Relevance of IgG Binding to FcRn in PBPK Models of Therapeutic mAbs

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Introduction

Physiologically-based pharmacokinetic (PBPK) models represent a primary choice to support PK modelling of monoclonal antibodies (mAbs) because they allow one to integrate detailed mechanisms involved in the disposition of mAbs.

So far, existing PBPK models in mice are not fully satisfactory because they either do not take into account tissue data or the endogenous immunoglobulin type G (IgGendo) for model building and are highly sensitive to parameter estimates which indicates an over-parameterization of the model.

We developed a simplified PBPK model for mAb, in mice, in the absence of target which is consistent with the mechanistic understanding of FcRn-binding and accounts for available plasma data and tissue data including the correction for residual blood.

Objectives

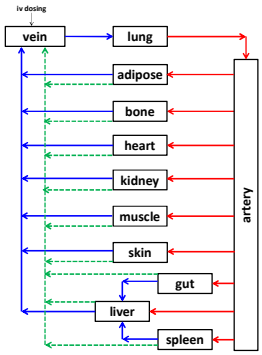
To understand the extent of the over-parameterization of the PBPK model by considering FcRn-binding in quasi-steady state.

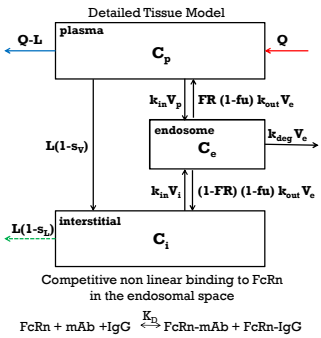
To derive a simplified Tissue model which implicitly consider endogenous IgG- and FcRn-model dependence to reliably perform the parameter estimation process.

Methods

The plasma concentration data of FcRn-knockout mice (KO) and wild type mice (WT) of endogenous IgG and mAb are issued from [1] and [2]. The mAb, 7E3, was administered intravenously at 8mg/kg.

The PBPK model includes 10 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:





•Modelling and simulations were performed in MATLAB R2010a.

Results

Insights into quasi-steady state approximation of FcRn-binding

We consider the following model of interaction between the unbound mAb (mAb_u) and unbound FcRn ($FcRn_u$) in the endosome:

$$mAb_u + FcRn_u \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} mAb_b, \quad mAb_u \xrightarrow{k_{deg}}, \quad mAb_b \xrightarrow{k_{out}}$$

Under a quasi-equilibrium assumption, the unbound concentration of the mAb is given by

$$mAb_u = \frac{K_D.mAb_b}{FcRn_{tot} - mAb_b}$$

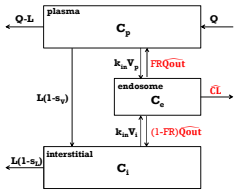
If the quasi steady state (QSS) is assumed, mAb_u is:

$$mAb_u = \frac{K_D.mAb_b}{FcRn_{eff} - mAb_b}, \text{ with } FcRn_{eff} = \frac{kon.FcRntot+kdeg}{kon}$$

The two expressions of mAb_u present the same algebraic form. Therefore, given only tissue data, it is not possible to discriminate between the two models when estimating parameters. This is reflected by comments in [2,3] reporting about difficulties in parameter estimation and high sensitivity of the PBPK model to parameters describing FcRn-binding.

Simplification of the Tissue Model

Figure I: Simplified tissue model



In a previous work we showed that the endosomal IgG level solely sets the saturation level of FcRn and therefore defines the linear clearance of mAbs. Hence, it is essential to consider its interaction with FcRn in the PBPK model.

Endogenous IgG and FcRn concentration are implicitly considered in the simplified tissue model by assuming fu constant and tissue-dependent.

As fu, Qout and CL are constant for a given tissue, we define:

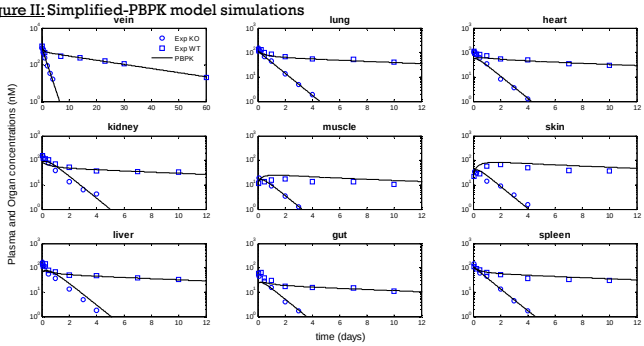
$\widehat{Qout}$ = (1-fu).Qout = (1-fu).kout.Ve

$\widehat{CL}$ = fu.CL = fu.ke.Ve

Given the new parameterization, 22 parameters were estimated, i.e. kin, identical for each tissue and $\widehat{Qout}$ and $\widehat{CL}$ for each of the 10 tissues.

Performance of the Simplified PBPK Model

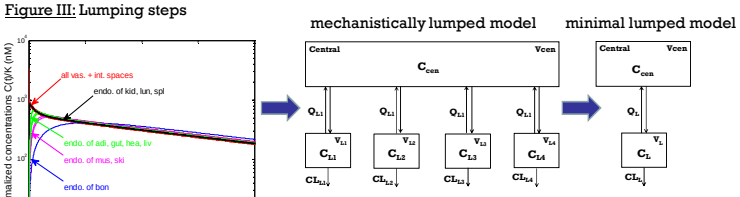
Figure II: Simplified-PBPK model simulations



The PBPK model accurately describes the venous plasma concentrations as well as tissue concentration time profiles in control and FcRn-knockout mice.

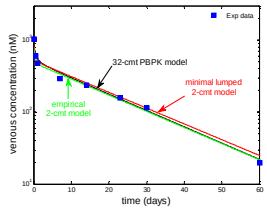
Lumping of the simplified PBPK Model of 7E3:

Figure III: Lumping steps



The concentrations in each sub compartment were normalized by their elimination corrected plasma partition coefficient. The spaces presenting similar kinetic behaviour and same mechanistic properties, i.e. eliminating spaces, were lumped to obtain the mechanistic 5-compartment lumped model. With the purpose to predict only venous plasma concentrations, all the endosomal spaces were lumped together to derive the 2-compartment minimal lumped model (MLM).

Figure IV: Comparison of the PBPK plasma predictions to the MLM and the empirical model



The venous plasma predictions from the MLM are in excellent agreement with the predictions from the full simplified PBPK model as well as the empirical model[1].

Conclusions

- The quasi-steady state approximations of FcRn-binding illustrate previous reports of the high sensitivity of PBPK models for mAbs to parameters involved in FcRn-binding including the total endosomal concentration of FcRn and its interaction with IgGendo.
- In order to circumvent parameter estimation problems, we derived a simplified PBPK model which implicitly considers the binding of IgGendo to FcRn and its implication in the linear clearance of mAbs.
- We applied the lumping strategy [4] to reduce the simplified 32-compartment PBPK model to a minimal 2-compartment lumped model.

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)
[3] Shah et al. J Pharmacokinetics Pharmacodynamics, Vol. 39, 67–86 (2012)
[4] Pilari et al. J Pharmacokinetics Pharmacodynamics, Vol. 37, 365–405 (2010)