# Scientific Basis for Comprehensive In vitro Proarrhythmia Assay

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## Disclaimer

The thoughts expressed here are those of the speaker and do not necessarily reflect those of the FDA.

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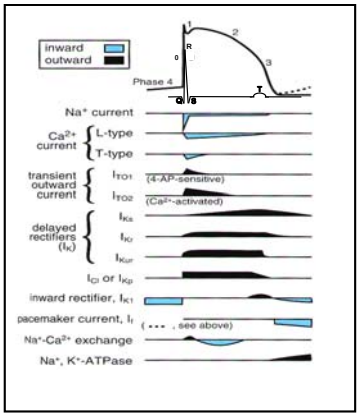
## Cardiac Ionic Currents




| Cardiac Channel Panel™ | AP Phase |
|---|---|
| Nav1.5 ($I_{Na}$) | 0, 2 |
| Cav1.2/ $\beta$ , $\alpha$ , $\delta$ , (L-type) | 2 |
| Cav3.2 (T-type) | 1 |
| Kv4.3 ($I_{TO1}$) | 1 |
| KvLQT1/minK ($I_{Ks}$) | 2 - 3 |
| hERG ($I_{Kr}$) | 2 - 3 |
| Kv1.5 ($I_{Kur}$) | 2 - 3 |
| Kir2.1 ($I_{K1}$) | 4 |
| HCN2 (pacemaker, $I_f$) | 4 |
| HCN4 (pacemaker, $I_f$) | 4 |
| Kir3.1/3.4 ($I_{K,ACh}$) | 4 |
| Kir6.2/SUR2A ($I_{K,ATP}$) | 4 |
| NCX1 (Na-Ca exchange) | 2 |

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# Why hERG?

- Major repolarizing current
- Inhibition responsible for TdP
  - Terfenadine
  - Cisapride
  - Bepridil
  - etc

# Evolution of thinking - hERG

- Blockade is bad - any dose/concentration
- Potency needs to be considered
- Potency relative to therapeutic concentration considered





# Multiple Ion Channel Inhibitors

- Consider both outward, e.g., hERG
- And inward currents, ICa, INa

# Multichannel Inhibitors

**Proarrhythmic**

- Quinidine
- Terfenadine
- Bepridil
- Terodiline

**Benign**

- Verapamil
- Ranolazine
- Tolterodine

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# MICE Models: Superior to the HERG Model in Predicting Torsade de Pointes

James Kramer[1]*, Carlos A. Obejero-Paz[1]*, Glenn Myatt[2], Yuri A. Kuryshev[1], Andrew Bruening-Wright[1], Joseph S. Verducci[3] & Arthur M. Brown[1]

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**Drug-induced block of the cardiac hERG (human Ether-à-go-go-Related Gene) potassium channel delays cardiac repolarization and increases the risk of Torsade de Pointes (TdP), a potentially lethal arrhythmia. A positive hERG assay has been embraced by regulators as a non-clinical predictor of TdP despite a discordance of about 30%. To test whether assaying concomitant block of multiple ion channels (Multiple Ion Channel Effects or MICE) improves predictivity we measured the concentration-responses of hERG, Nav1.5 and Cav1.2 currents for 32 torsadogenic and 23 non-torsadogenic drugs from multiple classes. We used automated gigaseal patch clamp instruments to provide higher throughput along with accuracy and reproducibility. Logistic regression models using the MICE assay showed a significant reduction in false positives (Type 1 errors) and false negatives (Type 2 errors) when compared to the hERG assay. The best MICE model only required a comparison of the blocking potencies between hERG and Cav1.2.**

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# hERG, ICa, INa

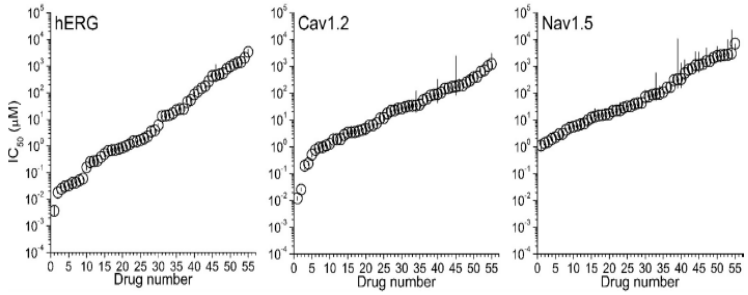


**Figure 1** | $IC_{50}$s **of the 55 drugs included in the dataset for hERG, Cav1.2 and Nav1.5.** Symbols indicate mean values and lines the 95% confidence intervals of data. Values for the three channels are plotted as a function of drugs numbered in decreased order of potency. The drug order for each channel is indicated in **Supplementary Table 3.**

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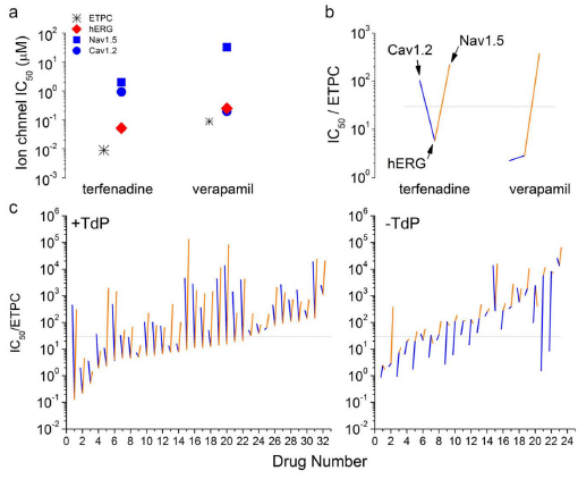


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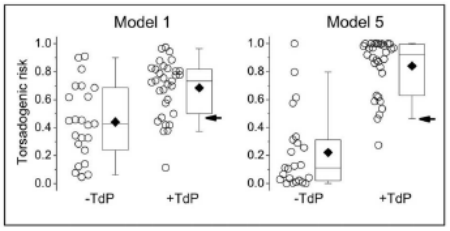


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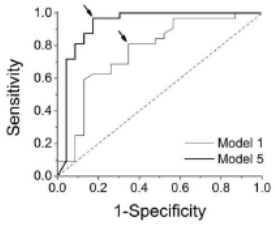


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**Model 1 ( 0.77 ± 0.07 )**

| | +TdP | -TdP |
|---|---|---|
| Correctly classified | 26 | 15 |
| Incorrectly classified | 6 | 8 |

| ***False Positives*** | ***False Negatives*** |
|---|---|
| ceftriaxone | amiodarone |
| linezolid | cilostazol |
| metronidazole | paroxetine |
| phenytoin | risperidone |
| piperacillin | solifenacin |
| ribavirin | sunitinib |
| telbivudine | |
| verapamil | |

**Model 5 ( 0.93 ± 0.04 )**

| | +TdP | -TdP |
|---|---|---|
| Correctly classified | 31 | 19 |
| Incorrectly classified | 1 | 4 |

| ***False Positives*** | ***False Negatives*** |
|---|---|
| dasatinib | voriconazole |
| donepezil | |
| loratadine | |
| telbivudine | |

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# Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk

**Gary R. Mirams[1]*, Yi Cui[2], Anna Sher[1], Martin Fink[1], Jonathan Cooper[3], Bronagh M. Heath[4], Nick C. McMahon[2], David J. Gavaghan[3], and Denis Noble[1]**

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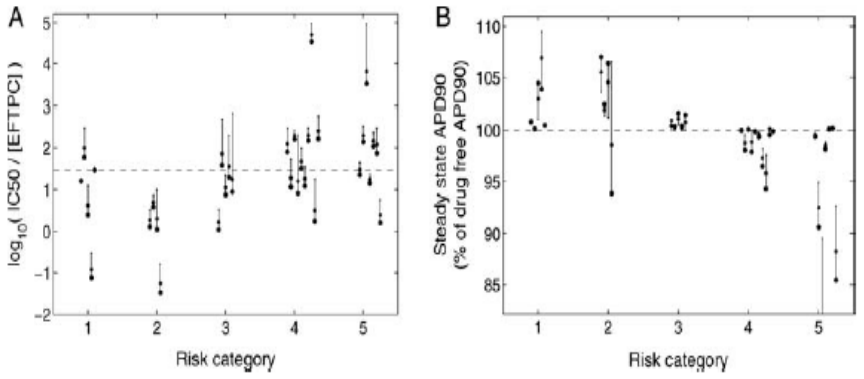
**Aims** The level of inhibition of the human Ether-à-go-go-related gene (hERG) channel is one of the earliest preclinical markers used to predict the risk of a compound causing Torsade-de-Pointes (TdP) arrhythmias. While avoiding the use of drugs with maximum therapeutic concentrations within 30-fold of their hERG inhibitory concentration 50% ($IC_{50}$) values has been suggested, there are drugs that are exceptions to this rule: hERG inhibitors that do not cause TdP, and drugs that can cause TdP but are not strong hERG inhibitors. In this study, we investigate whether a simulated evaluation of multi-channel effects could be used to improve this early prediction of TdP risk.

**Methods and results** We collected multiple ion channel data (hERG, Na, L-type Ca) on 31 drugs associated with varied risks of TdP. To integrate the information on multi-channel block, we have performed simulations with a variety of mathematical models of cardiac cells (for rabbit, dog, and human ventricular myocyte models). Drug action is modelled using $IC_{50}$ values, and therapeutic drug concentrations to calculate the proportion of blocked channels and the channel conductances are modified accordingly. Various pacing protocols are simulated, and classification analysis is performed to evaluate the predictive power of the models for TdP risk. We find that simulation of action potential duration prolongation, at therapeutic concentrations, provides improved prediction of the TdP risk associated with a compound, above that provided by existing markers.

**Conclusion** The suggested calculations improve the reliability of early cardiac safety assessments, beyond those based solely on a hERG block effect.

**Keywords** Computer modelling • Drug development • Pharmacology • Risk prediction • Torsade-de-pointes

# hERG vs Reconstructed APD

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# Comprehensive In vitro Proarrhythmia Assay (CIPA)

- Continuation of evolution
- More comprehensive than hERG alone
- Targeted towards prediction of proarrhythmic potential
- Available data supports the concept

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# Thank you