



Science For A Better Life

# Use of PBPK in Drug Development and Application to the Pediatric Setting

Innovative Approaches to Pediatric Drug Development and Pediatric Medical Countermeasures: A Role for Physiologically-Based PK?

FDA White Oak Campus – May 5, 2014

Dr. Jörg Lippert  
Vice President, Head Clinical Pharmacometrics



## Agenda

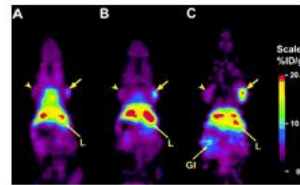
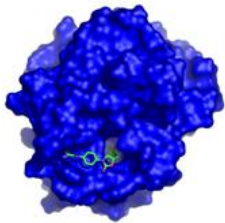
- Why do we use PBPK?
- How much biology can we capture with PBPK?
- How do we apply it?
- What is still missing?



## Agenda

- **Why do we use PBPK?**
- How much biology can we capture with PBPK?
- How do we apply it?
- What is still missing?

# The pharmaceutical R&D paradigm relies on indirect assessments



*PNAS July 18, 2000 vol. 97 no. 15 8495-8500*



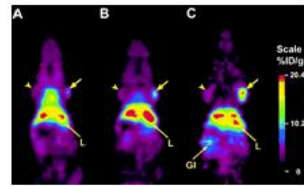
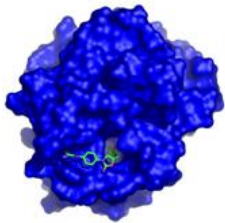
<http://www.damtp.cam.ac.uk/group/apde/people.html>

[http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472\\_468x313.jpg](http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472_468x313.jpg)

## Pathway? Target? Molecule? Dose? Patient?

# Integration and holistic interpretation of information is a major challenge

- Based on models and extrapolation



*PNAS July 18, 2000 vol. 97 no. 15 8495-8500*



<http://www.damtp.cam.ac.uk/group/apde/people.html>



[http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472\\_468x313.jpg](http://i.dailymail.co.uk/i/pix/2009/02/23/article-1152583-039B8A71000005DC-472_468x313.jpg)



- Distributed in a complex organization of highly specialized experts (time & space)
- Analytical and reductionist

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

# Output of Pharma R&D is a matter of debate for more than a decade



- Based on models and extrapolation

## Fundamental Challenge:

Understand and predict all consequences for **clinical** success!

⇒ **Identify and contain risks early!**

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...

# Output of Pharma R&D is a matter of debate for more than a decade



- Based on models and extrapolation

**Lack of understanding (explicit & implicit )  
and uncertainty translate into  
high development risks!**

Generated data, information, understanding & knowledge is  
broadly spread across heads, IT infrastructure...



# Output of Pharma R&D is a matter of debate for more than a decade



- Based on models and extrapolation

## How can PBPK modeling help?

Generated data, information, understanding & knowledge is broadly spread across heads, IT infrastructure...





# Why do we use PBPK?

- 1. PBPK provides the method for stringent integration of pharmacology relevant knowledge, assumptions and data – along the whole R&D process**
- 2. PBPK enables the identification of risks by revealing inconsistencies between different sources of information**
- 3. Based on a consistent representation of all information, directly drug related as well as independent prior information, PBPK allows prediction of most likely outcomes of future experiments and enables decision making and optimization of development strategies and study designs**



## Agenda

- Why do we use PBPK?
- **How much biology can we capture with PBPK?**
- How do we apply it?
- What is still missing?



ORIGINAL RESEARCH ARTICLE

Mol Diagn Ther 2012; 16 (1): 43-53  
1177-1062/12/0001-0043/\$49.95/0

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## Pharmacogenomics of Codeine, Morphine, and Morphine-6-Glucuronide

Model-Based Analysis of the Influence of CYP2D6 Activity, UGT2B7 Activity, Renal Impairment, and CYP3A4 Inhibition

*Thomas Eissing, Jörg Lippert and Stefan Willmann*

Competence Center Systems Biology and Computational Solutions, Bayer Technology Services GmbH, Leverkusen, Germany

### ARTICLES

nature publishing group

## Risk to the Breast-Fed Neonate From Codeine Treatment to the Mother: A Quantitative Mechanistic Modeling Study

<sup>1</sup>Competence Center Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany; <sup>2</sup>School of Pharmacy, University of Waterloo, Waterloo, Ontario, Canada; <sup>3</sup>Clinical Pharmacokinetics, Bayer HealthCare AG, Wuppertal, Germany. Correspondence: SWillmann ([stefan.willmann@bayertechnology.com](mailto:stefan.willmann@bayertechnology.com))

Received 30 April 2009; accepted 19 June 2009; advance online publication 26 August 2009. doi:10.1038/clpt.2009.151

VOLUME 86 NUMBER 6 | DECEMBER 2009 | [www.nature.com/cpt](http://www.nature.com/cpt)

# The use of codeine by breastfeeding mothers has been a matter of debate due to the risk of opioid intoxication of the child



**NATIONAL REVIEW**  
of MEDICINE  
ESSENTIAL NEWS FOR CANADA'S PHYSICIANS

JUNE 15, 2007 | VOLUME 4 NO. 11

PATIENTS & PRACTICE

## Codeine linked to breastfeeding danger

*Warnings and class action suit follow Toronto neonate's poisoning death*

BY OWEN DYER

A class action suit over the death of an apparently healthy Toronto newborn, who died last year from opiate toxicity from breast milk, has renewed the debate over prescribing Tylenol 3 to breastfeeding mothers. After the baby's death, doctors at Toronto's Hospital for Sick Children issued a warning that codeine given for postnatal pain can produce deadly concentrations of morphine in breast milk.

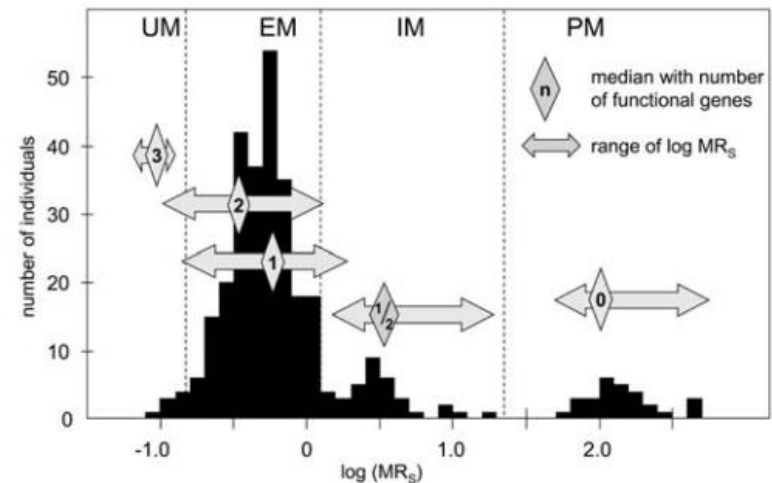
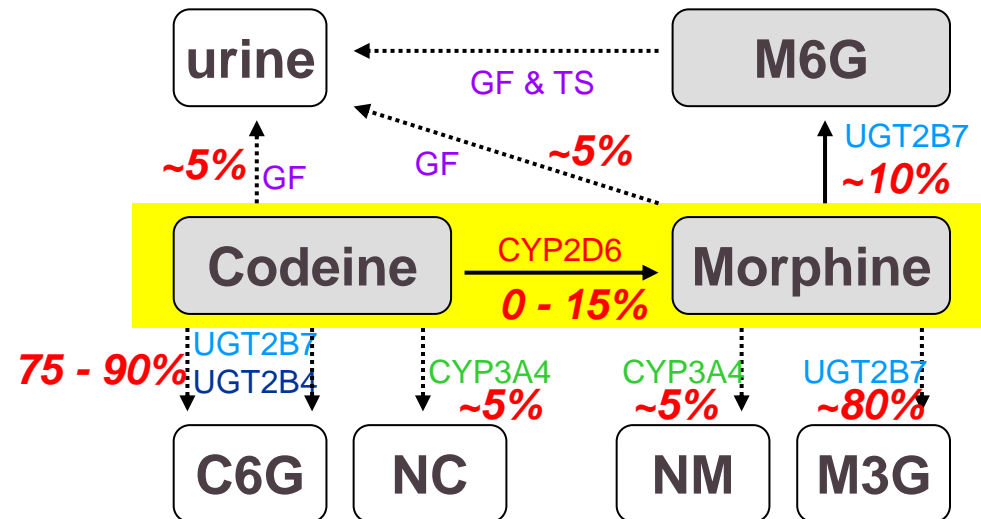
Tariq Jamieson was delivered vaginally at full term and healthy weight — everything appeared normal. His mother Rani suffered some lingering pain from an episiotomy so she was prescribed two tablets of Tylenol 3 twice daily — a common pain treatment for mothers who have just given birth. Doctors halved that dose after two days due to constipation and somnolence.

Tariq developed increasing lethargy from the seven-day mark, and at 11 days was brought to a pediatrician due to concerns about his sleep patterns and poor feeding.



Asian and African babies are at greater risk of rapidly metabolizing codeine

# Explicit representation of all mass-balance information is a strength of PBPK and key to robust models



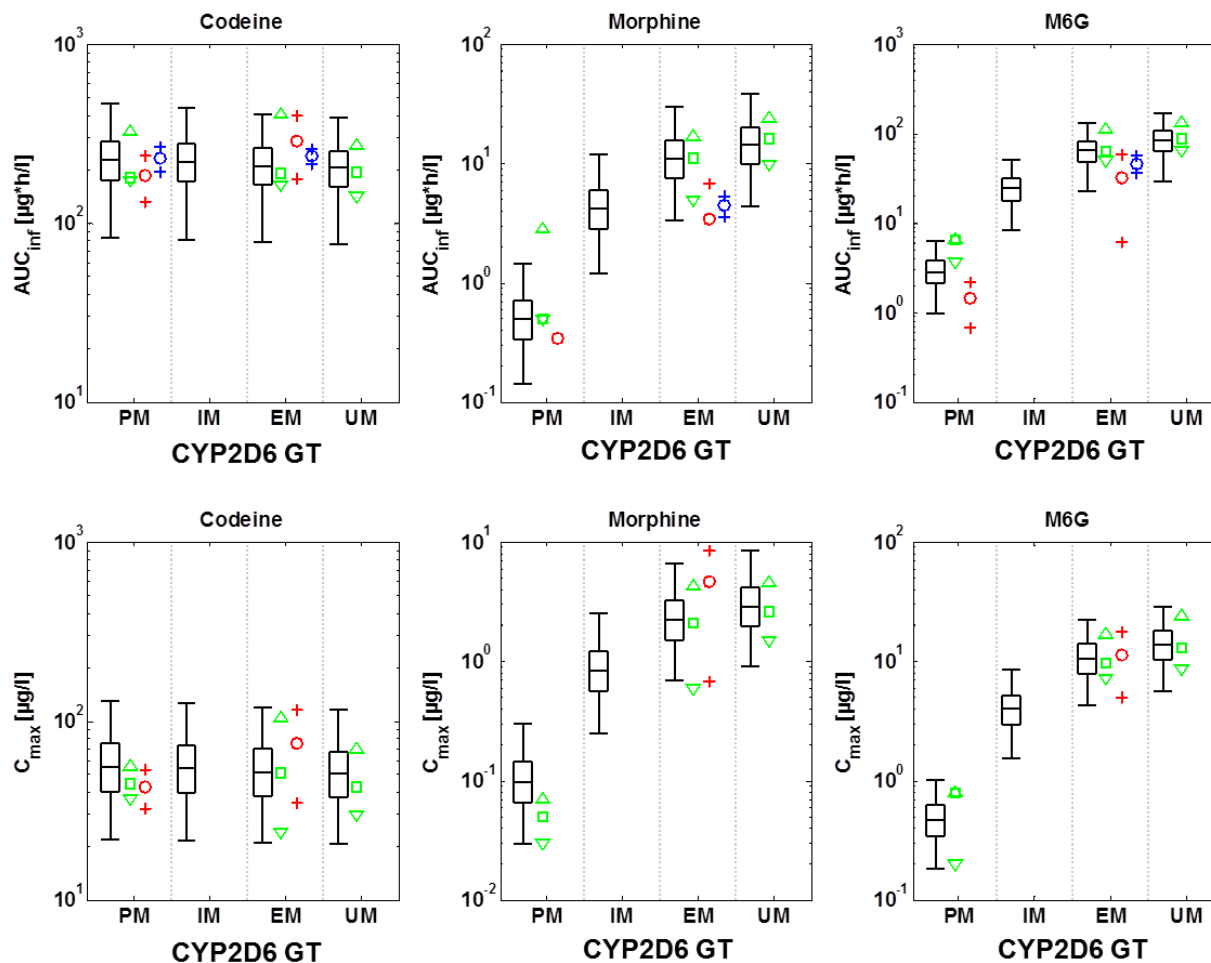
Naunyn-Schmiedeberg's Arch Pharmacol (2004) 369 : 23-37  
DOI 10.1007/s00210-003-0832-2

## REVIEW

Ulrich M. Zanger · Sebastian Raimundo  
Michel Eichelbaum

## Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry

# A systematic model validation requires comparison with all available data



## Simulation Results

Box-Whisker Plots  
Median, IQR, and  
95% C.I.

## Clinical Data

Kirchheiner et al.  
*Pharmacogen.* 2007

△ median  
□ min./max

## Yue et al.

*Br. J. Clin. Pharmacol.* 1991

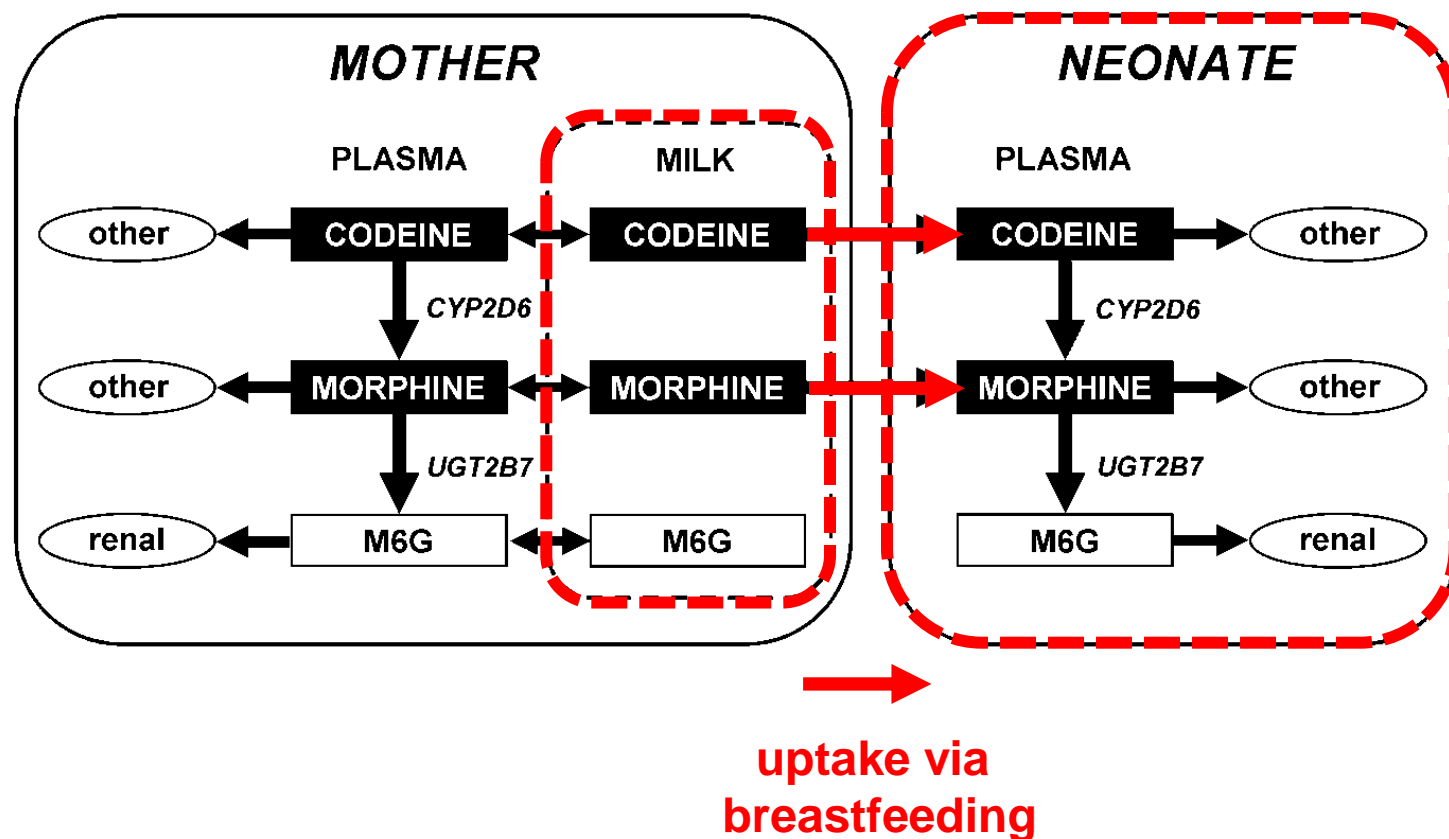
○ mean  
+ std.dev.

## Caraco et al.

*J. Pharm. Exp. Therap.* 1996

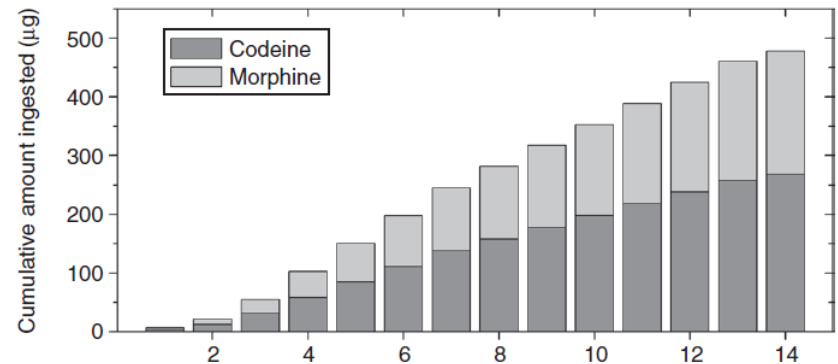
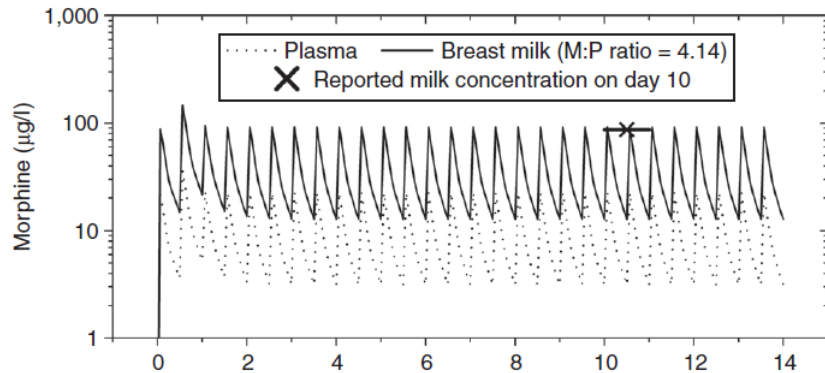
○ mean  
+ std.dev.

# Coupled models of codeine-morphine-M6G can be established to represent mother and child in a breastfeeding situation



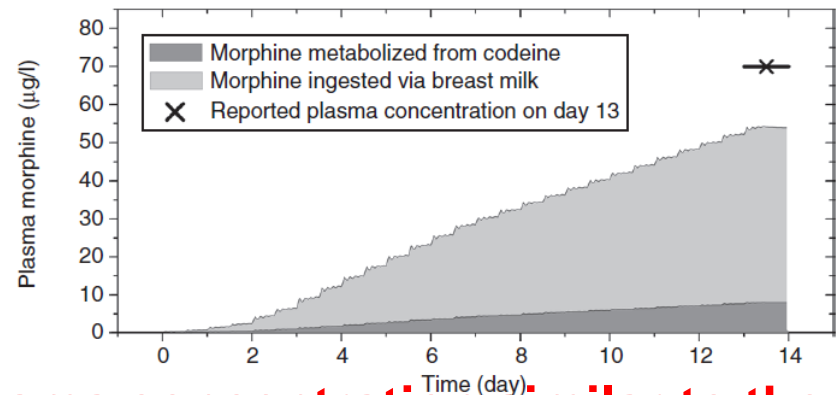


# The Toronto case – coupled PBPK models can be applied to simulate arbitrary scenario



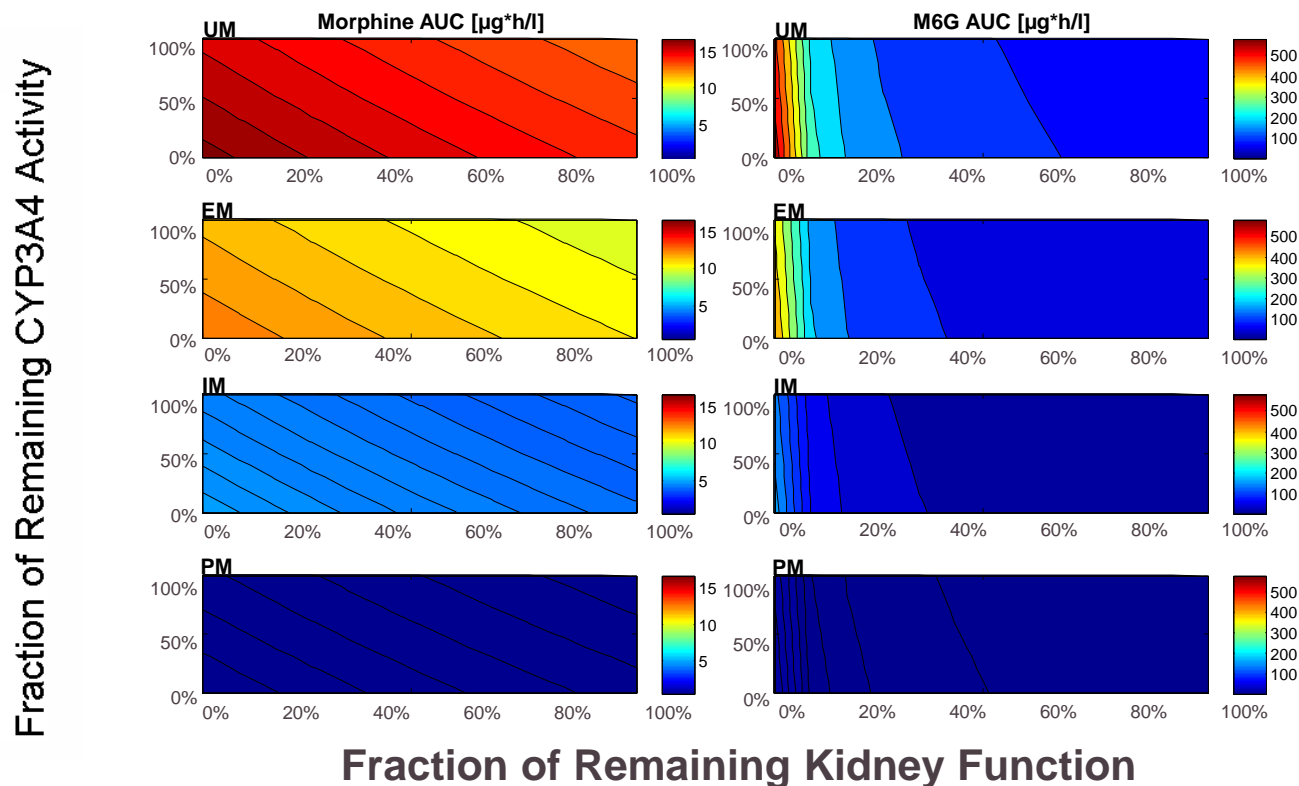
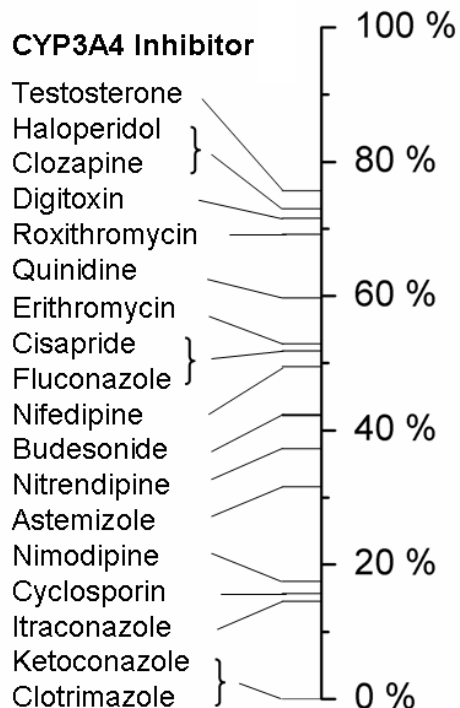
**Maternal codeine dose:** initially 120 mg/d, 60 mg/d from day 2 on

**Neonatal codeine and morphine dose:** calculated assuming a typical breast-feeding scenario



**Model shows neonatal morphine plasma concentration similar to the reported *post-mortem* level on day 13.**

# The systematic analysis of CYP3A4 related DDI and renal impairment are more common applications



Study of combined influence of CYP3A4 inhibition, renal impairment and CYP2D6 genotype reveals strongest influence of kidney function on active opioid exposure after codeine administration



# Active Transport

1521-009X/12/4005-892-901\$25.00  
DRUG METABOLISM AND DISPOSITION  
Copyright © 2012 by The American Society for Pharmacology and Experimental Therapeutics  
DMD 40:892-901, 2012

Vol. 40, No. 5  
43174/3761775

## Using Expression Data for Quantification of Active Processes in Physiologically Based Pharmacokinetic Modeling

Michaela Meyer, Sebastian Schneckener, Bernd Ludewig, Lars Kuepfer, and Joerg Lippert

*Systems Biology and Computational Solutions, Bayer Technology Services, Leverkusen, Germany*

Citation: CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e13; doi:10.1038/psp.2012.14  
© 2012 ASCPT All rights reserved 2163-8306/12

[www.nature.com/psp](http://www.nature.com/psp)

### ORIGINAL ARTICLE

## A Mechanistic, Model-Based Approach to Safety Assessment in Clinical Development

J Lippert<sup>1</sup>, M Brosch<sup>2</sup>, O von Kampen<sup>2</sup>, M Meyer<sup>1</sup>, H.-U Siegmund<sup>1</sup>, C Schafmayer<sup>3</sup>, T Becker<sup>3</sup>, B Laffert<sup>4</sup>, L Görlitz<sup>1</sup>, S Schreiber<sup>2</sup>, PJ Neuvonen<sup>5,6</sup>, M Niemi<sup>5,6</sup>, J Hampe<sup>2</sup> and L Kuepfer<sup>1</sup>

# OATP1B1 (SLCO1B1) genotype drives statin exposure and myopathy risk



## The NEW ENGLAND JOURNAL of MEDICINE

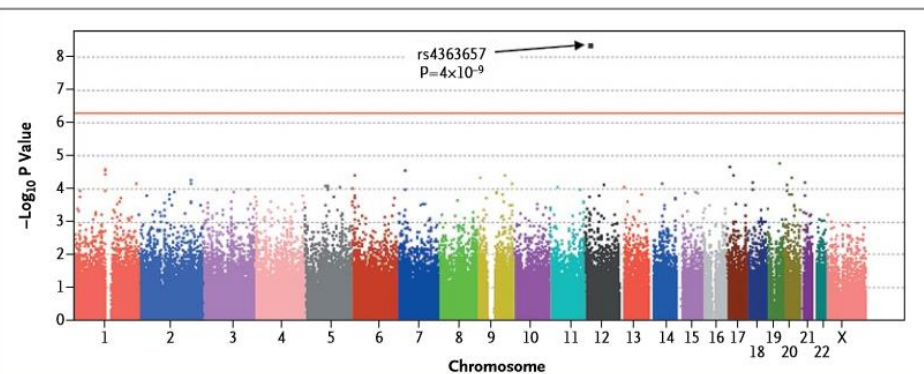
ESTABLISHED IN 1812

AUGUST 21, 2008

VOL. 359 NO. 8

### SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group\*



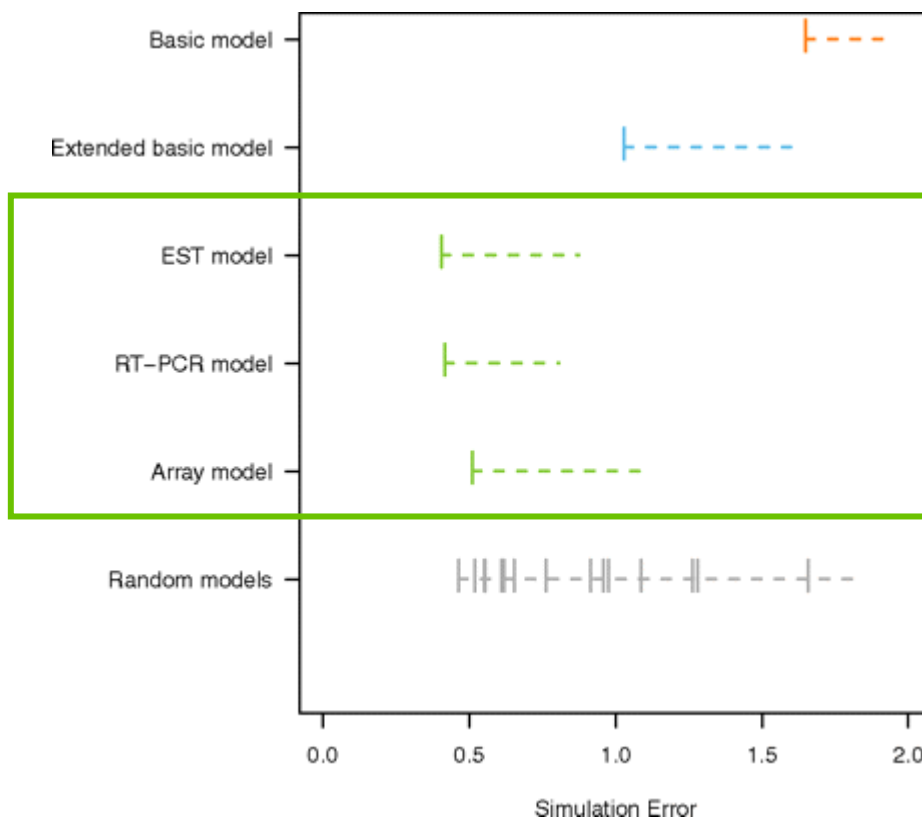
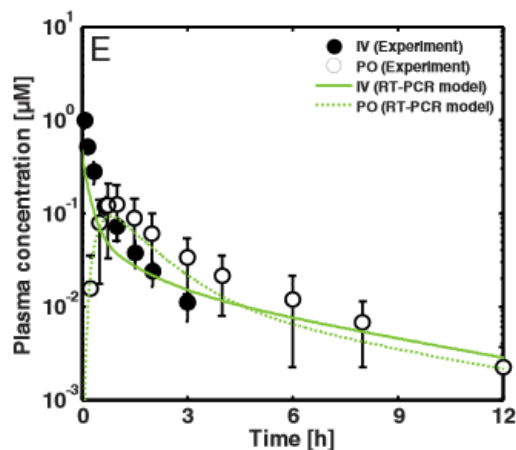
**Figure 1.** Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ( $P < 5 \times 10^{-7}$ ).

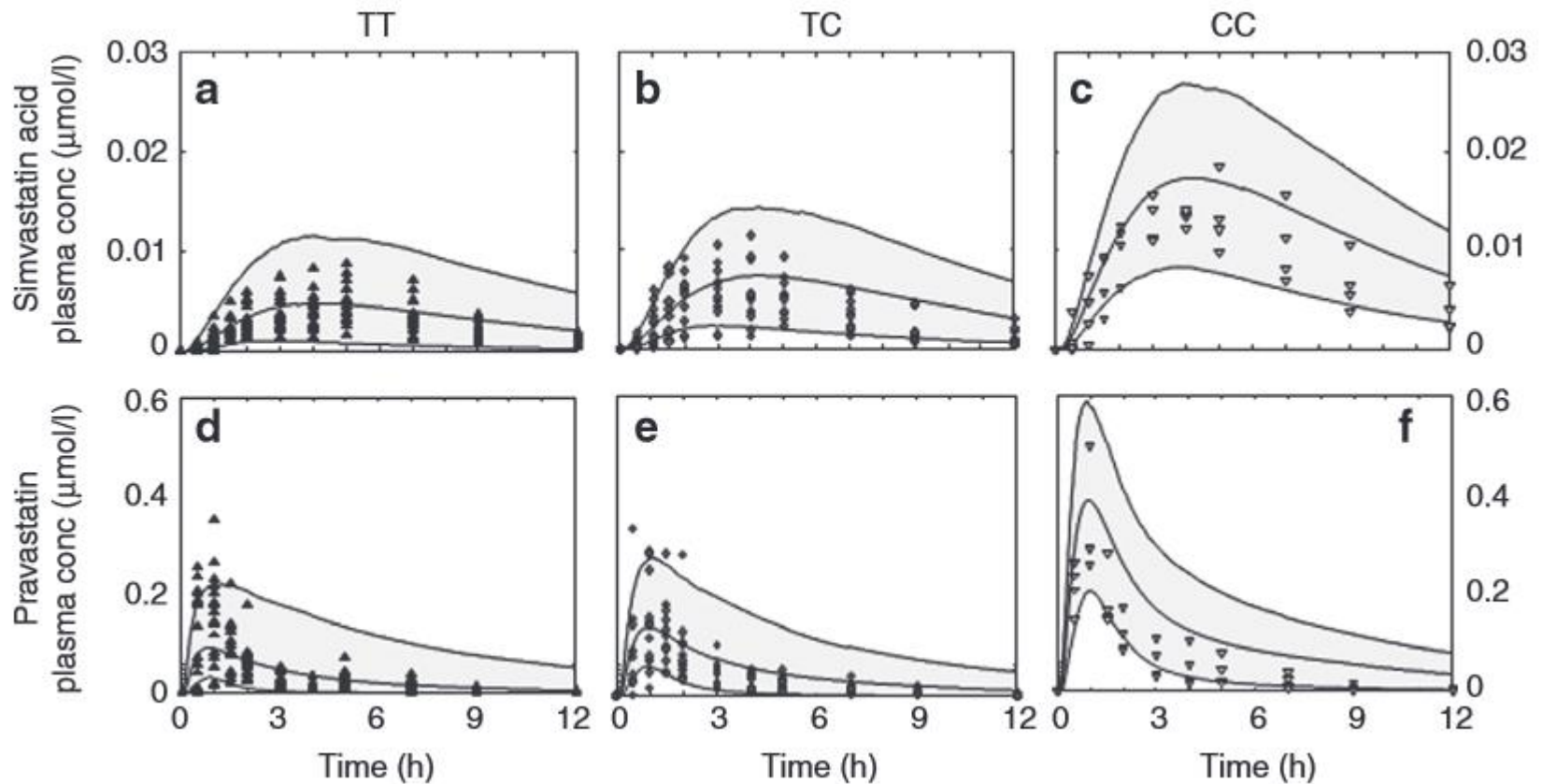
# Transporters and their tissue-specific expression once integrated into PBPK models improve performance



## Models representing transporter information show optimal performance



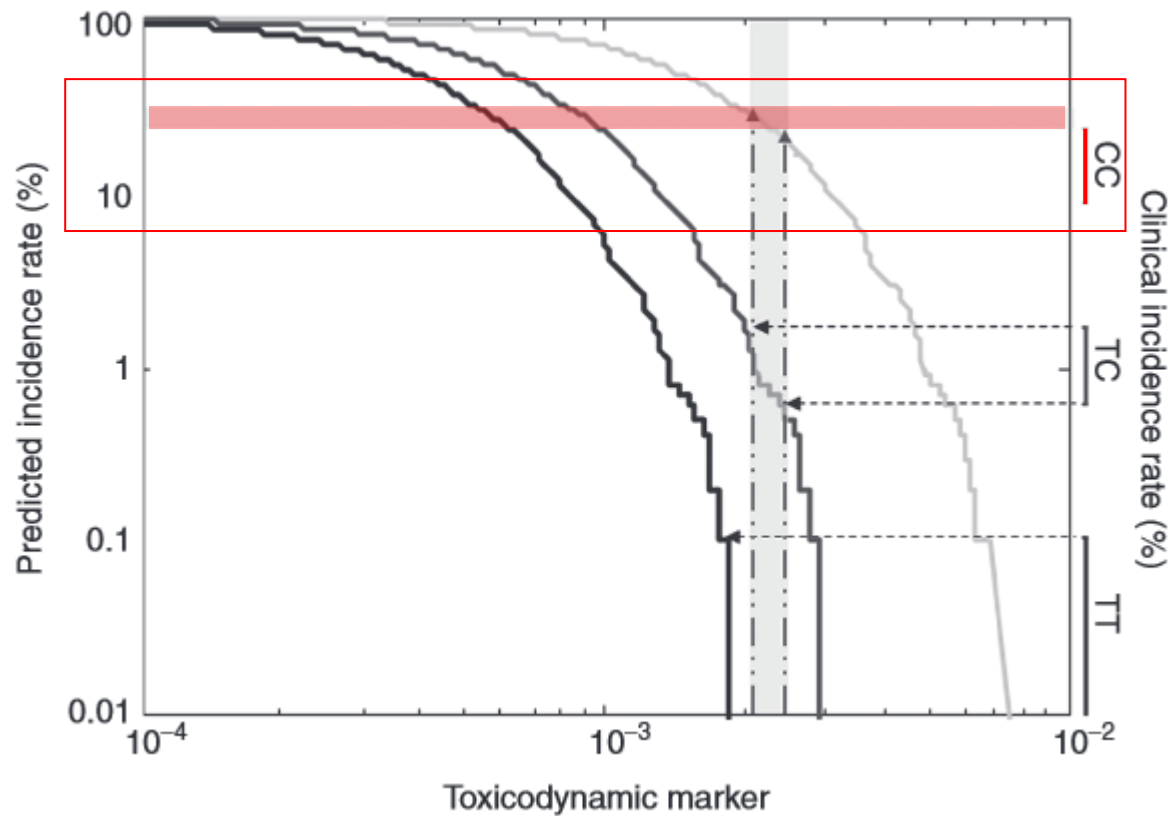
# The pharmacogenomics of transporter can be simulated accurately



# Event rates of relevant side effects in a small high risk subpopulations can be quantitatively predicted



Myopathy event rates by OATP1B1 genotype







# (Off-)Target Interaction

## Physiologically-based PK/PD modeling for oncology: structure and applications.

Michael Block<sup>1</sup>, Rolf Burghaus<sup>2</sup>, Kristin Dickschen<sup>1</sup>, Thomas Eissing<sup>1</sup>, Thomas Gaub<sup>1</sup>, Lars Küpfer<sup>1</sup>, Jörg Lippert<sup>2</sup>.

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<sup>1</sup> Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany.

<sup>2</sup> Bayer Pharma AG, Clinical Pharmacometrics, Wuppertal, Germany.

### Physiologically-based PK/PD modeling for oncology: structure and applications.

Michael Block<sup>1</sup>, Rolf Burghaus<sup>2</sup>, Kristin Dickschen<sup>1</sup>, Thomas Eissing<sup>1</sup>, Thomas Gaub<sup>1</sup>, Lars Küpfer<sup>1</sup>, Jörg Lippert<sup>2</sup>.

\* [michael.block@bayer.com](mailto:michael.block@bayer.com)

<sup>1</sup> Bayer Technology Services GmbH, Technology Development, Enabling Technologies, Computational Systems Biology, Leverkusen, Germany.  
<sup>2</sup> Bayer Pharma AG, Clinical Pharmacometrics, Wuppertal, Germany.

#### Motivation

A physiologically-based (PB) model applicable for oncological questions including a representation of tumor pharmacokinetics (PK) and pharmacodynamics (PD) was developed. It is aimed to represent all relevant processes for small molecules and biologics at a physiological level. Furthermore it determines a structure which can be applied in a full coupled PB/PD context. The modeling of the specific case antibody drug conjugates (ADC) has to respect the properties of the distribution of biologics combined with the release and distribution of the Toxopore in the tumor and off-target organ tissue. To overcome non-target-related effects which could lead to toxicity and still have sufficient efficacy naked antibody (nAb) pretreatment could be of high interest in drug development. The example of nAb pretreatment in the case of anti-TENB2/MMAE should provide insights into the possibility of this method and show up the potential of the ADC model.

#### Concepts

The PB model for oncology was developed by use of the systems biology platform for PBPK and PD modeling including PK-Sim and MoBi. Relevant processes concerning the representation of small molecules, antibodies (Ab) and antibody drug conjugates (ADC) were included as well as a structure which enables the model for species extrapolation [1-4]. In addition a PD model was integrated in order to represent tumor growth [5].

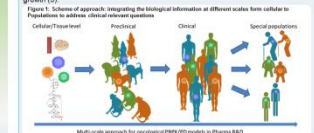


Figure 1: Scheme of approach, integrating the biological information at different scales from cellular to population to address clinical-relevant questions.

#### Model structure

As shown in Figure 2, the model structure consists of the full blown PBPK model for the ADC (here anti-TENB2/MMAE), the uncoupled naked Ab (here anti-TENB2), and the Toxopore (here Monomethyl Auristatin E, MMAE). As depicted in Fig 3 the model structure contains the processes from ADC distribution to the receptor at the tumor cell (A), the binding to the receptor (B), and the internalization and lysosomal degradation in the cell (C).

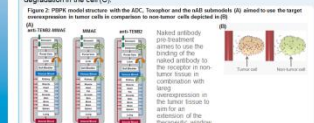


Figure 2: PBPK model structure with the ADC, Toxopore and the nAb submodels (B) aimed to use the target compartment in tumor cells in comparison to non-tumor cells related to (A) and (C).

In addition the model incorporates the process for the receptor synthesis and degradation in balance without dosing.

To explore the pharmacodynamics of the Toxopore a Simeoni model is incorporated to the structure. The approach follows the 4 step assessment of

- 1. PK without preloading; 2. PK with preloading; 3. consistency check of impact by naked Ab on off-target PK (small intestine, large intestine) and 4. representation of the corresponding tumor growth.

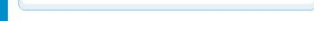


Figure 3: Required processes and related data to the distribution and binding of the ADC and the internalization of the ADC complex. Complex into the cell and further transport to the lysosome.

#### Results anti-TENB2/MMAE Pharmacokinetics

The pharmacokinetics of the ADC in no tumor bearing mice were simulated. As shown in Fig 4 the pharmacokinetics were well and represented by the model. It especially the timepoint of strong increase changes mediated clearance indicates that the model describes the target- and off-target effects on PK in a sufficient manner. To further validate the model and explore the nAb pretreatment effects the data from clinical trials taken (B) in mg/kg ADC and off-target pretreatment with nAb.

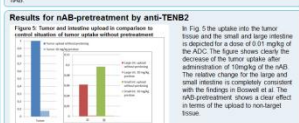


Figure 4: Comparison of the simulated ADC plasma time concentration time course to the observations in Bissler et al. (A) shows the pharmacokinetics for anti-TENB2/MMAE in mice bearing the tumor (B) the corresponding simulated vs. observed plot.

#### Results for nAb-pretreatment by anti-TENB2

Figure 5: Tumor and immune uptake in comparison to better illustrate of tumor uptake without preloading. The figure shows a bar chart comparing tumor uptake with and without nAb pretreatment.

In Fig 5 the uptake into the tumor tissue and the small and large intestine is depicted for a dose of 0.1 mg/kg of the ADC. The figure shows clearly the decrease of the tumor uptake after administration of 10 mg/kg of the nAb. The relative change for the large and small intestine is completely consistent with the findings in Bissler et al. The nAb-pretreatment shows a clear effect in terms of the uptake to non-target tissue.

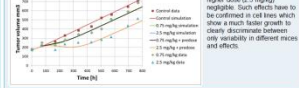


Figure 5: Tumor and immune uptake in comparison to better illustrate of tumor uptake without preloading.

#### Results Resulting pharmacokinetics for nAb pretreatment assessment

To explore if the efficacy is not affected by preloading the pharmacokinetics and the tumor growth was analyzed. In Figure 6 the change of pharmacokinetics under preloading is shown as observed (Bissler). The change in PK can best be reproduced. It can be seen that the preloading leads to a decrease of concentration in plasma indicating the amount-time uptake in tissue.

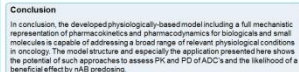


Figure 6: Resulting pharmacokinetics for nAb pretreatment assessment.

#### Model structure of the CV model. Separation of the model into target and organ with further detailing.

Figure 7 confirms that the impact of preloading on efficacy is different of tumor inhibition as for the higher dose 0.1 mg/kg nAb/kg. Such effects have to be confirmed in cell lines which show a much faster growth to clearly discriminate between nAb variability in different mice and effects.

Figure 7: Model structure of the CV model. Separation of the model into target and organ with further detailing.

#### Discussion

The results clearly show that we were able to cover the naked antibody pretreatment results observed for anti-TENB2/MMAE and anti-TENB2 by means of a full PBPK/PD structure. The model is able to cover the full range of PK of the ADC and related uptake of target and non-targeted tissue in a sufficient manner. Still it has to be explored that the positive (decrease of uptake) impact on some tissue does not lead to higher uptake and increasing risks in other tissues to validate the hypothesis of the potential to enlarge the therapeutic window.

#### Conclusion

In conclusion, the developed physiologically-based model including a full mechanistic representation of pharmacokinetics and pharmacodynamics for biologics and small molecules is capable of addressing a broad range of relevant physiological conditions in oncology. The model structure and especially the application presented here shows the potential of such approaches to assess PK and PD of ADC's and the likelihood of a beneficial effect by nAb preloading.

#### References

- 1. Bissler JJ, Geier PJ. *Ann. Rev. Med.* 2013;64:16-29.
- 2. Voggenreder V, et al. *Ther. PP. Oncol. LA. Leach MH, Wong J. *Bio. Chem.* 2012; 287:3617-32.*
- 3. Haddad-Dezaire M, et al. *Pharmacokinetic Pharmacodynamic*. 2010; 10:465-527.
- 4. Gray A, Bissler JJ. *Pharmacokinetic Pharmacodynamic*. 2007; 10:345-387-93.
- 5. Bissler et al. *Br. J. Pharmacol.* 2013; 169(2): 484-497.
- 6. Bissler et al. *J. Natl. Med.* 2012; 304(5): 1454-61.

# Protein PK, target binding and target mediated processes are available in commercial standard PBPK models

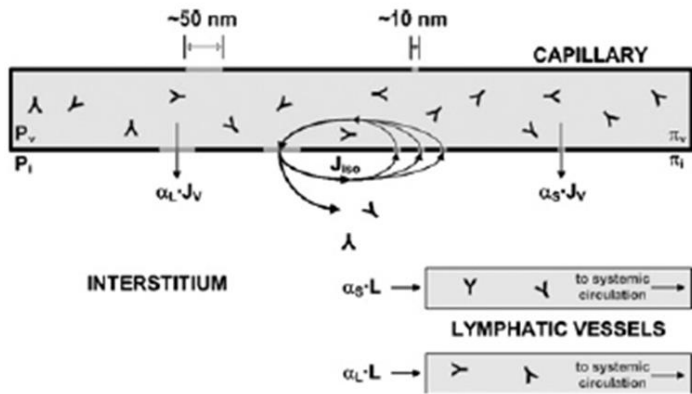


figure taken from Ferl et al., *Ann. Biomed. Eng.* 33, 1640 (2005)

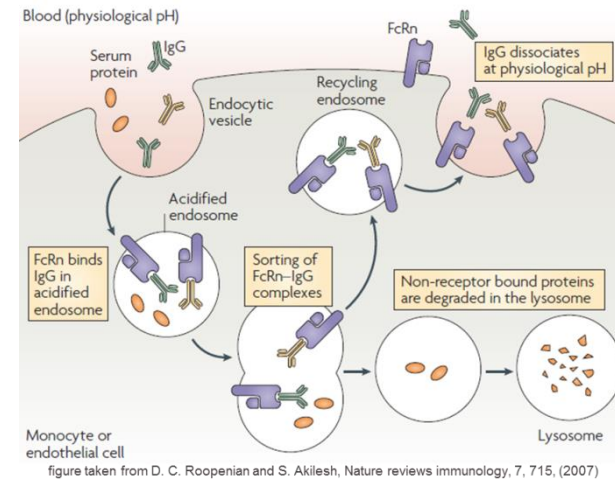
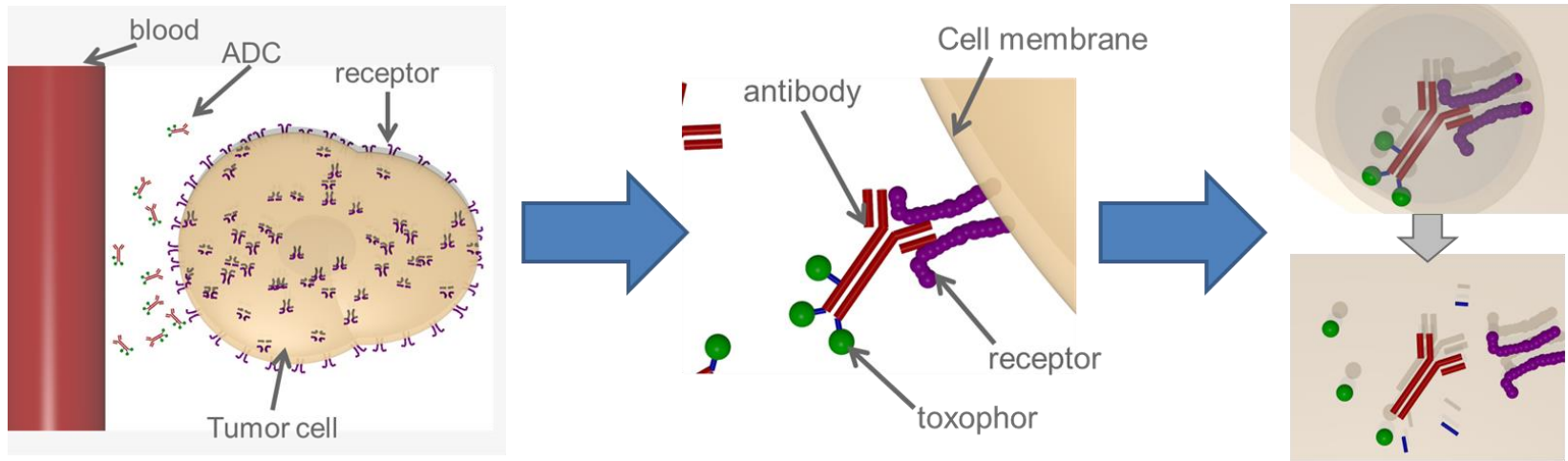


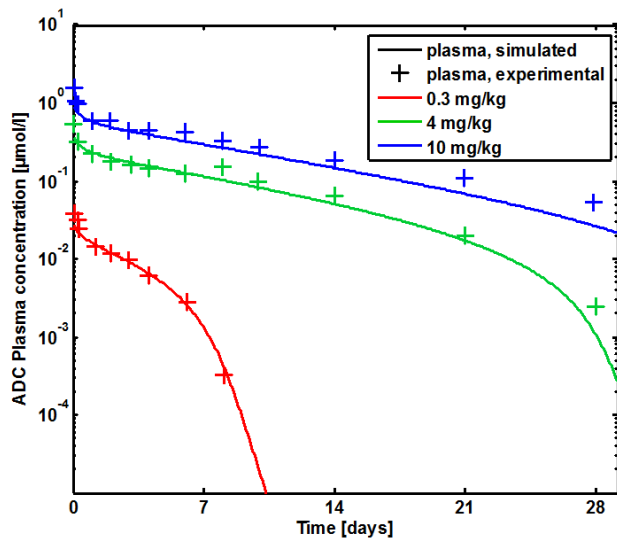
figure taken from D. C. Roopenian and S. Akilesh, *Nature reviews immunology*, 7, 715, (2007)



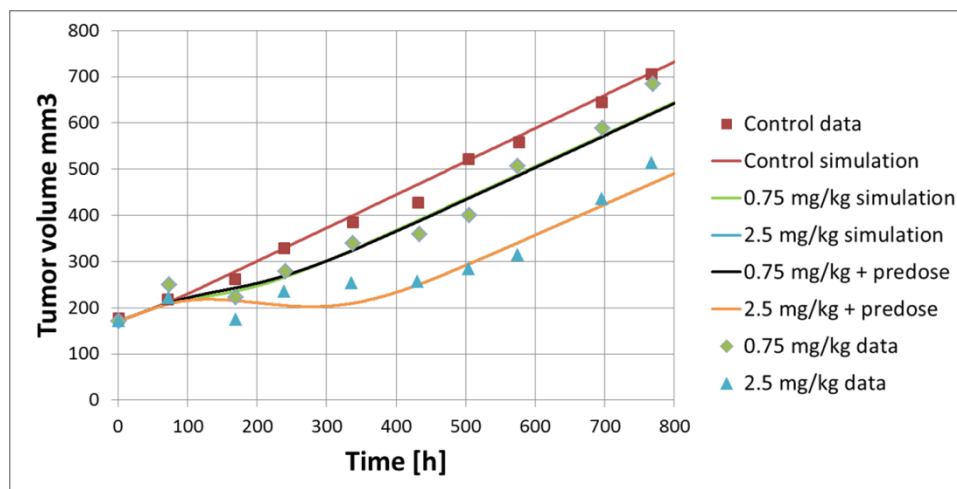
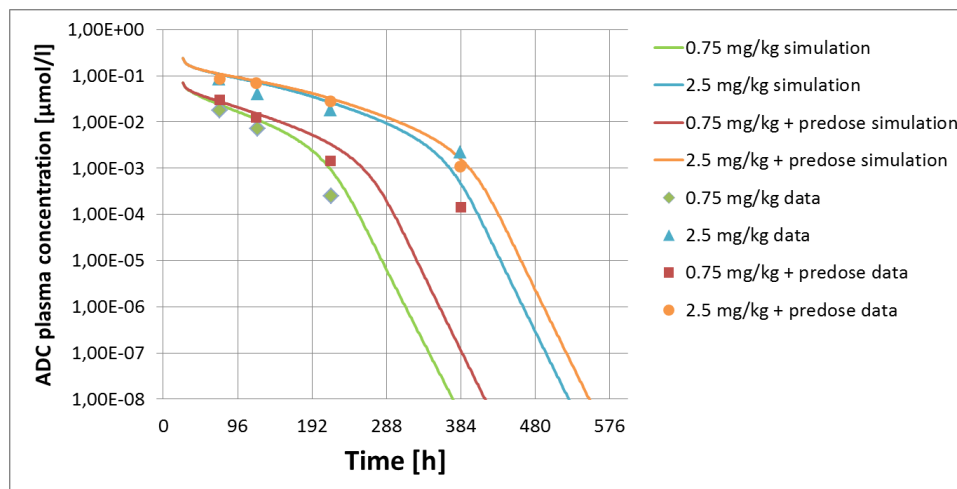
# Models for ADCs reflect all relevant properties and allow the simulation of complex scenarios such as nAb predosing



## PBPK-PD predictions for TENB2 - MMAE ADC PK and tumor growth



TENB2 - MMAE ADC data taken from  
 Boswell et al., Br J Pharmacol. Jan 2013; 168(2): 445–457.  
 Boswell et al., J Nucl Med. 2012 Sep;53(9):1454-61.





# Organ Physiology

frontiers in  
**PHYSIOLOGY**

**ORIGINAL RESEARCH ARTICLE**

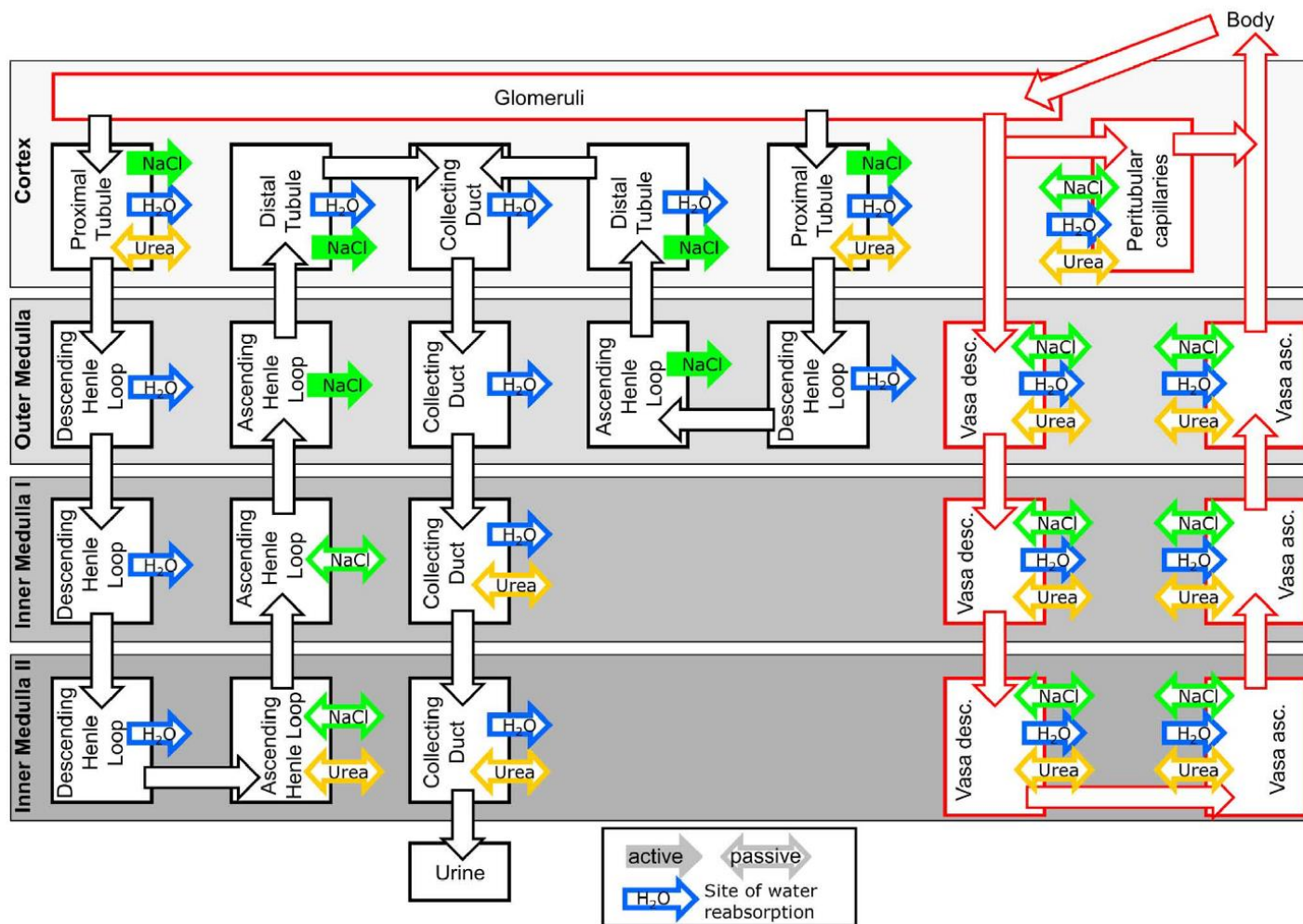
published: 24 January 2013  
doi: 10.3389/fphys.2012.00494



## Development of a physiologically based computational kidney model to describe the renal excretion of hydrophilic agents in rats

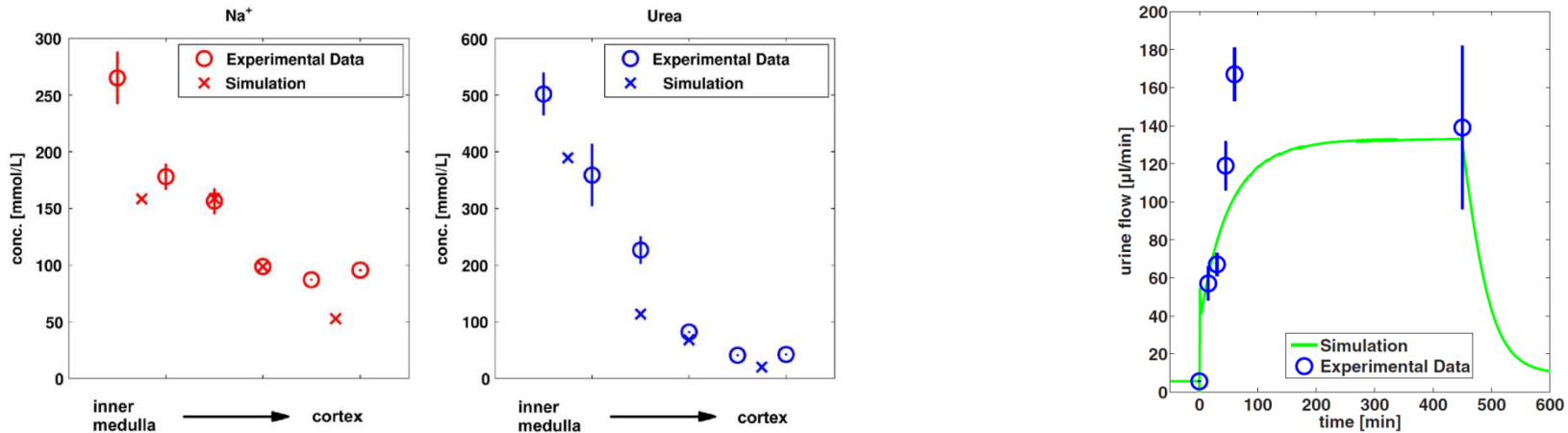
*Christoph Niederalt<sup>1\*</sup>, Thomas Wendl<sup>1</sup>, Lars Kuepfer<sup>1</sup>, Karina Claassen<sup>2</sup>, Roland Loosen<sup>1</sup>, Stefan Willmann<sup>1</sup>, Joerg Lippert<sup>1</sup>, Marcus Schultze-Mosgau<sup>3</sup>, Julia Winkler<sup>1</sup>, Rolf Burghaus<sup>4</sup>, Matthias Bräutigam<sup>5</sup>, Hubertus Pietsch<sup>6</sup> and Philipp Lengsfeld<sup>7</sup>*

# Standard PBPK models can be enhanced to represent organ function

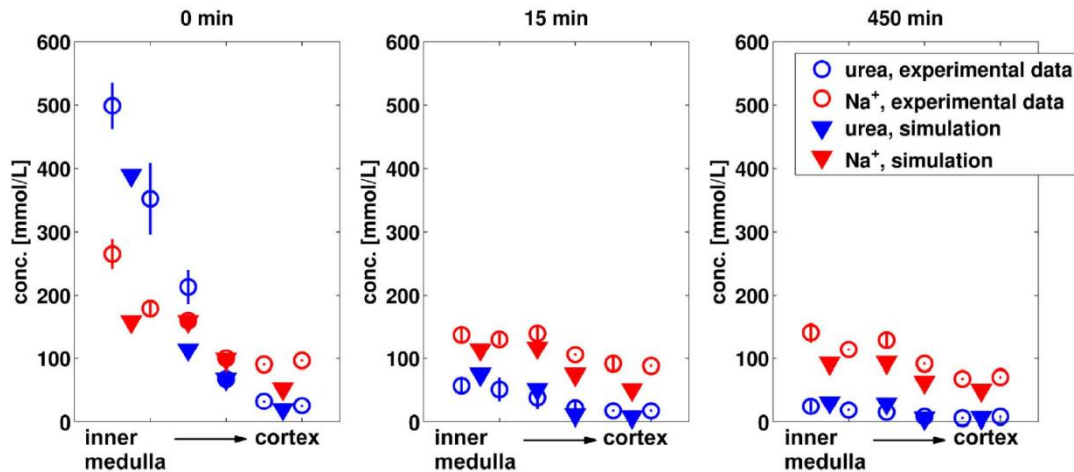




# The interaction between organ function and drugs can be studied mechanistically





## The impact of mannitol on urine flow and concentration profile



# How much biology can we capture with PBPK?



- Commercial state-of-the-art PBPK modeling platforms  **PK-Sim**<sup>®</sup> already provide implementations for all classical aspects of ADME, pharmacokinetics and pharmacogenomics
- Within these platforms models can be extended to  **MoBi**<sup>®</sup> customized PBPK-PD-physiology models to represent specific aspects relevant for a project / application
- PBPK is not constrained by modeling technology or feature lists of modeling tools but only by limits to our pharmacological understanding
- When applied systematically, PBPK can provide clinically relevant insights clearly beyond the limits of PK





## Agenda

- Why do we use PBPK?
- How much biology can we capture with PBPK?
- **How do we apply it?**
- What is still missing?

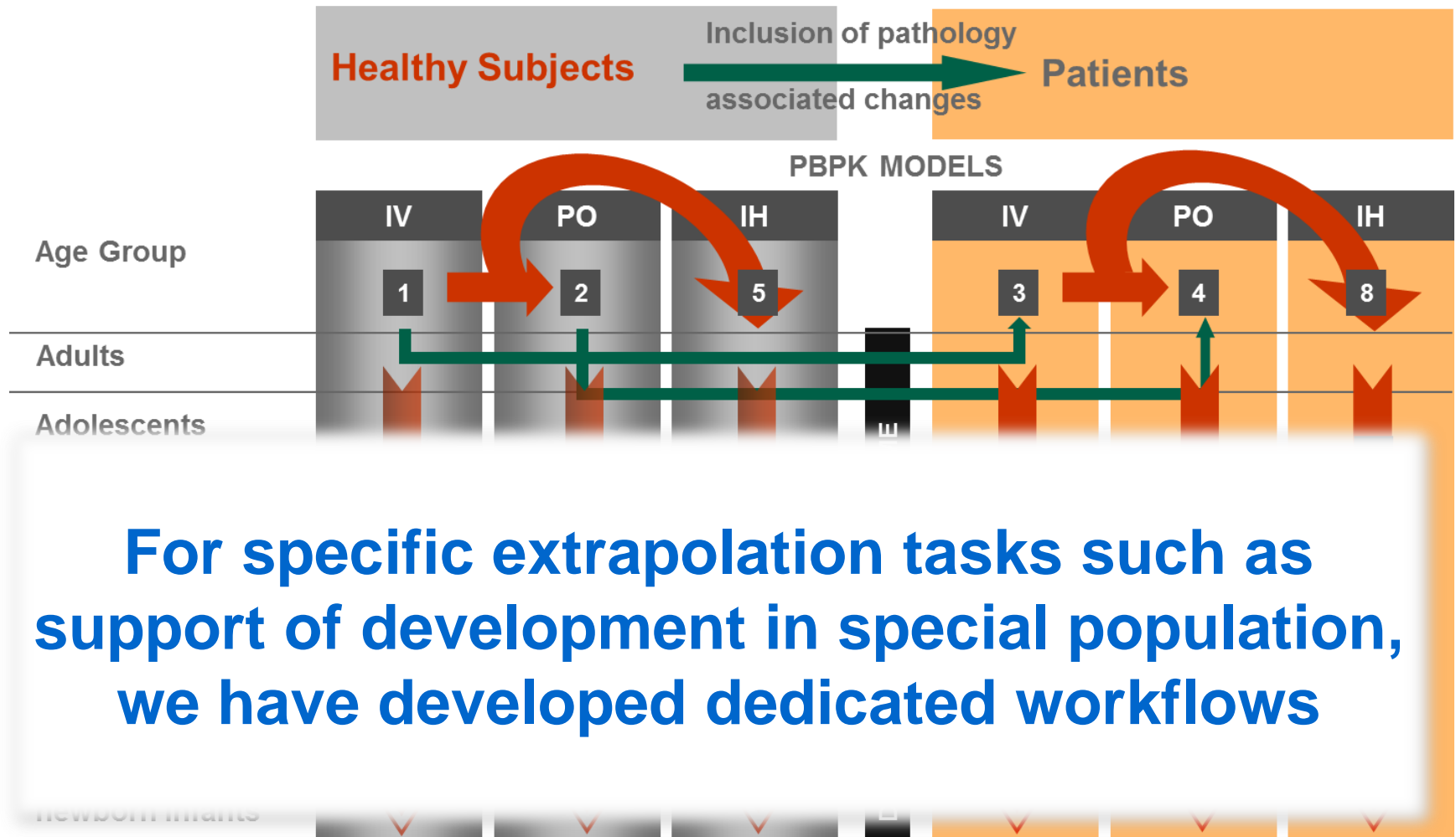
As a representation of information, data, and assumptions the PBPK model enables continuous explicit check of consistency



	Application		
Spec	<p><b>We continuously integrate “all” information from preclinical discovery on and try to follow a structured approach to either</b></p> <ul data-bbox="193 785 1700 1170" style="list-style-type: none"><li><b>• confirm consistency or</b></li><li><b>• identify inconsistency and guide active learning and obtain a better understanding</b></li></ul>		
	<p><b>Primary Objective:</b> Remove either consistency or understanding in each step</p>		



A systematic staggered approach minimizes uncertainty and risk



**For specific extrapolation tasks such as support of development in special population, we have developed dedicated workflows**



# Pediatric Scaling

Clin Pharmacokinet (2014) 53:89–102  
DOI 10.1007/s40262-013-0090-5

ORIGINAL RESEARCH ARTICLE

## **Development of a Paediatric Population-Based Model of the Pharmacokinetics of Rivaroxaban**

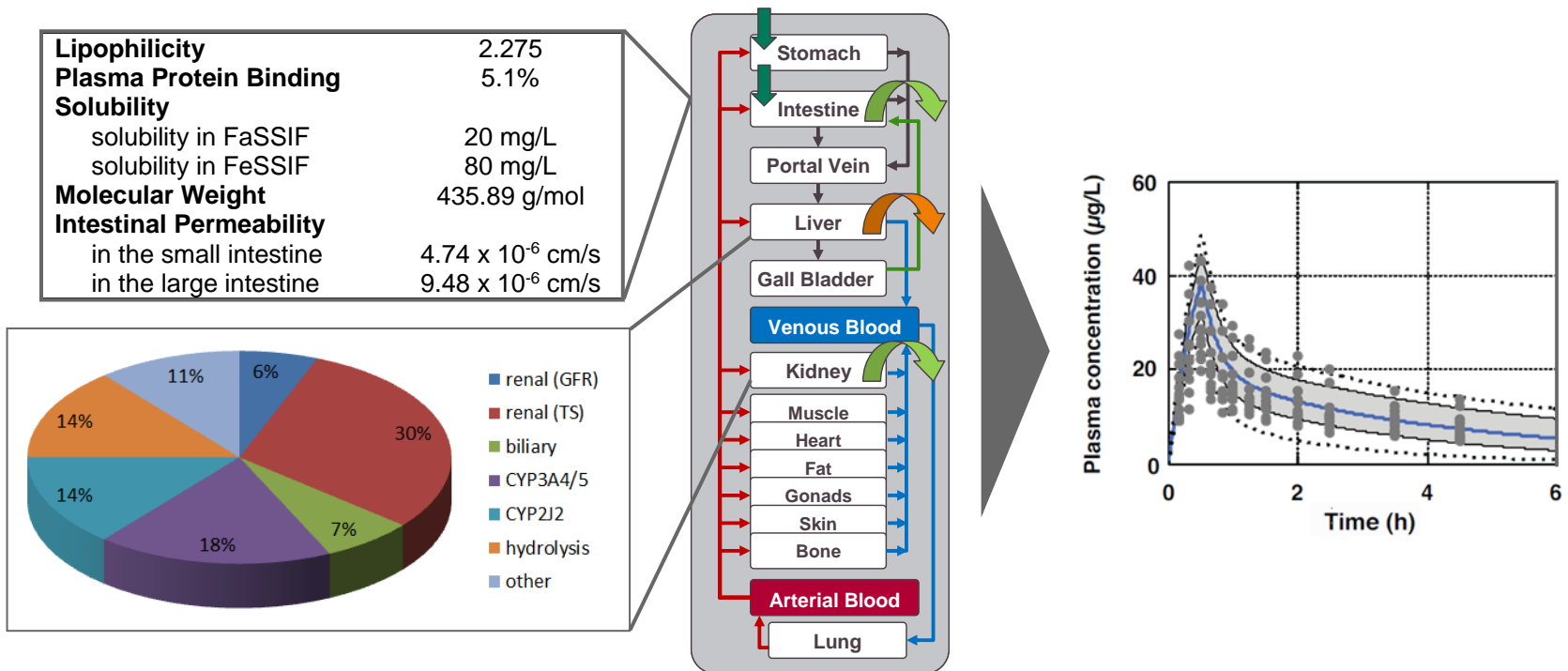
**Stefan Willmann · Corina Becker · Rolf Burghaus ·  
Katrin Coboeken · Andrea Edginton · Jörg Lippert ·  
Hans-Ulrich Siegmund · Kirstin Thelen · Wolfgang Mück**

# The PBPK model for rivaroxaban integrates all existing ADME information



## Step 1: Development and validation of a Rivaroxaban PBPK Model for Adults

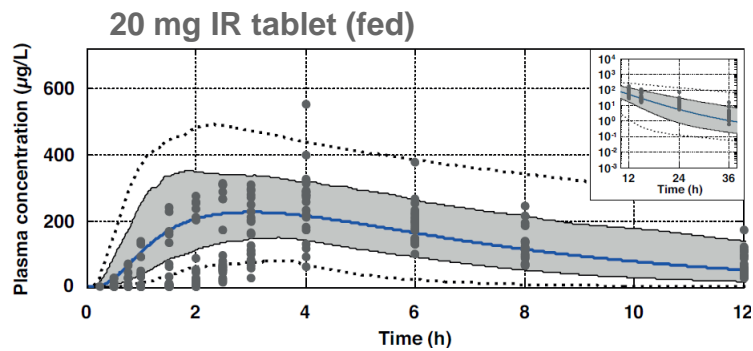
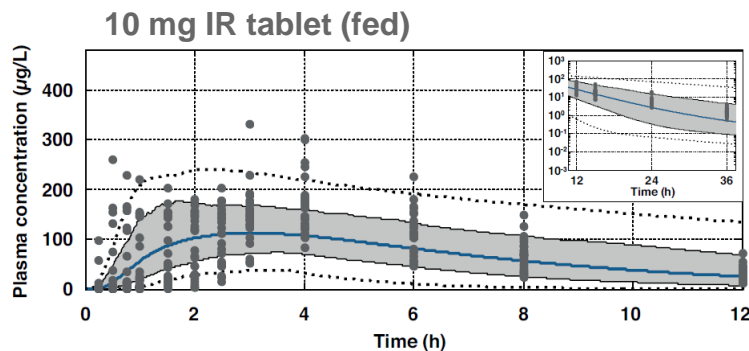
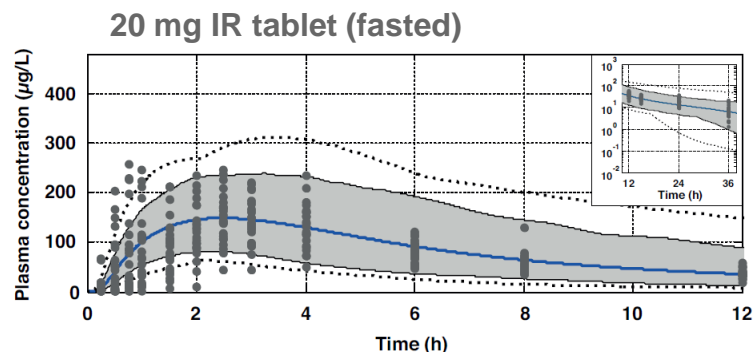
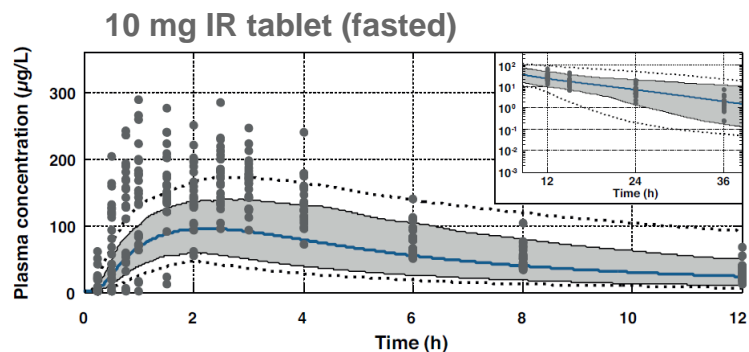
Development using physico-chemical data, preclinical and clinical IV/PO data:



# The model represents PK in adults

## Step 1: Validation of a Rivaroxaban PBPK Model for Adults

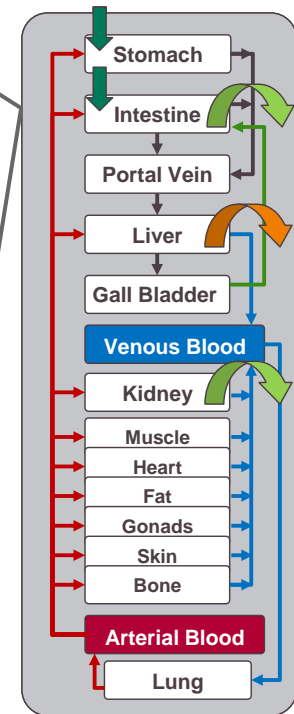
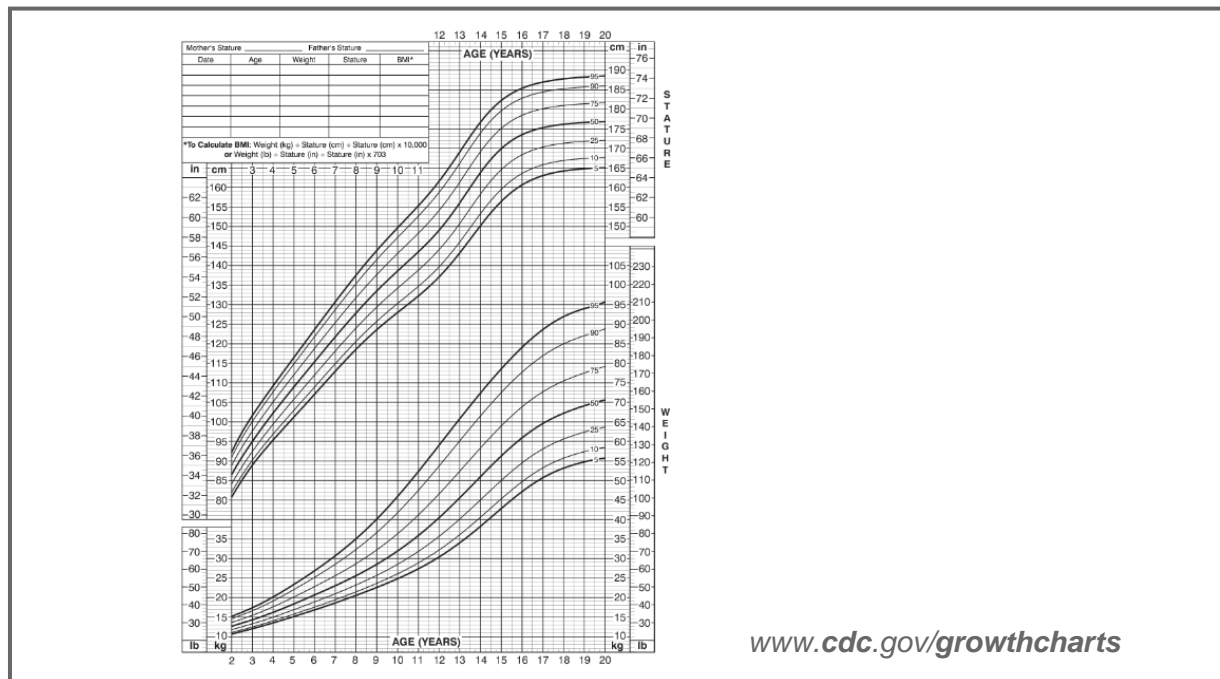
Validation: Comparison of PBPK model predictions with phase I study data



# The scaling to children is based on prior knowledge about 1. growth

**Step 2:** Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age





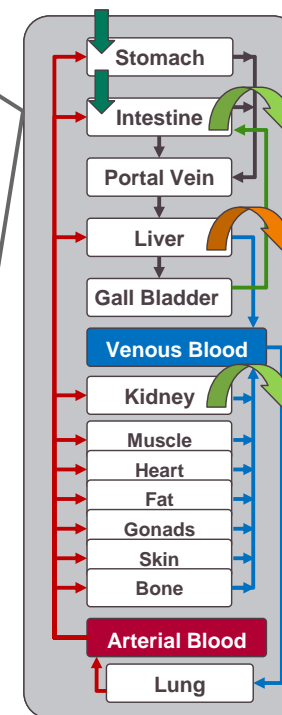
# The scaling to children is based on prior knowledge about 2. maturation

**Step 2:** Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of physiological/anatomical information vs. age

Parameter	Newborn	1y	5y	10y	15y	Adult (30y)
<b>Organ blood flow (mL/min)</b>						
adipose	30	12	171	250	315/484 <sup>a</sup>	325/502 <sup>a</sup>
brain	180	700	900	840/750 <sup>a</sup>	805/708 <sup>a</sup>	780/708 <sup>a</sup>
gonads	0.3	0.6	1.7/0.7 <sup>a</sup>	2.5/1.0 <sup>a</sup>	3.2/1.1 <sup>a</sup>	3.3/1.2 <sup>a</sup>
heart	24	48	136	200	252/285 <sup>a</sup>	260/295 <sup>a</sup>
kidneys	110	230	577	854	1335/950 <sup>a</sup>	1325/1120 <sup>a</sup>
large intestine	24	48	136	200	251/285 <sup>a</sup>	260/295 <sup>a</sup>
liver	39	78	221	325	409/370 <sup>a</sup>	423/383 <sup>a</sup>
muscle	31	72	212	429	941/646 <sup>a</sup>	1105/665 <sup>a</sup>
pancreas	6	12	34	50	63/57 <sup>a</sup>	65/59 <sup>a</sup>
skeleton	30	60	170	250	315/285 <sup>a</sup>	325/295 <sup>a</sup>
skin	30	60	170	250	315/285 <sup>a</sup>	325/295 <sup>a</sup>
small intestine	60	120	340	500	630/627 <sup>a</sup>	650/649 <sup>a</sup>
spleen	18	36	102	150	189/171 <sup>a</sup>	195/177 <sup>a</sup>
stomach	6.0	12	34	50	63/57 <sup>a</sup>	65/59 <sup>a</sup>
Portal blood flow (mL/min)	114	228	646	950/950 <sup>a</sup>	1197/1197 <sup>a</sup>	1235/1239 <sup>a</sup>
Q <sub>H</sub> (mL/min)	153	306	867	1275/1273 <sup>a</sup>	1600/1566 <sup>a</sup>	1660/1620 <sup>a</sup>
Bodyweight (kg)	3.5	10	19	32	56/53 <sup>a</sup>	73/60 <sup>a</sup>
Height (cm)	51	76	109	138	167/161 <sup>a</sup>	176/163 <sup>a</sup>

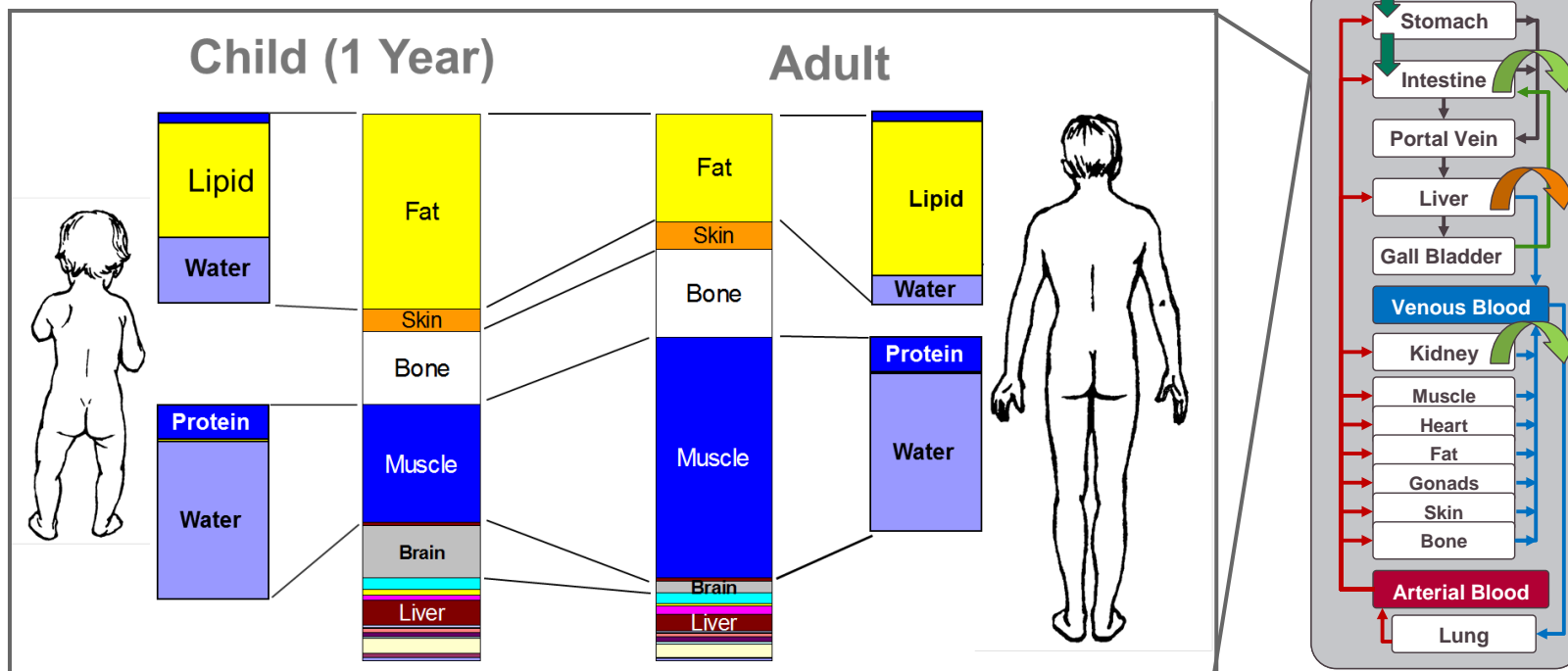
<sup>a</sup> Male/female.



# The scaling to children is based on prior knowledge about 2. maturation

**Step 2:** Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

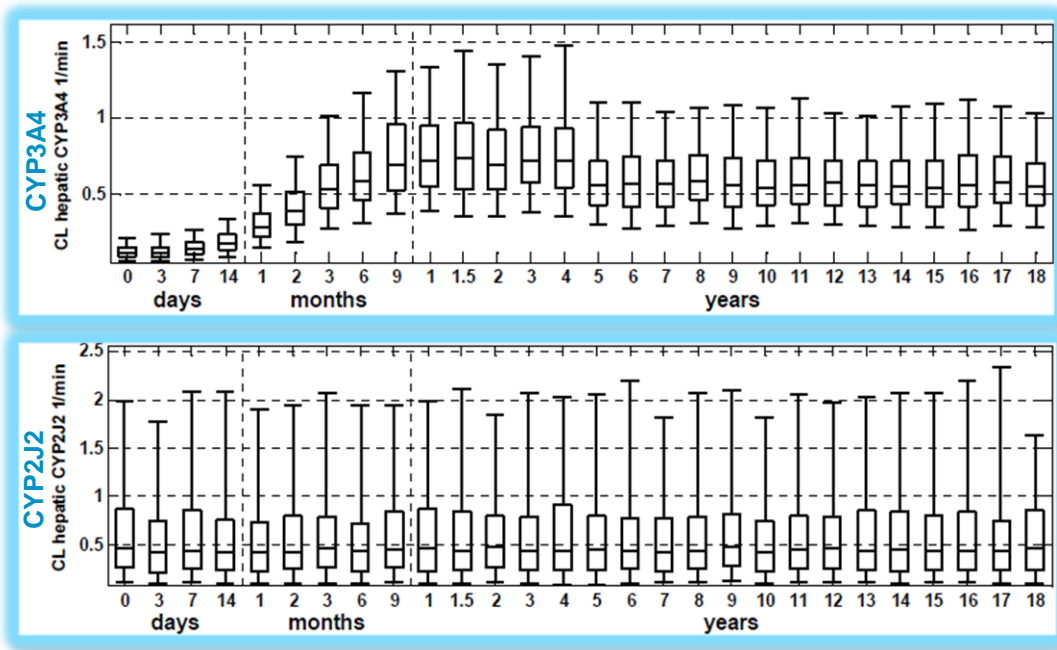
Inclusion of physiological/anatomical information vs. age



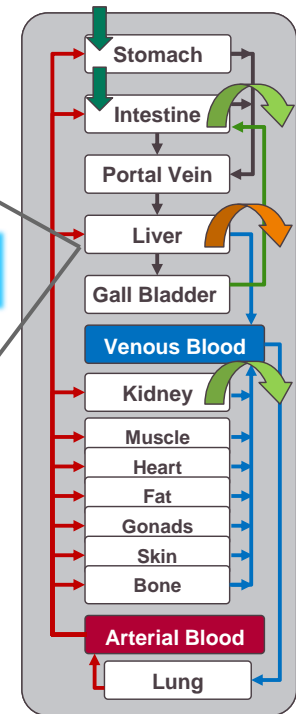
# The scaling to children is based on prior knowledge about 2. maturation

**Step 2:** Scaling of the adult PBPK model to children using prior physiological information about growth and maturation of relevant processes

Inclusion of ontogeny information for relevant processes



\* CYP3A4/5  
\* CYP2J2



# Population simulations provide expectations about exposure in children

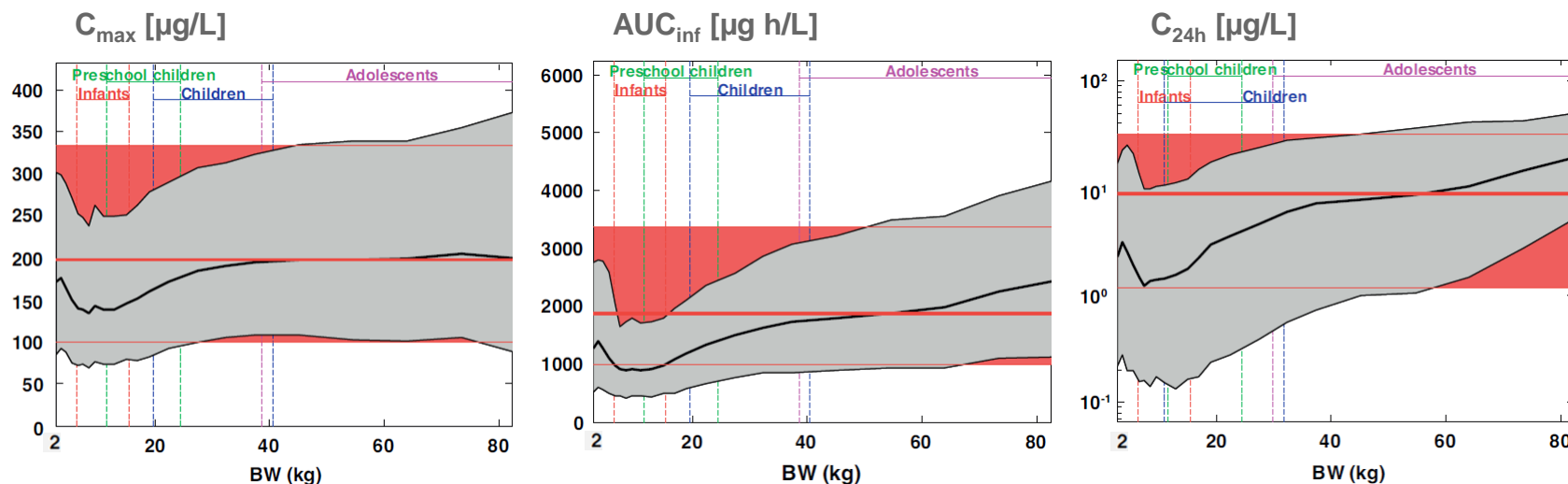


## Step 3: Prediction of Rivaroxaban pharmacokinetics in pediatric populations

Simulations of virtual pediatric populations according to study proposal

- mixed gender (male:female = 50:50), fasted:fed state = 50:50
- Rivaroxaban doses: 10 mg/70 kg and 20 mg/70 kg
- influence of formulation needs to be considered (tablet vs. suspension)

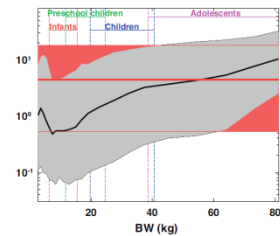
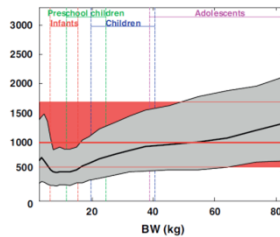
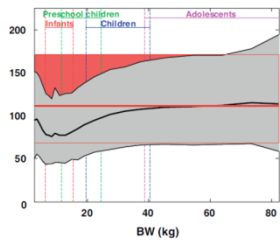
**Results** (dose = 20 mg/70 kg, pooled for gender and fasted/fed):



# To match exposure to levels known to be efficacious and safe in adults dose adjusted are calculated



## Step 3: Prediction of Rivaroxaban pharmacokinetics in pediatric populations



### Result: Age and body weight adapted dosing table

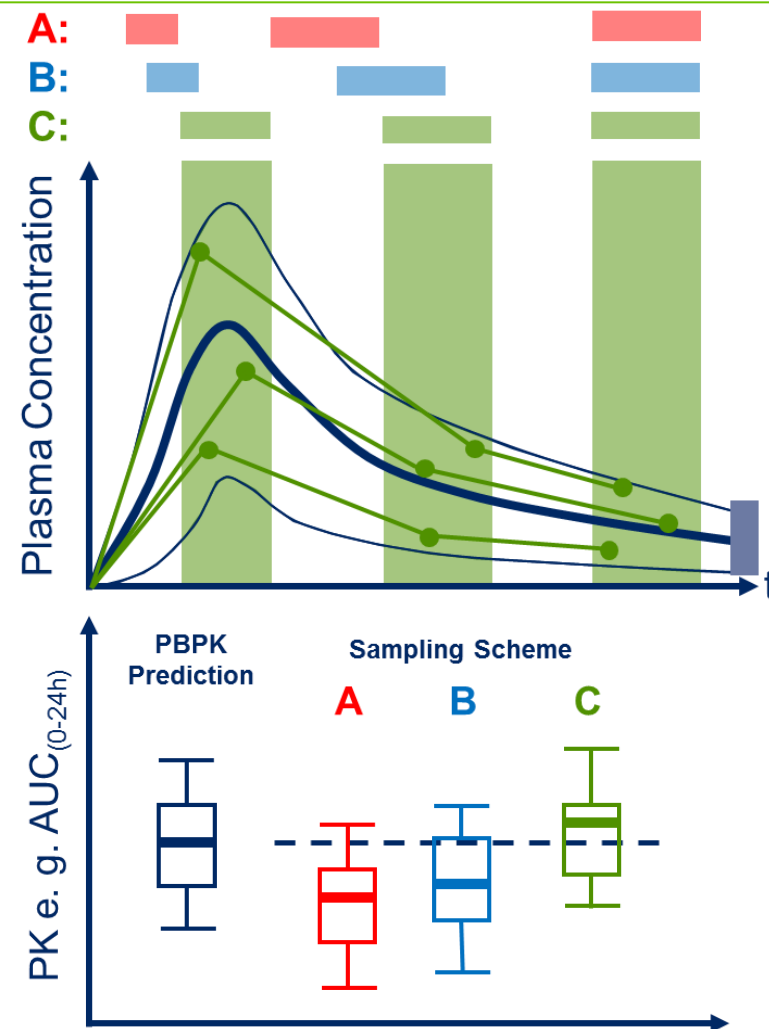
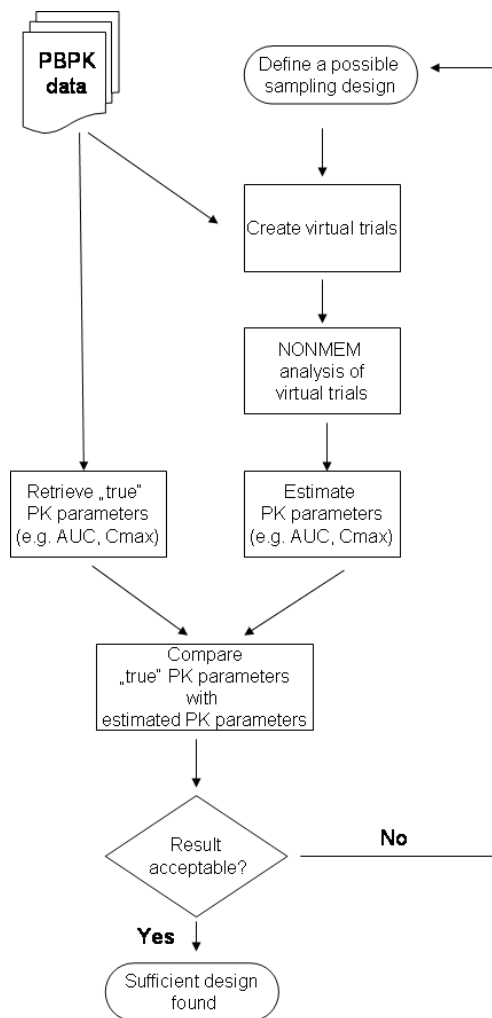
Age group	Body weight [kg]	Dose	
		Tablet	Suspension
Pre-school children (0-2 years)	5-8		200 mg
	8-12		200 mg
	12-18		200 mg
	18-25		200 mg
	25-35		200 mg
	35-50		200 mg
Infants (2-3 years)	10-15	200 mg	200 mg
	15-20	200 mg	200 mg
	20-25	200 mg	200 mg
	25-35	200 mg	200 mg
Children (3-12 years)	15-20	200 mg	200 mg
	20-25	200 mg	200 mg
	25-35	200 mg	200 mg
	35-50	200 mg	200 mg
Adolescents (12-18 years)	50-60	200 mg	200 mg
	60-80	200 mg	200 mg
Body weight	>100	200 mg	200 mg

# Clinical Trial Simulations with PopPK based on PBPK simulations help to optimize sampling design in pediatric trials



## Step 4:

Sampling schemes are optimized for accurate determination of PK parameters with a minimum of samples



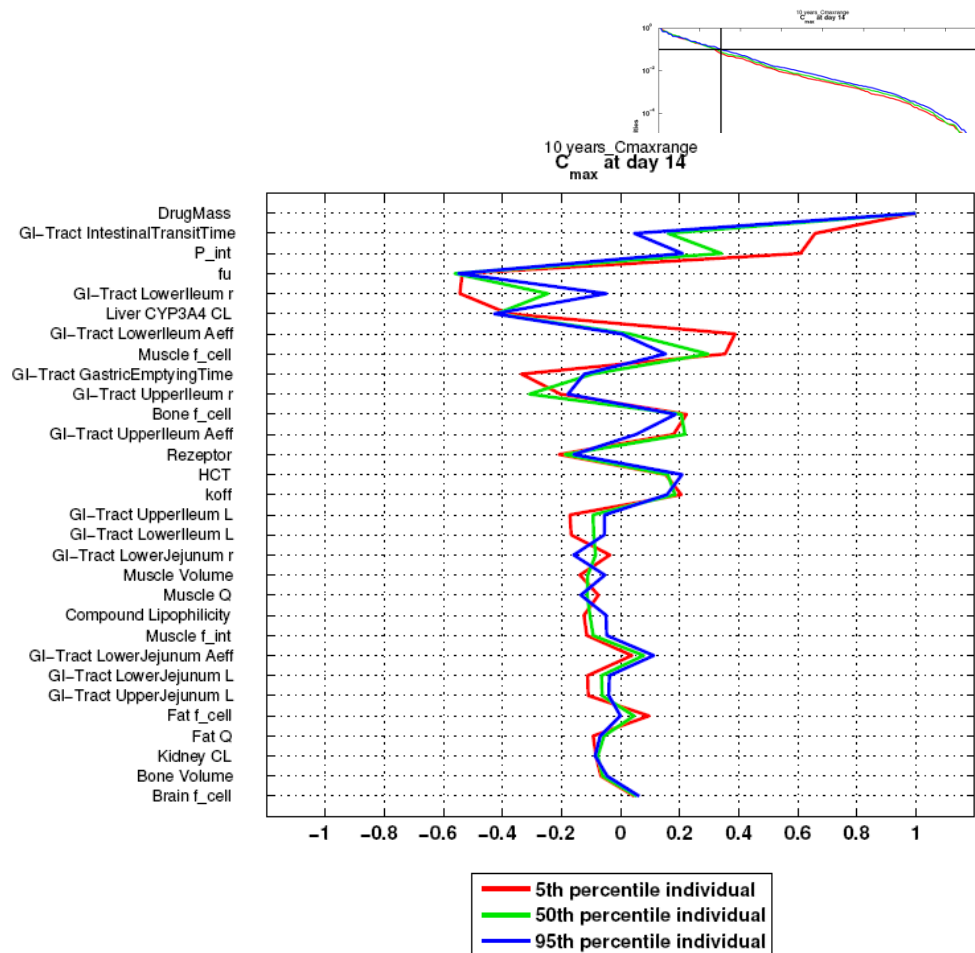
# Evaluation of the sensitivities of simulated outcomes to model parameters is a mandatory risk assessment measure



1. Determination of globally normalized sensitivities of all (independent) parameters
2. Determination of cut-off using integral sensitivity threshold
3. Detailed analysis and discussion of dominant “factors” using standard report format


## Check of understanding!

Discussion of sensitivities is the natural step for an assessment of uncertainty, lack of understanding and resulting risks!





# How do we apply it?

1. Continuous integration of all information and on-going check of consistency at each development (project) step
2. Consistent use of the same fully transparent base PBPK model across all therapeutic areas, projects and development stages from discovery to clinic 
3. Explicit formulation and documentation of all assumptions and evaluation of sensitivities of predictions to these

**Full transparency and explicit formulation of assumptions is key to identify non-characterized development risks!**

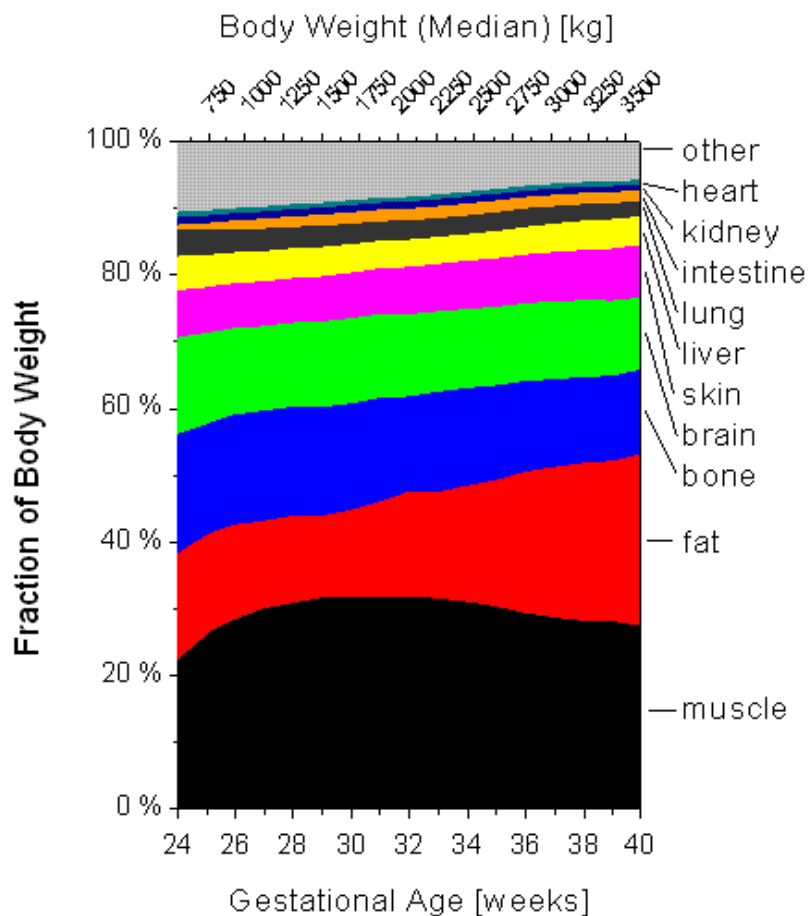




## Agenda

- Why do we use PBPK?
- How much biology can we capture with PBPK?
- How do we apply it?
- **What is still missing?**

# Existing information about anatomy and physiology of **preterm neonates** allows establishment of dedicated PBPK models

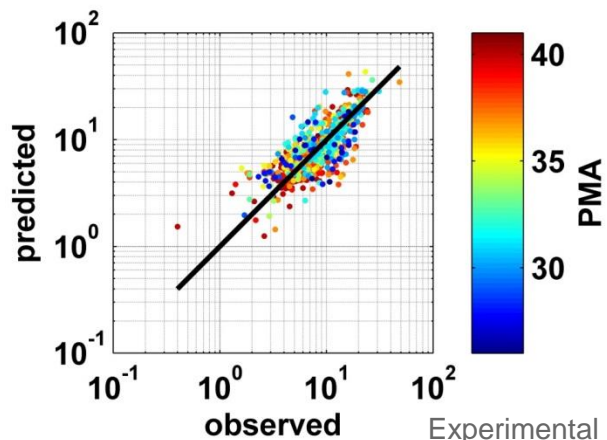
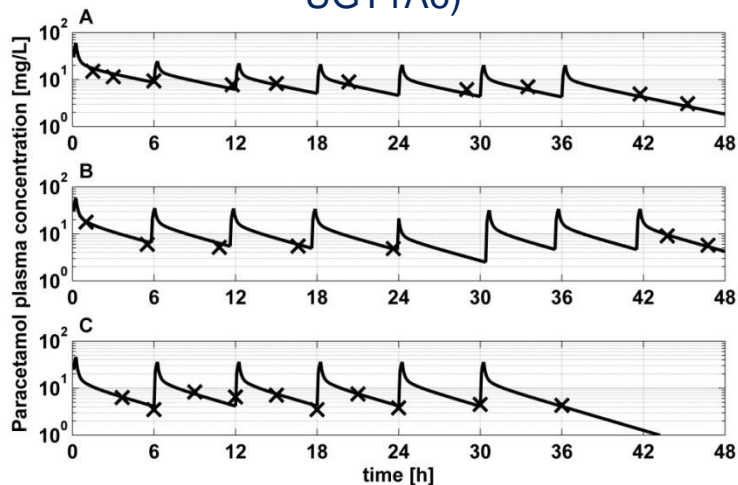


PK-Sim® Database	Early gestation	Mid gestation	Late gestation	postnatal
Oxidative enzymes				
Alcoholdehydrogenase				
ADH		31%*		45%
Cytochrome P450 system				
CYP 1A1		low or no expression*		
CYP 1A2		5%*		10%
CYP 1B1		undetectable*		
CYP 2A6		low or no expression*		
CYP 2A13		undetectable*		
CYP 2B6		50%		
CYP 2C		0%*		3%
CYP 2C9	0%	4-5%	10%	25%
CYP 2C18		undetectable*		
CYP 2C19	0%	1%	10-20%	50%
CYP 2D6	5%	5%	6%	9%
CYP 2E1	0%	0%	0%	10%
CYP 3A4		3%		13%
CYP 3A5		is present, no change as function of age*		
CYP 3A7		500%*		130%
FMO system				
FMO1	100%	50%	25%	0%
FMO3	0%	0%	0%	50%
Conjugation enzymes				
Epoxide hydrolase				
EPHX1	6%	10%	32%	50%
Glutathione S-transferases				
GSTM (GST1)		22%*		93%
GSTA (GST2)		25%*		62%
GSTP (GST3)		5300%*		2100%

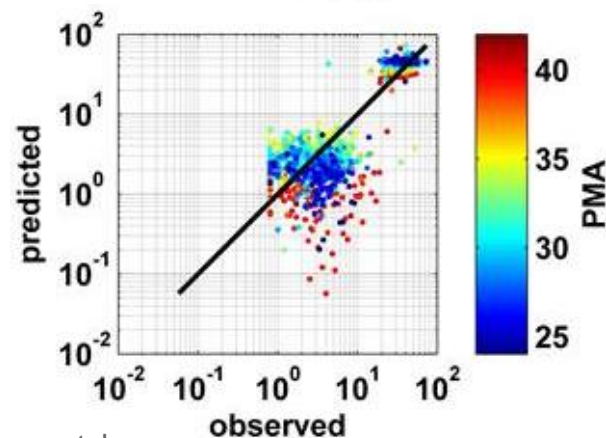
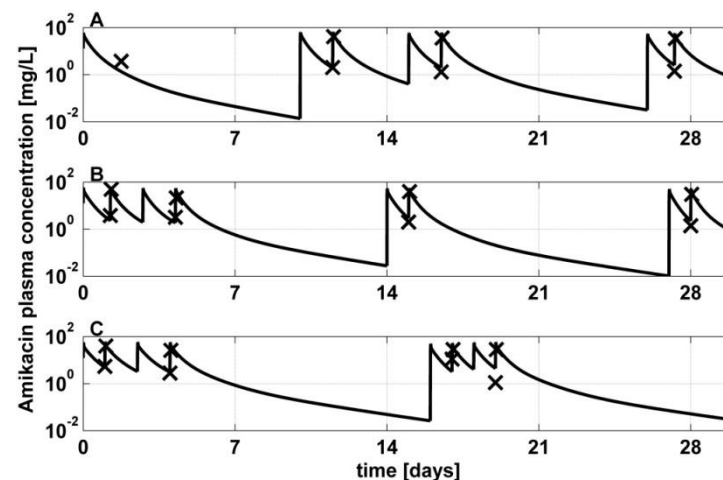
# Prediction of Therapeutic Drug Monitoring (TDM) data already shows promising performance but reveals current limitations



## Paracetamol TDM (CYP2E1, SULT1A1, and UGT1A6)



## Amikacin TDM (glomerular filtration)



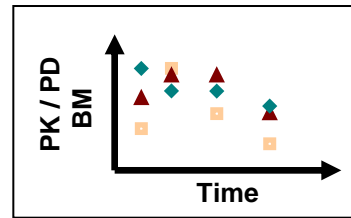
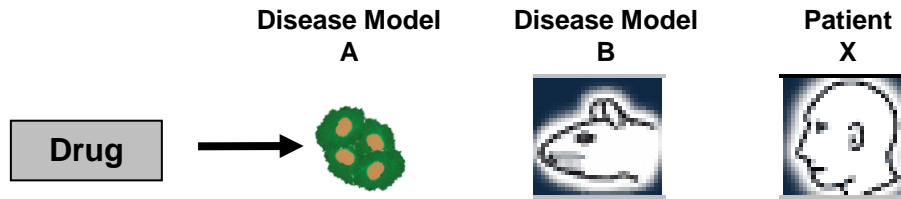
Experimental data provided by Dr. Karel Allegaert, Leuven



The knowledge base is broad,  
our knowledge gaps are significant

- Knowledge about anatomy, physiology and liver enzymes is already considerable
- In other highly relevant areas (**target, transporter proteins** etc.) we often rely on assumptions such as
  - constant specific expression level is assumed
  - target protein maturation is assumed to be similar to

**PBPK provides a means to systematically implement the Probe Study Concept to all trials in order to learn continuously and generalize knowledge**



Use of prior information →

**MCMC-based Bayesian Analysis**

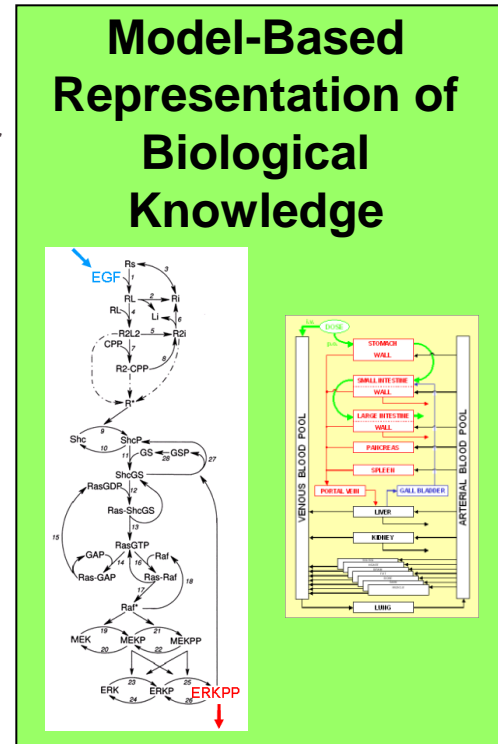
← Use of prior information

**Drug Property Knowledge**

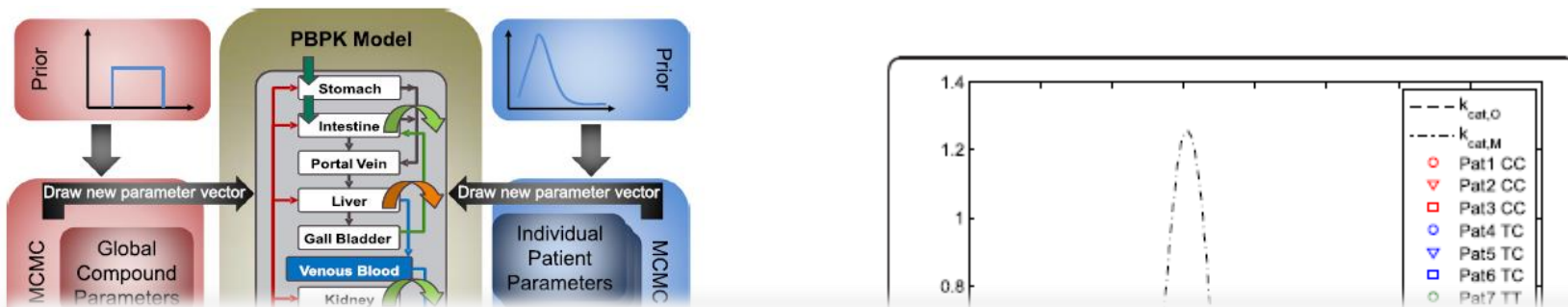
← Extraction of posterior information

**De-convolution & Identification of Systems Parameters, MoA & Drug Parameters**

→ Extraction of posterior information



# Application of Bayesian MCMC with PBPK to clinical data is feasible



**PBPK-MCMC platform allows companies the continuous build-up of proprietary knowledge bases.**

**Agencies could develop an across-industry knowledge base of priors for future data interpretation and predictions!**

Krauss  
http://

OR

Us  
int  
str

Mark

Stefan Wilmanns, Lars Koepfer, and Erno Somlai



# What is still missing?

Coordinated, state-of-the-art (Bayesian) exploitation of rapidly growing database of pediatric trial data and continuous improvement of all priors (anatomy, physiology,...) for PBPK modeling and simulation





Science For A Better Life

Thank you!