In Vitro to In Vivo Predictions of Drug Interactions: Going Beyond the I/Ki Ratio

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http://depts.washington.edu/pceut/faculty_research/
http://depts.washington.edu/uwscor/
Unadkat laboratory: Research Interests

• Elucidating mechanisms of transport and metabolism of antiviral and anticancer drugs in various tissues including the:
  • blood-brain barrier (P-gp transport and PET)
  • blood-placental barrier (P-gp, BCRP, and nucleoside transport)
  • intestinal and hepatic barriers (CYP metabolism, nucleoside, P-gp, and BCRP transport)
• Understanding the in vivo consequences of expression of transporters and metabolic enzymes on the PK and PD of antiviral/anticancer drugs including:
  • effect of pregnancy – Specialized Center Of Research or SCOR
  • metabolic and transport-based drug-drug interactions – Program Project grant on drug interactions
"In this laboratory we’re always pushing the envelope to the Max."
Predicting Competitive Metabolic In Vivo Drug Interactions

\[ \frac{\text{AUC}_{\text{inhibitor}}}{\text{AUC}} = 1 + \frac{[I]}{K_i} \]  

(1)

Assumptions

1) substrate conc. << Km
2) competitive interaction

e.g. effect of fluconazole on the \textit{in vivo} formation of sulfamethoxazole or dapsone hydroxylamine
**In-vitro to in-vivo correlation of inhibition of SMX hydroxylamine formation by fluconazole**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Fluconazole time-averaged concentration (µM)</th>
<th>% Inhibition in vivo</th>
<th>Predicted % Inhibition</th>
<th>In vivo Ki (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20.7</td>
<td>54</td>
<td>52</td>
<td>17.9</td>
</tr>
<tr>
<td>B</td>
<td>27.5</td>
<td>41</td>
<td>59</td>
<td>39.9</td>
</tr>
<tr>
<td>C</td>
<td>34.3</td>
<td>51</td>
<td>64</td>
<td>32.7</td>
</tr>
<tr>
<td>D</td>
<td>20.9</td>
<td>38</td>
<td>52</td>
<td>34.7</td>
</tr>
<tr>
<td><strong>Mean± SD</strong></td>
<td><strong>25.9± 6.5</strong></td>
<td><strong>46± 8</strong></td>
<td><strong>57± 9</strong></td>
<td><strong>31.3± 9.4</strong></td>
</tr>
</tbody>
</table>

In vitro estimates were 19µM for one-enzyme Michaelis-Menten models in human liver (HL) microsomes HL142 (competitive mechanism) and, 46µM for HL123 and 62µM for HL140 (non-competitive mechanism). * Time averaged concentration is the ratio of plasma AUC of fluconazole and Tau 0-12. Winter et al., Clin Pharmacol Ther 2004; 76:313–322
**In-vitro to in-vivo correlation of inhibition of Dapsone hydroxylamine formation by fluconazole**

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Fluconazole time-averaged concentration (µM)</th>
<th>% Inhibition <em>in vivo</em></th>
<th>Predicted % Inhibition</th>
<th><em>In vivo</em> Ki (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>60</td>
<td>61</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>59</td>
<td>55</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>34</td>
<td>65</td>
<td>60.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>25.9±5.2</td>
<td>51±15</td>
<td>60±5</td>
<td>30.6±25.7</td>
</tr>
</tbody>
</table>

The next frontier in predicting in vivo drug interactions

• Enzyme-based interactions
  – More complex interactions problematic – induction, inactivation, allostéricity

• Transporter-based interactions
  – which transporters are functionally important in the target tissue (e.g. intestine, liver, kidneys, BBB and blood-placental barriers)?
  – which transporters are important in the disposition of the victim drug and capable of being inhibited by the perpetrator?
  – Interspecies difference in expression of transporters
  – Can the I/Ki approach successfully predict in vivo interactions?
**Induction: in vitro to in vivo**

*Anti-HIV protease inhibitors*

- Potent CYP3A inhibitors but produce paradoxical interactions
- RIT – alprazolam interaction is significant when administered acutely but is abolished on chronic administration of RIT
- RIT induces CYP1A2 - 43% decrease in the AUC of theophylline.
- RIT induces CYP2C9 - decrease in the anticoagulant effect of warfarin and acenocoumarol.
- NEL induces CYP2C9 and/or CYP2C19 - increase in the oral clearance of phenytoin(17).
Induction: in vitro to in vivo

DRUG METABOLISM AND DISPOSITION Vol. 35, No. 10, 2007

Cytochrome P450 Enzymes and Transporters Induced by Anti-Human Immunodeficiency Virus Protease Inhibitors in Human Hepatocytes: Implications for Predicting Clinical Drug Interactions

Vaishali Dixit, Niresh Hariparsad, Fang Li, Pankaj Desai, Kenneth E. Thummel, and Jashvant D. Unadkat

NOTE:
• Induction by RIT, NEL or RIF
• phenotyping was done with microsomes, not with intact hepatocytes
Induction: in vitro to in vivo

In-Vivo CYP and P-gp activities in Healthy Volunteers after Multiple Dose administration of the anti-HIV protease inhibitors, Nelfinavir, Ritonavir, Rifampin

Brian Kirby, Ann C. Collier, Evan D. Kharasch, Dale Whittington, Kenneth E. Thummel, Jashvant D. Unadkat

ISSX meeting Puerto Rico, 2007

• Cocktail studies to phenotype CYP1A2, 2D6, 2C9, 3A4 (hepatic and intestinal) and P-gp

• Eliminated acute inhibition by withholding the protease inhibitors during phenotyping study.
**Induction in hepatocytes and in vivo: Rifampin, Ritonavir or Nelfinavir**

<table>
<thead>
<tr>
<th>Human Hepatocytes</th>
<th>In Vivo</th>
<th>( C_{\text{ave}} ) (( \mu \text{M} ))</th>
<th>( C_{\text{max}} ) (( \mu \text{M} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10 ( \mu \text{M} )</strong></td>
<td>Tolbutamide ( \text{CL}_{\text{oral}} )</td>
<td>OH-Tolbutamide ( \text{CL}_{\text{formation}} )</td>
<td>Total</td>
</tr>
<tr>
<td>Rifampin</td>
<td>3.3 ± 2.3</td>
<td>3.3 ± 2.2</td>
<td>2.9 ± 1.6</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>2.2 ± 1.2</td>
<td>2.0 ± 0.4</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>2.7 ± 1.6</td>
<td>1.5 ± 0.4</td>
<td>1.3 ± 0.3</td>
</tr>
</tbody>
</table>

Dixit V., *DMD* Epub July 16 2006

**Induction in hepatocytes and in vivo: Rifampin, Ritonavir or Nelfinavir**

<table>
<thead>
<tr>
<th>Human Hepatocytes</th>
<th>Fold Increase in CYP1A2 Activity</th>
<th>In Vivo Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caffeine CL&lt;sub&gt;Oral&lt;/sub&gt;</td>
<td>Paraxanthine CL&lt;sub&gt;formation&lt;/sub&gt;</td>
</tr>
<tr>
<td>10 µM</td>
<td>Caffeine</td>
<td>Total</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1.9 ± 0.4</td>
<td>2.5 ± 1.5</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>2.1 ± 0.3</td>
<td>3.6 ± 1.7</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>2.1 ± 0.2</td>
<td>2.6 ± 2.3</td>
</tr>
</tbody>
</table>

Dixit V., *DMD* Epub July 16 2006

JD Unadkat NEDMG Boston 2007

CYP3A Induction by Rifampin

- Rifampin ↑ midazolam GI intrinsic CL ~ 3.3-fold
- In hepatocytes rifampin (10 μM) induces CYP3A4 activity and mRNA by ~12 and 25-fold respectively.
- Are induction studies in hepatocytes representative of induction in the intestine? Tissue specific induction likely!

Induction in Intestinal Cells

Intestinal human colon adenocarcinoma cell line, LS180, is an excellent model to study PXR- but not CAR-mediated CYP3A4 and MDR1 induction: studies with Anti-HIV Protease Inhibitors

Anshul Gupta, Ganesh Mugundu, Pankaj B. Desai, Kenneth E. Thummel, Jashvant D. Unadkat

DMD: Manuscript In Revision
**Induction in LS180 cells**

*indicates p< 0.05 vs. DMSO*

- This induction can be knocked down by PXRsi
- Induction is PXR-mediated
- CAR is not expressed in LS180 cells
- Protease inhibitors do not activate CAR3.
Induction – Future Challenges

• Which *in vitro* systems are predictive of *in vivo* induction
• Quantitative Correlation
  – $EC_{50}$, $E_{\text{max}}$, $I_u$
• Is the steady state inducer concentration approach sufficient?
• Best model system to study intestinal CYP3A induction
  – LS180 cells?
• Inducer washout (*in vitro and in vivo*)
• Nuclear receptors involved
Inactivation: in vitro to in vivo correlation?

Model #1

\[
\frac{AUC'_{IV}}{AUC_{IV}} = \frac{1}{f_m + \frac{k_{inact} \times I_u}{1 + \frac{k_{deg} \times (K_I + I_u)}} + (1 - f_m) \lambda}
\]

- \(f_m\) - fraction metabolized
- \(k_{inact}\) – maximal inactivation rate
- \(k_{deg}\) – degradation rate of the enzyme
- \(K_I\) – conc. of the inactivator at 50% of \(k_{inact}\)

Model does not incorporate:
- induction
- blood flow
- competitive interaction

How does this model perform when the drugs (e.g. anti-HIV protease inhibitors) inactivate, induce and competitively inhibit CYP3A and other enzymes
Pharmacokinetics made simple
In vitro-in vivo prediction Model for IV administration (incorporating hepatic blood flow)

Model #2

\[
\frac{AUC_{IV}'}{AUC_{IV}} = \frac{1}{f_{\text{hep}} \left( \frac{1}{ER} - 1 \right) \left( \frac{\text{Comp}}{\text{Induc}} \right) \left( 1 + \frac{\lambda}{K_{\text{deg}}} \right) + 1 + (1 - f_{\text{hep}})}
\]

% Error Between Model 1 and 2
(Induction/comp. inhibition absent)

% Error Between Model 1 and 2
(Inactivation/comp. inhibition absent)
**Inactivation - HIV Protease Inhibitors Ritonavir or Nelfinavir**

### Average IV MDZ Plasma Profile

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Object</th>
<th>Observed AUC ratio in our study</th>
<th>Predicted AUC ratio (Model 1)#</th>
<th>Predicted AUC ratio Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>IV Midazolam</td>
<td>3.7 (95% CI: 3.0, 4.7)</td>
<td>9.2-9.8*</td>
<td>6.5 -6.6*</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>IV Midazolam</td>
<td>2.2 (95% CI: 1.5, 3.3)</td>
<td>4.6-7.9</td>
<td>3.3 -5.4</td>
</tr>
</tbody>
</table>

* Assuming t1/2 of CYP3A degradation of 9 and 44 h respectively

#Ernest C.S., *JPET* **312**:583-591 2005
Allosterism: R-Lansoprazole activation of Phenytoin hydroxylation (In-Vitro)

Fig. 2. Effect of racemic lansoprazole (○), R-lansoprazole (■), and S-lansoprazole (▲) on CYP2C9-catalyzed phenytoin 4-hydroxylation


Allosterism – Future Challenges

• Is allosterism consequential \textit{in vivo}?
• \textit{In vitro} methods to determine constants
• Quantitative prediction models yet to be developed
What are the challenges?

• Enzyme-based interactions
  – $I/K_i$ ratio for predicting *in vivo* competitive inhibition interactions has been largely successful
  – More complex interactions problematic – inactivation, induction, allosteric

• Transporter-based interactions
  – which transporters are functionally important in the tissue of interest (e.g intestine, liver, kidneys, BBB and blood-placental barriers)?
  – Identifying the transporters important in the disposition of the victim drug and capable of being inhibited by the perpetrator
  – Can the $I/K_i$ approach successfully predict *in vivo* interactions?
Can in vivo transporter-based interactions be predicted?

The role of transporters in drug interactions

Christopher J. Endres, Peng Hsiao, Francisco S. Chung, Jashvant D. Unadkat*

Department of Pharmaceutics, Box 357610, University of Washington, Seattle, WA 98195, United States
Quantitative Predictions of In Vivo P-gp Drug Interactions Based on In Vitro Data and Comparison With the Magnitude of Interaction Observed In Vivo

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Mechanism</th>
<th>Distribution</th>
<th>fu</th>
<th>K_i or IC_{50} (µM)</th>
<th>[I] (µM)</th>
<th>Unbound Drug (fu×[I])</th>
<th>Total Drug [I]</th>
<th>(\frac{Cl_{inhibit}}{Cl})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>CsA</td>
<td>brain distribution</td>
<td>0.02^a</td>
<td>0.46^b</td>
<td>2.9^c</td>
<td>0.88</td>
<td>0.14</td>
<td>0.56^c</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Itraconazole</td>
<td>oral Cl</td>
<td>0.002^d</td>
<td>0.5^e</td>
<td>0.3^f</td>
<td>1.0</td>
<td>0.63</td>
<td>0.67^f</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Quinidine</td>
<td>biliary Cl</td>
<td>0.13^d</td>
<td>2.2^g</td>
<td>4.5^h</td>
<td>0.79</td>
<td>0.33</td>
<td>0.65^h</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Verapamil</td>
<td>biliary Cl</td>
<td>0.1^d</td>
<td>2.2^l</td>
<td>0.13^m</td>
<td>0.98</td>
<td>0.94</td>
<td>0.57^m</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Itraconazole</td>
<td>biliary Cl</td>
<td>0.002^d</td>
<td>0.5^e</td>
<td>0.3^f</td>
<td>1.0</td>
<td>0.63</td>
<td>0.8^f</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ritonavir</td>
<td>oral Cl</td>
<td>0.01^d</td>
<td>3.8^i</td>
<td>6.2^j</td>
<td>0.98</td>
<td>0.38</td>
<td>0.70^j</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Ritonavir</td>
<td>oral Cl</td>
<td>0.01^d</td>
<td>3.8^i</td>
<td>8.2^k</td>
<td>0.98</td>
<td>0.32</td>
<td>0.58^k</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Quinidine</td>
<td>renal Cl</td>
<td>0.13^d</td>
<td>2.2^g</td>
<td>4.5^h</td>
<td>0.79</td>
<td>0.33</td>
<td>0.71^h</td>
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<td>0.01^d</td>
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<td>8.2^k</td>
<td>0.98</td>
<td>0.32</td>
<td>0.65^k</td>
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*Endres et al, Eu J Pharm. Sci 27:2006 501-07*
**P-glycoprotein based drug interaction at the BBB: CsA-verapamil**

MRI without CsA

11C-Verapamil

with CsA

11C-Verapamil

P-gp drug interactions at the human BBB

In vivo imaging protocol

• Healthy volunteers: $[^{11}\text{C}]-\text{verapamil}$ infused over 1 min ($\sim 0.2$ mCi/kg, $< 0.12$ $\mu$g/kg) -- brain PET images captured over 45 minutes
• P-gp inhibitor, cyclosporine (2.5 mg/kg/h), infused IV
• After $\sim 60$ min of cyclosporine infusion, $[^{11}\text{C}]-\text{verapamil}$ ($\sim 0.2$ mCi/kg, $< 0.12$ $\mu$g/kg) administered again, PET images captured for $\sim 45$ min.
• Arterial blood samples collected before and for 45 min after each $[^{11}\text{C}]-\text{verapamil}$ administration
**In vivo imaging protocol**

- Tissue blood flow measured before **each** $[^{11}C]$-verapamil study by IV administration of $[^{15}O]$ H$_2$O ($\leq 0.5$ mCi/kg or up to a maximum of 40 mCi).

- Tissue intravascular volume measured at the end of the study by $[^{11}C]$-CO (0.2 mCi/kg) inhalation.

- MRI images of the brain were taken for co-registration of PET data

- Blood and plasma samples counted and metabolite content determined by a rapid SPE/HPLC assay

- The ratios of AUC tissue : AUC blood were calculated. Compartmental modeling also conducted. Metabolism or plasma protein binding of verapamil or cerebral blood flow ($0.31 \pm 0.16$ vs. $0.29 \pm 0.16$ mL/min/g; $P = 0.10$) was not affected by CsA
### P-glycoprotein based drug interaction at the BBB: CsA-verapamil

Increase in $^{11}$C-radioactivity brain distribution in the presence of CsA

<table>
<thead>
<tr>
<th>Blood CsA</th>
<th>Ratio of $\text{AUC}<em>{\text{brain}}$:$\text{AUC}</em>{\text{blood}}$ (20 min)</th>
<th>Ratio of $\text{AUC}<em>{\text{brain}}$:$\text{AUC}</em>{\text{blood}}$ (45 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12*</td>
<td>μM</td>
<td>- CsA</td>
</tr>
<tr>
<td>Mean</td>
<td>2.8</td>
<td>0.42</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Max.</td>
<td>3.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Min.</td>
<td>2.1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

* 6 males, 6 females – no sig. difference between males and females

**Do the rodent models grossly overestimate P-gp based drug interactions at the human BBB?**

<table>
<thead>
<tr>
<th>Rodent PET study</th>
<th>Human PET +2.5 mg/kg/h CsA</th>
<th>20 Minutes post $^{11}$C-Verapamil</th>
<th>45 Minutes post $^{11}$C-Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 1 hour post $^{11}$C-verapamil</td>
<td>Brain : Blood (single point)</td>
<td>100% $\uparrow$</td>
<td>79% $\uparrow$</td>
</tr>
<tr>
<td>Mdr1a(-/-) mice</td>
<td>Brain : Blood (AUC)</td>
<td>87% $\uparrow$</td>
<td>88% $\uparrow$</td>
</tr>
<tr>
<td>Sprague Dawley Rat+50 mg/Kg CsA IV bolus</td>
<td>950% $\uparrow$</td>
<td>1,060% $\uparrow$</td>
<td></td>
</tr>
</tbody>
</table>
Concentration-dependent inhibition of P-gp at the rat BBB

EC50 = 7.2 µM (7%)
Emax = 1290% (7%)
γ = 3.8 (22%).

Hsiao et al J Pharmacol Exp Ther. 2006

JD Unadkat NEDMG Boston 2007
**P-glycoprotein based drug interaction at the BBB: CsA-verapamil**

**Comparison of human and rat data**

![Bar chart showing comparison of human and rat blood:brain ratios of total $^3$H-radioactivity with increasing CsA concentration.](chart)

- **Human**
- **Rat**

<table>
<thead>
<tr>
<th>Blood CsA concentration (µM)</th>
<th>Human</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>2.8</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>2.9</td>
<td>2.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

- **79%** Increase vs. control
- **75%**

*Hsiao et al J Pharmacol Exp Ther. 2006*
Can such In Vivo P-gp-based drug interactions be Predicted from In Vitro Studies?

In vivo unbound EC50 at the rat BBB 0.47 ± 0.004 µM
**P-glycoprotein based drug interaction at the BBB: CsA-verapamil**

Comparison of *in vitro* cell culture data and *in vivo* data in humans and rats

![Graph showing % increase in intracellular verapamil-bodipy accumulation and % increase in brain : blood \[^{11}C\] or \[^{3}H\]-radioactivity.](image)

- **LLCPK1-MDR1 Cell**
- **Rat Study**
- **Human PET study**

**EC50 values:**
- **CsA-verapamil**
  - EC50 0.47 ± 0.004 µM
  - EC50 0.6 ± 0.3 µM

_Hsiao et al DMD 2007 In Press_
**P-glycoprotein based drug interaction at the BBB: CsA-verapamil**

*Prediction from in vitro cell culture and in vivo rodent data*

![Graph showing brain: blood ratio of total [11C] or [3H]-radioactivity vs blood CsA concentration (μM)].

- Human
- Rat
- LLCPK1-MDR1 & Rat prediction for human

<table>
<thead>
<tr>
<th>Blood CsA concentration (μM)</th>
<th>Human</th>
<th>Rat</th>
<th>LLCPK1-MDR1 &amp; Rat prediction for human</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8</td>
<td>1.2</td>
<td>1.0</td>
<td>79%, n = 12</td>
</tr>
<tr>
<td>2.9</td>
<td>1.6</td>
<td>1.5</td>
<td>75%, n = 5</td>
</tr>
<tr>
<td>2.8</td>
<td>1.8</td>
<td>1.7</td>
<td>129%, n = 17</td>
</tr>
</tbody>
</table>

*Hsiao et al DMD In Press 2007*
**P-glycoprotein based drug interaction at the BBB and BPB: CsA-verapamil**

*Is Emax in the rodents and humans the same?*

---

Pre CsA | During CsA
---|---

- Brain
- Placenta
- Fetal Liver
- Liver
Inhibition of P-gp activity by CsA at the Non-Human-Primate BBB

$E_{\text{max}} = 3.97$
$EC_{50} = 18.7 \mu M$
Unbound $EC_{50} = 1 \mu M$
Inhibition of P-gp activity by CsA at the Human BBB

Prediction from in vitro cell culture and in vivo data in rodents and non-human primates

![Graph showing brain: blood ratio of total [14C] or [3H]-radioactivity vs. blood CsA concentration (µM) for different species and concentration levels.]
Predicting drug-drug interactions from in vitro to in vivo: challenges of the future

Summary

- Metabolic competitive interactions relatively well predicted – issue of which concentration of the inhibitor to use (transporter related?) remains – total or unbound?

- Induction – progress made in prediction, but models need to be refined to identify the inducer concentration to use in the intestine and liver. Need to take into consideration the dynamics of induction in intestine and liver.

- Models exist for predicting inactivation interaction, but validity needs to be widely tested and may need to be refined to incorporate induction.

- Cautious optimism in prediction of transporter-related competitive interactions. Many unanswered questions remain – which transporters are functionally important in various human tissues, the Ki of the inhibitors, the conc. of the inhibitor to use (total or unbound) etc.
ACKNOWLEDGMENTS

SMX/Dapsone work
Helen Winter and
The ACTG 283 team

Protease inhibitor studies
Pankaj Desai
Niresh Hariprasad
Fang Li
Vaishali Dixit
Anshul Gupta
Ganesh Mugundu
Brian Kirby
Ann Collier and her team
Kenneth Thummel
Evan Kharasch

NIH grants GM 54447, AI21766, MH 63641, P50HD44404, HD47892, GM032165, RR 00166

BBB studies
Unadkat team: Peng Hsiao, Lucy Sasongko,
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James Yang, Dale Whittington, Antoine Dupuis,
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