

A semi-physiologic mathematical model describing pharmacokinetic profile of an IgG monoclonal antibody mAbX after IV and SC administration in human FcRn transgenic mice.



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OBJECTIVES

To characterize the observed PK profiles of mAbX after IV and SC administration in variants of human FcRn transgenic mice in a mathematical model incorporating physiological elements of FcRn salvage.

INTRODUCTION

Neonatal Fc receptors (FcRn) are crucial in protecting antibodies from degradation. Following endocytosis, the acidification of the endosome leads to strengthened antibody-FcRn binding by which the recycling of antibodies to the cell surface is enhanced. Consequently, studies have shown that inhibiting FcRn binding or knock-out of FcRn have dramatic effects on antibody pharmacokinetics. FcRn is expressed in many organs, but its quantitative contribution in protecting IgG from degradation remains unclear. The vascular endothelium was previously associated to the main site of IgG protection from degradation because of the large FcRn expression and results from some in vitro studies. Using transgenic mice that differentially express human FcRn in bone marrow derived antigen-presenting cells (APC) and/or somatic cells (SOM), the Roopenian group has demonstrated that both cell types are involved in the FcRn-mediated salvage process [1]. With a series of semi-mechanistic models, we explore the FcRn-mediated salvage of IgG following IV and SC administration of IgG.

RESULTS DATA EXPLORATION

From PK profiles (figure 1, table 1), one already discussed [1]:

- The presence of FcRn in either somatic cells (SOM) or bone marrow derived antigen presenting cells (APC) decreases the overall clearance in both IV and SC profiles. This observation suggests that SOM and APC play a similar role in mAbX FcRn recycling. All models presented here (figure 3) capture this behavior.
- The data suggest that APC and not SOM are involved in first pass process of mAbX. However the final model depends on both APC and SOM while it appears to describe the observed data well.

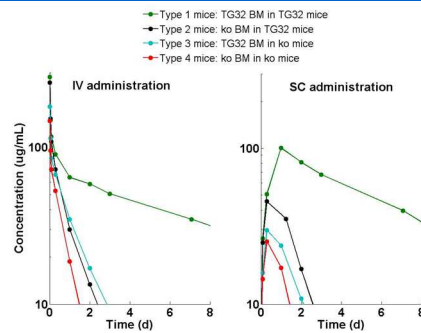


Figure 1: Observed Mean PK profile after IV (left) and SC (right) administration in 4 types of hFcRn transgenic mice

METHODS

In vivo experiments

Transgenic mice deficient of mouse FcRn and expressing human FcRn (hFcRn) were provided by Jackson Laboratory in Bar Harbor, Maine (USA) where also all in vivo PK studies were performed (presented at AAPS Annual Meeting in October 2012 [1]). In short, the PK of mAb X, a humanized IgG1 antibody, not cross reactive with the murine target, was investigated after administration of 10 mg/kg iv and sc administration. Mice expressing human FcRn either in somatic cells, in bone-marrow derived antigen presenting cells, in both cell types or none (4 groups, 8 animals per group and per route of administration) were prepared as described elsewhere for wild-type mice [2].

Modeling activity

A series of semi-mechanistic PK models (figure 3) derived from a general model (figure 2) were developed to reproduce observed PK data. Model parameters were simultaneously estimated for all type of mice and route of administration via population approach in MONOLIX® version 413 standalone LIXOFT S.A.S. As described elsewhere [6], "best" model is chosen according to system convergence (structural and parameter identifiability), fitting performance (Akaike criteria, comparison between observed AUC and predicted one), and diagnostic plots (Residuals and VPC not presented). Non compartmental analysis and graphical representations were performed under Matlab® environment.

		Type 1 mice: TG32 BM in TG32 mice	Type 2 mice: ko BM in TG32 mice	Type 3 mice: TG32 BM in ko mice	Type 4 mice: ko BM in ko mice
FcRn status	in APC	✓	X	✓	X
	in SOM	✓	✓	X	X
NCA analysis	AUC IV (ug.d.mL ⁻¹)	804	156	104	58.8
	Clearance (mL.d ⁻¹ .kg ⁻¹)	12.9	67.4	98.8	179
	AUC SC (ug.d.mL ⁻¹)	704	61.7	92.5	35.0
	Bioavailability (%)	87.6	39.5	89.2	59.5

Table 1: Observed mean PK parameters depending on FcRn status after IV and SC administration of mAbX

Conclusions (from table 1) already presented elsewhere [1]:

SOM and APC play a similar role in mAbX FcRn recycling
APC are involved into mAbX first pass process

RESULTS

MODEL STRUCTURE GENERAL MODEL

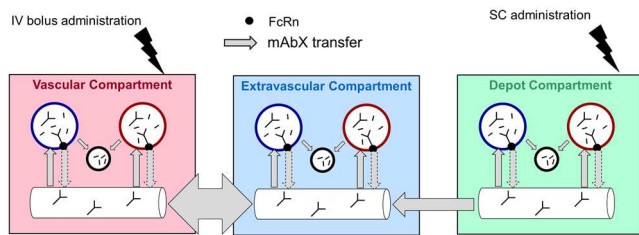


Figure 2: General model describing IgGX pharmacokinetic in mice. Blue, brown and black circle represent endosomes in SOM and APC and degraded material respectively. Recycling occurs only if FcRn is present (dashed arrow). Arrow size roughly represent proportions of parameters estimate.

General model construct (figure 2) describes all processes involving 20 parameters (20P) as follow:

- Compartmental structure: Volume of distribution in central compartment for each type of mice (4P).
 - Circulation in between compartments:
 - Extravasation from main circulation to extravascular compartment and vice versa (2P)
 - Absorption from depot compartment to Extravascular compartment (1P)
 - Circulation within compartments: endocytosis, re-circulation (if FcRn is present), and elimination (13P)
- Because of parameter identifiability limitations, elimination only occurs into lysosomes and at a unique rate.

RESULTS

MODEL STRUCTURE STRUCTURES DERIVED FROM GENERAL MODEL

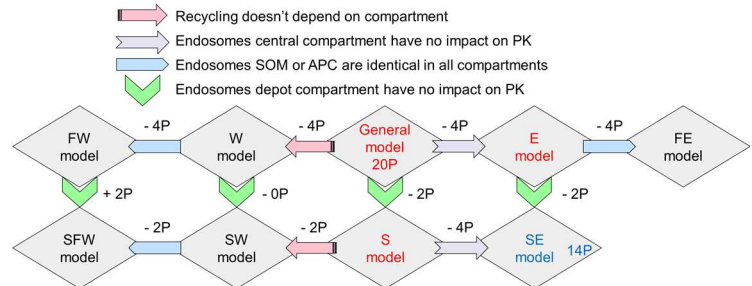


Figure 3: Flow chart to derive new structure from general model. Top-down oriented arrows assume mAbX distributing from depot to extravascular compartment and endosomes in that compartment. Models with poorly estimated parameters have parameters with residual standard error higher than 100%. The best model (SE) has the lowest values on the 3 selection criteria.

The SE model appears to be the "best" according to criteria presented in model selection section. Mechanistically, it suggests that:

- endosomes in the vascular compartment have no influence on PK.
- endosomes in the depot compartment have no influence on the absorption process and mAbX distributes from the depot compartment to the extravascular compartment and the endosomes in that compartment.

RESULTS

MODEL SELECTION

The models presented in figure 3 were compared according to following criteria:

- Poor estimation of parameters: a model is excluded when any fixed effect estimate has a residual standard error higher than 100% (models indicated in red color in figure 3 and 4).
- Goodness of fit: a model is favored when having low values in AUC difference, Akaike information criterion (AIC), and residual error. Evaluating the goodness of fit via AUC appeared to be important in checking that final model adequately reproduces observed profiles. The best model (SE model) has the lowest value on those criteria.

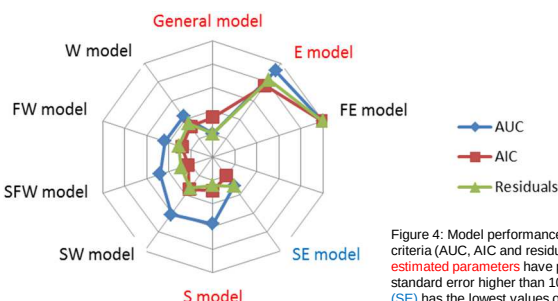


Figure 4: Model performance according to selected criteria (AUC, AIC and residuals). Models with poorly estimated parameters have parameters with residual standard error higher than 100%. The best model (SE) has the lowest values on the 3 selection criteria.

CONCLUSIONS

The contribution of both somatic and bone marrow derived cells in FcRn salvage from catabolism [3] is adequately described in the presented novel mathematical model, which reflects the various localizations of FcRn and associated salvage processes. It is an alternative to other models incorporating similar mechanism [4, 5, 6].

We find that the model part describing the SC absorption leaves some room for improvement, firstly for the goodness of fit and secondly as it seems not to capture fully the relative role of APC and SOM in this process.

All in all, by systematically investigating model variants and comparing them with objective criteria has allowed formulating new hypotheses on the differential role of APC and SOM in FcRn-mediated salvage. Furthermore, these insights may provide guidance to new experiments.

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