Open

Systems Pharmacology

Hands-On ADC Exercise – Stepwise Solution –

Disclaimer:

Examples described herein have been designed to teach physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) modeling with PK-Sim® and MoBi®. Cases may have been simplified to focus on relevant didactic aspects and may not necessarily describe the best model variant.

Exercise – Modeling biologics I (ADC)

Tutorial
Effects of antibody pre-treatment

Open Systems Pharmacology

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.

Tutorial
ADC exposure in non-tumor bearing mice

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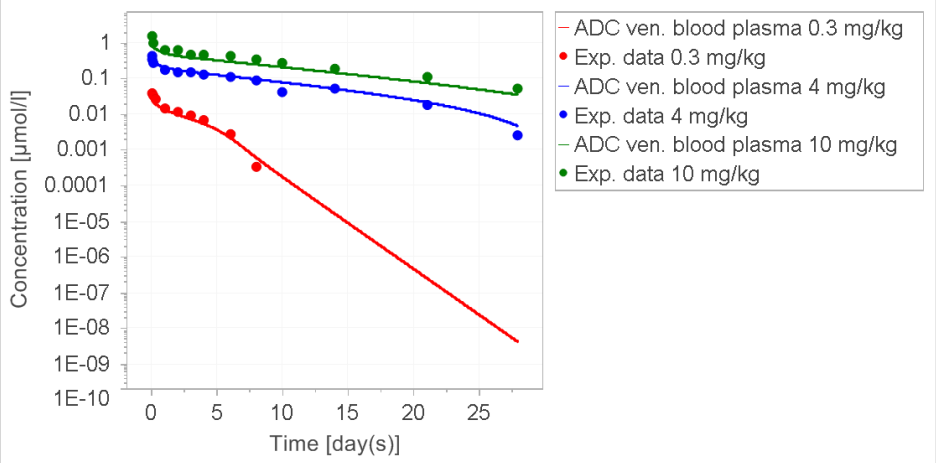

➔ **PK including target mediated clearance is represented well for different dosages**

Tutorial
PBPK Model Structure

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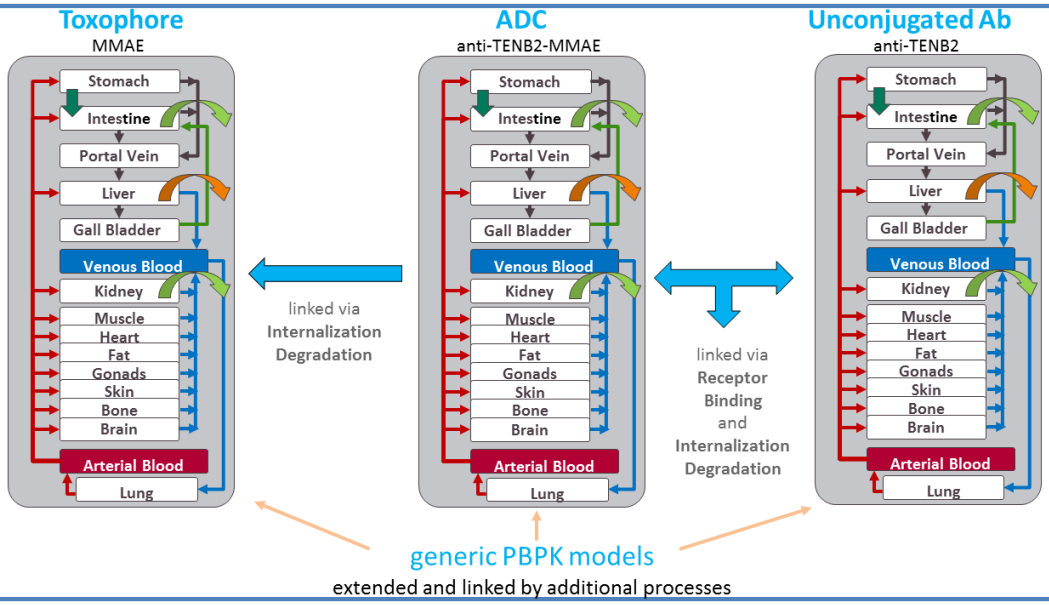


Tutorial
Modeling of biologics

Open Systems Pharmacology

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

Solution – Modeling biologics I (ADC)

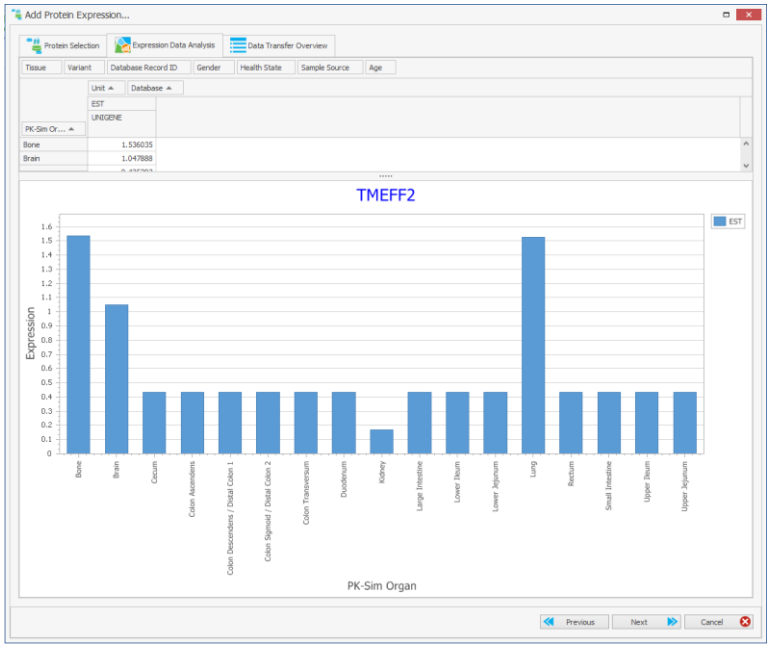
Objectives

- Learn to set up a simulation for an ADC and compare the simulation to observed data
- Examine the reason why the simulation does not fit the experimental data
- What processes are missing to describe the data?
- Think about how the toxophore should be modeled to describe toxophore release mechanistically

Open a new PK Sim Project

Create the individual

1. Click "**Individual**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Individuals**" in the "**Building Blocks**" Explorer and select "**Add Individual**".
2. Initialize the Individual by giving it a name (*here*: "**Mouse**").
3. Select "**Mouse**" as Species and click "**Next**".
4. Click "**Next**" to get to the "**Expression**" tab.
5. Add "**TENB2 (also called TMEFF2)"** as a protein binding partner:
    a. "**Right click**" on "**Protein Binding Partners**", choose "**Add Protein Binding Partner… (Database Query)**"
    b. Search for "**TENB2**"
    c. "**Double click**" on "**TENB2"**
    d. Check the available expression profile and click "**Next**"



e. Click "**OK**". The relative expression profile is added to your individual "**Mouse**"
f. Set "**Reference concentration**" to "**0.0005 µmol/l**".
g. Set "**Location in tissue**" to "**Extracellular membrane**"
h. Set "**Location on vasc. endothelium**" to "**basolateral**"

6. Click "OK". Your individual is created.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_1.pksim5**.

Create the compound

1. Click "**Compound**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Compounds**" in the "**Building Blocks**" Explorer and select "**Add Compound**".
2. Initialize the Compound by giving it a name (*here*: "**ADC**").
3. Uncheck the box "**Is small molecule**".
4. Define the compound data as depicted in the following table:

Properties of anti-TENB2		
	Value	**Unit**
Lipophilicity (log P)	-5	Log Units
Plasma fu	1	
Molecular Weight	148000	g/mol
aqueous solubility pH 7.0	999	mg/l
Radius (solute)*	5	nm
Kd (FcRn) in endosomal space*	1.5	µmol/l

*The parameters "**Radius (solute)**" and "**Kd (FcRn)**" can be found under "**Advanced Parameters**"

5. Click "**Next**" to go to the "**ADME**" tab (or click "**Previous**" when you have been in the "**Advanced Parameters**" tab)
6. "**Right click**" on "**Protein Binding Partners**". Select "**Add Protein Binding Partner**".
    a. Choose the target "**TENB2**" (it is named "**TMEFF2"** here, which is another synonym for the target) from the drop-down menu.

b. Type **"Exp_data"** as "**Data source**".
c. Set "**koff**" to "**0.9 1/min**" and "**Kd**" to "**0.01 µmol/l**".
d. Click "**OK**". Your compound is created.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_2.pksim5**.

Create the Administration Protocol

1. Click "**Administration Protocol**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Administration Protocols**" in the "**Building Blocks**" Explorer and select "**Add Administration Protocol**".
2. Initialize the Administration Protocol by giving it a name (*here*: "**i.v. 0.3 mg/kg**").
3. Set "**Dose**" to "**0.3 mg/kg**".
4. Click "**OK**". Your Administration protocol is created.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_3.pksim5**.

Create the Simulation

1. Click "**Simulation**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Simulations**" in the "**Simulations**" Explorer and select "**Add Simulation**".
2. Initialize the Simulation and name it (*here*: "**Mouse ADC i.v. 0.3 mg/kg**").
3. Under "**Model Settings**", choose the "**Model for proteins and large molecules**" in the drop-down menu
4. Click "**Next**"
5. Click "**Next**"
6. In the "**Processes**" tab, "**Protein in individual**" should be linked with the correct "**Binding process**"
7. Click "**Next**"
8. Choose the defined "**Administration**"
9. Click "**Next**" and then "**OK**"
10. The simulation is created

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_4.pksim5**.

Run the Simulation

1. "**Double click**" on the selected simulation.
2. Click "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" tab.
3. Select the predefined "**Venous Blood Plasma ADC Concentration**" and click "**OK**".
4. The simulation is processed.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_5.pksim5**.

Compare the simulation result with experimental data

1. Click "**Observed Data**" in the "**Import**" group of the "**Import/Export**" tab or right click on "**Observed Data**" in the "**Building Blocks**" Explorer and select "**Add Observed Data**".
2. Choose "**Exp_data.xlsx**" as experimental data set and click "**Open**".
3. Choose the data for "**0.3 mg_kg"** and click "**Import (1)**".
4. Choose "**ADC**" as "**Molecule**", "**Mouse**" as "**Species**" and "**Venous Blood"** as "**Organ**". Finally, choose "**Plasma**" as "**Compartment**".
5. Choose **"{File}.{Sheet}"** as the **"Naming pattern"** and click "**OK**".
6. The observed data are imported.
7. Open the **"Time Profile Analysis**" tab in the "**Simulation: Mouse ADC i.v. 0.3 mg/kg**" window and add the experimental data via drag and drop.
8. Open the "**Parameters**" tab in the "**Simulation: Mouse ADC i.v. 0.3 mg/kg**" window and click on "**Settings**".
9. Change the "**End Time**" of the simulation to 8 days.
10. Click "**Run**" in the "**Simulation**" group of the "**Run & Analyze**" tab.
11. Go back to the **"Time Profile Analysis**" tab in the "**Simulation: Mouse ADC i.v. 0.3 mg/kg**" window and compare the simulation with the data. Why the simulation does not fit the experimental data?

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_6.pksim5**.

Exercise – Modeling of Biologics II and Model Coupling

Tutorial
Modeling target-mediated drug clearance

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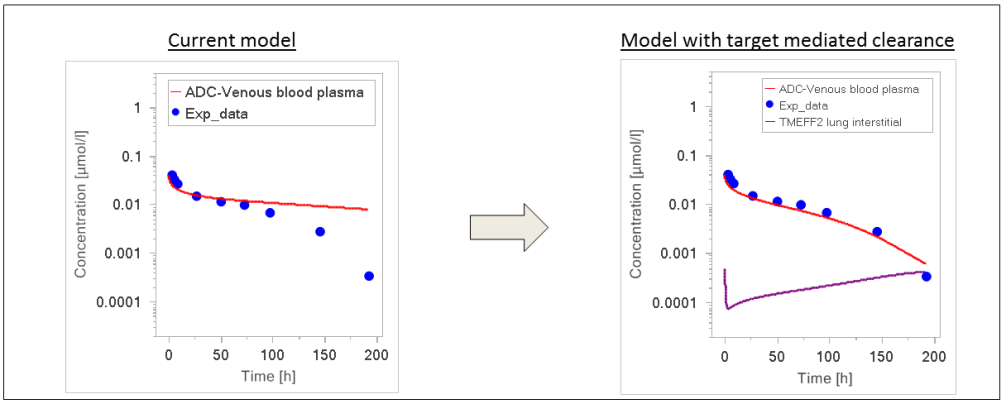
Which additional processes are needed to describe target mediated drug clearance?

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

Re-synthesis of TENB2 receptor allows target mediated clearance

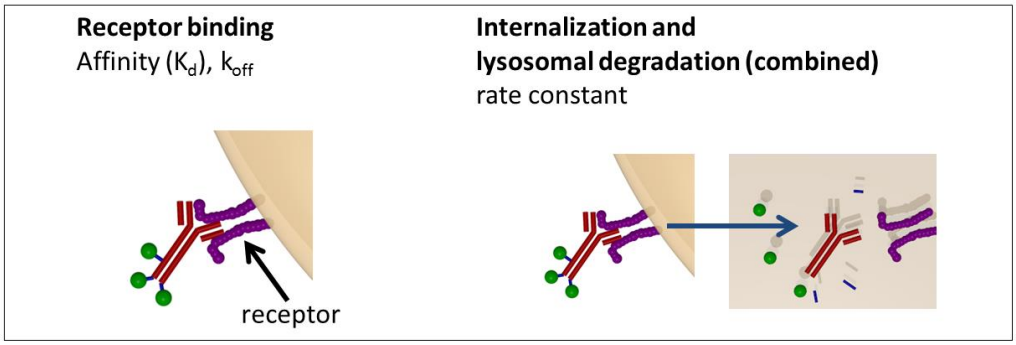


Tutorial
Release of the toxophore from the ADC

Open Systems Pharmacology

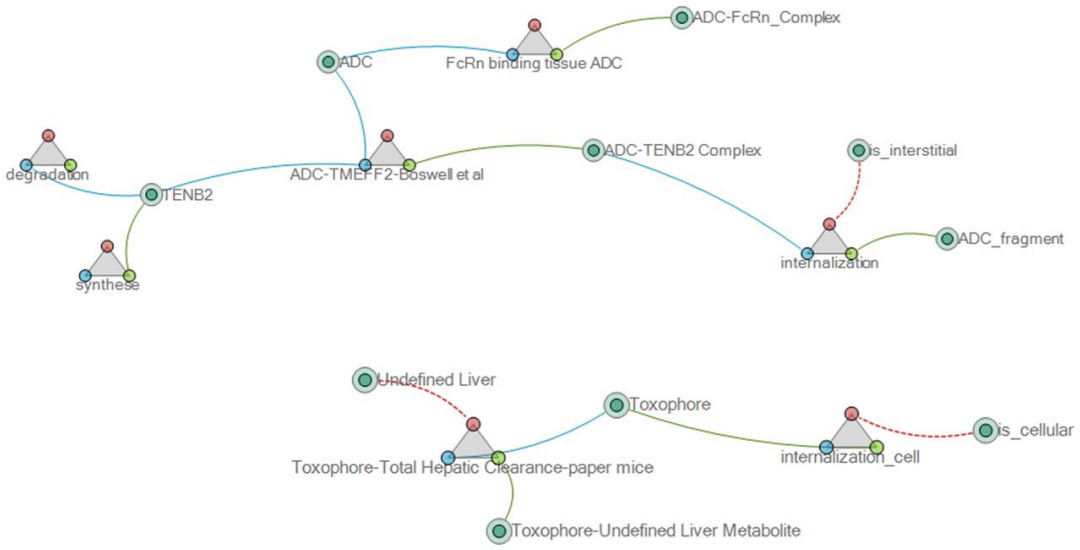
Which additional processes are needed to describe the release of the toxophore?

- 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



Reaction Network in MoBi

Open Systems Pharmacology



Tutorial
Establish a Complex ADC Model in MoBi

Open Systems Pharmacology

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?

Solution – Modeling of Biologics II and Model Coupling

Add the toxophore as a single compound and create a combined simulation of ADC and toxophore

1. Open the file: **Ex_1_ADC_Tox_Modeling_6.pksim5** or continue with your file of the first exercise.
2. Click "**Compound**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Compounds**" in the "**Building Blocks**" Explorer and select "**Add Compound**".
3. Initialize the Compound by giving it a name (*here*: "**Toxophore**") and define the compound data as depicted in the following table:

Properties of Toxophore		
	Value	**Unit**
Lipophilicity (log P)	3.2	Log Units
Plasma fu	0.49	
Molecular Weight	780	g/mol
aqueous solubility pH 7.0	10000	mg/l

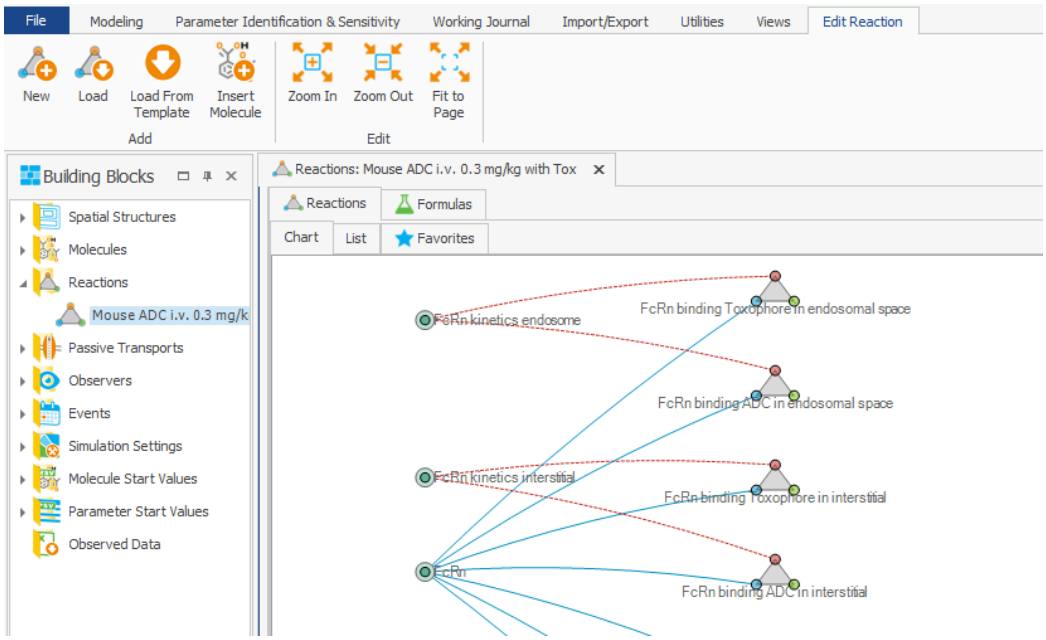
4. Click "**Next**" to go to the "**ADME**" tab.
5. "**Right click**" on "**Total Hepatic Clearance**". Select "**Add Total Hepatic Clearance Process**".
    a. Type "**Literature**" as "**Data source**".
    b. Choose "**Mouse**" as "**Species**" from the drop down menu.
    c. Choose **"Liver Plasma Clearance"** as the "**Process type"**
    d. Set "**Plasma clearance**" to "**8 ml/min/kg**". Click "**OK**".
    e. Click "**OK**". Your compound is created.
6. Click "**Simulation**" in the "**Create**" group of the "**Modeling**" tab or right click on "**Simulations**" in the "**Simulations**" Explorer and select "**Add Simulation**".
7. Initialize the Simulation by giving it a name (*here*: "**Mouse ADC i.v. 0.3 mg/kg with Tox**").
8. Select "**ADC**" and "**Toxophore**" as the compounds in the "**Compounds Selection**"
9. Under "**Model Settings**", choose the "**Model for proteins and large molecules**" in the drop-down menu.
10. Click "**Next**" and move forward to the **"Administration"** tab.

11. Choose the defined administration "**i.v. 0.3 mg/kg**" for ADC. Choose "**none**" as administration for Toxophore.
12. Click "**Next**" and then "**OK**".

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_7.pksim5**.

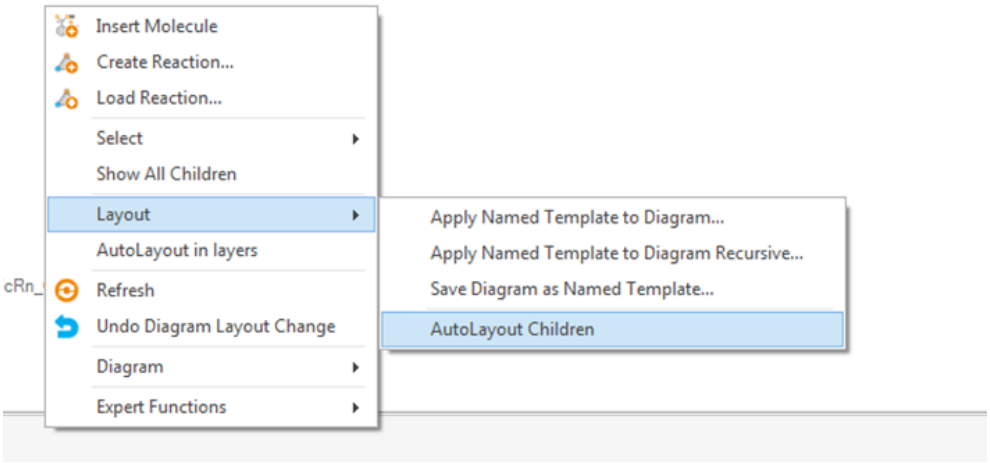
Export to MoBi

1. Select the simulation "**Mouse ADC i.v. 0.3 mg/kg with Tox**".
2. Right click on the simulation in the simulation block and select "**Send to MoBi**
3. Close PK-Sim.
4. Open the Reactions building block "**Mouse ADC i.v. 0.3 mg/kg with Tox**" via "**double click**".

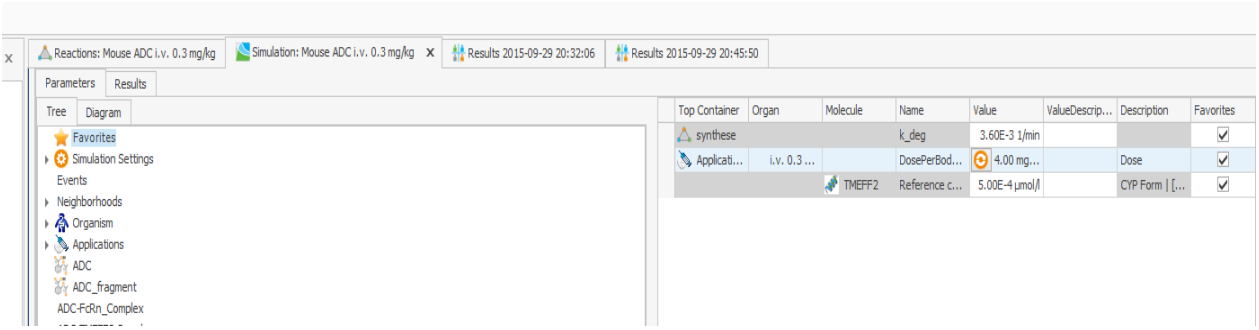


5. "**Right click**" in the reactions window. Select "**Load Reaction**" and choose the file "**ReactionsADCModel.pkml**".
6. Mark all four reactions via holding "**CTRL"** and click "**OK**".
7. The reactions are integrated.

8. “**Right click**” in the reactions window and select “**Layout**”. Within the “**Layout**” menu, select “**AutloLayout children**”.



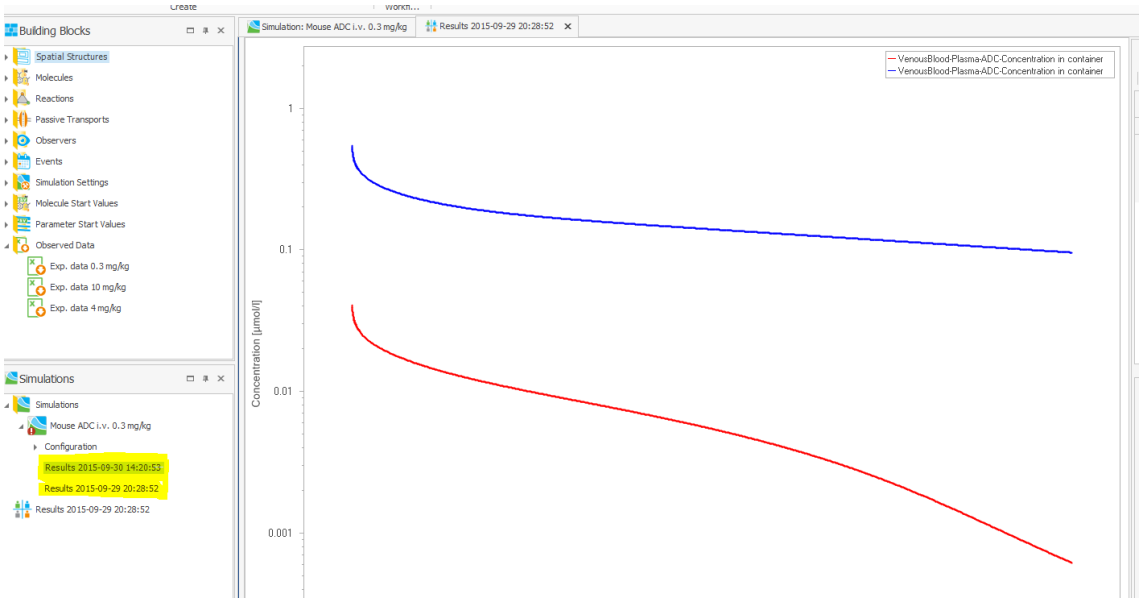
9. Check the reaction scheme. All important processes should be integrated now.
10. Close your MoBi project.
11. Open the File **Ex_1_ADC_Tox_Modeling_9.mbp3** where you find the combined model for ADC and Toxophore modeling together with experimental data. In the **“Favorites”** you can find the key parameters.



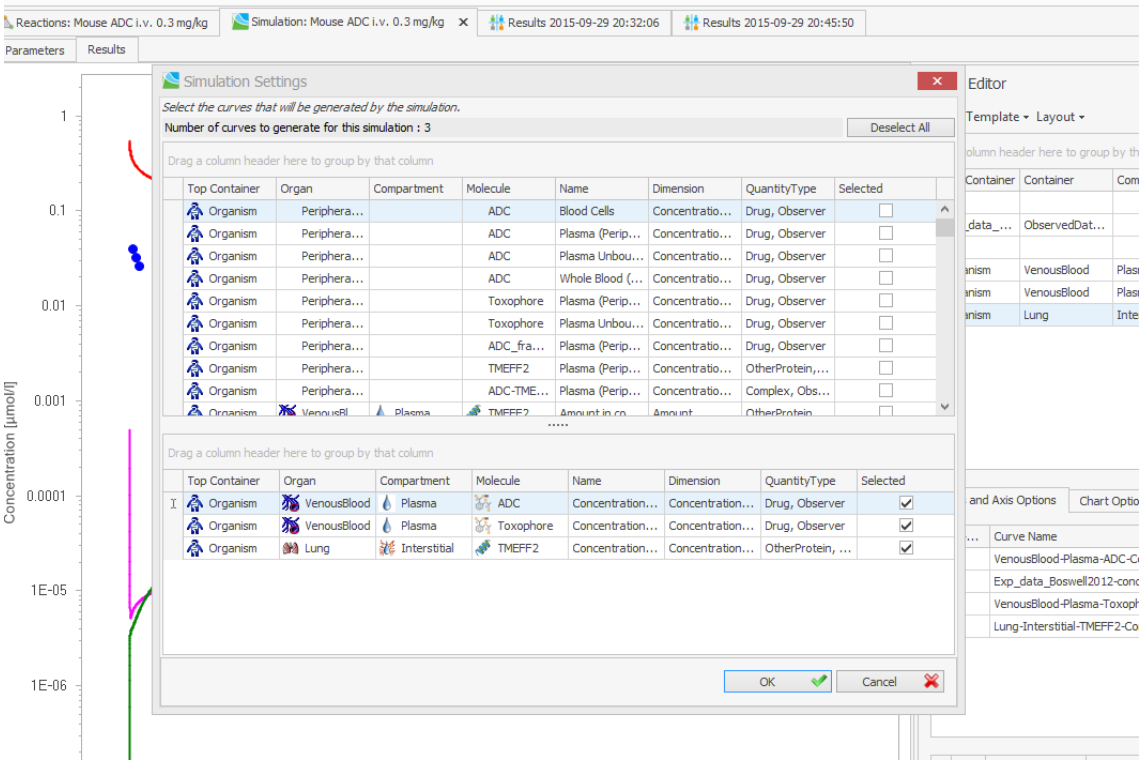
12. Simulate the model for several dosings and compare the results to the experimental data for 0.3 mg/kg, 4 mg/kg and 10 mg/kg

Tip:

- *You can create one simulation for one dose; however, it is also possible just to change the dose in the existing simulation.*
- *To compare several simulations in one window, you can double click on the Results of your last simulation. The Results open in a new window. Drag & drop other Results into this window to be able to illustrate them in the same window.*

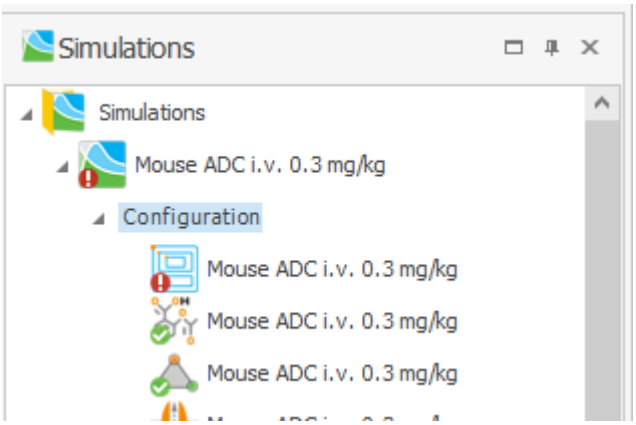


13. Which is the critical dose, where target mediated clearance needs to be taken into account?
14. Simulate and analyze the different behavior of the Toxophore concentration in venous blood and the TMEFF2 concentration in the interstitial of the lung for different doses.
15. *Optional: Change the degradation rate "**k_deg**" and "**reference concentration**" of TMEFF2 to analyze the effect of these parameters on the target-mediated drug clearance.*



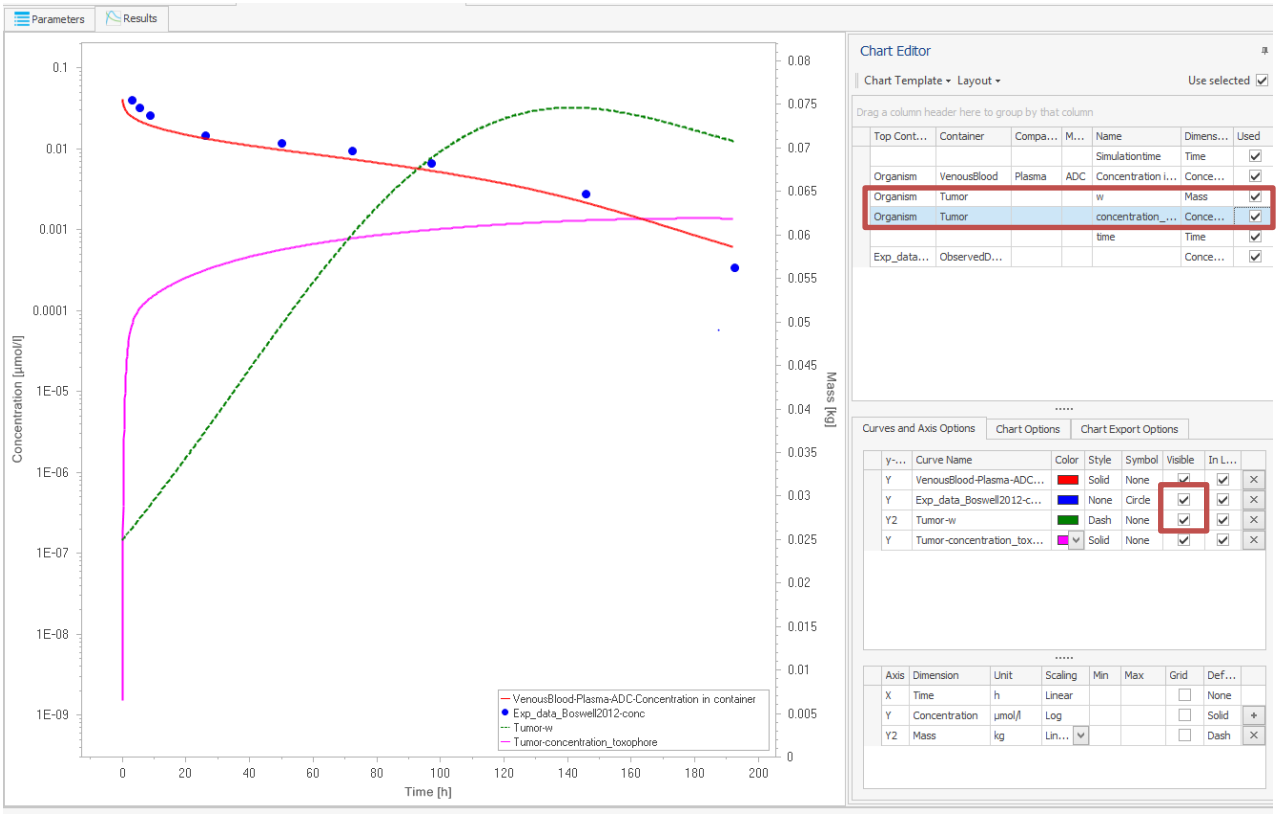
Add tumor growth model

1. Double click on **“Mouse ADC i.v. 0.3 mg/kg”** in the **“Spatial Structures”** building block.
2. In the **“Parameters”** tab select **“Organism”** within the **“Tree”** view tab.
3. Right click on **“Parameters”** and select **“Load Container…”**
4. Load the **“Tumor.pkml”** file and select **“Tumor”** in the **“Select container to load”** window.
5. Click **“OK”**. The tumor is now added to the organism structure.
6. A red circle with an exclaimation mark appears now on the simulation icon of **“Mouse ADC i.v. 0.3 mg/kg”** and on the underlying spatial structure.



7. Right click on the spatial structure **“Mouse ADC i.v. 0.3 mg/kg”** in the **“Simulations”** building block and select **“Update from building block”**.
8. The window **“Configure Simulation: Mouse ADC i.v. 0.3 mg/kg”** appears. Click **“OK”**
9. Double click on the simulation **“Mouse ADC i.v. 0.3 mg/kg”**.
10. Click on **“Define Settings and Run”** in the “**Run & Analysis”** tab.
11. Initiate the simulation by clicking **“OK”**
12. Select Tumor Mass and Tumor Concentration in the **“Chart Editor”** and mark them as **“visible”** in the **“Curves and Axis Options”** tab of the **“Chart Editor”**

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_1_ADC_Tox_Modeling_10.mbp3**.


Parameters
Results
Chart Editor
Chart Template
Layout
Use selected
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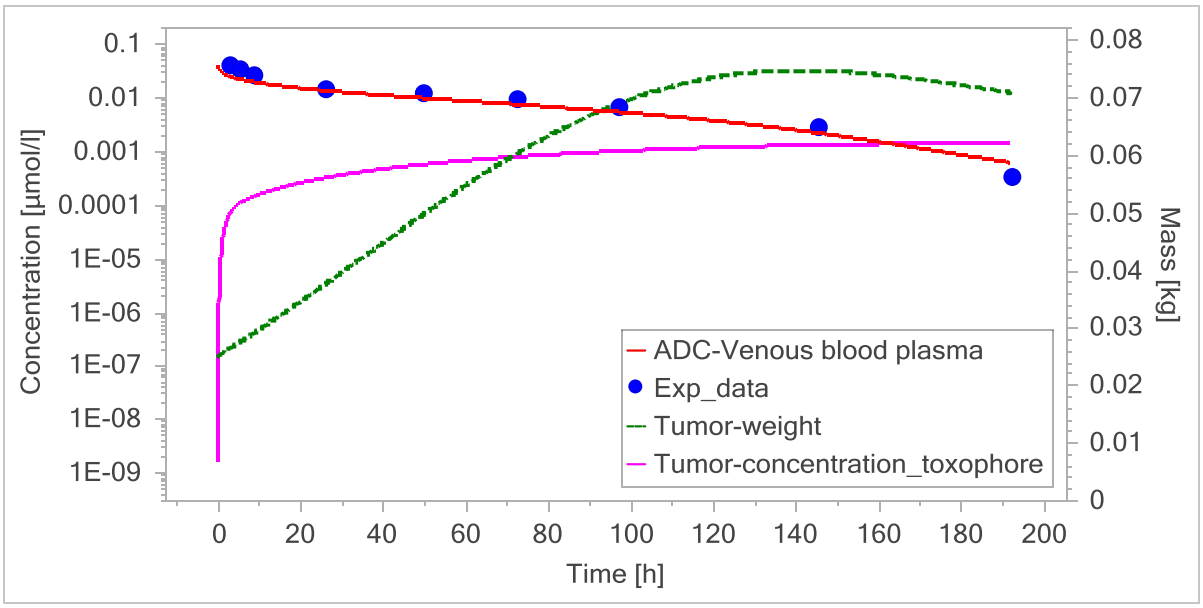
Curves and Axis Options
Chart Options
Chart Export Options
Concentration [µmol/l]
Mass [kg]
Time [h]
VenousBlood-Plasma-ADC-Concentration in container
Exp_data_Boswell2012-conc
Tumor-w
Tumor-concentration_toxophore


Concentration [µmol/l]
Mass [kg]
Time [h]
ADC-Venous blood plasma
Exp_data
Tumor-weight
Tumor-concentration_toxophore