Quantitative Systems Pharmacology Models in Health and Disease

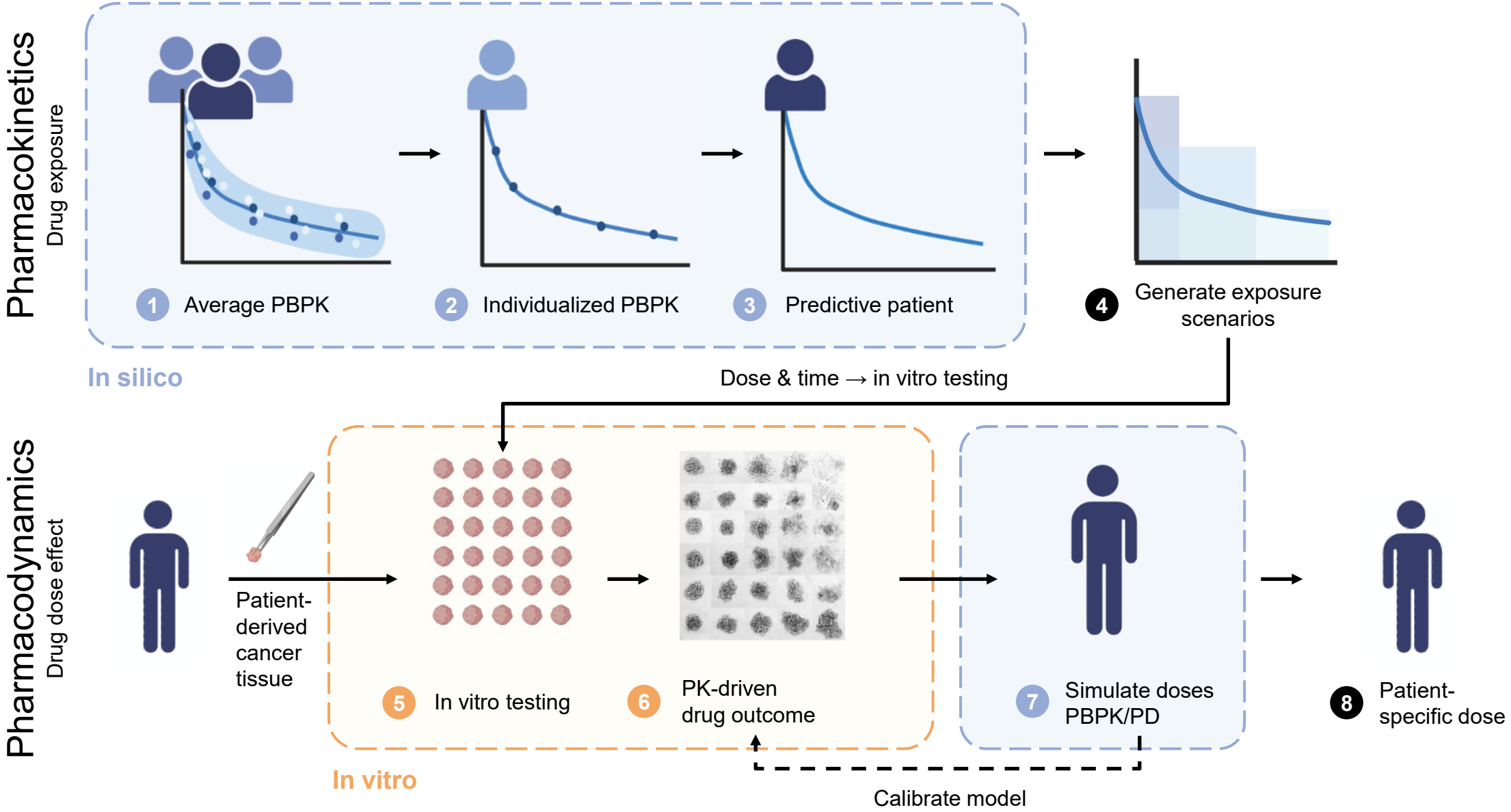
Lars Kuepfer

Institute for Systems Medicine with Focus on Organ Interactions
University hospital RWTH Aachen

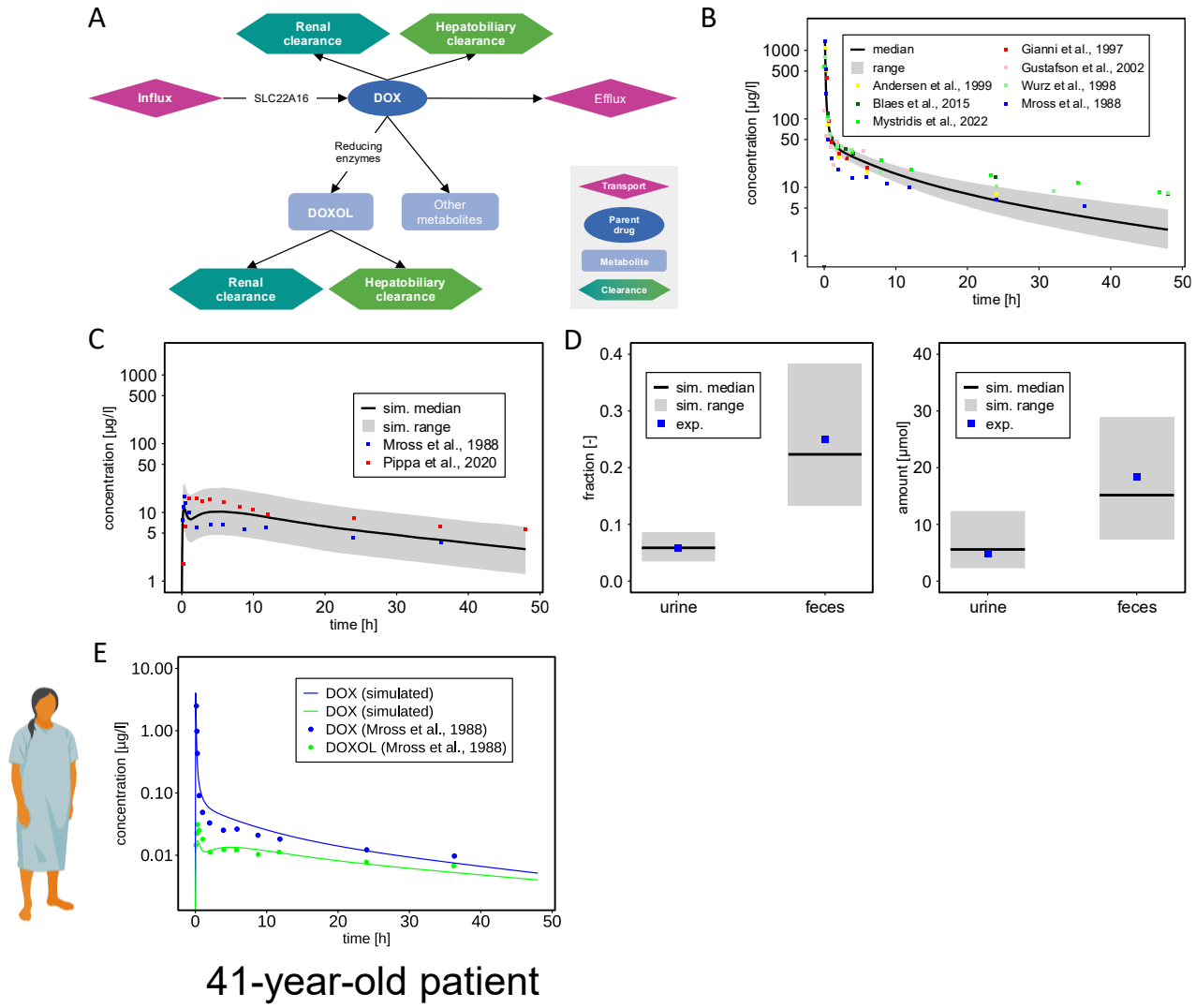
Outline

1. **Towards model-informed precision dosing in oncology**
2. Drug-induced liver injury
3. Conclusions and outlook

General concept



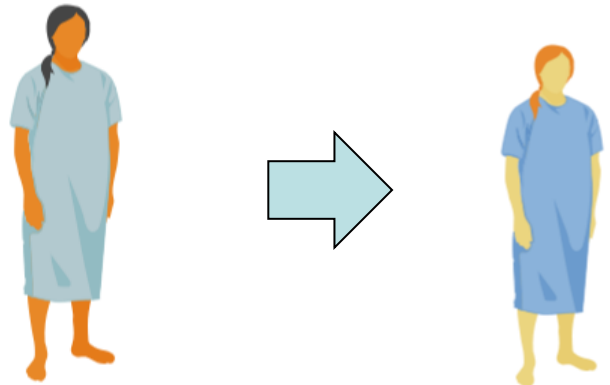
Doxorubicin (DOX) PBPK simulations for a 41-year-old breast cancer patient



41-year-old patient

Dorn *et al.*, re-*submitted*

PBPK model translation



41-year-old patient

16-year-old patient

Received: 16 December 2020 | Revised: 17 March 2021 | Accepted: 29 April 2021

DOI: 10.1002/psp4.12646

ARTICLE

Data-driven personalization of a physiologically based pharmacokinetic model for caffeine: A systematic assessment

Rebekka Fendt[1,2] | Ute Hofmann[3,4] | Annika R. P. Schneider[1,2] | Elke Schaeffeler[3,4] | Rolf Burghaus[1] | Ali Yilmaz[5] | Lars Mathias Blank[2] | Reinhold Kerb[3,4] | Jörg Lippert[1] | Jan-Frederik Schlender[1] | Matthias Schwab[3,6] | Lars Kuepfer[1,7]

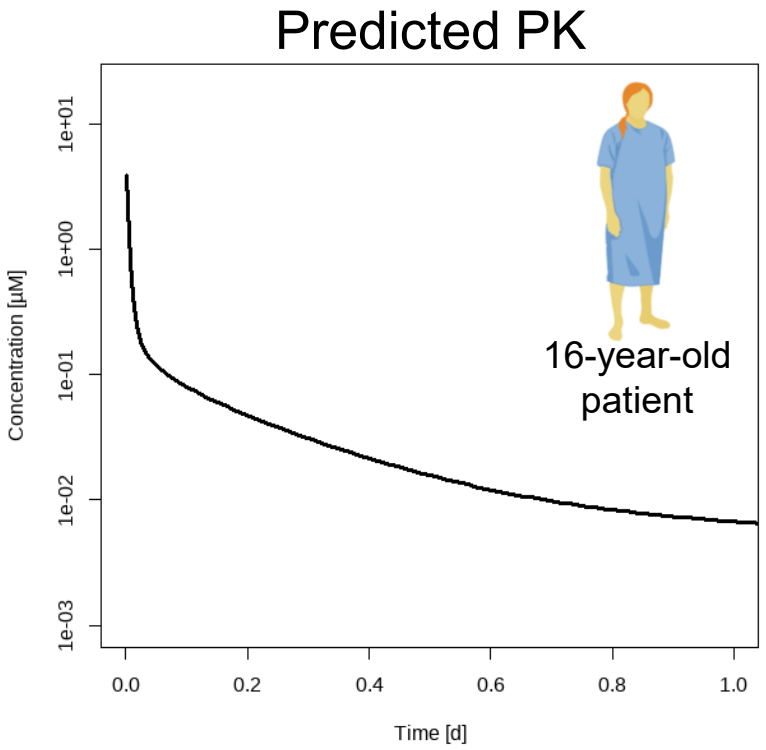
[1]Systems Pharmacology & Medicine, Bayer AG, Leverkusen, Germany

[2]Institute of Applied Microbiology, Aachen Biology and Biotechnology, Rheinisch-Westfaelische Technische Hochschule Aachen University, Aachen, Germany

[3]Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

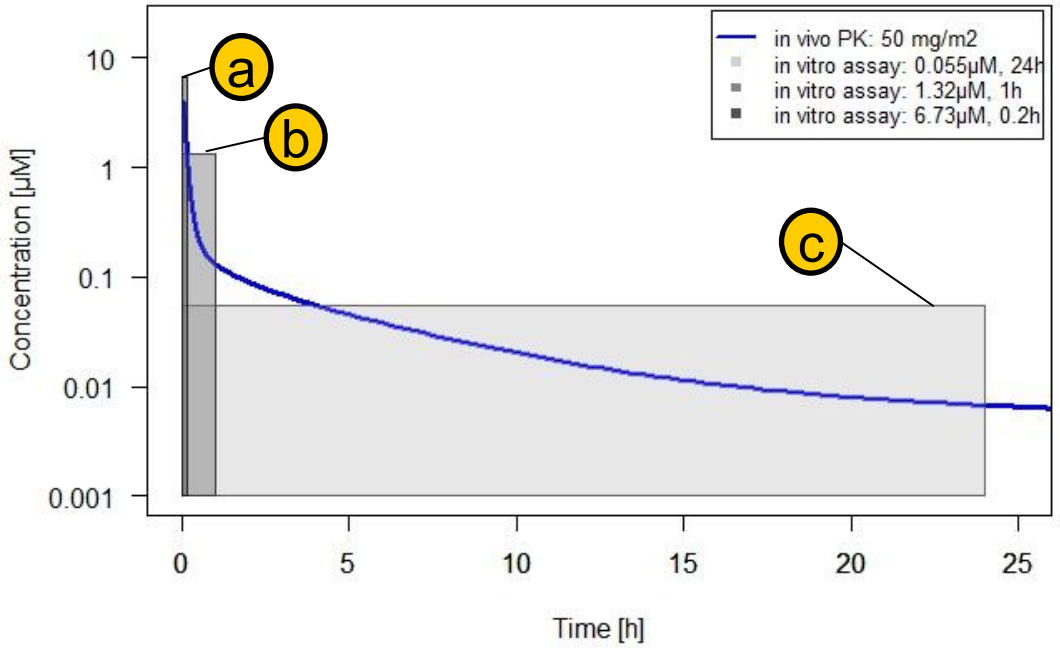
Abstract

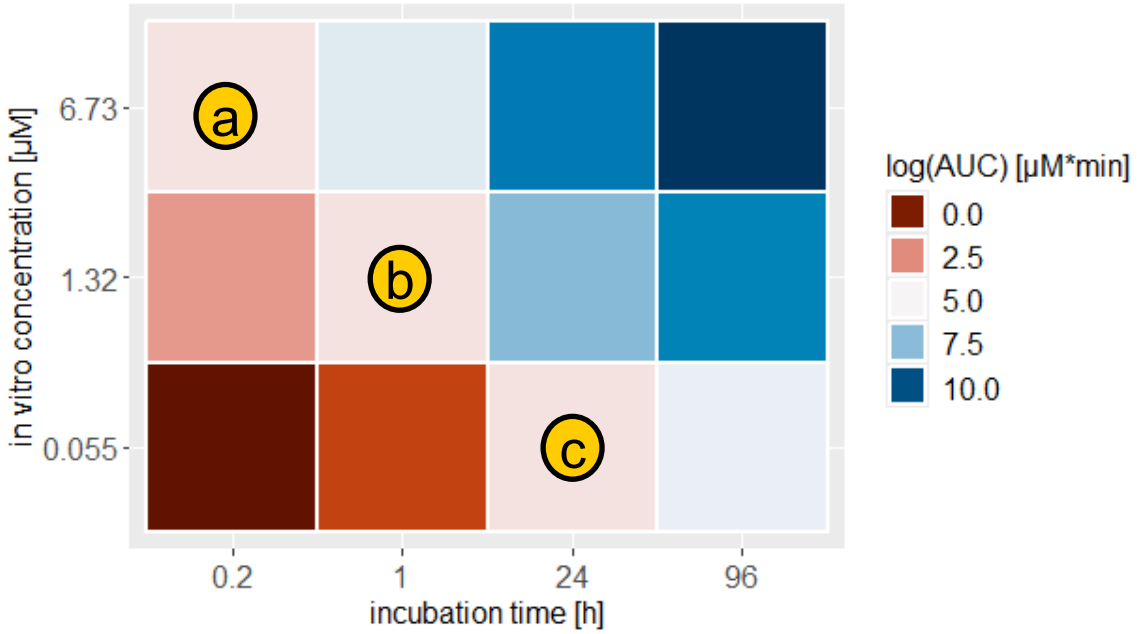
Physiologically based pharmacokinetic (PBPK) models have been proposed as a tool for more accurate individual pharmacokinetic (PK) predictions and model-informed precision dosing, but their application in clinical practice is still rare. This study systematically assesses the benefit of using individual patient information to improve PK predictions. A PBPK model of caffeine was stepwise personalized by using individual data on (1) demography, (2) physiology, and (3) cytochrome P450 (CYP) 1A2 pheno-



Dorn *et al.*, re-*submitted*

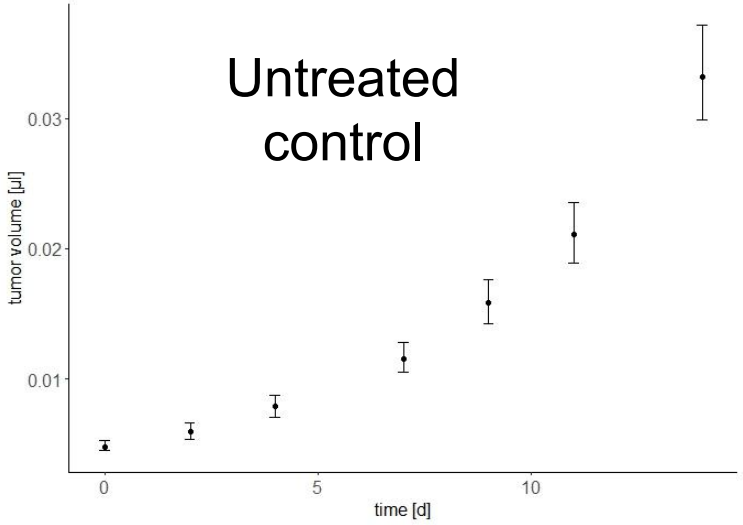
Model-based assay design:
In vivo-in vitro extrapolation

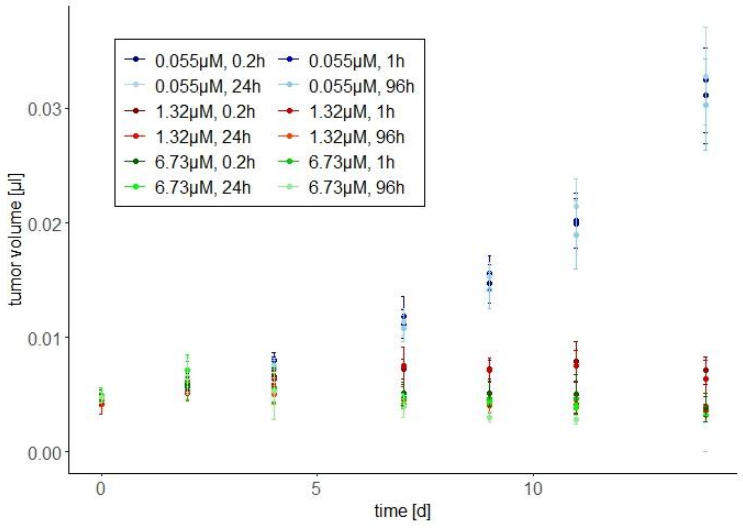


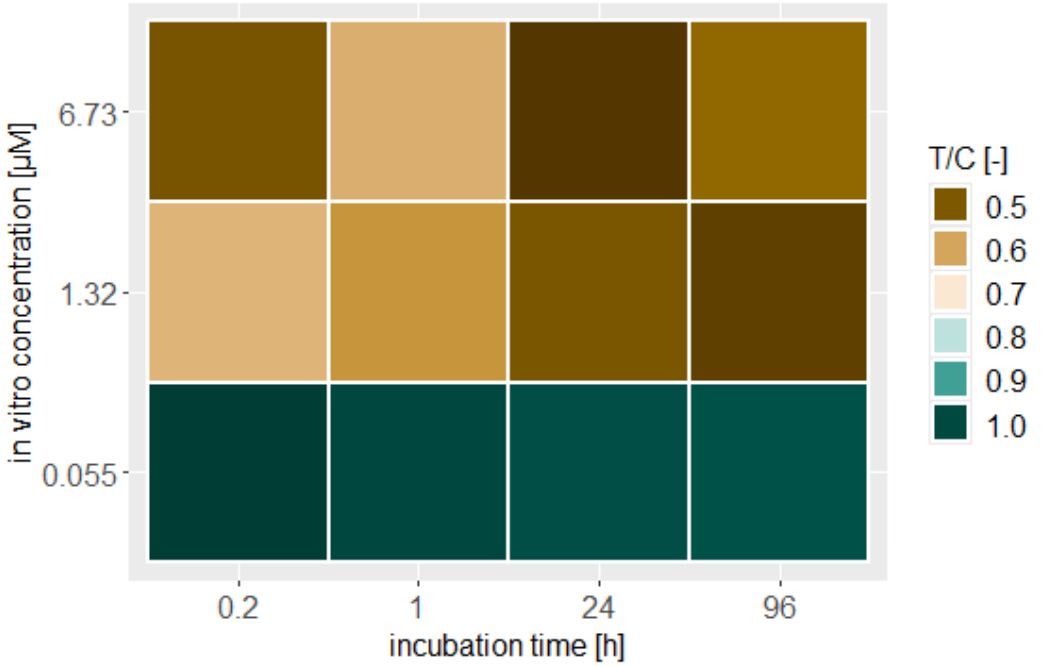


Dorn *et al.*, re-*submitted*

Growth of tumor spheroids



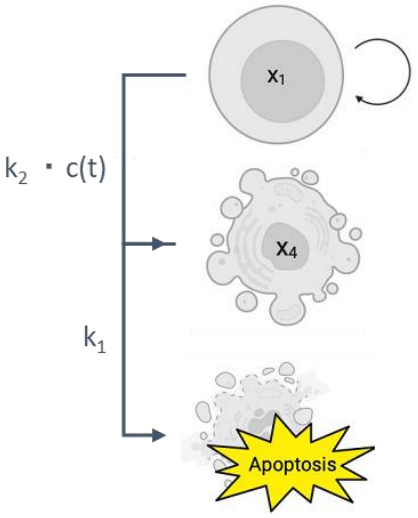


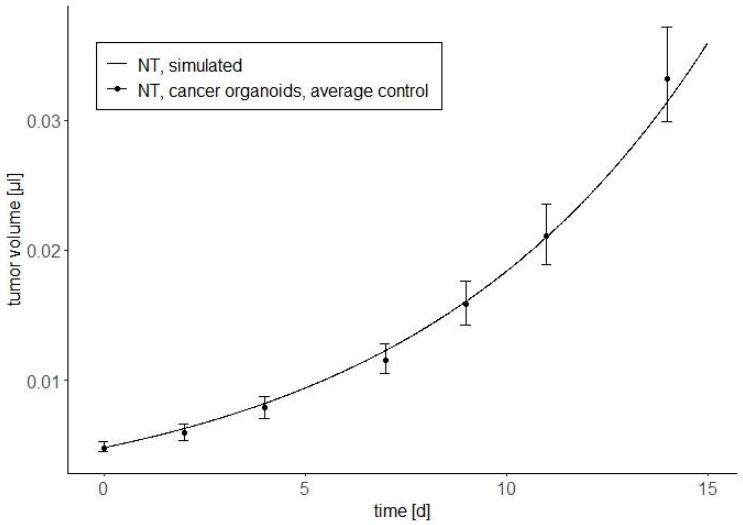


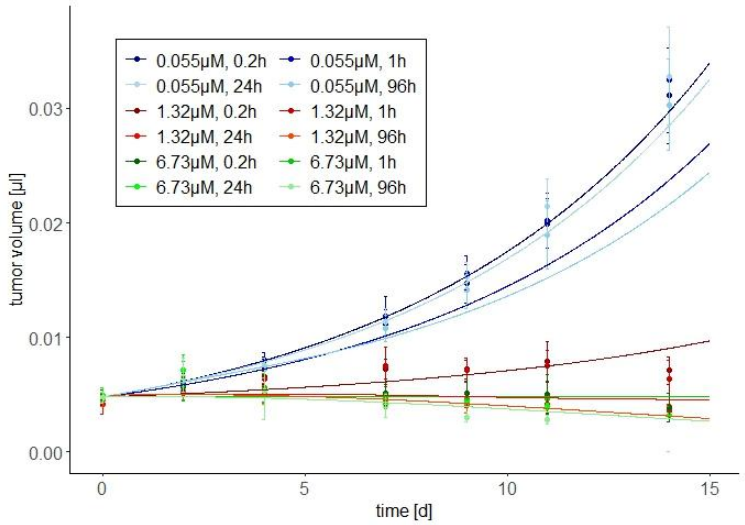
DOX concentration governs the antitumoral effect rather than the incubation time.

Dorn *et al.*, re-*submitted*

Growth of tumor spheroids

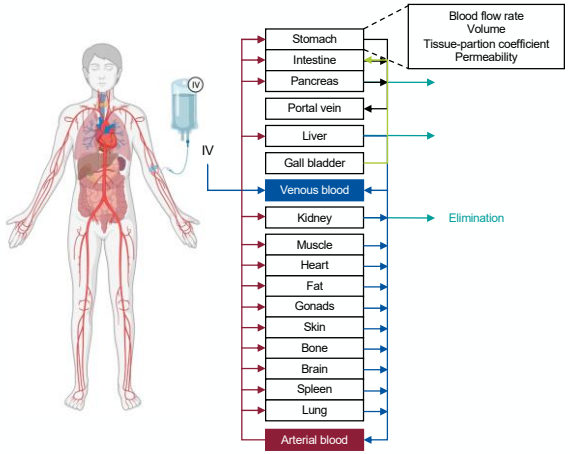


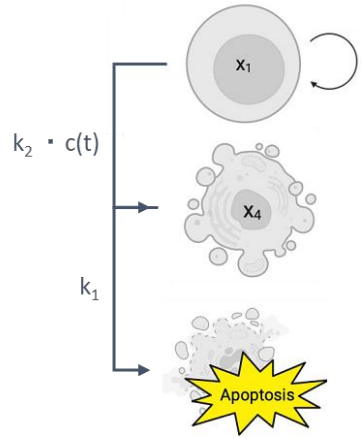


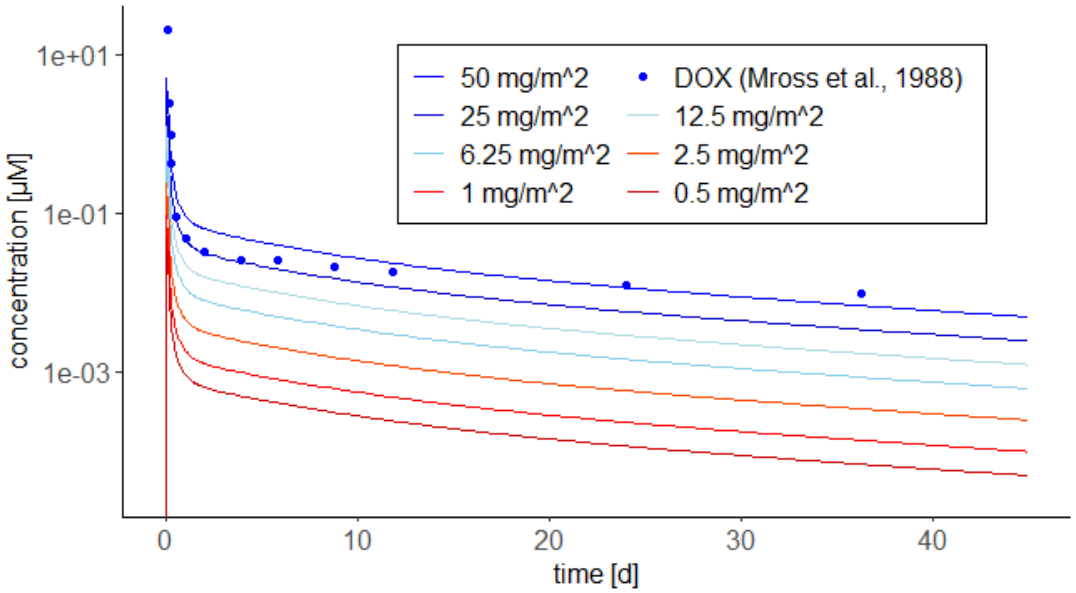


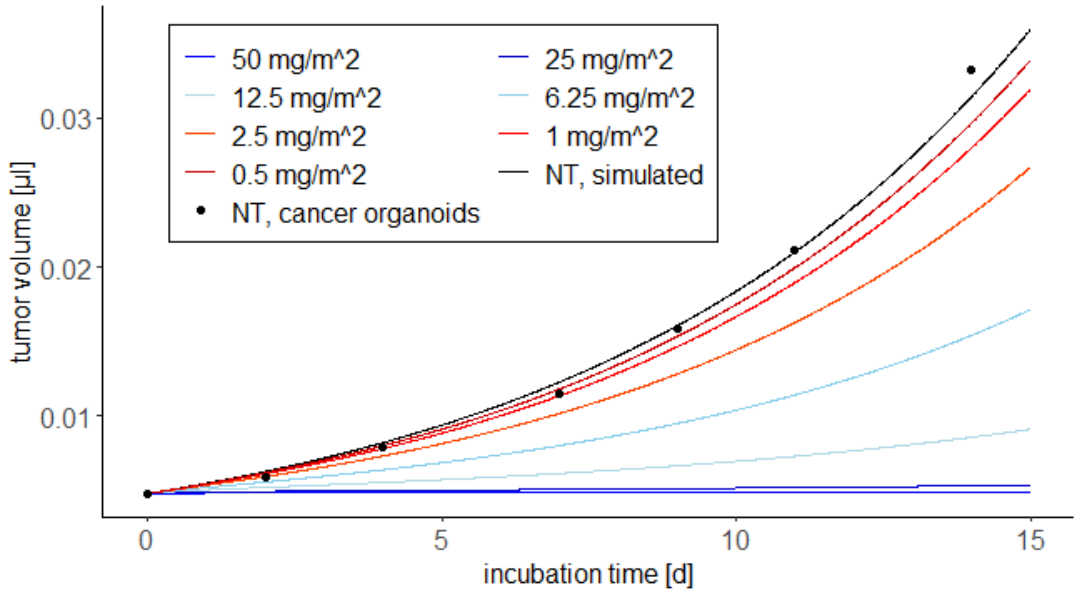
Dorn *et al.*, re-*submitted*
Simeoni et al., 2004

Personalised PBPK/PD simulations



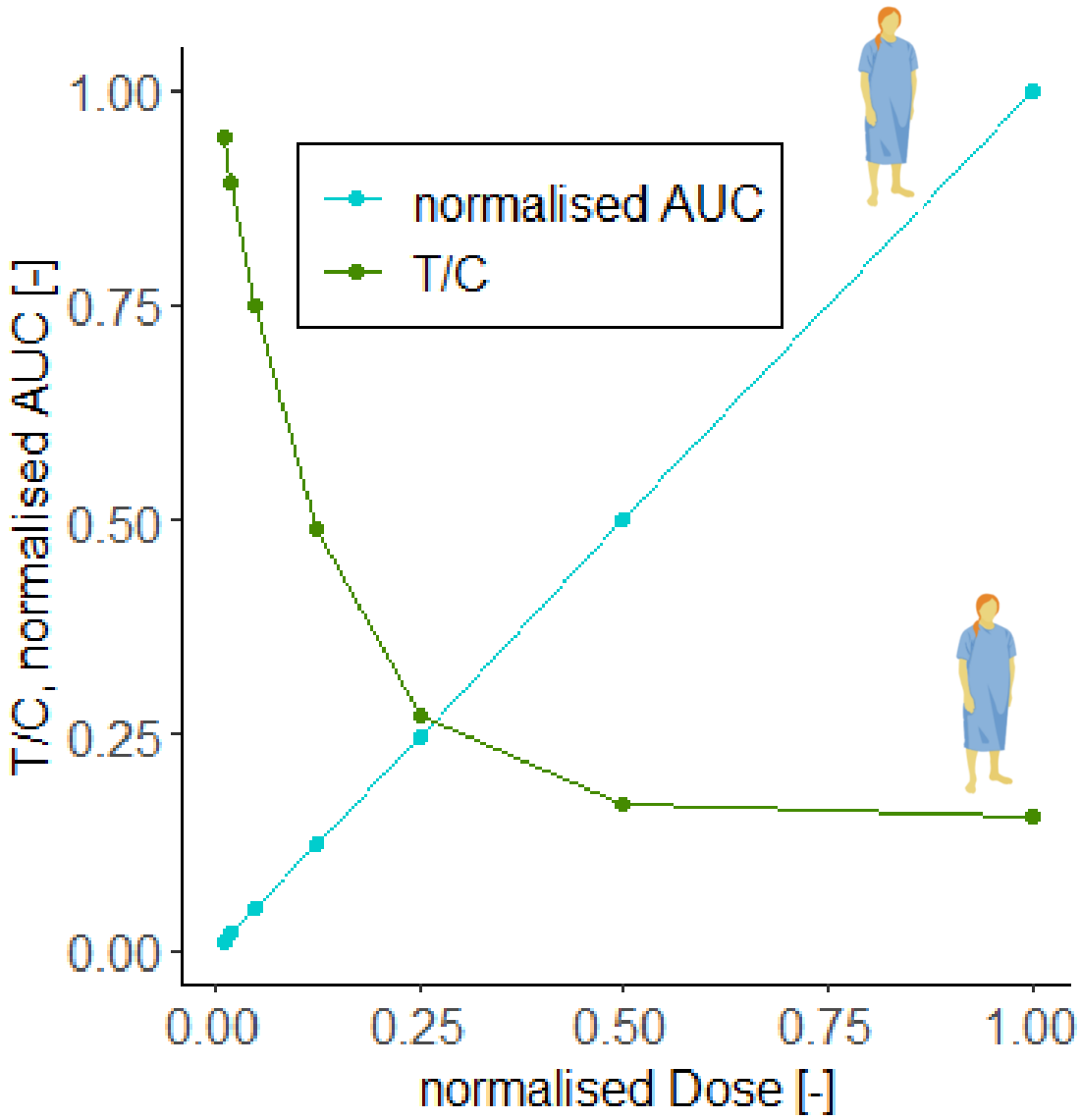






Dorn *et al.*, re-*submitted*

Personalised PBPK/PD simulations



While the DOX plasma AUC is linearly dependent on the administered dose, the induced drug effect T/C has a non-linear behavior and shows a clear saturation effect.

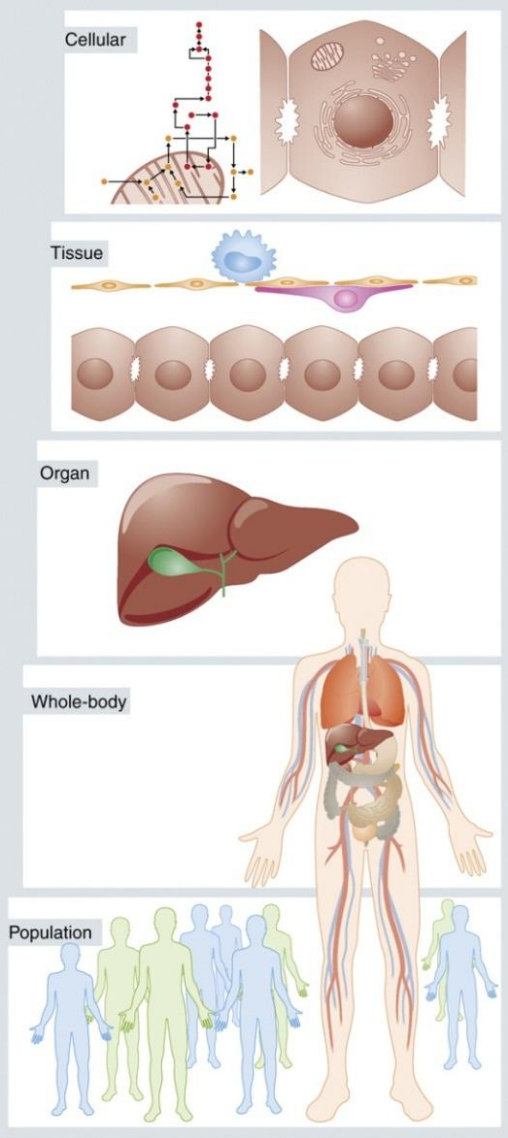
Critical cumulative dose of DOX per patient is 700 mg/m2 due to cardio-toxicity of anthracyclines.

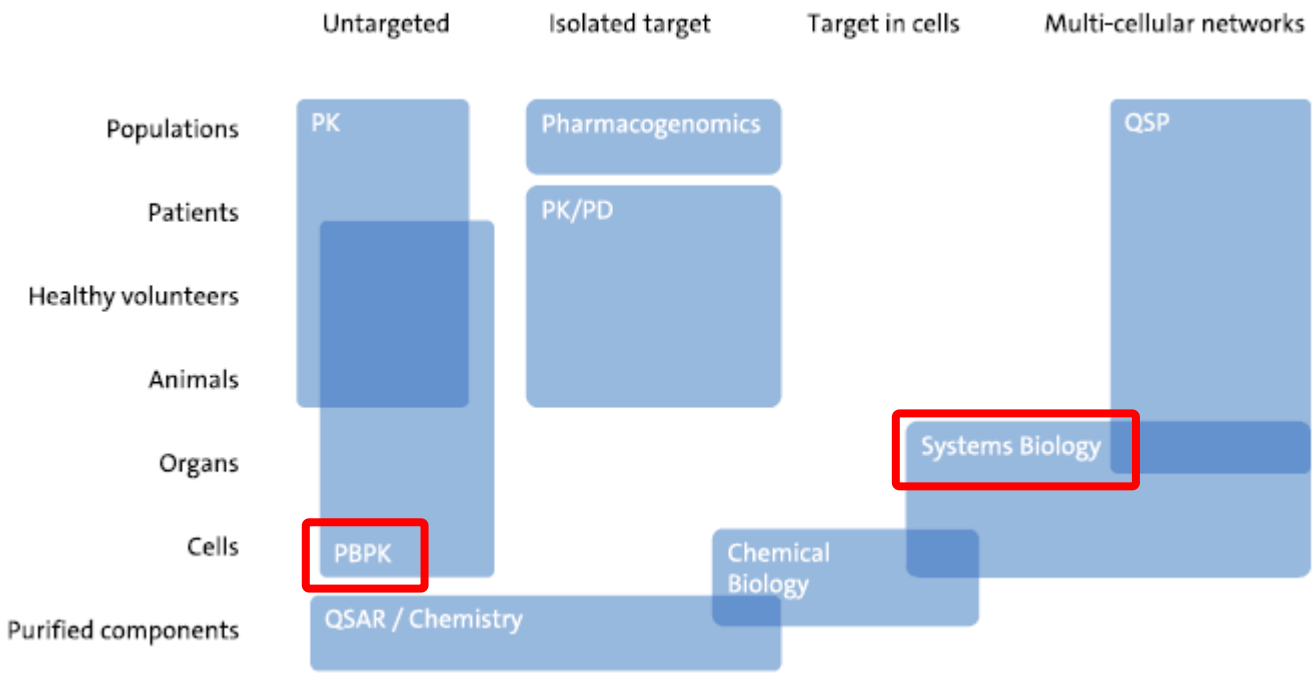
Dorn *et al.*, re-*submitted*

Outline

1. Towards model-informed precision dosing in oncology
2. **Drug-induced liver injury**
3. Conclusions and outlook

A QSP view on DILI





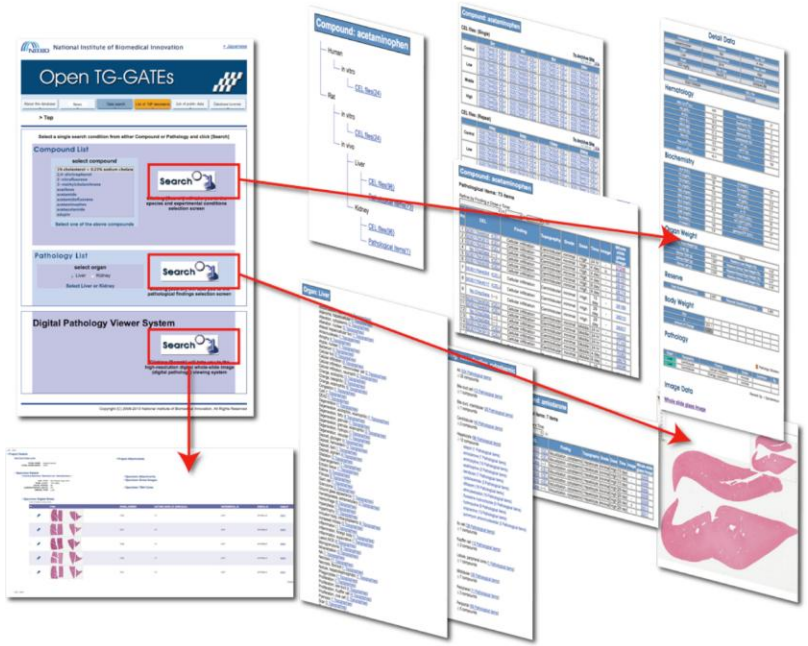
Kuepfer., *MSB*, 2010
Wicha and Kloft, *Curr. Opin. Sy.s. Biol.*, 2018

„Doses“ in in vitro toxicology and DILI

Open TG-GATEs: a large-scale toxicogenomics database

Yoshinobu Igarashi[1], Noriyuki Nakatsu[1], Tomoya Yamashita[1,2], Atsushi Ono[3], Yasuo Ohno[3], Tetsuro Urushidani[1,4] and Hiroshi Yamada[1,*]

[1]Toxicogenomics Informatics Project, National Institute of Biomedical Innovation, Osaka 567-0085, Japan, [2]Hitachi, Ltd. Information & Telecommunication Systems Company, Government & Public Corporation Information Systems Division, Tokyo 136-8832, Japan, [3]National Institute of Health and Sciences, Tokyo 158-0098, Japan and [4]Department of Pathophysiology, Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kyoto 610-0332, Japan

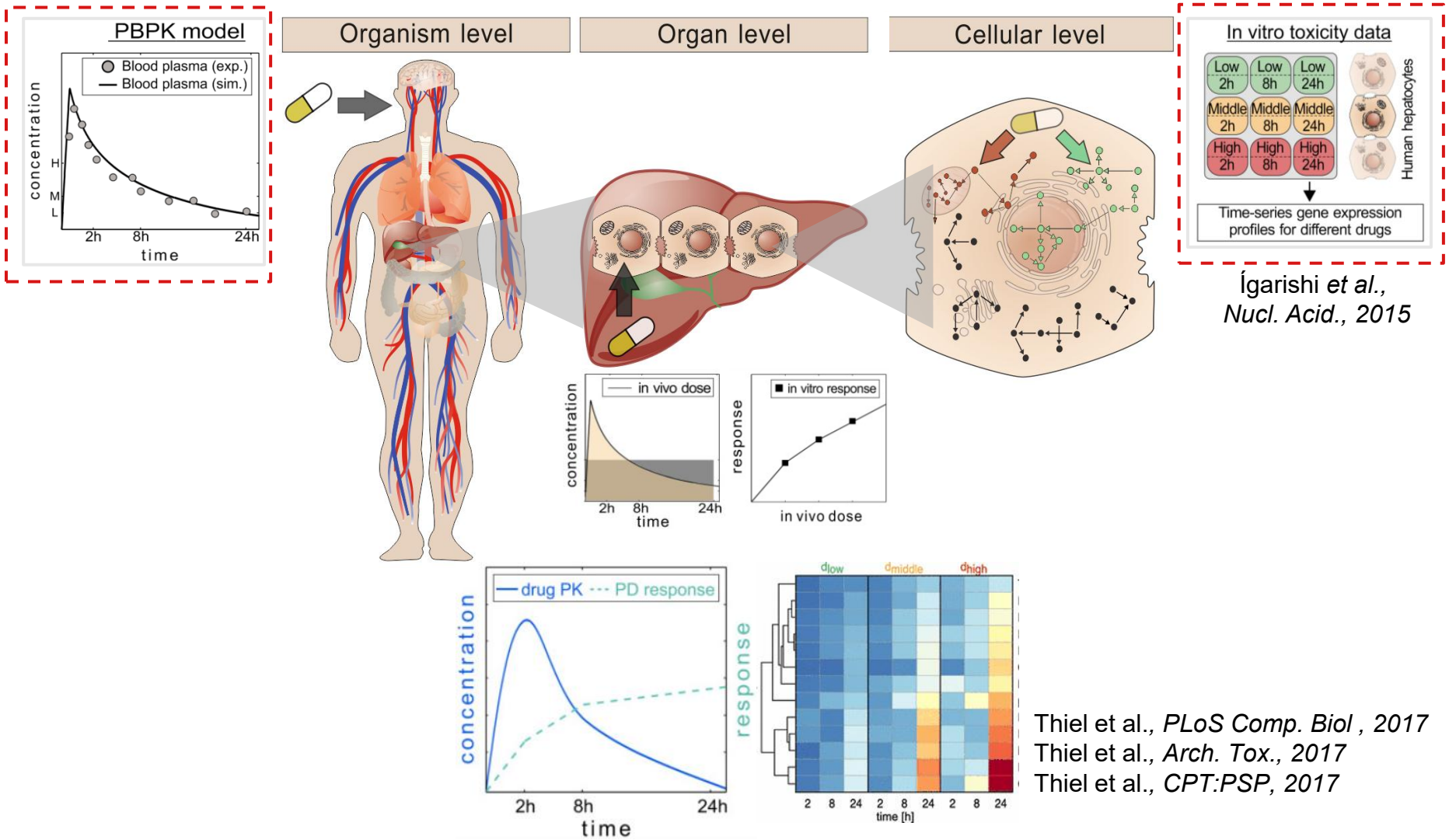


Dose setting

For the *in vivo* studies, the highest dose was selected to match the level demonstrated to induce the minimum toxic effect over the course of a 4-week toxicity study. In principle, the ratio of the concentrations for the low, middle and high dose levels was set as 1:3:10. For the *in vitro* studies, the highest concentration was defined as the dose level yielding an 80–90% relative survival ratio. However, for compounds that dissolved poorly in the vehicle, the highest concentration was defined by the maximum solubility of the compound. In principle, the ratio of the concentrations for the low, middle and high dose levels was 1:5:25.

Igarashi *et al.*, Nucl. Acids Res., 2014

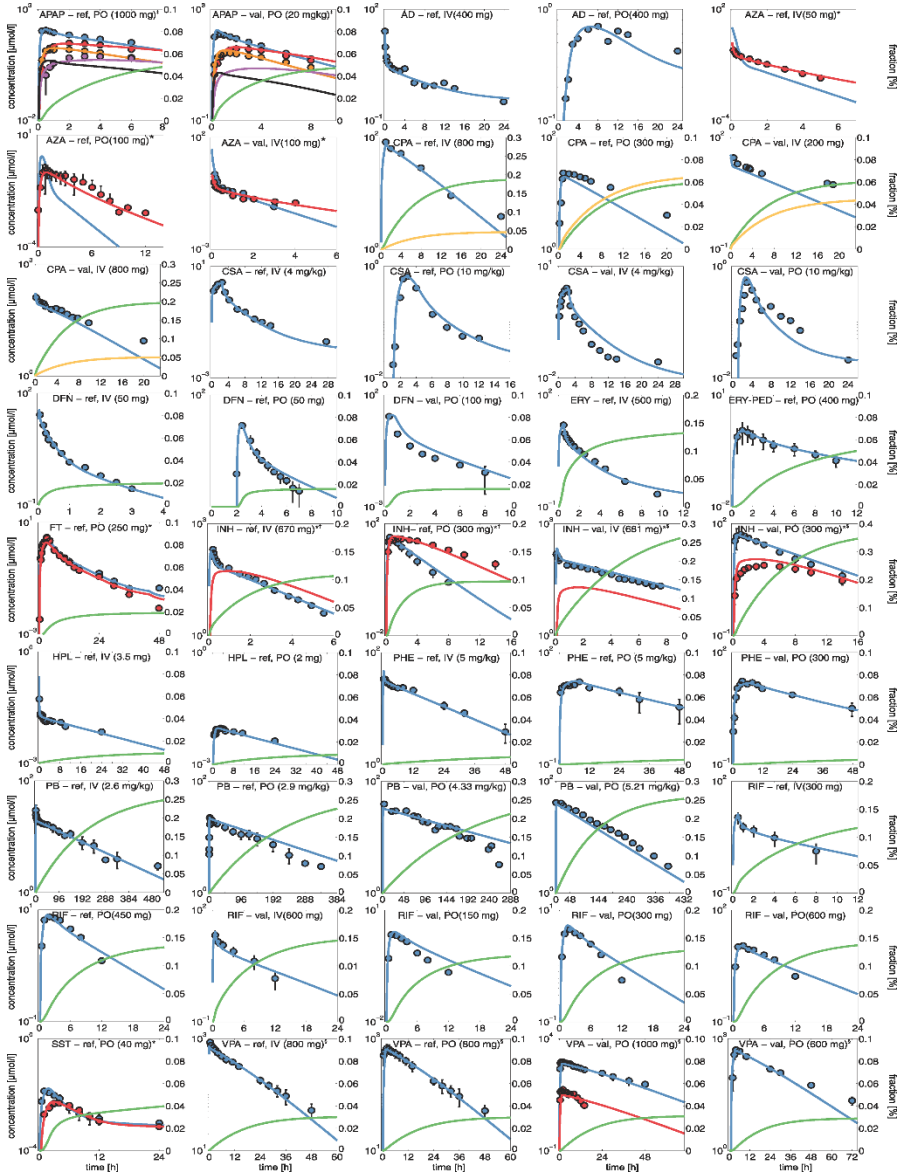
Reverse dosimetry for in vivo contextualization of in vitro toxicity data

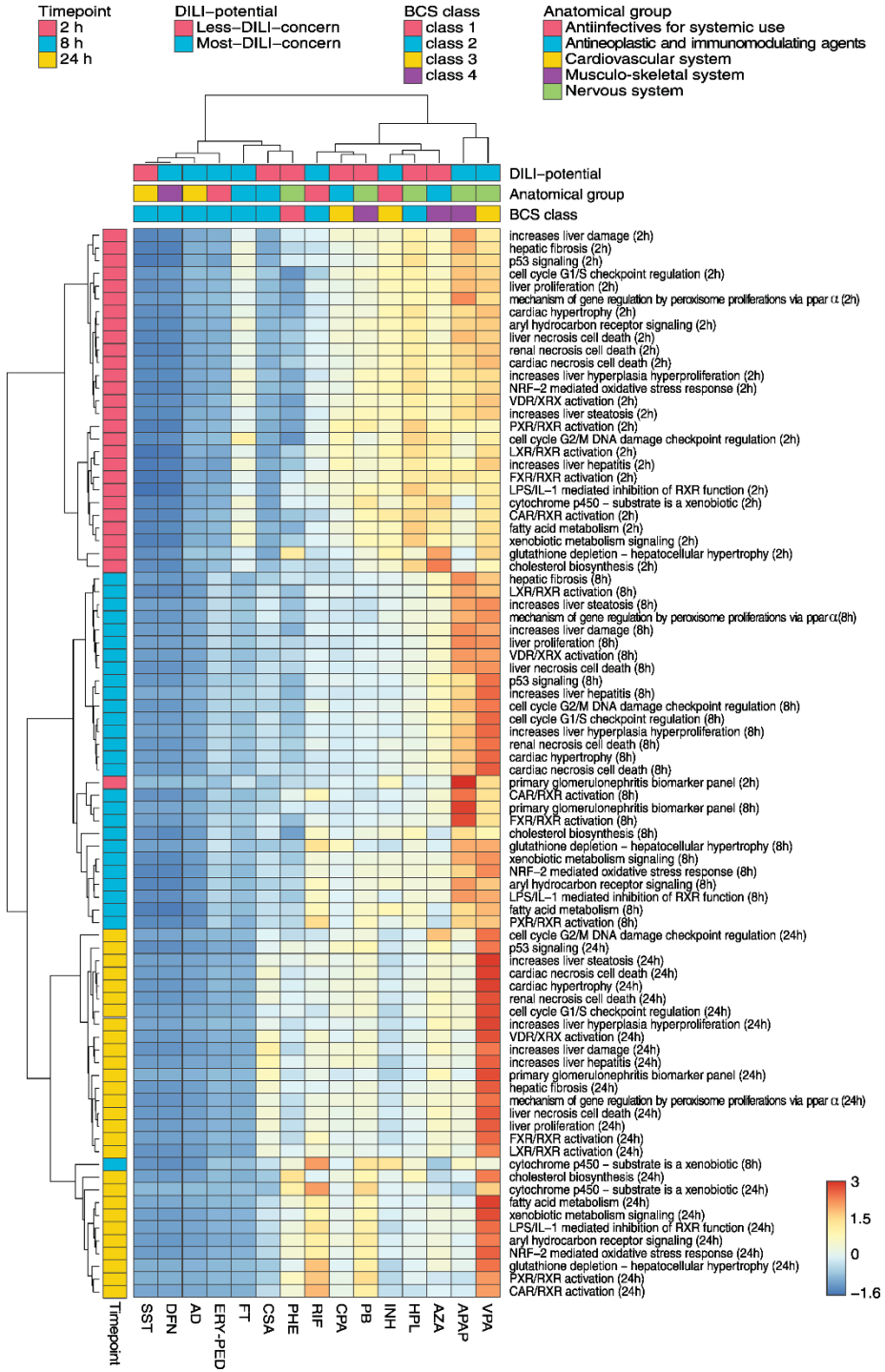


Ígarishi *et al.*, *Nucl. Acid., 2015*

Thiel et al., *PLoS Comp. Biol , 2017*
Thiel et al., *Arch. Tox., 2017*
Thiel et al., *CPT:PSP, 2017*

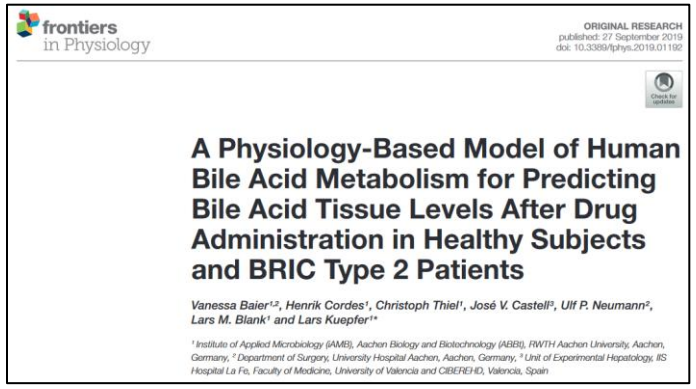
15 PBPK models





Thiel et al., *PLoS Comp. Biol* , 2017

PBPK models of bile acid and bilirubin metabolism


frontiers in Physiology

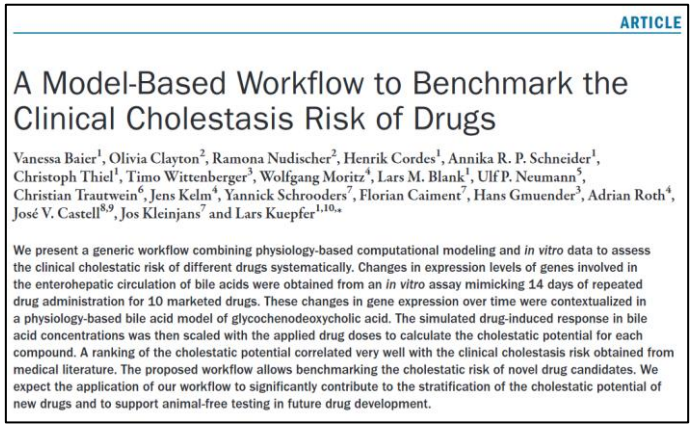
ORIGINAL RESEARCH
published: 27 September 2019
doi: 10.3389/fphys.2019.01192

A Physiology-Based Model of Human Bile Acid Metabolism for Predicting Bile Acid Tissue Levels After Drug Administration in Healthy Subjects and BRIC Type 2 Patients

Vanessa Baier[1,2], Henrik Cordes[1], Christoph Thiel[1], José V. Castell[3], Ulf P. Neumann[2], Lars M. Blank[1] and Lars Kuepfer[1]*

[1] Institute of Applied Microbiology (iAMB), Aachen Biology and Biotechnology (ABBt), RWTH Aachen University, Aachen, Germany, [2] Department of Surgery, University Hospital Aachen, Aachen, Germany, [3] Unit of Experimental Hepatology, IIS Hospital La Fe, Faculty of Medicine, University of Valencia and CIBEREHD, Valencia, Spain

Baier et al., Frontiers in Pharmacology, 2019

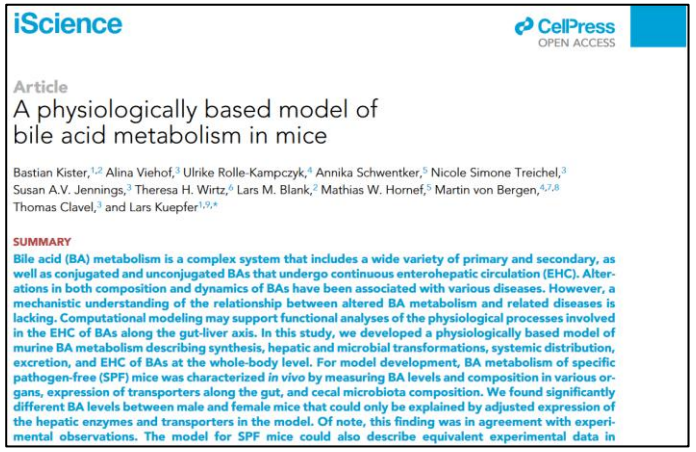

ARTICLE

A Model-Based Workflow to Benchmark the Clinical Cholestasis Risk of Drugs

Vanessa Baier[1], Olivia Clayton[2], Ramona Nudischer[2], Henrik Cordes[1], Annika R. P. Schneider[1], Christoph Thiel[1], Timo Wittenberger[3], Wolfgang Moritz[4], Lars M. Blank[1], Ulf P. Neumann[5], Christian Trautwein[6], Jens Kelm[4], Yannick Schrooders[7], Florian Caiment[7], Hans Gmuender[3], Adrian Roth[4], José V. Castell[8,9], Jos Kleinjans[7] and Lars Kuepfer[1,10,*]

We present a generic workflow combining physiology-based computational modeling and *in vitro* data to assess the clinical cholestatic risk of different drugs systematically. Changes in expression levels of genes involved in the enterohepatic circulation of bile acids were obtained from an *in vitro* assay mimicking 14 days of repeated drug administration for 10 marketed drugs. These changes in gene expression over time were contextualized in a physiology-based bile acid model of glycochenodeoxycholic acid. The simulated drug-induced response in bile acid concentrations was then scaled with the applied drug doses to calculate the cholestatic potential for each compound. A ranking of the cholestatic potential correlated very well with the clinical cholestasis risk obtained from medical literature. The proposed workflow allows benchmarking the cholestatic risk of novel drug candidates. We expect the application of our workflow to significantly contribute to the stratification of the cholestatic potential of new drugs and to support animal-free testing in future drug development.

Baier et al., CPT, 2021


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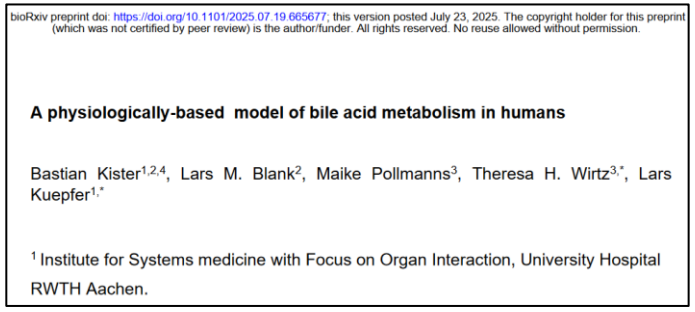
A physiologically based model of bile acid metabolism in mice

Bastian Kister,[1,2] Alina Viehof,[1] Ulrike Rolle-Kampczyk,[4] Annika Schwentker,[5] Nicole Simone Treichel,[1] Susan A.V. Jennings,[3] Theresa H. Wirtz,[6] Lars M. Blank,[2] Mathias W. Hornef,[5] Martin von Bergen,[4,7,8] Thomas Clavel,[3] and Lars Kuepfer[1,9,*]

SUMMARY

Bile acid (BA) metabolism is a complex system that includes a wide variety of primary and secondary, as well as conjugated and unconjugated BAs that undergo continuous enterohepatic circulation (EHC). Alterations in both composition and dynamics of BAs have been associated with various diseases. However, a mechanistic understanding of the relationship between altered BA metabolism and related diseases is lacking. Computational modeling may support functional analyses of the physiological processes involved in the EHC of BAs along the gut-liver axis. In this study, we developed a physiologically based model of murine BA metabolism describing synthesis, hepatic and microbial transformations, systemic distribution, excretion, and EHC of BAs at the whole-body level. For model development, BA metabolism of specific pathogen-free (SPF) mice was characterized *in vivo* by measuring BA levels and composition in various organs, expression of transporters along the gut, and cecal microbiota composition. We found significantly different BA levels between male and female mice that could only be explained by adjusted expression of the hepatic enzymes and transporters in the model. Of note, this finding was in agreement with experimental observations. The model for SPF mice could also describe equivalent experimental data in

Kister et al., iScience, 2023

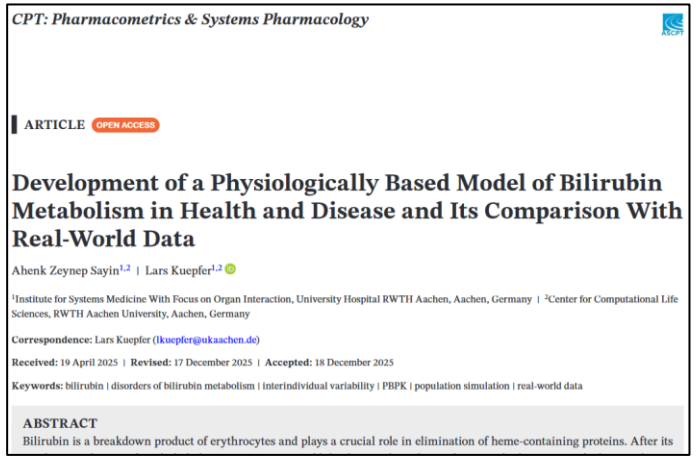

bioRxiv preprint doi: https://doi.org/10.1101/2025.07.19.665677; this version posted July 23, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A physiologically-based model of bile acid metabolism in humans

Bastian Kister[1,2,4], Lars M. Blank[2], Maike Pollmanns[3], Theresa H. Wirtz[3,*], Lars Kuepfer[1,*]

[1] Institute for Systems medicine with Focus on Organ Interaction, University Hospital RWTH Aachen.

Kister et al., bioRxiv, submitted


CPT: Pharmacometrics & Systems Pharmacology

ARTICLE OPEN ACCESS

Development of a Physiologically Based Model of Bilirubin Metabolism in Health and Disease and Its Comparison With Real-World Data

Ahenk Zeynep Sayin[1,2] | Lars Kuepfer[1,2]

[1]Institute for Systems Medicine With Focus on Organ Interaction, University Hospital RWTH Aachen, Aachen, Germany | [2]Center for Computational Life Sciences, RWTH Aachen University, Aachen, Germany

Correspondence: Lars Kuepfer (lkuepfer@ukaachen.de)

Received: 19 April 2025 | **Revised:** 17 December 2025 | **Accepted:** 18 December 2025

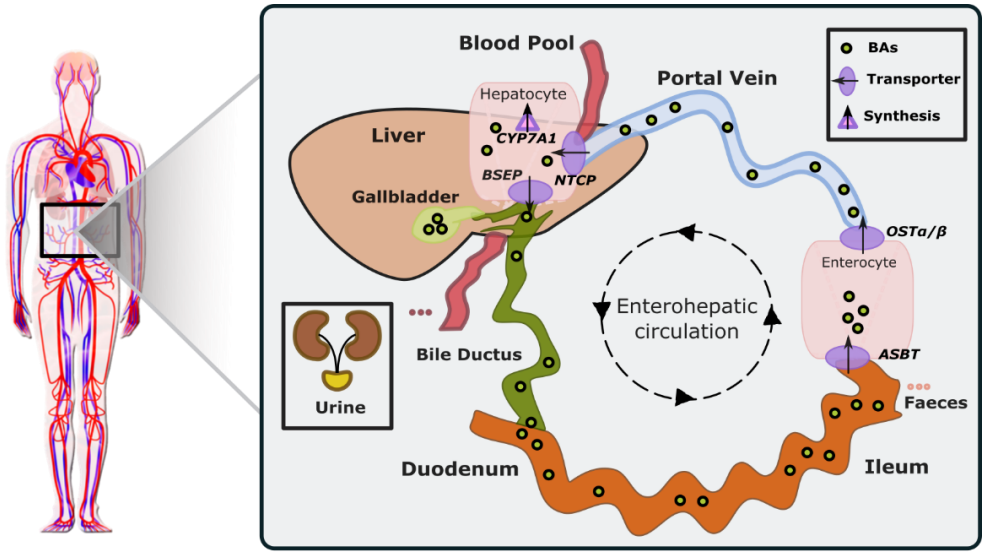
Keywords: bilirubin | disorders of bilirubin metabolism | interindividual variability | PBPK | population simulation | real-world data

ABSTRACT

Bilirubin is a breakdown product of erythrocytes and plays a crucial role in elimination of heme-containing proteins. After its

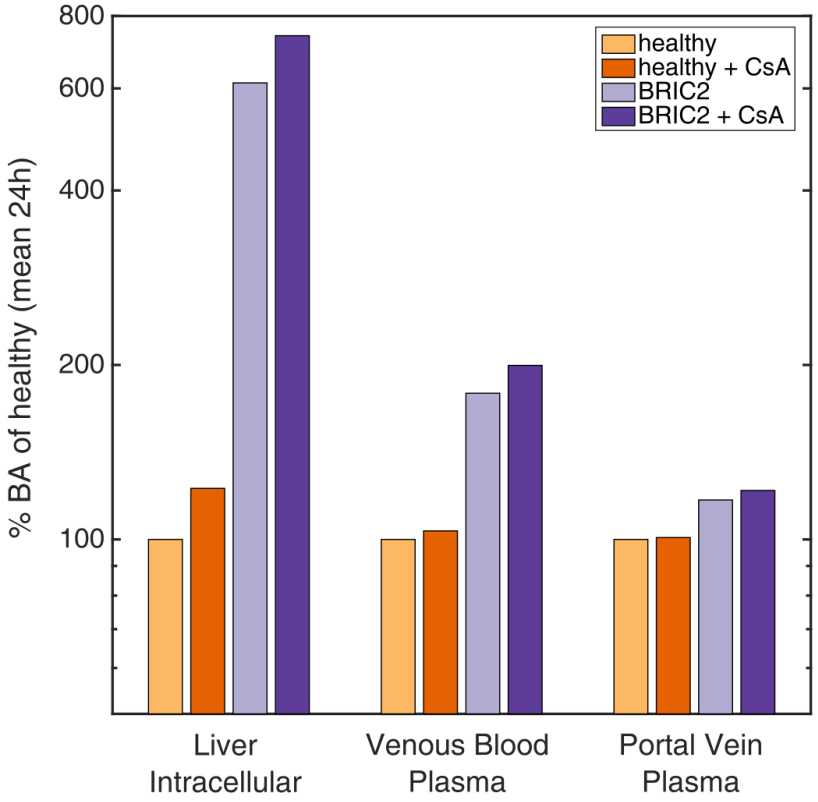
Sayin et al., CPT:PSP, 2026

Physiologically-based modelling of bile acid metabolism along the gut-liver axis



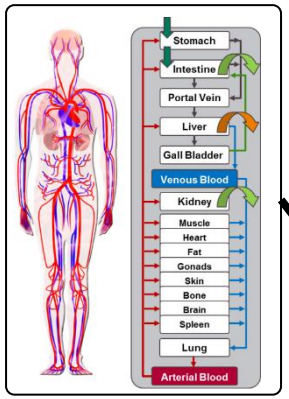
Validated for:

- bile acid concentration in venous blood
- bile acid concentration in portal vein blood
- bile acid concentration in gallbladder
- bile acid concentration in intestinal lumen
- bile acid concentration in liver cells
- total bile acid pool size
- synthesis rate
- faecal excretion rate
- secretion rate per meal



Baier *et al.*, *Front. in Physiol.*, 2019

PBPK-based assay design



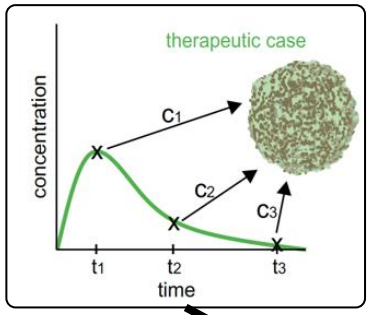
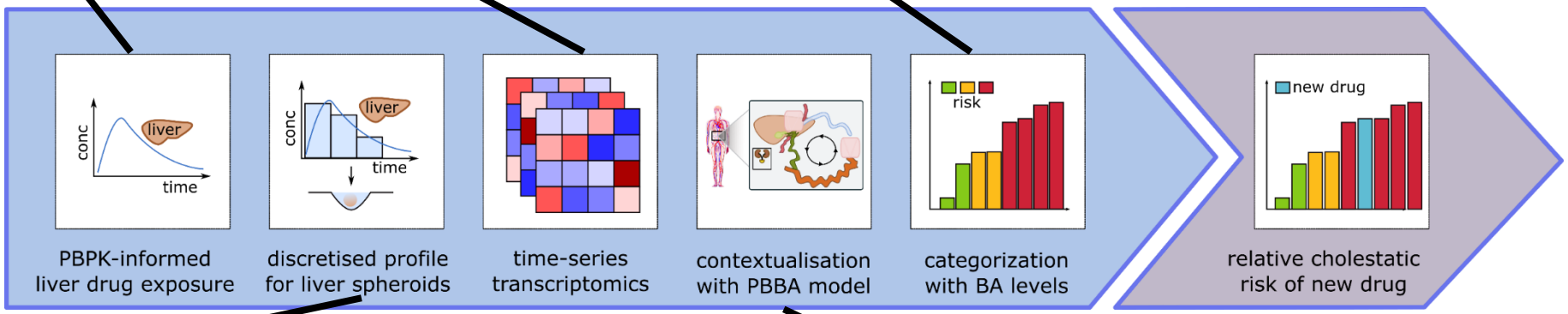
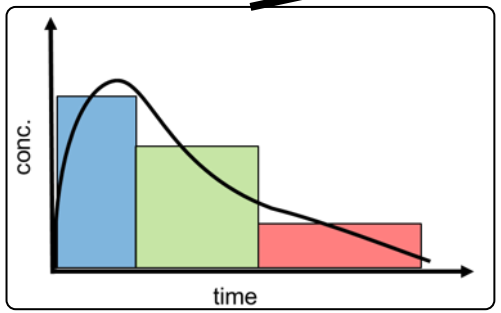


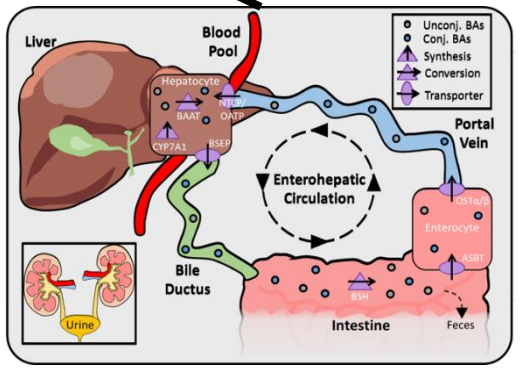
Table 2 Top ten implicated drugs in three prospective studies on DILI, DILIN study from the USA (Chalasani et al. 2008), a prospective study from Iceland (Björnsson et al. 2013) and Spain (Andrade et al. 2005)

DILIN study	Icelandic study	Spanish registry
Amoxicillin–clavulanate	Amoxicillin–clavulanate	Amoxicillin–clavulanate
Isoniazid	Diclofenac	Isoniazid
Nitrofurantoin	Azathioprine	RIP + INH + PIZ
SMZ/TMP	Infliximab	Flutamide
Minocycline	Nitrofurantoin	Ibuprofen
Azithromycin	Isotretinoin	Ebrotidina[a]
Ciprofloxacin	Atorvastatin	Diclofenac
Diclofenac	Doxycycline	Atorvastatin
Levofloxacin	Herbalife products	Ticlopidine

RIP + INH + PIZ: rifampin, isoniazid and pyrazinamide
SMZ/TMP sulfamethoxazole/trimethoprim
[a] Withdrawn from the Spanish market in 1998 due to hepatotoxicity

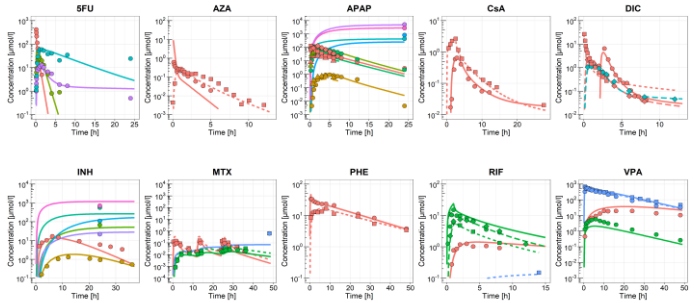


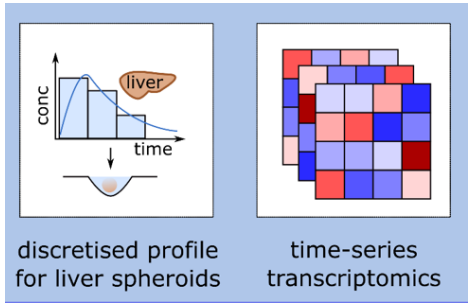


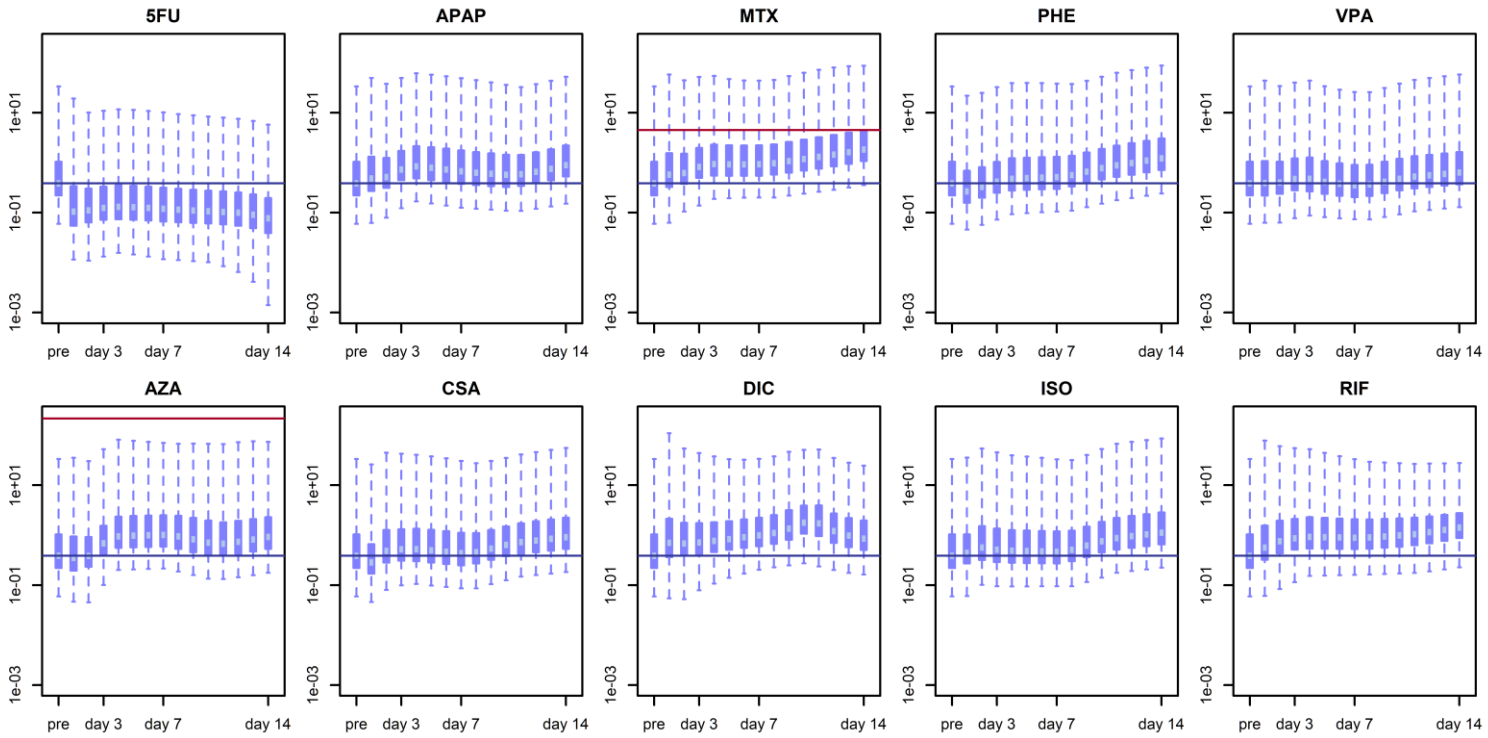


Baier *et al.*, *CPT*, 2021

Couping of PBPK models and bile acid model



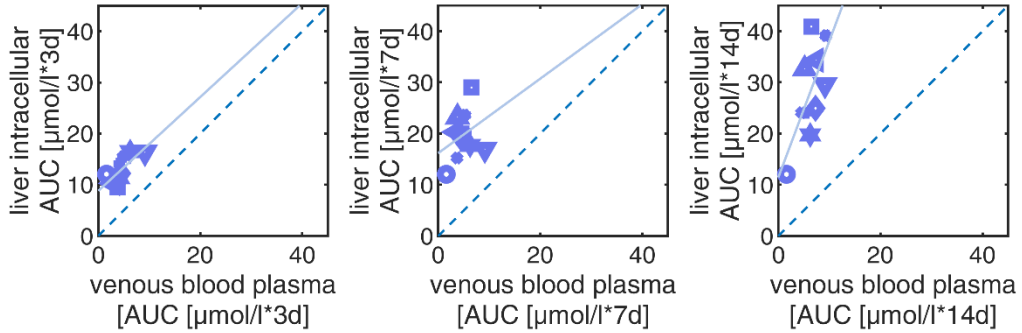




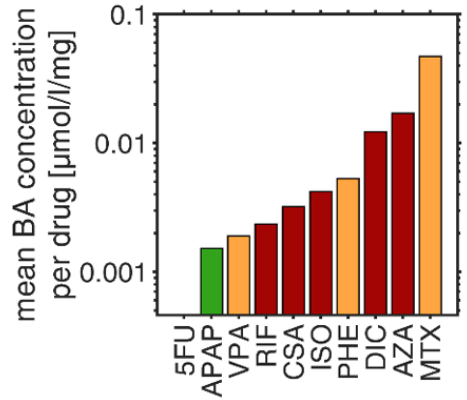
Baier *et al.*, *CPT*, 2021

Benchmark the clinical cholestasis risk of drugs

Venous blood vs. liver cells



Cholestatic potential

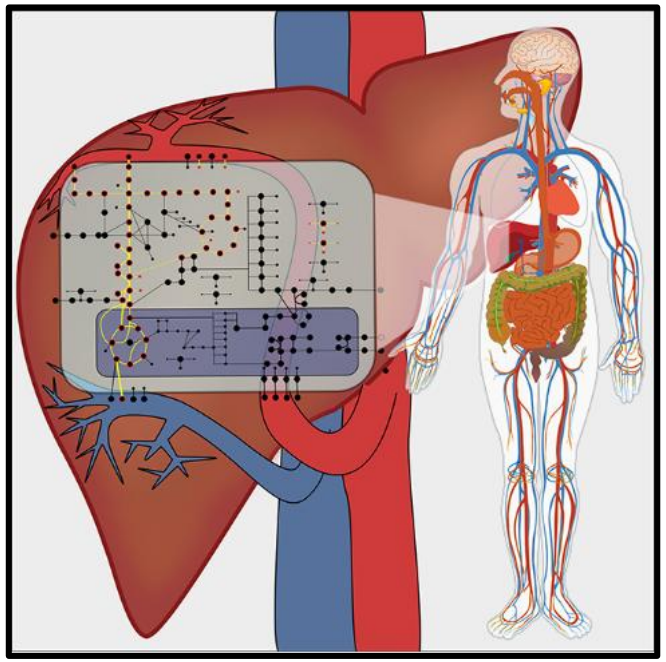


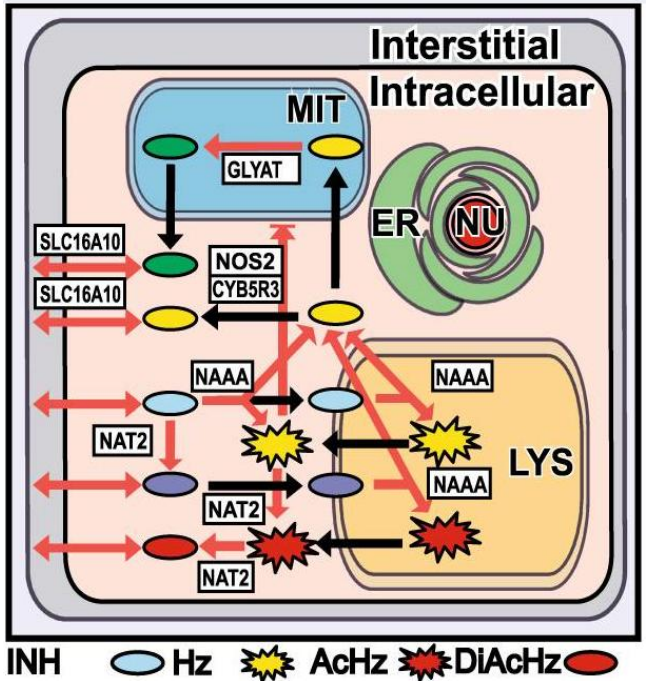
Clinical cholestasis risk

5FU	*APAP*	*MTX*	*PHE*	*VPA*	*AZA*	*CSA*	*DIC*	*ISO*	*RIF*
-	-	+	+	+	++++	++	++	+++	++

Baier *et al.*, *CPT*, 2021

Drug-induced metabolic perturbations

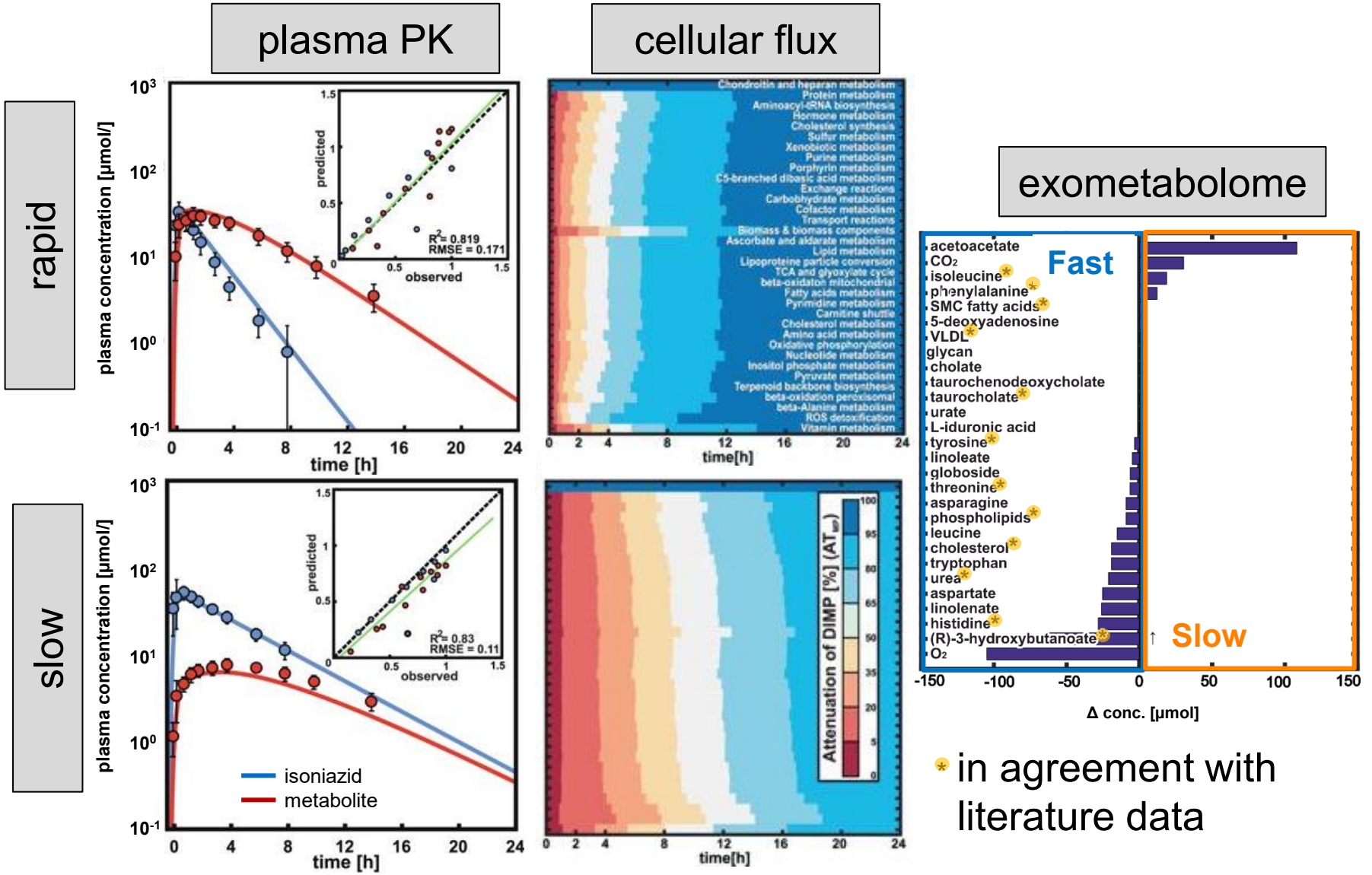




Coupling of endogenous and xenobotic metabolism through the **competitive demand** for redox cofactors and energy equivalents.

Krauss *et al*, *PLoS Comp Biol.*, 2012
Cordes *et al.*, *npj Sys. Biol and Appl.*, 2018

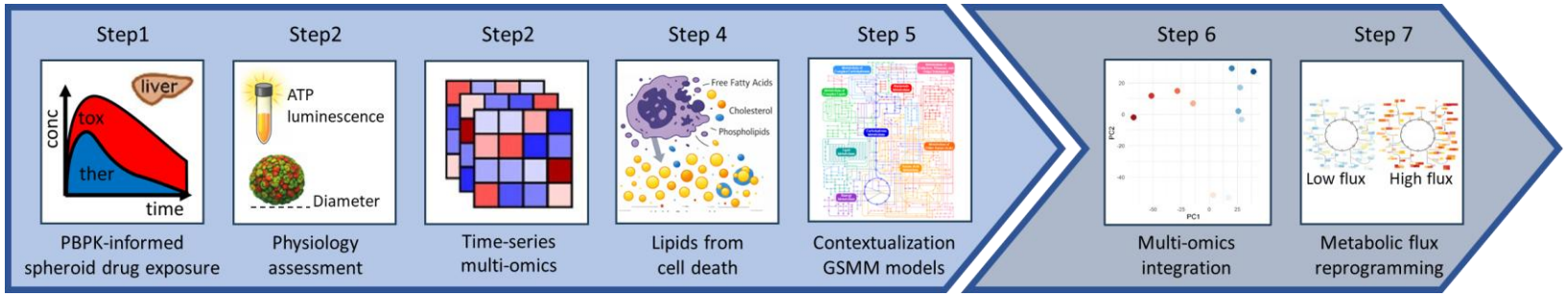
Metabolic response to isoniazid in rapid and slow NAT2 acetylators

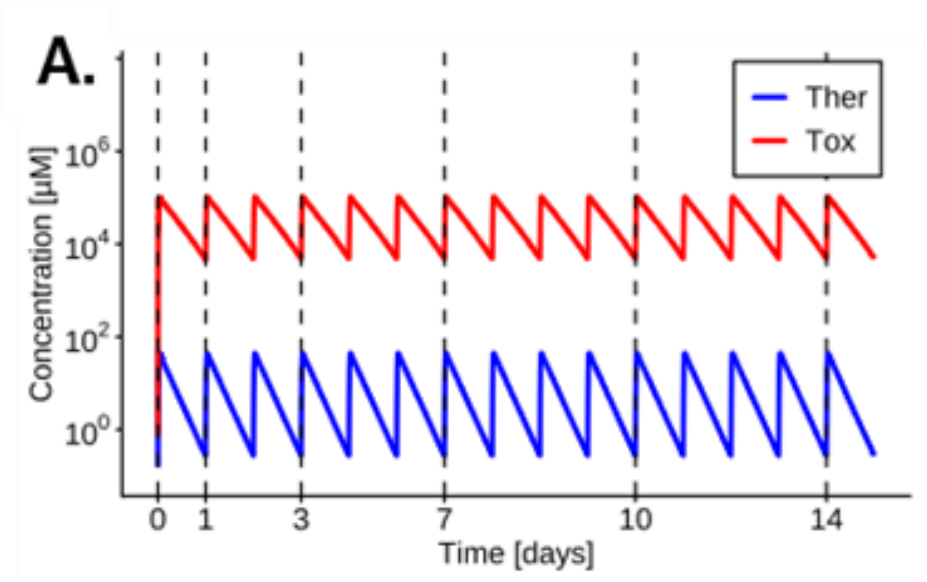


* in agreement with literature data

Cordes *et al.*, *Antimicrob Agents Chemother.* ,2016
Cordes *et al.*, *npj Sys. Biol and Appl.*, 2018

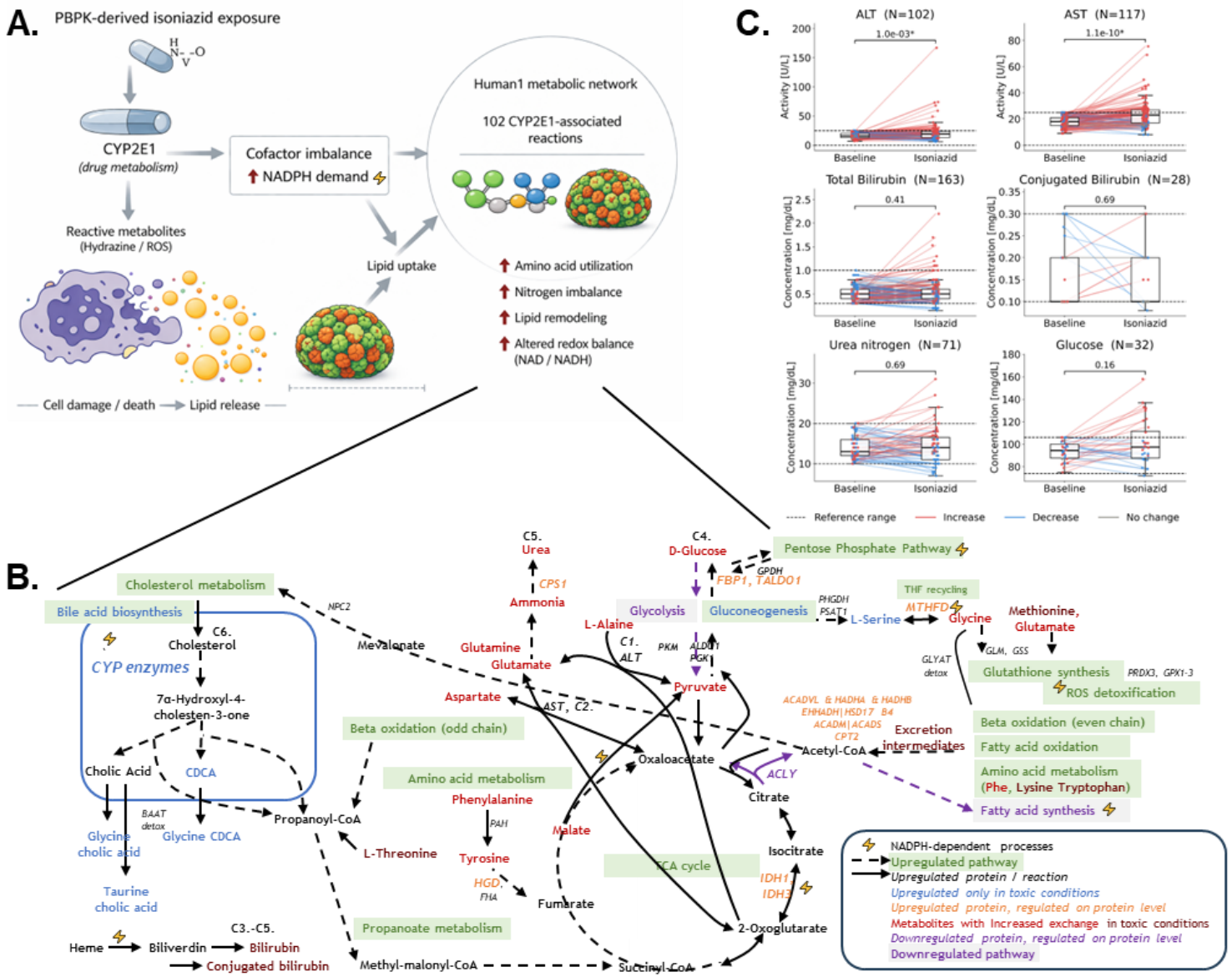
Physiologically relevant Multi-Omics Flux Analysis





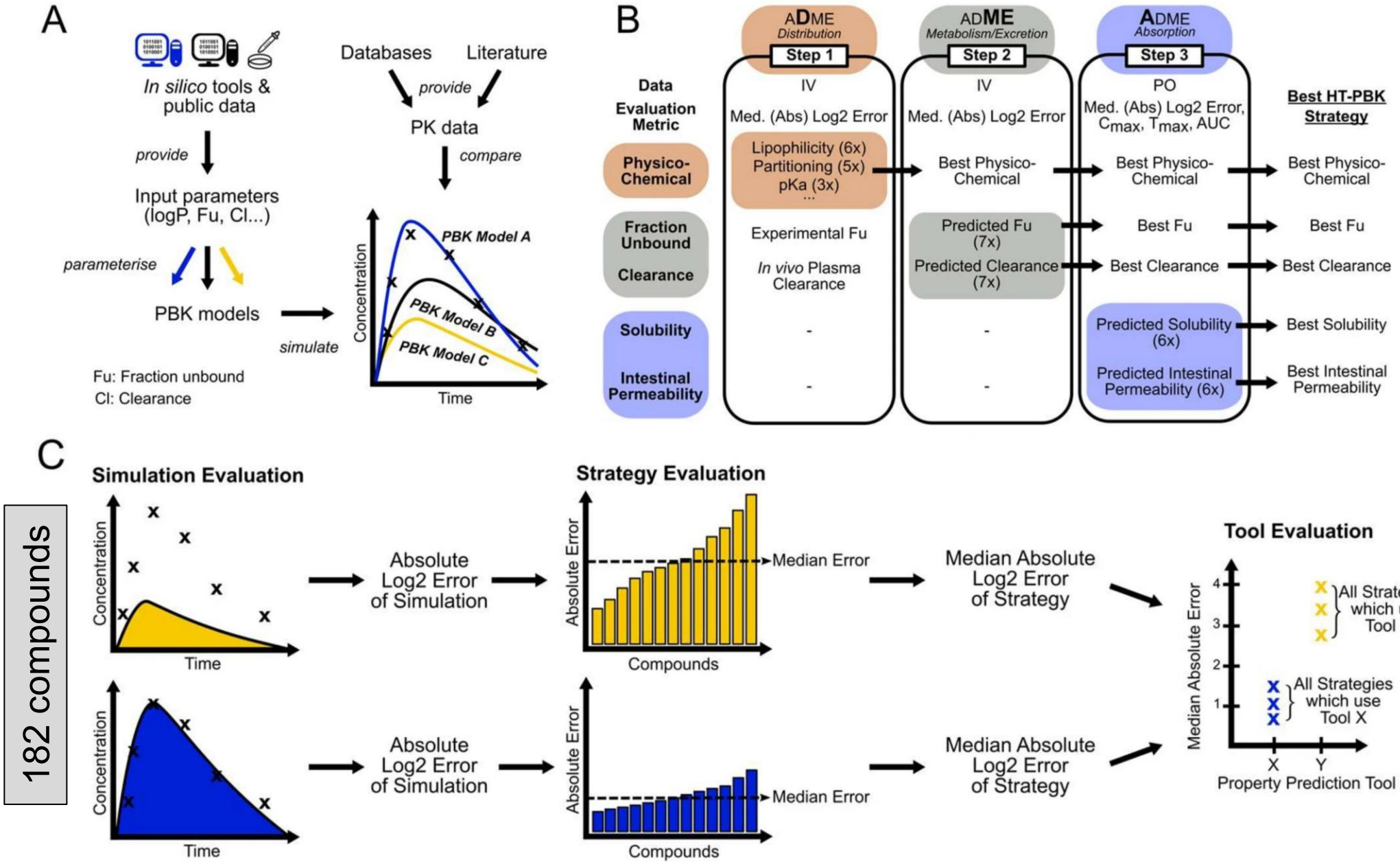
Soons *et al.*, *submitted*

Physiologically relevant Multi-Omics Flux Analysis



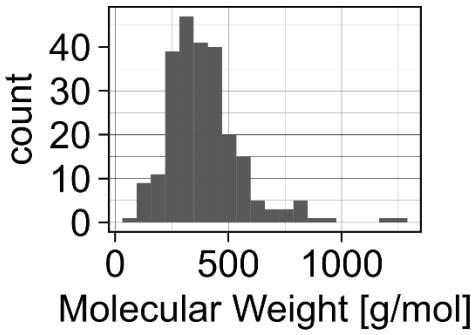
Soons *et al., submitted*

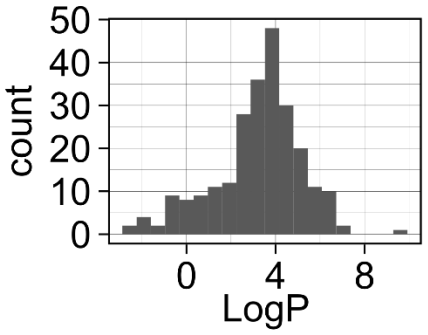
High-throughput PBPK models in humans

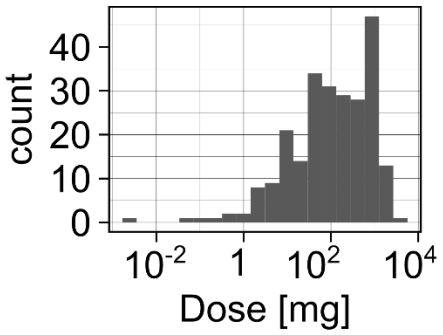


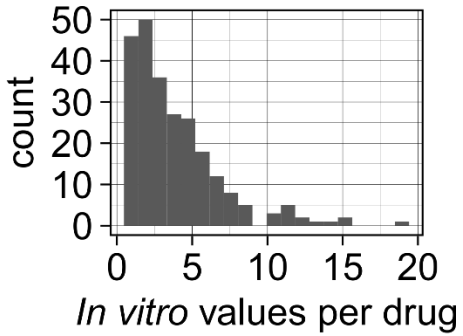
Geci et al. Archives of Toxicology, 2024

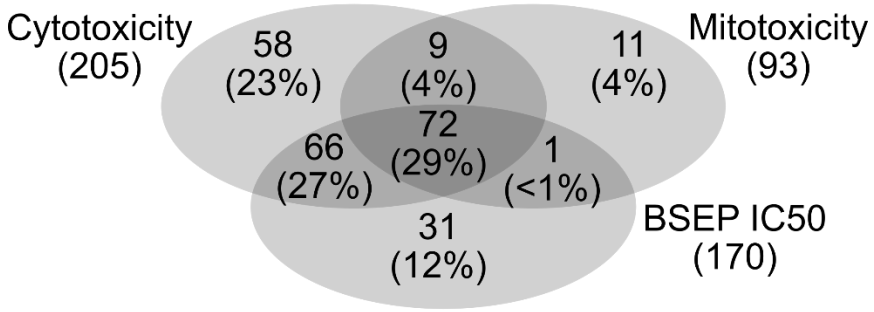
DILI datasets for 241 drugs

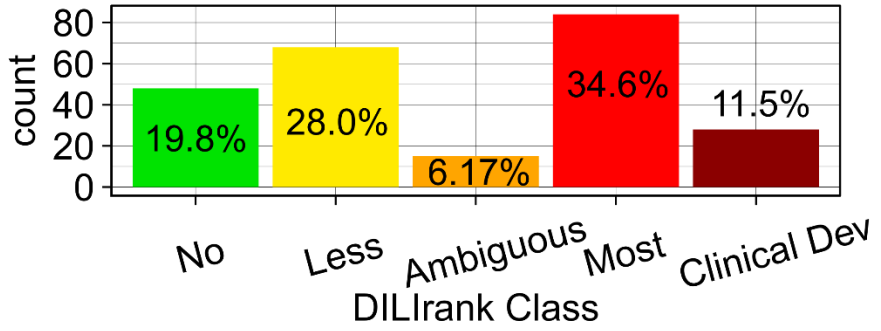






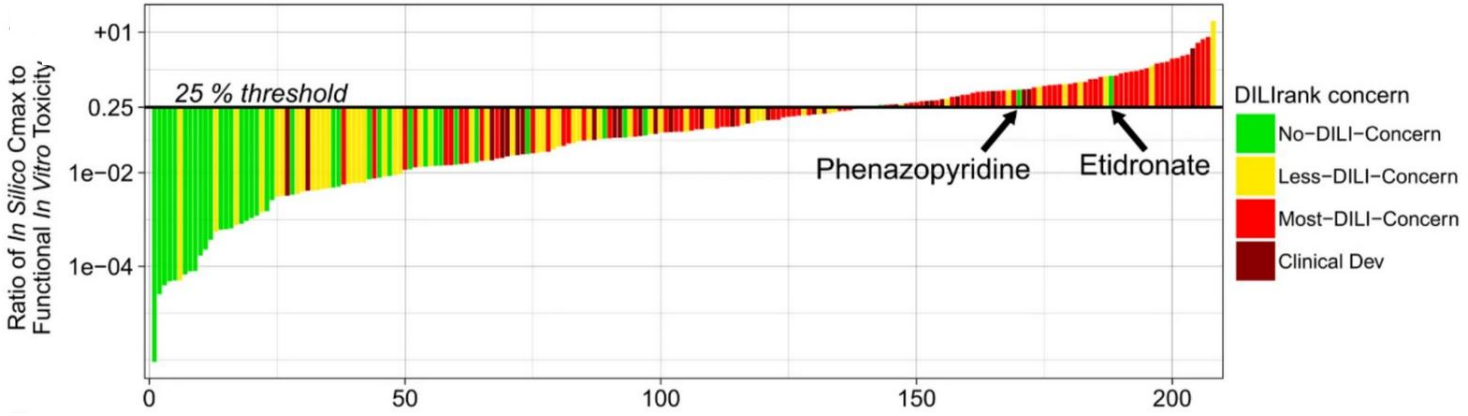


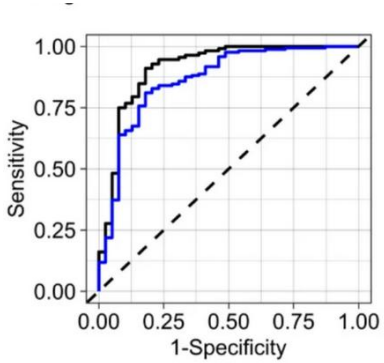


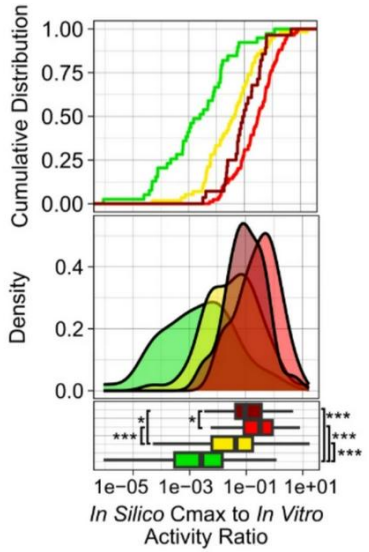


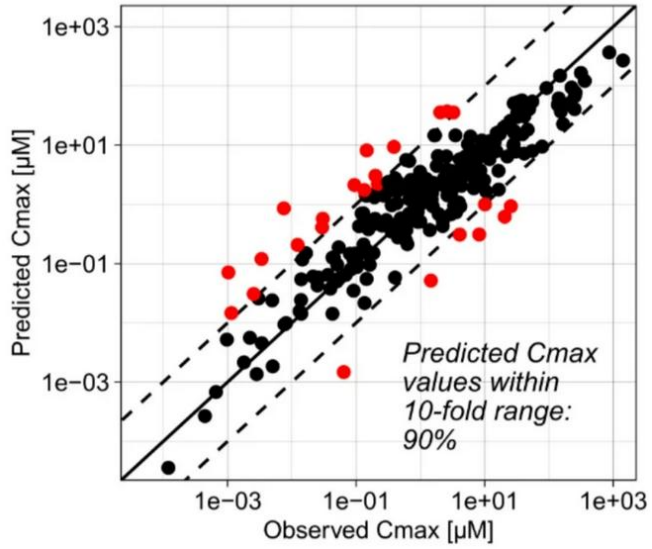
Geci et al. Archives of Toxicology, 2026

In silico Cmax to in vitro toxicity ratios: prospective DILI evaluation (ROC AUC: 0.86-0.91)





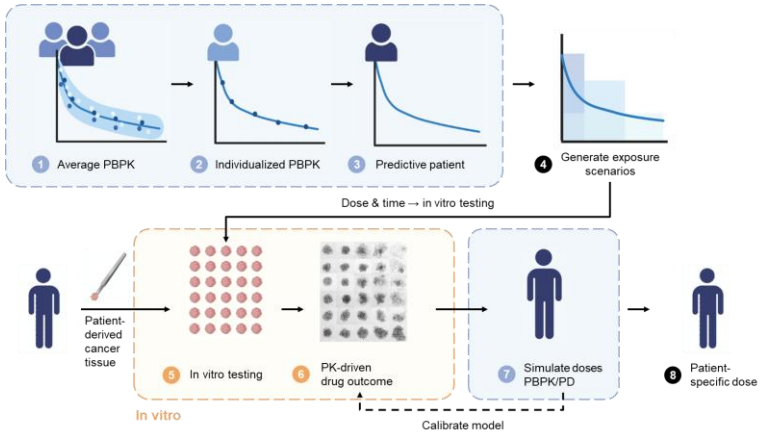




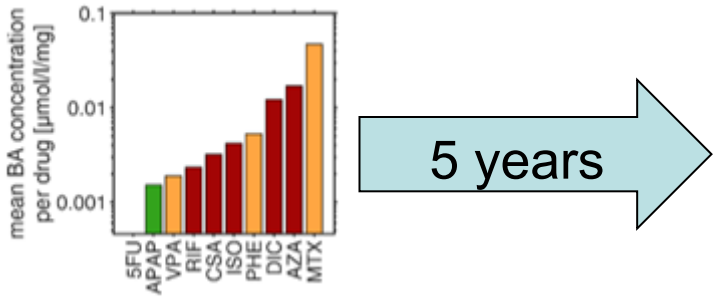
Geci et al. Archives of Toxicology, 2026

Conclusions

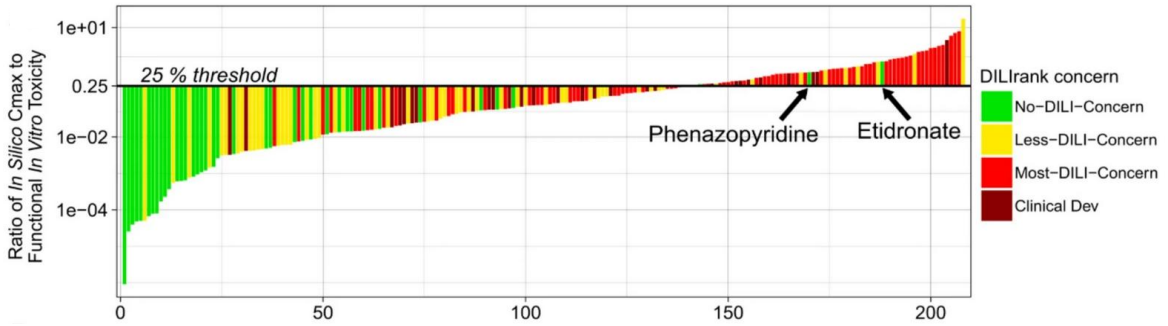
1. Towards model-informed precision dosing in oncology



2. Drug-induced liver injury



5 years



Acknowledgements

UNIKLINIK RWTH AACHEN

Vanessa Baier
Henrik Cordes
Christoph Thiel
Bastian Kister
Rebekka Fendt
Hannah Dorn
René Geci
Ravi Jairam
Si-Eun Lee
Ahenk Zeynep Sayin
Zita Soons

iAMB Institute of Applied Microbiology RWTH AACHEN

Lars M. Blank

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Stephan Schaller

PreComb Therapeutics

Micaela Freitas
Severin Manser
Jens Kelm

JÜLICH Forschungszentrum

Marco Oldiges

BAYER

Annika Schneider
Christoph Niederalt
Markus Krauss
Christian Scheerans
Rolf Burghaus
Jörg Lippert

Maastricht University

Jos Kleinjans

Instituto de Investigación Sanitaria La Fe

José V.Castell

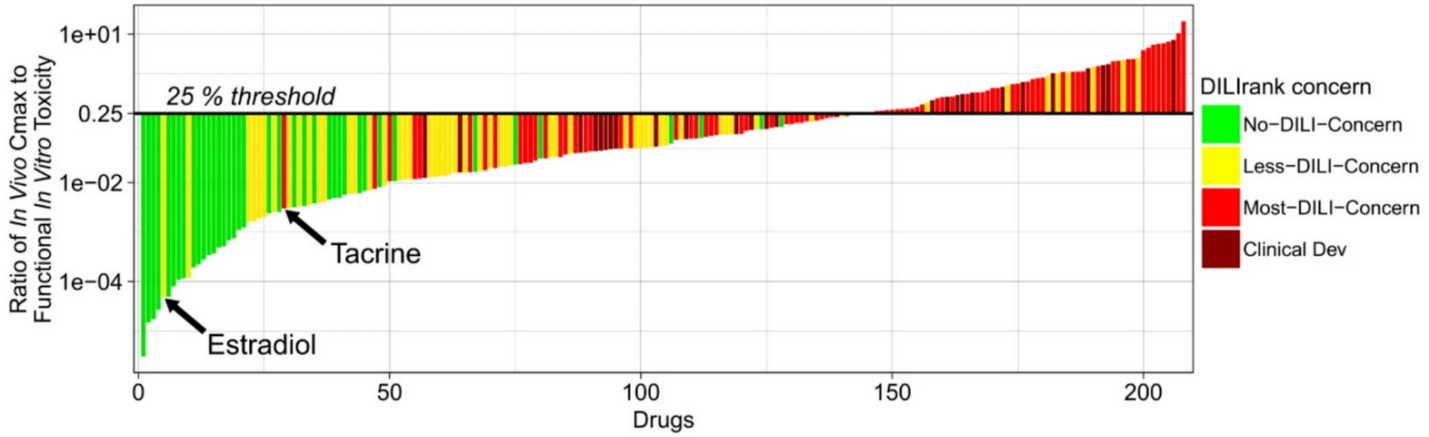
KiTZ Hopp-Kindertumorzentrum Heidelberg

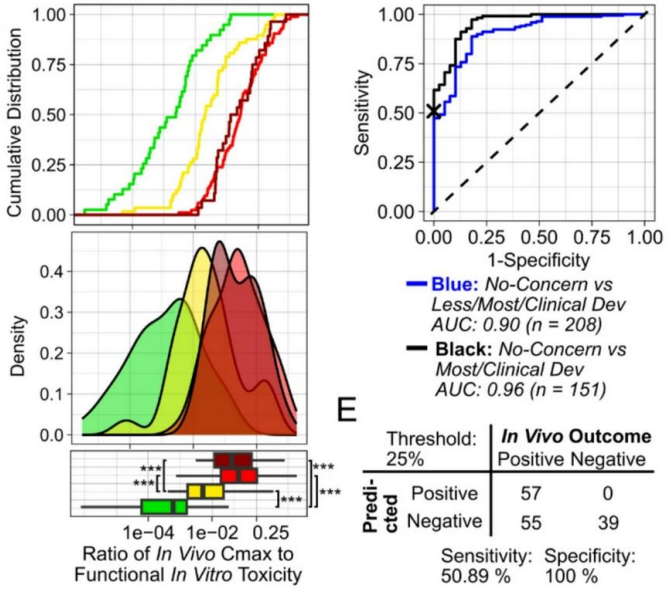
Ina Oehme
Marko Weidmann
Heike Peterziel
Olaf Witt

Roche

Adrian Roth

In vivo Cmax to in vitro toxicity ratios: retrospective DILI evaluation (ROC AUC: 0.9-0.96)

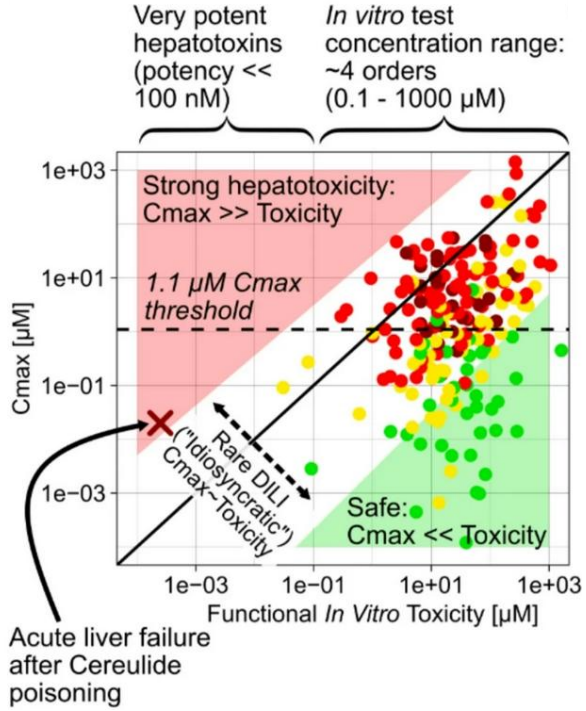




E

Threshold: 25%		*In Vivo* Outcome Positive	Negative
Predicted	Positive	57	0
	Negative	55	39

Sensitivity: 50.89 % Specificity: 100 %



Geci et al. Archives of Toxicology, 2026