



Science For A Better Life

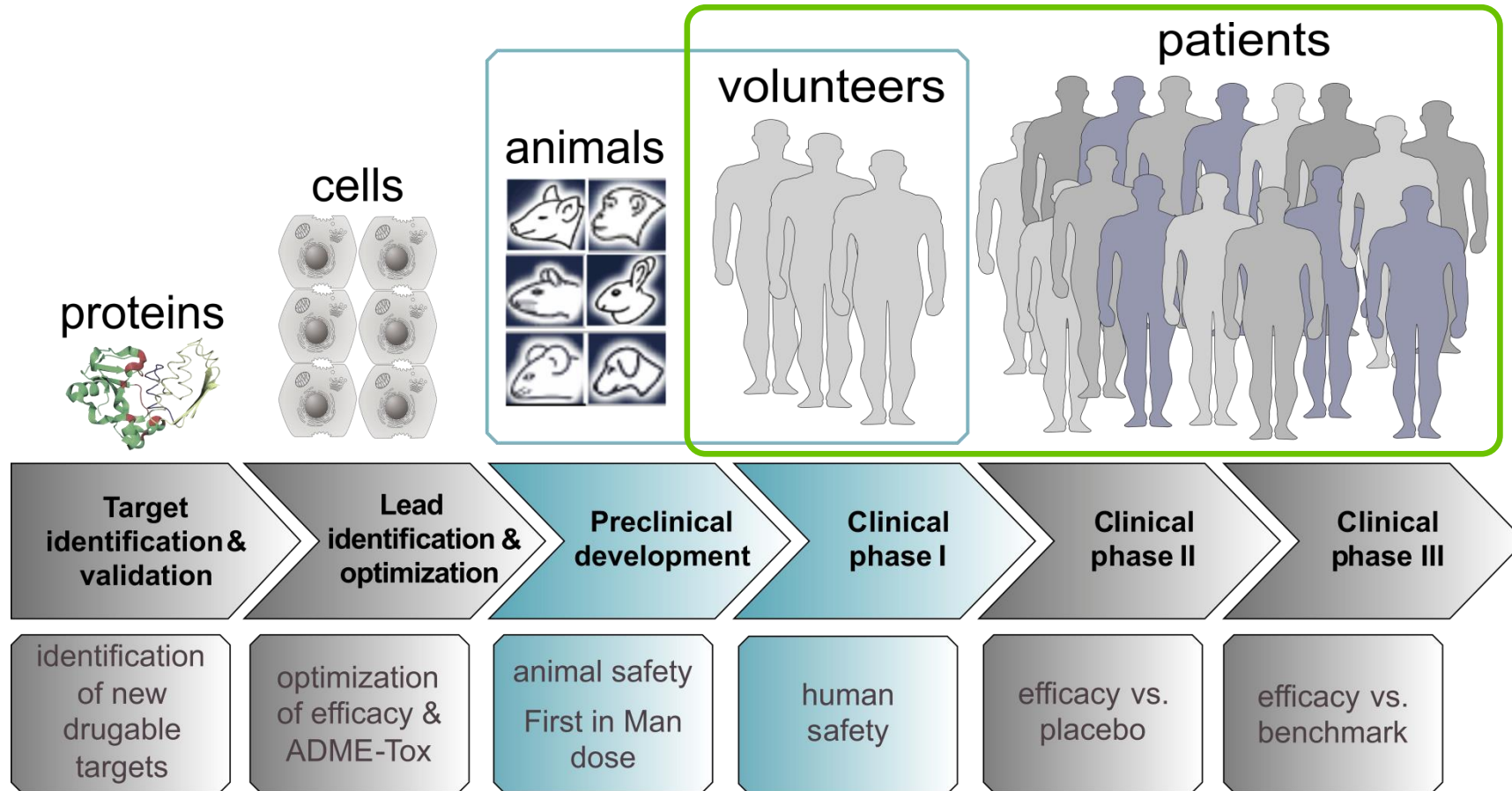


Translational systems pharmacology for acquisition of knowledge and prediction of drug pharmacokinetics across patient populations

Markus Krauß

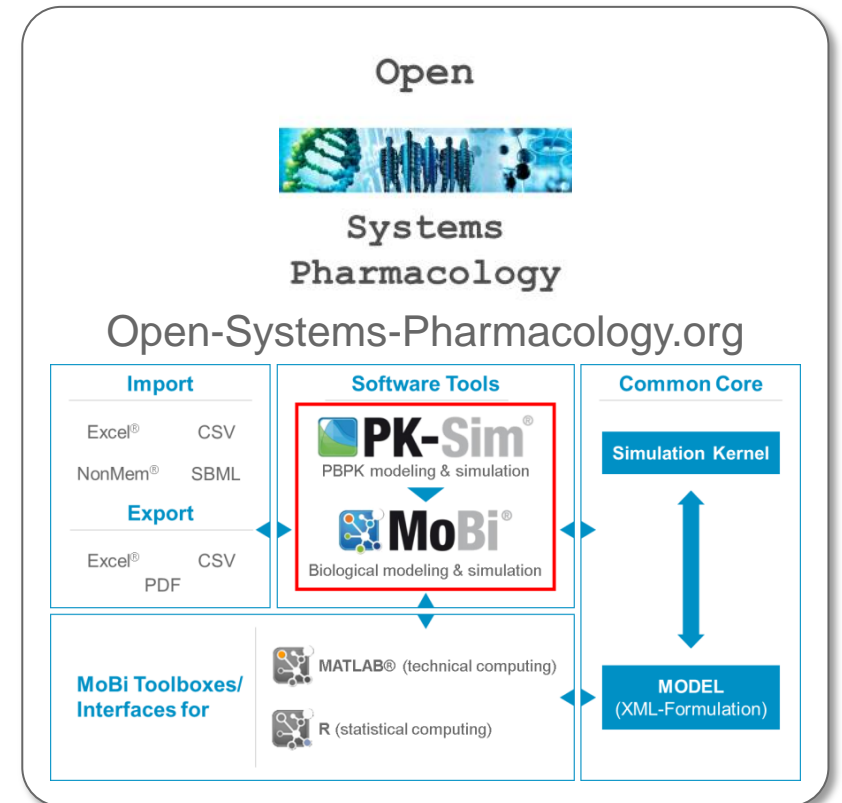
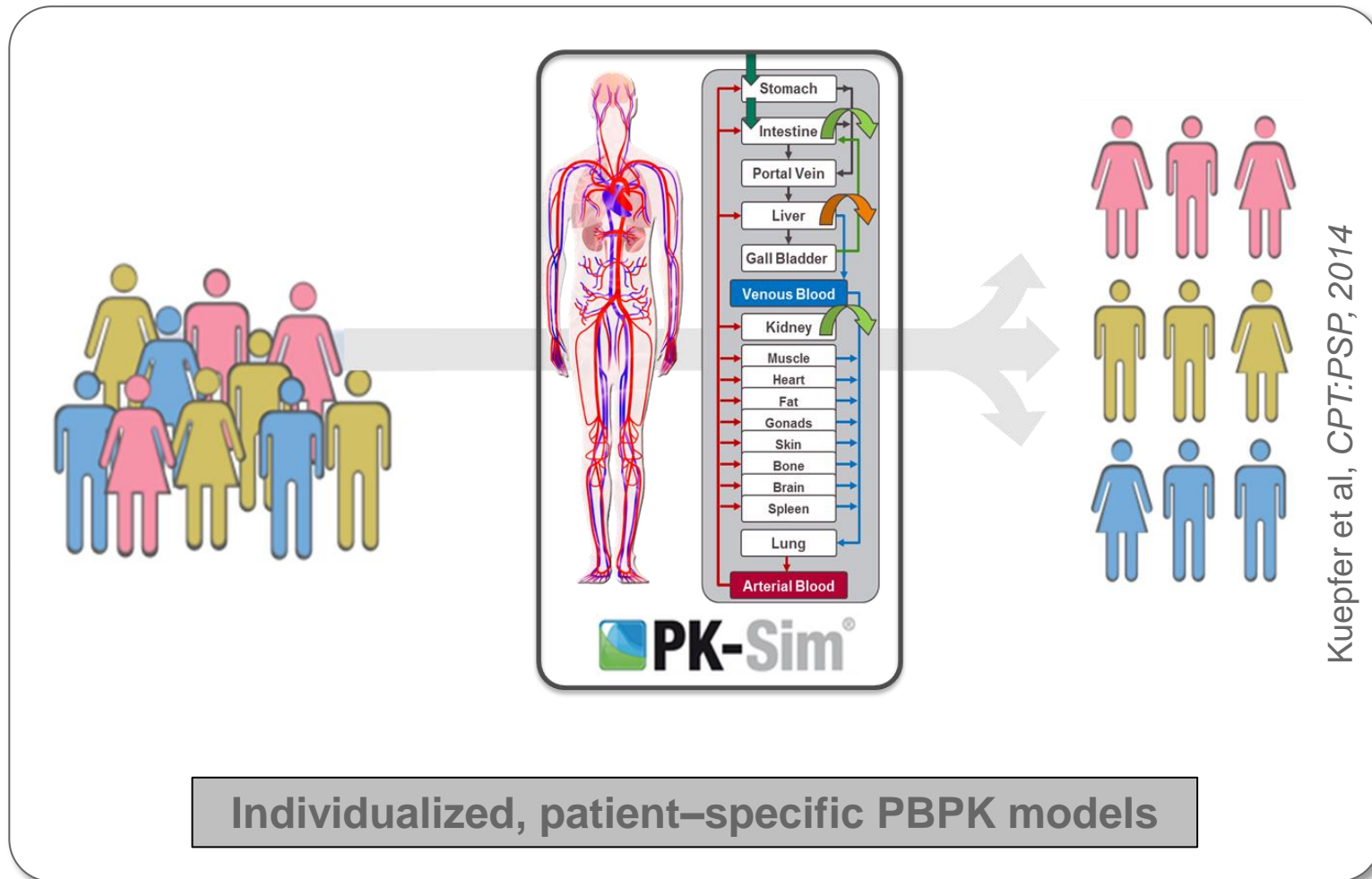
PAGE meeting - 09.06.2017

Translation of knowledge as a key challenge in clinical development

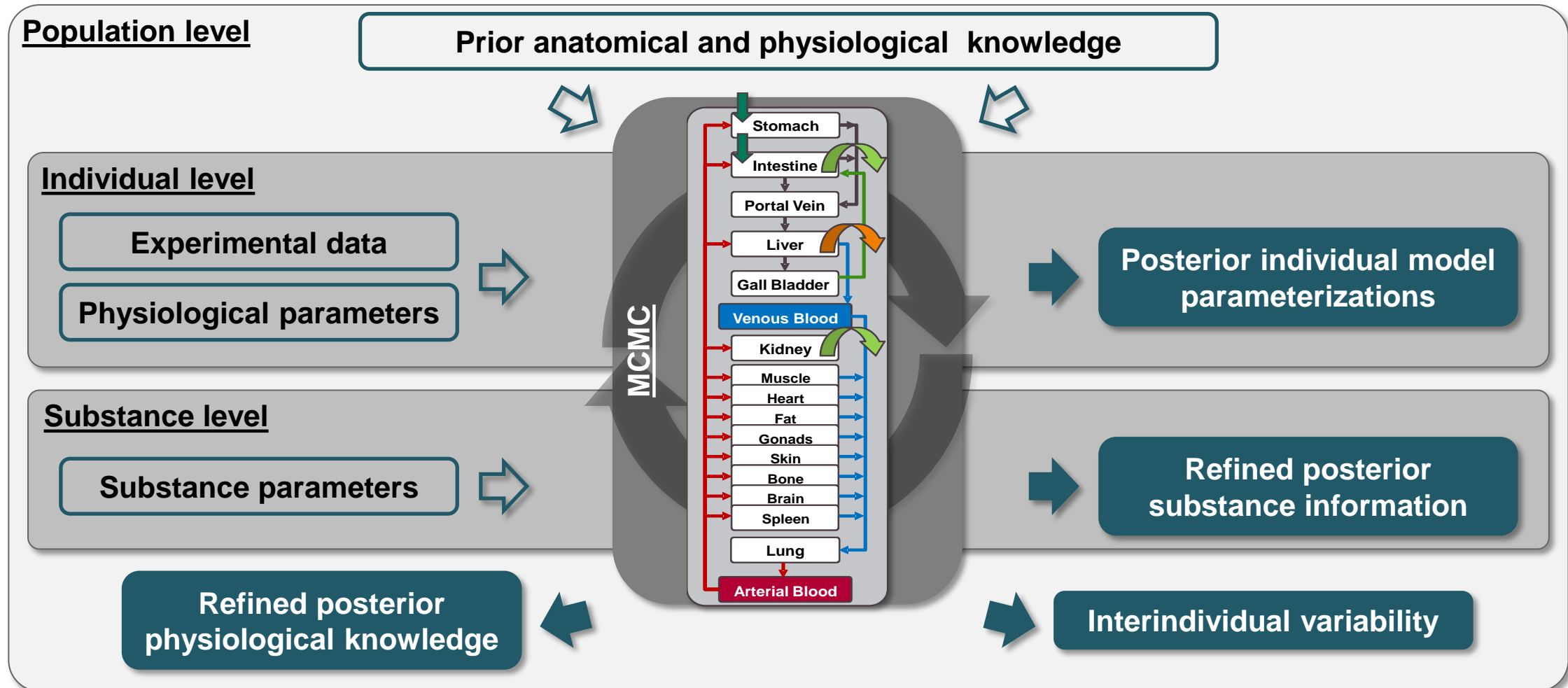


Thiel et al., Drug discov. today: disease models, 2017

Physiologically-based pharmacokinetic (PBPK) models enable patient stratification and individualization

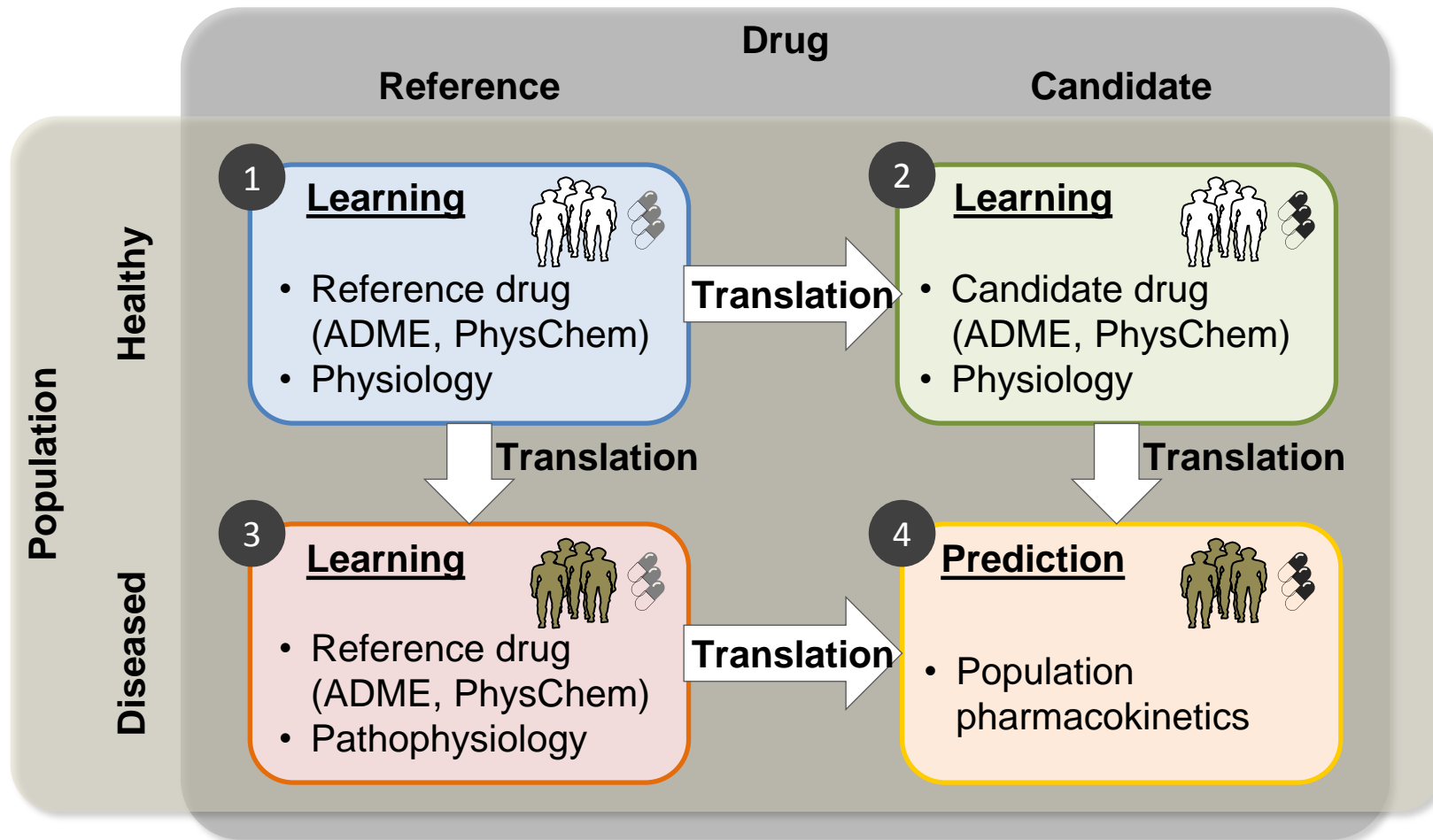


Bayesian population PBPK combines prior knowledge and information from experimental data



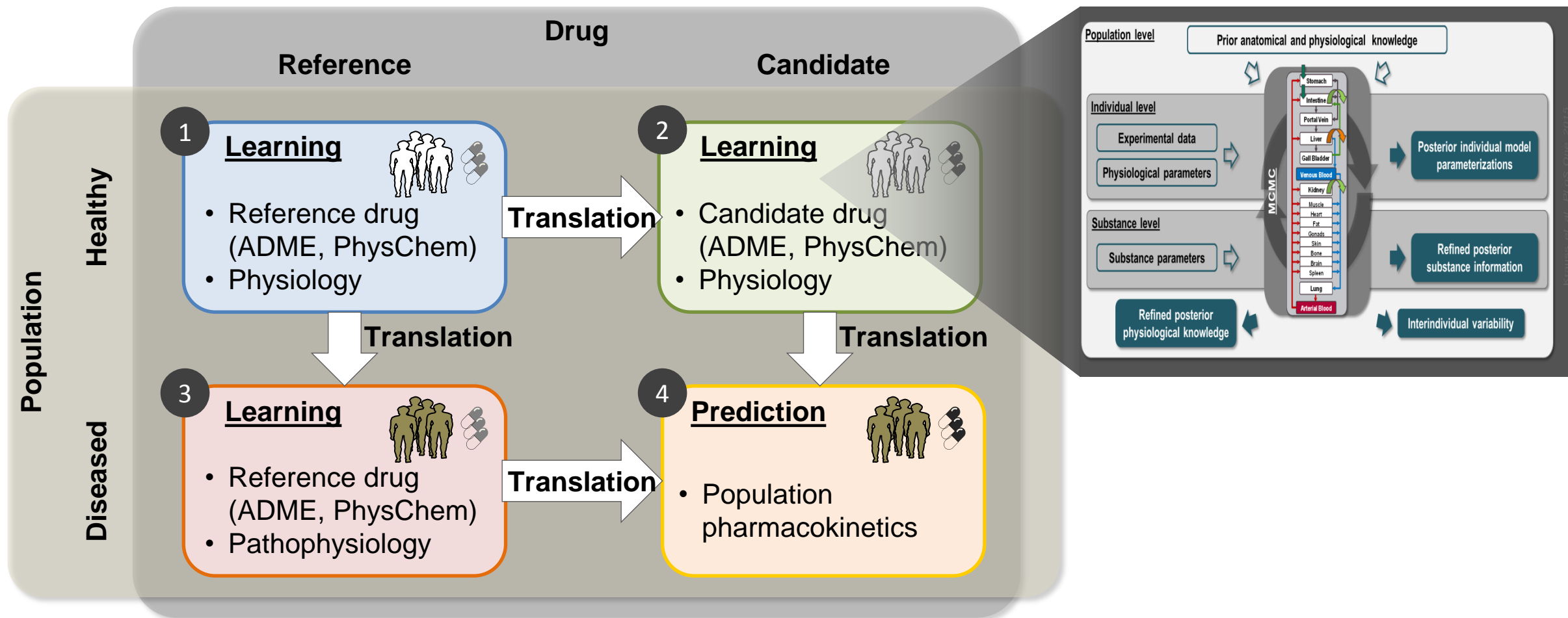
Krauss et al., PLoS One, 2015

A translational learning workflow for prediction of drug pharmacokinetics



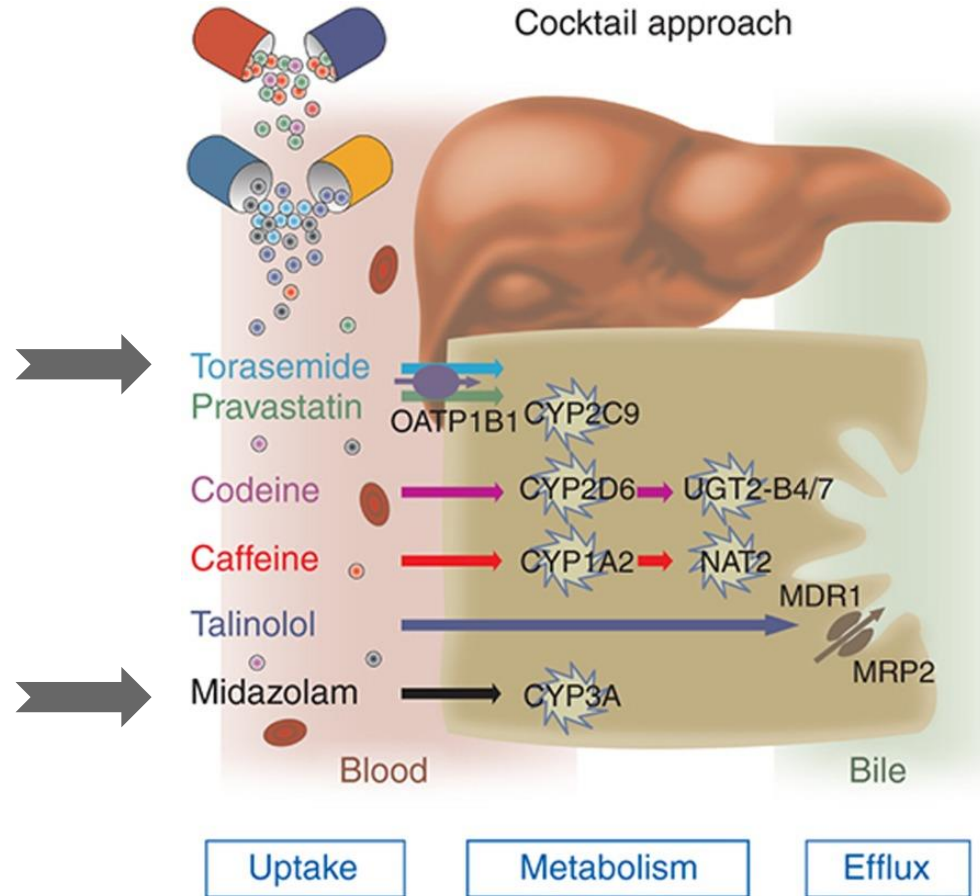
Krauss et al., *npj Syst. Biol & Appl.*, 2017

A translational learning workflow for prediction of drug pharmacokinetics



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

A specifically-designed drug cocktail probing study provides experimental data



Kuepfer et al, CPT:PSP, 2014

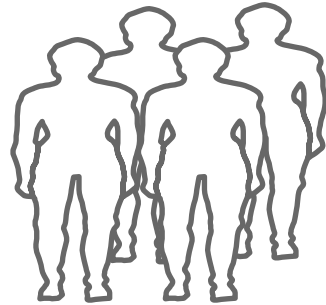


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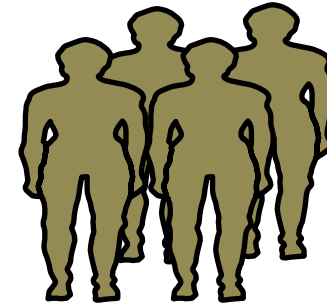


Federal Ministry
of Education
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The same experimental setting was considered for two different cohorts of individuals



Healthy cohort
103 healthy volunteers

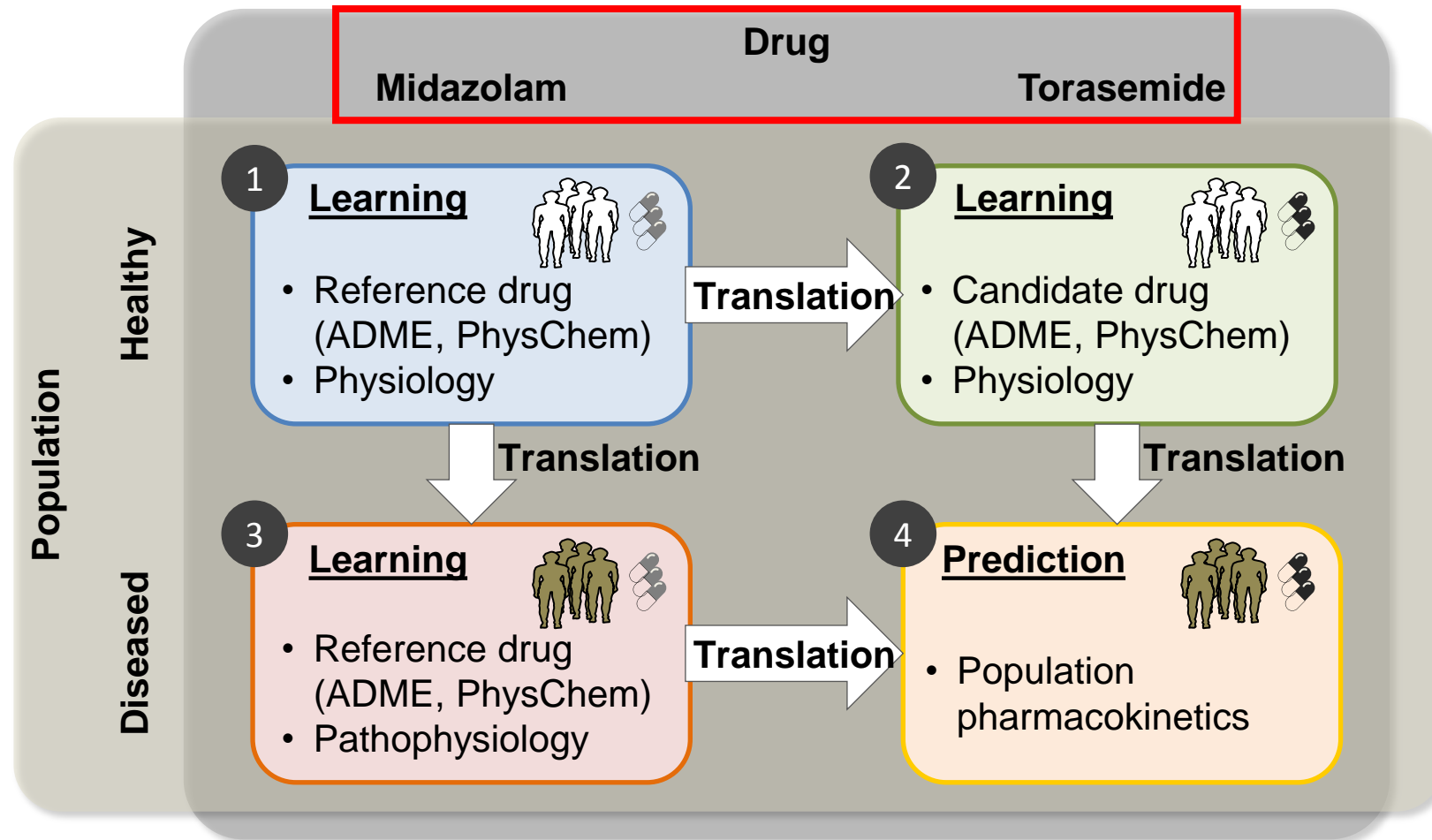


Diseased cohort
79 obese patients

	N	Male [#]	age [years]		body weight [kg]		body height [cm]		body mass index	
			median	[min max]	median	[min max]	median	[min max]	median	[min max]
healthy individuals	103	54	28	[18 56]	74.5	[48.5 113]	174	[154 194]	23.5	[18.8 32.3]
diseased patients	79	33	45	[20 77]	138	[52 206]	175	[156 192]	47.3	[19.7 67.1]

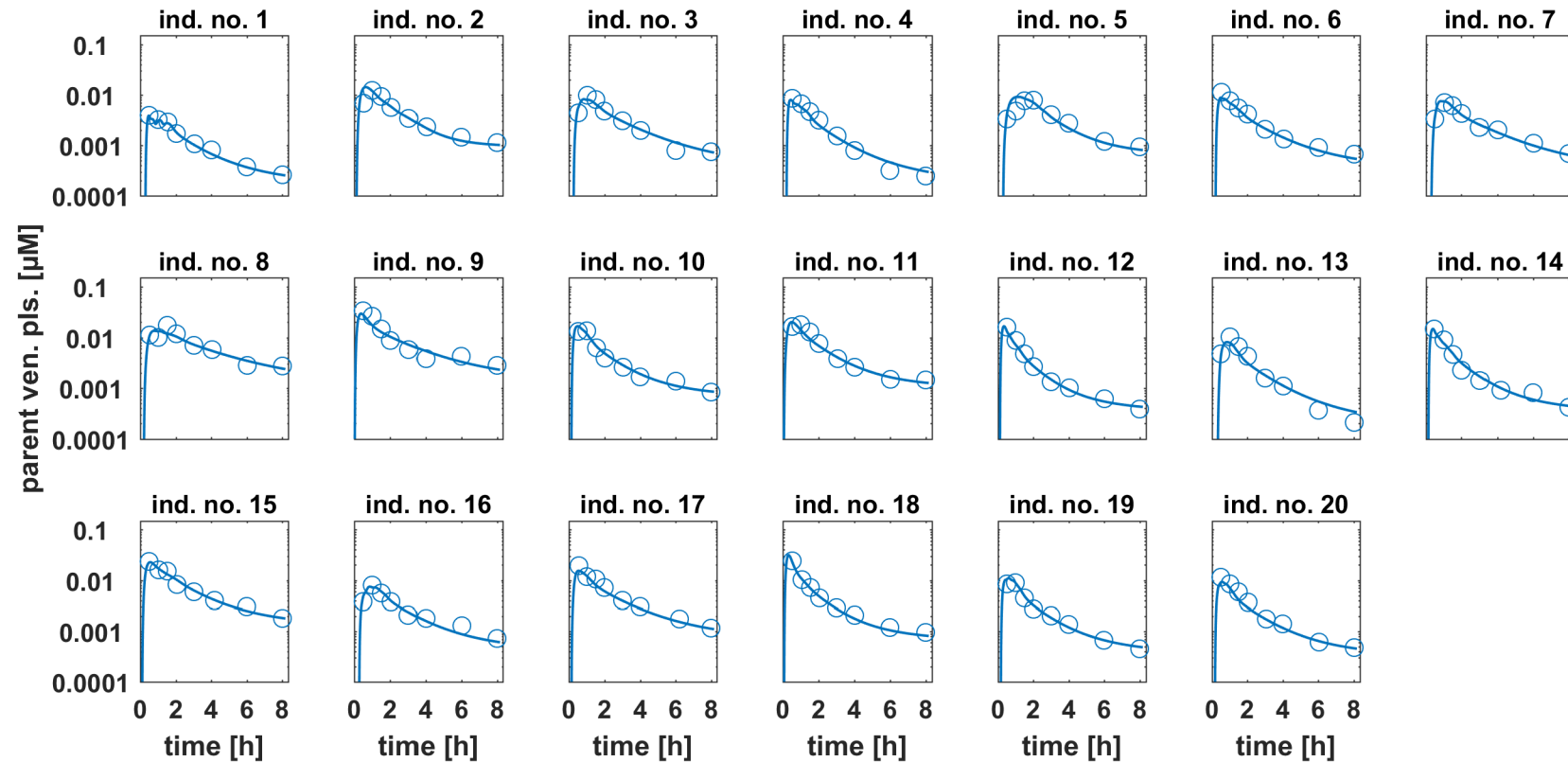
Krauss et al., npj Syst. Biol & Appl., 2017

Application of the developed workflow as a proof of concept study



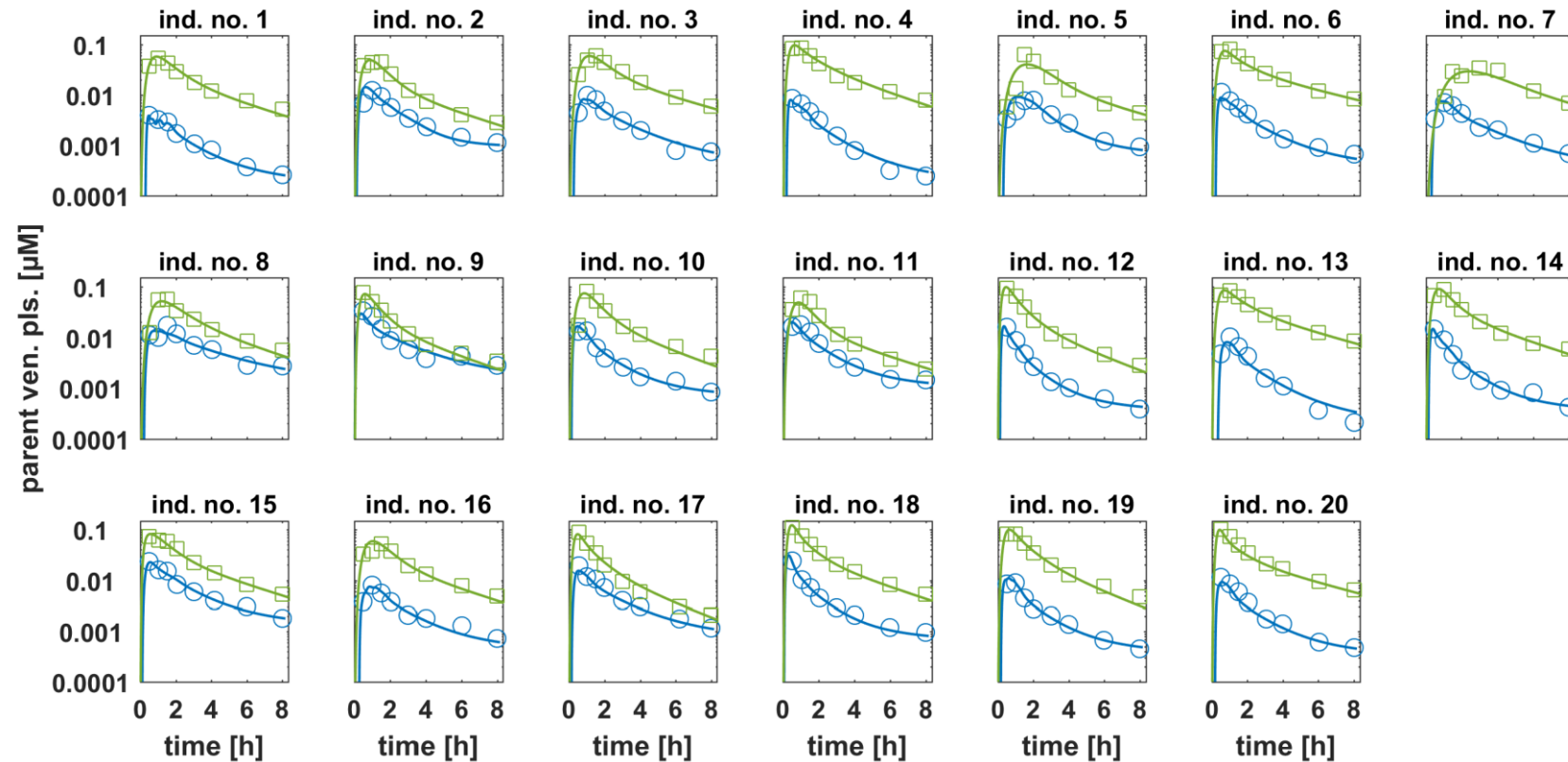
Krauss et al., npj Syst. Biol & Appl., 2017

Individualized PK simulations as a key result of each Bayesian PBPK learning step



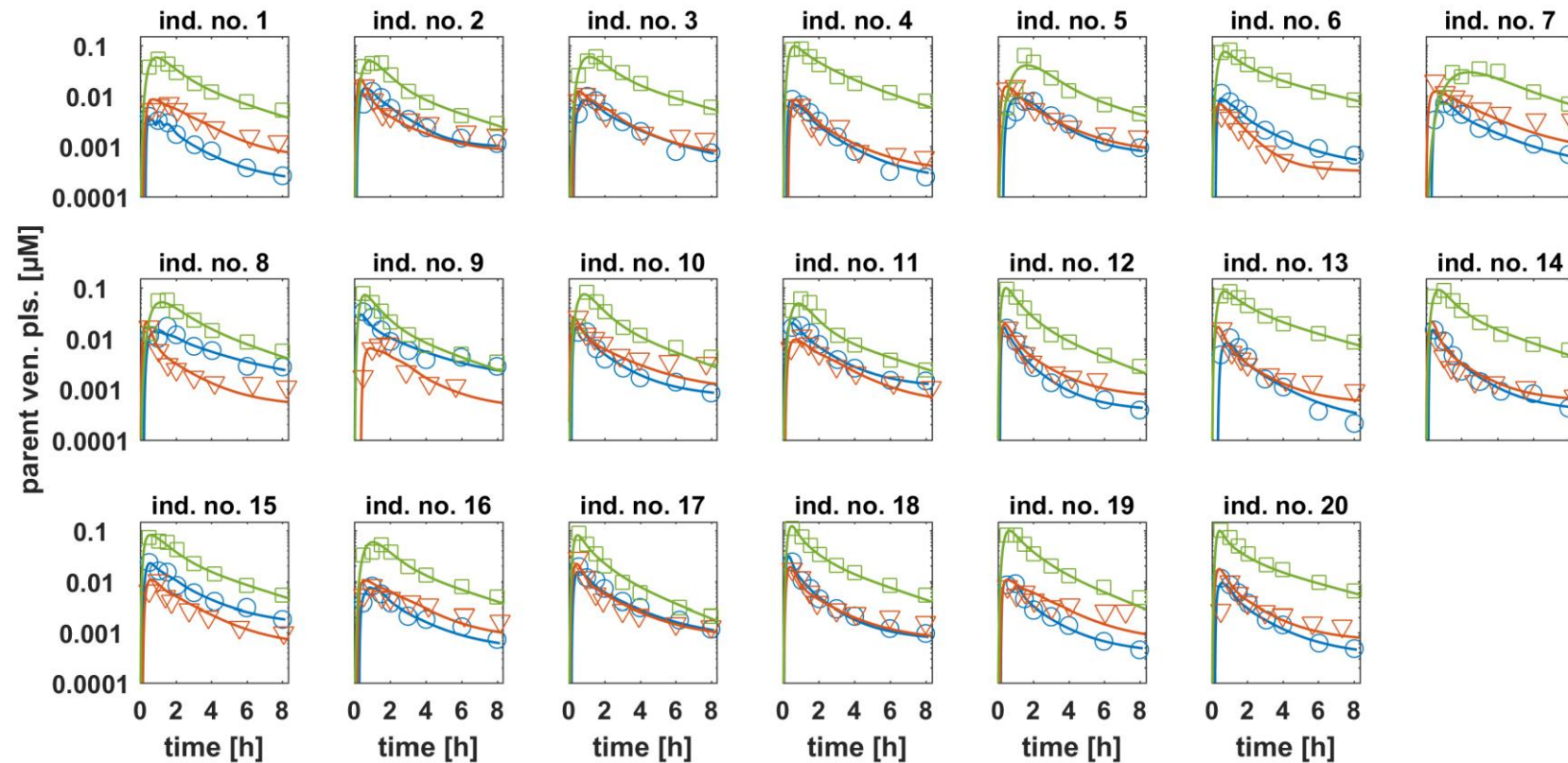
Krauss et al., *npj Syst. Biol & Appl.*, 2017

Individualized PK simulations as a key result of each Bayesian PBPK learning step



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

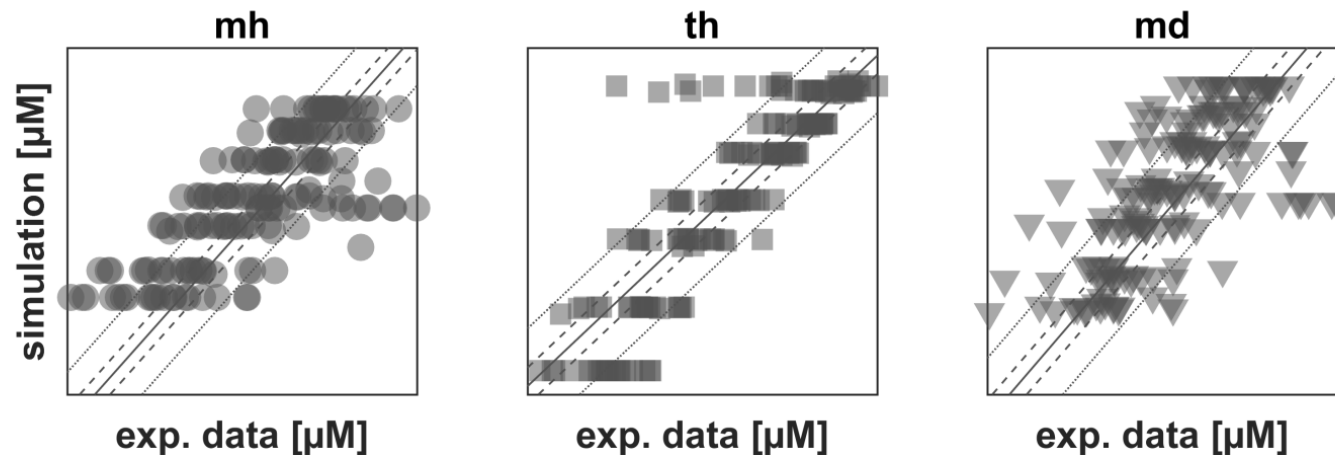
Individualized PK simulations as a key result of each Bayesian PBPK learning step



— midazolam, healthy — torasemide, healthy — midazolam, obese

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

Starting from mean patient models...



Prior

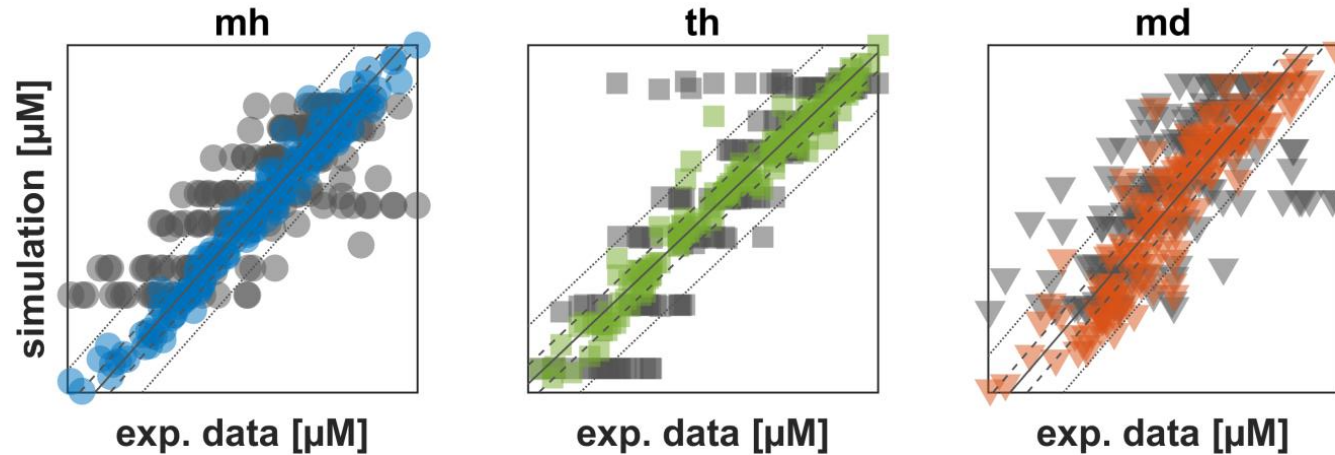
● midazolam, healthy

■ torasemide, healthy

▼ midazolam, diseased

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

... model individualization strongly improves model accuracy



Prior

● midazolam, healthy

■ torasemide, healthy

▼ midazolam, diseased

Posterior

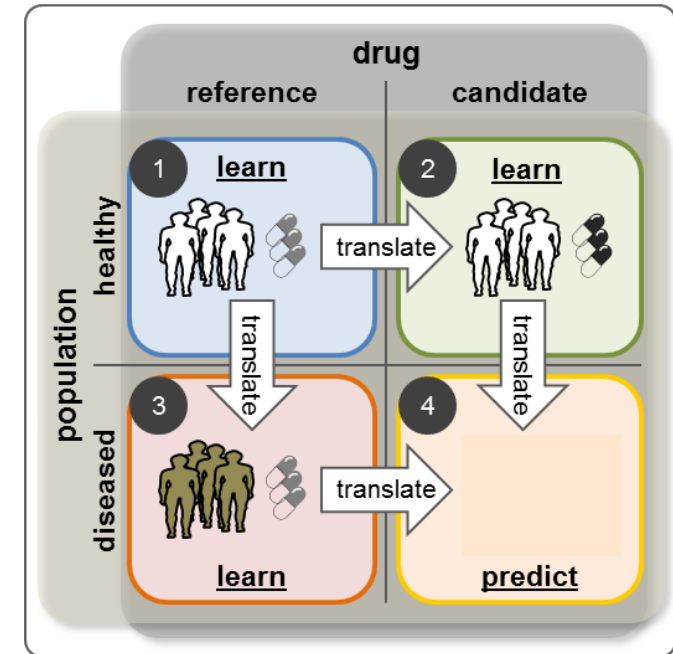
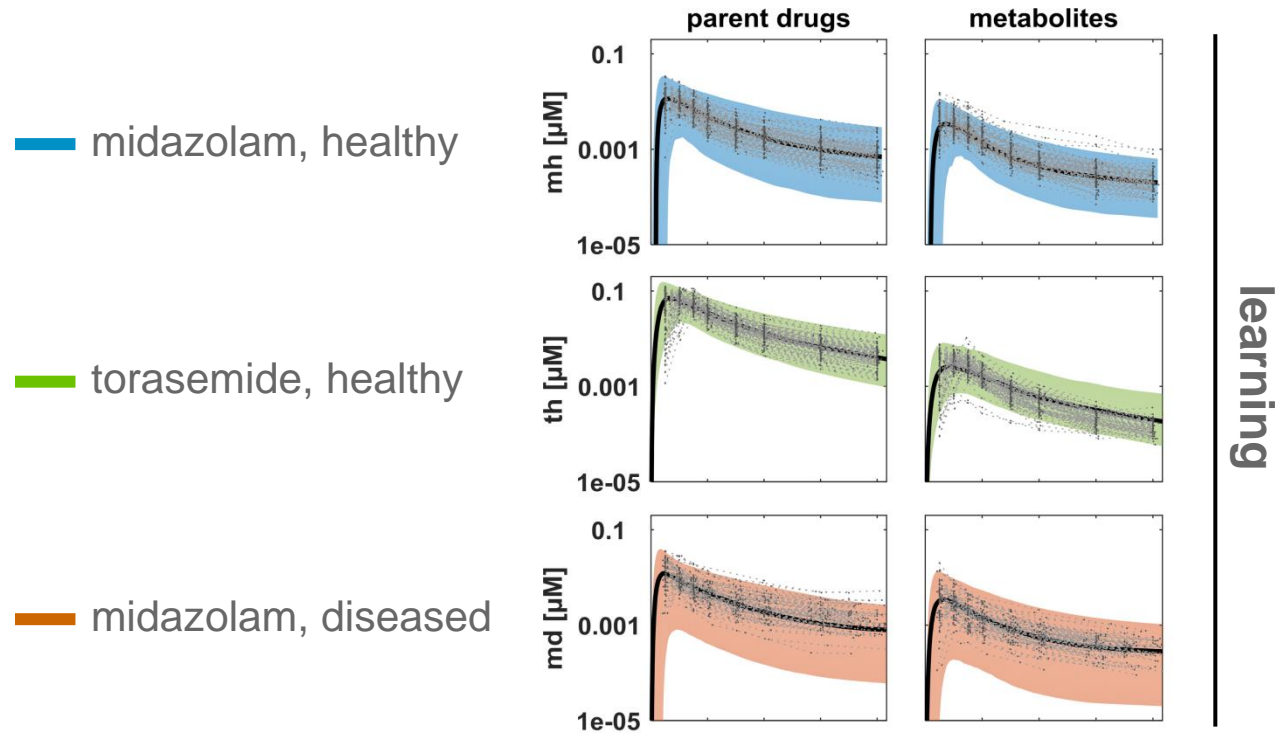
● midazolam, healthy

■ torasemide, healthy

▼ midazolam, diseased

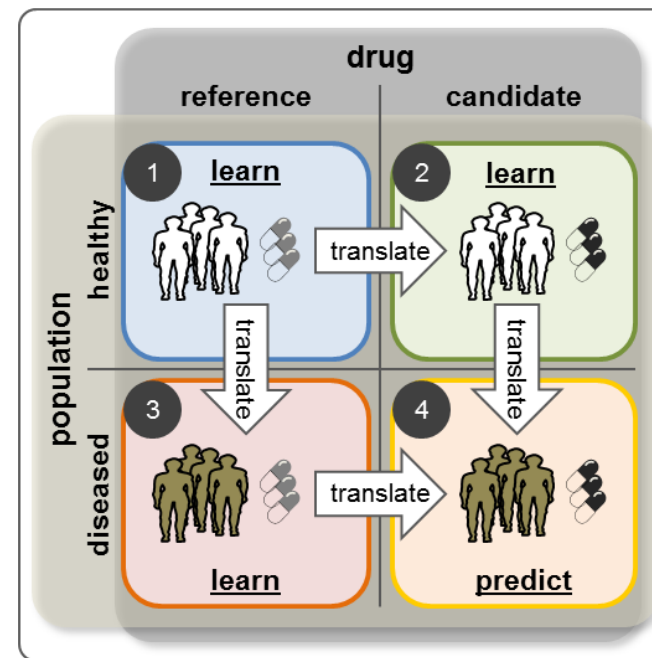
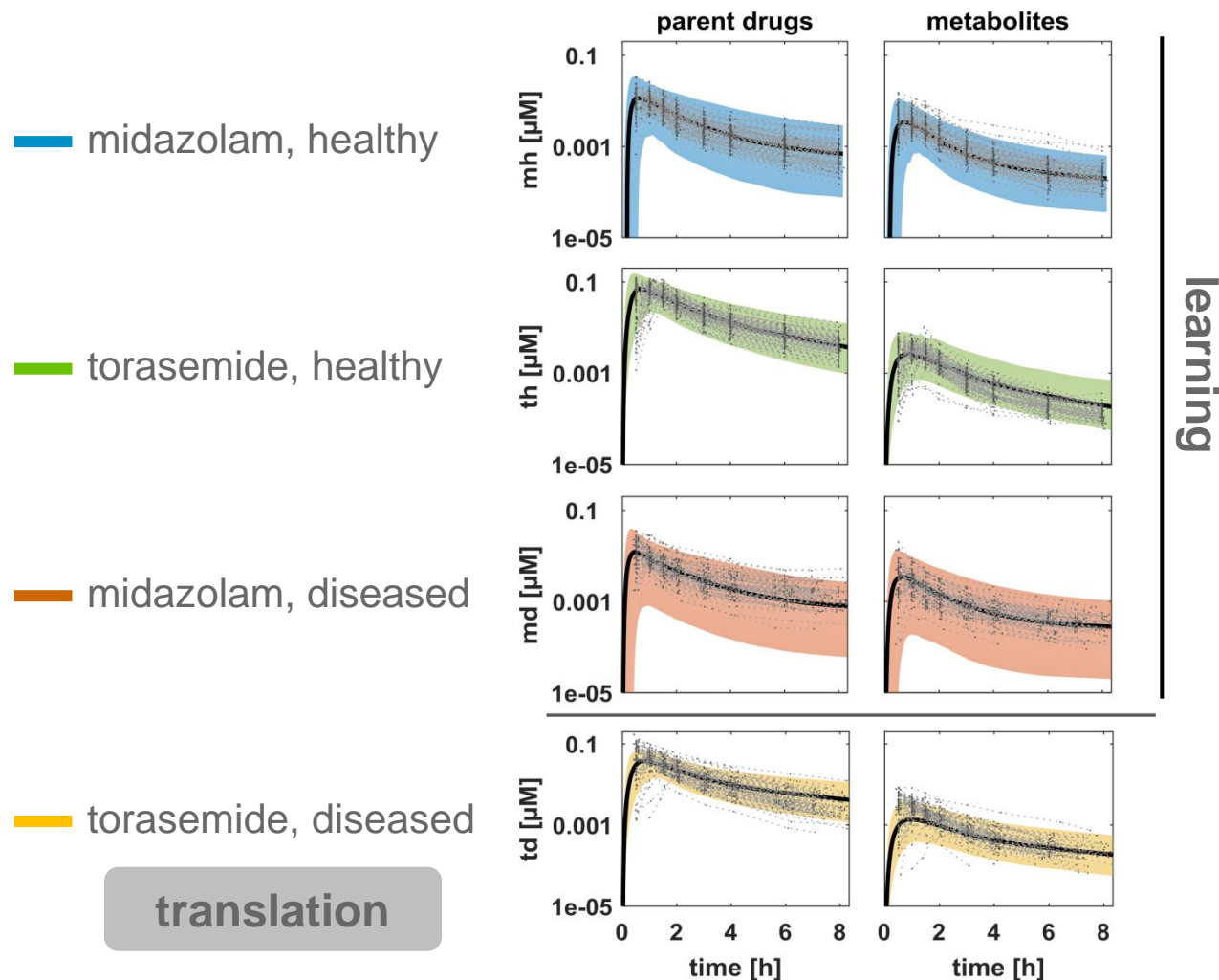
Krauss et al., *npj Syst. Biol & Appl.*, 2017

Qualified models on a population level...



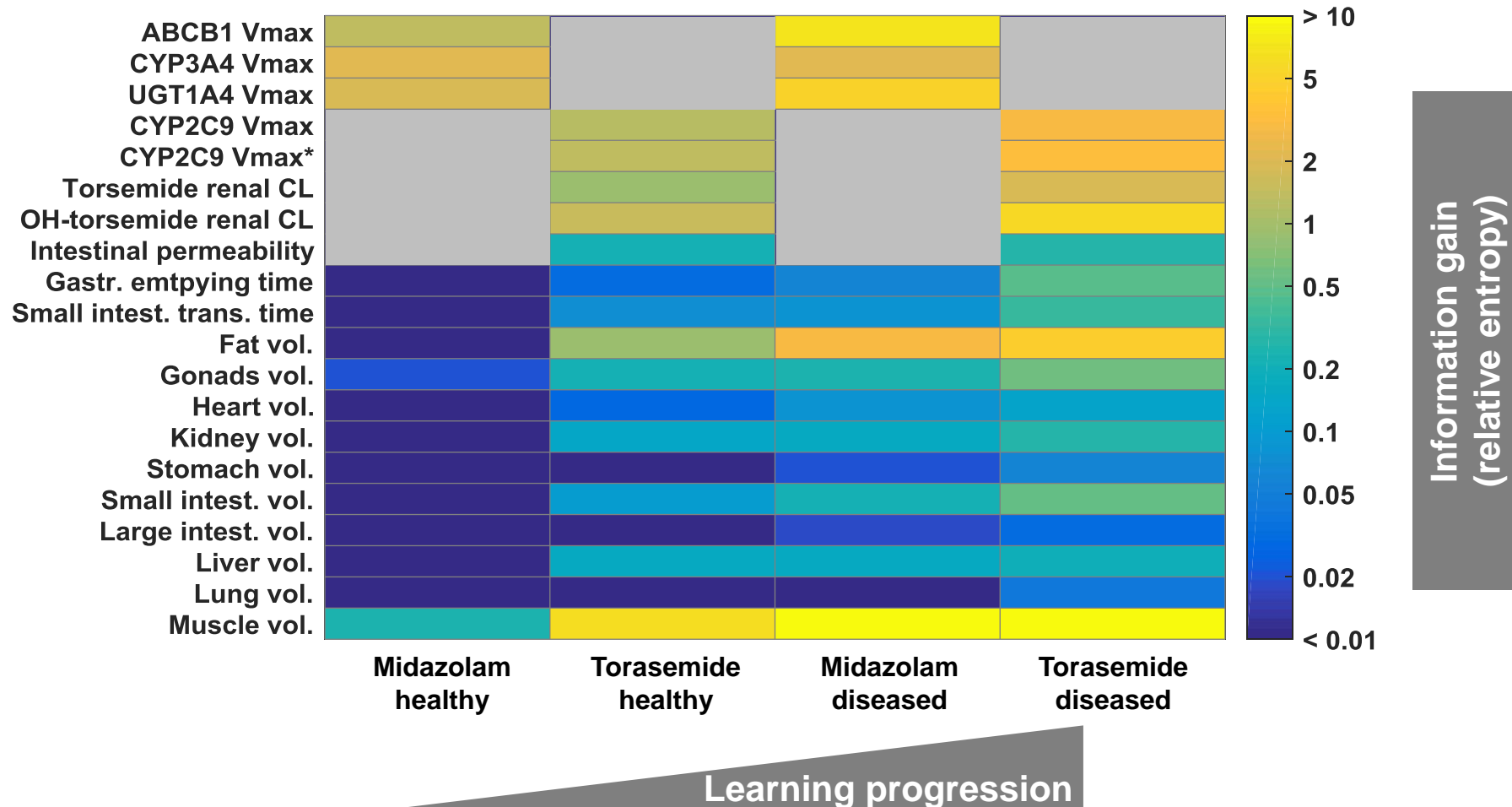
Krauss et al., *npj Syst. Biol & Appl.*, 2017

... allow translation and prediction of population PK

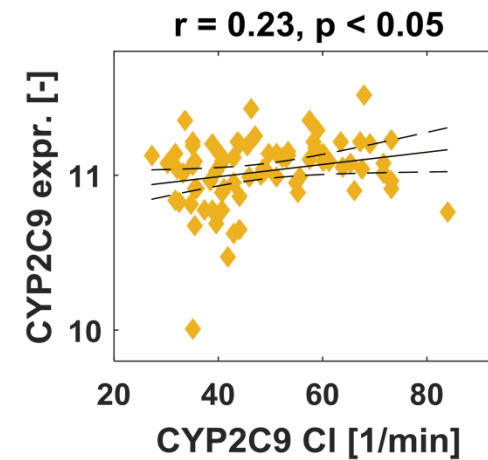
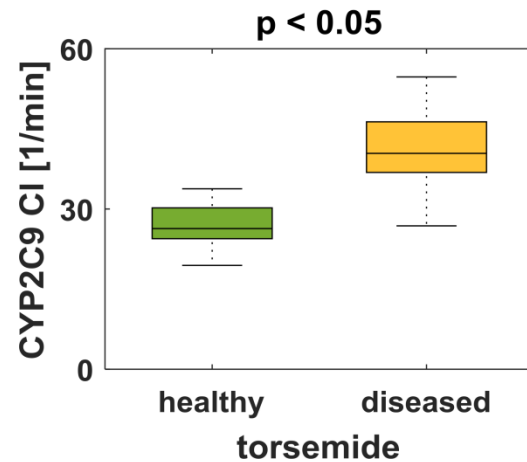
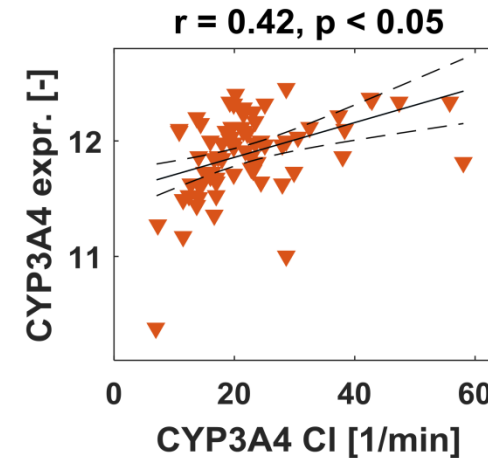
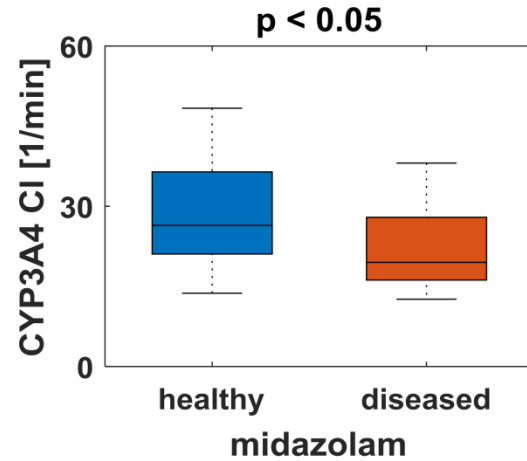


Krauss et al., npj Syst. Biol & Appl., 2017

Use of PBPK models allow to assess knowledge acquisition on a parameter level...



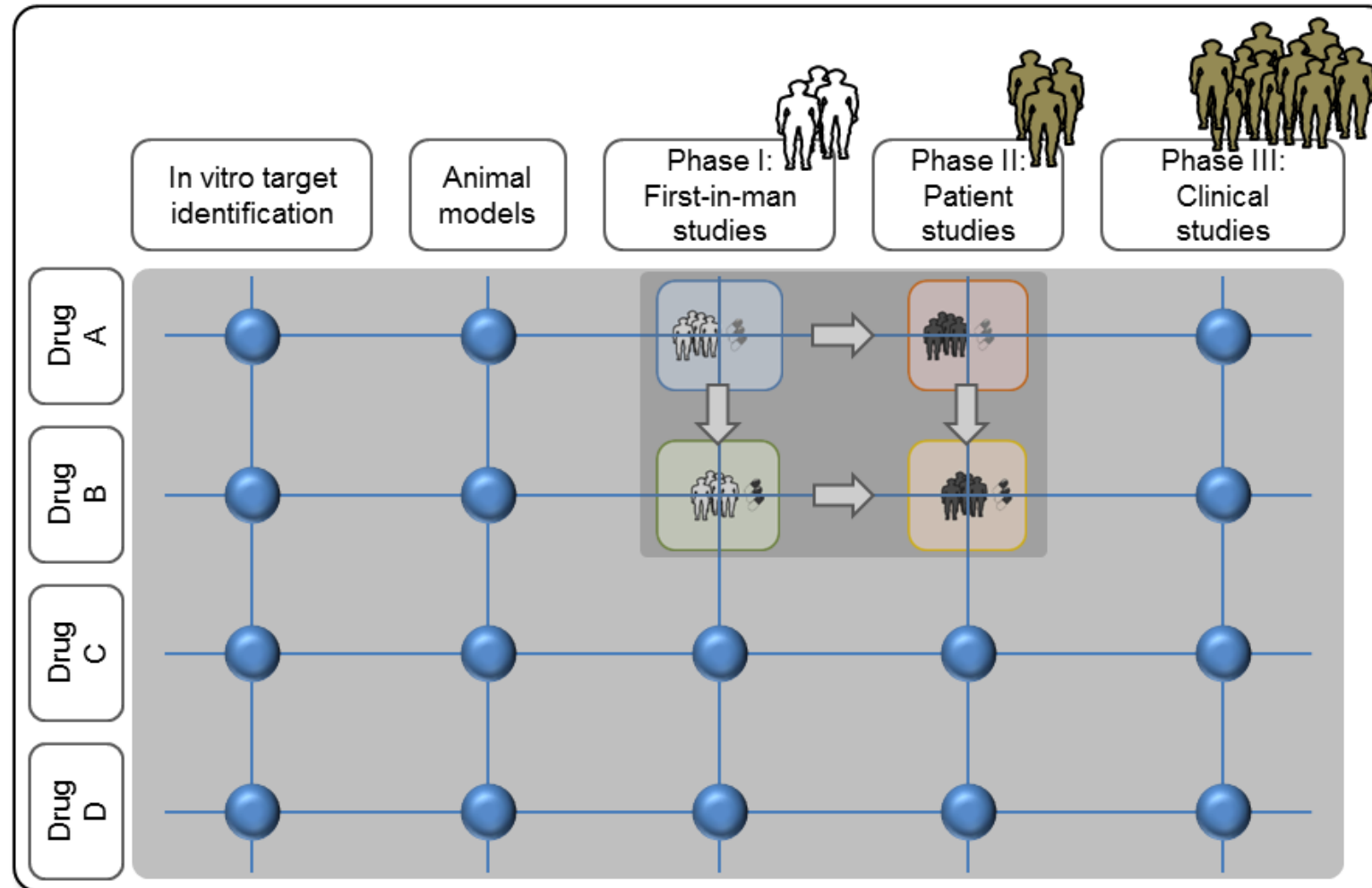
... and demonstrates potential for model-based pathophysiological characterization



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

Specific hepatic clearance correlates well with changes in gene expression

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

Universitätsklinikum
Carl Gustav Carus
DIE DRESDNER.



Mario Brosch

Jochen Hampe



Ute Hofmann

Reinhold Kerb

Matthias Schwab



Witigo v. Schönfels

Clemens Schafmayer

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Translational learning from clinical studies predicts drug pharmacokinetics across patient populations

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