Monoclonal Antibody Disposition beyond Target Binding: Impact of FcRn on Clearance and Derivation of Mechanistic Compartment Models

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Introduction

Monoclonal antibodies (mAbs) have been used in the treatment of various diseases for over 20 years and combine high specificity with generally low toxicity.

Their pharmacokinetic (PK) properties differ markedly from small molecule drugs.

While empirical PK modelling of small molecule drugs is widely understood and used, there is no clear standard to model mAbs data.

Lately, mechanistic and physiologically based pharmacokinetic (PBPK) models showed their importance in understanding the mechanism of elimination/salvage of mAbs via FcRn binding present in the endothelial cells.

Objectives

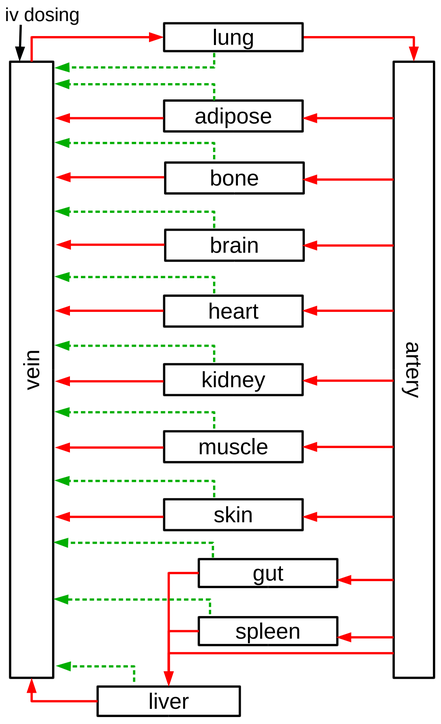
To explain the observed non-target specific linear clearance when FcRn-mediated salvage is saturable.

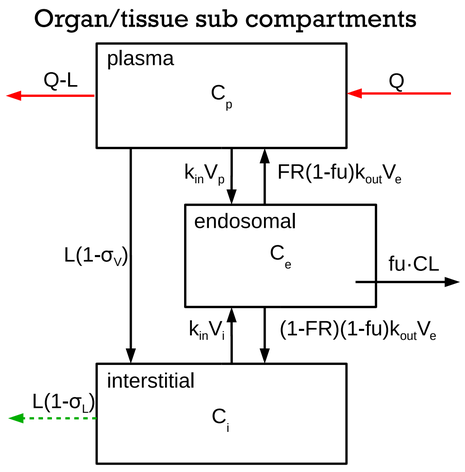
To derive a low-dimensional compartment model consistent with the knowledge present in the mechanistic PBPK model.

Methods

The plasma mice concentration data of endogenous IgG and mAb are issued from [1] and [2]. The mAb, 7E3, was administered intravenously at 8mg/Kg.

The PBPK model includes 11 organ/tissue compartments, plasma artery and plasma vein compartments. Organs/tissues and other spaces are interconnected by the plasma flows and the lymphatic system. Each organ/tissue is divided into vascular, endosomal and interstitial sub compartments as follows:





Competitive non linear binding to FcRn in the endosomal space

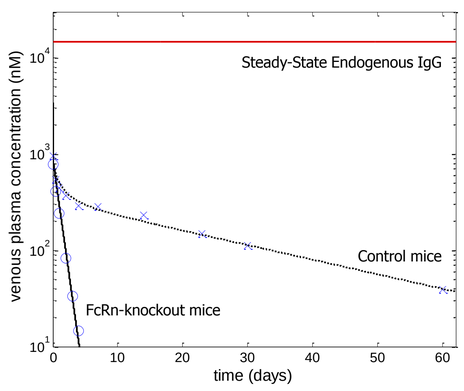
$$FcRn + mAb + IgG \overset{K_D}{\longleftrightarrow} FcRn\text{-}mAb + FcRn\text{-}IgG$$

•Modelling and simulations were performed in MATLAB R2010a.

Results

PBPK Modelling:

Figure I: Predictions from the PBPK model of venous plasma concentration time profiles in control and FcRn-knockout mice



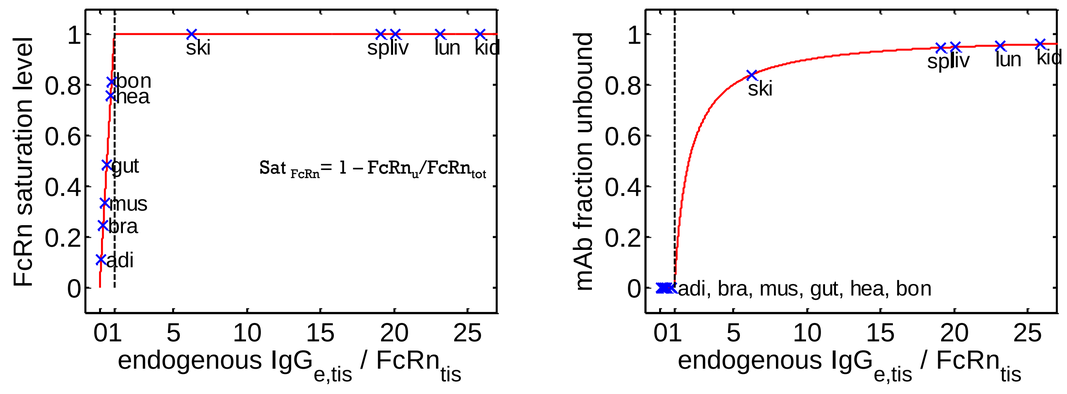
The PBPK model accurately describes the plasma concentration time profiles in control and FcRn-knockout mice.

The steady-state concentration level of endogenous IgG is 10 fold higher than the level of mAb in plasma and is not perturbed by mAb administration.

The saturation level of FcRn is therefore expected to be determined by only the concentrations of endogenous IgG.

Saturation level of FcRn and its impact on mAb clearance:

Figure II: FcRn saturation level (left) and fraction unbound of mAb (right) in each endosomal space



Assuming a quasi-steady state for FcRn yields

$$FcRn_u = \tfrac{1}{2}\,(FcRn_{tot} - IgG_{tot} - mAb_{tot} - K_D + sqrt[(FcRn_{tot} - IgG_{tot} - mAb_{tot} - K_D)^2 + 4K_D.FcRn_{tot})]$$

As in plasma and according to PBPK simulations, we expect mAb << IgG in the endosomal spaces. Assuming $FcRn_{tot}$ constant in each organ/tissue, the saturation level of FcRn only depends on IgG_{tot} (fig. II, left).

$IgG_{tot} \geq FcRn_{tot} \Rightarrow Sat_{FcRn} > 0.994$

$IgG_{tot} \leq 0.9\ FcRn_{tot} \Rightarrow Sat_{FcRn} \approx IgG_{tot}/FcRn_{tot}$

Consequently, FcRn is not fully saturated in all endosomal spaces.

Considering the same K_D for IgG and mAb, the fraction unbound of mAb in the endosomal space is given by $fu_{mAb} = K_D/(K_D+FcRn_u)$.

fu_{mAb} differs between the endosomal spaces (fig. II, right).

$IgG_{tot} \geq FcRn_{tot} \Rightarrow fu_{mAb} \approx 1\text{-}FcRn_{tot}/IgG_{tot}$

$IgG_{tot} \leq 0.9\ FcRn_{tot} \Rightarrow fu_{mAb} \leq 0.001$

According to the previous results and because IgG_{tot} concentration is not influenced by mAb administration, fu_{mAb} level is set by IgG_{tot} and remains constant over time, leading to a linear mAb clearance.

Lumping of the PBPK model of 7E3 in presence of endogenous IgG :

Figure III: Lumping steps

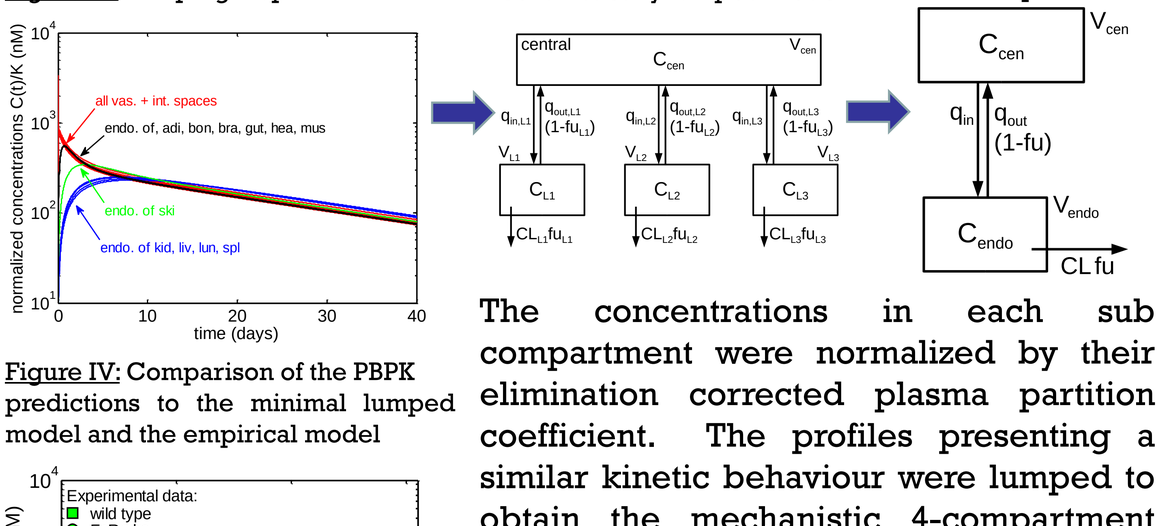
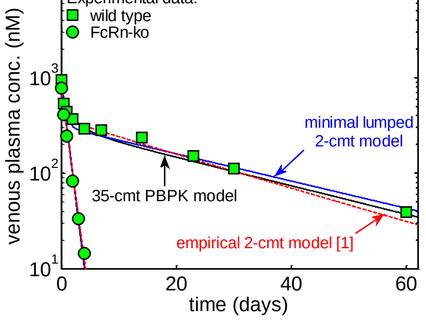


Figure IV: Comparison of the PBPK predictions to the minimal lumped model and the empirical model



The concentrations in each sub compartment were normalized by their elimination corrected plasma partition coefficient. The profiles presenting a similar kinetic behaviour were lumped to obtain the mechanistic 4-compartment lumped model. With the purpose to predict only plasma concentrations, all the endosomal spaces were lumped together to derive the 2-compartment minimal lumped model. This model provides a good fit compared to the full PBPK model and the existing empirical model [1].

Conclusions

- The saturation level of FcRn and the fraction unbound of mAb are set by the high steady-state concentrations of endogenous IgG. It results in a linear clearance of the mAb.
- For similar PK behaviours in plasma and interstitial compartments as well as in all endosomal spaces, the mechanistic 35-compartment PBPK model can be reduced to a minimal 2-compartment lumped model.
- These findings are a new step towards a standard for mAb modelling.

References

[1] Hansen et al. J Pharmaceutical Sc, Vol. 92, 1206–1215 (2003)

[2] Garg et al. J Pharmacokinetics Pharmacodynamics, Vol. 34, 687–707 (2007)