Induction: Drug Transporters versus Enzymes

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Transporter Induction: How Do We Inform Our Labels?

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed
Transporter Induction: Conservative/Minimal Guidance Due to Lack of Data

- Difficult to predict in vivo transporter induction liability from in vitro data
- P450 induction parity is assumed
- **Ultimately, overly conservative recommendations are adopted**
  - May restrict patient access to still efficacious therapy
- How do we fill in the gaps?
  - We generate data!

### FDA

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>Avasimibe, carbamazepine, phenytoin, rifampin, St. John’s wort, tipranavir/ritonavir</td>
</tr>
<tr>
<td>BCRP</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Not known</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>Not known</td>
</tr>
</tbody>
</table>

### EMA

If there are inducers of the transporter marketed within the EU, an interaction study with such an inducer is recommended.

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FDA. Guidance for industry: drug interaction studies 2012;
EMA. Guideline on the investigation of drug interactions 2013.
Rifampin: a Prototypical In Vivo PXR Agonist

<table>
<thead>
<tr>
<th>Probe Drug Cassette</th>
<th>Dose</th>
<th>Abbreviation</th>
<th>P450/Transporter</th>
<th>Cassette Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate*</td>
<td>75 mg</td>
<td>DE</td>
<td>P-gp</td>
<td>1</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>20 mg</td>
<td>PRA</td>
<td>OATP</td>
<td>3</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg</td>
<td>ROS</td>
<td>OATP/BCRP</td>
<td>5</td>
</tr>
<tr>
<td><strong>Cocktail</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>2 mg</td>
<td>MDZ</td>
<td>CYP3A</td>
<td></td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500 mg</td>
<td>TOL</td>
<td>CYP2C9</td>
<td>7</td>
</tr>
<tr>
<td>Caffeine</td>
<td>200 mg</td>
<td>CAF</td>
<td>CYP1A2</td>
<td></td>
</tr>
</tbody>
</table>

*DE was analyzed as total dabigatran (TDAB), the sum of conjugated and unconjugated active species.

- Are transporters as inducible as P450s?
- Can transport induction be predicted from P450s?
### Rifampin: Multiple Dose Levels to Elicit Weak, Moderate, and Strong Induction

**Study Design**

<table>
<thead>
<tr>
<th>Days</th>
<th>9–18</th>
<th>19–26</th>
<th>27–36</th>
<th>37–44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>Cassette</td>
<td>Cassette</td>
<td>RIF 75 mg qd</td>
<td>Cassette</td>
</tr>
<tr>
<td>Cohort 1 n=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>RIF 2 mg qd</td>
<td>RIF 600 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 2 n=20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Are transporters as inducible as P450s?
- Can transport induction be predicted from P450s?
Probe Induction As a Function of RIF Dose

- $E_{\text{max}}$ and $ED_{50}$ values were estimated for each probe
- AUC Ratio: Weak (0.5–0.8), moderate (0.2–0.5) and strong (<0.2) induction

$ED_{50} = 66 \text{ mg}$

$E_{\text{max}} = 13$
Dabigatran Is Less Inducible Than Midazolam

- $ED_{50} = 66 \text{ mg}$
- $E_{\text{max}} = 13$

- $ED_{50} = 31 \text{ mg}$
- $E_{\text{max}} = 2.0$

- Are differences due to probe sensitivity?
After Accounting for Probe Sensitivity: P-gp is Less Inducible than CYP3A

- $E_{\text{max},c} = E_{\text{max}}$ corrected for (divided by) differences in probe sensitivity ($f_{m/t}$)
- Strong P-gp induction (>5-fold CL increase) is unlikely to be observed

<table>
<thead>
<tr>
<th></th>
<th>Individual observed</th>
<th>Mean observed</th>
<th>Corrected</th>
<th>Weak</th>
<th>Moderate</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDZ AUCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF Dose, mg</td>
<td>1 10 100 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED$_{50}$</td>
<td>= 66 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>= 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{\text{max},c}$</td>
<td>= 14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|          |                     |               |           |      |          |        |
| P-gp     |                     |               |           |      |          |        |
| TDAB AUCR |                     |               |           |      |          |        |
| RIF Dose, mg | 1 10 100 1000 |               |           |      |          |        |
| ED$_{50}$  | = 31 mg             |               |           |      |          |        |
| $E_{\text{max}}$ | = 2.0             |               |           |      |          |        |
| $E_{\text{max},c}$ | = 3.6             |               |           |      |          |        |
Similar to P-gp, Only Moderate Induction of OATP and CYP2C9 Is Observed

- PRA and ROS results suggest that OATP, but not BCRP, is induced
- RIF may elicit weak induction of CYP1A2 via PXR crosstalk or weak AHR agonism
How Do We Characterize and Interpret Relationships Between Probes?

Can we predict Probe Y induction based on Probe X?
Linear Relationships Only Occur When $E_{\text{max}}/ED_{50}$ Are Similar

- Combining $E_{\text{max}}/ED_{50}$ curves allows for evaluation of PXR agonism, independent of RIF
- Gray areas represent similar induction between probes
Nonlinear Relationships Occur When Induction Capacity is Different

- $E_{\text{max},x} > E_{\text{max},y}$
- $E_{50,x} = E_{50,y}$

- Combining $E_{\text{max}}/ED_{50}$ curves allows for evaluation of PXR agonism, independent of RIF

- Gray areas represent similar induction between probes
Induction of P-gp is One DDI Category Weaker Than CYP3A

<table>
<thead>
<tr>
<th>Induction of P-gp</th>
<th>Weaker Than CYP3A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean observed ± 90% CI</td>
<td>Corrected</td>
</tr>
</tbody>
</table>

- Weak
- Moderate
- Strong
Similarly, OATP and CYP2C9 Induction Is Always Less than CYP3A

- This relationship holds true even after accounting for probe sensitivity.
P-gp, OATP and CYP2C9 Demonstrate Induction DDI Classification Equivalence

- The relationships between PRA, ROS and TOL approximate the line of unity
- Parity suggests simplicity in clinical interpretation and prediction
What are the Clinical Implications?

- Doses of <600 mg RIF can be tailored to represent weak, moderate and strong PXR-dependent induction

  Standardize DDIs and facilitates extrapolation
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  Standardize DDIs and facilitates extrapolation

♦ Compared to CYP3A, strong induction of P-gp, OATP or CYP2C9 is unlikely to be elicited by potent PXR agonists

♦ Observed relationships should apply to other inducers
  This hypothesis is currently being tested with rifabutin and carbamazepine
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♦ Application of these results could provide for
  
  – More informed labeling recommendations
  
  – Decreased # of DDI studies via better leveraging of available data
Acknowledgments

We extend our thanks to the study subjects.

This study was funded by Gilead Sciences, Inc.
$E_{\text{max,c}}$ is P450/transporter (not probe) specific $f_{m/t}$ only attenuates (not limits) AUCR

\[
f_{m/t} = 0.5 \text{ and } f_{m/t} = 0.9
\]

**Inhibition:**
Max AUCR $= \frac{1}{(1-f_{m/t})}$

**Induction:**
Max AUCR $= \frac{1}{(1+E_{\text{max,c}} \cdot f_{m/t})}$

Max $CL_i$ change $= 1+E_{\text{max,c}}$