MICE Assay Significantly Improves Predictivity of Cardiac Risk

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Case Study Why Drugs Fail: Terfenadine, hERG & Sudden Cardiac Death

Normal sinus rhythm (hr= 66 bpm)

Torsades de Pointes

A Control  B Terfenadine (Seldane)


Courtesy of Dr. A. J. Moss
Nonclinical Cardiac Risk Assessment (S7B)

Chemical/Pharmacological Class

*In vitro* $I_{Kr}$ assay  
*In vivo* QT assay

Relevant non-clinical & clinical information

Integrated Risk Assessment

Follow-up repolarization assays

Evidence of Risk

None  Weak  Strong

*In vitro*, it’s all about HERG!!
## Why Would It Be Just About HERG?

<table>
<thead>
<tr>
<th>Cardiac Channel Panel™</th>
<th>AP Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nav1.5 (I(_{Na}))</td>
<td>0, 2</td>
</tr>
<tr>
<td>Cav1.2/β(_2), α(_2)δ, (L-type)</td>
<td>2</td>
</tr>
<tr>
<td>Cav3.2 (T-type)</td>
<td>1</td>
</tr>
<tr>
<td>Kv4.3 (I(_{TO1}))</td>
<td>1</td>
</tr>
<tr>
<td>KvLQT1/minK (I(_{Ks}))</td>
<td>2 - 3</td>
</tr>
<tr>
<td>hERG (I(_{Kr}))</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Kv1.5 (I(_{Kur}))</td>
<td>2 - 3</td>
</tr>
<tr>
<td>Kir2.1 (I(_{K1}))</td>
<td>4</td>
</tr>
<tr>
<td>HCN2 (pacemaker, I(_f))</td>
<td>4</td>
</tr>
<tr>
<td>HCN4 (pacemaker, I(_f))</td>
<td>4</td>
</tr>
<tr>
<td>Kir3.1/3.4 (I(_{K,ACH}))</td>
<td>4</td>
</tr>
<tr>
<td>Kir6.2/SUR2A (I(_{K,ATP}))</td>
<td>4</td>
</tr>
<tr>
<td>NCX1 (Na-Ca exchange)</td>
<td>2</td>
</tr>
<tr>
<td>HERG Status</td>
<td>Concordance</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>- HERG</td>
<td>80/118 (68%) Concordant</td>
</tr>
<tr>
<td>+ HERG</td>
<td>19/118 (16%) False Pos</td>
</tr>
<tr>
<td>+ Impaired Repol (APD/QT)</td>
<td>- Impaired Repol -(APD/QT)</td>
</tr>
</tbody>
</table>

HERG and APD/QT discordances at CT, consistent with DeBruin et al odds ratio 1.93 for hERG assay safety margin and TdP (2005) & Wallis Pfizer study (2010)
IC$_{50}$s of 55 Drugs Included in Dataset for hERG, Cav1.2 & Nav1.5
SaVeTy (ETPC) Indexes of Torsadogenic & Non-Torsadogenic Drugs

(a) Ion channel IC$_{50}$ (μM)

(b) IC$_{50}$ / ETPC

(c) TdP

Drug Number
Association of Safety Margins & Torsadogenicity

(a) hERG
(b) Cav1.2
(c) Nav1.5
(d) CavD
CT MI CE Assay Significantly Improves Predictive Models for TdP

Model 1 (0.77 ± 0.07)

<table>
<thead>
<tr>
<th>Correctly classified</th>
<th>+TdP</th>
<th>-TdP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrectly classified</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

False Positives:
- ceftriaxone
- linezolid
- metronidazole
- phenytoin
- piperacillin
- ribavirin
- telbivudine
- verapamil

False Negatives:
- amiodarone
- cilostazol
- paroxetine
- risperidone
- solifenacin
- sunitinib

Model 5 (0.93 ± 0.04)

<table>
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<tbody>
<tr>
<td>Incorrectly classified</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

False Positives:
- dasatinib
- donepezil
- loratadine
- telbivudine

False Negatives:
- voriconazole

Diagram:
- Sensitivity vs. 1-Specificity for Model 1 and Model 5.
Avoid Unexpected Outcomes

Achieve Expected Outcomes
Summary: MICE vs hERG Assays

- The *in vitro* HERG assay has ~ 70% accuracy for predicting TdP.
- Type 1 errors are the most reported causes but Type 2 errors also occur.
- We hypothesized Multiple Ion Channel Effects (MICE) as responsible.
- We measured concentration-responses of hERG, Nav1.5 and Cav1.2 for 32 torsadogenic and 23 non-torsadogenic drugs from many chemotypes.
- We used automated *gigaseal* patch clamp to provide throughput with accuracy and robustness comparable to reference manual patch clamp.
- We constructed logistic regression models to compare the hERG and MICE assays.
- MICE increased accuracy to > 93% and significantly reduced Types 1 and 2 errors.
- Using QPatch, automation turn-around times are ~ 40 x faster and ~ 1.5 x costlier for MICE (hERG, Cav1.2 & Nav1.5) than manual patch clamp for hERG alone.
- **Cost is more but insignificant compared to speed, gain in predictivity and understanding of MoA.**
Thanks to all of my ChanTest Colleagues

Thanks for Your Attention