

Qualification of the Open Systems Pharmacology PBPK modeling Platform for simulation of transporter Drug-Drug-Interactions

Nina Hanke¹, Pavel Balazki², Stephan Schaller², Jose David Gomez-Mantilla¹, Thomas Wendl³, Thorsten Lehr⁴, Ibrahim Ince^{1,*}

¹ Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, ² ESQlabs GmbH, Germany, ³ Bayer AG, Germany, ⁴ Saarland University, Germany, *ibrahim.ince@Boehringer-Ingelheim.com



Objective

Our objective is to establish and qualify a network of transporter DDI substrate and perpetrator PBPK models for the OSP software (OSPS). An overview of currently available models for different transporter DDIs using an automated PBPK platform qualification of PK-Sim® PBPK M&S tool will be presented, and exemplary transporter DDI assessments using rosuvastatin [1] and verapamil [2] will be highlighted.

Introduction

- The success of applications of physiologically based pharmacokinetic (PBPK) modeling in drug development has led regulatory agencies to demand rigorous demonstration of the predictive capability of a PBPK platform for a specific intended application purpose, such as drug-drug interaction (DDI). Although the PBPK of CYP-mediated DDI is well established in the Open Systems Pharmacology (OSP) software [3], transporter-mediated DDI PBPK is less evaluated.
- Therefore, connected via the DDI Focus Group of the free open source and open science GitHub landscape of Open Systems Pharmacology, PBPK experts from Bayer, Saarland University, Boehringer Ingelheim and ESQlabs are collaborating to establish state of the art qualification packages for transporter substrates.



Transporter DDI Network

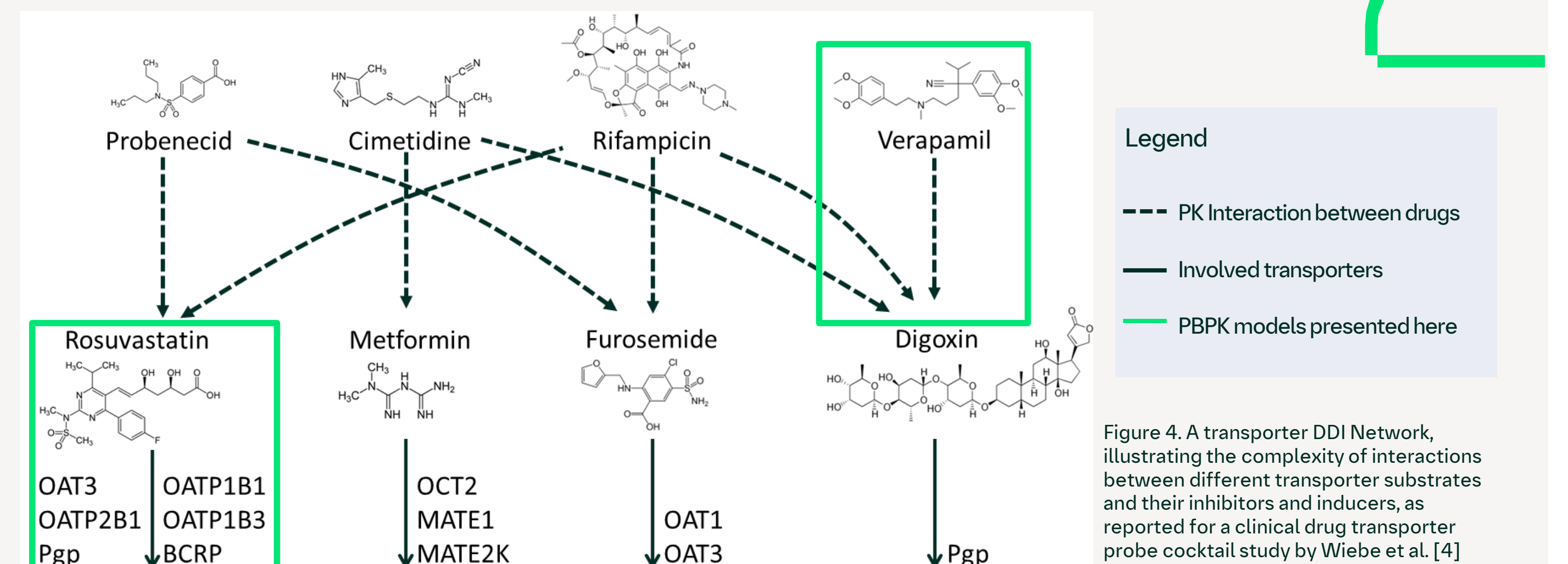


Figure 4. A transporter DDI Network, illustrating the complexity of interactions between different transporter substrates and their inhibitors and inducers, as reported for a clinical drug transporter probe cocktail study by Wiebe et al. [4]

Methods

- Both rosuvastatin and verapamil models were developed using the open-source PBPK software PK-Sim® as part of the OSPS.
- The rosuvastatin PBPK model has been developed and DDI studies with previously established models for rifampicin (inhibition of OATP2B1, Pgp, BCRP, OATP1B1/1B3 and CYP2C9), gemfibrozil (inhibition of OATP1B1/1B3, OAT3 and CYP2C9) and probenecid (inhibition of OATP1B1/1B3 and OAT3) as perpetrator drugs were included to qualify the model using in vitro inhibition constants without adjustments (figures 1 and 2).
- The verapamil PBPK model was developed and validated as a perpetrator for Pgp using digoxin as victim drug (figure 3).

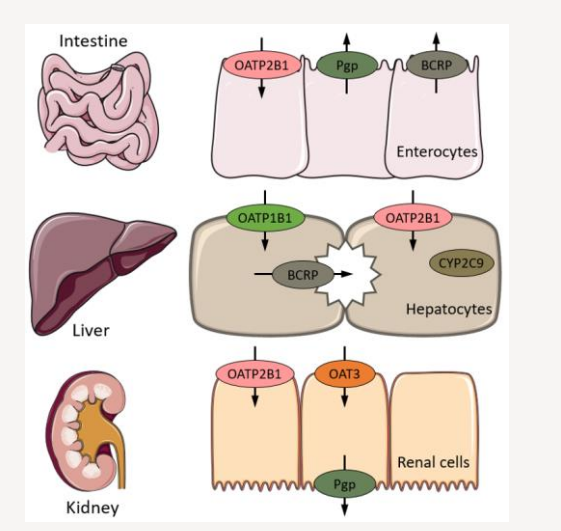
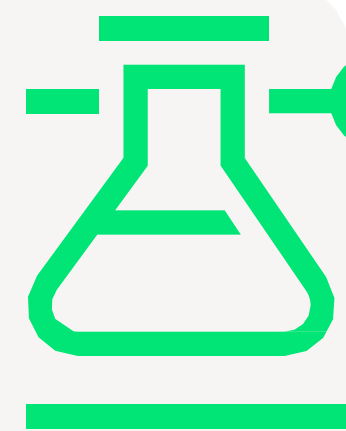


Figure 1. Rosuvastatin transport and metabolism. Main sites of action of the transporters and enzymes implemented to model the ADME of rosuvastatin. [1]

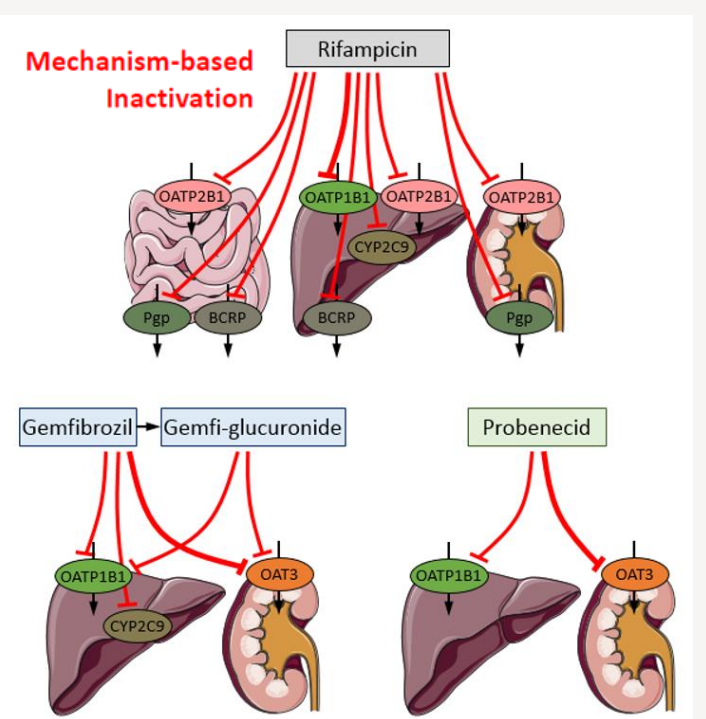
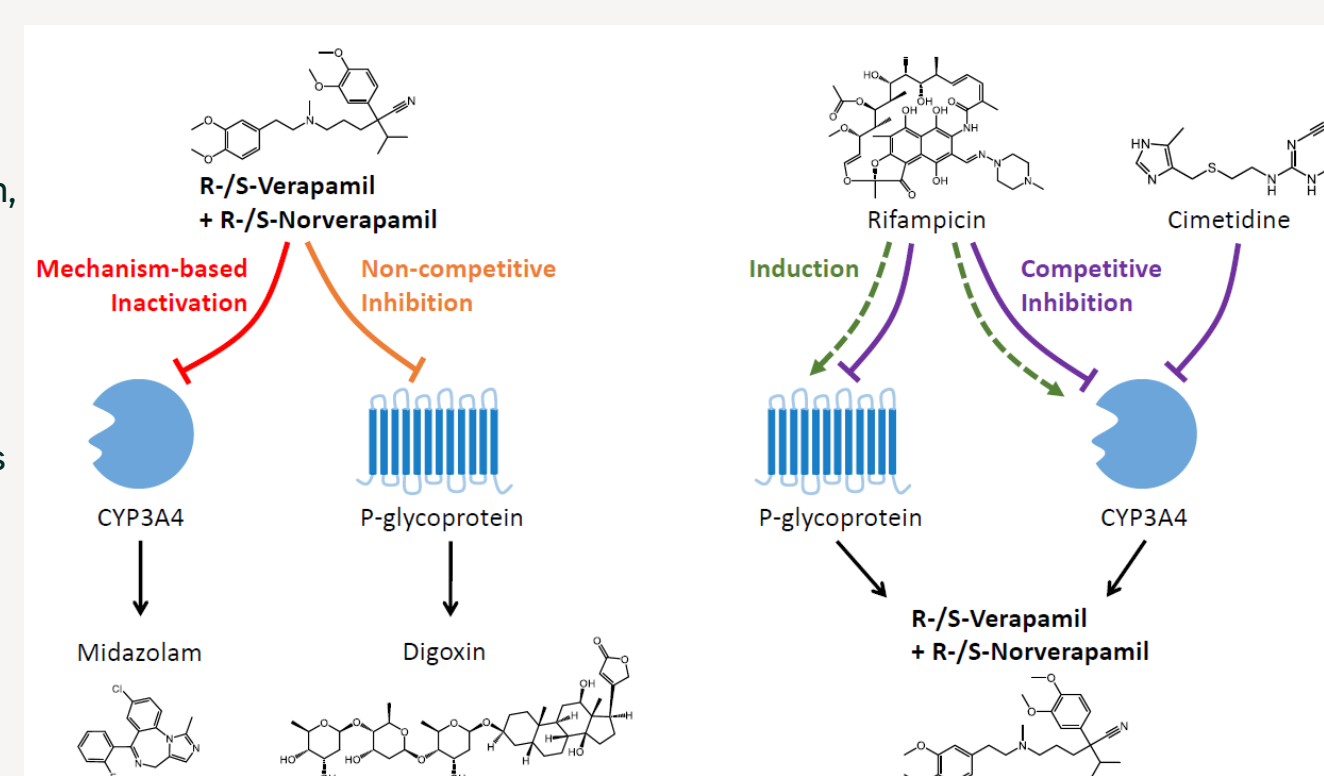


Figure 2. Schematic illustration of the rosuvastatin transporters and metabolic enzymes inhibited by rifampicin, gemfibrozil, gemfibrozil glucuronide and probenecid [1]

Figure 3. Schematic illustration of the modeled DDIs. Verapamil acts as the perpetrator in the DDIs with midazolam and digoxin, whereas it is the victim drug in the DDIs with rifampicin and cimetidine. Metabolism and transport of the victim drugs are shown as black arrows. Mechanism-based inactivation is shown as a red line, non-competitive inhibition as an orange line, competitive inhibition as purple lines, and induction as green dashed arrows.



Results



- Currently, the qualification of several transporter substrate PBPK models is ongoing, to assess DDIs using PK-Sim®.
- The processes implemented to describe the rosuvastatin pharmacokinetics and DDIs were active uptake by OATP2B1, OATP1B1/OATP1B3 and OAT3, active efflux by BCRP and Pgp, metabolism by CYP2C9 and passive glomerular filtration. The good prediction of DDIs was demonstrated by simulated rosuvastatin plasma profiles, DDI AUClast ratios (AUClast during DDI/AUClast without co-administration) and DDI Cmax ratios (Cmax during DDI/Cmax without co-administration), with all simulated DDI ratios within 1.6-fold of the observed values [1]. Result figures shown under “Model & DDI Predictions”.
- For the verapamil PBPK model, mechanism-based inactivation of CYP3A4 and non-competitive inhibition of Pgp by the verapamil and norverapamil enantiomers were incorporated based on in vitro literature data, and DDI performance was demonstrated by prediction of DDIs with midazolam, digoxin, rifampicin (not shown here), and cimetidine, with 21 out of 22 predicted DDI AUC ratios or Ctrough ratios within 1.5-fold of the observed values [2]. Result figures shown under “Model & DDI Predictions”.

Conclusions

Exemplary DDI models for transporter substrates or transporter perpetrator drugs, such as rosuvastatin and verapamil, were built and qualified for the prediction of their pharmacokinetics and transporter-mediated DDIs and will be part of the automated qualification framework.

The transporter DDI PBPK models demonstrate good model performance and are freely available in the Open Systems Pharmacology model repository [6], to support future investigations of DDI studies during model-informed drug discovery and development.

More qualifications of transporter packages are under development and will be freely available, thanks to the support of different contributors from pharmaceutical companies and universities.

Abbreviations

OSP, Open Systems Pharmacology; OSPS, Open Systems Pharmacology Suite; PBPK, Physiologically based pharmacokinetic; DDI, as drug-drug interaction; M&S, Modeling and Simulation; OATP, Organic anion transporting polypeptide; Pgp, permeability glycoprotein; BCRP, Breast Cancer Resistance Protein; CYP2C9, Cytochrome P450 2C19, AUClast, Area under the curve from the time of dosing to the time of the last observation; Cmax, Maximum concentration; Ctrough, through concentration.

References

- [1] Hanke et al. Physiologically Based Pharmacokinetic Modeling of Rosuvastatin to Predict Transporter-Mediated Drug-Drug Interactions. Pharm Res. 2021; 38(10): 1645–1661; <https://doi.org/10.1007/s11095-021-03109-6>
- [2] Hanke et al. A Mechanistic, Enantioselective, Physiologically Based Pharmacokinetic Model of Verapamil and Norverapamil, Built and Evaluated for Drug-Drug Interaction Studies. Pharmaceutics. 2020; 12(6): 556; <https://doi.org/10.3390/pharmaceutics12060556>
- [3] Open Systems Pharmacology. OSP DDI. Qualification_CYP3A4 v11.2 [Internet]. [cited 2024 Feb 26]. Available from: https://github.com/Open-Systems-Pharmacology/OSP-QualificationReports/tree/v11.2/DDI_Qualification_CYP3A4

- [4] Wiebe et al. Validation of a Drug Transporter Probe Cocktail Using the Prototypical Inhibitors Rifampin, Probenecid, Verapamil, and Cimetidine. Clin Pharmacokinet. 2020 Dec;59(12):1627–1639.
- [5] Guest et al. Critique of the two-fold measure of prediction success for ratios: Application for the assessment of drug-drug interactions. Drug Metab. Dispos. 2011, 39, 170–173.
- [6] Open Systems Pharmacology OSP PBPK substance model library - Release Version 11.2 [Internet]. [cited 2023 Sep 21]. Available from: <https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/releases/tag/v11.2>

