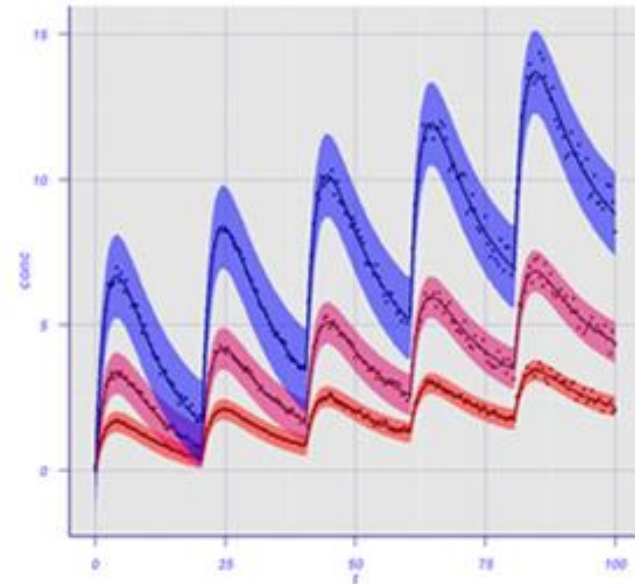# Open-Systems-Pharmacology.org

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PK-Sim/MoBi –
Open Systems Pharmacology Suite

Physiologically based pharmacokinetic and
pharmacodynamic modeling of antibody drug conjugates

2017-06-02 / J.-F. Schlender, R. Burghaus, M. Krauss, M. Block, M.Hobe

Disclaimer

The views expressed in this presentation are those of the speakers and may not reflect the position of Bayer AG.

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Open Systems Pharmacology Suite
PK-Sim®, MoBi® & toolboxes now open source freeware under GNU Public License v2.0

- Fully transparent open source development
- Open development of scientific content and qualification approaches
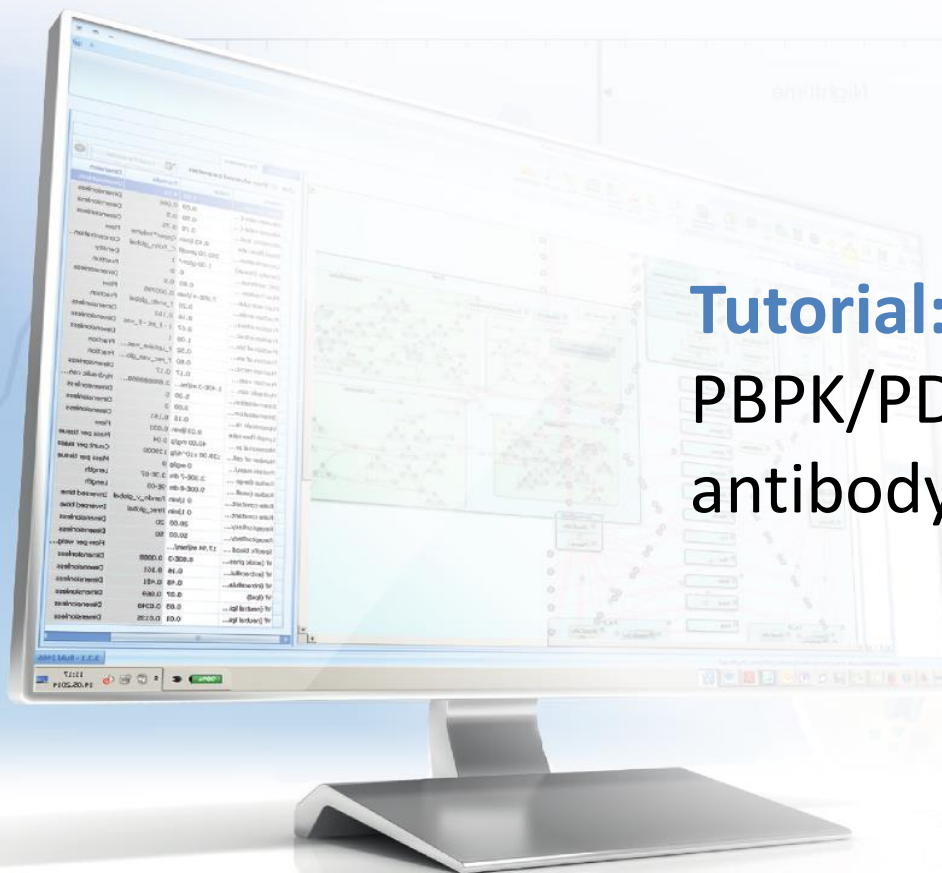- Repositories for open PBPK and Systems Pharmacology models

Join us!
Download and use the software!
Contribute bug reports, new feature proposals, PBPK & Systems Pharmacology models, code…
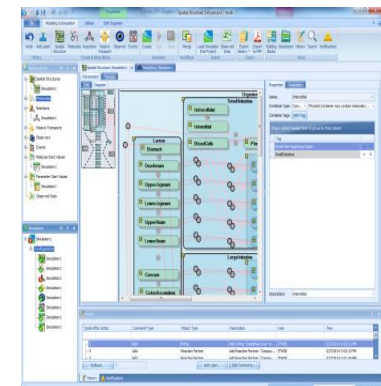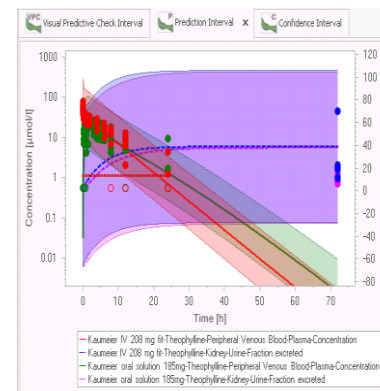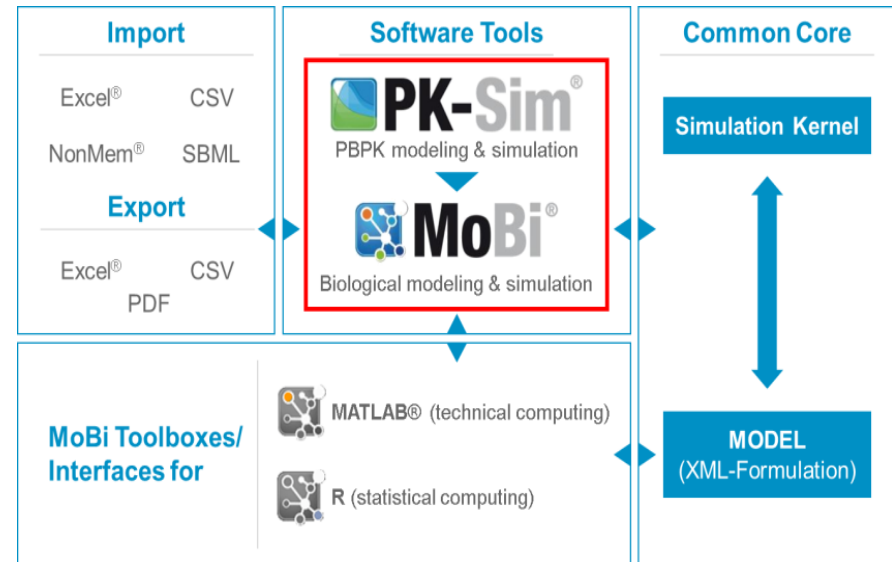
Tutorial:

PBPK/PD modeling of
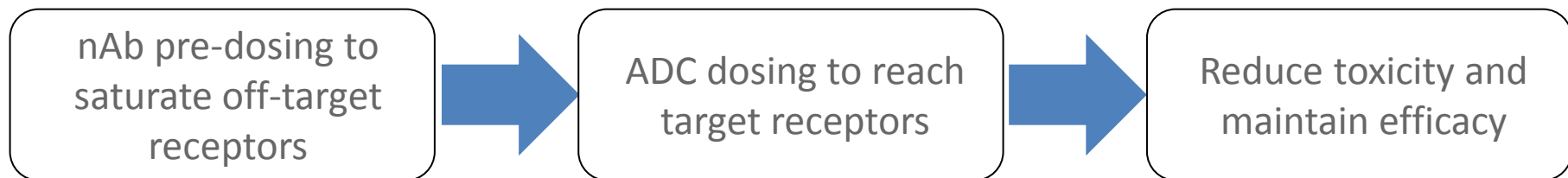antibody drug conjugates (ADCs)

Tutorial
Effects of antibody pre-treatment

Example: TENB2 ADC and anti-TENB2 pre-treatment

- published by Boswell *et al.*, Genentech[1,2]
- Toxophore: MMAE
- Linker: cleavable MC-vc-PAB
- Mouse, non-tumor-bearing mice and prostate cancer explant model (LuCaP 77)
- Intestines were identified to contribute to the target-mediated clearance of the anti-TENB2 antibody and its drug conjugate in rodents

Boswell et al., Br J Pharmacol. 2013; 168(2): 445–457.
Boswell et al., J Nucl Med. 2012; 53(9):1454-61.

| nAb pre-dosing to saturate off-target receptors | → | ADC dosing to reach target receptors | → | Reduce toxicity and maintain efficacy |

The goal is to extend the therapeutic window by reducing the uptake in non-tumor tissues while preserving tumor uptake and efficacy due to a target overexpression in the tumor tissue.
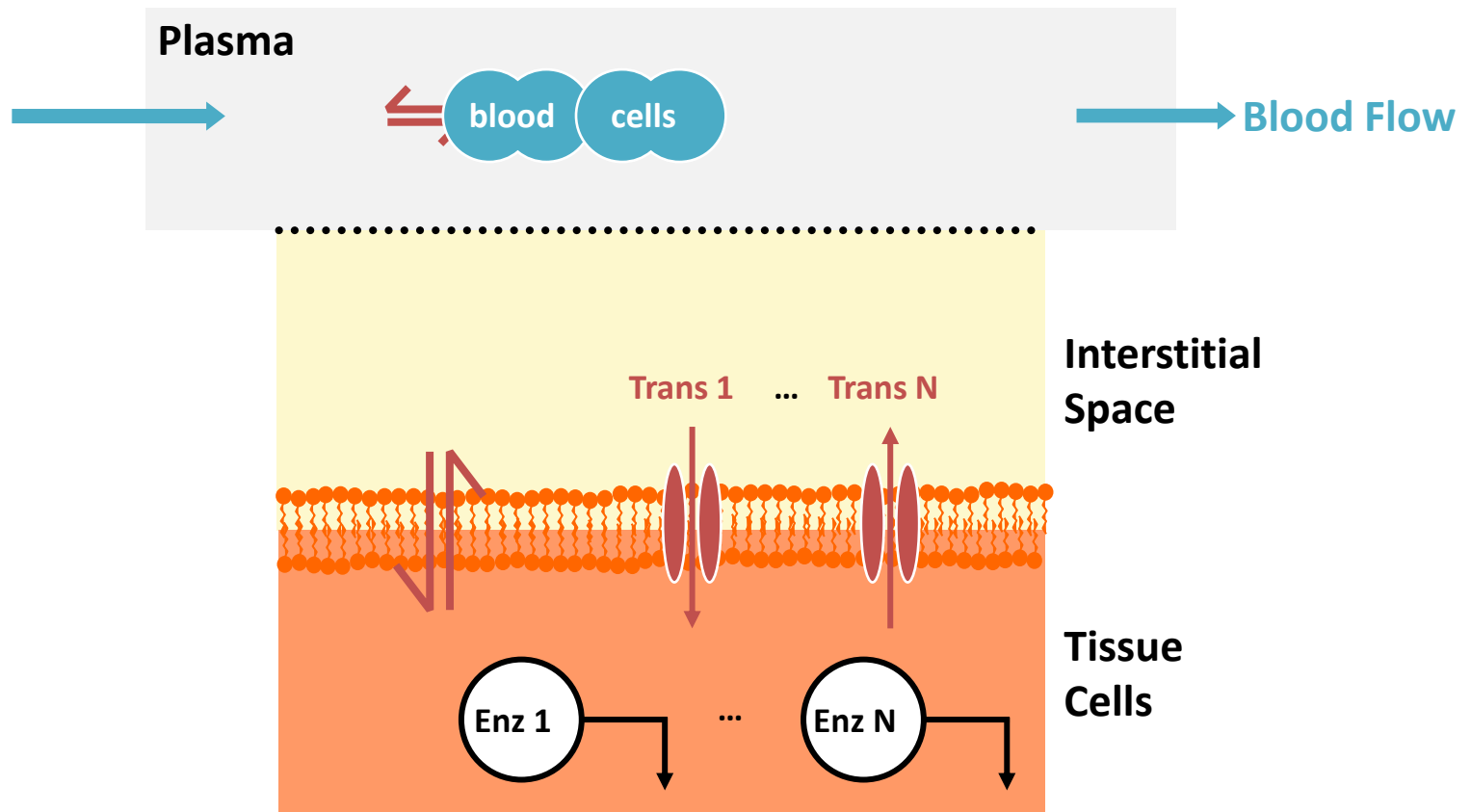
Background information
Distribution of small molecules in PK-Sim®

Plasma

blood cells

Blood Flow

Interstitial Space

Trans 1 ... Trans N

Tissue Cells

Enz 1 ... Enz N

> Parameters given by a-priori knowledge or prediction models
> Adjusted to data only in the second iteration

Kuepfer et al., *CPT Pharmacometrics Syst Pharmacol.* 2016

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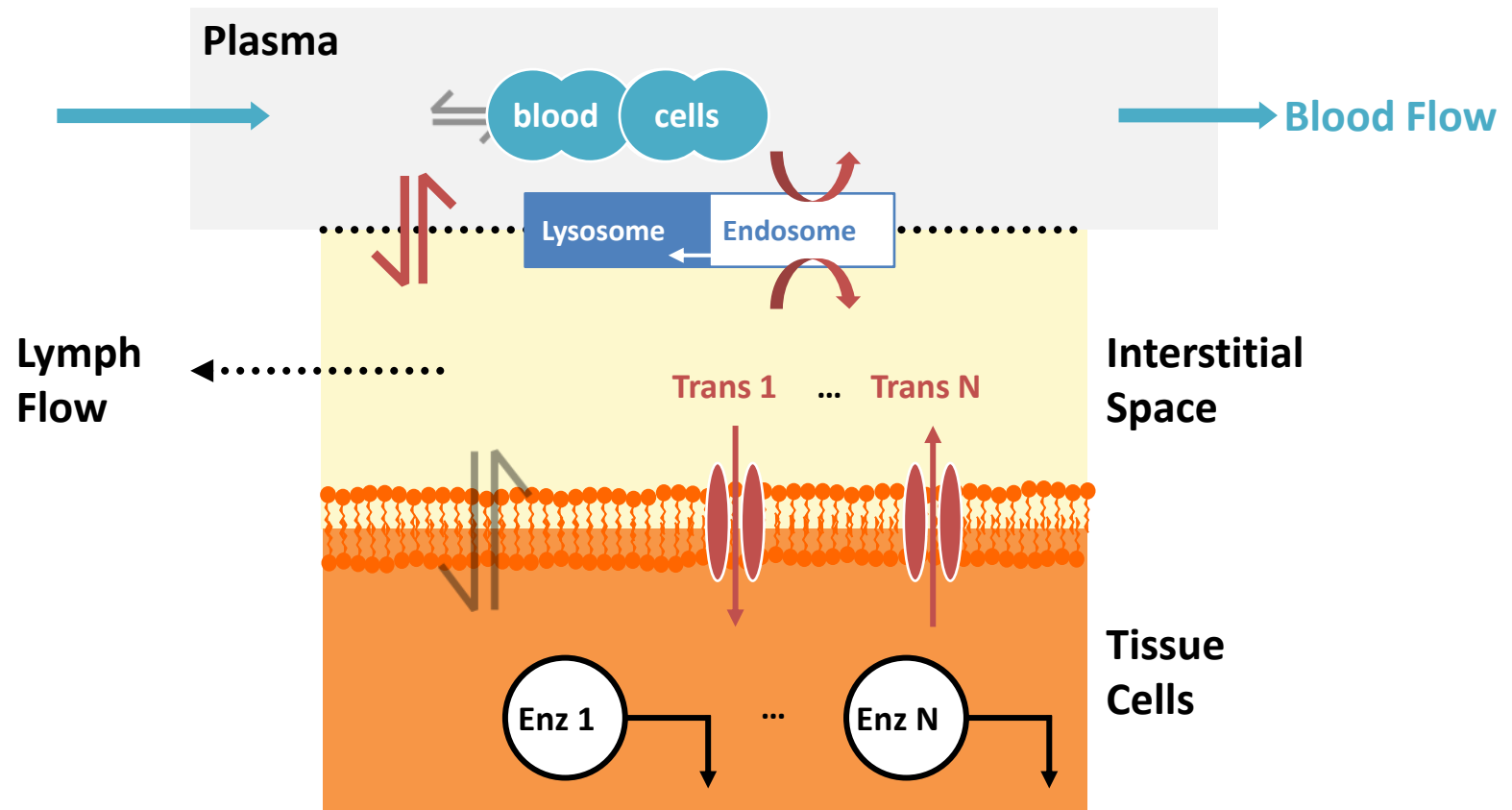# Background information
Distribution of large molecules in PK-Sim®

> ❯ **Parameters given by a-priori knowledge or prediction models**
> **Adjusted to data only in the second iteration**

Kuepfer et al., *CPT Pharmacometrics Syst Pharmacol.* 2016

Background information
Generic PBPK structure for FcRn- Binding

vascular space

K_d (pH 7.4)

IgG + FcRn ⇄ IgG-FcRn

blood cells

CL

endosomal space

K_d (pH 6.0)

IgG + FcRn ⇄ IgG-FcRn

exchange via pores

interstitial space

K_d (pH 7.4)

IgG + FcRn ⇄ IgG-FcRn

cellular space

Garg and Balthasar. *J. Pharmacokinet. Pharmacodyn.* 2007

Objectives

Set up a (mouse model) simulation for TENB2 ADC in PK-Sim and compare the result to observed data

1. Set up the building blocks for Individual, Compound and Administration Protocol

2. Set up the simulation and analyze the result

3. Import observed data ("Exp_data.xlsx") sheet "0.3 mg/kg" and drag & drop it to the figure panel

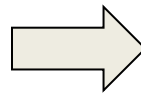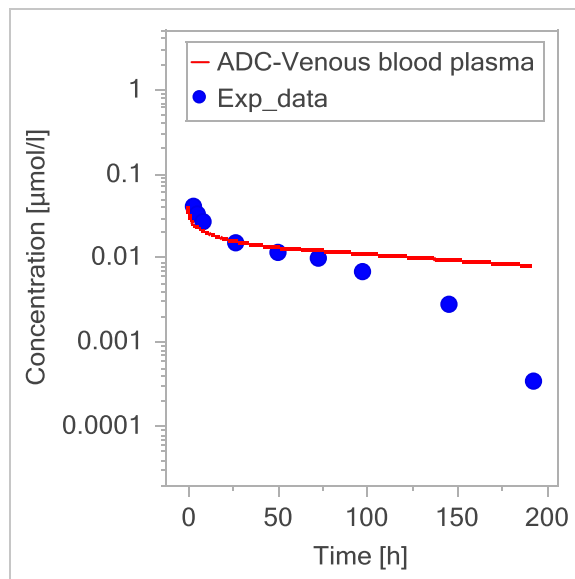4. Compare the observed data with your simulation results

Tutorial
Modeling target-mediated drug clearance

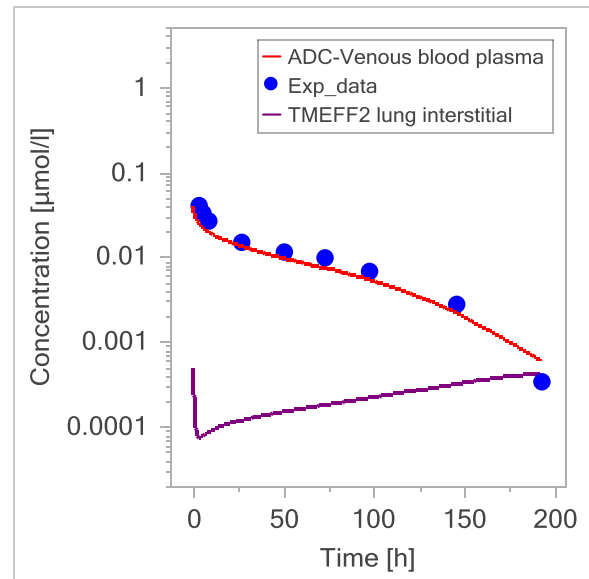Which additional processes are needed to describe target mediated drug clearance?

- Current receptor binding is insufficient
- Modeling of receptor synthesis and degradation required

Re-synthesis of TENB2 receptor allows target mediated clearance
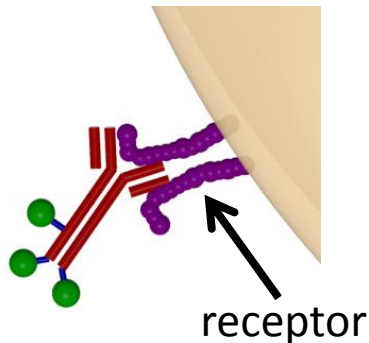
Tutorial
Release of the toxophore from the ADC

Which additional processes are needed to describe the release of the toxophore?

- Toxophore release is initiated after receptor binding of the ADC
- ADC-receptor complex is internalized and degraded in the lysosome
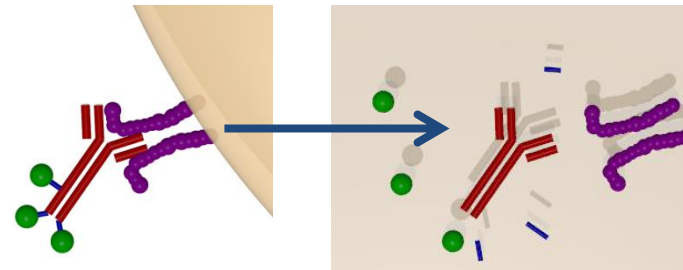- Toxophore is then released in the intracellular space

Receptor binding
Affinity (K_d), k_{off}

Internalization and lysosomal degradation (combined)
rate constant

receptor

Establish a Complex ADC Model in MoBi

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Objectives

Set up a combined simulation for the ADC and the toxophore including receptor dynamics and internalization of the ADC-receptor complex

1. Export established ADC and toxophore model to MoBi
2. Integrate the reactions for receptor dynamics and internalization of ADC-TMEFF2 complex (import "ReactionsADCModel.pkml")
3. Simulate the model for several dosings and compare the results to the observed data for 0.3 mg/kg, 4 mg/kg and 10 mg/kg
4. Simulate and analyze the different exposures of toxophore in venous blood and TMEFF2 in the interstitial space of the lung following the dose escalation
5. Which is the critical dose, where target mediated clearance needs to be taken into account?
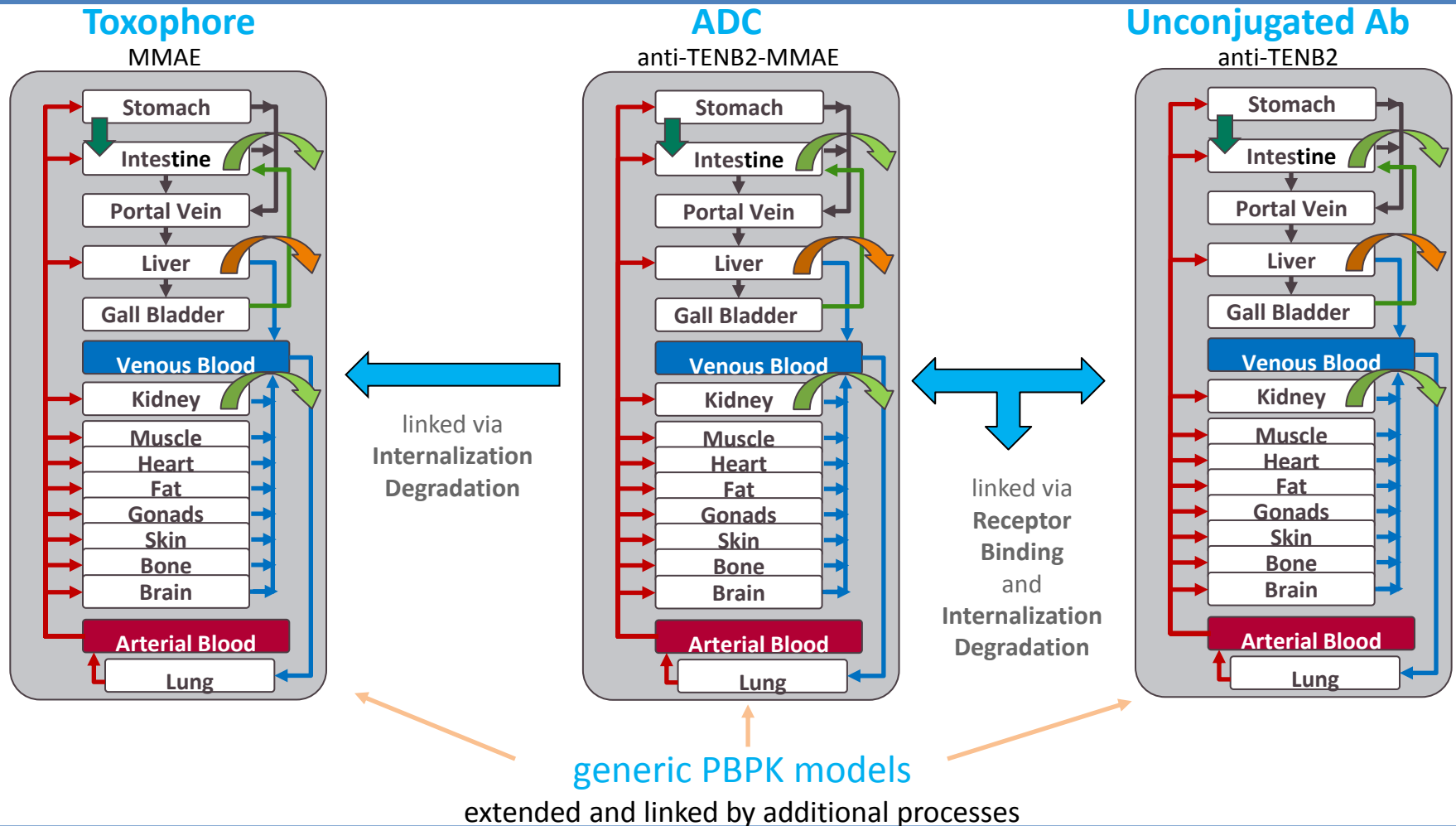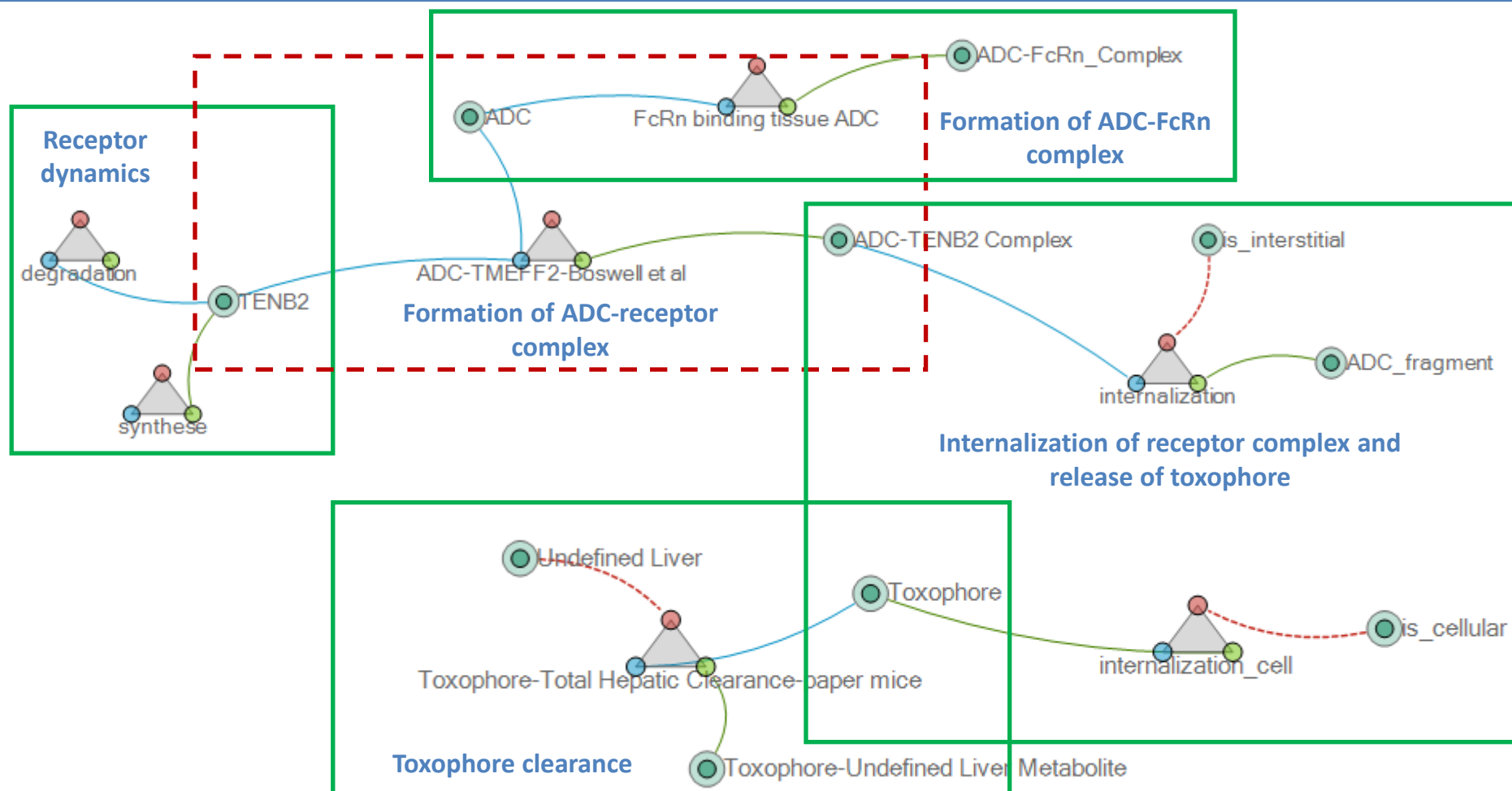
Tutorial
PBPK Model Structure

Toxophore
MMAE

ADC
anti-TENB2-MMAE

Unconjugated Ab
anti-TENB2

linked via **Internalization Degradation**

linked via **Receptor Binding** and **Internalization Degradation**

generic PBPK models
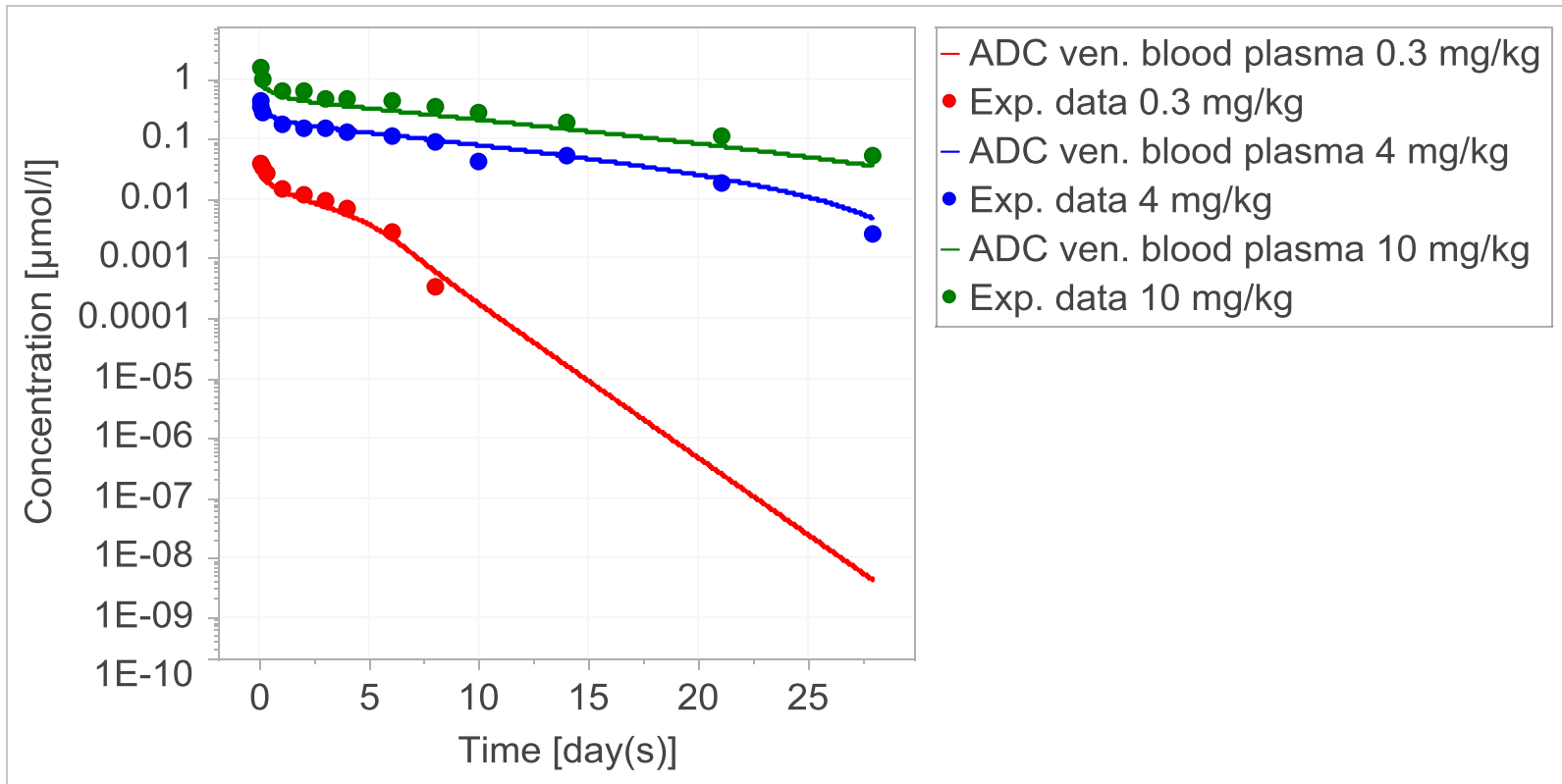extended and linked by additional processes

Reaction Network in MoBi

Tutorial
ADC exposure in non-tumor bearing mice

➔ **PK including target mediated clearance is represented well for different dosages**

Establish a Complex ADC Model in MoBi
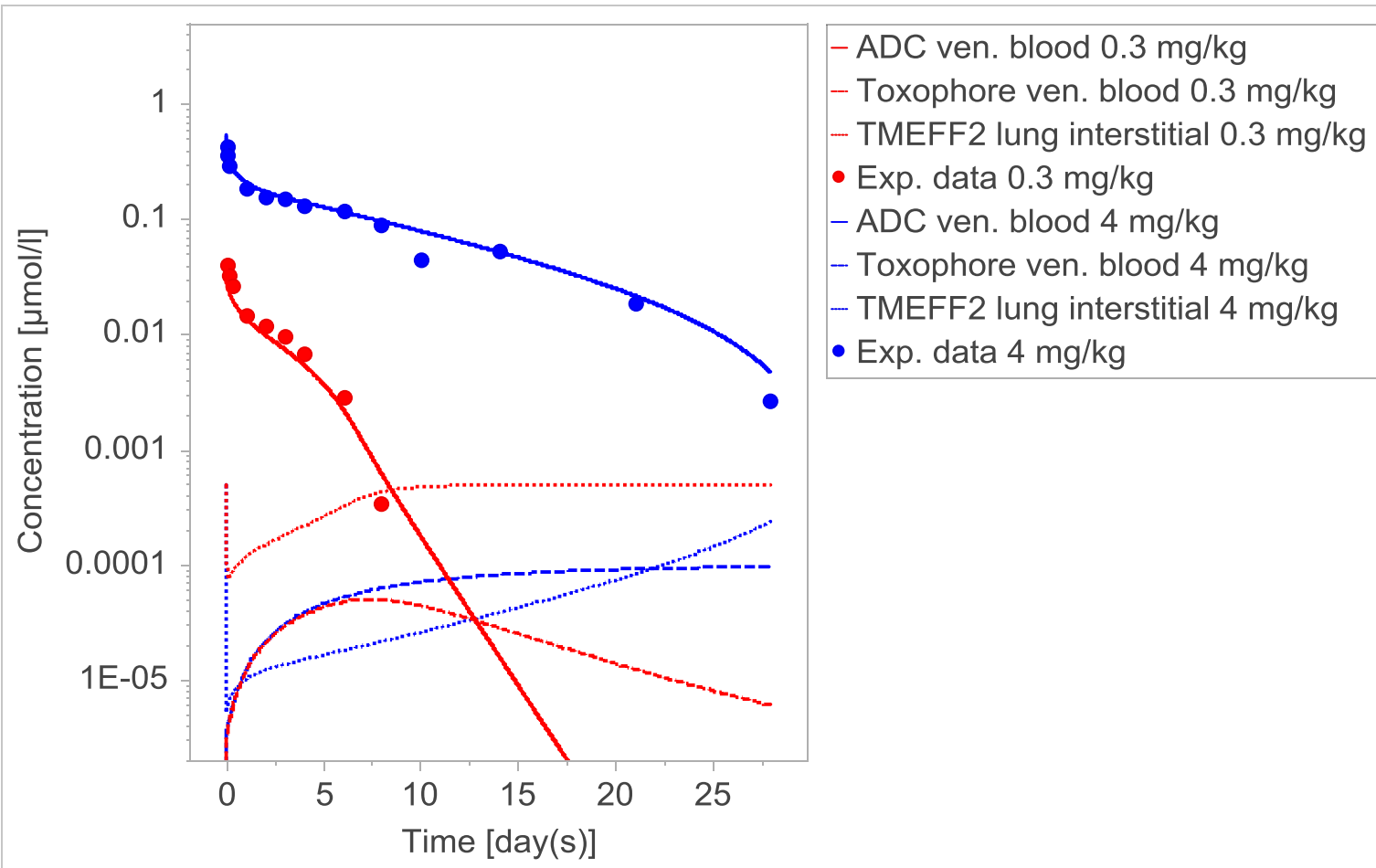
Tutorial
Add a tumor growth model in MoBi

Objectives

Add a predefined tumor growth model to the PBPK model structure and link it to the ADC exposure

1. Import a tumor to the PBPK model structure in MoBi
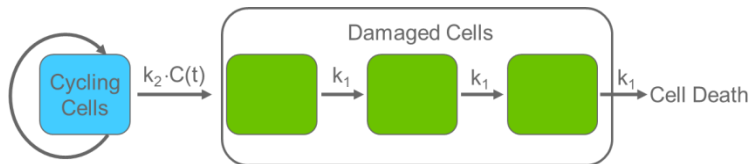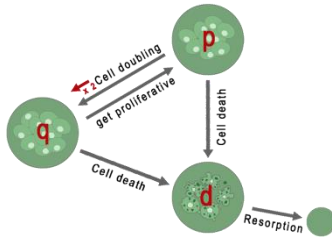2. Analyze the tumor growth under ADC treatment

Tutorial
Tumor growth models
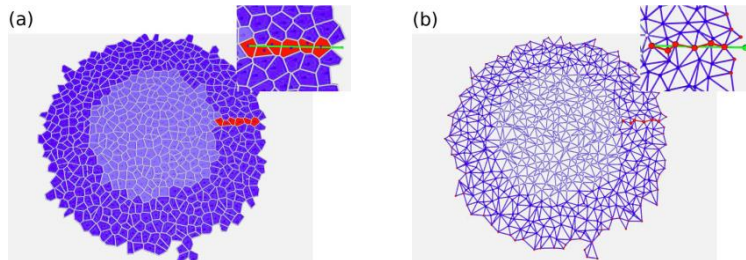
Which models for tumor growth?

Compartmental models

Mechanistic models at tissue level

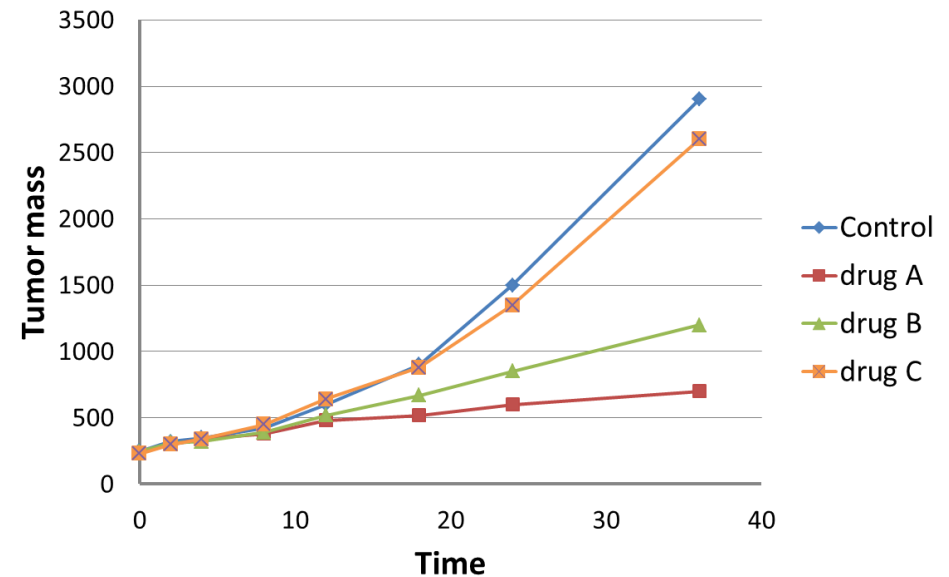Cellular automata and similar models



taken from Block, 2007

Tumor growth vs. time
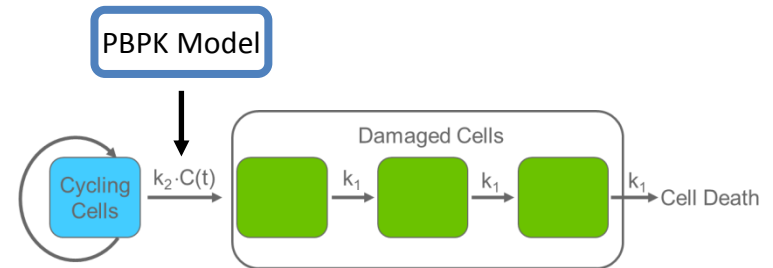

- Control
- drug A
- drug B
- drug C

Tutorial
Tumor growth models

Tumor growth model structure

- Compartmental model with one compartment including the proliferation of cells and secondary compartments describing the damaged cells getting necrotic

- Effect on cells by the drug is included by a dependency of the rate to secondary compartments
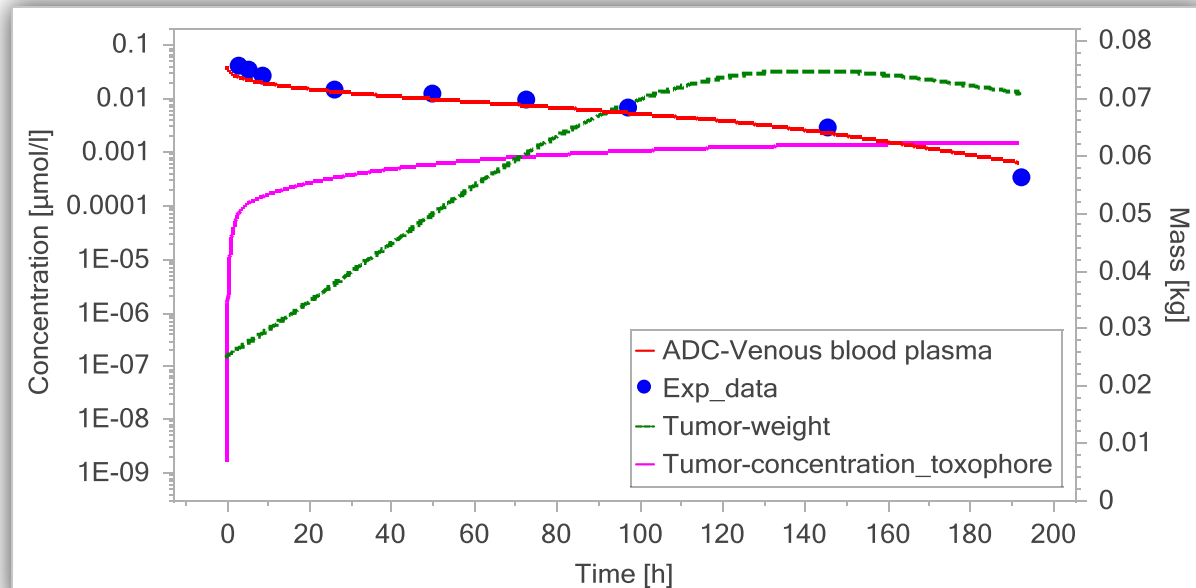
Summary & Conclusions

A coupled PBPK model was developed which allows simultaneously exploring the pharmacokinetics of

- the ADC

- the antibody

- the released small molecule toxophore

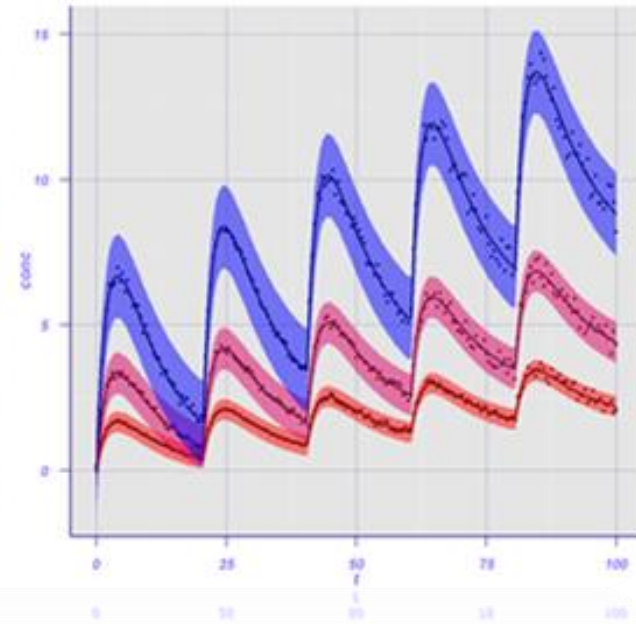- including receptor binding, dynamics, internalization and cleavage/release of the toxophore

It allows the use of prior knowledge for extrapolation as well as testing assumptions or hypotheses on relevant mechanisms

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Thank you!

We hope you enjoyed the tutorial!