Rechanneling the current cardiac risk paradigm: arrhythmia risk assessment during drug development without the thorough QT study.

What would success look like?

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What would success look like?

- Positive implications for industry?
- How would the approach be used?
- Next steps with respect to schema refinement?
Positive implications for industry

- Increase the likelihood of success of developing efficacious & safe medicines that would benefit patients
- Reduce the likelihood of discontinuing potentially valuable medicines (devoid of TdP risk or with an acceptable risk / benefit ratio)
- Support the selection of clinical candidates
- Better predict clinical outcome at early stage
Positive implications for industry: case studies

<table>
<thead>
<tr>
<th>Test system</th>
<th>Species</th>
<th>Viozan (Sibenadet)</th>
<th>Ranolazine (Ranexa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>in vivo</em> QT/QTc interval</td>
<td>Human</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Torsades de Pointes</td>
<td>Human</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Cardiac repolarisation models:**

| *in vitro* Ikr / hERG        | Human       | Negative           | Positive            |
| *in vitro* APD *             | Dog         | Negative           | Positive            |
| *in vivo* QT/QTc interval    | Dog         | Negative           | Positive            |

**Proarrhythmia models:**

| Isolated heart               | Rabbit      | Negative           | Negative            |
| Wedge preparation            | Dog         | -                  | Negative            |
| Isolated myocyte             | Guinea-pig  | -                  | Negative            |
| A-V block *in vivo*          | Dog         | -                  | Negative            |

- Other examples may include: Alfuzosin, Verapamil, Ebastine, Clozapine...
- Can the assessment of the proarrhythmic potential of drugs add value to the drug development paradigm?
- **Negative** in non-clinical assays: no statistically/biologically significant effect at exposures $\geq100$-fold the therapeutic free plasma concentration. * Purkinje fibre and epicardial cells for Viozan and Ranolazine.

Data extracted from: Viozan: Newbold et al., Br J Clin Pharmacol 2007; Valentin et al., JPTM, 2006
Ranolazine: Antzelevitch C., J Electocardiol, 2004; Scham et al., BJP 2004; Song et al., JCP 2004; Antzelevitch C et al., JCPT 2004; Antzelevitch C et al., Circulation 2004; Belardinelli et al., 2003; Anon., FDA Briefing Information
(http://www.fda.gov/ohrms/dockets/ac/03/briefing/4012B2.htm)
How would the new approach be used?

Current vs. Proposed (?) screening paradigm


<table>
<thead>
<tr>
<th></th>
<th>Target to Hit</th>
<th>Hit to Lead</th>
<th>Lead Opti.</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Post-approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Projects</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nb cpds</td>
<td>&gt;10^6</td>
<td>10 000</td>
<td>7500</td>
<td>12</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Current paradigm “basic” S7B-E14</td>
<td></td>
<td></td>
<td></td>
<td>GLP-hERG GLP-NR-Telemetry</td>
<td></td>
<td></td>
<td></td>
<td>TQT</td>
</tr>
<tr>
<td>Current paradigm “enhanced”</td>
<td></td>
<td></td>
<td></td>
<td>GLP-hERG GLP-NR-Telemetry</td>
<td></td>
<td></td>
<td></td>
<td>ECG TQT</td>
</tr>
<tr>
<td>Proposed paradigm “basic”</td>
<td></td>
<td></td>
<td></td>
<td>•GLP-hERG •GLP-NR-Telemetry •Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proposed paradigm “enhanced”</td>
<td>•Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG</td>
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<td>•Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG</td>
<td>•GLP-hERG •GLP-NR-Telemetry •Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG</td>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### How would the approach be used?

Pre-clinical screening & Clinical (TQT) costs - Estimates (detailed breakdown)

- Assume 2 TQTS at $2M each

<table>
<thead>
<tr>
<th>Testing Candidate Drugs only</th>
<th>ICH S7B &amp; E14</th>
<th>New Paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>$1.44M</td>
<td>$1.80M</td>
</tr>
<tr>
<td>TQTS</td>
<td>$4.00M</td>
<td>$0.00M</td>
</tr>
<tr>
<td>GRAND TOTAL</td>
<td>$5.44M</td>
<td>$1.80M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testing multiple compounds</th>
<th>ICH S7B &amp; E14</th>
<th>New Paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical</td>
<td>$3.44M</td>
<td>$38.69M</td>
</tr>
<tr>
<td>TQTS</td>
<td>$4.00M</td>
<td>$0.00M</td>
</tr>
<tr>
<td>GRAND TOTAL</td>
<td>$7.44M</td>
<td>$38.69M</td>
</tr>
</tbody>
</table>

- Companies may decide to implement different pre-clinical approaches from minimalistic to comprehensive.
- Discovery and/or Development time, cost and level of de-risking may vary.
Next steps with respect to schema refinement? Confidence in non-clinical testing cascade

- A multi-dimensional framework approach:
- **What?** Quantitative method to relate preclinical safety data to clinical outcome in man
  - Trepakova et al., (2009) *JPTM* 60:45-50
- **How?** A multi-dimensional framework approach to assess confidence in the:
  - Biology
  - Translation
  - Model / Assay

<table>
<thead>
<tr>
<th>Confidence in the biology</th>
<th>Confidence in translation</th>
<th>Confidence in model / assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Ideal</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Ideal state:
- Low confidence in the biology
- Medium confidence in translation
- High confidence in model / assay
### Conscious dog telemetry model

<table>
<thead>
<tr>
<th>Model</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching the clinical end point (x2)</td>
<td></td>
<td></td>
<td></td>
<td>Measure same end point in humans and dogs</td>
</tr>
<tr>
<td>Matching the pathway/mechanism (conservation of pathways) (x1)</td>
<td></td>
<td>Close similarity between receptors, ion channels, intracellular pathways etc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matching the physiology (x1)</td>
<td></td>
<td>Similar anatomy and physiology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall confidence:** High

### Conscious rat telemetry model

<table>
<thead>
<tr>
<th>Model</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching the clinical end point (x2)</td>
<td></td>
<td></td>
<td></td>
<td>Measure same end point in humans and rats</td>
</tr>
<tr>
<td>Matching the pathway/mechanism (conservation of pathways) (x1)</td>
<td></td>
<td>Some similarity between receptors, ion channels, intracellular pathways etc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matching the physiology (x1)</td>
<td></td>
<td>Repolarisation driven by (I_h) current; physiology dissimilar</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall confidence:** Medium

### Larval zebrafish ‘QT’ model

<table>
<thead>
<tr>
<th>Model</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching the clinical end point (x2)</td>
<td></td>
<td></td>
<td></td>
<td>Image synchronicity of contraction between atria and ventricle</td>
</tr>
<tr>
<td>Matching the pathway/mechanism (conservation of pathways) (x1)</td>
<td></td>
<td></td>
<td></td>
<td>Some similarity between receptors &amp; ion channels (based on limited validation data)</td>
</tr>
<tr>
<td>Matching the physiology (x1)</td>
<td></td>
<td></td>
<td></td>
<td>Anatomy and physiology of the heart dissimilar</td>
</tr>
</tbody>
</table>

**Overall confidence:** Low

---

2. Confidence in the translation: non-clinical to humans

- Compare the response to drugs in the model and in humans
- Quantification using a statistical approach:

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

- Overall predictive capacity = (True Negatives + True Positives) / Total
  - A value of 50% is no better than chance!

If a compound is ‘negative’ in human, what is the probability that the animal model will correctly identify it.

If a compound is ‘positive’ in human, what is the probability that the animal model will correctly identify it.

-灵敏度 (Sensitivity) = TP / (TP + FN)
- 特异性 (Specificity) = TN / (TN + FP)
- 阳性预测值 (Positive Predictive Value) = TP / (TP + FP)
- 阴性预测值 (Negative Predictive Value) = TN / (TN + FN)

Depend upon prevalence

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<table>
<thead>
<tr>
<th>Test system end-point</th>
<th>Species</th>
<th>Exp. conditions</th>
<th>Clinical endpoint</th>
<th>Exposure multiple</th>
<th>Number of drugs</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Predictability %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>QT interval</td>
<td>3</td>
<td>44</td>
<td>17</td>
<td>91</td>
<td>70</td>
<td>Koerner et al., 2012</td>
</tr>
<tr>
<td>APD</td>
<td>Rabbit, Dog, Guinea-P</td>
<td>In vitro</td>
<td>QT interval</td>
<td>3</td>
<td>43</td>
<td>0</td>
<td>93</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>QTc interval</td>
<td>Dog</td>
<td>In vivo</td>
<td>QT interval</td>
<td>3</td>
<td>47</td>
<td>20</td>
<td>100</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Integrated</td>
<td>All of the above</td>
<td>In vitro &amp; In vivo</td>
<td>QT interval</td>
<td>3</td>
<td>88</td>
<td>17</td>
<td>92</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>QTc interval</td>
<td>Dog</td>
<td>In vivo</td>
<td>QT interval</td>
<td>3</td>
<td>114</td>
<td>80</td>
<td>70</td>
<td>?</td>
<td>Ewart et al., 2012</td>
</tr>
<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>QT interval</td>
<td>2-3</td>
<td>19</td>
<td>82</td>
<td>75</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>APD</td>
<td>Dog</td>
<td>In vitro</td>
<td>QT interval</td>
<td>2-3</td>
<td>19</td>
<td>20</td>
<td>100</td>
<td>53</td>
<td>Wallis R., 2010</td>
</tr>
<tr>
<td>QTc interval</td>
<td>Dog</td>
<td>In vivo</td>
<td>QT interval</td>
<td>2-3</td>
<td>19</td>
<td>83</td>
<td>86</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>hERG + QTc</td>
<td>Human &amp; Dog</td>
<td>In vitro &amp; In vivo</td>
<td>QT interval</td>
<td>2-3</td>
<td>19</td>
<td>90</td>
<td>88</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>QT interval</td>
<td>45</td>
<td>39</td>
<td>64</td>
<td>88</td>
<td>79</td>
<td>Gintant G., 2011</td>
</tr>
<tr>
<td>QTc interval</td>
<td>Dog</td>
<td>In vivo</td>
<td>QT interval</td>
<td>ND</td>
<td>17</td>
<td>100</td>
<td>90</td>
<td>95</td>
<td>Toyoshima et al., 2005</td>
</tr>
<tr>
<td>QTc interval</td>
<td>Monkey</td>
<td>In vivo</td>
<td>QT interval</td>
<td>ND</td>
<td>16</td>
<td>100</td>
<td>73</td>
<td>86</td>
<td>Ando et al.,</td>
</tr>
<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>Torsades de P</td>
<td>30</td>
<td>28</td>
<td>89</td>
<td>100</td>
<td>93</td>
<td>Webster et al., 2002</td>
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<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>Torsades de P</td>
<td>30</td>
<td>52</td>
<td>96</td>
<td>69</td>
<td>81</td>
<td>Redfern et al., 2003</td>
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<tr>
<td>Screenit</td>
<td>Rabbit</td>
<td>In vitro</td>
<td>Torsades de P</td>
<td>30</td>
<td>64</td>
<td>65</td>
<td>89</td>
<td>75</td>
<td>Lawrence et al., 2006</td>
</tr>
<tr>
<td>hERG</td>
<td>Human</td>
<td>In vitro</td>
<td>Torsades de P</td>
<td>ND</td>
<td>12</td>
<td>100</td>
<td>83</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>APD</td>
<td>Dog</td>
<td>In vitro</td>
<td>Torsades de P</td>
<td>ND</td>
<td>12</td>
<td>33</td>
<td>83</td>
<td>58</td>
<td>Hanson et al., 2006</td>
</tr>
<tr>
<td>QTc interval</td>
<td>Dog</td>
<td>In vivo</td>
<td>Torsades de P</td>
<td>ND</td>
<td>12</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

ECVAM criteria (Genschow et al., 2002): <65% not sufficient; 65 – 74%: sufficient; 75 – 84%: good; > 85%: excellent
2. Confidence in the translation

Impact of Prevalence – in 1000 Compounds

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>+ve</th>
<th>-ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>8</td>
<td>198</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>792</td>
</tr>
<tr>
<td>10%</td>
<td>80</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>720</td>
</tr>
<tr>
<td>30%</td>
<td>240</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>560</td>
</tr>
</tbody>
</table>

Sensitivity 80%  Specificity 80%

FP  FN

Impact of Prevalence on Predictive Value (80% sensitivity & specificity)

Courtesy of Dr Derek J. Leishman, Eli Lilly and Company.
3. Confidence in the model

- **Parameters:**
  - Numerous parameters to take into account.
  - May vary from model to model.
  - E.g., Intra & inter laboratories reproducibility; Responsiveness to positive & negative agents; Baseline values; Performance of the assay, screen or model; Understanding of strengths & limitations of the model; Availability of data in the public domain – see next slide
  - E.g., In vivo cardiovascular assessment in non-rodent: D. Leishman et al., *JPTM* 2012.

- **Logistic:**
  - Compatibility with the Design – Make – Test – Analyse cycle of drug discovery
  - Cost; Throughput; Turnaround Time; Availability; Capital investment & depreciation....
## 3. Confidence in the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>QT in telemetered dogs</th>
<th>hERG electrophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assay screen or model performance</strong></td>
<td>Vehicle and positive control within historical range</td>
<td>Z’ &gt;0.6. Reference IC$_{50}$ within 3-fold of historical</td>
</tr>
<tr>
<td><strong>Protocol/study design</strong></td>
<td>Ability to detect compounds which affect cardiovascular parameters (haemodynamics, ECG intervals, contractility)</td>
<td>Ability to detect compounds which are either blockers or activators. Distinguish use/state dependence. Detect slow onset of effect.</td>
</tr>
<tr>
<td><strong>Reproducibility of test system within laboratory</strong></td>
<td>Power analysis and historical reference ranges</td>
<td>Z’ &gt;0.6. Reference IC$_{50}$ within 3-fold of historical</td>
</tr>
<tr>
<td><strong>Reproducibility of test system between laboratories</strong></td>
<td>Compare power analysis and historical reference ranges across sites</td>
<td>Absolute IC$_{50}$ values are protocol-dependent so may vary between laboratories, but rank order of potency for reference compounds should be identical. Risk that different platforms (e.g IonWorks, Patch Clamp, Qpatch) may bias towards particular kinds of interaction</td>
</tr>
<tr>
<td><strong>Inclusion of both known positive and negative agents</strong></td>
<td>Vehicle routinely included in each study. Reference compound can be included in each study</td>
<td>Reference compound and vehicle included in each assay</td>
</tr>
<tr>
<td><strong>Method limitations</strong></td>
<td>Animal variability. Lots of parameters assessed; a single positive control can not demonstrate sensitivity to all parameters</td>
<td>IC$_{50}$ is dependent on assay protocol so translation requires a “standard curve”</td>
</tr>
<tr>
<td><strong>Data supporting validity</strong></td>
<td>Extensive literature evaluation of several different assay platforms. Strong evidence for correlation between in vivo and clinical effects</td>
<td>Extensive literature evaluation of several different assay platforms. Strong evidence for correlation between in vitro activity and in vivo effect pre-clinically and clinically. Risk that much attention is focussed on a single target, at the expense of other mechanisms</td>
</tr>
</tbody>
</table>
Next steps with respect to schema refinement?

- What confidence do we have in existing & emerging models?
  - E.g., Non-Rodent telemetry to predict QT prolongation 😊
  - E.g., hERG to predict QT prolongation 😊
  - E.g., hSC-CM to predict Torsades de Pointes ?

1. Confidence in the biology
2. Confidence in translation
3. Confidence in model / assay

- Low               Medium              High
- Low               Medium              High
- Low               Medium              High

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Summary & next steps

• Which pre-clinical assays should be used?
  – In silico, in vitro & in vivo? Key stakeholders agreement e.g. Industry, Regulators
• For each relevant assay, develop confidence in biology, translation and model?
• If focusing on the proposed scheme:
  – Decide which channels should be investigated, which parameters to be measured, define protocols, optimize automated platforms, etc
  – Develop in silico methods (ion channels, action potential, ECG)
  – Stem cells: in parallel, standardize stem cell preparation
  – Compare stem cell data vs. transfected cells vs. freshly isolated cardiac myocytes
• Question: Who would be doing what, where & when? Pharma & Biotech Industry, Service / Equipment providers, Consortia: CSRC, HESI, FDA, SPS...........
Acknowledgements

• AstraZeneca colleagues:
  – David Baker
  – Joanne Bowes
  – Chris Pollard
  – Will Redfern

• Industry colleagues:
  – Peter K. Hoffmann, Novartis
  – Derek J. Leishman, Eli Lilly and Company
  – Michael Pugsley, Johnson & Johnson
  – Hugo Vargas, Amgen
Pierre Fabre died Saturday the 20th of July, aged 87. The pharmaceutical and cosmetics company which he founded in 1961 employs 10,000 people and had a turnover of ~2billion € last year. “Since its creation in 1961 and until these last few days, Mr. Fabre has dedicated all his energy to building the 3rd largest French pharmaceutical company. He led, steered and masterminded all the different stages of its development and has built, stone by stone, an international company”.