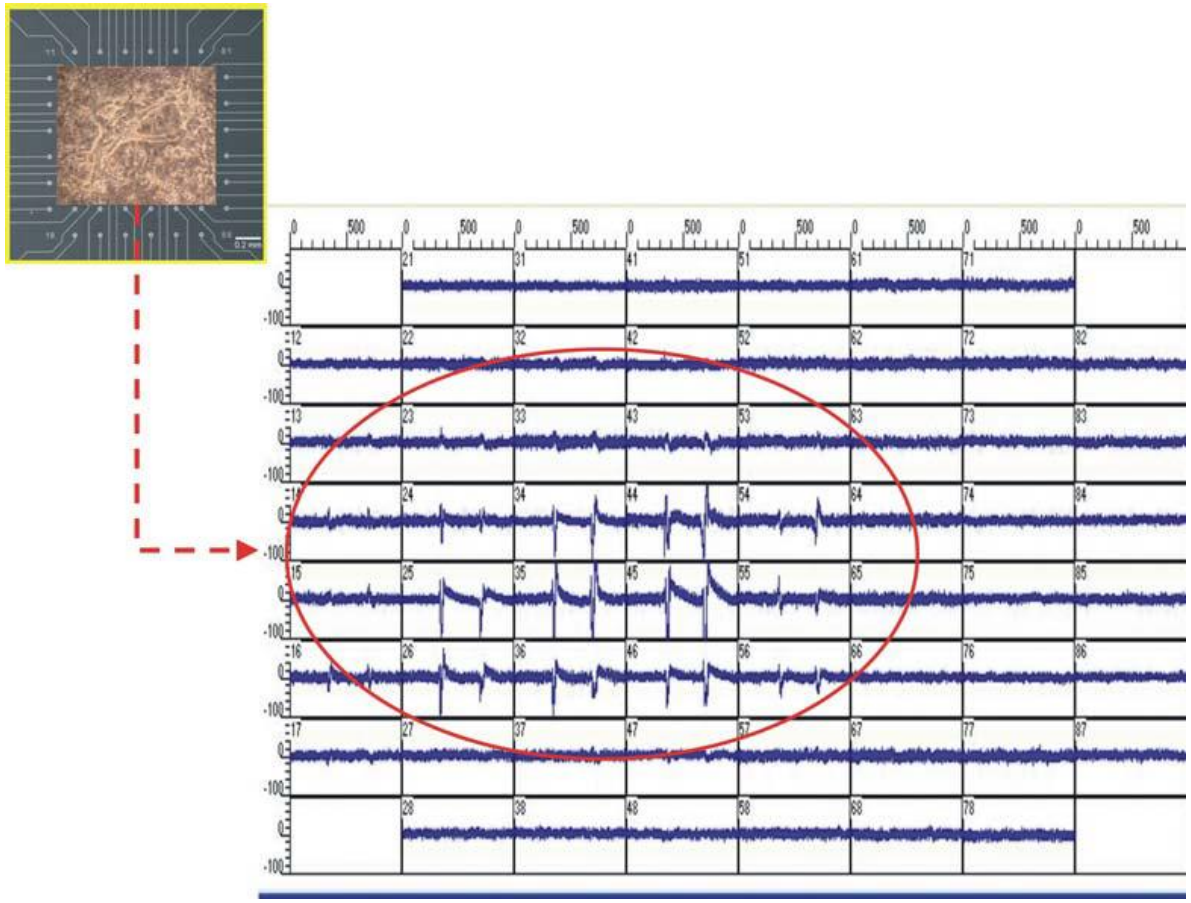
- Suffices to model single cell (not heart!)
- Exact proarrhythmia metric is under debate
- …but is likely to involve proximity to having EADs

T.J. O'Hara, L. Virág, A. Varró, Y. Rudy,
"Simulation of the undiseased human cardiac ventricular action potential:
Model formulation and experimental validation"
PLoS Computational Biology 2011; 7(5): e1002061.
doi:10.1371/journal.pcbi.1002061

Ion channel effects



MEA recordings from myocytes



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