The role of non-clinical assays in determining the level of clinical QT assessment

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Introduction

• Role of non-clinical studies are to identify signals of risk for humans
  – Magnitude of signal that is a concern
  – FIH vs. TQT study

• Inhibition of hERG channel is a significant risk for QT prolongation, especially with evidence of translation e.g. Purkinje fiber or in vivo data

<table>
<thead>
<tr>
<th>Normalized response in hERG assay</th>
<th>Man</th>
<th>Dog</th>
<th>G.Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT prolongation in man (msec)</td>
<td>105</td>
<td>59</td>
<td>41</td>
</tr>
<tr>
<td>$E_{\text{max}}$ (ms)</td>
<td>386</td>
<td>212</td>
<td>148</td>
</tr>
<tr>
<td>$E_0$ (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% increase</td>
<td>27</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

10 msec in human = 5-6 msec in dog?

• Non-hERG mediated QT prolongation is less reliably detected in non-clinical assays e.g PDE5i. However, these may be detected in FIH studies

• A number of datasets are becoming available to study translation of non-clinical data to the clinic

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### Understanding translation

<table>
<thead>
<tr>
<th>Human</th>
<th>Animal +ve</th>
<th>Animal -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>-ve</td>
<td>False +ve (FP)</td>
<td>True -ve (TN)</td>
</tr>
<tr>
<td>+ve</td>
<td>True +ve (TP)</td>
<td>False -ve (FN)</td>
</tr>
</tbody>
</table>

**If the assay is +ve or −ve, what are the chances of the compound being +ve or −ve in humans?**

**Knowing the clinical outcome is +ve or −ve, what are the chances of the assay is +ve or −ve?**

- **+ve predictive value**: $TP/(TP+FP)$
- **-ve predictive value**: $TN/(TN+FN)$

**Assay specificity**: $TN/(TN+FP)$

**Assay sensitivity**: $TP/(TP+FN)$
**Animal Model Framework**

A framework to assess the translation of safety pharmacology data to humans

Jean-Pierre Valentin a,1, Russell Bialecki b, Lorna Ewart a,2,3, Tim Hammond a, Derek Leishmann c, Silvana Lindgren d, Vicente Martinez e, Chris Pollard f, Will Redfern f, Rob Wallis f

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<table>
<thead>
<tr>
<th>Confidence in model</th>
<th>Confidence in translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Med</td>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

- **Cross-pharma dataset of 114 compounds**
- **FIH data - +ve or –ve for QTc changes**
  - 14 compounds reported an increase QTc and 2 compounds decrease
  - No quantification of the magnitude
- **Reviewed dog telemetry data**
  - Magnitude of change at multiples of human exposure
The dog telemetry model adequately predicts QT changes in man based on the data from the 114 compounds.

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**ROC Curves for QTC**

- **Cut-off = 12%**
  - Sens = 75 (30, 95)
  - Spec = 87 (71, 95)

- **Cut-off = 3%**
  - Sens = 80 (49, 94)
  - Spec = 68 (57, 77)

- **Cut-off = 7%**
  - Sens = 78 (45, 94)
  - Spec = 77 (64, 86)
TI-Pharma – PK/PD Approach

- Developing PK/PD models for ~6 compounds across species (dog, monkey and man) and applying a probabilistic analysis for a QT effect

- Attractive approach
  - Exposure response
  - Time course
  - Other factors e.g. metabolites
## hERG Translation to dog

<table>
<thead>
<tr>
<th>Compound</th>
<th>hERG IC&lt;sub&gt;20&lt;/sub&gt; (µM)</th>
<th>Modelled [µM] for 10 msec change in dog</th>
<th>Fraction of hERG IC&lt;sub&gt;20&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6.9</td>
<td>2.3</td>
<td>0.33</td>
</tr>
<tr>
<td>B</td>
<td>0.57</td>
<td>0.29</td>
<td>0.51</td>
</tr>
<tr>
<td>C</td>
<td>2.04</td>
<td>0.63</td>
<td>0.31</td>
</tr>
<tr>
<td>D</td>
<td>1.6</td>
<td>0.4</td>
<td>0.23</td>
</tr>
<tr>
<td>E</td>
<td>16.7</td>
<td>7.6</td>
<td>0.45</td>
</tr>
<tr>
<td>F</td>
<td>2.5</td>
<td>2.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Moxi</td>
<td>12.8</td>
<td>3.5</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Predicting QTc Changes in Human TQT study

• 26 compounds tested in Pfizer ‘TQT studies’
  – Including 7 comparator agents/positive controls
• All studies were designed to rule out a 7 to 10 msec change in QTc
• Positive QTc study was defined if the QTc change exceeded the pre-defined sensitivity
• Data derived from clinical study report
• Non-clinical analysis based on
  – 1/10 hERG IC$_{50}$ value
  – Purkinje fibre Studies powered to detect 8% change with 90% power using n=5
  – In vivo studies powered to detect ~5 msec QTc change with 90% power using n=4 cross over design
Predicting QTc Changes in Human TQT study

<table>
<thead>
<tr>
<th>Multiple of clinical</th>
<th>hERG</th>
<th>Purkinje</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>X2</td>
<td>0.86</td>
<td>0.92</td>
<td>0.25</td>
</tr>
<tr>
<td>x10</td>
<td>0.92</td>
<td>0.5</td>
<td>0.44</td>
</tr>
<tr>
<td>X30</td>
<td>0.9</td>
<td>0.17</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Issues

• No harmonized study design
  – For some compounds inhibition of hERG current is very much protocol dependent – potency can vary by ~10-fold
    • Not an issue if taken as safety signal, critical for understanding potential exposures that may prolong QTc interval

• Most in vivo CV studies are designed to detect large effects of concern for FIH studies. May not have appropriate assay sensitivity to detect changes of 5 to 10 msec
  – Potential to detect larger effects at higher multiples of human exposure
    • May not study such high multiples
    • Potential to dismiss effect as not relevant because only observed at high doses
    • Assumes some understanding of exposure response relationship

• Issue of assay sensitivity has been discussed at Safety Pharmacology Society sponsored workshop
  – Key recommendations
    • Define hypothesis to be tested
      – E.g. detect a 5 msec change in QTc or 10% (25 msec)
    • Does the study design have the potential to detect desired effect?
      – Power calculations
    • Understand ability of the study design to detect known agents of concern
      – Reference agent
    • Support conclusions based on ability of the specific study to detect change
Conclusions

• Non-clinical assays can detect agents that prolong QT interval via hERG inhibition
  – Robust in vitro assays
  – Assays to confirm translation (re-verapamil)
• More robust application of PK/PD modeling can define exposure response relationships to aid translation to man
  – Model potential exposures to cause ‘small changes’ of concern in the TQT study
• Need to prospectively define study objectives
  – Cannot claim lack of QT signal of regulatory concern if the *in vivo* assay is not appropriately powered
• Non-clinical assays do not detect all QTc prolonging agents e.g. mild vasodilators – PDE5i
  – These mechanisms are detected in FIH studies
• Combination of robust non-clinical and FIH studies has the potential to detect small QT changes of regulatory concern.