

PBPK-Modeling of IgG Plasma and Tissue Kinetics In Wild-Type And FcRn-Knockout Mice

Objectives

- Set up a PBPK-model in mice describing protein PK in PK-Sim® including FcRn mediated protection from degradation
- Explore the influence of FcRn mediated recycling

Create An Individual

- Click **“Individual”** in the **“Create New Building Blocks” Group** of the **“Modeling” Tab** or right click on **“Individuals”** in the **“Building Block” Explorer** and select **“Add Individual”**.
- Initialize the **Individual** by giving it a name (*here: “Mouse WT”*).
- Select **“Mouse”** as **Species** and click **“Next”**.
- The settings in the **“Anatomy & Physiology”** as well as **“Expression” Tab** can be left as is, so finish the creating process by clicking **“OK”**.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Modeling of Biologics/Ex IgG 1.pksim5](#).

Create A Compound

- Click **“Compound”** in the **“Create New Building Blocks” Group** of the **“Modeling” Tab** or right click on **“Compounds”** in the **“Building Block” Explorer** and select **“Add Compound”**.
- Initialize the **Compound** by giving it a name (*here: “IgG”*) and define the compound data as depicted in the following table:

Properties of IgG		
Property	Value	Unit
Lipophilicity (log P)	-5	Log Units
Plasma fu	1	
Molecular Weight	150000	g/mol
aqueous solubility pH 7.0	999	mg/l

- Uncheck the “**Is Small Molecule**” attribute.
- The “**Biological Properties**” Tab can be left as is. Change to the “**Advanced Parameters**” Tab.
- Set the “**Radius**” (**Solute**) and the “**Kd**” (**FcRn**) of the compound to the values mentioned in the table

Radius (solute)	5.34	nm
Kd (FcRn) in endosomal space	0.75	μmol/l

- Now finish editing the new **Compound** by clicking “**OK**”.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Modeling of Biologics/Ex IgG 2.pksim5](#).

Create an Administration Protocol

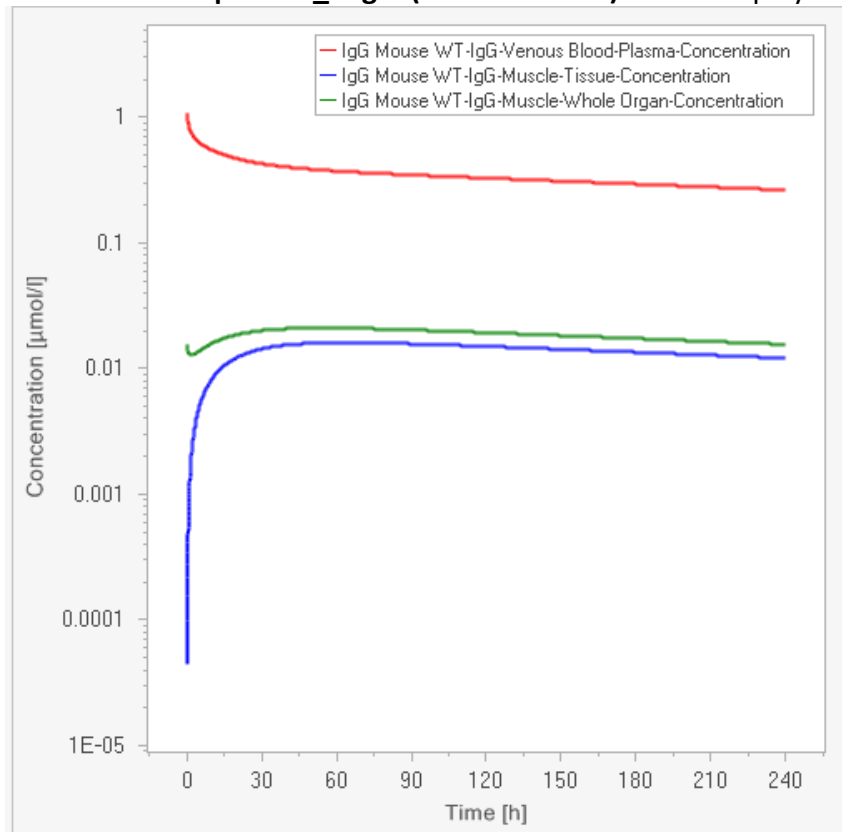
- Click “**Administration Protocol**” in the “**Create New Building Blocks**” Group of the “**Modeling**” Tab or right click on “**Administration Protocols**” in the “**Building Block**” Explorer and select “**Add Administration Protocol**”.
- Initialize an “**Administration Protocol**” by defining a name (*here: “**IV Bolus**”*). Set the “**Dose**” to “**8 mg/kg**” and click “**OK**”.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Modeling of Biologics/Ex IgG 3.pksim5](#).

Set Up A Simulation

- Click “**Create**” in the “**Simulation Building Blocks**” Group of the “**Modeling**” Tab.
- Initialize the **Simulation** by naming it “**IgG Mouse WT**”. Select “**Mouse WT**” as **Individual** and choose the Compound “**IgG**”. Change the “**Model Settings**” to “**Model for Proteins and large Molecules**” and click “**Next**”.
- Leave the “**Partition coefficients**”, “**Cellular permeabilities**”, and “**Intestinal permeabilities**” on default (“**PK-Sim Standard**”). Click “**Next**”.
- Click “**Next**”. No **Processes (Metabolism, Transport)** have been defined.

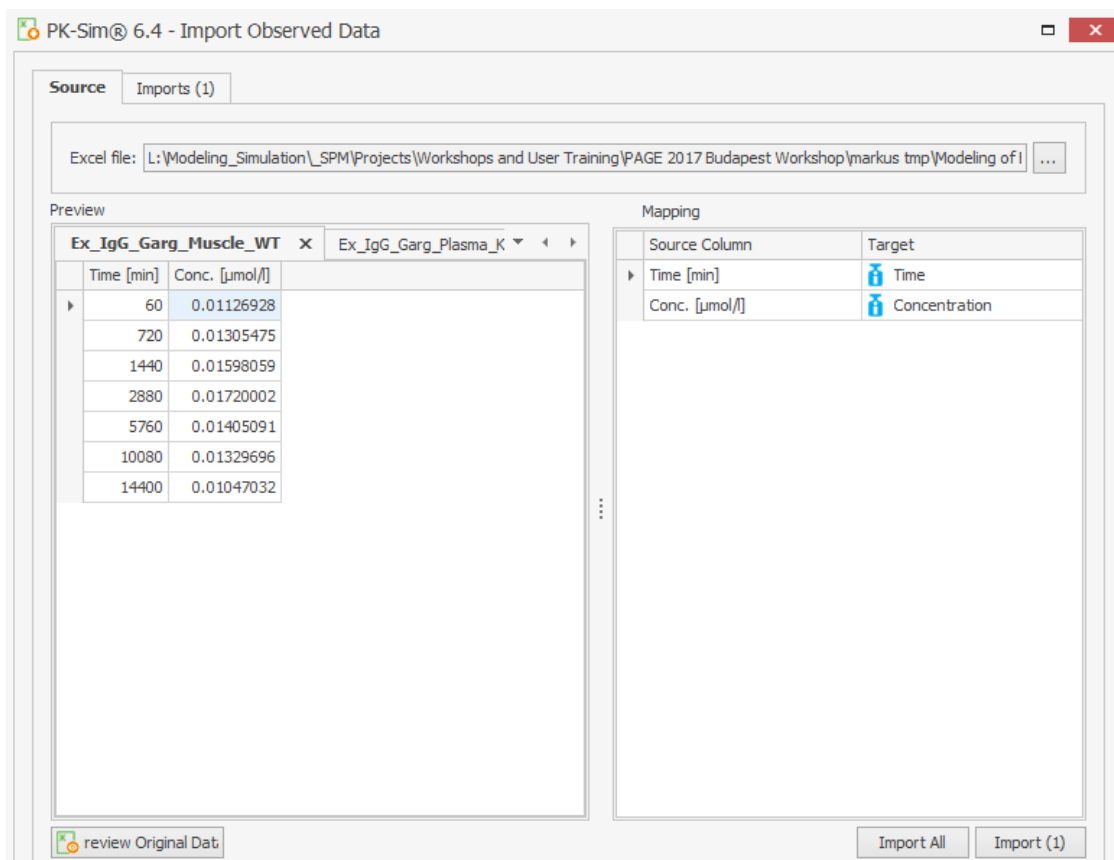
- Choose the **Administration Protocol “IV Bolus”** if not already chosen and finish the setup of the **Simulation**. No **Event** has been defined in this project.
- A **Simulation** is set up now. Set the “**End time**” to “**10 days**” and click “**Run**”.
- Choose “**Venous Blood Plasma Concentration**”, “**Muscle|Tissue(Concentration)**” and “**Muscle|Whole_Organ(Concentration)**” to be displayed in 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 [Modeling of Biologics/Ex_IgG_4.pksim5](#).

Load And Compare To Observed Data

- Click “**Observed Data**” in the “**Import Building Blocks**” Group of the “**Modeling**” Tab.
- Choose the right path to your **Observed Data**, select the **Excel File** “**ExperimentalData_IgG_FcRn.xls**”.
- Select the **Excel Sheet** “**Ex_IgG_Garg_Plasma_WT**” and click “**Import (1)**”. Then go back to the tab “**Source**” and select the Excel Sheet “**Ex_IgG_Garg_Muscle_WT**” and click “**Import (1)**”.



- Check for correct mapping of **“Time”** and **“Concentration”**.
- As Naming Pattern, choose **{File}.{Sheet}** from the drop-down menu.
- Choose **“Molecule”** (**“IgG”**), **“Species”** (**“Mouse”**), **“Organ”** (**“Venous Blood”, “Muscle”**), and **“Compartment”** (**“Plasma”, “Tissue”**) referring to the **Data Sheet** and click **“OK”**.
- Drag and drop the imported **Observed Data** into the **Results Window**.
- In the **Chart Editor** on the right side choose the curves **“IgG_Mouse_WT|Muscle|Tissue(Concentration)”** and **“IgG_Mouse_WT|Muscle|Whole_Organ(Concentration)”** to be displayed.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file Modeling of Biologics/Ex IgG 5.pksim5.

Create An Individual

- Click **“Individual”** in the **“Create New Building Blocks” Group** of the **“Modeling” Tab** or right click on **“Individuals”** in the **“Building Block” Explorer** and select **“Add Individual”**.
- Initialize the **Individual** by giving it a name (*here: “Mouse KO”*).
- Select **“Mouse”** as **“Species”** and click **“Next”**.
- In the **“Anatomy & Physiology” Tab** change to an advanced view by clicking on **“Advanced”** in the drop down menu at the lower right side of the window
- Set the **“Start concentration of free FcRn”** to **“0”**. You can find this **Parameter** at **“Physiology|Vascular_Physiology|Endosomal_Clearance”** in the tree view.
- Now finish editing the new **Individual** by clicking **“OK”**.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file [Modeling of Biologics/Ex IgG 6.pksim5](#).

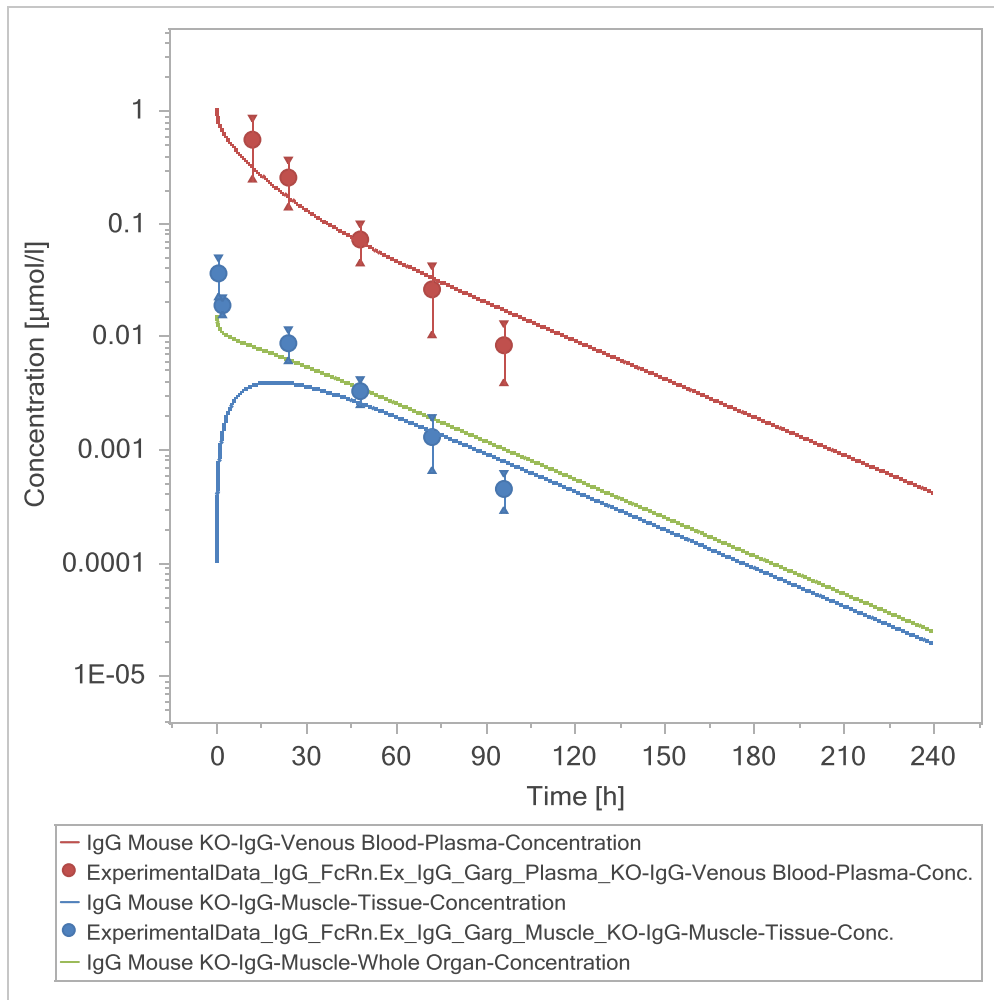
Set Up A Simulation

- Click **“Create”** in the **“Simulation Building Blocks” Group** of the **“Modeling” Tab**.
- Initialize the **Simulation** by naming it **“IgG Mouse KO”**. Select **“Mouse KO”** as **Individual** and choose the Compound **“IgG”**. Change the **“Model Settings”** to **“Model for Proteins and large Molecules”** and click **“Next”**.
- Leave the **“Partition coefficients”**, **“Cellular permeabilities”**, and **“Intestinal permeabilities”** on default (**“PK-Sim Standard”**). Click **“Next”**.
- Click **“Next”**. No **Processes (Metabolism, Transport)** have been defined.
- Choose the **Administration Protocol “IV Bolus”** if not already chosen and finish the setup of the **Simulation**. No **Event** has been defined in this project.
- A **Simulation** is set up now. Set the **“End Time”** to **“10 days”** and click **“Run”**.
- Choose **“Venous Blood Plasma Concentration”**, **“Muscle|Tissue(Concentration)”** and **“Muscle|Whole_Organ(Concentration)”** to be displayed in 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 [Modeling of Biologics/Ex IgG 7.pksim](#).

Load And Compare To Observed Data

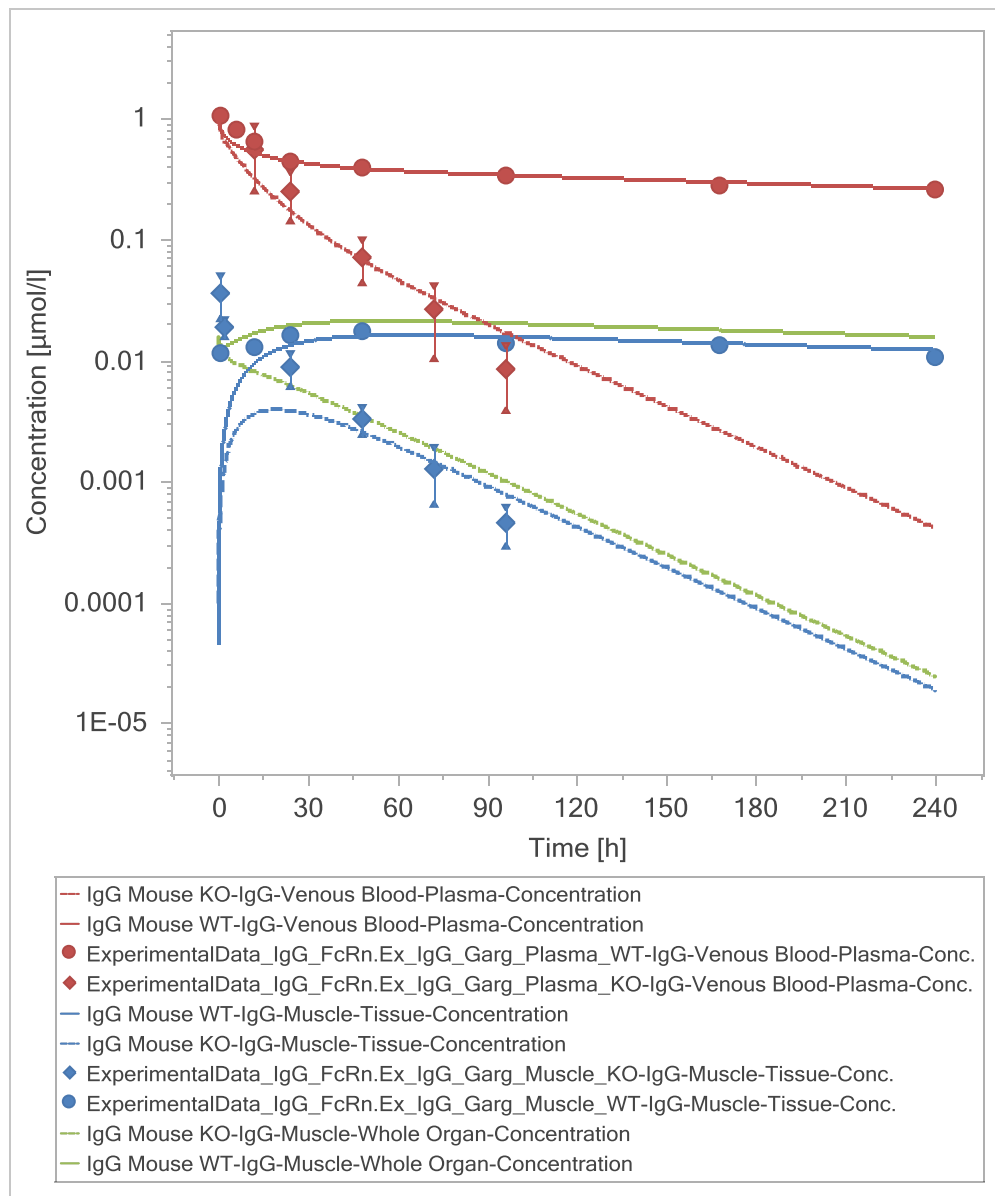
- Click **“Observed Data”** in the **“Import Building Blocks” Group** of the **“Modeling” Tab**.
- Choose the right path to your **Observed Data**, select the **Excel File “ExperimentalData_IgG_FcRn.xls”**
- Select the **Excel Sheet “Ex_IgG_Garg_Plasma_KO”** and click **“Import (1)”**. Then go back to the tab **“Source”** and select the Excel Sheet **“Ex_IgG_Garg_Muscle_KO”** and click **“Import (1)”**.
- Check for correct mapping of **“Time”**, **“Concentration”** and **“Error”** and click **“Import”** to import each **Data Sheet**.
- As Naming Pattern, choose **{File}.{Sheet}** from the drop-down menu.
- Choose **“Molecule”** (**“IgG”**), **“Species”** (**“Mouse”**), **“Organ”** (**“Venous Blood”**, **“Muscle”**), and **“Compartment”** (**“Plasma”**, **“Tissue”**) referring to the **Data Sheet** and click **“OK”**.
- Drag and drop the imported **Observed Data** into the **Results Window**.
- In the **Chart Editor** on the right side choose the curves **“IgG_Mouse_KO|Muscle|Tissue(Concentration)”** and **“IgG_Mouse_KO|Muscle|Whole_Organ(Concentration)”** to be displayed.
- *Additionally:* Change the scale of the Y-axis to **Logarithmic** and change the **colors** of the different curves in order to improve the appearance.



*In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Modeling of Biologics/Ex_IgG_8.pksim.***

Task

- Compare the **Simulations** in a **Summary Chart**. To do so click on “**Individual Simulations**” in the “**Compare Results**” Group of the “**Modeling**” Tab. Drag and drop the **Simulations** into the white field. In the **Chart Editor** select the curves you wish to be displayed.



*In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Modeling of Biologics/Ex IgG End.pksim.***