

Predictiveness of the human CYP3A4 transgenic mouse model (Cyp3aXAV) for human drug exposure assessed using a population pharmacokinetic approach

David Damoiseaux (1), Wenlong Li (2), Alejandra Martínez-Chávez (2), Jos H. Beijnen (1, 3), Alfred H. Schinkel (2), Alwin D.R. Huitema (1, 4, 5), Thomas P.C. Dorlo (1)

(1) Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, (2) Division of Pharmacology, The Netherlands Cancer Institute, Amsterdam, the Netherlands, (3) Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands, (4) Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands, (5) Princess Máxima Center for Pediatric Oncology, Utrecht University, Utrecht, The Netherlands.

Introduction

Approximating the human pharmacokinetic (PK) profile as closely as possible in preclinical settings can still be a struggle in the context of predicting first-in-human doses and drug-drug interactions. For safety reasons a 4-fold margin is currently recommended for interspecies extrapolation of PK.

Human CYP3A4 transgenic (Cyp3aXAV) mice were mainly developed to assess the effect of CYP3A4 in a qualitative manner. This might be a more representative animal model for the pharmacokinetics of CYP3A4-metabolized compounds in human. We hypothesized that this murine model could also yield improved quantitative predictions of human exposure, using a compartmental population PK (PopPK) approach.

Objectives

- To model murine Cyp3aXAV data using a PopPK approach and investigate the predictive value and the accurateness of a quantitative extrapolation of this mouse model to humans for CYP3A4-metabolized compounds.
- Acceptance criterium of a 2-fold difference in terms of exposure and assessment of the overall predictiveness of the shape of the extrapolated human PK curve.

Methods

- PopPK models for lorlatinib, brigatinib, fisogatinib and ribociclib in mice were developed. To account for differences between wild type (WT) and Cyp3aXAV mice, strain was evaluated as a covariate on clearance (CL) and bioavailability (F)
- Extrapolation of typical parameters of mice model to humans by means of allometric scaling
- Run simulations for the human model from literature and the extrapolated model (100 individuals with random weights)
- Compare the simulations of both models (AUC_{inf}, C_{max}, T_{max}, concentration-time curves)

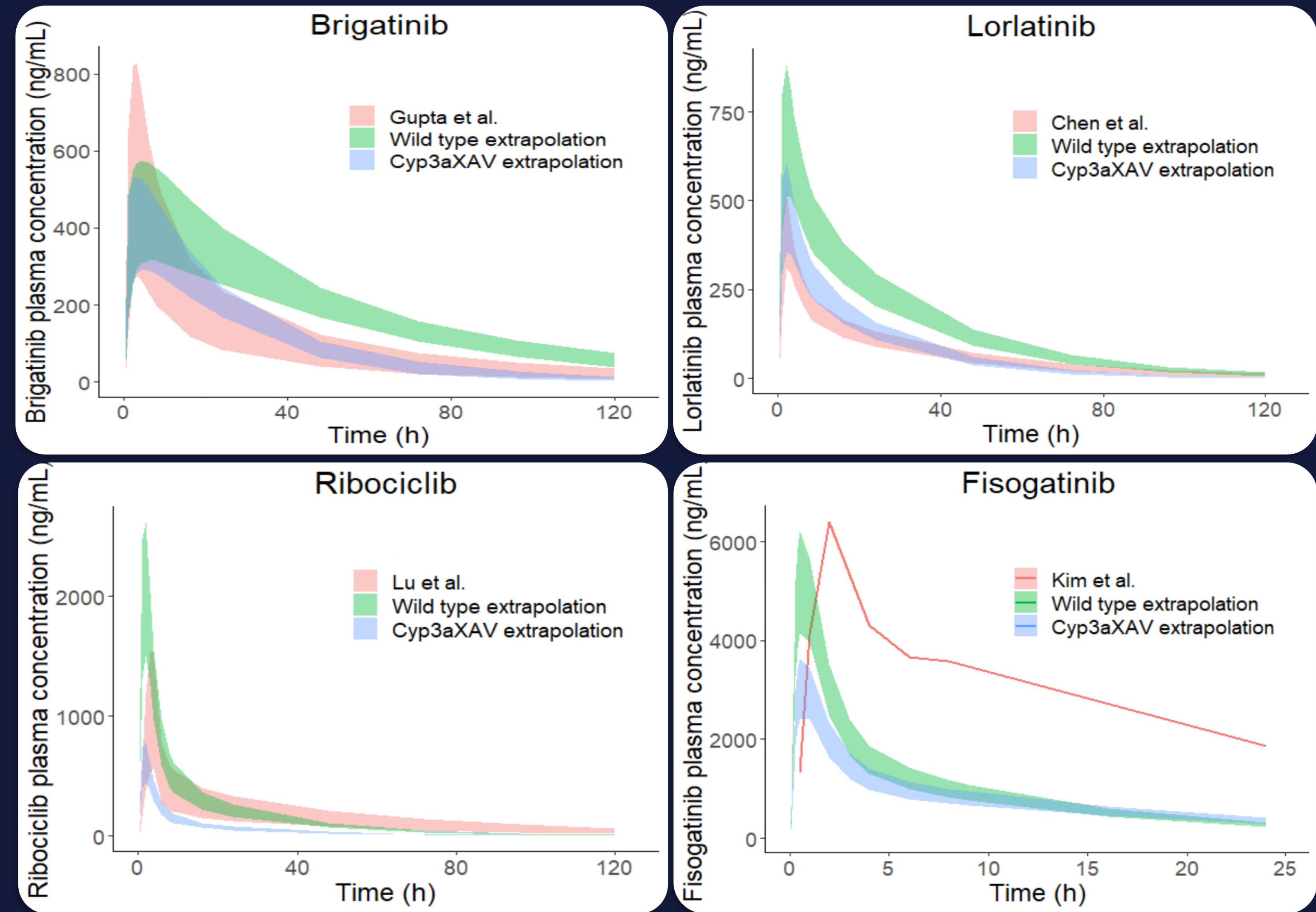
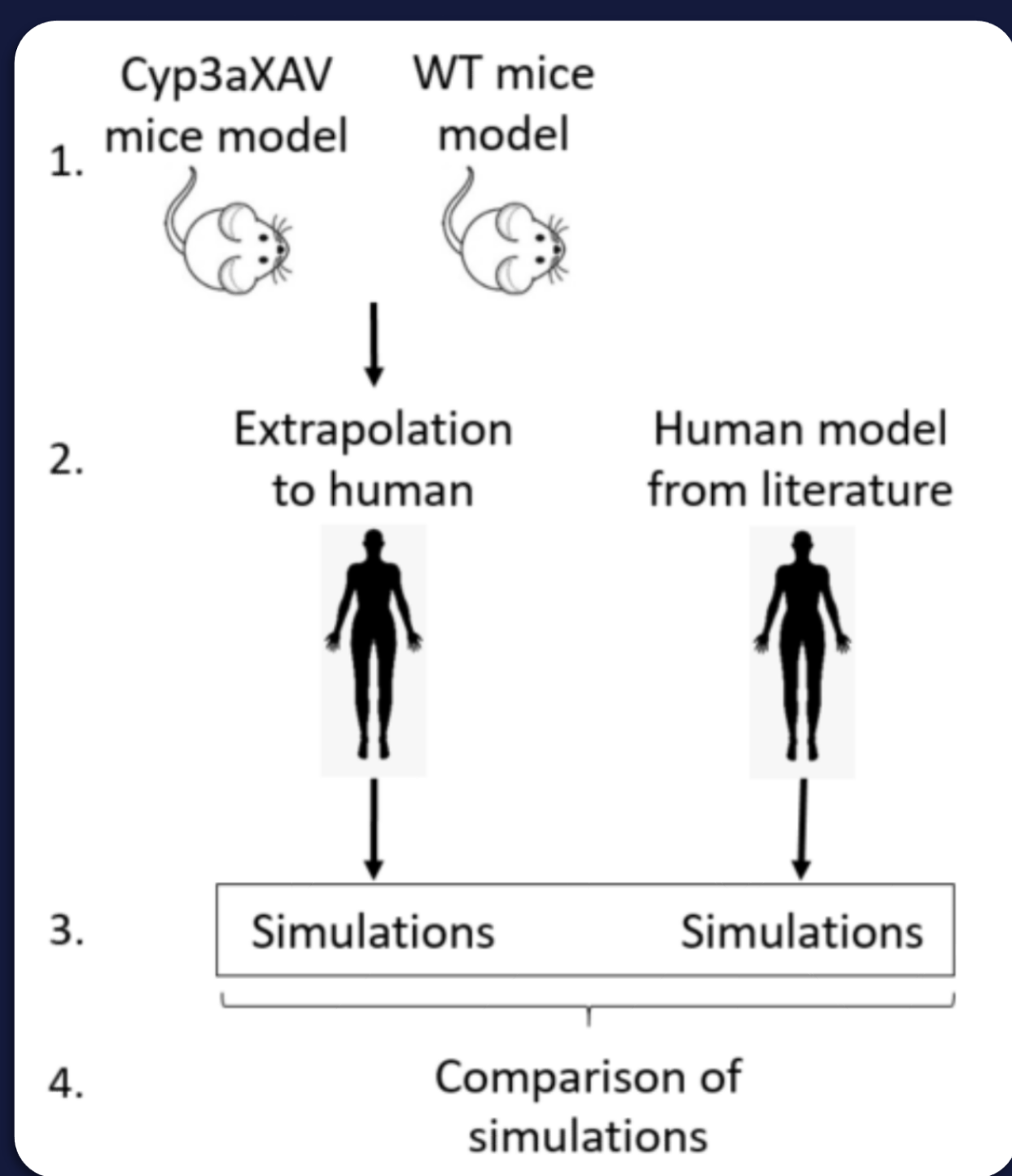


Figure: concentration-time curves (50% prediction intervals of simulations) of the in literature published PopPK model for humans (red), the extrapolated wild type mice model (green) and the extrapolated Cyp3aXAV mice model (blue)

	Lorlatinib	Brigatinib	Ribociclib	Fisogatinib
Covariates (Cyp3aXAV vs. WT)	0.71x lower F	1.91x higher CL	0.30x lower F	0.61x lower CL 0.57x lower F
Median AUC _{inf} ratio WT	2.08 fold	1.80 fold	1.00 fold	-
Median AUC _{inf} ratio Cyp3aXAV	1.12 fold	0.99 fold	0.30 fold	-
Median C _{max} ratio WT	1.85 fold	0.82 fold	1.82 fold	0.84 fold
Median C _{max} ratio Cyp3aXAV	1.24 fold	0.77 fold	0.55 fold	0.50 fold

Results

- The models that best fitted the data were a 2-compartment model with a dual first-order absorption for lorlatinib, a 2-compartment model with an exponential dose effect on BB for brigatinib, a 1-compartment model with transit compartments and an enterohepatic circulation model (EHC) for fisogatinib and a 2-compartment model with an EHC for ribociclib.
- Although EHC and exponential dose effect on BB led to significant model improvements for ribociclib, brigatinib and fisogatinib in mice, these turned out to be redundant model properties for the extrapolation to human and were omitted for human extrapolation.
- The extrapolation of the Cyp3aXAV model for both lorlatinib and brigatinib gave adequate predictions of clinical PK profiles (figure and table). Extrapolation of ribociclib, led to less adequate overlap of the prediction intervals, suggesting that certain PK properties were not well covered in the extrapolation (figure). Due to the lack of clinical data for fisogatinib, only the C_{max} could be compared for which both WT and Cyp3aXAV achieved the target (table).

Conclusion

- Extrapolation based on Cyp3aXAV mice led to a more accurate prediction of exposure in humans than WT mice for both lorlatinib and brigatinib, with predicted median AUC_{inf} deviating less than 12%. The curve shapes visually matched the human PK curves, suggesting that this model is an appropriate model to predict the human PK of lorlatinib and brigatinib.
- In contrast, a higher than 2-fold deviation in AUC_{inf} and some deviations in the curve shapes of ribociclib suggested that the Cyp3aXAV model is not fully representative of the human PK.

Table: Significant covariates identified on CL and F for Cyp3aXAV mice relative to WT mice for each compound (first row) and the fold changes in AUC_{inf} and C_{max} of the simulations of the extrapolated WT and Cyp3aXAV mice models compared to the in literature published PopPK model for humans

References:
Gupta, N., et al., Population Pharmacokinetics of Brigatinib in Healthy Volunteers and Patients With Cancer. Clin Pharmacokinet, 2021. 60(2): p. 235-247.
Lu, Y., et al., Ribociclib Population Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analysis of Neutrophils in Cancer Patients. J Clin Pharmacol, 2021.
Chen, J., et al., Population pharmacokinetic model with time-varying clearance for lorlatinib using pooled data from patients with non-small cell lung cancer and healthy participants. CPT Pharmacometrics Syst Pharmacol, 2021. 10(2): p. 148-160.
Kim, R.D., et al., First-in-Human Phase I Study of Fisogatinib (BLU-554) Validates Aberrant FGF19 Signaling as a Driver Event in Hepatocellular Carcinoma. Cancer Discov, 2019. 9(12): p. 1696-1707.