Comparative Pharmacophore Modeling of Organic Anion Transporting Polypeptides (OATP)

A Meta-analysis of Rat Oatp1a1, Human OATP1B1 and OATP1A2

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Rationale

• Pharmacophore modeling has been applied successfully to many biological systems
  – ligand-receptor interactions
  – lead identification via database screening
• Issues with consistent datasets for transporter study

Objective

• To derive OATP meta-pharmacophores that can utilize data from diverse experimental systems
Biology

OATP: Membrane transporter proteins that mediate sodium-independent transport of a diverse array of amphipathic organic compounds.

Hagenbuch B, Meier PJ. *Biochimica et Biophysica Acta* 1609 (2003) 1
Phylogenetic Analysis
Tissue Distribution

Hagenbuch B, Meier PJ. *Pflugers Arch.* 2004 Feb;447(5):653
Significance of OATPs

• Critical role in drug-drug interactions (DDI), e.g.
  – Cerivastatin and gemfibrozil (Shitara et al., 2004 *J Pharmacol Exp Ther.*).

• Potential Pharmaceutical Application
  – Identify DDI in early drug discovery
  – Co-administration of OATP inhibitors to improve bioavailability
Methods

- Complete literature search and captured data on molecule, \( K_m \), cell system and species

<table>
<thead>
<tr>
<th></th>
<th>Cell Line</th>
<th>Substrates</th>
<th>( K_m ) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B1</td>
<td>Oocytes</td>
<td>12</td>
<td>0.0076 – 17</td>
</tr>
<tr>
<td>Oatp1a1</td>
<td>HEK-293</td>
<td>12</td>
<td>0.1 – 268</td>
</tr>
<tr>
<td></td>
<td>Oocytes</td>
<td>14</td>
<td>0.015 – 3300</td>
</tr>
<tr>
<td></td>
<td>CHO</td>
<td>12</td>
<td>3 – 3000</td>
</tr>
<tr>
<td></td>
<td>HeLa</td>
<td>9</td>
<td>3.1 – 214</td>
</tr>
<tr>
<td>OATP1A2</td>
<td>Oocytes</td>
<td>15</td>
<td>2.5 – 5500</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Meta</td>
<td>18</td>
<td>0.0076 – 268</td>
</tr>
<tr>
<td>Oatp1a1</td>
<td>Meta</td>
<td>26</td>
<td>0.015 – 3300</td>
</tr>
</tbody>
</table>
Methods

• Generated pharmacophores for each cell system
  – Correlation and total energy cost

• Merged pharmacophores for the same transporter

• Generated Meta-pharmacophores using combined data

• Validated models using scrambling and test sets

• Performed drug database searches to identify molecules
Results: OATP1A2

Oocytes $r=0.89$
(N-methyl-quinidine)

Blue = Hydrophobic; Red = H-bond Acceptor; Arrow = Direction of Vector
OATP1B1

Blue = Hydrophobic; Red = H-bond Acceptor; Arrow = Direction of Vector
Oatp1a1

Blue = Hydrophobic; Red = H-bond Acceptor; Yellow = Negative Ionizable; Arrow = Direction of Vector
Meta Models

A. OATP1B1 $r = 0.92$
   (Bilirubin)

B. Oatpl1 $r = 0.90$
   (Aldosterone)

Blue = Hydrophobic; Red = H-bond Acceptor; Arrow = Direction of Vector
Bilirubin Controversy

Cui Y, et al., 2001
*J Biol Chem*
276:9626-30.

Briz O, et al., 2003
*Biochem J*
371:897-905.

Wang P, et al., 2003
*J Biol Chem*
278:20695-9.

OATP1B1 w/o Bilirubin $r=0.92$
(Bilirubin monoglucuronide)
Qualitative Testing of Meta Models

• BSP(bromosulfophthalein)-GSH is transported by Oatp1a1, while enalaprilat, hippuric acid, benzoic acid, and harmol sulfate were not (Pang et al., 1998 Hepatology 28:1341)

<table>
<thead>
<tr>
<th>Test compounds</th>
<th>Predicted $K_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Hippuric acid and benzoic acid</td>
<td>Failed to fit</td>
</tr>
<tr>
<td>– Harmol sulfate</td>
<td>550 µM</td>
</tr>
<tr>
<td>– Enalaprilat</td>
<td>69 µM</td>
</tr>
<tr>
<td>– BSP-GSH</td>
<td>23 µM</td>
</tr>
</tbody>
</table>

• OATP1B1 inhibitor indocyanine green (Cui et al., 2001 J Biol Chem 276:9626)
  – Predicted $K_m$ 6.3 µM
Qualitative Testing of Meta Models

- Troglitazone & its metabolites produce statistically significant inhibition of estrone-3-sulfate uptake in OATP1B1 (Nozawa et al., 2004 *Drug Metab Dispos* 32:291).

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<thead>
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<th>Test compounds</th>
<th>Predicted $K_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>– troglitazone</td>
<td>7.9 µM</td>
</tr>
<tr>
<td>– troglitazone glucuronide-M2</td>
<td>1.6 µM</td>
</tr>
<tr>
<td>– troglitazone sulfate-M1</td>
<td>5.6 µM</td>
</tr>
<tr>
<td>– troglitazone quinone-M3</td>
<td>6.7 µM</td>
</tr>
<tr>
<td>– pioglitazone</td>
<td>14 µM</td>
</tr>
<tr>
<td>– rosiglitazone</td>
<td>9.9 µM</td>
</tr>
</tbody>
</table>
Database Screening

- In-house database of 576 widely prescribed drugs (Gomella L and Haist S, *Clinician's pocket drug reference* 2004)

- OATP1B1 (w/o Bilirubin) meta model hits: 220

- Oatp1a1 meta model hits: 187

- Recent QSAR study for Oatp1a5
  - One hydrophobic area flanked by a H-bond acceptor feature and a negative charge feature

Conclusion

• Predictive meta pharmacophores from different experimental systems were generated for Oatp1a1 and OATP1B1.

• Both Oatp1a1 and OATP1B1 require centrally clustered hydrophobic features and 2 H-bond acceptor features at extremities.

• OATP1A2 is a less selective transporter requiring clustered hydrophobic features and 1 H-bond acceptor feature.

• Database screening results suggest broad range of potential substrates.
Acknowledgment

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