Development of network-based PBPK models to enhance the confidence in drug-drug interaction predictions

Revathi Chapa, Suvarchala Avvari, Saima Subhani, Inger Darling, Grace Fraczkiewicz, Tarang Vora, Haiying Zhou, Jeffry Adiwidjaja, Joyce Macwan, John Chung, Ke Xue Szeto, Jeremy Perrier, Rebecca Graves, Celeste Vallejo, Jasmina Novakovic, Peter Kilford, Xinyuan Zhang, Michael B. Bolger, Viera Lukacova

Simulations Plus Inc.

peter.kilford@simulations-plus.com

Introduction: The use of physiologically based pharmacokinetic (PBPK) modeling in regulatory submissions has advanced significantly over time. Among the various applications of PBPK, drug-drug interactions (DDIs) are the most commonly addressed. For DDI predictions involving an investigational drug, probe substrates and modulator drugs (either inhibitors or inducers) are crucial. Inadequate models for probe substrates or modulator drugs can result in the rejection of PBPK analysis in a new drug application. To enhance the reliability of PBPK DDI predictions supporting regulatory decision-making, network-based PBPK models for probe substrates and modulators have been developed.

Objectives: The goal of this study is to develop and cross-validate network-based PBPK models for probe substrates and perpetrators, specifically targeting the CYP3A4, CYP2C8/OATP, and P-gp pathways.

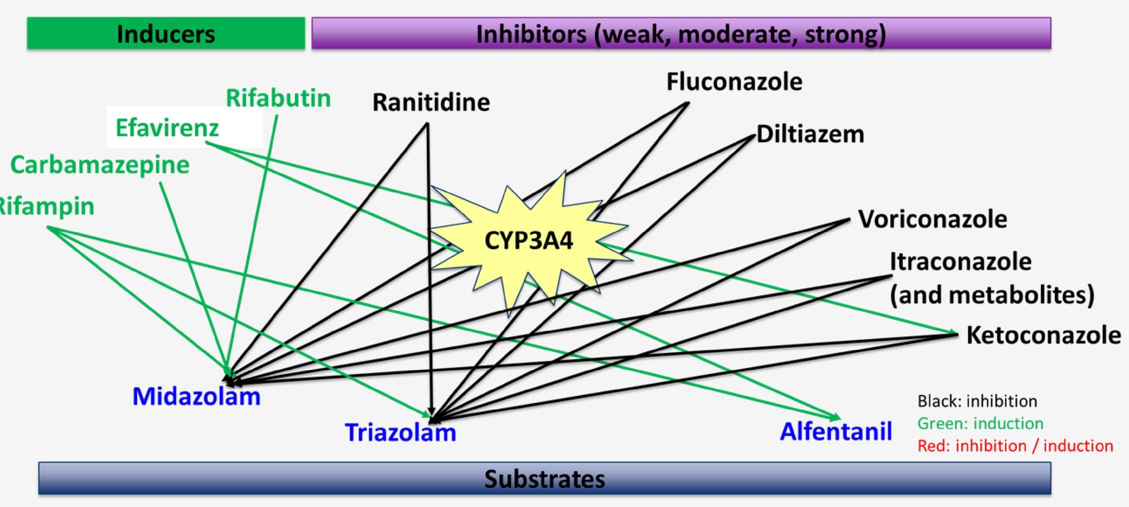
Methods: Fully mechanistic PBPK models were developed in GastroPlus® Version 9 or above (Simulations Plus, Inc.) for the CYP3A4, CYP2C8/OATP, and P-gp pathways. For the CYP3A4 network, models were developed for sensitive substrates (midazolam, triazolam, and alfentanil), strong inhibitors (ketoconazole, itraconazole, and voriconazole, clarithromycin), moderate substrates (atorvastatin, clarithromycin) and moderate inhibitors (diltiazem, fluconazole), weak inhibitors (ranitidine), strong inducers (rifampin, carbamazepine), and moderate inducers (efavirenz and rifabutin). For the CYP2C8/OATP network, models were developed for rosiglitazone (a substrate of CYP2C8, CYP2C9, and CYP3A4), repaglinide (a substrate of CYP2C8, CYP3A4, and OATP1B1), pravastatin (a substrate of OATP1B1), rosuvastatin (a substrate of OATP1B1/3, BCRP), gemfibrozil and its glucuronide metabolite (an OATP1B1/3 inhibitor and a strong CYP2C8 inhibitor), and rifampicin (an OATP1B1/3 inhibitor). For the P-gp network, models were developed for P-gp substrates (fexofenadine, digoxin, and edoxaban), P-gp inhibitors (itraconazole, quinidine), and P-gp inhibitors/inducers (rifampin and efavirenz). Each mechanistic PBPK model incorporates ACAT™ (Advanced Compartmental Absorption and Transit) and whole-body PBPK models. The models were verified against published PK data (including multiple formulations when available) and DDI studies.

Results: PBPK models were developed for the CYP3A4 (13 compounds), CYP2C8/OATP (6 compounds), and P-gp (7 compounds) pathways and were fully verified against published PK data from multiple studies and formulations, when available. The predicted PK parameters generally fall within 2-fold of the corresponding observed values. Additionally, the PBPK models were further cross validated against multiple published DDI studies for the same interaction pathways. The predicted DDI magnitudes typically fall within the established Guest criteria limits.

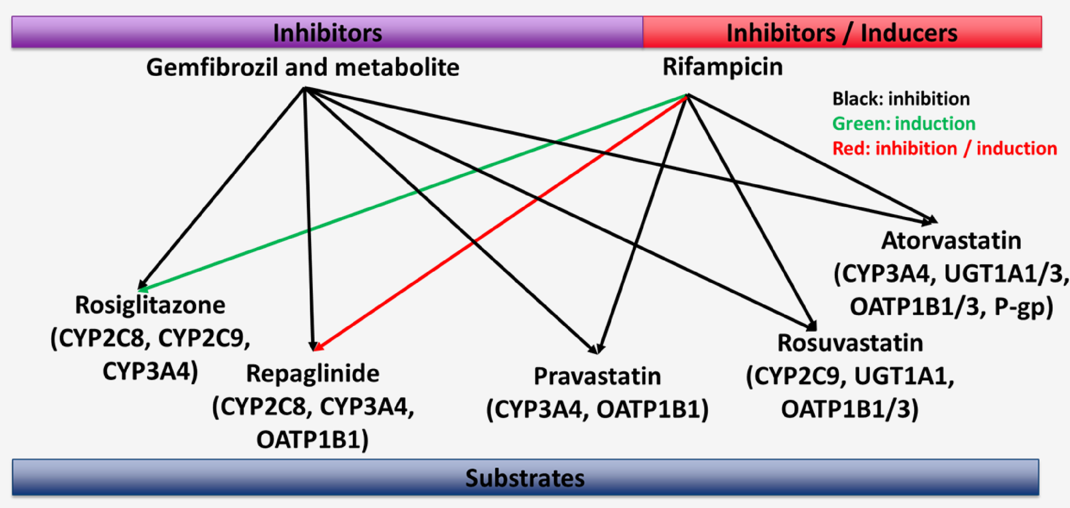
Conclusion: Probe substrate and modulator models are developed for the CYP3A4, CYP2C8/OATP, and P-gp interaction networks. For each network, multiple PBPK models were created and cross-validated, ensuring acceptable model performance. Each PBPK model consisted of a mechanistic ACAT and full-body distribution model, which allowed mechanistic interactions at tissue level (such as in the gastrointestinal tract, liver, and kidney). In addition, these models offered flexibility to incorporate relevant pathways for future updates requiring minimal or no changes in model structure. The development and validation of network-based PBPK models will strengthen confidence in DDI predictions, supporting both drug development and regulatory decision-making.

THE PBPK NETWORKS FOR DDI EVALUATION

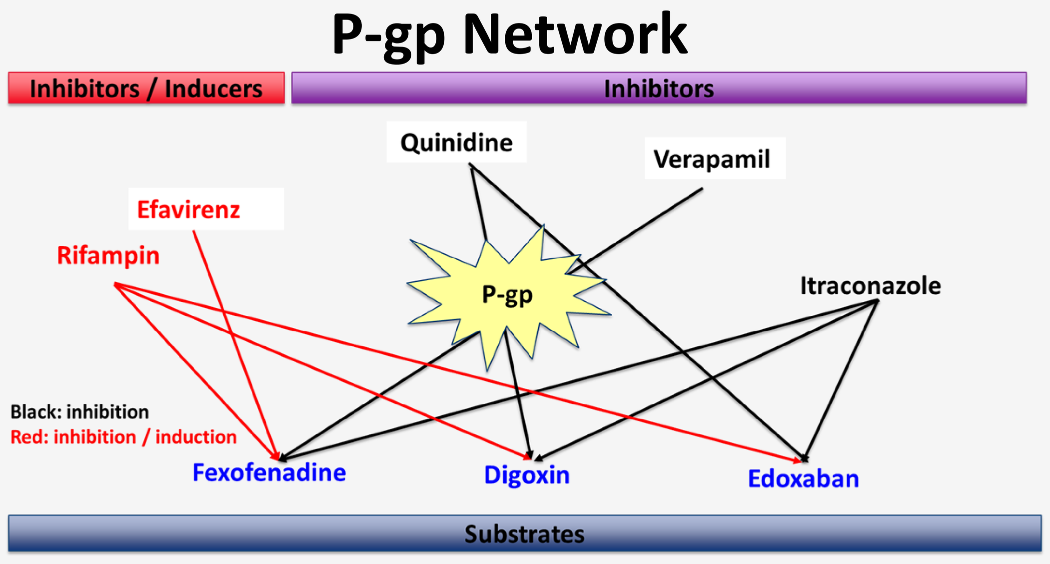
CYP3A4 Network



CYP2C8 – OATP Network



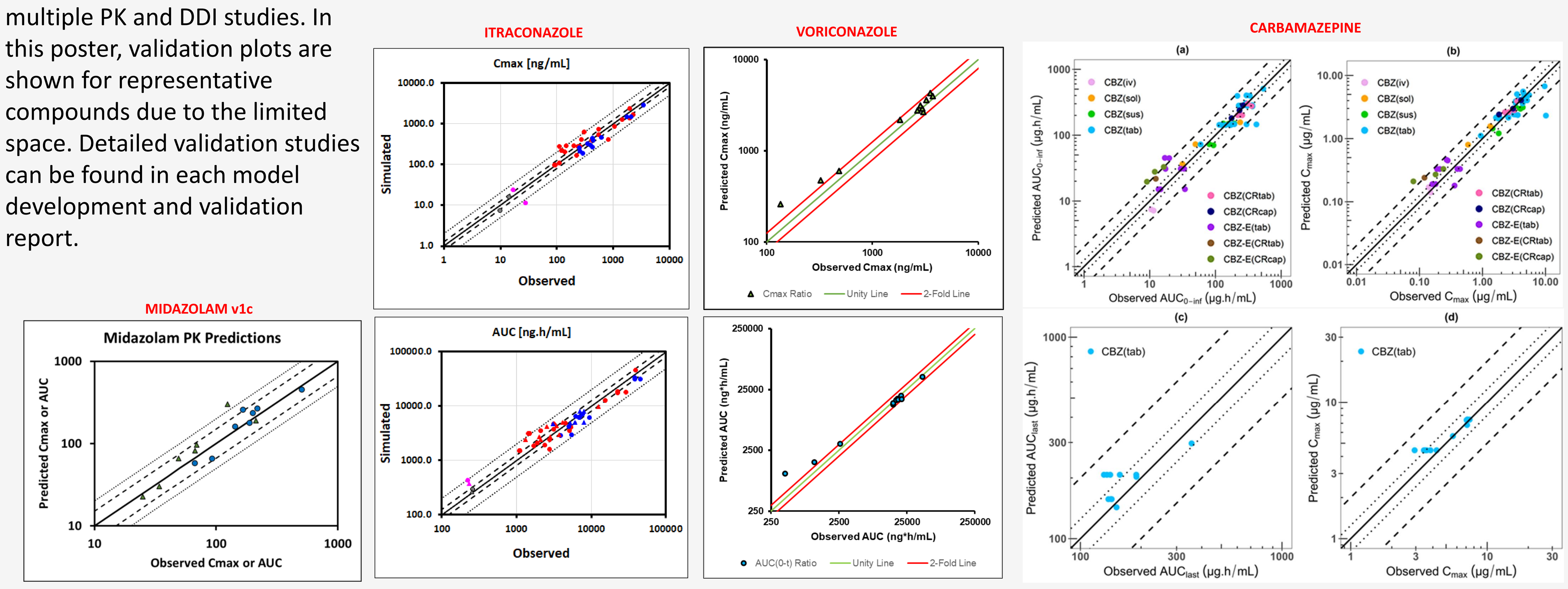
P-gp Network



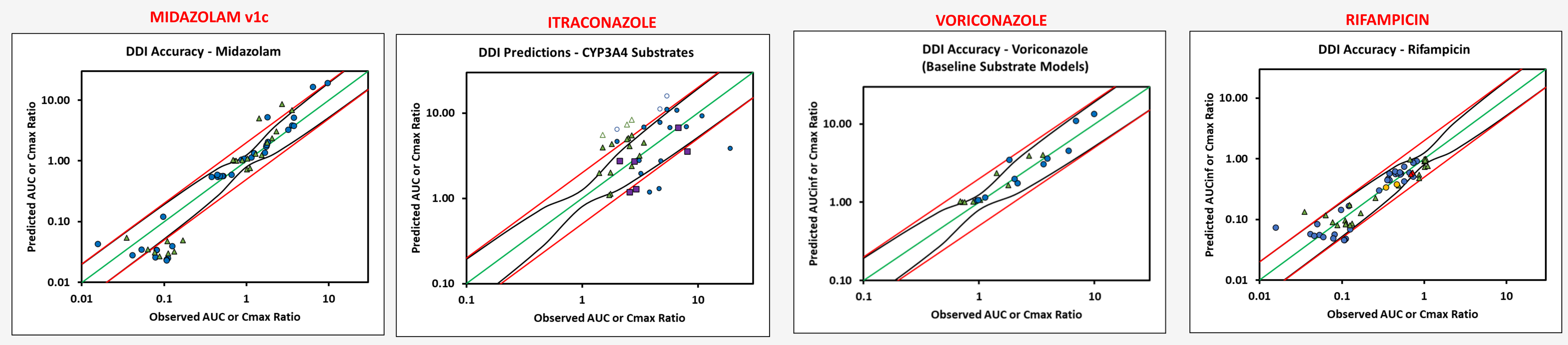
THE CYP3A4 NETWORK MODEL VALIDATION EXAMPLES

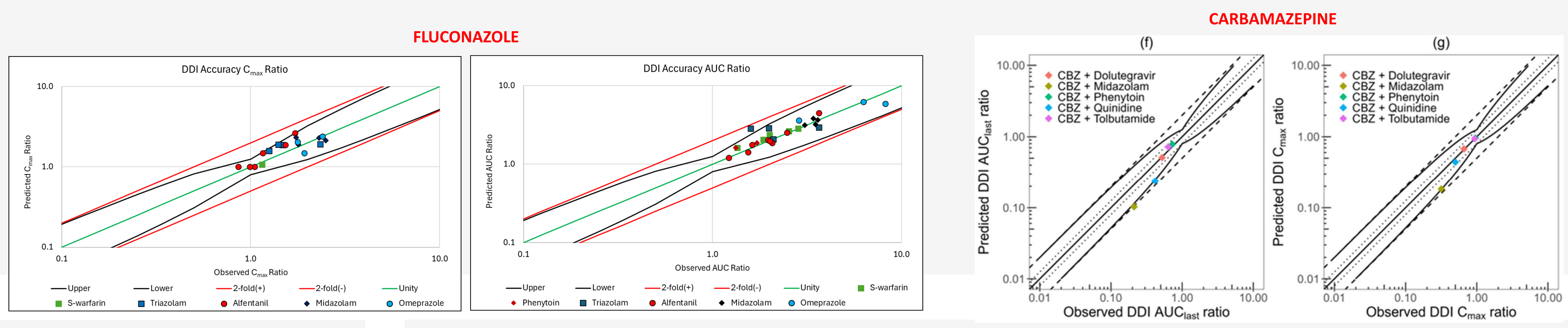
Each model is validated against multiple PK and DDI studies. In this poster, validation plots are shown for representative compounds due to the limited space. Detailed validation studies can be found in each model development and validation report.

Validation against available PK data



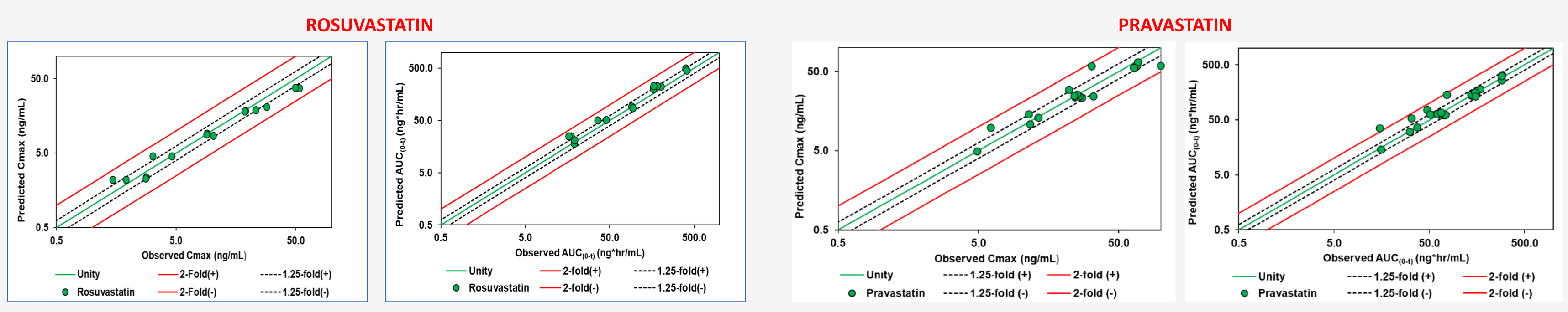
Validation against available DDI studies



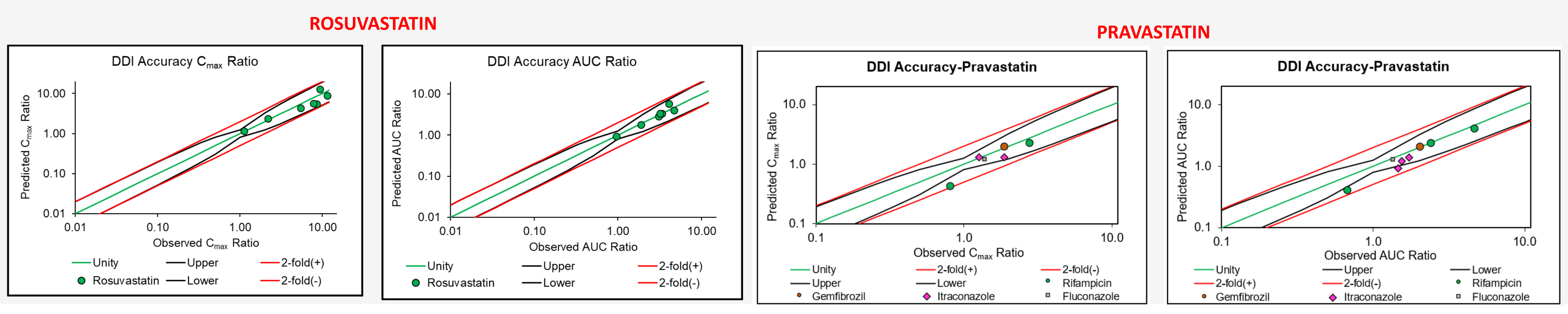


THE CYP2C8-OATP NETWORK MODEL VALIDATION EXAMPLES

Validation against available PK data

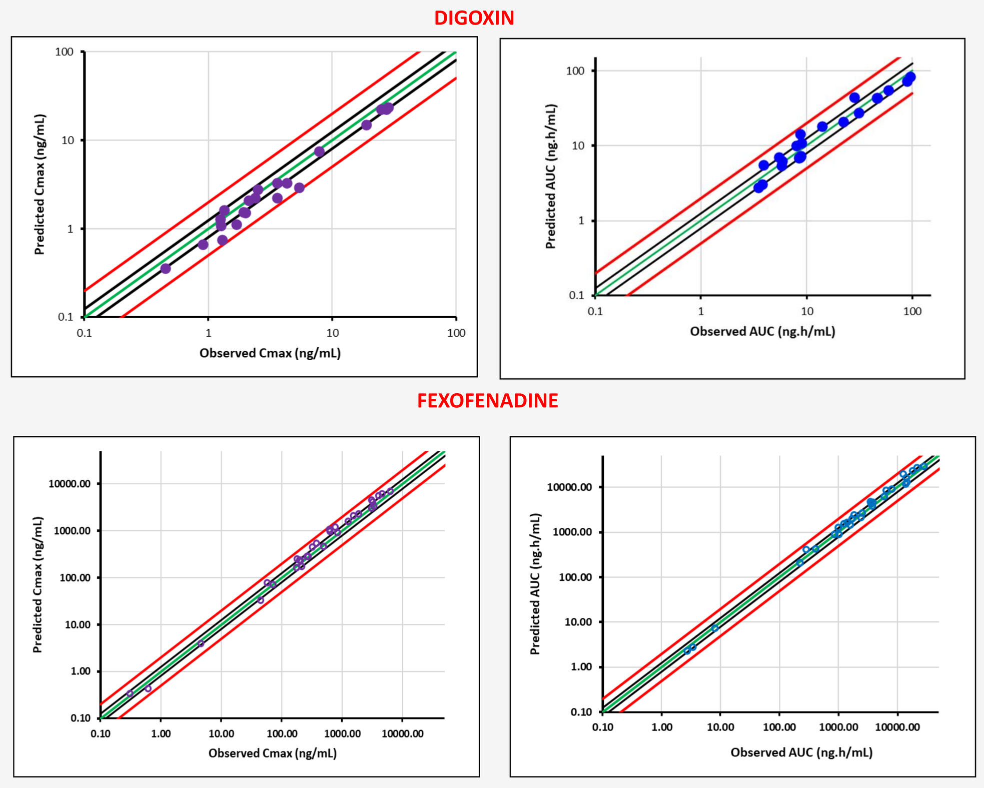


Validation against available DDI studies

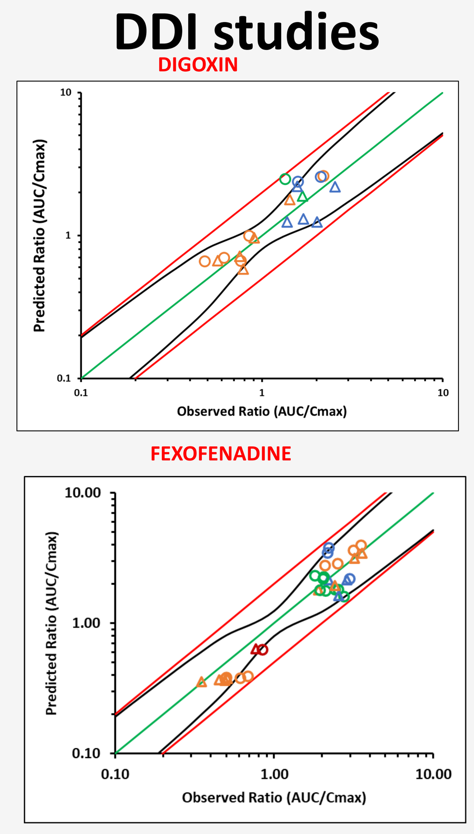


THE P-GP NETWORK MODEL VALIDATION EXAMPLES

Validation against available PK data



Validation against available DDI studies



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