Physiologically Based Pharmacokinetic Modeling of Imatinib Using Simcyp
Deshun Lu1, Kundan Kunapareddy2, Edward Simpson3,4, Nimita Dave1, Sara Quinney4,5,6
1Division of Clinical Pharmacology, 2School of Informatics and Computing; 3Department of Bioinformatics; 4Center for Computational Biology
and Bioinformatics; 5Department of OB/GYN; 6ICTSI Disease and Therapeutic Response Modeling Program, Indiana University School of
Medicine, Indianapolis, Indiana

**Objectives:** We utilized PBPK modeling and mouse tissue distribution data to predict human brain and liver concentrations of imatinib, and used
this model to predict the effect of CYP3A inhibition.

**Methods:** A mouse full-body PBPK model for imatinib was developed using Simcyp v15 Animal (Certara®). Partition coefficients (Kp) were
derived from published plasma, liver, and brain concentrations1. A full-body PBPK model for imatinib was developed using Simcyp V15. Liver
and brain Kp’s were adapted from the mouse model; default values were used for other distribution parameters. Clearance was calculated based
upon published *in vitro* intrinsic clearance2. The effect of ketoconazole, a CYP3A inhibitor, on imatinib disposition was predicted using the default
ketoconazole inhibitor profile3.

**Results:** We estimated Kp values of 2.8 and 0.1 for liver and brain based upon mouse data. Using these values, the predicted:observed plasma
AUC ratio following a 200 mg oral dose of imatinib mesylate in humans was 1.16 (Table 1), with AUC in liver and brain estimated as 2.9x and
0.1x plasma AUC, respectively. Ketoconazole was predicted to increase imatinib exposure 30% in plasma and 33% in liver and brain.

**Conclusions:** The imatinib PBPK model predicted plasma concentration in good agreement with experimental data. Uptake to liver and brain
were predicted based on mouse data. The model was able to adequately predict the effect of ketoconazole on imatinib plasma disposition. Continued
development of the model, including incorporation active transport, will improve the prediction of brain tumor oncentrations of imatinib.

**References:**
2. Filppula et al. Drug Metab Dispos 41:50 (2013)

**Table 1:** Predicted and observed changes in imatinib (200 mg PO) plasma AUC and Cmax when coadministered with ketoconazole (400 mg PO).

<table>
<thead>
<tr>
<th></th>
<th>Predicted</th>
<th></th>
<th>Observed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- KTZ</td>
<td>+ KTZ</td>
<td>Ratio</td>
<td>- KTZ</td>
</tr>
<tr>
<td><strong>AUC (mg/L*h)</strong></td>
<td>16.5</td>
<td>22.0</td>
<td>1.3</td>
<td>14.2</td>
</tr>
<tr>
<td><strong>Cmax (mg/L)</strong></td>
<td>0.91</td>
<td>1.0</td>
<td>1.1</td>
<td>0.94</td>
</tr>
</tbody>
</table>