Metabolomic and Genome-wide Association Studies Reveal Potential Endogenous Biomarkers for OATP1B1

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Transporter Mediated Drug-Drug Interactions Can Cause Toxicities

- **Cerivastatin** was withdrawn from market in 2001 because of many cases of rhabdomyolysis
- Half of the cases where patients using cerivastatin + gemfibrozil

Problem With Current Decision Tree To Determine Need for Transporter-Mediated Clinical DDI Study


If the IC$_{50}$ of the NME \leq 10 times unbound C$_{\text{max}}$ then Clinical DDI Study is needed

Limitation

Several False Positive Results of Transporter-Mediated DDI


Motivation: Measuring Biomarkers of Transporters To Determine The Need for Conducting Clinical DDI Study
Several OATP1B1 Biomarkers Were Identified Through Targeted Approaches

Bile acids, Bilirubin and glucuronide, Coproporphyrins I and III, Glycocholic acid, Taurocholic acid, Thyroxine

Motivation: Are There Other OATP1B1 Biomarkers That May Be A Better OATP1B1 Biomarkers (e.g. selective for OATP1B1)?

PMID: 19387419, 21245207, 22232210, 25813937, 26907622
Unbiased Approach To Discover Endogenous Metabolites of *SLCO1B1*

N > 7,000 Individuals Blood Sample*

500 Metabolites

Genomewide Chip

Genomewide Association Studies

Which metabolites associate with *SLCO1B1, 521T>C* (Val174Ala)?

*Shin et al., Nature Genetics, 2014*  
*Clin Pharmacol Ther. 2016 Nov;100(5):524-536*
20 Metabolites Associated with SNPs in the SLCO1B1 Locus with $P<5\times10^{-8}$

*glycochenodeoxycholate glucuronide

$P$-value = $5.5 \times 10^{-315}$

$P$-value = $1.6 \times 10^{-61}$

$P$-value = $3.4 \times 10^{-59}$

SLCO1B1, 521T>C (Val174Ala) cause increase level of the metabolites
Validate Metabolites as Biomarkers of OATP1B1: Using Pravastatin-CSA Interaction Study

Determine whether the metabolites also increase in patients treated with cyclosporine.

12 Potential Metabolites as Biomarkers of OATP1B1

**OATP1B1 Inhibitor, Cyclosporine, increased level of the metabolites**

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Placebo</th>
<th>CSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-11529</td>
<td>0.6</td>
<td>1.5</td>
<td>0.0017</td>
</tr>
<tr>
<td>TDA</td>
<td>0.9</td>
<td>1.2</td>
<td>0.0013</td>
</tr>
<tr>
<td>HDA</td>
<td>0.8</td>
<td>1.2</td>
<td>1x10^-5</td>
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</tbody>
</table>
Validate TDA and HDA as Substrates of OATP1B1

TDA and HDA Are Dicarboxylate Fatty Acids

TDA and HDA are not substrates and inhibitors of OATP1B3, OATP2B1 and OATP1A2

TDA: Tetradecanedioic Acid
HDA: Hexadecanedioic Acid

Summary and Future Studies

1. Unbiased approach with GWAS reveal novel metabolites which are substrates of OATP1B1.

1. These metabolites were also increased after administration of OATP1B1 inhibitor in human subjects.

2. In vitro studies confirmed that TDA and HDA metabolites are novel substrates of OATP1B1.

3. **Future studies:**
   - Determine whether TDA and HDA also increased upon administration of other OATP1B1, OAT1 and OAT3 inhibitors.
   - Determine the sensitivity, selectivity, other factors that could modulate these biomarkers.
Propose To Measure Biomarkers in Phase I Clinical Study

Phase I Study of NME

Measure Biomarker Before And After NME Administration

If Biomarker(s) Increases:
Consider Clinical DDI Study

If No Increase:
No Clinical DDI Study
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TDA and HDA Are Also Substrates of Other Organic Anion Transporters