

Science For A Better Life

Using physiology-based pharmacokinetic modelling for mechanistic analyses of drug action in disease and special populations

Tobias Kanacher



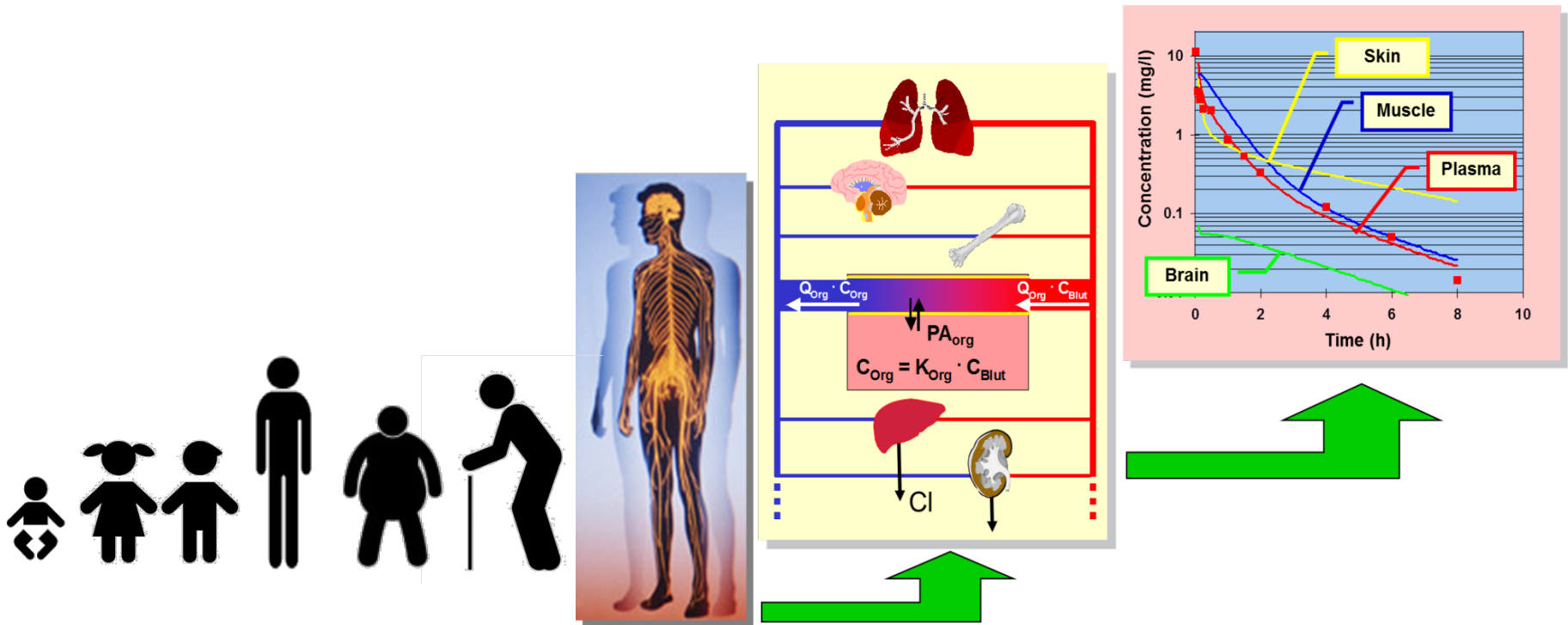
Agenda

- Definition of PBPK Modelling
- Physiology based PK Modelling in Preterms
Karina Blei et al.
- PBPK concept study in oncology: simulations of naked antibody predosing
Michael Block et al.
- Model-based risk assessment statin induced myopathies
Jörg Lippert, ...Lars Küpfer et al.

Definition of PBPK Modelling

Wikipedia:

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species



The Very Special Populations



Courtesy of www1.wdr.de

- Up to 93% of **preterm born neonates** in ICU care receive at least one unlicensed and/or off-label use of a drug.

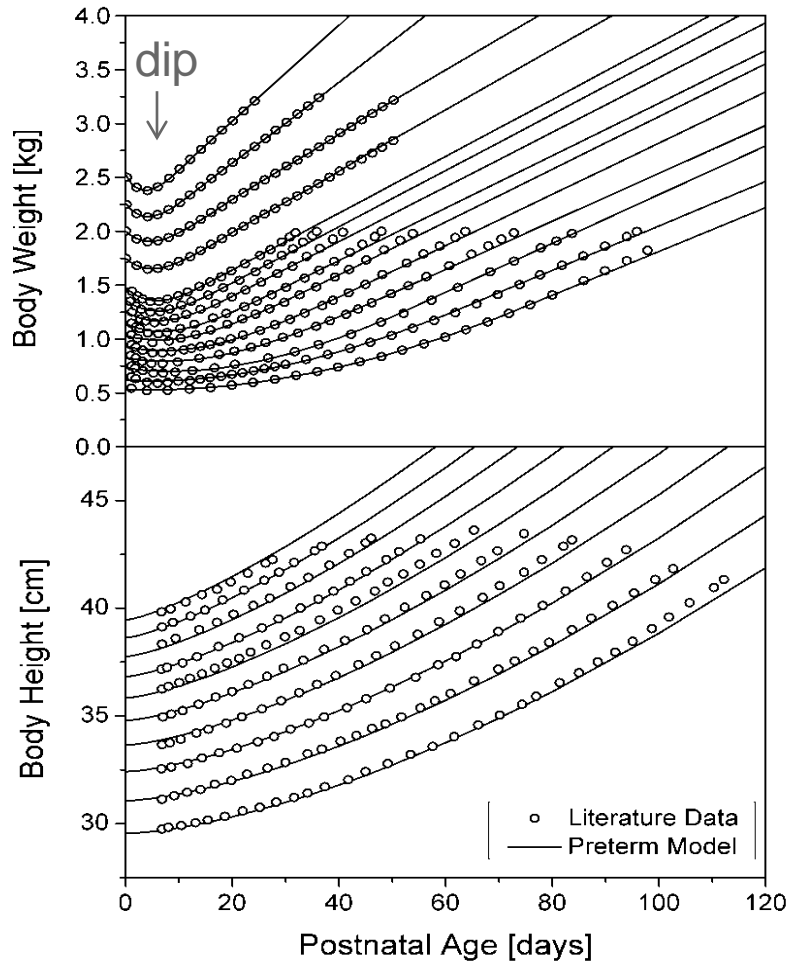
Motivation – need for a PBPK model of preterm born children



http://www.healthynewbornnetwork.org/sites/default/files/images/2012-07-07__health01.jpg

- Scaling of models to children and term born neonates is quite established
- Preterm born neonates differ from term born neonates considerably.
- Rapid developmental changes in neonates strongly impact PK of drugs
- Maturation of certain clearances triggered by birth e.g. CYP3A4 and tubular secretion

Preterm born infants show no loss of fat and water during the first days of life...



Because they have really nothing left to lose!

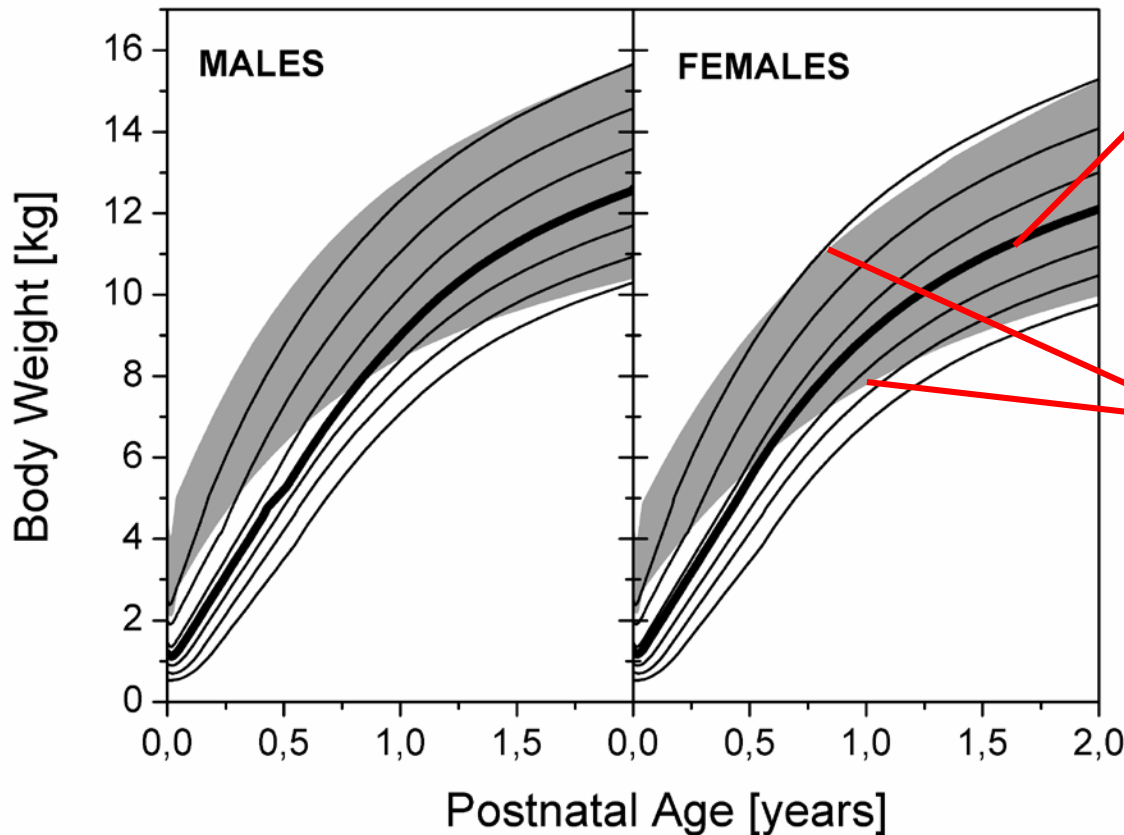
Preterm PBPK model incorporates many physiological changes:

- Postnatal growth
- Organ weights
- Blood flow
- Renal function
- Hepatobiliary function

Literature data from Dancis et al., 1948 and Ehrenkranz et al., 1999

Preterm born children show a “catch up grow” in the first 2 years.

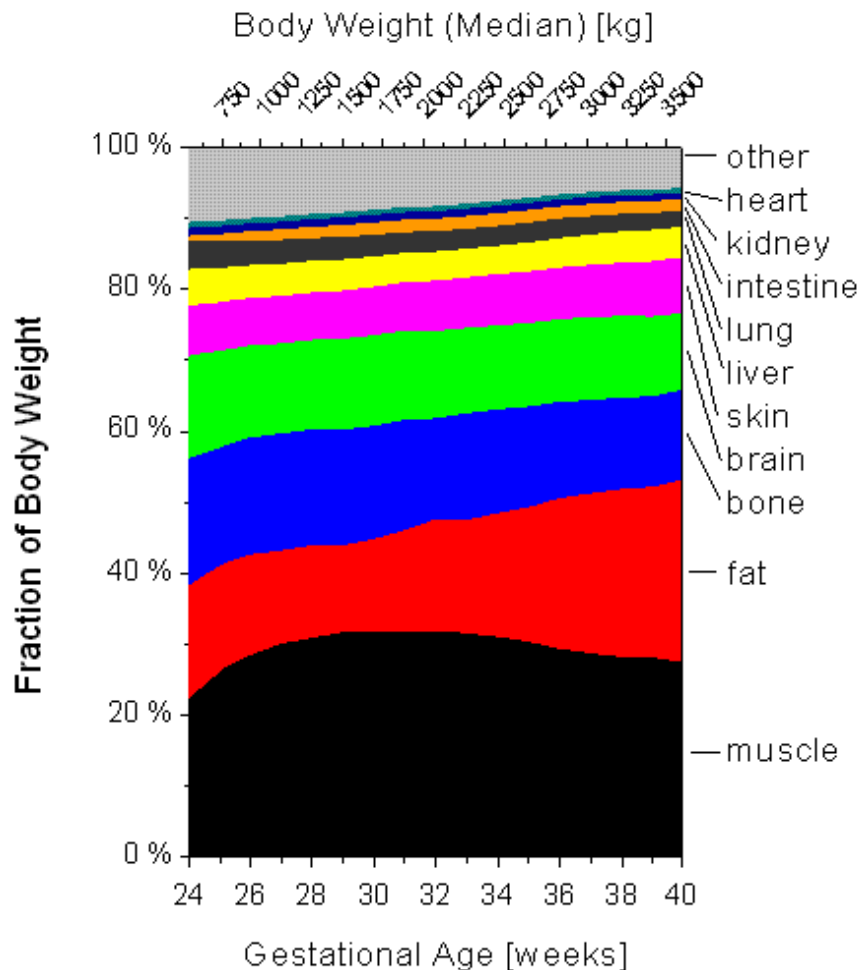
Growth Model for Preterms



Mean preterm born individual based on the PBPK model for preterm infants pooled in different weight

5-95% of term born infants matched to the growth charts of the “Centers for Disease Control and Prevention”

Organ growth in preterm born infants



- Data from many different data sources
- Checked for consistency
- If possible only continuous data from 24 to 40 weeks postmenstrual age has been included
- Inclusion of as much in vivo imaging data as possible
- Further differentiation of the GI tract (not shown)



Evaluation of the preterm PBPK model in a population simulation of Amikacin administration

Amikacin is an antibiotic which is often given for preterms to prevent infection

Population simulation using a validated and published adult PBPK model (Wendl. et al. 2011):

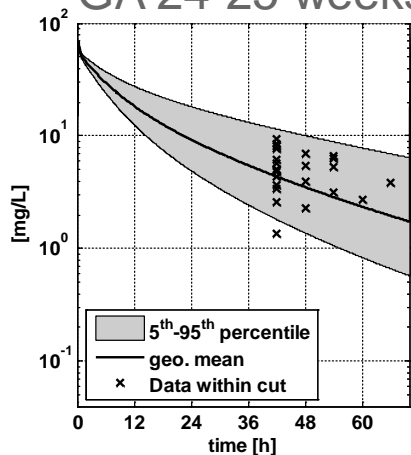
- Drug-related parameters as defined in the adult model.
- Age-dependent parameters in anatomy and physiology
- Developmental changes in drug clearance: GFR is primarily responsible for Amikacin clearance

- simulated populations: 500 male/500 female subjects per GA; GA ranging from week 24 to 40; GA groups pooled in two- and three-week intervals.

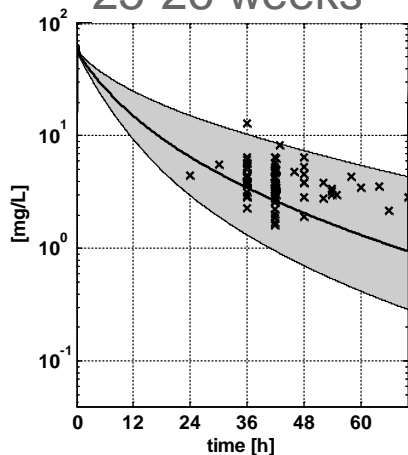
Evaluation of the preterm PBPK model – clinical data from preterms of different gestational age



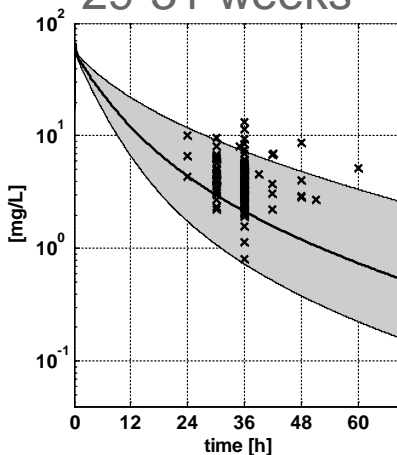
GA 24-25 weeks



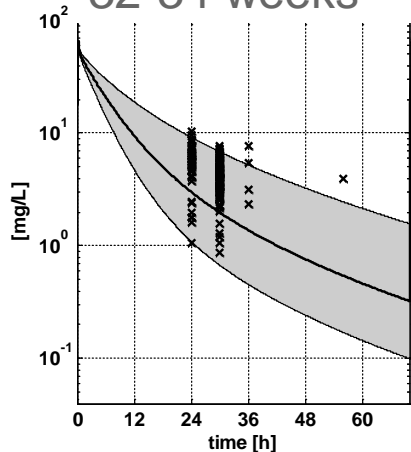
25-26 weeks



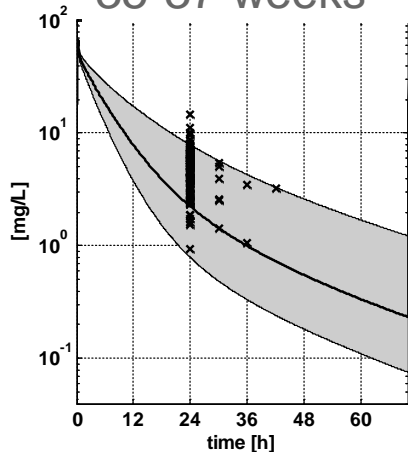
29-31 weeks



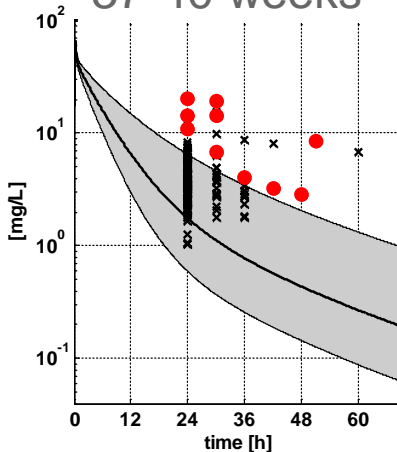
32-34 weeks



35-37 weeks



37-40 weeks



Prediction of plasma conc. based on knowledge about kidney maturation e.g. developmental changes in GFR.

Date from Allegaert et al. 2008

Outliers at week 37-40 have $SCr \geq 1.5$ mg/dL (red marks), points to loss of renal function as they already have an infection.



2nd data set for evaluation of the preterm PBPK model – Paracetamol

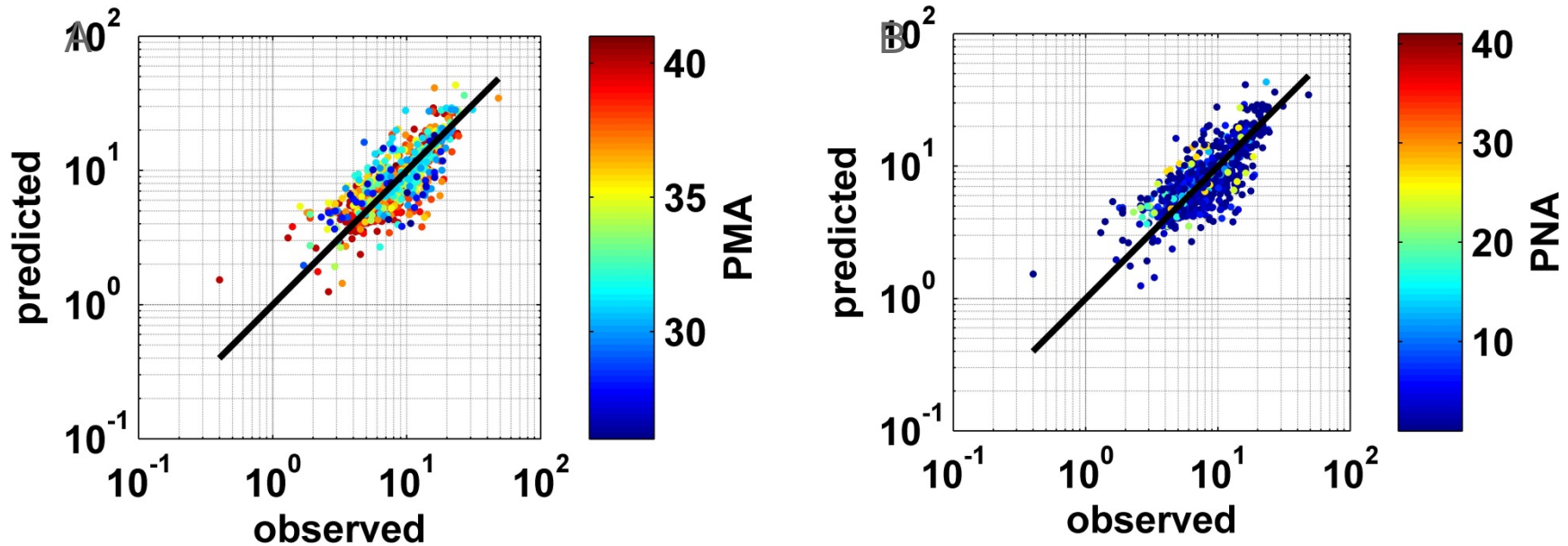
To evaluate that also liver metabolism and maturation is represented correctly

Population simulation using a validated and published adult PBPK model (Thelen et al. 2011):

- Drug-related parameters as defined in the adult model.
 - Age-dependent parameters in anatomy and physiology
 - Developmental changes in CYP2E1, SULT1A1, UGT1A6 in liver
-
- simulated populations:
500 male/500 female subjects per GA; GA ranging from week 24 to 40.
 - GA groups pooled in two- and three-week intervals.



2nd Evaluation of the preterm PBPK model – Paracetamol



Comparison of observed (Allegaert et al. 2004a, b) versus predicted plasma paracetamol concentrations from population simulations in preterm neonates at (A) different postmenstrual and (B) different postnatal ages.

Preterm PBPK model can support dose finding in clinics for and helps to make off label drug use safer



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PBPK/ PD Concept for simulations of naked antibody predosing

Background:

- Concept study from Genentech claims that naked antibody pretreatment (antibody without the toxophore) can reduce off-target effects and potentially extend the therapeutic window in cancer treatment. Antibody-drug conjugate (ADC) used is Anti-TENB2-MMAE (Boswell 2012, Boswell 2013)

Objective:

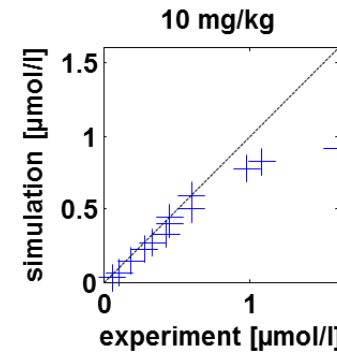
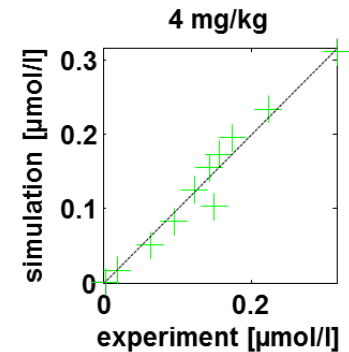
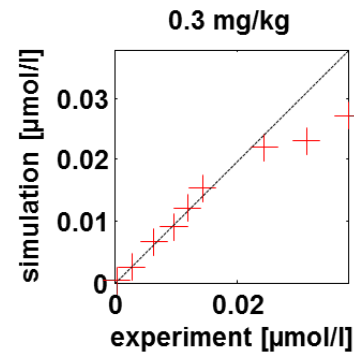
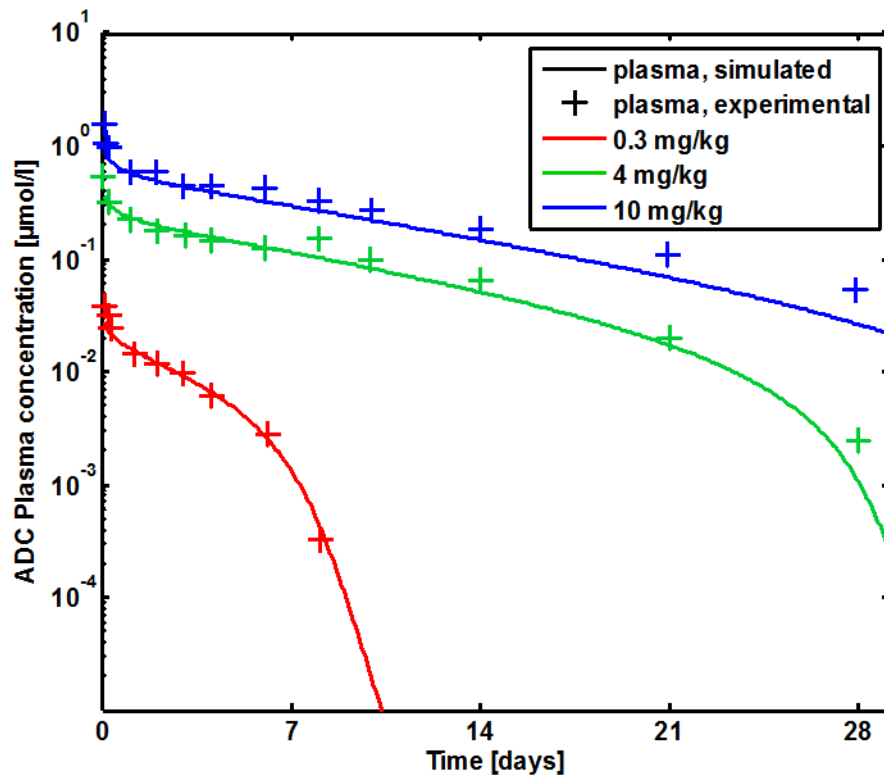
- Use established PBPK/PD model structure to investigate, if literature data can be described.

Approach

1. Development a coupled PBPK model for ADC, the antibody, and the toxophore to describe PK in plasma
2. Exploration of positive effects of antibody pretreatment on tissue uptake
3. Use the model to validate the PBPK/PD relationship for the nAB-pretreatment

PBPK Modell can describe target mediated disposition like behavior PK of the ADC

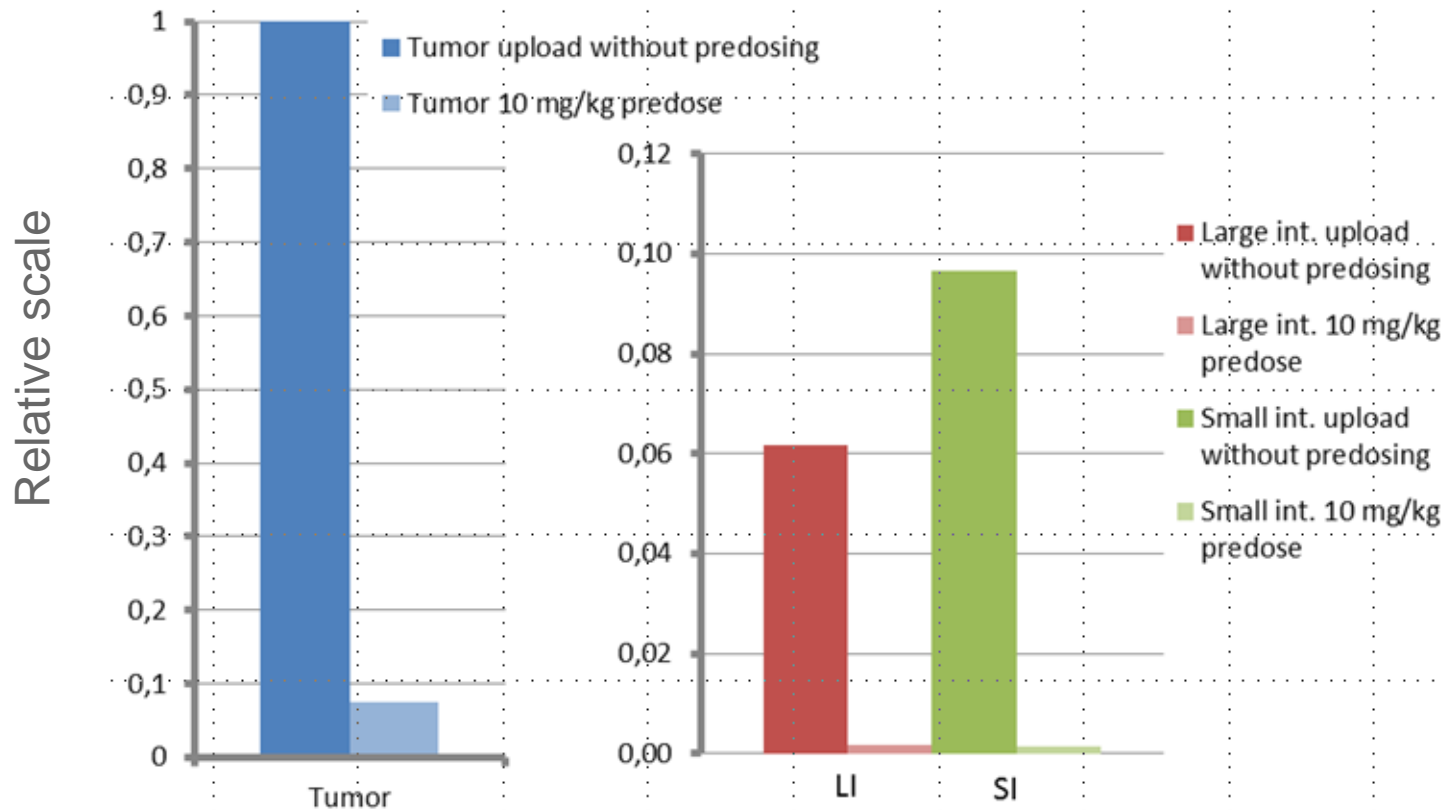
Apparent nonlinear behavior in the PK is very well represented by the model for all doses (observed data from Boswell)



PBPK Modell can describe the decrease of ADC upload after naked anti body pretreatment

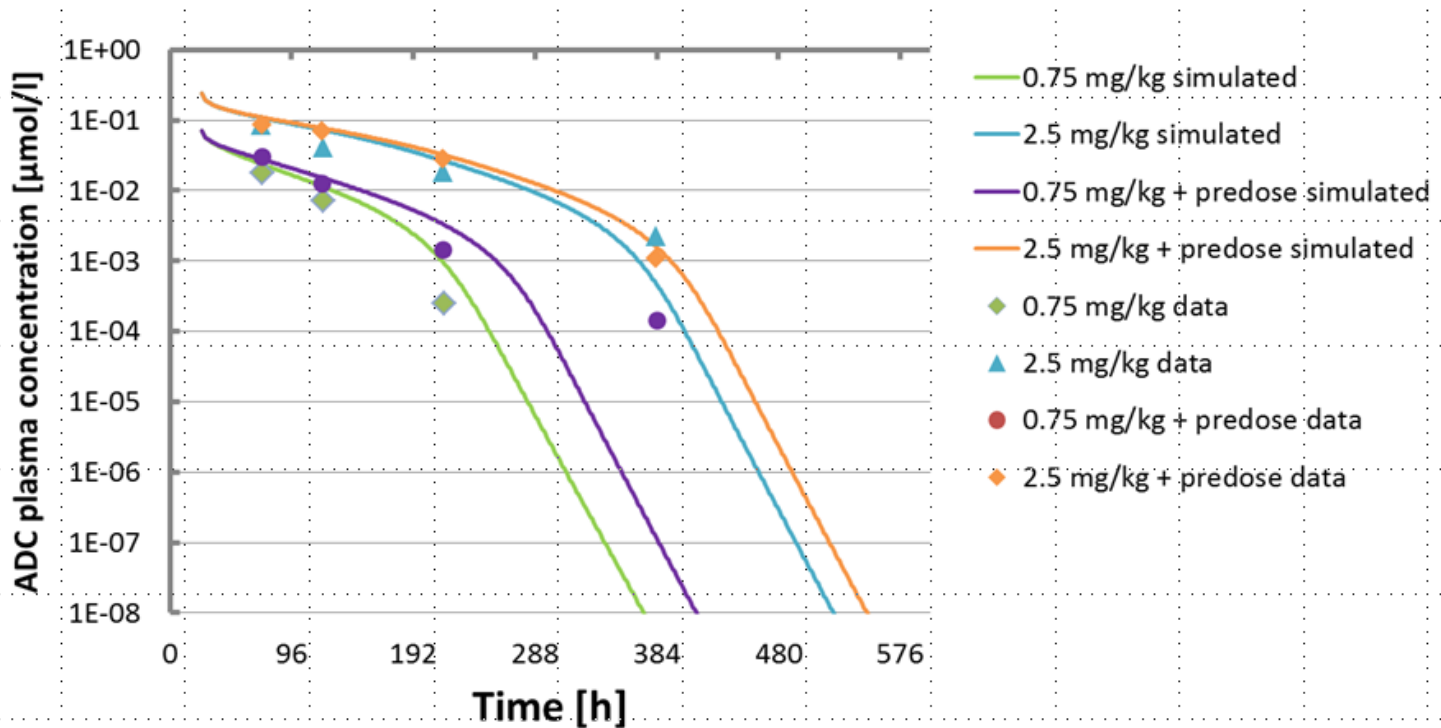
Upload of ADC strongly decreases after nAB-pretreatment (dose for ADC was only 0.01mg/kg)

- Model simulations are in good agreement with the observations



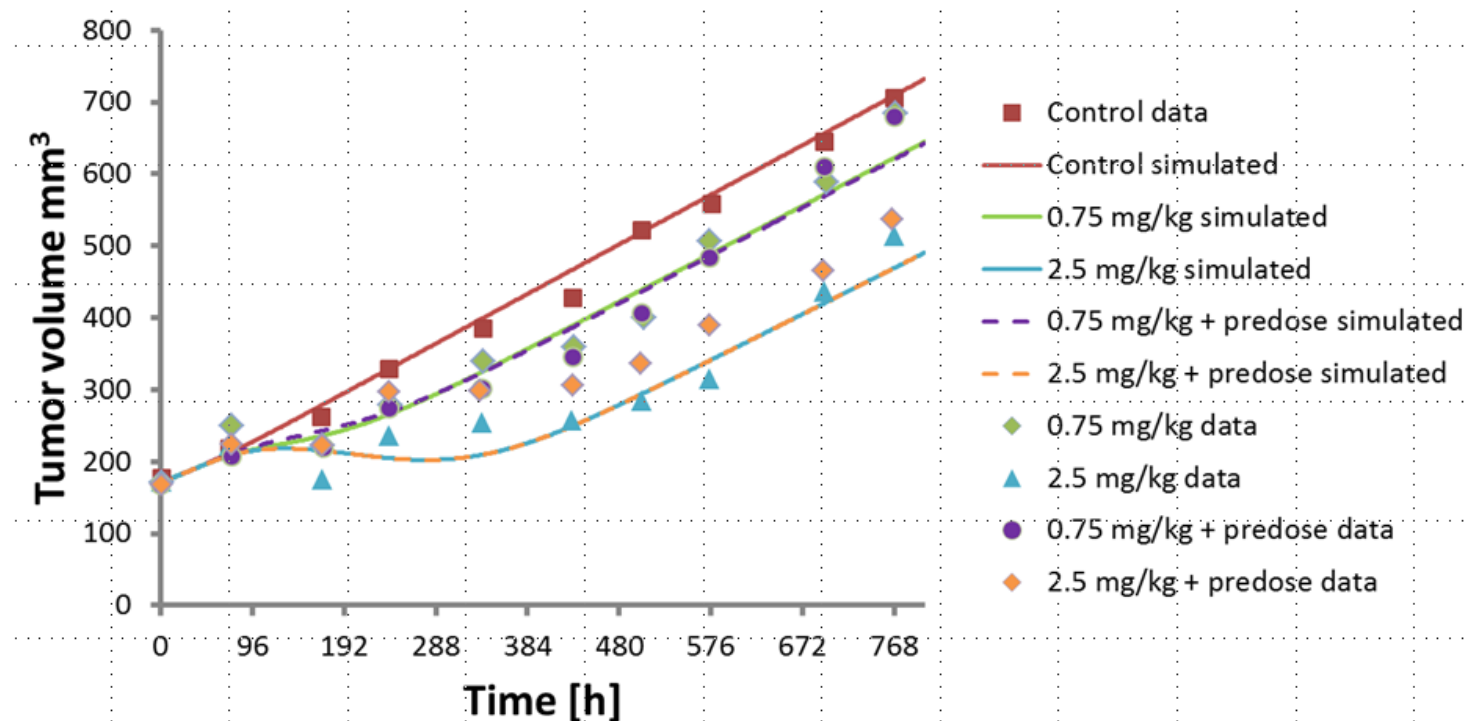
PBPK Modell can describe plasma concentrations of ADC with and without predosing

Therapeutically dosing schemes with and without pretreatment can be well represented by the model



PBPK Modell can inhibition of tumorgrow by ADC with and without predosing

Tumor growth inhibition after predosing shows no relevant effect in the model as observed



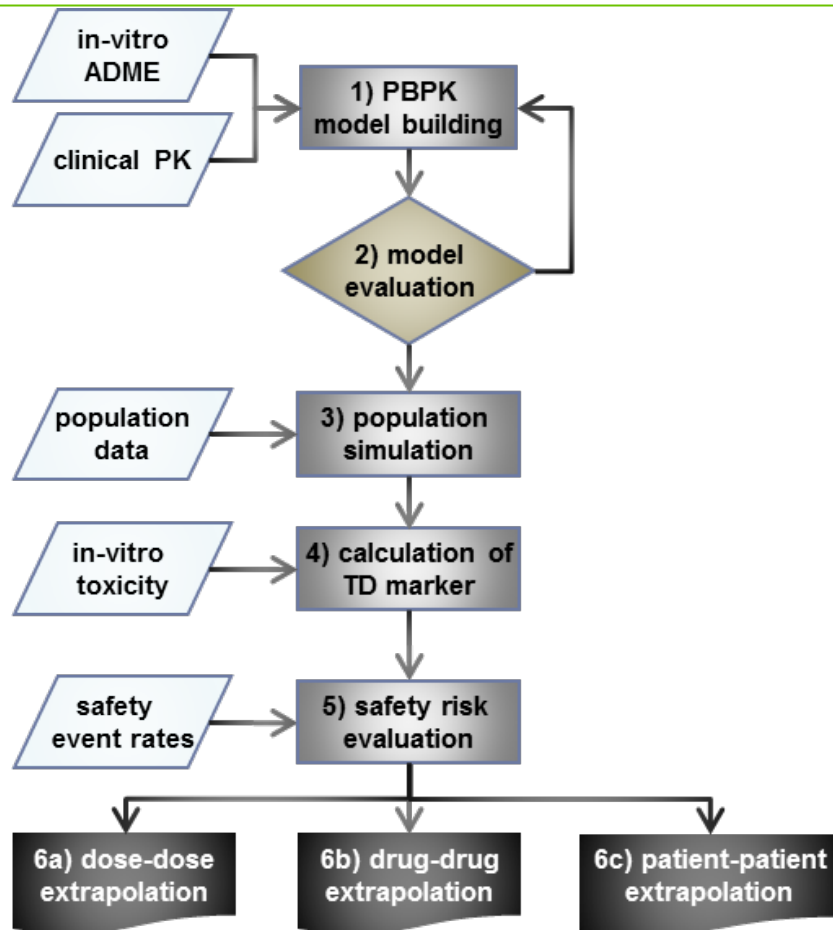
PBPK/PD example shows that the model structure model can describe in vivo data correctly and can support development of oncology drugs



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- Definition of PBPK Modelling
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Karina Blei et al.
- Simulations of naked antibody predosing (positive control example anti-TENB2-MMAE)
Michael Block et al.
- **Model-based risk assessment of statin induced myopathies**
Lippert, Küpfer et al.

Model-based risk assessment in pharmaceutical R&D



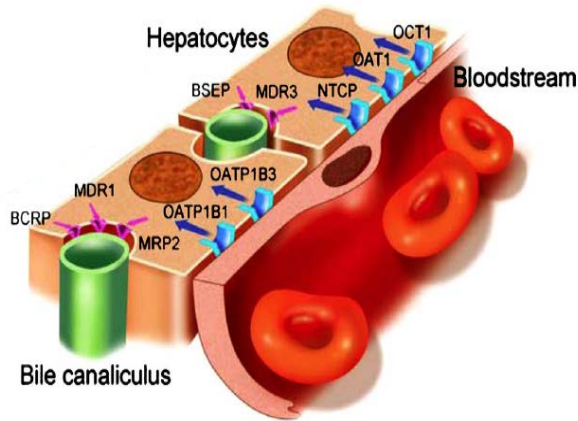
1. establishment of reference PBPK models
2. model evaluation at relevant scales
3. simulation of virtual populations and model evaluation
4. calculation of toxicodynamic (TD) markers
5. evaluation of the safety risk
6. prediction of drug safety
 - a. dose to dose
 - b. drug to drug
 - c. patient to patient extrapolation

Lippert et al., *CPT:PSP*, 2012

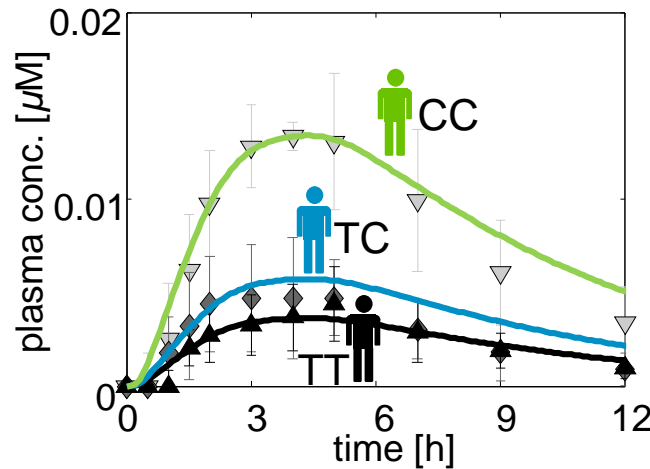
The risk for Statin induced myopathy seems to be linked to gene function



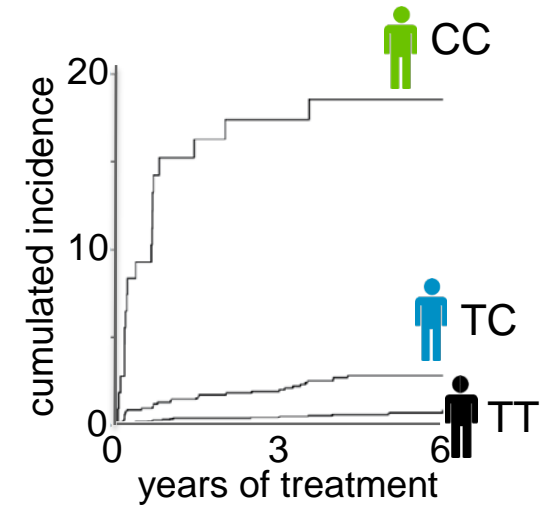
Physiology



Statin PK



GWAS of myopathy

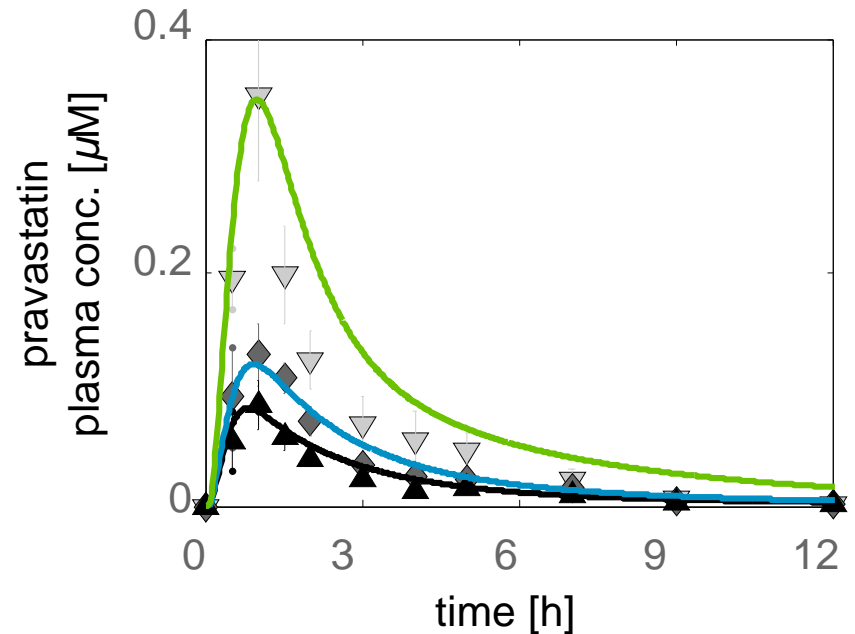
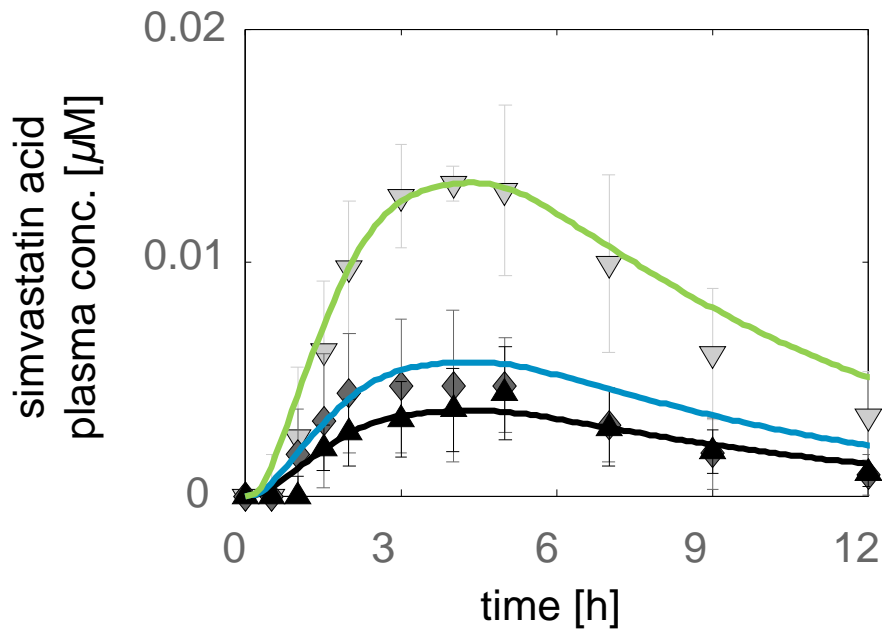


Hepatic uptake by OATP1B1

Genotype-phenotype correlation (c.521T>C SNP)

A mechanistic explanation, however, is lacking as of now

Validating the predictive power for PK genotypes



TT genotype



CC genotype

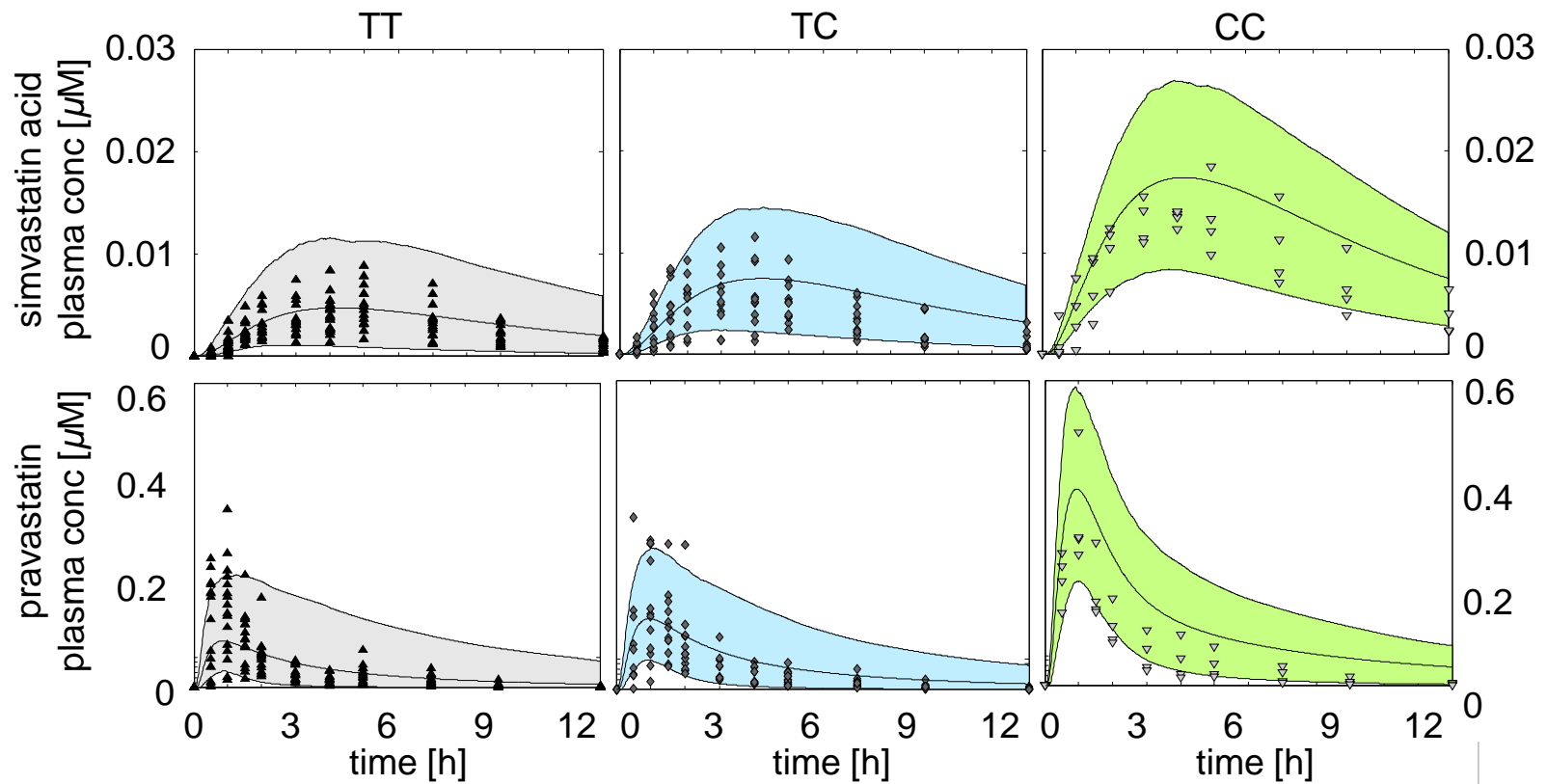


TC genotype

Model is predictive for pharmacokinetic phenotypes

Population simulations

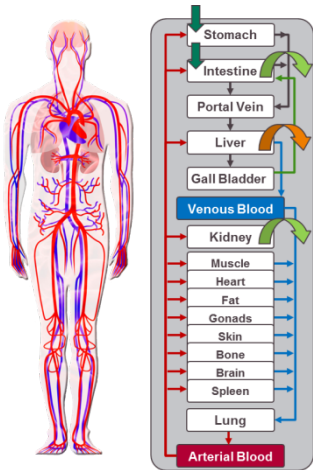
Genotype-specific virtual patient populations
(n=1000 individuals).



Pasanen et al., *Pharmacogenet Genomics*, 2006

Niemi et al., *Clin Pharmacol Ther*, 2006

Calculation of a toxicodynamic (TD) marker for statin toxicity



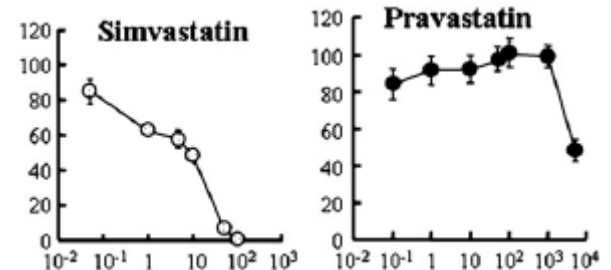
$$TD = \frac{C_{max} \text{ Muscle}}{IC50}$$

Model-based estimation of drug exposure in the target tissue

An *in vivo* marker for statin toxicity

$IC50_{\text{Simvastatin}} = 3.99 \mu\text{M}$

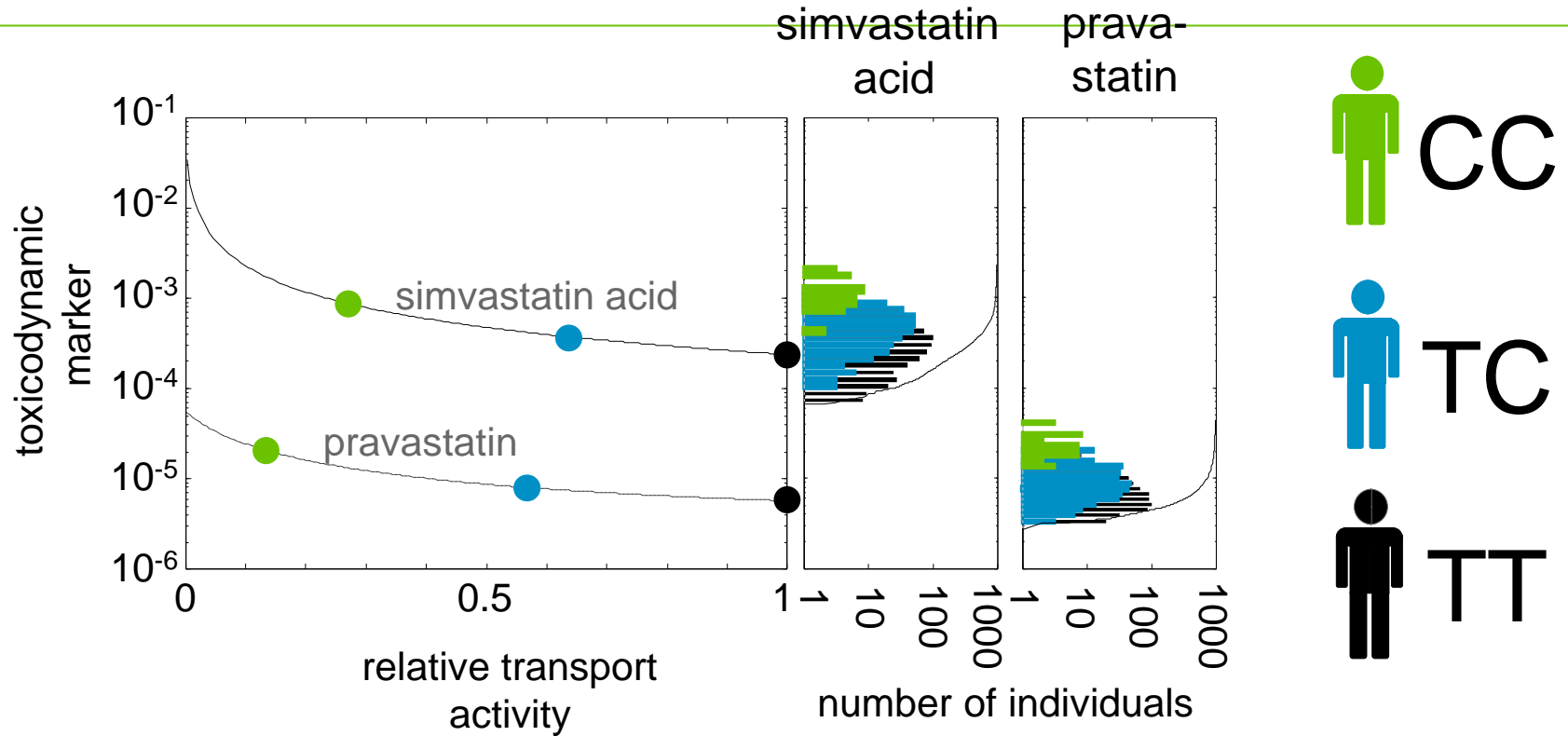
$IC50_{\text{Pravastatin}} = 4890 \mu\text{M}$



In vitro toxicity (IC50 values) in embryonal rhabdomyosarcoma cells

Kobayashiet al., Life Sciences, 2008

Population simulations describe distributions of the toxico-dynamic marker for different genotypes

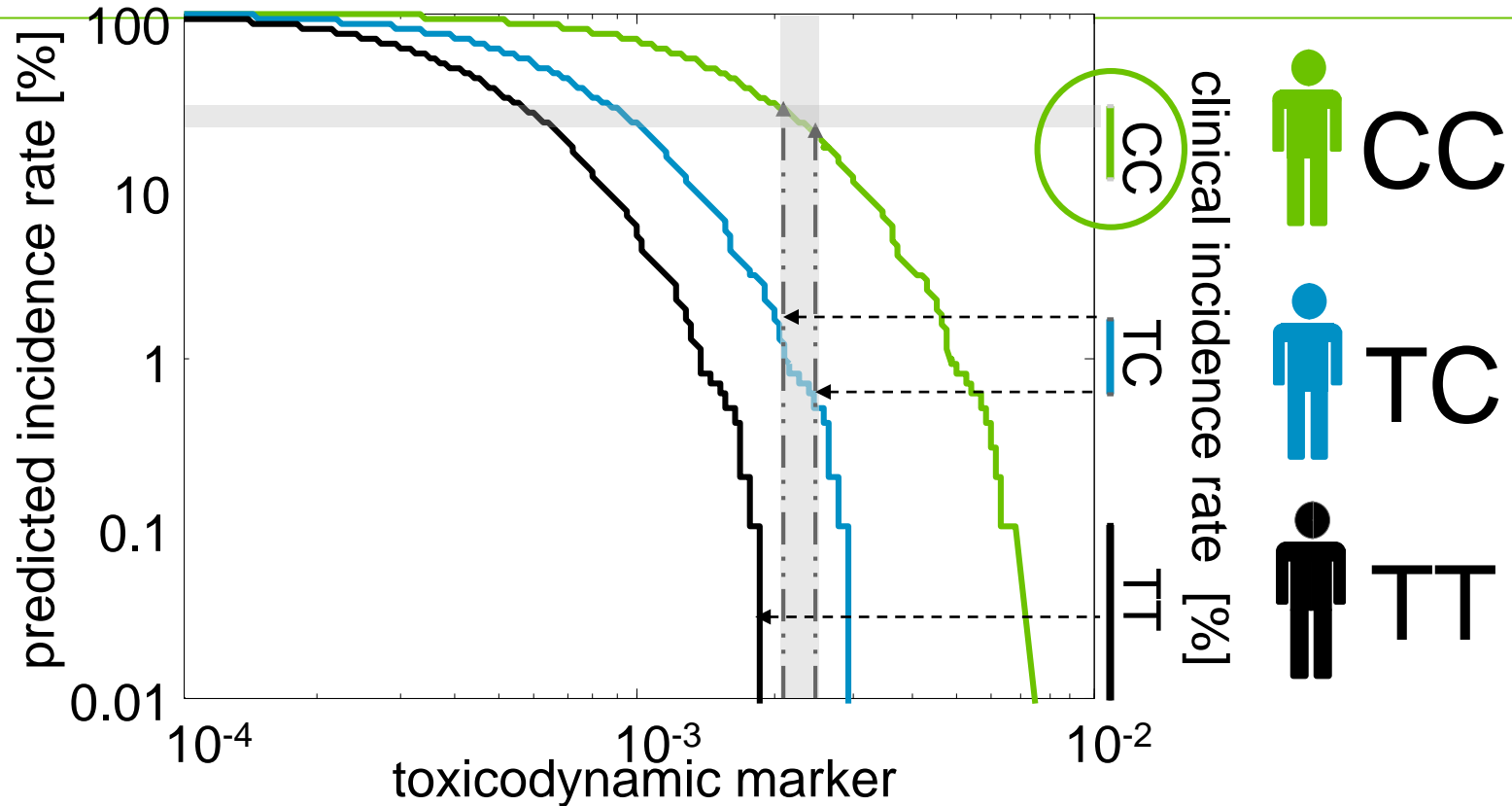


Lippert et al., CPT:PSP, 2012

The toxicodynamic marker is considerably higher for simvastatin, and highest in CC genotypes (as seen in clinics).



Prediction of clinical incidence rates for the rare CC-subpopulations.



Model predicted Risk: 22.2% - 29.6% in range with SEARCH study: [8.8%;23.1%]

PBPK based concept applicable to estimate risk in other statins as well



Summary

- Physiology-based pharmacokinetic (PBPK) models enable the mechanistic investigation of drug PK at a mechanistic level of detail even in very special populations like preterm born neonates
- The methods presented outline how computational models together with targeted experimental data allow a mechanistic investigation of drug kinetics, efficacy and even toxicity.
- Such integrative approaches may have significant implications for the development of individualized therapeutic strategies with a favorable risk-benefit profile in the future.



Thank you

Preterm PBPK Model

Karina Blei, Kirstin Thelen, Katrin Coboeken, Thomas Gaub, Jörg Lippert, Karel Allegaert, Stefan Willmann

Naked Antibody Example for oncology

Michael Block, Rolf Burghaus, Kristin Dickschen, Thomas Eissing, Thomas Gaub, Lars Kuepfer, Jörg Lippert.

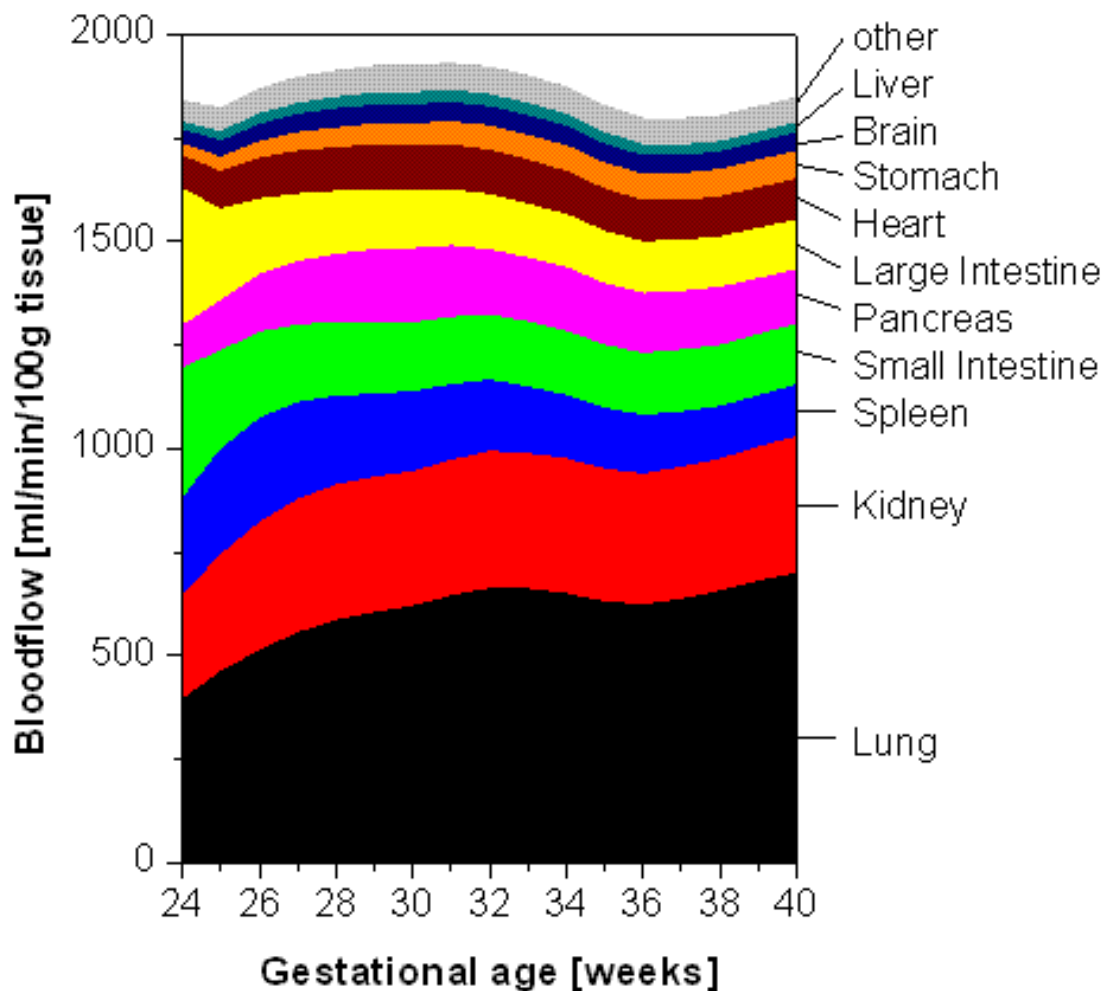
Model-based risk assessment of statin induced myopathies

J Lippert, M Brosch, O von Kampen, M Meyer, H.-U Siegmund, C Schafmayer, T Becker, B Laffert, L Görlitz, S Schreiber, PJ Neuvonen, M Niemi, J Hampe and L Kuepfer

Back up



Appendix: Blood flow in preterm born infants



Techniques need to be non-invasive

No data available:

- Fractions of blood flow from the term newborn were assumed to be constant.
- Fractions have been applied to the cardiac output of preterm newborns.
- Good correlation with data for renal blood flow values.



Thanks

Development of a Physiologically-Based Pharmacokinetic Model for
Preterm Neonates (in Press)

**Karina Blei, Kirstin Thelen, Katrin Coboeken, Thomas Gaub, Jörg
Lippert, Karel Allegaert, Stefan Willmann**