Using a physiological based pharmacokinetic model to evaluate the influence of covariates on sunitinib exposure

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Sunitinib

- Anti-tumour Tyrosine Kinase Inhibitor
- mRCC, GISTs and pancreatic tumours
- Toxicities limit dosing to 50 mg OD for 4 weeks followed by 2 off weeks
- Css trough < 50 ng/mL associated with decreased efficacy\(^1\)
- Css trough > 100 ng/mL associated with increased toxicity
- Substantial between individual pharmacokinetic variability
- Largely unknown which physiological variables drive the variability in concentrations?

Aim

• Develop a full physiological based pharmacokinetic (full-PBPK) model to evaluate the influence of covariates on sunitinib exposure
Methods

- Full PBPK model built in Simcyp 15.1®
- Profile built based on *in vitro* and physiochemical data
- Trained against single dose healthy volunteer data
- Validated against population exposure data
- Used to assess the potential impact of age, gender, ethnicity, disease states
- Used in a virtual study (phase imaginary study) to identifying the most promising precision medicine markers
SimCYP

Input

Mathematical Model

Simulated PK and Population Data

Mechanistic Population Model

Mechanistic Drug Model

Physiochemical, *In Vitro* and *In Vivo* Data

Mechanistic Population PBPK Model

Pharmacokinetics and Population Output
Sunitinib Profile

**Physiochemical Properties**

- Molecular weight: 398.47
- $\log P_{o:w}$: 2.6
- $pK_a$: 11.3

**Protein Binding**

- B/P: 0.623
- $F_{up}$: 0.050

**Absorption (ADAM model)**

- PSA: 77.2
- HBD: 3
- $P_{eff,man}$ ($10^{-4}$ cm/s): 0.590

**Distribution (full PB-PK model)**

- $V_{ss}$ (L/kg): 27.57

**Metabolism ($CL_{int}$; $\mu$L/min/mg)**

- CYP2C8: 1.57
- CYP3A4: 106.01

**Transport ($CL_{int}$; $\mu$L/min)**

- Intestinal Efflux (P-gp): 37.34
- Passive diffusion ($CL_{PD}$): 0.1
- Hepatic Efflux (P-gp): 37.34
## Single Dose Simulations

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Simulated Cohort</th>
<th>mean AUC ± 95% CI (ng/mL/hr)</th>
<th>% Difference of the Mean</th>
<th>Known influence</th>
<th>Concordance with literature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (50 mg)</td>
<td>1201 ± 142</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>1037 ± 137</td>
<td>-13.7</td>
<td></td>
<td>Females have a 50% higher exposure than males</td>
<td>✓</td>
</tr>
<tr>
<td>Female</td>
<td>1571 ± 172</td>
<td>30.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbid Obesity</td>
<td>1785 ± 222</td>
<td>48.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geriatric</td>
<td>2252 ± 310</td>
<td>147.0</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
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<tr>
<td>Japanese</td>
<td>1605 ± 245</td>
<td>33.6</td>
<td></td>
<td>Increased exposure in Asians</td>
<td>✓</td>
</tr>
<tr>
<td>Chinese</td>
<td>2423 ± 330</td>
<td>101.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Patients</td>
<td>1483 ± 300</td>
<td>23.5</td>
<td></td>
<td>▲ Inter and intra-individual variability</td>
<td>✓</td>
</tr>
<tr>
<td>Child-Pugh C</td>
<td>6985 ± 1191</td>
<td>481.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR &lt; 30 ml/min</td>
<td>1694 ± 165</td>
<td>41.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>25 mg</td>
<td>601 ± 71</td>
<td></td>
<td></td>
<td>Dose proportional in normal dose range</td>
<td>✓</td>
</tr>
<tr>
<td>37.5 mg</td>
<td>901 ± 106</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62.5 mg</td>
<td>1501 ± 178</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exposure Variability Between Populations

Physiology
- Morbidly Obese
- Control
- Males
- Females
- Geriatric

Ethnicity
- Control
- Japanese
- Chinese

Disease
- GFR < 30
- Control
- Cancer
- Cirrhosis

Kichenadasse et al. 2017 Unpublished data
Clinical significance of the differences between the populations?

Physiological variables driving concentration variability?

Use simCYP to conduct a virtual study (a phase imaginary study)
Phase imaginary studies

- *Phase i* trials use mechanistic models (physiological models) to simulate virtual population outcomes from which the factors driving individual differences can be determined

Virtual trials in virtual patients

*Is this how we will accelerate progress in personalised treatments?*
Indentify the Model Variables that Predict Exposure to Sunitinib

• Simulated steady state concentrations of sunitinib in 1000 virtual cancer patients within the simCYP database

• The characteristic of these virtual patients were then assessed for their predictive performance on a sunitinibCss trough < 50 ng/mL

• Characteristics Tested:
  1. Baseline physiological variables (Age, Sex, Weight, BMI > 35, BSA, GFR)
  2. Baseline enzyme abundances (CYP1A2, CYP2C9, CYP2C8, CYP3A4, Pgp, BCRP abundances)
Baseline Physiological Variable Model

- Model developed through the backwards deletion (AIC) of the significant physiological on univariate analysis
- Model included – Age, Weight and BSA

Sensitivity (True positive rate) = Rate of correctly predicting concentrations below 50 ng/ml

1 - Specificity (True negative rate) = Rate of correctly predicting concentration above 50 ng/ml
Baseline Physiological + Enzyme Abundance Model

• Model developed through the backwards deletion (AIC) of the enzyme abundances significant on univariate analysis

• Model included – Baseline physiological variables and log of CYP3A4, P-GP & BCRP abundances

Sensitivity (True positive rate) = Rate of correct predicting concentrations below 50 ng/ml

1 - Specificity (True negative rate) = Rate of correctly predicting concentration above 50 ng/ml

AUC 0.86
Accuracy 0.77
Conclusion

• Developed a sunitinib PBPK model consistent with reported exposures
• Demonstrated concentration variability for under studied populations
• Via a virtual trial, demonstrated that enzyme abundances appear to drive pharmacokinetic variability
Acknowledgments:
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Ganessan Kichenadasse

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NBCF
Ramaciotti Foundation
NHMRC
Flinders Foundation
Thank you:

Questions/Discussion
<table>
<thead>
<tr>
<th>Logistic Regression Variable</th>
<th>OR</th>
<th>2.50%</th>
<th>97.50%</th>
<th>P - value</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.966</td>
<td>0.953</td>
<td>0.979</td>
<td>&lt;0.001</td>
<td>0.588</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>1.240</td>
<td>0.966</td>
<td>1.593</td>
<td>0.091</td>
<td>0.527</td>
</tr>
<tr>
<td>Weight</td>
<td>1.015</td>
<td>1.006</td>
<td>1.024</td>
<td>0.002</td>
<td>0.559</td>
</tr>
<tr>
<td>BMI &gt; 35</td>
<td>0.738</td>
<td>0.339</td>
<td>1.60</td>
<td>0.437</td>
<td>0.504</td>
</tr>
<tr>
<td>BSA</td>
<td>4.009</td>
<td>2.063</td>
<td>7.88</td>
<td>&lt;0.001</td>
<td>0.572</td>
</tr>
<tr>
<td>Cardiac.Output</td>
<td>1.011</td>
<td>1.007</td>
<td>1.015</td>
<td>&lt;0.001</td>
<td>0.594</td>
</tr>
<tr>
<td>log(GFR)</td>
<td>1.973</td>
<td>1.272</td>
<td>3.077</td>
<td>0.003</td>
<td>0.554</td>
</tr>
<tr>
<td>log(CYP1A2)</td>
<td>1.394</td>
<td>1.162</td>
<td>1.678</td>
<td>&lt;0.001</td>
<td>0.563</td>
</tr>
<tr>
<td>log(CYP2C9)</td>
<td>1.48</td>
<td>1.223</td>
<td>1.797</td>
<td>&lt;0.001</td>
<td>0.576</td>
</tr>
<tr>
<td>log(CYP2C8)</td>
<td>1.371</td>
<td>1.162</td>
<td>1.621</td>
<td>&lt;0.001</td>
<td>0.56</td>
</tr>
<tr>
<td>log(CYP3A4)</td>
<td>6.086</td>
<td>4.804</td>
<td>7.825</td>
<td>&lt;0.001</td>
<td>0.815</td>
</tr>
<tr>
<td>log(P.gp)</td>
<td>2.8</td>
<td>2.232</td>
<td>3.541</td>
<td>&lt;0.001</td>
<td>0.665</td>
</tr>
<tr>
<td>log(BCRP)</td>
<td>2.232</td>
<td>1.708</td>
<td>2.935</td>
<td>&lt;0.001</td>
<td>0.606</td>
</tr>
</tbody>
</table>
Cancer Population Exposure

Pop PK Model = Khosravan et al. 2016 (Population Pharmacokinetic/Pharmacodynamic Modeling of Sunitinib by Dosing Schedule in Patients with Advanced Renal Cell Carcinoma or Gastrointestinal Stromal Tumor)