The New Paradigm: Next Steps

Norman Stockbridge, MD, PhD
Director, Division of Cardiovascular and Renal Products
FDA

Oct 31, 2013
Time has come

• Urgency
  – We have probably labeled drugs as risky when there is none
  – Drug developers are probably making suboptimal decisions about which compounds to bring forward in development

• Feasibility
  – Basis of TdP pretty well understood
    • Vulnerable repolarization
    • Asynchronous activity
  – Vulnerability can be assessed now in human ion channels
Contributors to assessment of feasibility

• Darell Abernethy/FDA
• Arthur Brown/ChanTest
• Thomas Colatsky/FDA
• Christine Garnett/Pharsight
• Gary Gintant/AbbVie
• Craig January/U Wisconsin
• Lars Johannesen/FDA
• John Koerner/FDA
• James Kramer/ChanTest
• Naomi Kruhlak/FDA

• Derek Leishman/Lilly
• Marek Malek/U London
• Sebastian Polak/Simcyp
• Philip Sager/Stanford Univ
• David Strauss/FDA
• Robert Temple/FDA
• Nick Thomas/GE
• Douglas Throckmorton/FDA
• Jiwen Zhang/GE
Engineering team - 1

- HESI ProArrhythmia Working Group, Safety Pharmacology Society, FDA
  - What channels to study
  - What voltage clamp protocols
  - Other aspects of protocol specification
### Pulse sequences: Ito

<table>
<thead>
<tr>
<th>ID</th>
<th>Channel /Current</th>
<th>Species/cells</th>
<th>CPD</th>
<th>Temp</th>
<th>Vh (mV)</th>
<th>Prepulse (ms, mV)</th>
<th>Activation (ms, mV)</th>
<th>Voltage -Dependence (ms, mV)</th>
<th>Interval/ frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>hKv4.3/hKChIP2.2</td>
<td>CHO</td>
<td>Methadone</td>
<td>RT</td>
<td>-90</td>
<td>300, 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>rKv4.3</td>
<td>Mouse/L cell</td>
<td>Vanoxerine</td>
<td>RT</td>
<td>-80</td>
<td>300, 20</td>
<td></td>
<td></td>
<td>15s</td>
</tr>
<tr>
<td>50</td>
<td>hKv4.3</td>
<td>HEK293</td>
<td>Alfuzosin</td>
<td>RT</td>
<td>-80</td>
<td>300, 20</td>
<td></td>
<td></td>
<td>15s</td>
</tr>
<tr>
<td>206</td>
<td>Ito</td>
<td>Rat/VM</td>
<td>Zacopride</td>
<td>24</td>
<td>-40</td>
<td>n/a</td>
<td>500, -40 to 80 (Δ10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>210</td>
<td>Ito</td>
<td>Human/AM</td>
<td>Cyamemazine</td>
<td>32-34</td>
<td>-50</td>
<td>500, 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>214</td>
<td>Kv4.3</td>
<td>Monkey/COS7</td>
<td>Pentamidine</td>
<td>n/a</td>
<td>-80</td>
<td>n/a</td>
<td>500, -40 to 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>215</td>
<td>Ito</td>
<td>Canine/VM</td>
<td>Pioglitazone</td>
<td>n/a</td>
<td>-80</td>
<td>n/a, 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>220</td>
<td>Ito</td>
<td>Rat/VM</td>
<td>Ajmaline</td>
<td>RT</td>
<td>-75</td>
<td>300, 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221</td>
<td>rKv4.2, rKv4.3</td>
<td>HEK293</td>
<td>RSD1235</td>
<td>25</td>
<td>-80</td>
<td>250, 60</td>
<td></td>
<td>1Hz</td>
<td></td>
</tr>
<tr>
<td>222</td>
<td>Ito</td>
<td>Rat/VM</td>
<td>FK-506</td>
<td>22-24</td>
<td>-80</td>
<td>n/a, 50</td>
<td>1000, -50 to 70</td>
<td>0.1Hz</td>
<td></td>
</tr>
<tr>
<td>224</td>
<td>hKv4.3</td>
<td>HEK293</td>
<td>Allitridi</td>
<td>22-23</td>
<td>-80</td>
<td>300, 60</td>
<td>300, -80 to 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>245</td>
<td>Ito</td>
<td>Human/AM</td>
<td>DPO</td>
<td>RT</td>
<td>-80</td>
<td>150, 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>256</td>
<td>Ito</td>
<td>Rabbit/VM</td>
<td>Carvedilol</td>
<td>34</td>
<td>-60</td>
<td>300, 40</td>
<td>300, -50 to 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>263</td>
<td>Kv4.3</td>
<td>CHO (transient)</td>
<td>Spironolactone canrenonic acid</td>
<td>RT</td>
<td>-80</td>
<td>250, 50</td>
<td>250, -90 to 50</td>
<td>10s</td>
<td></td>
</tr>
<tr>
<td>267</td>
<td>Ito</td>
<td>rat/VM</td>
<td>Ebastine</td>
<td>n/a</td>
<td>-90</td>
<td>n/a, 75</td>
<td>n/a, -30 to 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>273</td>
<td>Ito</td>
<td>Canine/VM</td>
<td>Thymol</td>
<td>37</td>
<td>-80</td>
<td>400, 50</td>
<td>400, -10 to 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>281</td>
<td>rKv1.4</td>
<td>Xenopus Oocyte</td>
<td>Haloperidol</td>
<td>22</td>
<td>-80</td>
<td>300, 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>283</td>
<td>Ito</td>
<td>Human/AM</td>
<td>Clotrimaxole</td>
<td>21-22</td>
<td>-50</td>
<td>300, 50</td>
<td>300, -40 to 60</td>
<td>0.2Hz</td>
<td></td>
</tr>
</tbody>
</table>

VM= ventricular myocyte. AM= Atrial myocyte

From EJ Park, FDA
Engineering team - 2

• FDA, academia, pharma
  – What channel models to use
  – What proarrhythmia metric
  – How to fit drug effect data
O’ Hara-Rudy model of human myocyte
Engineering team - 3

• HESI Myocyte Working Group?
  – Can you confirm the adequacy of voltage clamp assessment of drug effects?
  – What is the best cell line?
  – What is the best approach to recording?
  – Can these cells be made more like the adult human?
Engineering Team - 4

• Cardiac Safety Research Consortium, ICH E14 Working Group
  – What drugs, performance would allow one to replace the TQT study?
  – What would go into a Drug Development Tool Qualification package?
Future vision

• Relabeling of some existing drugs
• Better labeling for future drugs
• More and better drugs in development
• More efficient drug development
• No TQT studies
Work plan in progress

Myocyte Stream
- Best Practices - Myocyte CC
- Consensus Protocol - Myocyte CC
- Power Estimate - Myocyte CC

Voltage Clamp Stream
- Best Practices - VC Protocols
- Literature Review - VC Protocols
- Consensus - VC Protocols
- Consensus - Channels
- Power Estimate - VC

Validation/Calibration
- VC and CC Data on Test Drugs
- Process Validation Dataset

Regulatory Stream
- Consensus - Drugs to Test
- Drug Development Tool Qualification Submission
- DDT Qualification Review
- Withdraw from ICH E14
- Workshop on New Paradigm
- CIPA in Production

In Silico Stream
- Model development
  - Determine Heart Conductances
  - Determine Myocyte Conductances
  - Voltage Clamp Data Format
  - Algorithms for VC-to-Model Parameters
  - Algorithm for ProA Metric
  - Infrastructure Development
  - In Silico Infrastructure - Design
  - In Silico Infrastructure - Website

July 2015
Call to action

• Whether this happens “on time” – or at all – depends upon the cooperative efforts of many stakeholders. Volunteer.

  – https://www.ilsieextra.org/hesi/science/cardiac/cipa/SitePages/Home.aspx
  – Norman.Stockbridge@fda.hhs.gov
  – Psager@Stanford.edu
  – Gary.Gintant@abbvie.com