Translational systems pharmacology for acquisition of knowledge and prediction of drug pharmacokinetics across patient populations

Markus Krauß

PAGE meeting - 09.06.2017
Translation of knowledge as a key challenge in clinical development

Thiel et al., Drug discov. today: disease models, 2017
Physiologically-based pharmacokinetic (PBPK) models enable patient stratification and individualization.

Kuepfer et al., CPT:PSP, 2014

Individualized, patient–specific PBPK models
Bayesian population PBPK combines prior knowledge and information from experimental data.
A translational learning workflow for prediction of drug pharmacokinetics

Reference drug
(ADME, PhysChem)

Pathophysiology

Population

Healthy

Diseased

Learning

Reference

Drug

Candidate

Learning

Prediction

Population pharmacokinetics

Krauss et al., npj Syst. Biol & Appl., 2017
A translational learning workflow for prediction of drug pharmacokinetics

<table>
<thead>
<tr>
<th>Population</th>
<th>Drug</th>
<th>Reference</th>
<th>Learning</th>
<th>Translation</th>
<th>Candidate</th>
<th>Learning</th>
<th>Translation</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td></td>
<td>Reference</td>
<td>Reference drug (ADME, PhysChem)</td>
<td>Physiology</td>
<td>Candidate drug (ADME, PhysChem)</td>
<td>Physiology</td>
<td>Population pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Diseased</td>
<td></td>
<td>Reference</td>
<td>Reference drug (ADME, PhysChem)</td>
<td>Pathophysiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Krauss et al., npj Syst. Biol & Appl., 2017
A specifically-designed drug cocktail probing study provides experimental data

Kuepfer et al, CPT: PSP, 2014
The same experimental setting was considered for two different cohorts of individuals

![Diagram showing healthy and diseased cohort](image)

<table>
<thead>
<tr>
<th></th>
<th>Healthy cohort</th>
<th>Diseased cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals</td>
<td>103 healthy volunteers</td>
<td>79 obese patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Male [#]</th>
<th>age [years]</th>
<th>body weight [kg]</th>
<th>body height [cm]</th>
<th>body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median</td>
<td>[min max]</td>
<td>median</td>
<td>[min max]</td>
</tr>
<tr>
<td>healthy individuals</td>
<td>103</td>
<td>54</td>
<td>28</td>
<td>74.5</td>
</tr>
<tr>
<td>diseased patients</td>
<td>79</td>
<td>33</td>
<td>45</td>
<td>138</td>
</tr>
</tbody>
</table>
Application of the developed workflow as a proof of concept study

Krauss et al., npj Syst. Biol. & Appl., 2017

1. **Learning**
   - Reference drug (ADME, PhysChem)
   - Physiology

2. **Learning**
   - Candidate drug (ADME, PhysChem)
   - Physiology

3. **Learning**
   - Reference drug (ADME, PhysChem)
   - Pathophysiology

4. **Prediction**
   - Population pharmacokinetics
Individualized PK simulations as a key result of each Bayesian PBPK learning step

Krauss et al., npj Syst. Biol. & Appl., 2017
Individualized PK simulations as a key result of each Bayesian PBPK learning step
Individualized PK simulations as a key result of each Bayesian PBPK learning step

Krauss et al., npj Syst. Biol. & Appl., 2017
Starting from mean patient models…

Prior
- midazolam, healthy
- torasemide, healthy
- midazolam, diseased
… model individualization strongly improves model accuracy

Prior
- midazolam, healthy
- torasemide, healthy
- midazolam, diseased

Posterior
- midazolam, healthy
- torasemide, healthy
- midazolam, diseased

Krauss et al., npj Syst. Biol. & Appl., 2017
Qualified models on a population level…

- midazolam, healthy
- torasemide, healthy
- midazolam, diseased

Krauss et al., npj Syst. Biol & Appl., 2017
... allow translation and prediction of population PK

- midazolam, healthy
- torasemide, healthy
- midazolam, diseased
- torasemide, diseased

Krauss et al., npj Syst. Biol & Appl., 2017
Use of PBPK models allow to assess knowledge acquisition on a parameter level…

Information gain (relative entropy)

Krauss et al., npj Syst. Biol & Appl., 2017
... and demonstrates potential for model-based pathophysiological characterization

Specific hepatic clearance correlates well with changes in gene expression

Krauss et al., npj Syst. Biol. & Appl., 2017
The presented prototypical workflow could provide a basis for iterative use in pharmaceutical development.

Krauss et al., npj Syst. Biol. & Appl., 2017
Acknowledgements

Lars Kuepfer
Linus Goerlitz
Jan-F. Schlender
Christian Müller
Andreas Schuppert
Michael Block
Rolf Burghaus
Jörg Lippert

Mario Brosch
Jochen Hampe
Reinhold Kerb
Matthias Schwab

Witigo v. Schönfels

Translational learning from clinical studies predicts drug pharmacokinetics across patient populations

Markus Krauss, Ute Hofmann, Clemens Schafmayer, Svitlana Igel, Jan Schlender, Christian Mueller, Mario Brosch, Witigo von Schoenfels, Wiebke Erhart, Andreas Schuppert, Michael Block, Elke Schaeffeler, Gabriele Boehmer, Linus Goerlitz, Jan Hoecker, Joerg Lippert, Reinhold Kerb, Jochen Hampe, Lars Kuepfer, and Matthias Schwab

www.nature.com/npjsba
Thank you!
Open Systems Pharmacology Suite
PK-Sim®, MoBi® & toolboxes now open source freeware under GNU Public License v2.0

• Fully transparent open source development
• Open development of scientific content and qualification approaches
• Repositories for open PBPK and Systems Pharmacology models

Join us!
Download and use the software!
Contribute bug reports, new feature proposals, PBPK & Systems Pharmacology models, code…