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FcRn modelling in the OSP suite

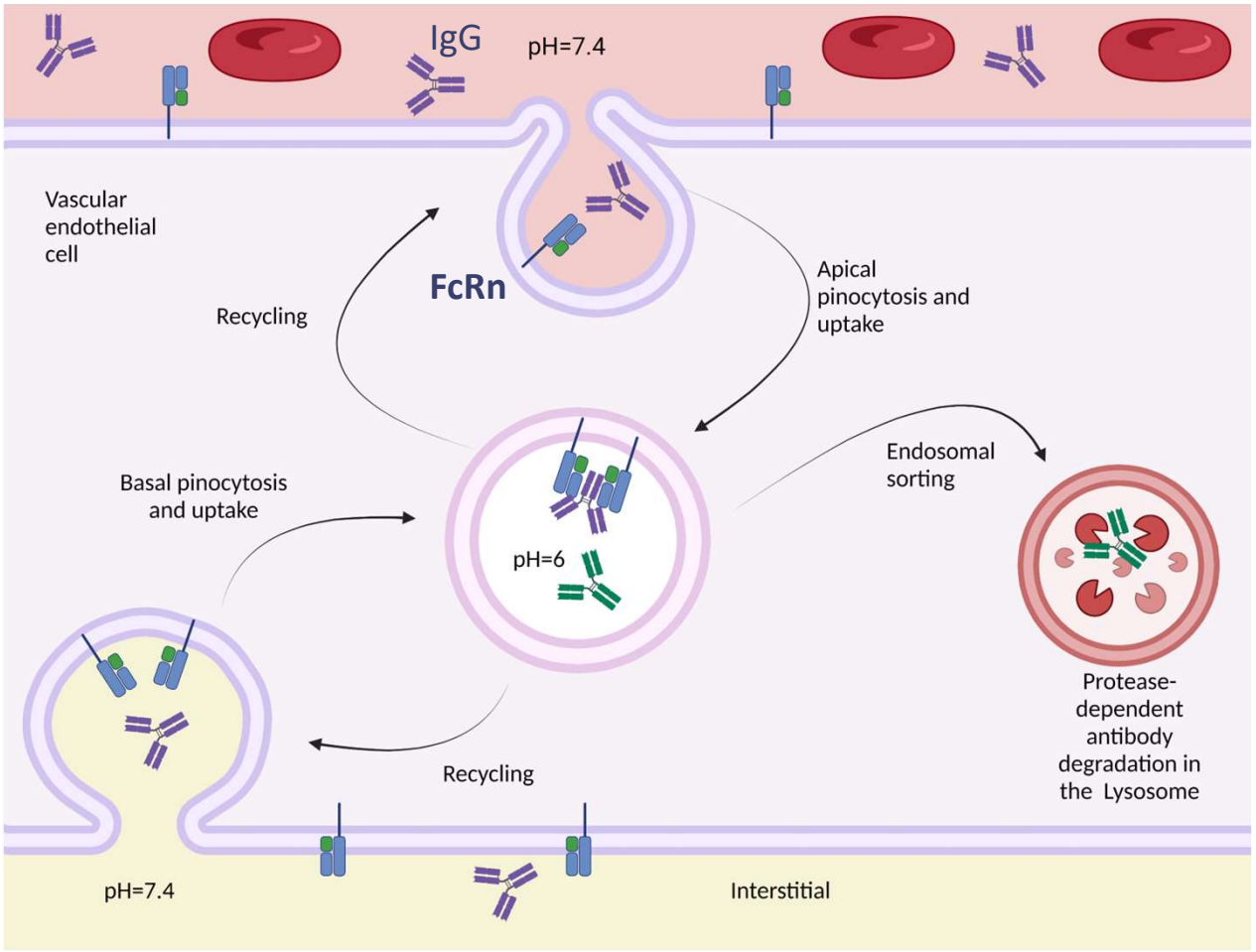
Wilbert de Witte

01

Introduction

FcRn Biology and therapeutic potential

What is FcRn and what is its function?



- pH-dependent binding of IgG (mAbs) and Albumin
- Binding to IgG in a 1:2 complex
- Endosomal binding and recycling increases half-life of IgG and Albumin

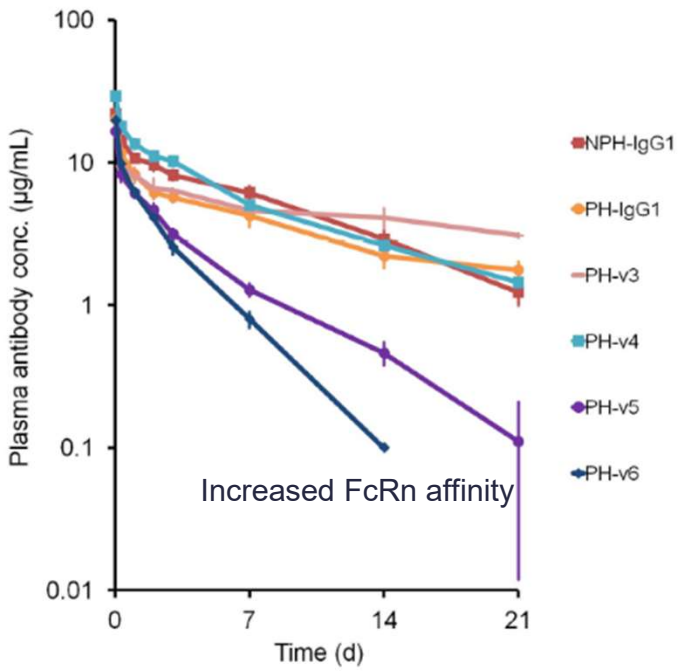
DOI: 10.3390/ijms22063048
Figure created with Biorender.com

FcRn and its therapeutic potential

- FcRn binding affinity in endosomes can be used to fine-tune the half-life of biologics
  - Fc mutations (e.g. YTE) have been reported to achieve up to 90-day half-lives in humans
  - Fc-silenced mAbs have a half-life of ~ 5 days in humans

- FcRn inhibitors: **FcRn binding affinity in plasma** can be used to increase drug concentrations in endosomes, and inhibit the FcRn binding of endogenous IgG, thereby reducing its concentration (e.g. efgartigimod, nipocalimab, batoclimab)

- FcRn-mediated sweeping: **FcRn binding affinity in plasma** and pH dependent soluble target binding can be used to increase soluble target concentrations in endosomes, and increase their clearance. E.g. GYM329, PhII/III



02

Mechanistic FcRn modelling

How does the default model work and how can it be changed for FcRn inhibitors?

How to explain a decreasing half-life with increasing plasma affinity?

Community engagement

wilbertdew commented on Dec 30, 2019

Hi All,

Can anybody give me some pointers to better underdstand FcRn kinetics in PK-Sim/Mobi?
Currently, I have the impression that no turnover of FcRn or degradation for the drug-FcRn complex is implemented. I do understand that FcRn binding is meant to minimize this degradation, but I would like to be able to implement it to describe the short half-life of drugs that bind to FcRn at neutral pH as well. In Mobi, I can implement degradation of the complex, but then I also want to implement degradation of FcRn itself (to avoid changing FcRn concentrations as a consequence of drug binding) for which I need to compensate with FcRn synthesis. I am now in doubt whether I need to use the endosomal or the membrane concentration of FcRn to calculate synthesis rate and if the latter is actually a parameter in the model. Also, I cannot find the reactions in mobi describing transfer of FcRn to endosome, or is this not defined as a reaction?
Thanks for your help and already a happy new year to everyone!
Wilbert

tobiasK2001 commented on Dec 31, 2019 Member

Dear Wilbert,

please find the details how the FcRn mediated recycling for large molecules in PK-sim described here
https://link.springer.com/article/10.1007/s10928-017-9559-4

Hope this might help you.

Best, Tobias

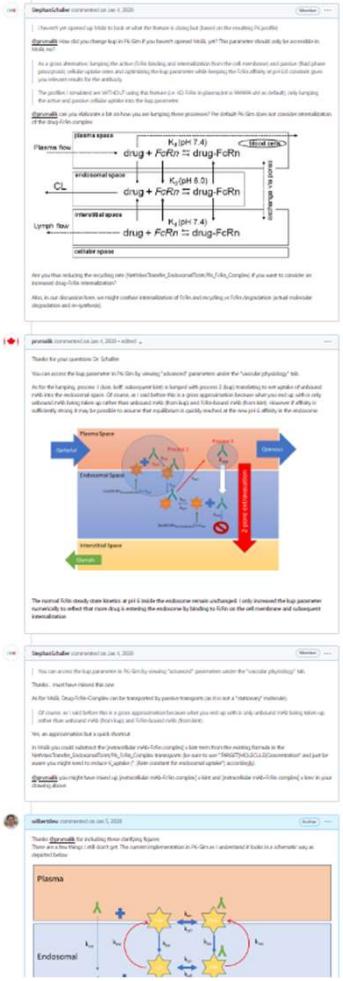
StephanSchaller commented on Dec 31, 2019 • edited Member

Dear Wilbert,

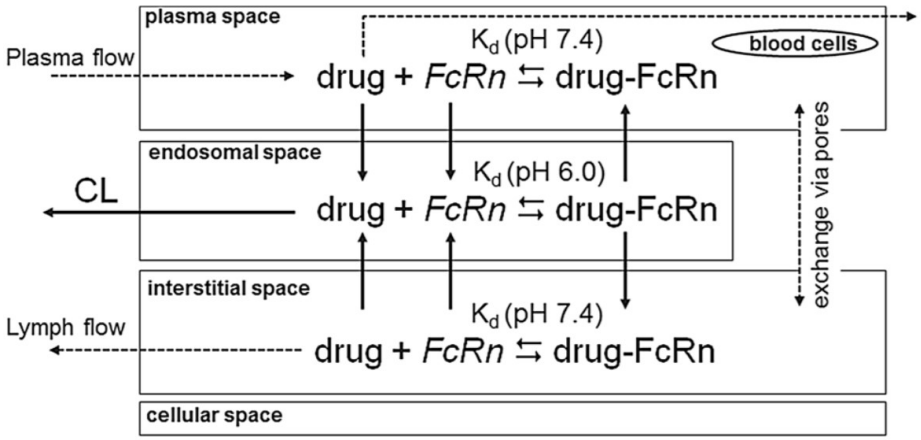
yes, you are absolutely right that there is no turnover of FcRn implemented. While the publication that @tobiasK2001 mentions gives you an oversight, it will not help you understand the explicit implementation of what you are trying to do. Section 5 in the Supplementary Information might help you understand how the FcRn SteadyState is defined.

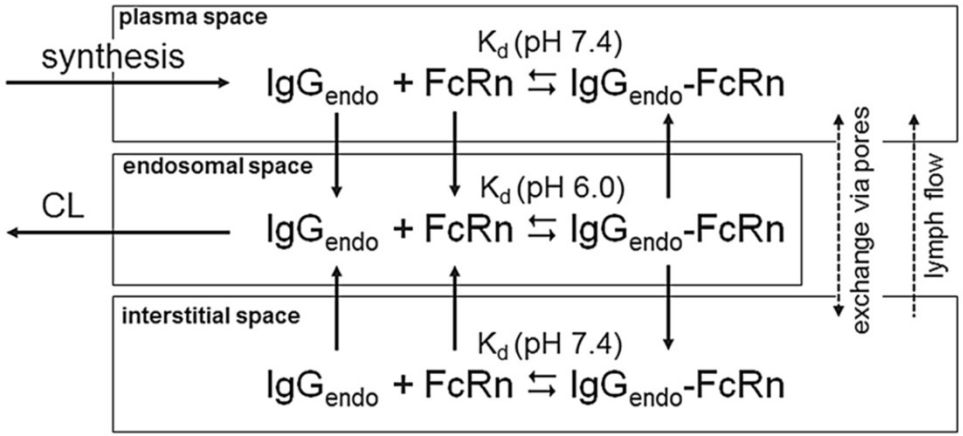
FcRn is located in the "Endogeneous_IgG" Organ. While the initial concentration in the endosome is defined (Parameter "..|Start concentration of free FcRn (endosome)" as a Parameter in the FcRn molecule in you Molecules BuildingBlock), the initial concentrations in Plasma and Interstitium are then calculated based in this value and the initial value of endogenous IgG.

I would thus suggest to create a turnover reaction for FcRn in the endosome of the Endogenous_IgG Organ using "..|Start



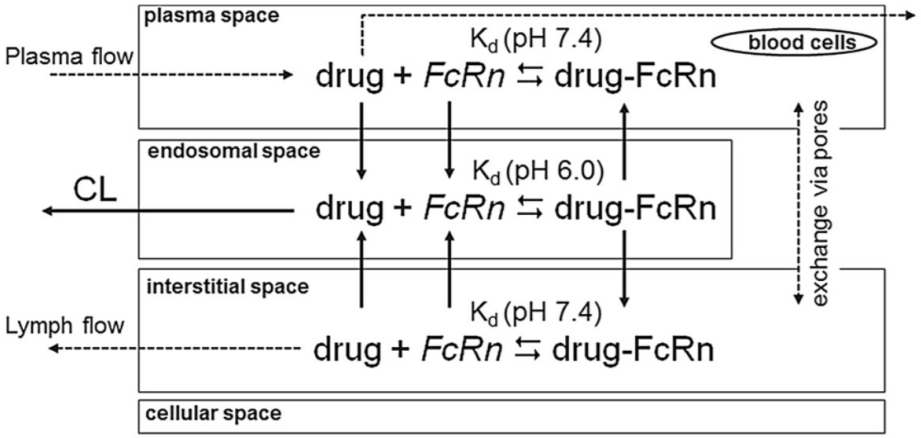
Implementation of FcRn processes in PK-Sim





Niederalt *et al.* J Pharmacokinet Pharmacodyn (2018) 45: 235.

Implementation of FcRn processes in PK-Sim



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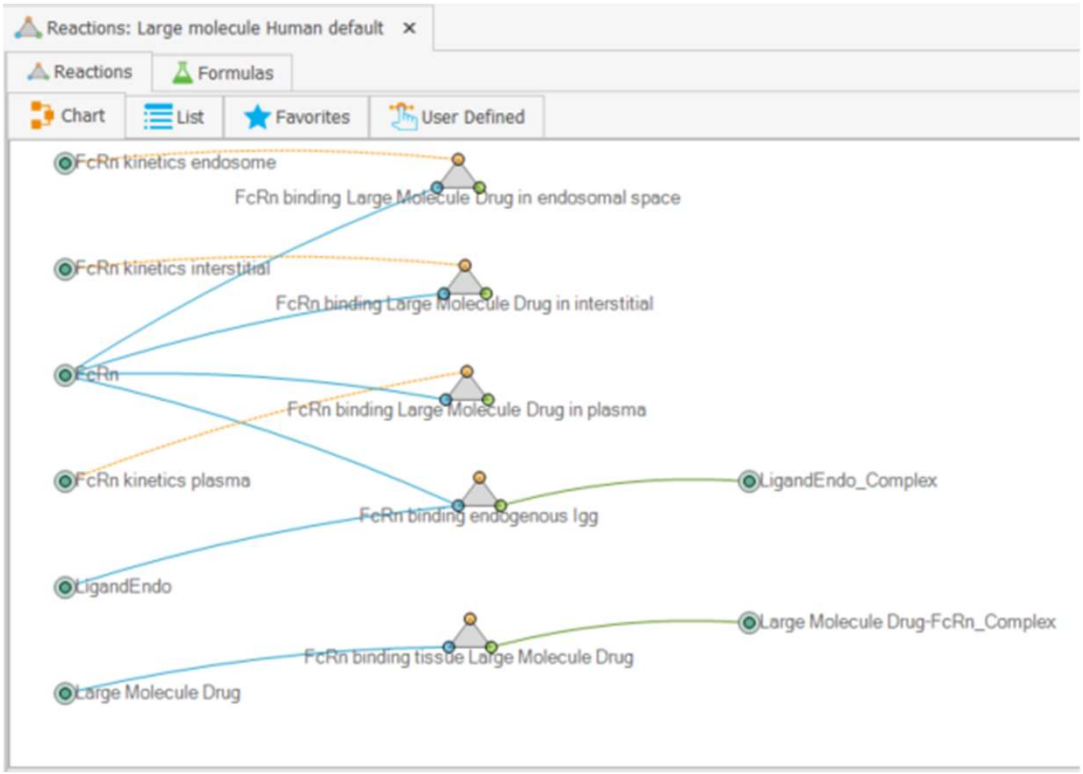
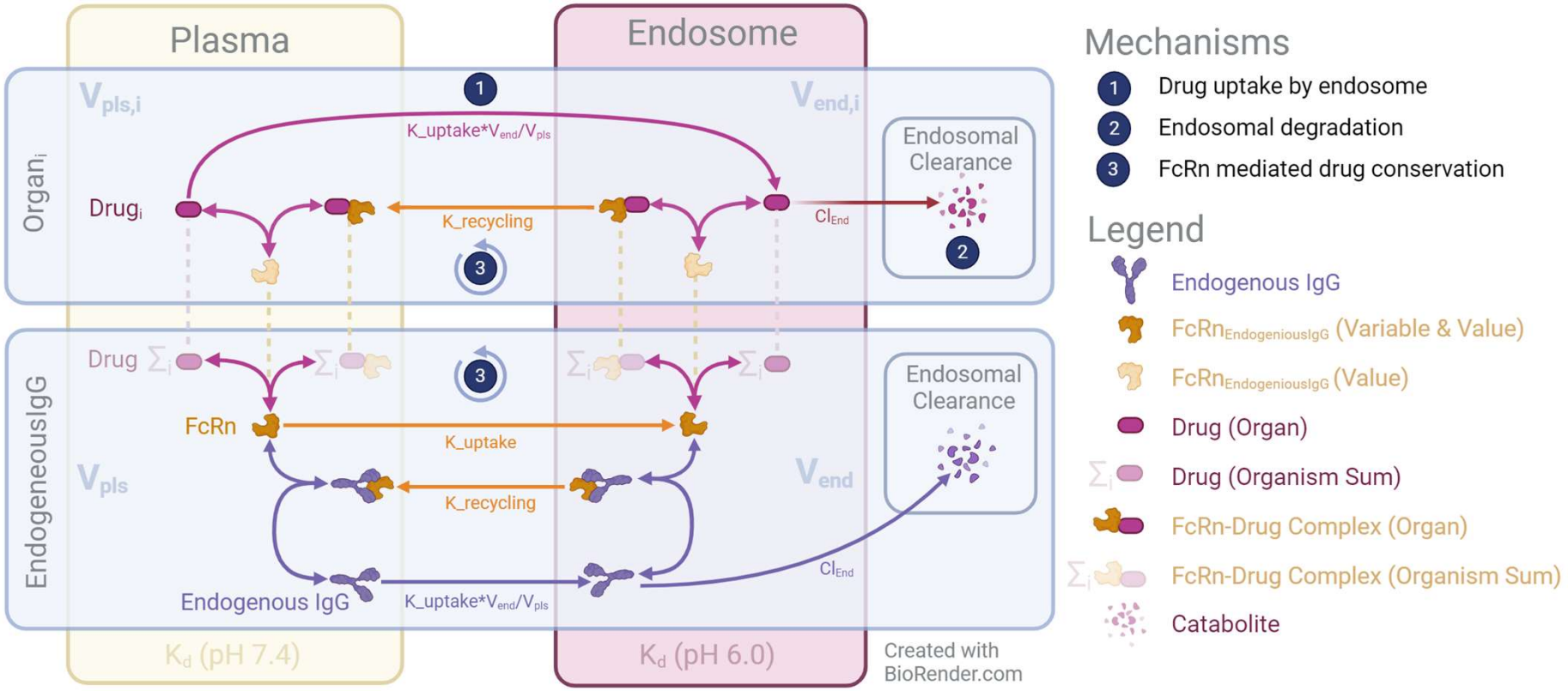


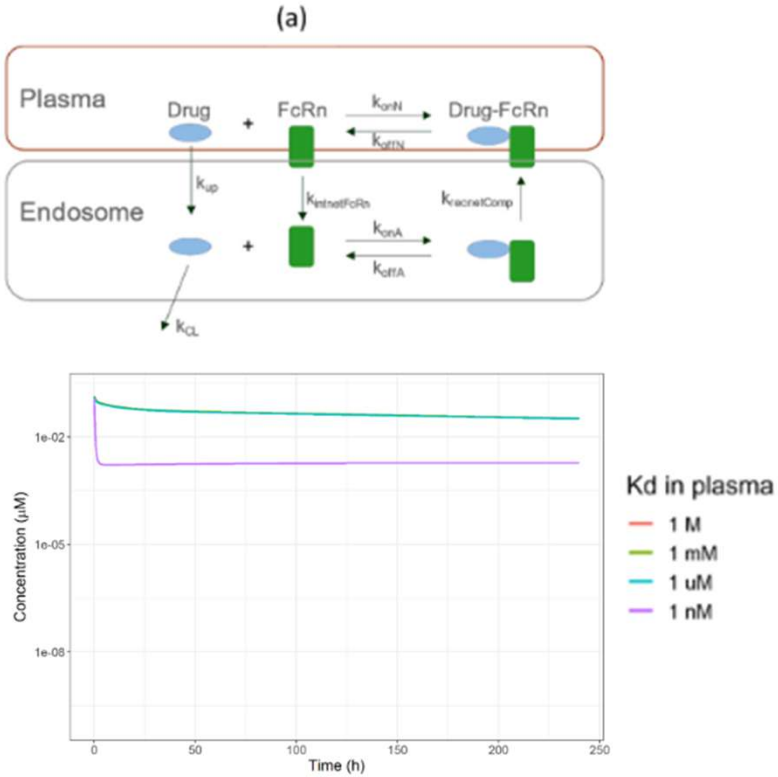
Implementation of FcRn processes in PK-Sim

Handling of (endogenous) IgG in PK-Sim



The impact of FcRn binding in plasma

Extension of FcRn cycling in PK-Sim



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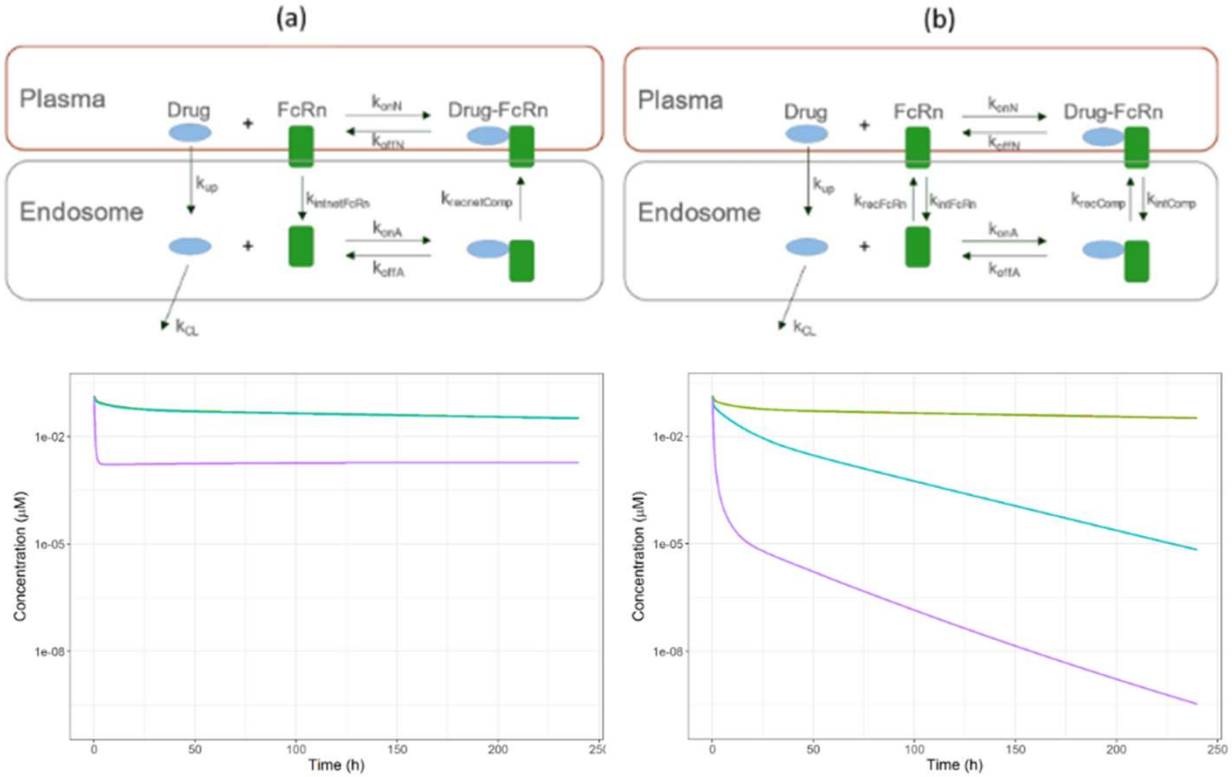


Journal of Pharmacokinetics and Pharmacodynamics (2023) 50:229–241
https://doi.org/10.1007/s10928-023-09849-9

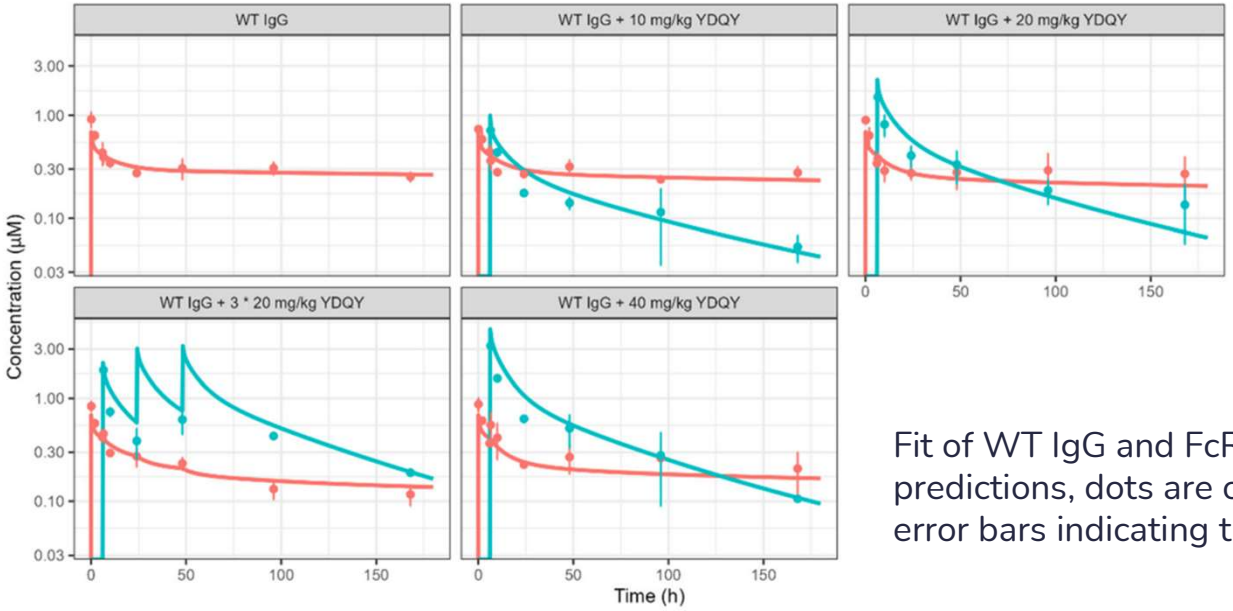
ORIGINAL PAPER

Mechanistic incorporation of FcRn binding in plasma and endosomes in a whole body PBPK model for large molecules

Wilhelmus E. A. de Witte[1,2] · Lindsay B. Avery[3] · Brian C. Mackness[3] · Tom Van Bogaert[1] · Anna Park[3] · Maria Laura Sargentini-Maier[1]

Implementation of FcRn processes in PK-Sim

Application of the extended model de describe FcRn inhibitor PK and its impact on WT PK



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Fit of WT IgG and FcRn inhibitor concentrations. Lines are the model predictions, dots are observed mean plasma concentration data with error bars indicating the standard deviations

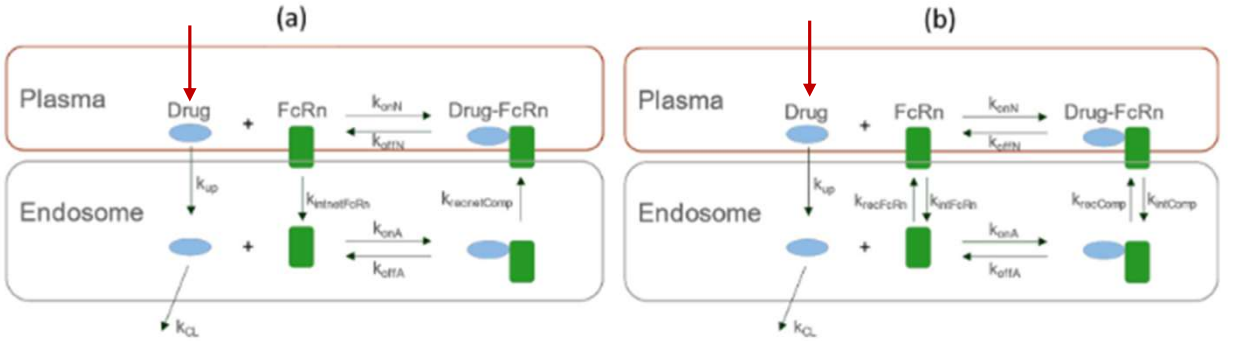
03

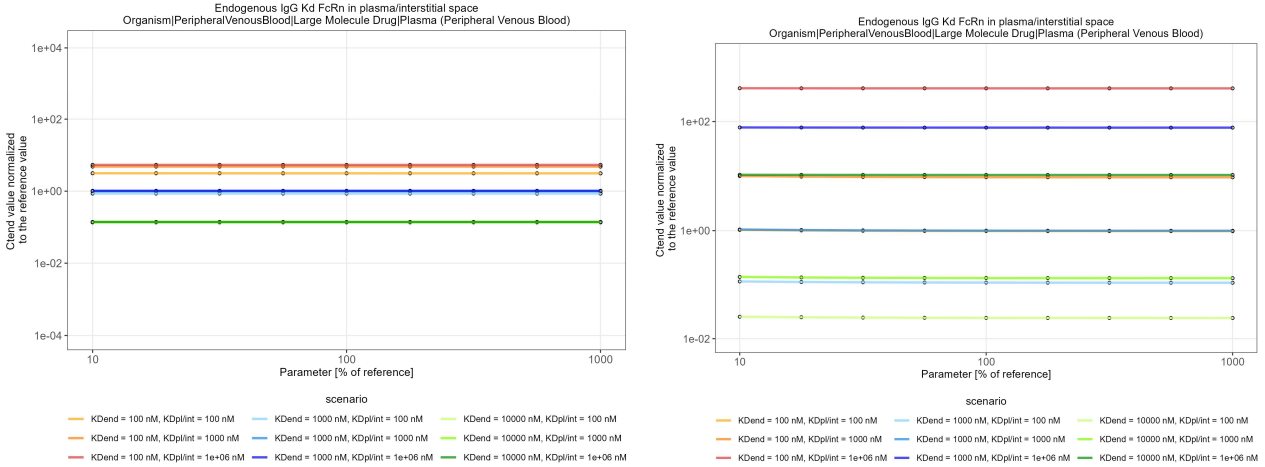
Model analysis

Focus on the default PK-Sim model

Getting a more complete understanding of the FcRn models

Application of a repeated sensitivity analysis with continuous infusion

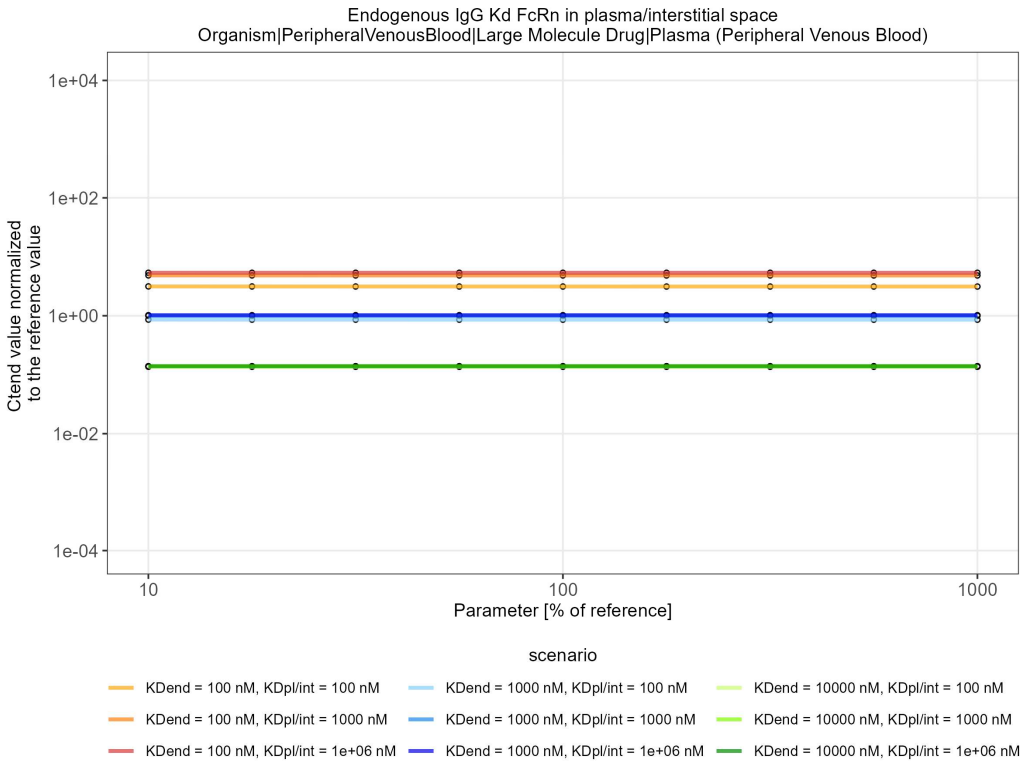




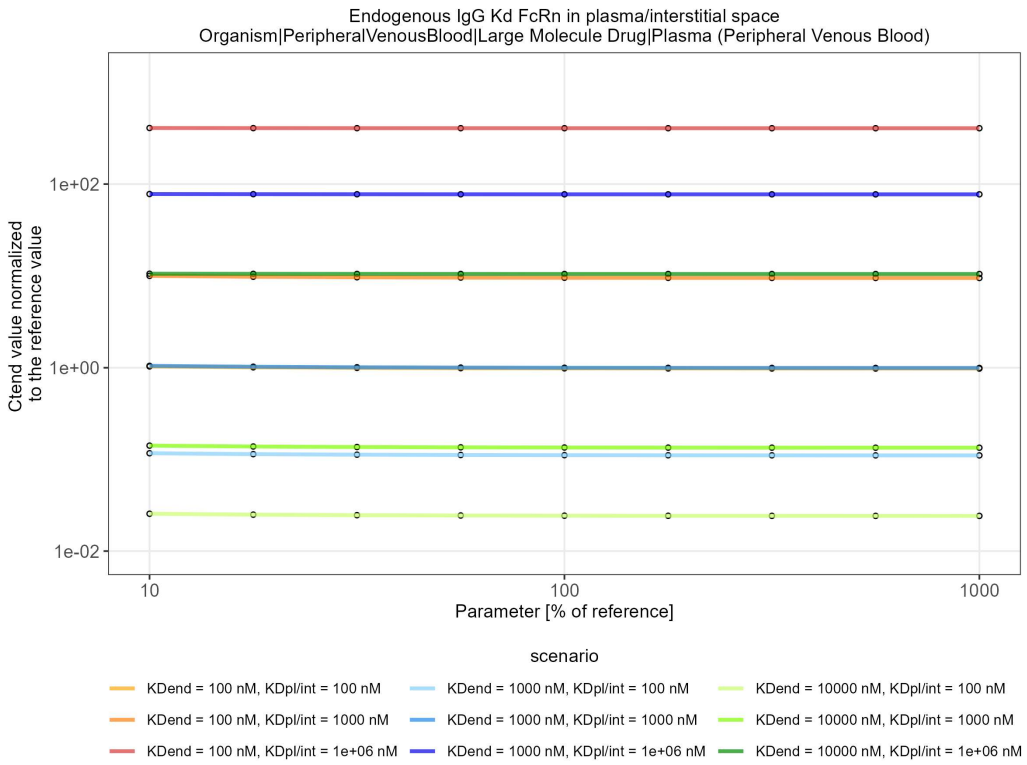
Getting a more complete understanding of the FcRn models

Application of a repeated sensitivity analysis with continuous infusion

Default model



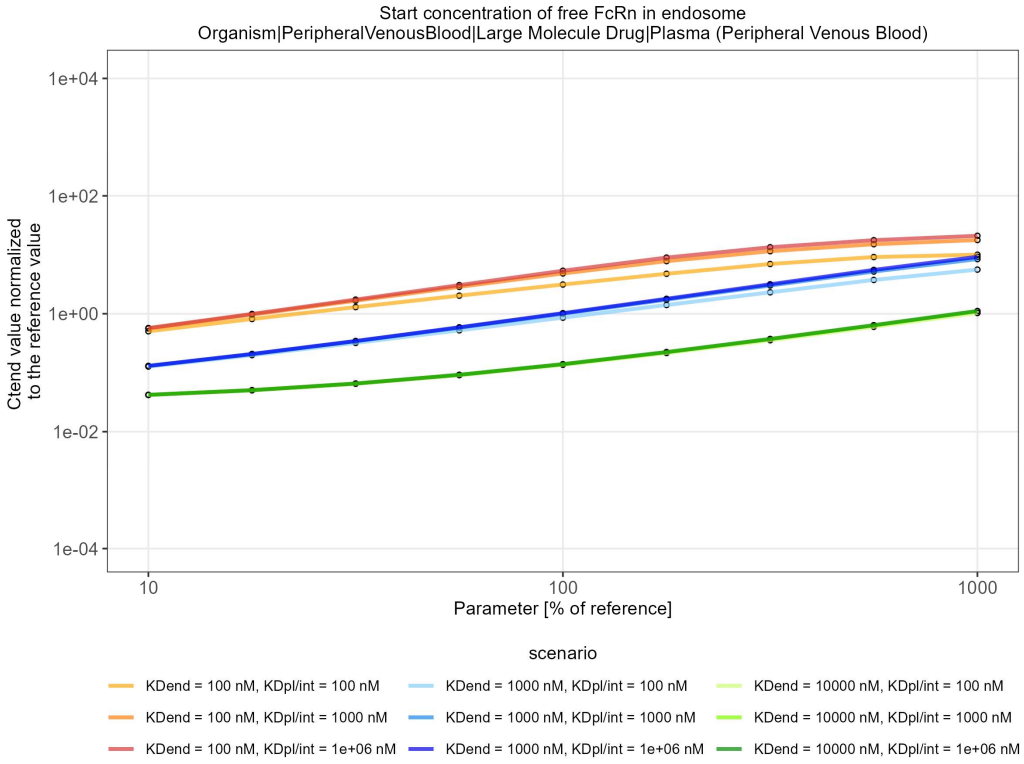
Extended model



Getting a more complete understanding of the FcRn models

What happens if the start concentration of free FcRn is changed?

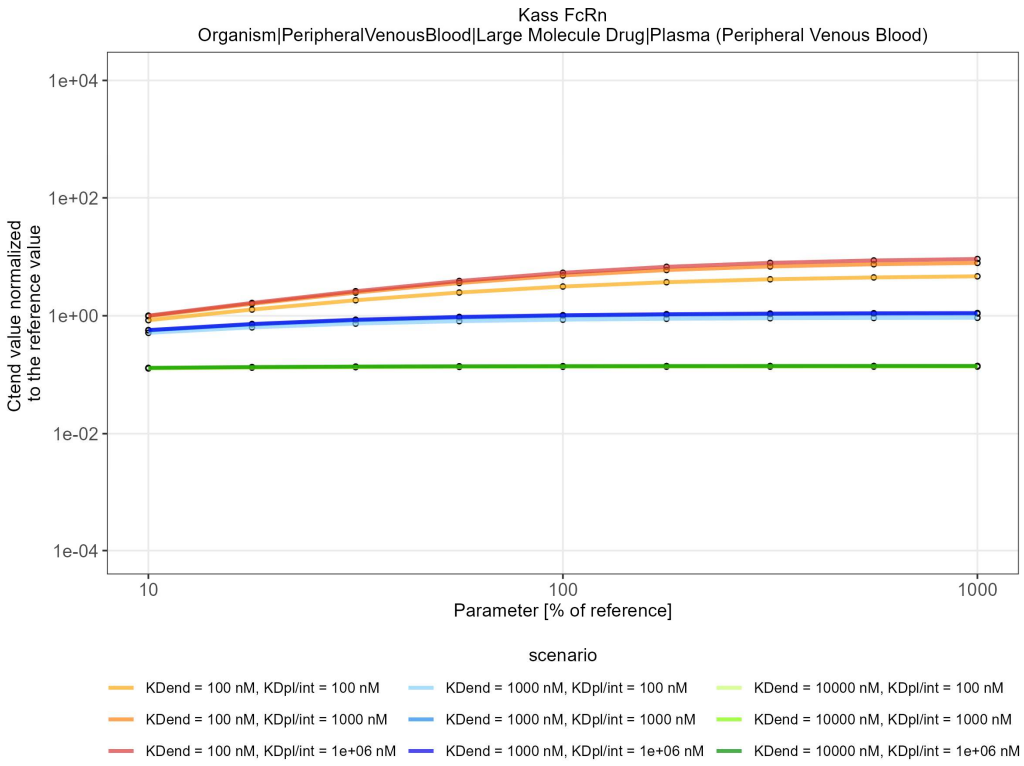
Default model



Getting a more complete understanding of the FcRn models

Some parameters have different sensitivities for different compounds

Default model

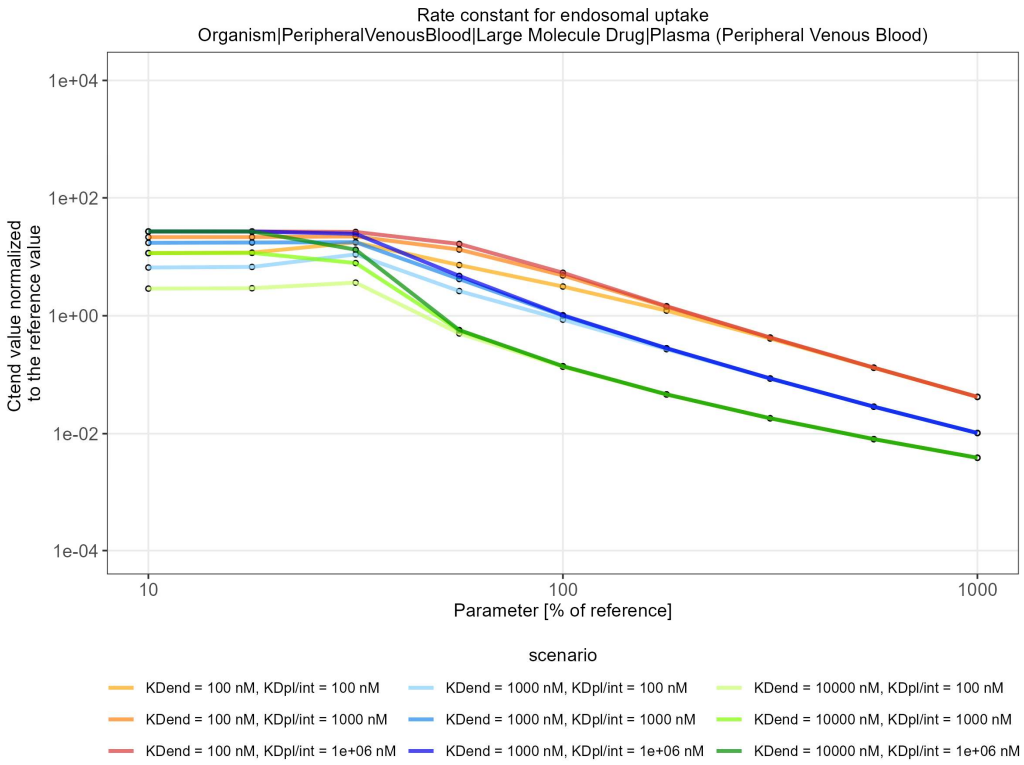


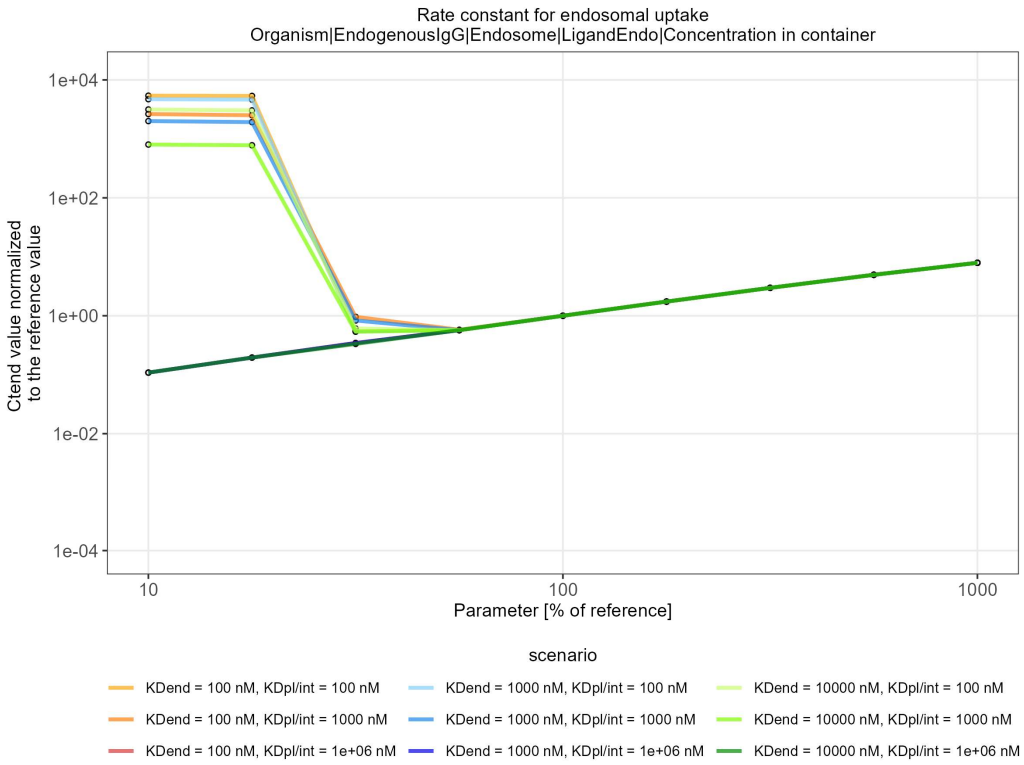
Getting a more complete understanding of the FcRn models

Be careful with adapting the uptake rate constant

Default model

Clend = max(K_uptake - K_rec , 0)

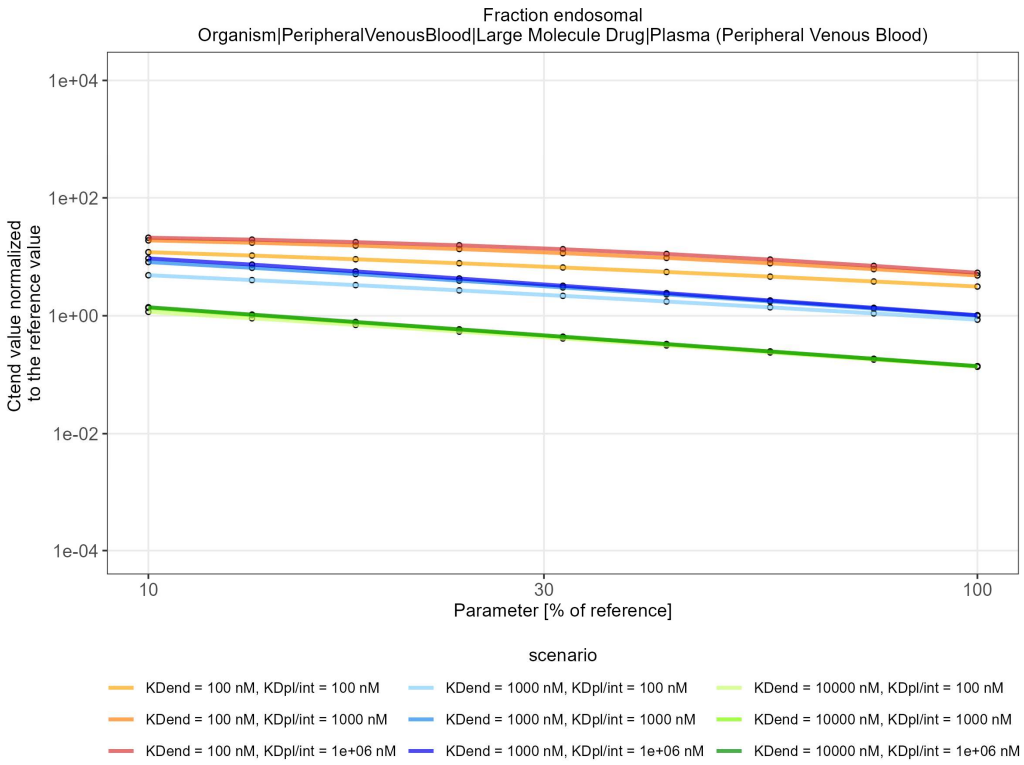


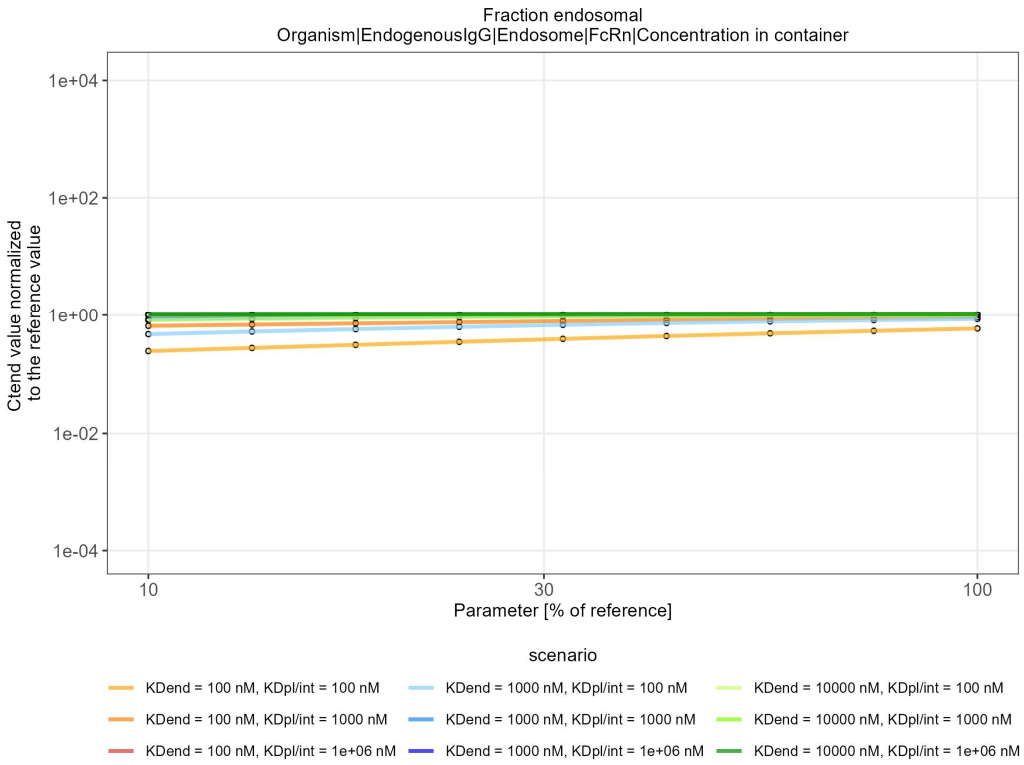


Getting a more complete understanding of the FcRn models

Changing endosomal volumes to affect drug PK selectively

Default model

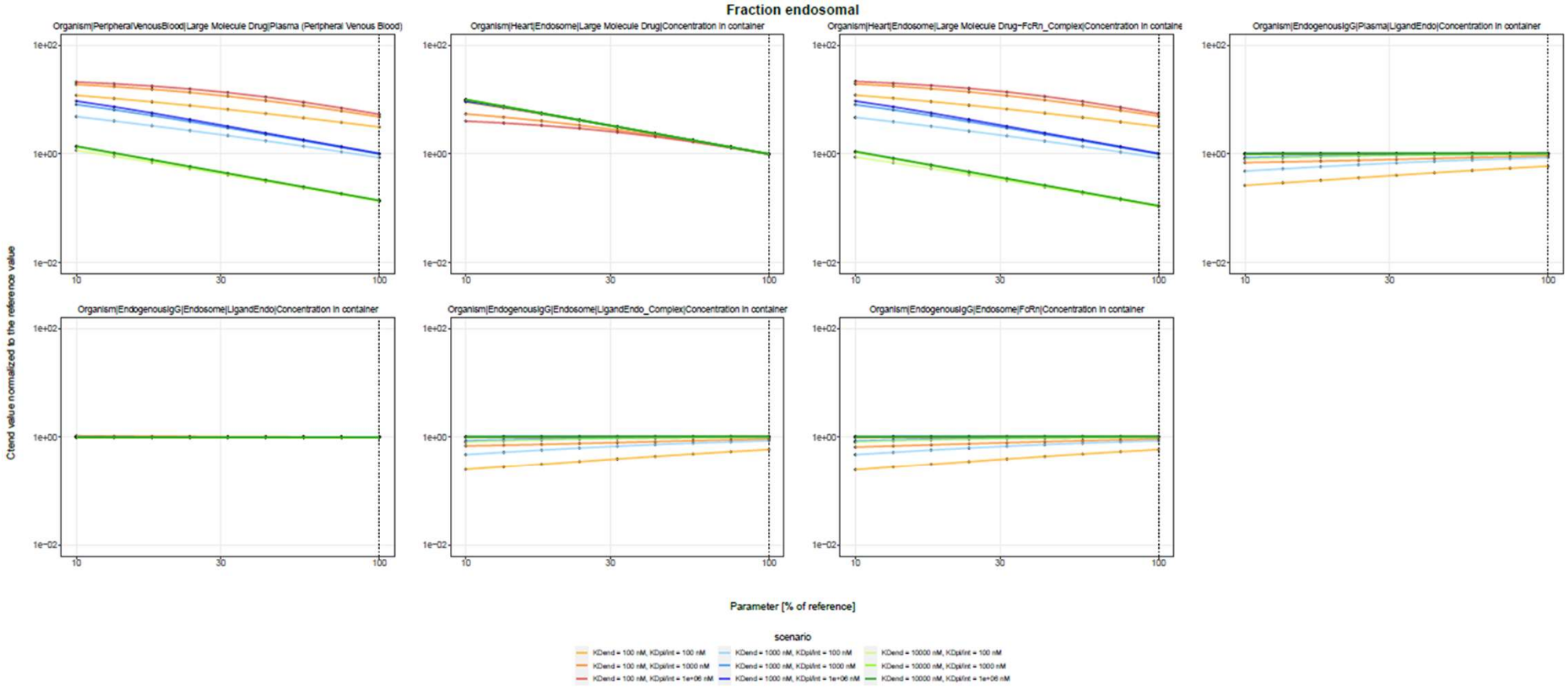




Getting a more complete understanding of the FcRn models

A comprehensive understanding requires a look at all relevant outputs

Default model



SUMMARY

- The default PK-Sim model is preferably only used for **molecules that do not bind FcRn in plasma**
- This model can be easily extended to cover other molecules like **FcRn inhibitors or FcRn-mediated sweeping antibodies**
- The default PK-Sim model comprises of FcRn binding of a drug and endogenous IgG, which happens in **organs and in the EndogenousIgG compartment**
- Adaptation of any of the FcRn parameters requires **careful consideration of the impact** on the drug and the rest of the FcRn model
- Adapting clearance of a drug trough the FcRn parameters without affecting FcRn or endogenous IgG can be obtained trough adapting the **“fraction endosomal” parameter**