Evaluation of Drug-Drug Interactions
FDA Perspective

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Evolution of FDA Guidances Related to DDI Evaluation

• 1997 (In vitro)
• 1999 (In vivo)
• 2006 (In vitro and In vivo)
  – P-gp
• 2012 (In vitro and In vivo)
  – More transporters
  – Model-based DDI
• 2017 (under clearance)
  – Two separate guidances: in vitro and in vivo
  – Additional harmonization and coordination of prediction approaches between FDA, EMA, and PMDA.
Today’s theme....
What is in the forest?

• Forest
  – The big picture
  – Constant

• Trees
  – Key issues
  – Slow to change

• Weeds
  – Details
  – Subject to change
Objectives of Drug Interaction Program
THE FOREST

Determine the potential for clinically significant DDIs

Determine management strategies for clinically significant DDIs
Objectives of Drug Interaction Program
THE TREES

Determine:

- Whether the investigational drug alters the pharmacokinetics of other drugs
- Whether other drugs alter the pharmacokinetics of the investigational drug
- The magnitude of changes in pharmacokinetic parameters
- The clinical significance of the observed or expected DDIs
- The appropriate management strategies for clinically significant DDIs
Evaluation of DDIs- INTO THE WEEDS

Inhibitors
Substrates
Inducers
Cut-off values (in vitro to in vivo)
Equations
Specific transporters
and much more!!
How do we navigate the process?

- Clinical relevance
- Communication
- Science
- Strategy
Major PK Drug Interaction Mechanisms

Inhibition or Induction of Metabolizing Enzymes and/or Transporters
Useful resources

Clinical Drug-Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access

Dinko Rekic, Kellie S. Reynolds, Ping Zhao, Lei Zhang, Kenta Yoshida, Madhav Sachar, Micheline Piquette Miller, Shiew-Mei Huang, Issam Zineh


In Vitro-In Vivo Extrapolation of Metabolism and Transporter-Mediated Drug-Drug Interactions- Overview of Basic Prediction Methods

Kenta Yoshida, Ping Zhao, Lei Zhang, Darrell R. Abernethy, Dinko Rekic, Kellie S. Reynolds, Aleksandra Galetin, Shiew-Mei Huang

Useful resources

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm

www.fda.gov
In vitro evaluation
Metabolizing Enzyme-Mediated Drug Interactions

- Determine if NME is a substrate of metabolizing enzymes
- Determine if NME is an inhibitor of metabolizing enzymes
- Determine if NME is an inducer of metabolizing enzymes

- Key enzymes of interest- CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5

Modified from Lei Zhang
Determine if NME is a Substrate of Metabolizing Enzymes

• Reaction phenotyping: two commonly used methods
  – (1) chemicals or antibodies as specific enzyme inhibitors
  – (2) individual human recombinant enzymes
  – Both methods should be performed to identify the specific enzyme(s) responsible for a drug’s metabolism.
  – A list of probe substrates, inhibitors, and inducers for in vitro evaluation can be found at the [FDA’s Web site on Drug Development and Drug Interactions](https://www.fda.gov).

• Significant contribution: enzyme is responsible for > 25% of the drug’s elimination (vitro phenotyping; human PK)
  – In vivo evaluation is needed

Modified from Lei Zhang
Determine if NME is an Inhibitor of Metabolizing Enzymes

Reversible inhibition - the basic model - two common equations (additional equations for time dependent inhibition)

- $\frac{Imax}{Ki} \geq 0.1$ (FDA recommendation in 2012 draft guidance and MHLW recommendation in 2014 draft guideline)
  - $Imax$: maximum total (unbound + bound) inhibitor concentrations in plasma

- $\frac{Imax,u}{Ki} \geq 0.02$ (EMA recommendation in 2013 guideline)
  - $Imax,u$: maximum unbound inhibitor concentrations in plasma

Recent analysis suggests these criteria performed similarly in predicting reported DDIs


Note: also consider inhibition in the gut for CYP3A
Determine if NME is an Inducer of Metabolizing Enzymes

- Evaluate CYP1A2, CYP2B6, and CYP3A4/5 initially.
- If no induction of CYP3A4/5 is observed, evaluating the induction potential of CYP2C enzymes is not necessary because both CYP3A4/5 and CYP2C enzymes are induced via activation of the pregnane X receptor (PXR).
- If the drug induces CYP3A4/5, evaluate the drug’s potential to induce CYP2C enzymes.

- P-gp and certain Phase II enzymes (e.g., UGT) may be co-induced with CYP3A.

Modified from Lei Zhang
Determine if NME is an Inducer of Metabolizing Enzymes

• Fold-change method
  – Examine the fold-change in CYP enzyme mRNA levels when incubated with the investigational drug
  – Use a cutoff determined from known positive and negative controls to calibrate the system.

• Correlation method
  – Predicted positive criteria defined by known positive (e.g., known inducers of the same enzyme) and negative controls

• Basic kinetic model


Modified from Lei Zhang
Determine if NME is an **Inhibitor** or **Inducer** of Metabolizing Enzymes

- **Mechanistic, static**
- **Mechanistic, dynamic (including PBPK)**

**Determine in vitro parameters**

**Basic Model**

- Mechanistic, static
- Mechanistic, dynamic (including PBPK)

**In vivo DDI study**

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CYP inhibitor (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A)

CYP inducer (CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A)

From Lei Zhang
Transporter-Mediated Drug Interactions

- Determine if NME is a substrate of transporters
- Determine if NME is an inhibitor of transporters
- Determine if NME is an inducer of transporters*

*in vitro transporter induction is not recommended; evaluate P-gp in vivo if CYP3A induction is observed
Investigational Drug as a Substrate of Transporters

*Does the drug level depend on a given transporter?*

- **In vitro assessments**—Which transporters?
  - Route of elimination
  - Rate-limiting step
  - Other (physicochemical properties and structure)

- **In vivo transporter DDI evaluation may be relevant**
  - P-gp and BCRP
    - Knowledge about tissue penetration is critical (safety or efficacy reasons)
    - Intestinal absorption may lead to variability in drug response
  - OATP1B1 and OATP1B3
    - Hepatic uptake is needed for effect
    - Hepatic elimination is significant
  - OAT1, OAT3, OCT2, MATE
    - Active renal secretion or concerns about renal toxicity

From Lei Zhang
In vitro assessment—Basic Models for Predicting NME as Transporter Inhibitor
Is relevant inhibitor concentrations \([I]/\text{in vitro IC}_{50} \geq \text{cutoff value?}
If yes, inhibition is possible

<table>
<thead>
<tr>
<th>Relevant Inhibitor Concentration</th>
<th>(P)-gp, BCRP:</th>
<th>Gut concentration</th>
<th>([I]_2 = \frac{\text{Dose}}{250 \text{ mL}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(OATP1B:)</td>
<td>Free hepatic inlet concentration</td>
<td>(I_{\text{u,in,max}} = f_{u,p} \times \left(\frac{(C_{\text{max}} + (F_a F_g \times k_a \times \text{Dose}))}{Q_h / R_B}\right))</td>
<td></td>
</tr>
<tr>
<td>(OAT/OCT:)</td>
<td>Free systemic concentration</td>
<td>(I_u = C_{\text{max},u})</td>
<td></td>
</tr>
<tr>
<td>(MATE:)</td>
<td>Free systemic concentration</td>
<td>(I_u = C_{\text{max},u})</td>
<td></td>
</tr>
</tbody>
</table>

(as a “surrogate” and a different cutoff may be warranted)

Modified from Lei Zhang
### P-gp: Comparison of prediction performance with different cut-off criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>EMA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>PMDA&amp; FDA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>I₂/IC₅₀ alone (#1)</th>
<th>I₂/IC₅₀ alone (#2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I₁u/IC₅₀ ≥0.02 OR I₂/IC₅₀ ≥10</td>
<td>I₁/IC₅₀ ≥0.1 OR I₂/IC₅₀ ≥10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN (#)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>FP (#)</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>7</td>
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<td>TN (#)</td>
<td>16</td>
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<td>21</td>
</tr>
<tr>
<td>TP (#)</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>61</td>
<td>61</td>
<td>63</td>
<td>71</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>73</td>
<td>73</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Likelihood ratio positive (LR+)</td>
<td>1.77</td>
<td>1.77</td>
<td>1.94</td>
<td>2.72</td>
</tr>
<tr>
<td>Likelihood ratio negative (LR-)</td>
<td>0.420</td>
<td>0.420</td>
<td>0.395</td>
<td>0.427</td>
</tr>
</tbody>
</table>

<sup>1</sup> 2012 EMA DDI guideline; <sup>2</sup> 2014 PMDA draft DDI guideline and 2012 FDA draft DDI guidance.  I₂=gut concentration.

All methods showed similar results. When considering I₂/IC₅₀ alone, I₂/IC₅₀ ≥10 (#1) showed a slightly better numerical result with the lowest likelihood of false negative predictions as compared to other criteria (lowest LR-);
## OATP1B1: Comparison of prediction performance with different methods and cutoff criteria

<table>
<thead>
<tr>
<th>Method</th>
<th>1: ( \frac{I_{\text{max}}}{K_i} \geq 0.1 )</th>
<th>2: ( \frac{I_{u,\text{max}}}{K_i} \geq 0.02 )</th>
<th>3: ( R \geq 1.04 ) (EMA)(^1)</th>
<th>4: ( R \geq 1.1 )</th>
<th>5: ( R \geq 1.25 ) (PMDA)(^2)</th>
<th>6: ( \frac{I_{\text{max}}}{K_i} \geq 0.1 ) and ( R \geq 1.25 ) (FDA 2-step)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FN</td>
<td>12</td>
<td>17</td>
<td>8</td>
<td>12</td>
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<td>FP</td>
<td>27</td>
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<td>22</td>
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<td>22</td>
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<td>35</td>
<td>44</td>
<td>40</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>PPV</td>
<td>60%</td>
<td>69%</td>
<td>57%</td>
<td>65%</td>
<td>70%</td>
<td>73%</td>
</tr>
<tr>
<td>NPV</td>
<td>70%</td>
<td>70%</td>
<td>73%</td>
<td>73%</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>LR+</td>
<td>1.57</td>
<td>2.31</td>
<td>1.41</td>
<td>1.92</td>
<td>2.45</td>
<td>2.85</td>
</tr>
<tr>
<td>LR-</td>
<td>0.453</td>
<td>0.461</td>
<td>0.385</td>
<td>0.385</td>
<td>0.407</td>
<td>0.428</td>
</tr>
</tbody>
</table>

\(^1\) 2012 EMA DDI guideline; \(^2\) 2014 PMDA draft DDI guideline; \(^3\) 2012 FDA draft DDI guidance.

R\( \geq 1.04 \) (Criterion #3) and R\( \geq 1.1 \) (Criterion #4) had the lowest likelihood of false negative predictions as compared to other criteria (lowest LR-). Criterion #4 appears to be reasonable with a lower false positive prediction (higher LR+).
# OAT1/OAT3: Comparison of prediction performance with different cut-off criteria

<table>
<thead>
<tr>
<th>C&lt;sub&gt;max,u&lt;/sub&gt;/ IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>All substrates (59 DDI Studies)</th>
<th>OAT1-specific substrates (13 DDI Studies)</th>
<th>OAT3-specific substrate (32 DDI Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMA ≥0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FDA ≥0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PMDA ≥0.25&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>FN</td>
<td>0</td>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
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</tr>
<tr>
<td>TN</td>
<td>17</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>PPV</td>
<td>52%</td>
<td>64%</td>
<td>72%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>96%</td>
<td>97%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Criteria suggested in 2012 EMA DDI guideline.  
<sup>b</sup> Criteria suggested in 2012 FDA draft DDI guidance.  
<sup>c</sup> Criteria suggested in 2014 PMDA draft DDI guideline.  
<sup>d</sup> The false negative prediction using 0.1 (also 0.25) as a cut-off was for a study between etoricoxib and methotrexate (MTX) where AUC of MTX increased by 27% with etoricoxib. In another study conducted by the same authors, AUC of MTX was only increased by 4.9% with etoricoxib (J Clin Pharmacol. 49(10):1202-1209, 2009). The 27% increase may reflect cross study variability because the study design between the 2 studies was very similar.

From Lei Zhang
# OCT2/MATEs: Comparison of prediction performance of different cut-off criteria

<table>
<thead>
<tr>
<th></th>
<th>EMA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ITC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>PMDA&lt;sup&gt;c&lt;/sup&gt;</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8</th>
<th>#9</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max,u}}/\text{IC}_{50} )</td>
<td>oct2 ( \geq 0.02 ) \text{ OR } oct2 ( \geq 0.1 ) \text{ OR } oct2 ( \geq 0.25 ) \text{ OR } OCT2 \geq 0.02 \text{ OR } OCT2 \geq 0.1 \text{ OR } OCT2 \geq 0.25 \text{ OR } \text{ MATEs} \geq 0.02 \text{ OR } \text{ MATEs} \geq 0.1 \text{ OR } \text{ MATEs} \geq 0.25</td>
<td>\text{ MATEs} \geq 0.02 \text{ OR } \text{ MATEs} \geq 0.1 \text{ OR } \text{ MATEs} \geq 0.25</td>
<td>\text{ MATEs} \geq 0.02 \text{ OR } \text{ MATEs} \geq 0.1 \text{ OR } \text{ MATEs} \geq 0.25</td>
<td>\text{ MATEs} \geq 0.02 \text{ OR } \text{ MATEs} \geq 0.1 \text{ OR } \text{ MATEs} \geq 0.25</td>
<td>\text{ MATEs} \geq 0.02 \text{ OR } \text{ MATEs} \geq 0.1</td>
<td>\text{ MATEs} \geq 0.25</td>
<td>\text{ FN}</td>
<td>\text{ FP}</td>
<td>\text{ TP}</td>
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<td></td>
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<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0</td>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>FP</td>
<td>10</td>
<td>9</td>
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<td>5</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>PPV</td>
<td>64%</td>
<td>64%</td>
<td>75%</td>
<td>64%</td>
<td>64%</td>
<td>64%</td>
<td>73%</td>
<td>67%</td>
<td>65%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>75%</td>
<td>77%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>82%</td>
<td>100%</td>
<td>70%</td>
</tr>
</tbody>
</table>

<sup>a</sup> A cut-off of 0.02 applied to unbound \( C_{\text{max,u}}/\text{IC}_{50} \) for OCT2 or for MATEs was suggested in 2012 EMA DDI guideline;  
<sup>b</sup> A cut-off of 0.1 for OCT2 or for MATEs was suggested in ITC paper (Hillgren KM, et. al, *Clin Pharm Ther*, 94(1):52-63, 2013). As of note, 2012 FDA’s draft DDI guidance has a cutoff of 0.1 only for OCT2;  
<sup>c</sup> A cut-off of 0.25 was suggested in 2014 PMDA draft DDI guideline.  
<sup>d</sup> Among these false negatives, two DDI records were between ranolazine (inhibitor, different doses) and metformin (substrate) (Zack J, *Clin Pharm in Drug Develop*, 4(2) 121–129, 2015). The other DDI study was between isavuconazole and metformin (Clinical Pharmacology and Biopharmaceutical review for NDA 207-500 from Drugs@FDA).  


From Lei Zhang
In vivo evaluation
Types of DDI Studies

- Prospective and Retrospective
- Index studies (studies with index perpetrators and index substrates)
- Concomitant use studies
- In silico studies
Prospective and Retrospective Studies

• Prospective (stand-alone or nested)
  – specifically designed to detect DDI
  – DDI objective
  – often stand alone

• Retrospective
  – no DDI objective in protocol
  – results may be difficult to interpret
Index studies

• Use perpetrators or substrates with well defined properties (level of inhibition, induction, and metabolic pathway)
  – Investigate drug as substrate: Use index inhibitors and inducers (strong = worst case)
  – Investigate drug as inhibitor or inducer: Use index substrate (sensitive = worst case)
• Extrapolate to other substrates and perpetrators
• May not be clinically relevant for intended patient population
Concomitant use studies

- Drugs relevant to intended population
- Potential to interact (mechanism)
- May be difficult to extrapolate to other drug pairs (or groups)
In silico DDI studies

• PBPK models can replace some in vivo studies
• Verify model by comparing clinical and PBPK evaluation: effect of strong perpetrator
• Use model to predict effect of moderate or weak perpetrator
• Some labeling examples
  – impact of weak and moderate CYP2D6 and 3A4 inhibitors
  – impact of weak and moderate CYP3A4 inducers
In silico DDI studies- example

• Sonidegib capsules (Odomzo)- trt of locally advanced basal cell carcinoma

• CYP3A substrate

• In vivo studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  – with keto- AUC increased 2.2x; Cmax increased 1.5x
  – with rif- AUC decreased 72%; Cmax decreased 54%

From Odomzo® (sonidegib) approved prescribing information
In silico DDI studies- example

Sonidegib, continued

• In vivo studies were conducted with strong CYP3A inhibitor (ketoconazole) and strong CYP3A inducer (rifampin)
  – with keto- AUC increased 2.2x; Cmax increased 1.5x
  – with rif- AUC decreased 72%; Cmax decreased 54%

• PBPK
  – with moderate inhibitor (erythromycin)- AUC would increase 1.8x (14d) and 2.8x (4 months)
  – with moderate inducer (efavirenz)- AUC would decrease 56% (14d) and 69% (4 months)

From Odomzo® (sonidegib) approved prescribing information
Investigational drug as a CYP-substrate

• Start with a strong index inhibitor and strong index inducer (worst case)
  – If no clinically significant interaction- STOP!!
  – If clinically significant interaction
    • evaluate moderate inhibitor or inducer
    • consider relevant concomitant med studies

• Evaluation of polymorphic enzyme- PM vs EM evaluation may be appropriate
Index inhibitors and inducers

• Based on OCP systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates.

• Strong index inhibitors:
  – CYP1A2: fluvoxamine
  – CYP2C8: gemfibrozil, clopidogrel
  – CYP2C9: fluconazole (moderate inhibitor)
  – CYP2C19: fluvoxamine
  – CYP2D6: fluoxetine, paroxetine
  – CYP3A: clarithromycin, itraconazole

• Strong index inducers:
  – CYP1A2: none identified
  – CYP2B6: rifampin (moderate inducer)
  – CYP2C8: rifampin (moderate inducer)
  – CYP2C9: rifampin (moderate inducer)
  – CYP2C19: rifampin
  – CYP3A: rifampin, phenytoin

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm
(FDA Drug Development and Drug Interaction page)
Investigational drug as an inhibitor or inducer of CYP enzymes

• Start with a sensitive index substrate (worst case)
  – If no clinically significant interaction- STOP!!
  – If clinically significant interaction
    • consider relevant concomitant med studies
  – Substrates may not be specific for one enzyme and may also be substrate for transporters.
    • Consider selectivity of investigational drug for the enzyme under study
**Sensitive index substrates**

- Based on OCP systematic review of clinical DDI studies between FDA recommended index perpetrators and sensitive substrates.

- Sensitive index substrates:
  - CYP1A2: caffeine, tizanidine
  - CYP2C8: repaglinide
  - CYP2C9: warfarin, tolbutamide (both are moderately sensitive substrates)
  - CYP2C19: omeprazole
  - CYP2D6: desipramine, dextromethorphan, nebivolol
  - CYP3A: midazolam, triazolam

[http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm](http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm)

(FDA Drug Development and Drug Interaction page)
Investigational drug as substrate of transporters

- In vivo transporter DDI evaluation may be relevant
  - Pgp and BCRP
    - knowledge about tissue penetration is critical (safety or efficacy reasons)
    - intestinal absorption may lead to variability in drug response
  - OATP1B1 and OATP1B3
    - hepatic uptake is needed for effect
    - hepatic elimination is significant
  - OAT1, OAT3, OCT2, MATE
    - active renal secretion or concerns about renal toxicity
Investigational drug as a substrate of transporters

• Conduct DDI study with a known inhibitor
• Select inhibitor based on the goal of the study
• Usually select inhibitor based on likelihood of co-administration (lack of index inhibitors)
• Possible worst case evaluation
  – Cyclosporine inhibits multiple transporters (Pgp, OATP, BCRP)
  – If positive, use inhibitor that is more selective
• Another approach- begin with more selective inhibitors
• Studies are not easily extrapolated to other drugs
Investigational drug as an inhibitor or inducer of transporters

**Inhibition** -
- Determine whether studies are relevant
  - likely concomitant medications and their safety profile
- Select substrate for DDI study
  - Most transporter substrates are not selective
  - Can select based on likely concomitant drugs

**Induction** - discuss need for study (case by case)
Study Results and Interpretation

• Out of the weeds....observe the trees.....
Classifying drug as a CYP inhibitor or inducer

• Base on the effect on index CYP substrate
  – strong inhibitor increases the AUC ≥ 5-fold
  – moderate inhibitor increases the AUC ≥ 2- to < 5-fold
  – weak inhibitor increases the AUC ≥ 1.25- to < 2-fold

  – strong inducer decreases the AUC ≥ 80 percent
  – moderate inducer decreases the AUC ≥ 50 to < 80 percent
  – weak inducer decreases the AUC ≥ 20 to < 50 percent
Interpreting study results

The question - Is there a clinically significant increase or decrease in substrate exposure in the presence of the perpetrator?

• Determine no-effect boundaries
  – Preferred approach - use knowledge of the concentration-response relationship
  – In the absence of concentration-response information, use 80-125 default 90% CI
  – Interpretation of effect of drug as a perpetrator requires knowledge about other drugs
DDI Management Strategies

• When: co-administration of drugs leads to concerns greater than those present when the drugs are administered alone

• Some considerations:
  – distribution of DDI data (proportion of patients expected to have too high or too low concentrations)
  – anticipated duration of concomitant use
  – medical need for the drugs, including alternatives
  – availability of monitoring parameters (PK or PD)
DDI Management Strategies

• Possible instructions for management
  – change dose level or frequency
  – stagger administration
  – prohibit concomitant use
  – monitor concentration, lab results, signs, or symptoms (and adjust dose)

• Not helpful- “use with caution”
A concluding view of the forest

When evaluating the DDI potential of a drug...

• Keep the big picture in mind
  – determine whether there are clinically significant DDIs

• Address key issues
  – evaluate specific interactions and their magnitude; interpret significance

• Details are relevant
  – the key to scientific and clinical relevance
  – be aware of regulatory documents and current literature
Acknowledgements

(Collaborators in the journey through the DDI forest)
Lei Zhang
Shiew-Mei Huang
Dinko Rekic*
Ping Zhao*
Kenta Yoshida*
Joseph Grillo
Darrell Abernethy
Issam Zineh

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