

FcRn modelling in the OSP suite

Wilbert de Witte

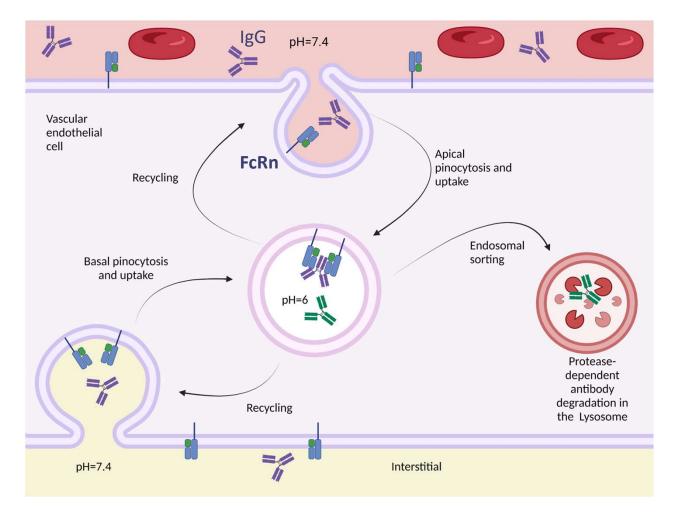
01

Introduction

FcRn Biology and therapeutic potential



What is FcRn and what is its function?



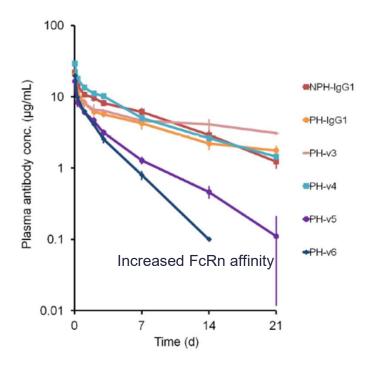
- pH-dependent binding of IgG (mAbs) and Albumin
- Binding to IgG in a 1:2 complex
- Endosomal binding and recycling increases halflife of IgG and Albumin

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 halflives 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



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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?

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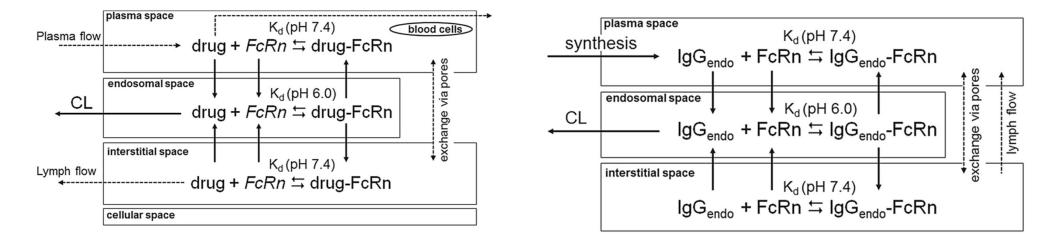
Community engagement			
vilbertdew commented on Dec 30, 2019		94.5 - 640 - 440 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4 - 4	
łi All,			
Ian anybody give me some pointers to better underdstand FCRn kinetics in PK-Sim/Mobi? Jurrently, I have the impression that no turnover of FCRn or degradation for the drug-FCRn 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 hort 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 liso 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 oncentration of FCRn to calculate synthesis rate and I' the latter is actually a parameter in the model. Also, I cannot find the eactions in mobil 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			
Dear Wilbert,		L = Man, I Mary	
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		(*)	
lope this might help you.		brui High	
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tephanSchaller commented on Dec 31, 2019 • edited 👻	Member ····		
Dear Wilbert,		30.00 9000 0.17 51.0	
es, you are absolutely right that there is no turnover of FcRn implemented. While the publication that <u>@t</u> jives you an oversight, it will not help you understand the explicit implementation of what you are trying 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 define concentration of free FcRn (endosome)" as a Parameter in the FcRn molecule in you Molecules BuildingBlo concentrations in Plasma and Interstitium are then calculated based in this value and the initial value of er	to do. Section 5 in the ed (Parameter " Start bck), the initial		

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

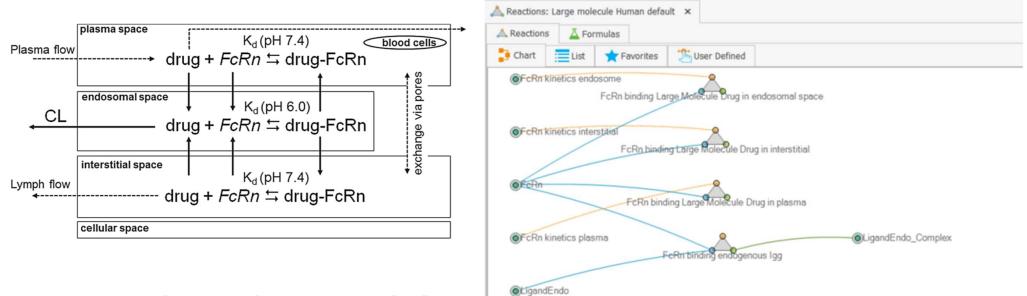
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Niederalt et al. J Pharmacokinet Pharmacodyn (2018) 45: 235.



Ocarge Molecule Drug

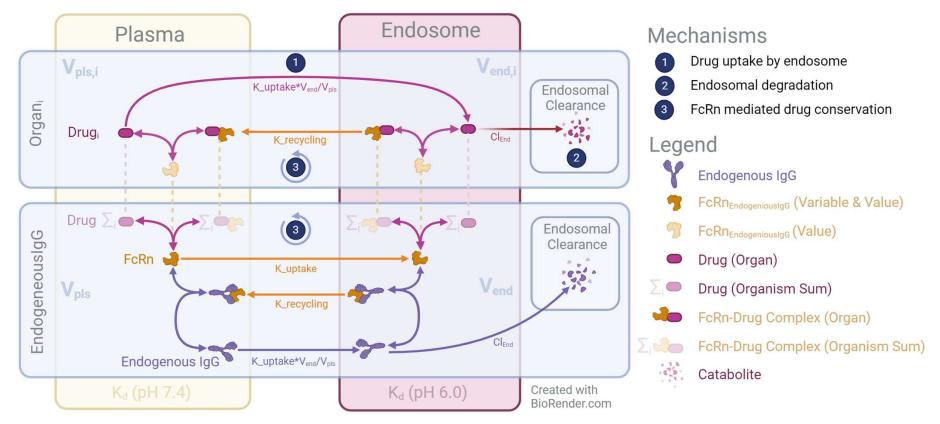
Niederalt et al. J Pharmacokinet Pharmacodyn (2018) 45: 235.

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OLarge Molecule Drug-FcRn_Complex

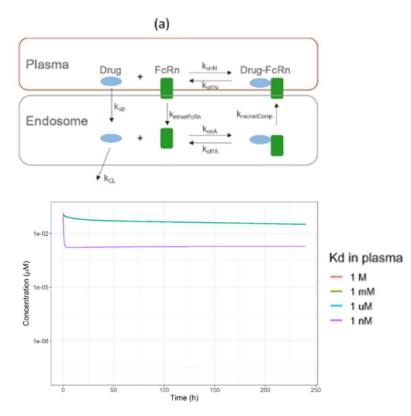
FCRn binding tissue Large Molecule Drug

Handling of (endogenous) IgG in PK-Sim



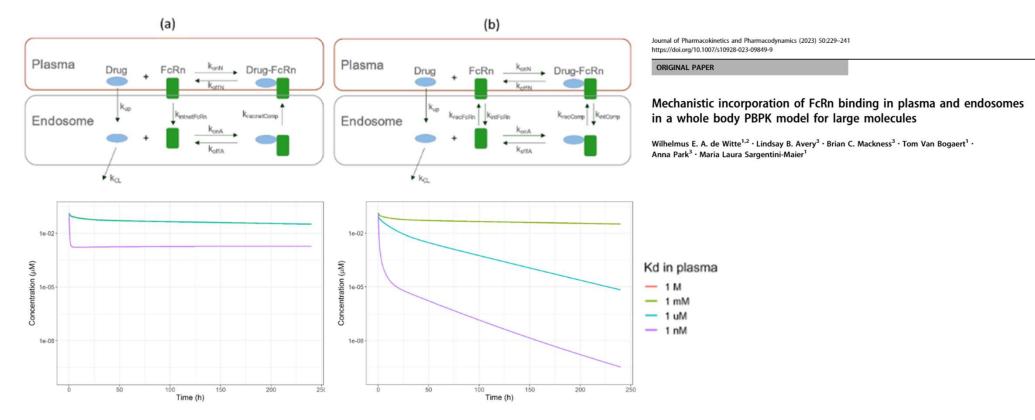
The impact of FcRn binding in plasma

Extension of FcRn cycling in PK-Sim

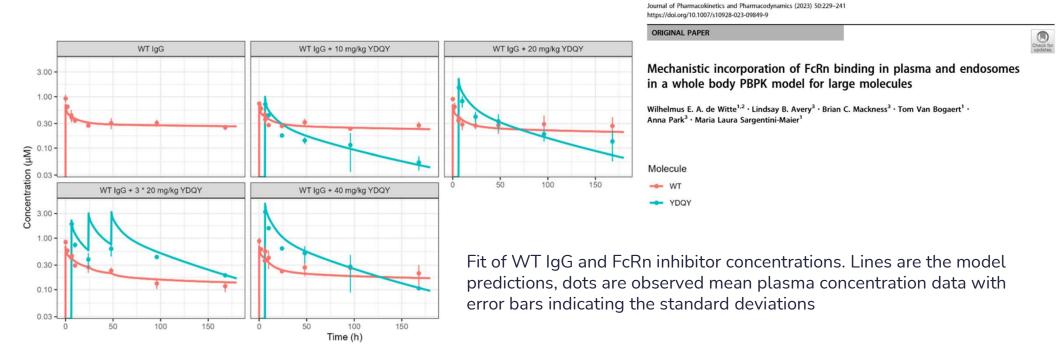


The impact of FcRn binding in plasma

Extension of FcRn cycling in PK-Sim



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

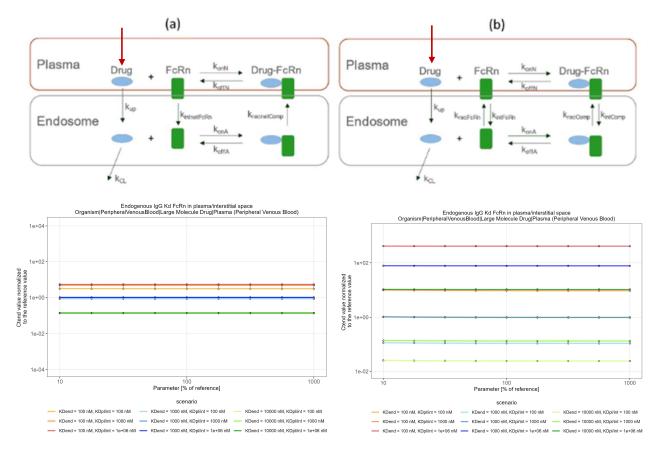


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Model analysis Focus on the default PK-Sim model



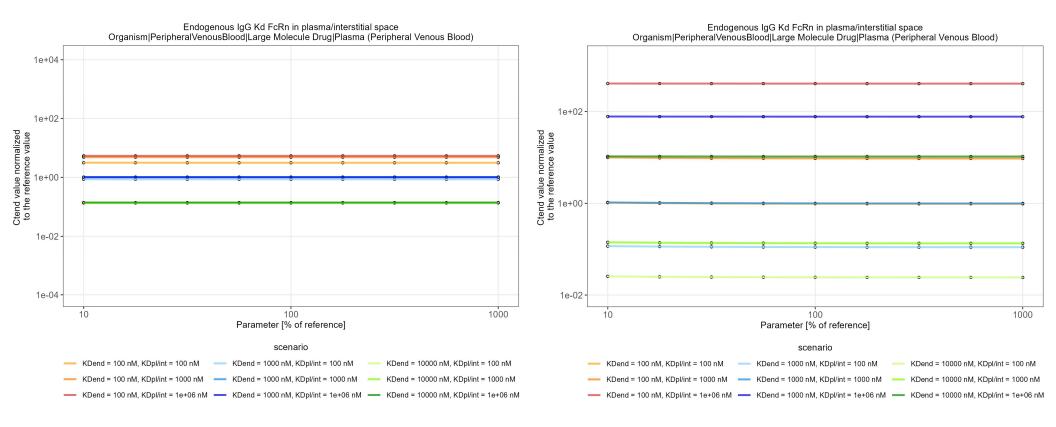
Application of a repeated sensitivity analysis with continuous infusion



Application of a repeated sensitivity analysis with continuous infusion

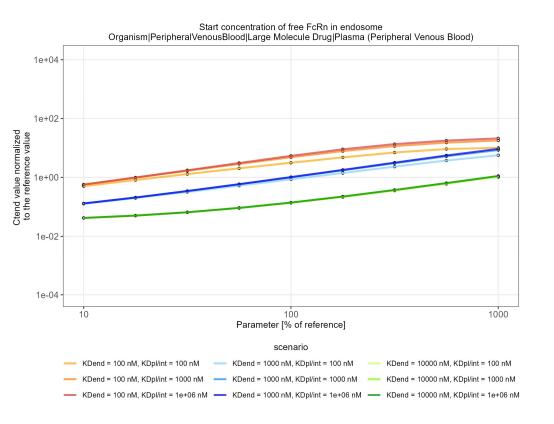
Default model

Extended model

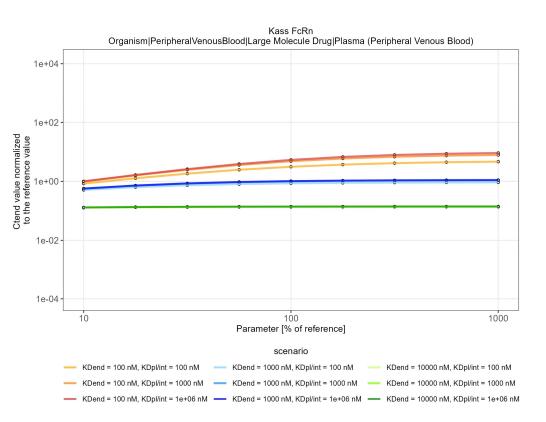


What happens if the start concentration of free FcRn is changed?

Default model

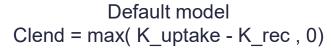


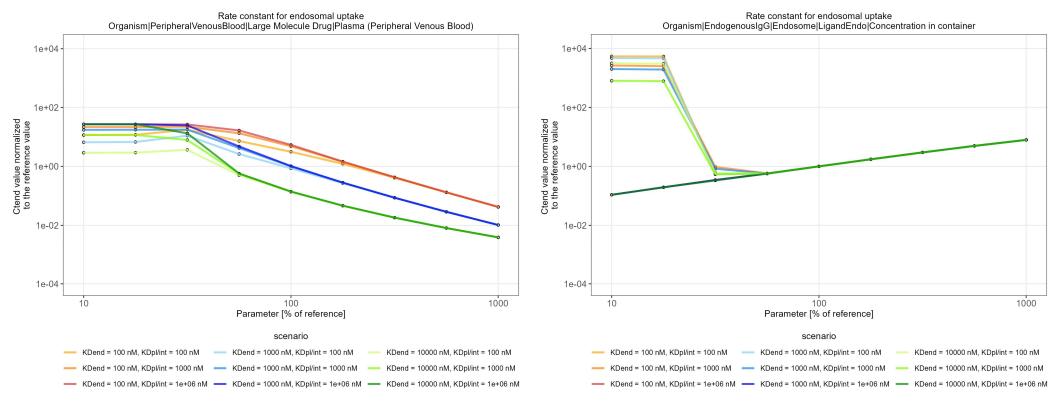
Some parameters have different sensitivities for different compounds



Default model

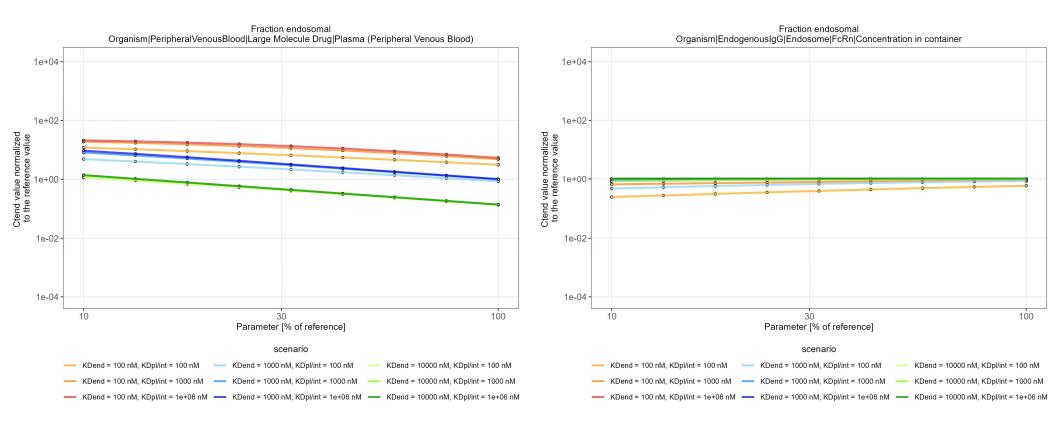
Be careful with adapting the uptake rate constant



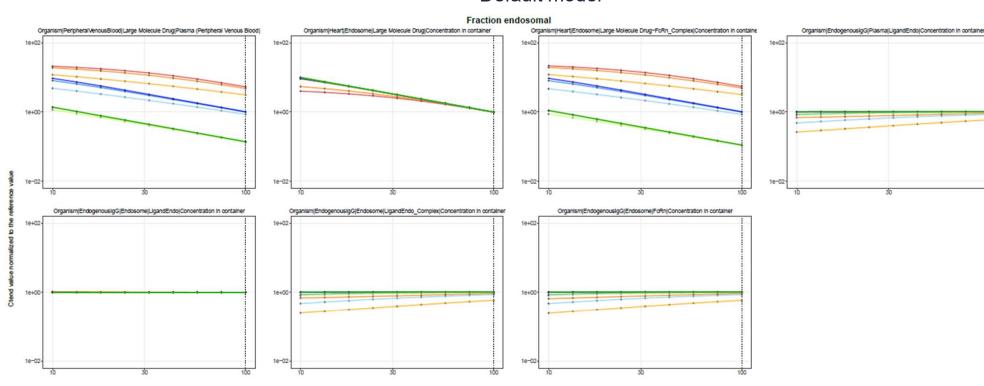


Changing endosomal volumes to affect drug PK selectively





A comprehensive understanding requires a look at all relevant outputs



Default model

Parameter [% of reference]

scenario

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- 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