Pursuing the holy grail of predicting and verifying tissue drug concentrations: A proteomics and PET imaging approach

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Failure Rate and Reasons for Failure in Drug Development

b Cumulative success rate Phase I to launch
Percentage likelihood of moving from Phase I to launch

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>1996–1999</td>
<td>16.4</td>
</tr>
<tr>
<td>2000–2003</td>
<td>10.8</td>
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<tr>
<td>2004–2007</td>
<td>10.0</td>
</tr>
<tr>
<td>2008–2011</td>
<td>7.5</td>
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<tr>
<td>2012–2014</td>
<td>11.6</td>
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</tbody>
</table>

b Reason for failure in phase II

<table>
<thead>
<tr>
<th>Year</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Commercial and strategy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008–2010</td>
<td>51</td>
<td>48</td>
<td>29</td>
<td>24</td>
</tr>
<tr>
<td>2011–2012</td>
<td>19</td>
<td>22</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>2013–2015</td>
<td>25</td>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

One Possible Reason for Lack of Drug Efficacy & Safety

• Unable to measure or predict tissue conc. of drugs

• Unbound plasma conc. $\neq$ unbound tissue conc. if transporters are involved, i.e. asymmetry between blood and tissue drug conc. (e.g. liver:blood due to OATPs)
Asymmetry In Brain: Blood Drug Conc. Due to Blood-Brain Barrier Efflux Transporters

Eyal, Hsiao & Unadkat Pharmacol. Ther., 2009
**P-gp at the Rat BBB Results in Asymmetry in Brain:Blood Conc. of Verapamil (P-gp substrate)**

- **Human PET study**
- **Mouse KO study**

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**Graph:**

- **X-axis:** Blood CsA concentration (μM)
- **Y-axis:** Percent increase in brain: blood $[^3]$H-radioactivity

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*Hsiao et al J Pharmacol Exp Ther. 2006*
Asymmetry in Drug Conc. at the Human Brain: Blood Barrier: P-gp Efflux of $^{11}$C-Verapamil

$^{11}$C-verapamil $\text{AUC}_{\text{brain}}:\text{AUC}_{\text{blood}}$ (20 min) - 0.42 ± 0.04

Eyal et al., *Clin Pharmacol Ther.* 2010
Asymmetry in Tissue: Blood Drug Conc. - Liver

Blood

\[ \text{CL}^s_{\text{in}} \text{ [D]} \]

\[ \text{CL}^s_{\text{ef}} \]

e.g. OATPs

Bile

\[ \text{CL}^s_{\text{bile}} \]

\[ \text{CL}^s_{\text{met}} \]

e.g. P-gp, BCRP, MRP2
Asymmetry in Liver Tissue: Plasma Conc. when $C_{in}^s$ is the Rate-Determining Step

i.e. $CL_{met+bile} >> CL_{ef}^s$

Blood

Liver

\[ 0 \quad 0.2 \quad 0.4 \quad 0.6 \]
\[ 0 \quad 10 \quad 20 \quad 30 \quad 40 \quad 50 \quad 60 \]

Concentration (mg/L) Time (min)

Assumptions:
- Liver is the only eliminating organ
- 90% inhibition

Patilea-Vrana & Unadkat. CPT. 2016
Asymmetry in Hepatic Blood Conc. of $^{11}$C-Rosuvastatin in the Rat

Coronal 2 min SUV images of $^{11}$C-Rosuvastatin

He et al., Mol Pharm., ‘14
Changes in Rat Liver Exposure to Rosuvastatin ± Rifampin

2.3 fold increase in RSV plasma AUC but NO significant increase in RSV liver AUC

He et al., Mol Pharm. 2014
Biodistribution of $^{11}$C-rosuvastatin in humans

Billington et al., In progress
How Can we Predict Tissue Drug Conc. in Humans?

• PET imaging (MRI and other imaging modalities do not have the required sensitivity):
  – Requires sophisticated equipment and radiochemistry
  – Costly (about $20-40K/experiment/subject)

• Therefore we need alternative methods that will allow us to predict tissue conc. of drugs in humans
APPLICATION OF PROTEOMICS DATA TO PREDICT PK AND TISSUE CONC. OF DRUGS
**Hypothesis:** Predict transporter-mediated in-vivo CL and tissue concentration of drugs in humans from in-vitro studies

1. transporter-mediated drug CL
2. transporter abundance using quantitative proteomics
3. Obtain transporter scaling factor

**Predict in-vivo**
CL and tissue conc.
using transporter scaling factor

**Verify predictions**
using PET imaging
Hepatic Uptake and Biliary Excretion of $^{11}$C-Rosuvastatin in the Rat

Coronal 2 min SUV images of $^{11}$C-Rosuvastatin

He et al., Mol Pharm., '14
Successful prediction of the hepatobiliary clearance of rosvastatin using cell lines, sandwich-cultured rat hepatocytes and quantitative proteomics

Ishida et al., DMD, 2018
Rat Hepatic Rosuvastatin Conc. well Predicted

Observed value
predicted value
95% CI of observed data

Hepatic concentration (kBq/mL) vs. Time (min)
Can Rosuvastatin Hepatobiliary CL and Hepatic Conc. be Predicted in Humans?
Total transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes and liver tissue

Data removed as not published

Kumar et al.,
Unpublished data
Plasma membrane transporter abundance in suspended (SH), plated (PH), sandwich-cultured (SCH) hepatocytes cf liver tissue

Kumar et al., Unpublished data
Transporter-expressing cells better predict in-vivo (IV) human rosvastatin hepatic uptake clearance than hepatocytes

Data removed as not published

\[ CL_h = \frac{Q_h \cdot f_u \cdot CL_{s,uptake}}{Q_h + f_u \cdot CL_{s,uptake}} \]

*Assuming sinusoidal uptake is the rate determining step in RSV plasma CL


RSV uptake CL scaled on the basis of hepatocellularity *(Classical method)*

*88 mg protein/g human liver


Metformin renal clearance is reasonably well-predicted using OCT2 expressing cells

Kumar et al., DMD 2018

Observed metformin renal secretory clearance in humans: 432 (range 215-643) mL/min
Summary

• Predicting tissue concentration and therefore efficacy and toxicity of a drug is the next frontier in ADME research
• The hepatic ECL model clarifies when transporters will or will not affect the systemic and tissue PK of a drug
• Tissue conc. measurement is possible using PET. However, this method cannot be routinely applied
• IVIVE using transfected cells and quantitative transporter proteomics is a promising technique to predict tissue drug conc.
• These predictions should be validated using PET imaging probes that interrogate multiple drug transporters
ATP \rightarrow ADP + Pi

Genentech, Merck, Biogen, Gilead, BMS, Takeda, Pfizer
Other Collaborators

Dept. of Radiology: Jeanne Link, David Mankoff, Todd Richards, Janet Eary, Satoshi Minoshima, Ken Maravilla, Mark Muzi, Steve Shoner, David Lewis, Jean Lee and the PET suite team

Dept. of Medicine: Ann Collier and her team; Scott Lee and his team

Dept. of Anesthesiology: Karen Domino, Matthew Pennington

Dept. of Pharmaceutics: Bhagwat Prasad, Edward Kelly, Carol Collins, Joanne Wang

Kidney Research Institute: Jonathan Himmelfarb

Univ. of Greifswald: Stefan Oswald and team

Children’s Mercy Hospitals: Steven Leeder and team

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