

Saskia Fuhrmann^{1,2}, Charlotte Kloft³, Wilhelm Huisinga²

¹ Graduate Research Training Program PharMetriX: Pharmacometrics & Computational Disease Modeling, Potsdam/Berlin;

² Institute of Mathematics / Institute of Biochemistry and Biology, Potsdam University, Potsdam, Germany;

³ Institute of Pharmacy, Freie Universitaet Berlin, Berlin, Germany.

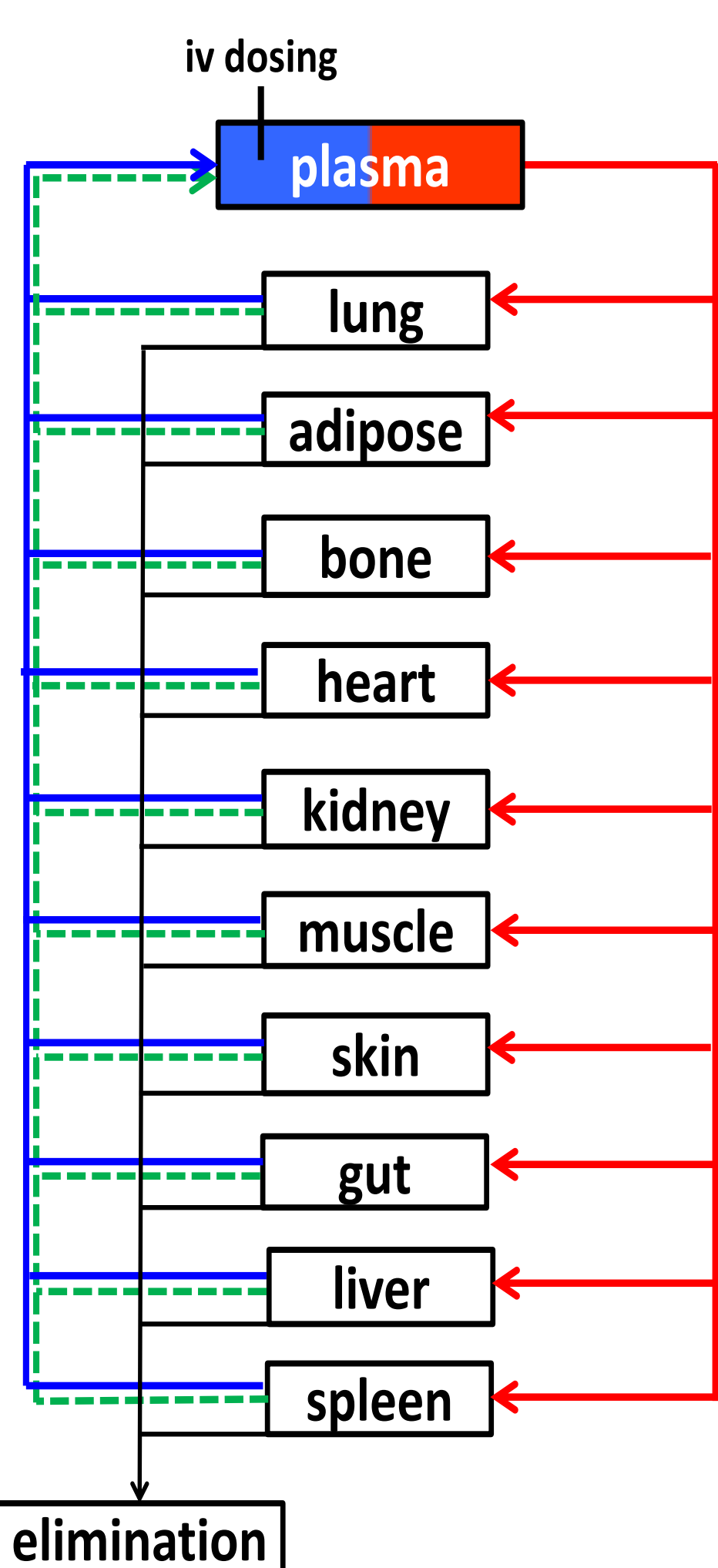
Motivation & Objectives

Immunodeficient mouse models are frequently used to study the PK and PD of monoclonal antibodies (mAbs). Protection from elimination by binding to the FcRn receptor is known to be a major process influencing the kinetics of mAbs as well as endogenous IgG (IgG_{endo}). Since in non-immunodeficient mice the therapeutic mAb concentrations following clinically relevant doses are manifold below the IgG_{endo} concentration, the clearance of mAb by this pathway appears to be linear. The levels of IgG_{endo} in immunocompromised mice, however, are reduced, and this effect on mAb PK has not yet been studied.

Objective:

- Investigation of the impact of FcRn level and low IgG_{endo} in immunodeficient mice on mAb clearance in a PBPK context

Simplified PBPK model with extravasation rate-limited tissue distribution



Parameterization of the simplified PBPK model [1]:

- plasma and interstitial tissue volumes
- lymph flows L_{tis} (convection) and tissue-specific vascular reflection coefficients σ_{tis} (one-pore theory)
- tissue partition coefficients K_{tis} (related to Antibody Biodistribution Coefficients, ABCs)

$$\hat{K}_{tis} = (1 - E_{tis}) \cdot K_{tis}$$

$$ABC_{tis} = (1 - \sigma_{tis}) \cdot \hat{K}_{tis}$$

- linear plasma and/or intrinsic tissue clearance
- implicit consideration of endosomal space and FcRn-mediated salvage mechanism, based on the assumption:

$$WTmice : mAb \ll IgG_{endo}$$

- Rate of change of tissue and plasma concentrations:

$$V_{tis} \frac{d}{dt} C_{tis} = L_{tis} \cdot \left((1 - \sigma_{tis}) C_{pla} - \frac{C_{tis}}{K_{tis}} \right) - CL_{int,tis} \cdot C_{tis}$$

$$V_{pla} \frac{d}{dt} C_{pla} = L_{pla} \cdot \left(C_{in} - (1 - \sigma_{pla}) C_{pla} \right) - CL_{pla} \cdot C_{pla}$$

Tissue-to-plasma concentration ratios $ABC_{tis} = C_{tis} / C_{pla}$ derived from the ABCs in [7] and tissue volume fractions from [2].

tissue	adipose	bone	gut	heart	kidney	lung	muscle	skin	spleen	liver
ABC_{tis}	0.05	0.07	0.05	0.10	0.14	0.15	0.04	0.16	0.13	0.12

Methods: Modelling the impact of IgG_{endo} on mAb disposition in PBPK context

- We studied the influence of the immune system on mAb PK by extension of the simplified PBPK model [1] to describe different scenarios, i.e. (i) non-immunodeficient FcRn wild-type (WT) mice following intravenous immunoglobulin (IVIG) therapy, (ii) non-immunodeficient rats following intravenous immunoglobulin (IVIG) therapy and (iii) immunodeficient i.e. SCID mice.
- Physiological parameters were taken from [2]. The experimental plasma and tissue data of mAb (7E3), administered i.v. at 8mg/kg following 3 different doses of IVIG, were extracted from [3] for FcRn WT mice and for rat [5]. For SCID mice, the experimental plasma and tissue data of mAb (8C2), administered at 1mg/kg and 25 mg/kg, were extracted from [4]. MATLAB R2013a was used for modelling and simulations.

PBPK Model with FcRn-protected elimination in tissues:

- extraction ratios implicitly determine intrinsic clearance from two groups of tissues (based on tissue properties)

$$E_{tis} = \frac{CL_{int} \cdot K_{tis}}{L_{tis} + CL_{int} \cdot K_{tis}}$$

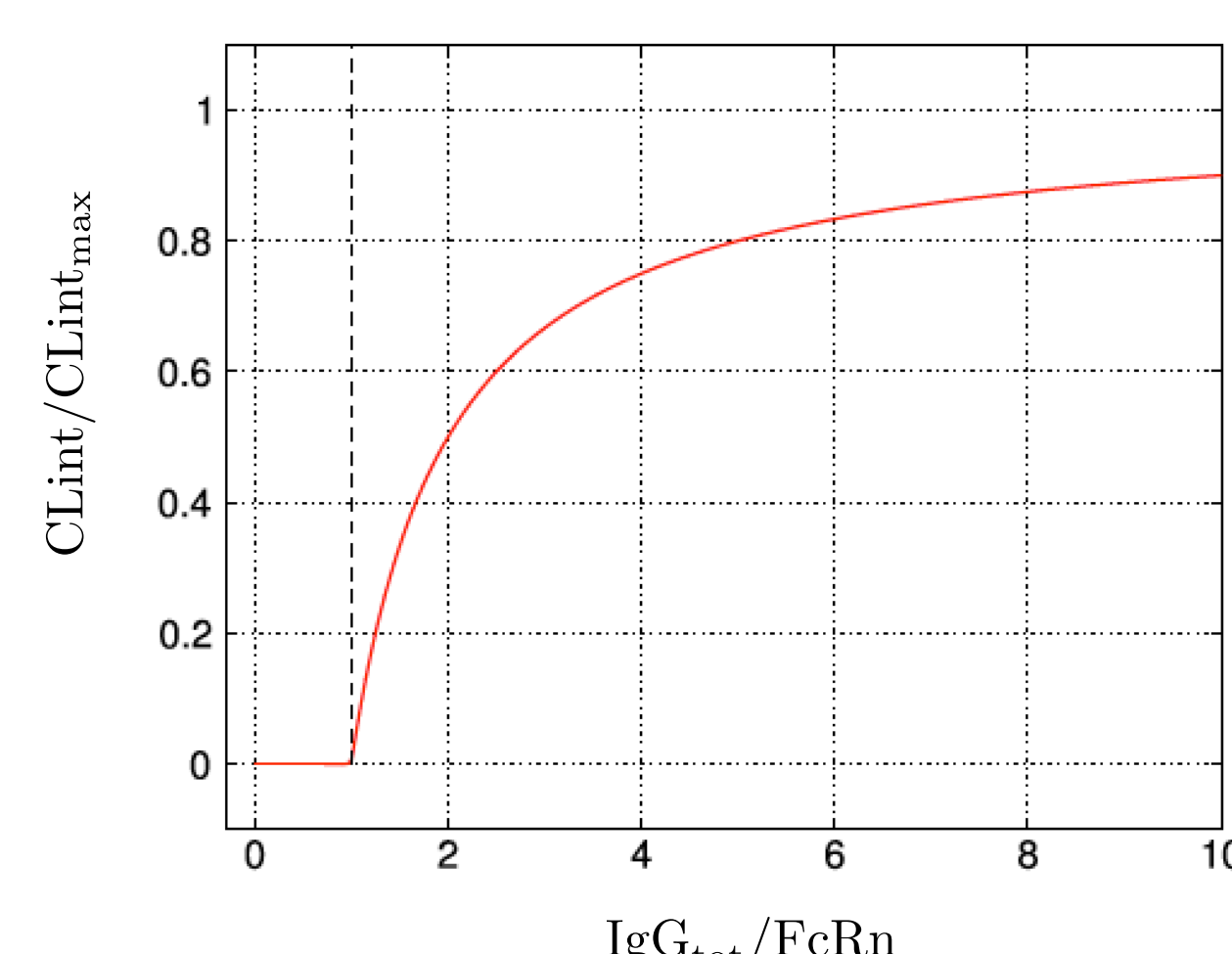
- tissue elimination linked to FcRn expression in tissues

$$CL_{int} = CL_{int,u} \cdot \left(1 - \frac{FcRn}{IgG_{tot}} \right)$$

- fraction unbound to FcRn

$$f_u = 1 - \frac{FcRn}{IgG_{tot}}$$

- total IgG concentration with plasma concentration of IgG_{endo} for WT mice, rat [5] and SCID mice [6]



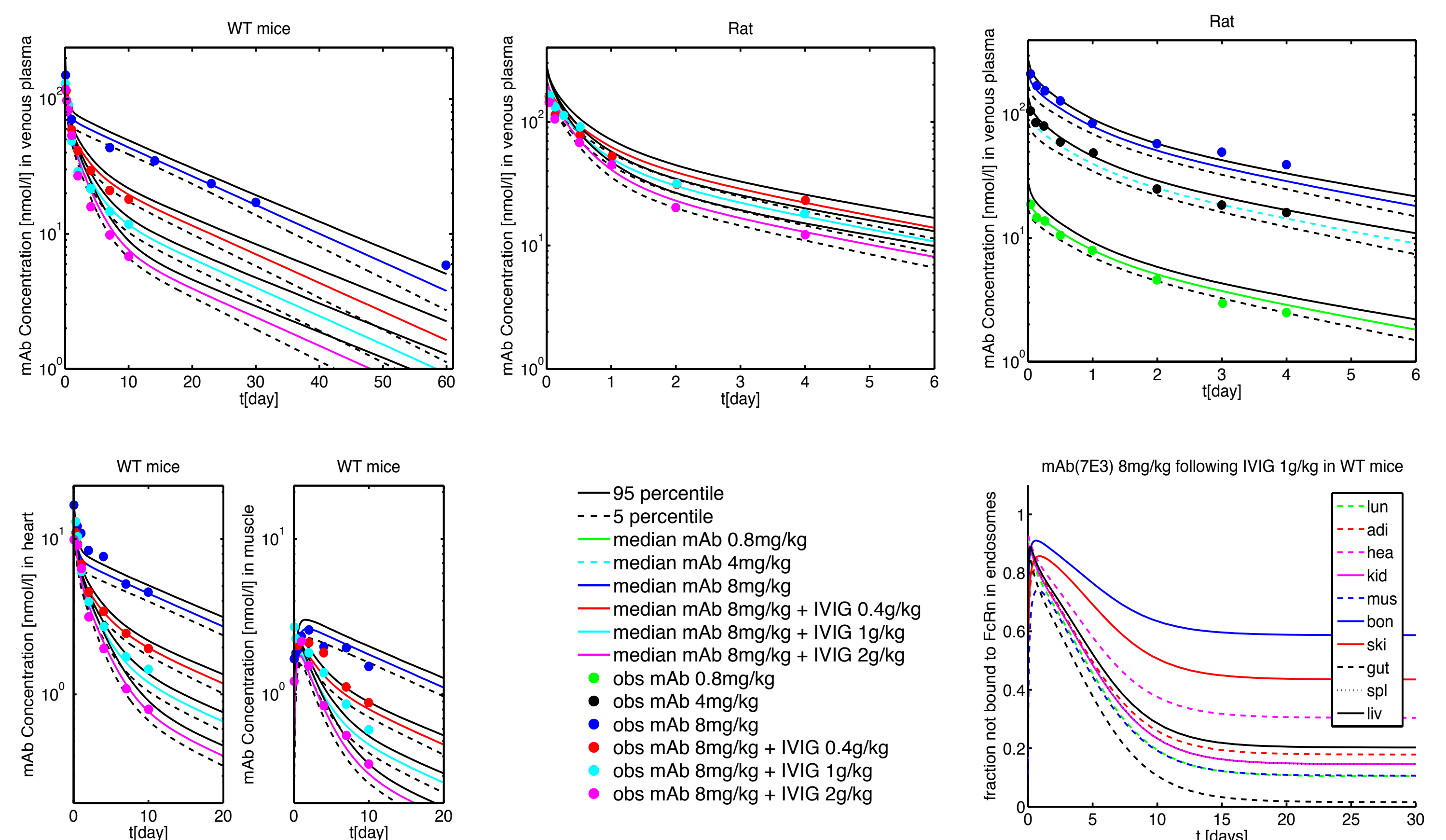
$$Rat, WTmice : IgG_{tot} = IgG_{endo} + mAb + IVIG$$

$$SCIDmice : IgG_{tot} = IgG_{endo} + mAb$$

Results: Performance of the model in WT mice and Rat following different doses of IVIG

Observation:

- The simplified PBPK Model with linear clearance from plasma and implicit consideration of FcRn cannot predict mAb 7E3 concentration-time profile after 8mg/kg dose in WT mice following IVIG therapy in rats and WT mice.
- The PBPK Model with FcRn-protected elimination in plasma could not predict the IVIG data.
- The PBPK Model with FcRn-protected elimination in tissues accurately characterized the impact of IVIG on mAb (7E3) PK. Interestingly, we observed higher extraction ratios for tight tissues than in leaky tissues and only negligible clearance from plasma. The model can predict both plasma and tissue data for rat and WT mice.

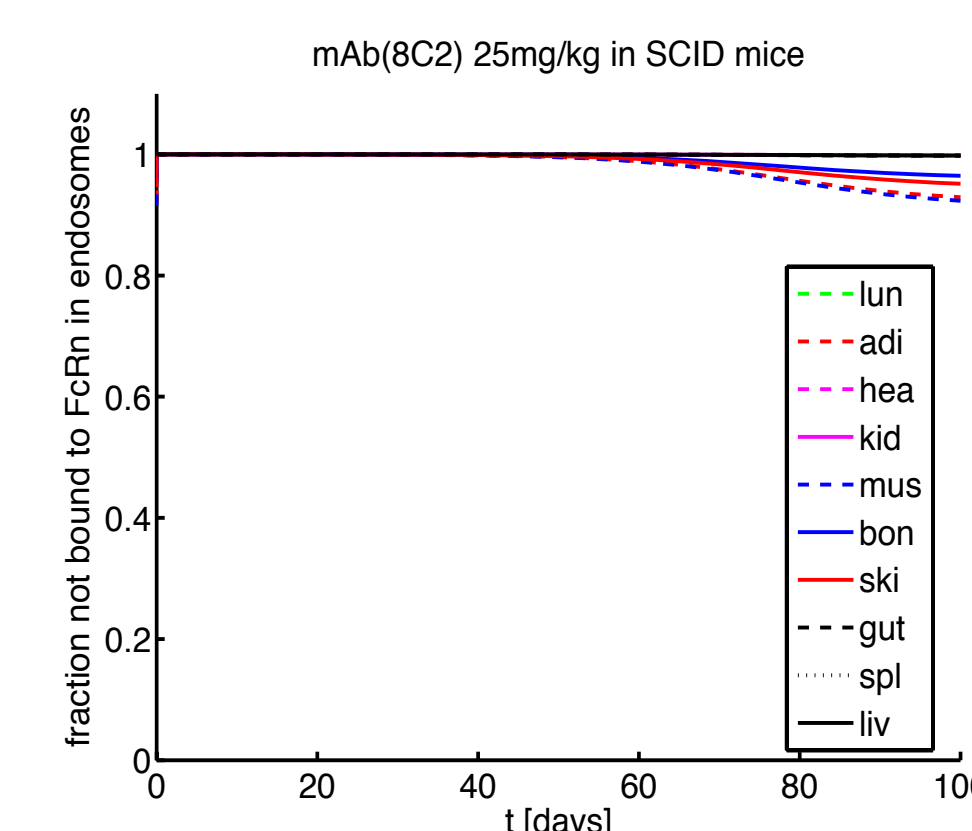
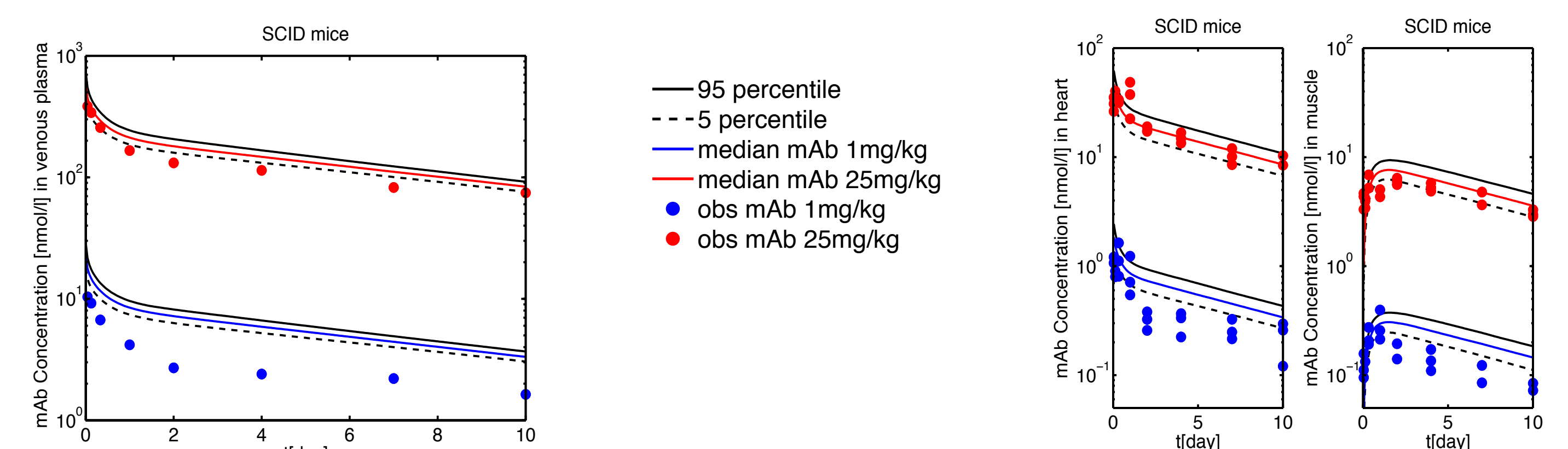


Percentiles for simulated data are based on predictions with variability in blood flow and blood volume ($\pm 20\%$), hematocrit and mAb dose ($\pm 10\%$).

Prediction of plasma concentrations at different dose levels in SCID mice

Observation:

- The simplified PBPK Model with linear clearance from plasma and implicit consideration of FcRn can predict the experimental data of SCID mice following two different doses.
- The PBPK Model with FcRn-protected elimination in tissues can capture the experimental data of SCID mice with estimated FcRn levels manifold lower compared to WT mice. For mAb dose 25 mg/kg plasma and tissue data are predicted accurately, whereas for mAb dose 1mg/kg plasma data is overestimated.



With estimated low FcRn levels and low endogenous IgG in SCID mice we observe a high fraction unbound to FcRn, leading to saturation of FcRn at therapeutic mAb doses. Therefore we alternatively can model the SCID data using a linear clearance.

$$SCIDmice : mAb \gg IgG_{endo}$$

Conclusion

Total IgG, FcRn level and elimination from tissues have a relevant impact on the PK of mAbs. For immunodeficient mice with low endogenous IgG we observe lower FcRn level than WT mice leading to saturation of mAb at therapeutic mAb doses and linear elimination pathway. Based on these results, FcRn and IgG_{endo} can be considered implicitly in the PBPK model when investigating tumour disposition from xenograft data. Tissues xenografted in immunodeficient mice are crucial models to evaluate the effectiveness of therapeutic drugs.

References

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