Research Article

Simplification of Complex Physiologically Based Pharmacokinetic Models of Monoclonal Antibodies

Mohamed Elmeliegy,¹ Philip Lowe,² and Wojciech Krzyzanski^{1,3}

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Abstract. Monoclonal antibodies (mAbs) exhibit biexponential profiles in plasma that are commonly described with a standard two-compartment model with elimination from the central compartment. These models adequately describe mAb plasma PK. However, these models ignore elimination from the peripheral compartment. This may lead to underestimation of the volume of distribution of the peripheral compartment and thus over-predicts concentration in the peripheral compartment. We developed a simple and physiologically relevant model that incorporates information on binding and dissociation rates between mAb and FcRn receptor, mAb uptake, reflection, and catabolic degradation. We employed a previously published PBPK model and, with assumptions regarding rates of processes controlling mAb disposition, reduced the complex PBPK model to a simpler circular model with central, peripheral, and lymph compartments specifying elimination from both central and peripheral. We successfully applied the model to describe the PK of an investigational mAb. Our model presents an improvement over standard two-compartmental models in predicting whole-body average tissue concentrations while adequately describing plasma PK with minimal complexity and physiologically more meaningful parameters.

KEY WORDS: compartmental models; monoclonal antibodies; PBPK.

INTRODUCTION

Monoclonal antibodies (mAbs) have become vital therapeutic modalities as anti-cancer, anti-inflammatory, or immune-modulatory agents (1,2). More than 26 mAbs are approved by the FDA and many antibody-based therapies are undergoing different phases of preclinical and clinical development (3). These molecules exhibit complex pharmacokinetic and pharmacodynamic properties which provide different challenges than those encountered with small molecules (4). Accurate description of these processes is crucial for both understanding drug disposition and for an efficient drug development process answering typical questions arising on the mechanisms of action through binding the intended target, especially in tissues.

Monoclonal antibodies display bi, or tri, phasic profile in plasma (5). A common and successful approach to describe

mAb concentrations in plasma is fitting classical compartmental models, *e.g.*, two-compartment model with linear or nonlinear elimination from the central compartment, to plasma or blood data (6). Fitting a two-compartmental model to plasma mAb PK data typically yields estimates of the volume of central compartment, V_C , of 2.4 to 5.5 L, close to that of plasma (6). This estimate is considered to be physiologically reasonable given the hydrophilic nature and large molecular size of mAbs which are expected to be distributed mainly in plasma. However, estimates of the volume of the peripheral compartment V_P are typically underestimated at 1.3 to 6.8 L (6), given the volume of interstitial space is 11.3 L for a 71 kg male (7). Underestimation of the volume of distribution at steady state (V_{SS}) of mAbs by classical models is explained, at least partially, by the fact that these models assume elimination from the central compartment only. This assumption is not adequate in the case of large molecules where V_P , not V_C , represents the main elimination site (8).

MABs are predominantly eliminated *via* proteolytic catabolism after transit and sorting through endosomes (4). During this process, mAbs are taken into the endosome *via* fluid-mediated endocytosis where they bind to the Fc receptor of the neonate (FcRn) (9). FcRn-unbound mAbs in the endosomes are destined for lysosomes, where they are degraded. Owing to the ubiquitous presence of endosomes and FcRn expression in the human body, primarily in

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¹Department of Pharmaceutical Sciences, School of Pharmacy & Pharmaceutical Sciences, University at Buffalo—State University of New York, 370 Kapoor Hall, Buffalo, New York 14214, USA.

²Novartis Pharma AG, Basel, Switzerland.

³To whom correspondence should be addressed. (e-mail: wk@buffalo.edu)

endothelial cells, elimination of mAbs can occur from either side of the endothelial cells, that is, from tissue interstitial spaces as well as from plasma. Thus, PK models that ignore elimination from peripheral compartments are simplistic and primarily designed to describe the PK in the central compartment. Further, classical models do not consider lymphatic circulation and uptake from endothelial space in peripheral tissues back to the vasculature (*i.e.* central compartment). Underestimation of V_p by the classical model leads to over predicting whole-body average peripheral tissue concentrations. This hinders the use of classical models in tissue target-mediated disposition models or predicting pharmacodynamic response to mAb based on *in vitro* estimates of binding affinities or effective concentrations in cellular assays.

A more mechanistic approach is the use of physiologically based PK (PBPK) models. Few PBPK models have been developed to integrate *in vitro* and *in vivo* data to describe mAb disposition in compartments such as the plasma, lymph node, as well as major peripheral organs (10). Models describing disposition in vascular, interstitial, and endosomal subcompartments of each organ were published (11–14). These models provide a useful tool to predict tissue concentrations, understand mAbs disposition in different compartments, and for extrapolation or prediction. However, these models are characterized by large number of parameters and differential equations. The high complexity and dimensionality of PBPK may exceed the capabilities of some simulation software and certainly take far longer to write and explain to team members. Finally, the large number of parameters makes PBPK models less suitable for estimation of individual parameters in a population analysis of clinical trial data.

An intermediate approach that reflects the physiological processes of mAb binding, transfer, and elimination in a simple compartmental model can be helpful. For example, Cao *et al.* proposed a general minimal PBPK model that incorporates physiological and anatomical information (15) and recently extended this approach to mAbs (16). In the current work, a previously published PBPK model (13) has been employed with several simplifying physiological assumptions regarding mAb disposition. The simplified physiological model was applied to describe the PK of an illustrative mAb in a patient cohort using the population approach and compared with a classical two-compartment model.

MATERIALS AND METHODS

Overall Simplification Methodology

Simplification of the full PBPK model was conducted *via* several broad classes of assumptions which fall under one of the following broad classes:

- Comparing the time scale of a process relative to others (*e.g.* fast transfer from one compartment to another, one organ to another, or fast receptor binding/dissociation). Both physiological and numerical factors were considered in each assumption.
- Similarity of transfer rates of mAb/IgG between body organs, within a predefined range, to allow lumping of body organs.

- Assumptions to rearrange inter-compartmental transfer rates, reduce model dimensions, and improve identifiability. These assumptions considered the numerical similarity of transfer rates as well as the direction of each process. This allowed for grouping of several processes in one term.

In each of the seven steps described below, assumptions are applied to the differential equations and a new set of differential equations was derived (Appendices 1–9). Simulations from each intermediate step were performed and plasma profile was used to compare the effects of each simplification step.

Full PBPK Model

We applied a previously published PBPK model that describes mAb PK in plasma, lymph, and body tissues (13). Transfer of mAbs is mediated *via* plasma and lymphatic flow (Fig. 1a, b). Each tissue was divided into three subcompartments (vascular, endosomal, and interstitial spaces). The endosomal space was described as a series of transit compartments with different pH levels. Following mAb uptake from vascular and interstitial spaces to the initial endosomal subcompartment, mAb is transferred through endosomal subcompartments with the same transit time, τ which was calculated as:

$$\tau = \frac{\text{Total endosomal transit time}}{N_{\text{Transit}}} \quad (1)$$

where N_{Transit} is the number of transit events. In the initial endosomal subcompartment (pH 7.4), negligible binding is assumed (k_{on} and k_{off} are set to 0). Through the intermediate and terminal subendosomal compartments, pH decreases and thus binding affinity increases. In the terminal compartment, FcRn-bound mAb is recycled to vascular and interstitial compartments while unbound mAb is degraded *via* proteolytic clearance (13). Endogenous IgG and mAb compete for FcRn binding and were assumed to have the same FcRn binding affinity.

Convective movement from vascular to interstitial space and from interstitial space back to the circulation were represented using vascular and lymph reflection coefficients (σ_{VAS} and σ_{LY} , respectively). Interstitial fluid from all organs was drained by the lymphatic circulation and collected in the lymph node compartment. A fraction of the mAb collected in the lymph node (F_{return}) was returned to the systemic circulation with a transit time (τ_{LN}).

The physiological values for plasma flow rate, vascular, interstitial, and total tissue volume were obtained from the literature (10). Other model-specific parameters such as tissue-specific FcRn expression, tissue endosomal volume, uptake rate of mAb from vascular to endosomal compartments, reflection coefficients, and binding/dissociation rate constants were obtained from the original model (13). The fraction of FcRn-bound IgG recycling to the vascular compartment was obtained from (11). Parameters and variables used in the full model and the simplification steps are defined in Table I. Model equations were written for the amounts of mAb or endogenous IgG (Appendix 1). Rate constants were obtained by dividing clearances by the volume

Fig. 1. a Schematic representation of the PBPK model of mAb disposition. Plasma flow is represented by solid arrows and lymph flow by dashed arrows. Organs are shaded in groups to demonstrate the lumping and/or fast transfer assumption applied. Heart, kidney, skin, and muscle are lumped in one compartment. GIT and spleen are lumped in one compartment. Fast transfer assumption was applied from liver to lung, from lung to plasma, and from lymph node to plasma (red arrows). **b** Intra-tissue compartmental model. Each tissue is divided into vascular, endosomal, and interstitial spaces. The endosomal space is subdivided into five compartments with pH ranging from 7.4 to 6.0, to represent gradual acidification of endosomes

of the appropriate compartment. The volume of each endosomal subcompartment (V_{END}^{Organ}) was calculated as:

$$V_{END}^{Organ} = \frac{V_{Total\ END}^{Organ}}{N_{END\ comp.}} \quad (2)$$

where $V_{Total\ END}^{Organ}$ is the volume of the endosomal compartment obtained from (13), and $N_{END\ comp.}$ is the number of endosomal subcompartments per organ (i.e., 5).

In this study, initial FcRn concentration in each tissue was used as a model parameter (R_{total}) and the free receptor is calculated as the difference between R_{total} and FcRn-bound mAb and endogenous IgG complexes. The dose used for simulations was 8 mg/kg assuming a 25-g mouse. The

initial condition for mAb in the plasma compartment was the dose. For all other mAb compartments, the initial condition was set to 0. Endogenous IgG plasma amounts were fixed to 5.8 nmol (determined *via* enzyme-linked immune-sorbent assay (ELISA) in (13)) and steady state values were obtained by simulations of IgG levels for 200 days and used as initial conditions.

In the original publication, the authors estimated two coefficients (F_1 and F_2) to reflect the non-FcRn dependent tissue uptake of mAb (e.g., surface charge) which was not explained by the model (13). In our study, simulations were performed without these coefficients to be able to compare the effects of different simplification assumptions on processes explained by the model. The impact of removing F_1 and F_2 on mAb plasma PK is displayed in Supplementary Fig. 1.

Rapid Binding and Fast Endosomal Transfer (Step 1) (Appendix 2)

In order to simplify the subendosomal compartments, several assumptions were made. First, we assumed that the rate of inter-endosomal compartment transfer rate ($1/\tau$) is faster than other processes such as the uptake process to the endosome and FcRn binding (17). Thus, input from vascular and interstitial compartments in the initial endosomal compartment was rapidly transferred to the terminal compartment (Appendix 9). This assumption holds true for earlier compartments where FcRn binding is considered negligible (in the first endosomal subcompartment) or low (in intermediate compartments). As the drug transfers to later compartments, rate of binding increases. Thus, rapid equilibrium between the binding and dissociation is assumed in the terminal compartment where the majority of FcRn binding occurs (18). This allowed the equations for the complex to be solved in terms of the free drug and the total FcRn receptor. Simulations from the full PBPK model supported the following assumptions: free mAb/IgG amounts ($A_{END}^{Organ-5}$) was 4,000- to 6,000-fold lower than the equilibrium dissociation constant, KD_{END} , in the terminal subendosomal compartment (Supplementary Figures 2 and 3), and that the total mAb in the terminal compartment was in equilibrium (Supplementary Figure 4). This allowed solving the complex in compartment 5 ($ARCPX_{Organ-5}^j$), which was recycled to vascular and interstitial compartments, as a function of the free amounts in vascular and interstitial compartments. This solution was then used to substitute $ARCPX_{Organ-5}^j$ in differential equations for the vascular and interstitial compartments. Model equations to reflect the simplified model are provided in Appendix 3 (Fig. 2).

Lumping Tissues with Similar Transfer Rate Constants (Step 2) (Appendix 4)

In this step, rate constants governing the transfer of species in tissues sharing similar anatomical locations within the full model were compared. Processes within 20-fold difference between tissues were assumed to be kinetically similar. Thus, these tissues can be explicitly lumped. Median of the rate constants for the original tissues was used to

Table I. Glossary for Parameters and Variables

Parameter/variable (unit)	Definition	References/remarks
Full PBPK model		
- Parameters		
K_0 (M/h)	Endogenous IgG production rate	(13)
Q_{organ} (L/h)	Plasma Flow rate to each organ	(10)
L_{organ} (L/h)	Lymphatic Flow rate to each organ	(10)
$CL_{\text{Uptake}}^{\text{Organ}}$ (L/h)	Endosomal uptake rate of unbound antibody	(13)
$CL_{\text{Proteolysis}}^{\text{Organ}}$ (L/h)	Clearance rate of unbound antibody <i>via</i> proteolytic degradation in the endosome	Same value for $CL_{\text{Uptake}}^{\text{Organ}}$
$k_{\text{on-X}}$ ($\text{M}^{-1} \text{h}^{-1}$)	mAb-FcRn association constant in each subendosomal compartment X	(13) Assumed similar for IgG and mAb
$k_{\text{off-X}}$ (h^{-1})	mAb-FcRn dissociation constant in each subendosomal compartment X	(13) Assumed similar for IgG and mAb
KA (M) ⁻¹	Equilibrium binding association affinity	$KA = \frac{k_{\text{on}}}{k_{\text{off}}}$
$R_{\text{totalOrgan-X}}$ (moles)	Initial amount of free FcRn receptor in subendosomal compartment X	obtained by multiplying FcRn concentration reported in (13) by $V_{\text{END}}^{\text{Organ}}$
F_{return} (no units)	Fraction of antibody returning from lymph node to plasma	$= 0.28 + 0.72 * \left(\frac{KA}{KA + 650000} \right)$ (13)
τ (h)	Transit time between endosomal compartments	(13) (0.045)
τ_{uLN} (h)	Transit time from lymph node to plasma	(13) (9.1)
σ_{VAS} (no unit)	Vascular reflection coefficient	Same for all organs (0.95) (11)
σ_{LY} (no unit)	Lymph reflection coefficient	Same for all organs (0.2)
FR (no unit)	Recycling fraction of the bound antibody from endosomal to vascular and interstitial subcompartments	(11) (0.715)
$V_{\text{VAS}}^{\text{Organ}}$ (L)	Volume of vascular compartment in each organ	(11)
$V_{\text{ISF}}^{\text{Organ}}$ (L)	Volume of interstitial compartment in each organ	(11)
$V_{\text{END}}^{\text{Organ}}$ (L)	Volume of each endosomal subcompartment in each organ	(11)
V_{Plasma} (L)	Volume of plasma	(11)
- Variables		
$A_{\text{Plasma}}^{\text{J}}$ (moles)	Amount of endogenous IgG or mAb in plasma	
A_{LN}^{J} (moles)	Amount of endogenous IgG or mAb in lymph node	
$A_{\text{VAS}}^{\text{J}}$ (moles)	Amount of endogenous IgG or mAb in vascular space	
$A_{\text{ISF}}^{\text{J}}$ (moles)	Amount of endogenous IgG or mAb in interstitial space	
$A_{\text{END}}^{\text{J}}$ (moles)	Amount of endogenous IgG or mAb in subendosomal compartment X	
$ARCPX_{\text{Organ-X}}^{\text{J}}$ (moles)	Amount of endogenous IgG-FcRn or mAb-FcRn receptor complex in subendosomal compartment X	
Step 1 (Fig. 2)		
- Parameters		
$k_{\text{VAS-circul.}}^{\text{Organ}}$ (h^{-1})	Transfer rate from vascular compartment to lung or, in case of lung, from lung to plasma	$\frac{Q_{\text{Organ}} - L_{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}}$
$k_{\text{circul.-VAS}}^{\text{Organ}}$ (h^{-1})	Transfer rate from plasma to vascular compartment	$\frac{Q_{\text{Organ}}}{V_{\text{Plasma}}}$
$(1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Organ}}$ (h^{-1})	Transfer from vascular to interstitial compartment <i>via</i> lymphatic flow	$(1 - \sigma_{\text{VAS}}) \times \frac{L_{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}}$
$k_{\text{VAS-EL}}^{\text{Organ}}$ (h^{-1})	Elimination from vascular compartment	$\frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}}$
$k_{\text{VAS-VAS}}^{\text{Organ}}$ (h^{-1})	Input from vascular compartment to itself. Reflect endosomal contribution to vascular compartment	$\frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times k_1$
$k_{\text{VAS-ISF}}^{\text{Organ}}$ (h^{-1})	Transfer from vascular to interstitial compartment	$(1 - FR) \times \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times k_1$
$k_{\text{ISF-VAS}}^{\text{Organ}}$ (h^{-1})	Transfer from interstitial to vascular compartment	$FR \times \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times k_2$
$(1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Organ}}$ (h^{-1})	Transfer from interstitial compartment to lymph node <i>via</i> lymphatic flow	$(1 - \sigma_{\text{LY}}) \times \frac{L_{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}}$
$k_{\text{ISF-EL}}^{\text{Organ}}$ (h^{-1})	Elimination from interstitial compartment	$\frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}}$

Table I. (continued)

Parameter/variable (unit)	Definition	References/remarks
$k_{\text{ISF-ISF}}^{\text{Organ}} (\text{h}^{-1})$	Input from interstitial compartment to itself. Reflect endosomal contribution to interstitial compartment	$\frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2$
KD_{END} (moles)	Equilibrium dissociation constant for mAb binding to FcRn receptor in amounts	$\frac{k_{\text{off}}}{k_{\text{on}}}$ $V_{\text{Organ}}^{\text{END}}$
K_0 (M/h)	Endogenous IgG production rate	(13)
- Variables		
$A_{\text{END Total Organ-X}}^{\text{I}}$ (moles)	Total amount of endogenous IgG or mAb (bound and free) in subendosomal compartment X	
Steps 2 and 3 (Fig. 3a and b)		
- Parameters		
Q_{Visceral} (L/h)	plasma Flow rate to the visceral compartment	$Q_{\text{Heart}} + Q_{\text{Kidney}} + Q_{\text{Skin}} + Q_{\text{Muscle}}$
$Q_{\text{Splanchnic}}$ (L/h)	plasma Flow rate to the splanchnic compartment	$Q_{\text{GIT}} + Q_{\text{Spleen}}$
L_{Visceral} (L/h)	Lymph Flow rate to the visceral compartment	$L_{\text{Heart}} + L_{\text{Kidney}} + L_{\text{Skin}} + L_{\text{Muscle}}$
$L_{\text{Splanchnic}}$ (L/h)	Lymph Flow rate to the splanchnic compartment	$L_{\text{GIT}} + L_{\text{Spleen}}$
- New compartments resulting from model simplification		
<i>Splanchnic</i>	GIT and spleen	
<i>Visceral</i>	Heart, kidney, skin, and muscle lumped	
Steps 4, and 5 (Fig. 3c and d)		
- Parameters		
$Q_{\text{Peripheral}}$ (L/h)	Plasma Flow rate to the Peripheral compartment	$Q_{\text{Visceral}} + Q_{\text{Splanchnic}}$
$L_{\text{Peripheral}}$ (L/h)	Lymph Flow rate to the Peripheral compartment	$L_{\text{Visceral}} + L_{\text{Splanchnic}}$
- New compartments resulting from lumping		
<i>Peripheral</i>	Visceral and splanchnic	
Step 6 (Fig. 3e)		
- Parameters		
$k_{\text{EL}}^{\text{Central}} (\text{h}^{-1})$	Elimination rate from the central compartment	
$(1-\sigma_{\text{VAS}}) \times k_{\text{LY Central-Per}}^{\text{Central}} (\text{h}^{-1})$	Transfer rate from the central to interstitial (<i>i.e.</i> , peripheral) compartment <i>via</i> lymphatic flow	
$k_{\text{Central}}^{\text{Central}} (\text{h}^{-1})$	First-order input from central compartment to itself which reflects the impact of recycled drug from endosomal compartment	
$k_{\text{Central-ISF}}^{\text{Central}} (\text{h}^{-1})$	First-order input from central to interstitial (<i>i.e.</i> , peripheral) compartment	
$k_{\text{ISF-Central}}^{\text{Peripheral}} (\text{h}^{-1})$	Transfer from interstitial (<i>i.e.</i> , peripheral) to central compartments	
$(1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Peripheral}} (\text{h}^{-1})$	Transfer from interstitial (<i>i.e.</i> , peripheral) compartment to lymph node <i>via</i> lymphatic flow	
$k_{\text{ISF-ISF}}^{\text{Peripheral}} (\text{h}^{-1})$	Input from Peripheral compartment to itself. Reflect endosomal contribution to interstitial compartment	
$\frac{1}{\tau_{\text{AuLN}}} (\text{h}^{-1})$	Transfer from lymph node to Central compartment	
Variables		
A_{Central} (moles)	Amount of mAb in the central compartment (<i>i.e.</i> , plasma and Vascular subcompartments in equilibrium)	
$A_{\text{Peripheral}}$ (moles)	Amount of mAb in the Peripheral compartment	
Step 7 (Fig. 3f)		
- Parameters		
$k_{\text{EL}}^{\text{C}} (\text{h}^{-1})$	Elimination rate from the central compartment after subtracting the contribution of the endosomal compartment	
$k_{\text{EL}}^{\text{P}} (\text{h}^{-1})$	Elimination rate from the peripheral compartment after subtracting the contribution of the endosomal compartment	
$k_{\text{Cen-Per}} (\text{h}^{-1})$	Reflection of the fraction mAb-FcRn complex recycled	
$(1-\sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} (\text{h}^{-1})$	Transfer of the mAb from Central to Peripheral compartments <i>via</i> lymphatic flow	
$k_{\text{CP}} (\text{h}^{-1})$	Transfer of the mAb from Central to Peripheral compartments <i>via</i> two processes, a- the lymphatic flow and b- the reflection of the fraction mAb-FcRn complex recycled	$(1-\sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} + k_{\text{Central-ISF}}^{\text{Central}}$
$(1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Peripheral}} (\text{h}^{-1})$	Transfer from interstitial (<i>i.e.</i> , peripheral) compartment to lymph node <i>via</i> lymphatic flow	
$\frac{1}{\tau_{\text{AuLN}}} (\text{h}^{-1})$	Transfer from lymph node to Central compartment	

Table I. (continued)

Parameter/variable (unit)	Definition	References/remarks
Final simplified model (Fig. 4)		
- Parameters		
V_C (L)	Volume of the Central Compartment	
k_{EL} (h^{-1})	Elimination rate from the central and peripheral compartments	
k_{CP} (h^{-1})	Transfer of the mAb from Central to Peripheral compartments <i>via</i> two processes, a- the lymphatic flow and b- the reflection of the fraction mAb-FcRn complex recycled	$(1 - \sigma_{VAS}) * k_{LY-ISF}^{Central} + k_{Central-ISF}^{Central}$
k_{LN} (h^{-1})	Transfer from interstitial (<i>i.e.</i> , peripheral) compartment to lymph node <i>via</i> lymphatic flow and Transfer from lymph node to Central compartment	

describe the lumped compartment. Two groups of tissues were distinguished. First, the gastrointestinal tract (GIT) and spleen can be lumped into a “splanchnic” compartment which feeds into the liver *via* entero-hepatic circulation. The second group is the heart, kidney, skin, and muscle that can be lumped into a “Peripheral” compartment. Rate constants governing transfer of species in GIT and spleen, and that for heart, kidney, skin, and muscle are provided in Supplementary Tables 1 and 2, respectively (Fig. 3a).

Fast Transfer from Liver to Lung (Step 3) (Appendix 5)

In this step, fast transfer from liver vascular compartment to lung was assumed. Thus, amount in the liver compartment was neglected and input into the liver was introduced to the lung compartment. Input into the liver, which comes from two processes namely the entero-hepatic circulation and systemic circulation, were introduced into the following sequential compartment, *i.e.*, lung. In this case, direct input from the plasma was introduced to the lung *via* a first-order rate constant $\left(\frac{Q_{Liver}}{V_{Plasma}}\right)$ (Fig. 3b).

Lumping Splanchnic and Visceral Compartments into a Peripheral Compartment (Step 4) (Appendix 6)

Similar to Step 2, rate constants governing the transfer of species in splanchnic and visceral compartments were compared (Supplementary Table 3) (Fig. 3c).

Fast Transfer from Lung to Plasma (Step 5) (Appendix 7)

In this step, fast transfer from lung to plasma was assumed. Thus, the amount in the lung compartment was neglected and input into the lung was introduced to the plasma compartment. Input into the lung, which comes from two processes, namely the venous return and the remaining input to the liver compartment, were introduced into the following sequential compartment, *i.e.*, plasma. In this case, the remaining input to liver compartment from plasma will cancel out in the plasma equation (Fig. 3d).

Rapid Equilibrium Between Plasma and Vascular Compartments to Form Central Compartment (Step 6) (Appendix 8)

In this step, we assume that the rate of transfer from plasma to vascular compartment $\left(\frac{Q_{Peripheral}}{V_{Plasma}}\right)$ was of the same order as transfer rate from the vascular compartment back to plasma ($K_{VAS-circul.}^{Peripheral}$) while both rates are faster than vascular-interstitial transfer rates. Further, we assume that the vascular compartment is in rapid equilibrium such that the rate of change is negligible. Further, these two rates were considered faster than rates governing transfer between vascular and that the vascular compartment is in rapid equilibrium (*i.e.*, $\frac{dA_{VAS-Peripheral}}{dt} = 0$) (Supplementary Table 3) (Fig. 3e).

Rearrangement of Inter-Compartmental Transfer Rates (Step 7) (Appendix 8)

Further reduction in model dimensionality and number of parameters was achieved by regrouping the rates of inter-compartmental transfer processes that act in similar or opposite directions. The following regrouping was considered: (a) recycling of mAb from endosomal back to central compartment ($k_{Central}^{Central}$) acted in opposite direction and slower magnitude compared with the elimination from the central compartment, $k_{EL}^{Central}$ (see Supplementary Table 4). Thus, $k_{Central}^{Central}$ was subtracted from $k_{EL}^{Central}$ yielding a slower elimination rate, k_{EL}^C . (b) Similar consideration was applied to the peripheral compartment, (c). transfer from central to peripheral compartments *via* lymphatic flow and the reflection of the fraction mAb-FcRn complex recycled are combined into one term that describes the sum of the 2 processes. Finally, the rate of return of mAb to the lymph node *via* lymphatic flow was considered faster than the reflection of the fraction mAb-FcRn complex recycled ($k_{ISF-Central}^{Peripheral}$) (Fig. 3f).

Identifiability Assumptions

To be able to identify the simple physiological model and estimate model parameters with appropriate precision from biexponential plasma profile, the following

Fig. 2. Intra-tissue compartments after simplification with rapid binding and fast transfer between endosomal compartments. Contribution of endosomal compartment to vascular and interstitial compartments is represented by first order rate inputs ($k_{VAS-VAS}$) and ($k_{ISF-ISF}$). The self-input to vascular and interstitial compartments is a reflection of the input to the first endosomal compartment, rapid binding to FcRn, fast endosomal transit, and recycle of the mAb-FcRn complex from the terminal endosomal compartment. Elimination at this stage is assumed to occur from vascular and interstitial compartments (k_{VAS-EL}) and (k_{ISF-EL})

assumptions were made: (a) rate of return from peripheral compartment to lymph node was proportional to rate of return from lymph node to central compartment, and (b) rates of elimination from both peripheral and central compartments were similar, yielding one elimination rate from both compartments, k_{EL} . One rate constant, k_{C-P} was used to describe the sum of two processes: transfer from central to peripheral compartments was estimated as the sum of two processes, *i.e.*, convection *via* lymphatic flow, $(1 - \sigma_V) \times k_{LY\ Cen-Per}$, and reflection of the fraction of mAb-FcRn complex that recycles to the peripheral compartment, $k_{Cen-Per}$. This model was then used to describe population PK of mAb in patients (Fig. 4).

Non-Compartmental and Population Pharmacokinetic Analysis of mAb in Patients

In a phase I study, an investigational mAb was administered at doses of 0.3, 1, 3, and 10 mg/kg as IV infusion at days 1 and 14. Plasma samples ($n=594$) were obtained from 25 patients (5 to 6 patients/dose level) and analyzed for mAb concentrations using ELISA. The clinical protocols were approved by Institutional Review Boards and informed consent was obtained from every patient prior to enrollment. Non-compartmental analysis was conducted to test for linear

Fig. 3. Schematic representation of simplification steps. **a** (Step 2), lumping GIT and spleen to splanchnic and lumping heart, kidney, skin, and muscle to visceral. **b** (Step 3), fast transfer from liver to lung. **c** (Step 4), lumping splanchnic and visceral to Peripheral. **d** (Step 5), fast transfer from lung to plasma, intra-tissue compartments are shown. **e** (Step 6), equilibrium between plasma and Vascular compartments forming a Central compartment. **f** (Step 7) final simplified model

Fig. 4. Final identifiable model for estimation of population PK parameters. Four parameters will be estimated k_{EL} , k_{LN} , k_{C-P} and V_C

PK. Two models were used to fit the data: (a) a standard two-compartmental model with linear elimination from the central compartment, and (b) our simplified physiological model. The model fittings and simulations were performed by nonlinear mixed effect modeling using Phoenix Version 6.4 (Pharsight, St. Louis, MO). An exponential model was used to describe the inter-individual variability (IIV) in PK parameters. Proportional and combined additive and proportional residual error models were tested. Full covariance matrix for the IIV was estimated. All estimations were carried out using the quasi-random parametric expectation maximization option (QRPEM).

RESULTS AND DISCUSSION

Simulations from Full PBPK Model Reveal Contribution of Different of Compartments to mAb Disposition

Simulations using an adapted PBPK model (13) were performed (Supplementary Figure 3). A biexponential profile in plasma was observed. Non-compartmental analysis revealed a half-life of 25.9 days consistent with typical mAb PK. The lymph node contributed highly to the mass of mAb in the body which highlights the importance of the lymph node as a transit compartment where mAb is collected from peripheral tissues. Tissue PK profiles were consistent with the observed data reported in (11). Peripheral tissues concentrations were lower than plasma concentration.

Amounts in the interstitial spaces of individual tissues were ~100-fold lower than that in plasma reflecting a slow and inefficient transfer of mAb from plasma to peripheral tissues. The amount of mAb in the vascular compartment was higher than that in the interstitial compartment. Concentrations in the vascular compartments of all tissues rapidly equilibrated with plasma concentrations (Supplementary Figure 3).

Formation of FcRn-mAb complex was higher in the terminal compared to intermediate subendosomal compartments while free mAb disposition was similar in the first four subendosomal subcompartments and dropped 10-fold in the terminal compartment where high degree of binding to FcRn and proteolytic elimination of the free mAb occurs. It is

worth mentioning that the contribution of the endosomal compartment as a whole to the amounts of mAb was negligible relative to that of interstitial and vascular compartments (Supplementary Figure 2 and 3).

Rapid Binding and Fast Endosomal Transfer Assumptions Simplifies Intra-Tissue Compartment Model

Applying fast endosomal transfer, rapid binding, and negligible free endosomal mAb amounts compared to KD_{END} , allowed reduction of the PBPK model by eliminating the endosomal compartment (Appendices 2 and 3) (Fig. 2). Contribution of endosomal compartment to vascular and interstitial compartments was represented by first-order rate input from vascular compartment to itself ($k_{VAS-VAS}$) and from interstitial compartment to itself ($k_{ISF-ISF}$). In contrast to classical models which assume elimination from the central compartment only, elimination was assumed to occur from vascular and interstitial compartments accurately reflecting the physiology of mAb elimination. The rate of elimination from vascular and interstitial compartments (k_{VAS-EL}) and (k_{ISF-EL}), is within two- to three-fold of each other. Transfer from the vascular to the interstitial compartment is governed by two processes namely, the convective movement via lymphatic flow, and the reflection of the fraction mAb-FcRn complex recycled ($k_{VAS-ISF}$) and ($k_{ISF-VAS}$), with the former process being ~4,000-fold faster than the latter (Supplementary Tables 2–4). Simulations from the reduced model showed similar plasma profiles to full PBPK model (Fig. 5).

PBPK Tissues Lumped into Two Compartments (Splanchnic and Visceral) (Appendix 4)

A common conundrum in tissue lumping in PBPK is how close time constants of a certain group of tissues should be to be considered for lumping. Nestorov *et al.* emphasized that no universal rule can be applied for PK equivalence since each case should be considered separately. In our case, most transfer rates compared were within two- to three-fold difference with the exception of the transfer rate from the interstitial compartment to the LN which is 12- and 19-fold higher for heart than skin and muscle (Supplementary Tables 1–2). This reflects physiological differences in structural properties of skin and muscle tissues which possess continuous capillary structure with an uninterrupted lining rich in tight junctions. Further, pore size of lymphatic vessels is likely smaller in skin and muscle compared to highly perfused organs such as heart and kidney (19). However, the relatively high concentrations observed in skin, as reported in (11) and supported by simulations from the full PBPK model (Supplementary Figure 5), reflects some model insensitivity for these two parameters and the difficulty of identifying distinct set of tissues with significantly different concentration profiles compared to others. Consequently, we decided to lump the skin and muscle to the rest of the tissues to provide a whole-body average tissue concentration. This approach is different from that of Cao *et al.* where body tissues were categorized according to their endothelial vessel structure into leaky (e.g., spleen and liver) and tight (e.g., skin and muscle) (16). The model proposed by Cat *et al.* assumes a tri-phasic distribution which might not be distinguished from the commonly observed biexponential plasma profile for mAbs.

Fig. 5. Simulations comparing the effect of consecutive simplifying assumptions on plasma concentrations. Concentrations are shown on linear scale. For Steps 6 and 7, amount of drug in plasma is calculated as a proportion of the drug in the central (*i.e.*, vascular and plasma) compartments

Thus, GIT and spleen were explicitly lumped into a single compartment (splanchnic) which feeds into the liver *via* entero-hepatic circulation. Heart, kidney, skin, and muscle were lumped into another compartment (visceral). This step can be modified to express the concentration in a certain tissue of interest. For example, if the purpose of the study is to determine mAb disposition in the muscle, other organs (*i.e.*, heart, kidney, and skin) can be lumped while muscle remains as distinct compartment. This will result in additional compartment and thus data from the tissue of interest is needed to resolve the additional complexity from additional parameters incorporated in the model. Simulations from the reduced model showed slight deviation from the full model (98% AUC agreement with full PBPK) (Fig. 5).

Fast Transfer from Liver Shows Minimal Impact on Plasma Profile (Appendix 5)

Nestorov *et al.*, showed that for PBPK models where tissue disposition is governed *via* simple processes such as tissue to plasma partition coefficient, ratios of the Laplace transforms of the input and output transfer functions can be used to obtain the equivalent transfer function for the lumped compartment (20). This transfer function can be expressed as the sum or the product of the Laplace transform for the individual tissues arranged in parallel or series, respectively. However, with the complexity of the current mAb PBPK that exhibits nonlinear binding behavior and more than eight different processes controlling mAb tissue disposition, derivation of Laplace transforms is not feasible. Thus, to bypass lumping of tissues arranged in series, the rate of transfer from the liver to lung ($k_{VAS-circul.}^{Liver}$) was assumed to be faster than the input rate to the liver ($\frac{Q_{Liver}}{V_{Plasma}}$). Numerical evaluation showed that (k_{VAS-

Fig. 5) since all input to the liver was added to the next serially located compartment in the model (*i.e.* lung) and thus, negligible amount of drug is lost from the system. The slight increase in plasma PK can be attributed to the loss of liver space (volume) from the model.

Lumping Splanchnic and Visceral to Peripheral Compartment (Appendix 6)

Similar to Step 2, transfer rates in splanchnic and visceral compartments were found to be within three-fold difference (Supplementary Table 3) and thus they were lumped into a single compartment (peripheral). Simulations showed slight deviation from the full model (97% AUC agreement with full model and 99% with Step 3) (Fig. 5).

Fast Transfer from Lung to Plasma (Appendix 7)

Transfer from lung to plasma ($k_{VAS-circul.}^{Lung}$) was assumed to be faster than the input rate into the lung ($k_{VAS-circul.}^{Peripheral}$). Numerical evaluation of these rates showed that $k_{VAS-circul.}^{Lung}$ is more than 19-fold higher than ($k_{VAS-circul.}^{Peripheral}$) and 161-fold higher than the input rate to the liver ($\frac{Q_{Liver}}{V_{Plasma}}$). Thus, amount in the lung compartment was neglected and input into the lung was introduced to the plasma compartment. The remaining input from the liver was introduced in the plasma equation where it canceled out. This step resulted in relatively high deviations from the full model which can be attributed to the additional amount introduced into the plasma compartment and the loss of a distribution compartment (*i.e.*, lung) (Fig. 5).

Plasma and Vascular Compartments in Rapid Equilibrium (Appendix 8)

The plasma compartment was assumed to be in rapid equilibrium with the vascular compartment in tissues. This assumption was supported by three observations. First, the rate transfer from plasma to vascular compartment of

Liver
circul.) is eight-fold higher than $\frac{Q_{Liver}}{V_{Plasma}}$. This assumption suggests that liver does not contribute to the mass of mAb. While we acknowledge that this assumption is inaccurate, large molecules are not specifically eliminated from the liver as opposed to small molecules where liver may represent an important elimination compartment. Interestingly, fast transfer assumption from the liver lead to a minimal increase in plasma profile

peripheral organs ($\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}$) is proportional to the transfer rate from the vascular compartment of peripheral organs to plasma ($k_{\text{VAS-circul.}}^{\text{Peripheral}}$). Second, these two rates are more than 9,000-fold faster than other processes. Finally, simulations showed that concentrations in plasma and vascular compartment of the peripheral organs are in rapid equilibrium (Supplementary Figure 3). Thus, the total amount of mAb in plasma and vascular compartments are represented by a new variable (A_{Central}). Amount of mAb in plasma was represented as a fraction of the total amounts in the central compartment. Simulations of plasma concentrations showed a biexponential profile close to that of the full PBPK model. Given this model structure, the “central” compartment resembles the rapid distribution compartment in classical two-compartment models as it includes spaces with rapid distribution properties (plasma and tissue vasculature). However, in contrast to two-compartmental models, the central compartment in our model exhibits clear physiological/anatomical definitions and retains the elimination of mAb from the central compartment, k_{EL}^{C} .

Final Simplified Physiological Model with Identifiable Parameters (Appendix 8)

In the final step, we considered regrouping transfer processes by adding processes that act in similar transfer direction or subtracting these that act in opposite direction (e.g., subtracting the rate of recycling of mAb from the endosomal space to peripheral and central spaces ($k_{\text{Central}}^{\text{Central}}$ and $k_{\text{Peripheral}}^{\text{Peripheral}}$) from the elimination rate from these compartments). This implies that $k_{\text{EL}}^{\text{Central}} > k_{\text{Central}}^{\text{Central}}$ and that $k_{\text{EL}}^{\text{Peripheral}} > k_{\text{Peripheral}}^{\text{Peripheral}}$, which was confirmed by numerical evaluation (Supplementary Table 4). This simplification results in slower elimination rates (k_{EL}^{C} and k_{EL}^{P}). Data collected in routine clinical trials usually involve samples from plasma but not from tissues and thus k_{EL}^{P} would be unidentifiable. Given that k_{EL}^{C} and k_{EL}^{P} are within two-fold difference, we assumed that rates of elimination from both central and peripheral compartments were similar, yielding one identifiable elimination rate from both compartments, k_{EL} .

Comparing the rates of processes involved in the transfer of mAb from the peripheral compartment, namely, the return to the lymph node *via* lymphatic flow and the reflection of the fraction mAb-FcRn complex recycled ($k_{\text{ISF-VAS}}$), showed that the return *via* convective movement is dominant ($> 2 \times 10^7$ fold higher) and thus $k_{\text{ISF-VAS}}$ was considered negligible and the loss of drug from the peripheral compartment was assumed to take place only *via* convective movement to the lymph node. Finally, the rate of return from peripheral compartment to lymph node, $(1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}}$, was found comparable to rate of return from lymph node to central compartment, $(\frac{1}{\tau_{\text{AuLN}}})$. Thus, we assumed these two rates to be equal and the term k_{LN} (calculated as the average of the two rates) was used. This renders the lymph node as a transit compartment that reflects the delayed return of mAb to the circulation. Simulation from the final model was almost identical to that of the full model.

Neither the full PBPK model nor the simplified model consider binding to the specific target. Target-mediated clearance represents an important elimination pathway for mAbs and is responsible for the rapid clearance of mAbs observed at lower doses in dose escalation trials. This nonlinear clearance pathway can be considered, if needed, within the proposed physiological model. The elimination rate, k_{EL} , can be replaced by Michaelis–Menten elimination terms V_{MAX} and K_{M} and or more complex TMDD models. Estimability of these parameters depends on the type and richness of the data (for example multiple doses before and after target saturation and at long sampling intervals with low concentrations).

Population Analysis and Model Parameters Estimation

Non-compartmental analysis showed linear PK across all doses tested. Initial estimates for the two-compartmental model were obtained from the literature (13). For the simple physiological model, physiological values for the transfer rates obtained during model simplification were used and the volumes of plasma in human was used as initial estimate for the volume of central compartment (3 L). The profile of the tested mAb was well characterized by both two-compartment model and the simple physiological model (Fig. 6). The residuals plots, visual predictive checks, and model selection criteria (e.g., AIC) all suggest similar fit for both models (Fig. 6 and Supplementary Figure 6). The estimated parameter values for both models are shown in Tables II and III. The estimate for V_{C} was the same in both models (3.8 L) with comparable IIV. Estimate for V_{P} in the classical two-compartmental model was 4.6 L which agrees with the range reported in the literature (1.3 to 6.8 L) (13). According to the structure of the simple physiological model, V_{P} cannot be directly estimated from our model without additional information on, for example, peripheral tissue concentrations.

However, the volume of the peripheral compartment (V_{P}) can be inferred as a secondary parameter from the simple physiological model by considering the convective clearance for mAbs from the tissues to lymph. Human plasma flow rate (4,368 L/day) can be referenced from the literature (7). Applying the same assumptions from the full PBPK model that lymph flow is proportional to plasma flow (i.e., lymph flow = 0.2% of plasma flow), and that the lymphatic reflection coefficient is 0.2, the convective clearance from the peripheral compartment to the lymph node, ($\text{CL}_{\text{Per-LN}}$) can be calculated as $(1 - \sigma_{\text{LY}}) \times L$ (i.e., 6.9 L/day), which allows calculation of V_{P} as the ratio between the convective clearance and k_{LN} ($V_{\text{P}} = \frac{\text{CL}_{\text{Per-LN}}}{k_{\text{LN}}} = \frac{6.9}{0.51} = 13.7 \text{ L}$). This estimate is a much better approximation of the reported estimate of the physiological volume of the interstitial space (~11.7 L) (7) and allows better prediction of the peripheral tissue concentrations compared to two-compartmental models (Supplementary Figure 7).

The utility of any model depends on the purpose of the modeling exercise. Both classical and simple physiological models were capable of capturing the plasma concentrations of the example used. However, if the model aims to predict whole-body average concentrations in peripheral tissues, classical models will underestimate the volume of distribution

Fig. 6. Visual predictive check for different dose levels, *open symbols* represent the observed plasma concentrations, *solid line* represents the 50th percentile and the *dotted lines* represent the 5th and 95th percentiles of the model predicted data

at steady state (V_{SS}) which is calculated as the sum of V_C and V_P (common (V_{SS}) estimates for mAbs are $\sim 5\text{--}7$ L) which is

Table II. Estimated Classical Two-compartment Model Parameters for the Population

Parameter (unit)	Population mean final estimate (%CV)	Inter-individual variance final estimate (%CV)
Volume of central compartment, V_C , (L)	3.8 (7.4)	33.9 (28.9)
Volume of peripheral compartment, V_P , (L)	4.8 (12.7)	45.1 (33.2)
Elimination clearance, CL , (L/h)	0.29 (7.4)	30.3 (30.47)
Distributional clearance, Q , (L/h)	1.47 (15.4)	23.1 (37.68)
Model AIC	5797	

almost half of the volume of interstitial space (~ 11.3 L) (8). Underestimation of V_{SS} in classical compartmental models will lead to over predicting whole-body average peripheral tissue concentrations as shown in (Supplementary Figure 7).

Table III. Estimated Simple Physiological Model Parameters for the Population

Parameter (unit)	Population mean final estimate (%CV)	Inter-individual variance final estimate (%CV)
Volume of central compartment, V_C , (L)	3.8 (7.3)	33.9 (29.1)
$k_{Cen-Per}$ (day) $^{-1}$	0.36 (16.87)	17.1 (30.2)
k_{LN} (day) $^{-1}$	0.51 (16.09)	43.6 (31.6)
k_{EL} (day) $^{-1}$	0.044 (3.9)	22.8 (30.7)
Model AIC	5,796	

This might be explained, at least partially, by the following two reasons: First, the classical model assumes elimination from the central compartment only. The impact of ignoring peripheral elimination on estimation of PK parameters of muscle relaxants which undergo extensive peripheral elimination has been studied. Ignoring peripheral elimination in a classical two-compartment model resulted in underestimation of several exit-site dependent PK parameters of which V_{SS} is the most clinically significant (21). According to the physiological and PK of mAbs, both V_P and V_C , represents an elimination site which is misrepresented in classical models. Second, classical models do not consider lymphatic circulation and uptake from endothelial space in peripheral tissues back to the vasculature (*i.e.*, central compartment). On the other hand, the physiological model provided reasonable representation of the whole-body average tissue concentrations. This was confirmed by calculating the ratio between average tissue and plasma concentrations from the full PBPK model (0.1) and comparing it to that obtained from the simple physiological model predictions (0.18). The classical model showed much higher ratio (0.92).

CONCLUSION

In this work, our goal was to reduce the dimensionality and complexity of a PBPK model into a simple compartmental model. The full PBPK model used provides close description of several important processes in mAb disposition such as the gradual change in endosomal pH, the change in mAb and FcRn association and dissociation affinities, mAb uptake in to the endosome, convective movement of mAb into tissue, and convective return of the antibody to blood *via* the lymphatic circulation (13). Using a series of physiologically plausible and consecutive assumptions, we employed a top-down approach to translate prior physiological information from the full PBPK model to a simple compartmental model. This model provides fewer compartments than PBPK but more physiologically meaningful

parameters than traditional mammillary systems that can be estimated in a population approach with minimal complexity. The final model was successfully applied to describe the PK of a development mAb using the population approach.

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Conflict of Interest The authors declare no conflict of interest

APPENDICES

Appendix 1: Original Model Equations

Notes:

1. A superscript J is used to denote endogenous IgG or mAb in most equations. If the equations describing the mAb and IgG are different two independent systems of equations are used.
2. Dependent variables are described in amounts, not concentrations, as in (13).
3. The original model (13) described binding to FcRn receptor as the change from initial FcRn concentration in different tissues and the initial conditions for this change is set to 0. In this work, FcRn receptor amounts were expressed as $R_{free, Organ-X}$.
4. The original model used two estimated coefficients to reflect the non-FcRn dependent tissue uptake of mAb (13). In our study, simulations were performed without these coefficients.

I. plasma
Endogenous IgG

$$\begin{aligned} \frac{dA_{plasma}^{endo}}{dt} = & K_0 \times V_{Plasma} + \frac{Q_{Lung} - L_{Lung}}{V_{VAS}^{Lung}} \times A_{VAS\ Lung}^{endo} - \frac{L_{GIT} + L_{Spleen}}{V_{Plasma}} \times A_{Plasma}^{endo} \\ & - \frac{Q_{Liver} + Q_{Heart} + Q_{Kidney} + Q_{Skin} + Q_{Muscle}}{V_{Plasma}} \times A_{Plasma}^{endo} + \frac{1}{\tau_{LN}} \times A_{LN}^{endo} \times F_{return} \\ IC = & A_{plasma}^{endo} SS \end{aligned} \quad (3)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{plasma}}{dt} = & \frac{Q_{Lung} - L_{Lung}}{V_{VAS}^{Lung}} \times A_{VAS\ Lung} - \frac{L_{GIT} + L_{Spleen}}{V_{Plasma}} \times A_{Plasma} \\ & - \frac{Q_{Liver} + Q_{Heart} + Q_{Kidney} + Q_{Skin} + Q_{Muscle}}{V_{Plasma}} \times A_{Plasma} + \frac{1}{\tau_{LN}} \times A_{LN} \times F_{return} \\ IC = & Dose_{mAb} \end{aligned} \quad (4)$$

II. Organs

A. Vascular Space

Equations for the vascular compartment in liver and lung are different from other organs.

i. lung

$$\begin{aligned}
 \frac{dA_{VAS\ Lung}^J}{dt} = & \frac{Q_{Liver}-L_{Liver}}{V_{VAS}^{Liver}} \times A_{VAS\ Liver}^J + \frac{Q_{Heart}-L_{Heart}}{V_{VAS}^{Heart}} \times A_{VAS\ Heart}^J + \frac{Q_{Kidney}-L_{Kidney}}{V_{VAS}^{Kidney}} \times A_{VAS\ Kidney}^J \\
 & + \frac{Q_{Skin}-L_{Skin}}{V_{VAS}^{Skin}} \times A_{VAS\ Skin}^J + \frac{Q_{Muscle}-L_{Muscle}}{V_{VAS}^{Muscle}} \times A_{VAS\ Muscle}^J - \frac{Q_{Lung}-L_{Lung}}{V_{VAS}^{Lung}} \times A_{VAS\ Lung}^J \\
 & - \frac{CL_{Uptake}^{Lung}}{V_{VAS}^{Lung}} \times A_{VAS\ Lung}^J - (1-\sigma_{VAS}) \times \frac{L_{Lung}}{V_{Lung}} \times A_{VAS\ Lung}^J + FR \times \frac{CL_{Uptake}^{Lung}}{V_{END}^{Lung}} \\
 & \times ARCPX_{Lung-5}^J \\
 A_{VAS\ Lung}^{endo} IC = & A_{VAS\ Lung}^{endo} SS; A_{VAS\ Lung}^{exo} IC = 0
 \end{aligned} \tag{5}$$

ii. liver

$$\begin{aligned}
 \frac{dA_{VAS\ Liver}^J}{dt} = & \frac{Q_{GIT}-L_{GIT}}{V_{VAS}^{GIT}} \times A_{VAS\ GIT}^J + \frac{Q_{Spleen}-L_{Spleen}}{V_{VAS}^{Spleen}} \times A_{VAS\ Spleen}^J + \frac{L_{GIT} + L_{Spleen}}{V_{Plasma}} \times A_{Plasma}^J \\
 & + \frac{Q_{Liver}-Q_{GIT}-Q_{Spleen}}{V_{Plasma}} \times A_{Plasma}^J - \frac{Q_{Liver}-L_{Liver}}{V_{VAS}^{Liver}} \times A_{VAS\ Liver}^J - \frac{CL_{Uptake}^{Liver}}{V_{VAS}^{Liver}} \times A_{VAS\ Liver}^J \\
 & - (1-\sigma_{VAS}) \times \frac{L_{Liver}}{V_{Liver}} \times A_{VAS\ Liver}^J + FR \times \frac{CL_{Uptake}^{Liver}}{V_{END}^{Liver}} \times ARCPX_{Liver-5}^J \\
 A_{VAS\ Liver}^{endo} IC = & A_{VAS\ Liver}^{endo} SS; A_{VAS\ Liver}^{exo} IC = 0
 \end{aligned} \tag{6}$$

iii. Other Organs (heart, kidney, skin, muscle, GIT, spleen)

$$\begin{aligned}
 \frac{dA_{VAS\ Organ}^J}{dt} = & \frac{Q_{Organ}}{V_{Plasma}} \times A_{Plasma}^J - \frac{Q_{Organ}-L_{Organ}}{V_{Organ}^{VAS}} \times A_{VAS\ Organ}^J - \frac{CL_{Uptake}^{Organ}}{V_{Organ}^{VAS}} \times A_{VAS\ Organ}^J - (1-\sigma_{VAS}) \\
 & \times \frac{L_{Organ}}{V_{Organ}} \times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times ARCPX_{Organ-5}^J \\
 A_{VAS\ Organ}^{endo} IC = & A_{VAS\ Organ}^{endo} SS; A_{VAS\ Organ}^{exo} IC = 0
 \end{aligned} \tag{7}$$

B. Interstitial Space (Applies for all organs including liver and lung, all termed “Organ”)

$$\begin{aligned}
 \frac{dA_{ISF\ Organ}^J}{dt} = & (1-\sigma_{VAS}) \times \frac{L_{Organ}}{V_{Organ}^{VAS}} \times A_{VAS\ Organ}^J - (1-\sigma_{LY}) \times \frac{L_{Organ}}{V_{ISF}^{Organ}} \times A_{ISF\ Organ}^J + (1-FR) \\
 & \times \frac{CL_{Uptake}^{Organ}}{V_{Organ}^{END}} \times ARCPX_{Organ-5}^J - \frac{CL_{Uptake}^{Organ}}{V_{Organ}^{ISF}} \times A_{ISF\ Organ}^J \\
 A_{ISF\ Organ}^{endo} IC = & A_{ISF\ Organ}^{endo} SS; A_{ISF\ Organ}^{exo} IC = 0
 \end{aligned} \tag{8}$$

C. Endosomal Space (Applies for all organs including liver and lung, all termed “Organ”)

i. Subcompartment 1

Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{END Organ-1}}^{\text{endo}}}{dt} &= \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^{\text{endo}} + \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^{\text{endo}} - k_{\text{on-1}} \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-1}}^{\text{endo}} \\ &\quad \times \left(R_{\text{total Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} \right) + k_{\text{off-1}} \times \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} - \frac{1}{\tau} \\ &\quad \times A_{\text{END Organ-1}}^{\text{endo}} \\ A_{\text{END Organ-1}}^{\text{endo}} \text{IC} &= A_{\text{END Organ-1}}^{\text{endo}} \text{SS} \end{aligned} \quad (9)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{\text{END Organ-1}}^{\text{exo}}}{dt} &= \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^{\text{exo}} + \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^{\text{exo}} - \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-1}}^{\text{exo}} \\ &\quad \times \left(R_{\text{total Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} - \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} \right) + k_{\text{off-1}} \times \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} - \frac{1}{\tau} \\ &\quad \times A_{\text{END Organ-1}}^{\text{exo}} \\ A_{\text{END Organ-1}}^{\text{exo}} \text{IC} &= 0 \end{aligned} \quad (10)$$

Endogenous IgG-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-1}}^{\text{endo}}}{dt} &= \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-1}}^{\text{endo}} \times \left(R_{\text{total Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} \right) - k_{\text{off-1}} \\ &\quad \times \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} - \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} \\ \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} \text{IC} &= \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} \text{SS} \end{aligned} \quad (11)$$

Exogenous mAb-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-1}}^{\text{exo}}}{dt} &= \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-1}}^{\text{exo}} \times \left(R_{\text{total Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} - \text{ARCPX}_{\text{Organ-1}}^{\text{endo}} \right) - k_{\text{off-1}} \\ &\quad \times \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} - \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} \\ \text{ARCPX}_{\text{Organ-1}}^{\text{exo}} \text{IC} &= 0 \end{aligned} \quad (12)$$

ii. Subcompartments 2, 3 and 4 ($i = 2, 3, 4$)

Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{END Organ-i}}^{\text{endo}}}{dt} &= \frac{1}{\tau} \times A_{\text{END Organ-(i-1)}}^{\text{endo}} - \frac{k_{\text{on-i}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-i}}^{\text{endo}} \times \left(R_{\text{total Organ-i}} - \text{ARCPX}_{\text{Organ-i}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-i}}^{\text{exo}} \right) \\ &\quad + k_{\text{off-i}} \times \text{ARCPX}_{\text{Organ-i}}^{\text{endo}} - \frac{1}{\tau} \times A_{\text{END Organ-i}}^{\text{endo}} \\ A_{\text{END Organ-i}}^{\text{endo}} \text{IC} &= A_{\text{END Organ-i}}^{\text{endo}} \text{SS} \end{aligned} \quad (13)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{\text{END Organ-}i}^{\text{exo}}}{dt} &= \frac{1}{\tau} \times A_{\text{END Organ-}(i-1)}^{\text{exo}} - \frac{k_{\text{on-}i}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}i}^{\text{exo}} \times \left(R_{\text{total Organ-}i} - \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} - \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} \right) \\ &\quad + k_{\text{off-}i} \times \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} - \frac{1}{\tau} \times A_{\text{END Organ-}i}^{\text{exo}} \\ A_{\text{END Organ-}i}^{\text{exo}} \text{IC} &= 0 \end{aligned} \quad (14)$$

Endogenous IgG-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-}i}^{\text{endo}}}{dt} &= \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-}(i-1)}^{\text{endo}} + \frac{k_{\text{on-}i}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}i}^{\text{endo}} \times \left(R_{\text{total Organ-}i} - \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} - \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} \right) \\ &\quad - k_{\text{off-}i} \times \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} - \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} \\ \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} \text{IC} &= \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} \text{SS} \end{aligned} \quad (15)$$

Exogenous mAb-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-}i}^{\text{exo}}}{dt} &= \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-}(i-1)}^{\text{exo}} + \frac{k_{\text{on-}i}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}i}^{\text{exo}} \times \left(R_{\text{total Organ-}i} - \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} - \text{ARCPX}_{\text{Organ-}i}^{\text{endo}} \right) \\ &\quad - k_{\text{off-}i} \times \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} - \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} \\ \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} \text{IC} &= 0 \end{aligned} \quad (16)$$

iii. Subcompartment 5 Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{END Organ-}5}^{\text{endo}}}{dt} &= \frac{1}{\tau} \times A_{\text{END Organ-}4}^{\text{endo}} - \frac{k_{\text{on-}5}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}5}^{\text{endo}} \times \left(R_{\text{total Organ-}5} - \text{ARCPX}_{\text{Organ-}5}^{\text{endo}} - \text{ARCPX}_{\text{Organ-}5}^{\text{exo}} \right) \\ &\quad + k_{\text{off-}5} \times \text{ARCPX}_{\text{Organ-}5}^{\text{endo}} - \frac{\text{CL}_{\text{Proteolysis}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}5}^{\text{endo}} \\ A_{\text{END Organ-}5}^{\text{endo}} \text{IC} &= A_{\text{END Organ-}5}^{\text{endo}} \text{SS} \end{aligned} \quad (17)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{\text{END Organ-}5}^{\text{exo}}}{dt} &= \frac{1}{\tau} \times A_{\text{END Organ-}4}^{\text{exo}} - \frac{k_{\text{on-}5}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}5}^{\text{exo}} \times \left(R_{\text{total Organ-}5} - \text{ARCPX}_{\text{Organ-}5}^{\text{exo}} - \text{ARCPX}_{\text{Organ-}5}^{\text{endo}} \right) \\ &\quad + k_{\text{off-}5} \times \text{ARCPX}_{\text{Organ-}5}^{\text{exo}} - \frac{\text{CL}_{\text{Proteolysis}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{Organ}}} \times A_{\text{END Organ-}5}^{\text{exo}} \\ A_{\text{END Organ-}5}^{\text{exo}} \text{IC} &= 0 \end{aligned} \quad (18)$$

Endogenous IgG-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-5}}^{\text{endo}}}{dt} &= \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-4}}^{\text{endo}} + \frac{k_{\text{on-5}}}{V_{\text{Organ-5}}^{\text{endo}}} \times A_{\text{Organ-5}}^{\text{endo}} \times \left(R_{\text{total Organ-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} \right) \\ &\quad - k_{\text{off-5}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ-5}}}{V_{\text{Organ-5}}^{\text{endo}}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} \end{aligned} \quad (19)$$

$$\text{ARCPX}_{\text{Organ-5}}^{\text{endo}} \text{IC} = \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} \text{ss}$$

Exogenous mAb-FcRn complex

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-5}}^{\text{exo}}}{dt} &= \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-4}}^{\text{exo}} + \frac{k_{\text{on-5}}}{V_{\text{Organ-5}}^{\text{exo}}} \times A_{\text{Organ-5}}^{\text{exo}} \times \left(R_{\text{total Organ-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} \right) \\ &\quad - k_{\text{off-5}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ-5}}}{V_{\text{Organ-5}}^{\text{exo}}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} \end{aligned} \quad (20)$$

$$\text{ARCPX}_{\text{Organ-5}}^{\text{exo}} \text{IC} = 0$$

III. Lymph Node

$$\begin{aligned} \frac{dA_{\text{LN}}^{\text{J}}}{dt} &= (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Lung}}}{V_{\text{ISF}}^{\text{Lung}}} \times A_{\text{ISF Lung}}^{\text{J}} + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Liver}}}{V_{\text{ISF}}^{\text{Liver}}} \times A_{\text{ISF Liver}}^{\text{J}} + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{GIT}}}{V_{\text{ISF}}^{\text{GIT}}} \times A_{\text{ISF GIT}}^{\text{J}} \\ &\quad + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Spleen}}}{V_{\text{ISF}}^{\text{Spleen}}} \times A_{\text{ISF Spleen}}^{\text{J}} + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Heart}}}{V_{\text{ISF}}^{\text{Heart}}} \times A_{\text{ISF Heart}}^{\text{J}} + (1-\sigma_{\text{LY}}) \\ &\quad \times \frac{L_{\text{Kidney}}}{V_{\text{ISF}}^{\text{Kidney}}} \times A_{\text{ISF Kidney}}^{\text{J}} + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Skin}}}{V_{\text{ISF}}^{\text{Skin}}} \times A_{\text{ISF Skin}}^{\text{J}} + (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Muscle}}}{V_{\text{ISF}}^{\text{Muscle}}} \\ &\quad \times A_{\text{ISF Muscle}}^{\text{J}} - \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^{\text{J}} \end{aligned} \quad (21)$$

$$A_{\text{LN}}^{\text{endo}} \text{IC} = A_{\text{LN}}^{\text{endo}} \text{ss}; A_{\text{LN}}^{\text{exo}} \text{IC} = 0$$

Appendix 2: Fast Endosomal Transfer and Rapid Binding Assumptions

Transfer of mAb/IgG between endosomal compartments is fast relative to the time scale of other processes such as changes in plasma and lymph as well as the rate of binding of mAb/IgG to FcRn. The assumption that the endosomal transfer rate is faster than FcRn binding process holds true for earlier compartments where FcRn binding is considered negligible (in the first endosomal

subcompartment) or low (in intermediate compartments). As the drug is transferred to later compartments, rate of binding increases and thus rapid binding assumption is applied to the last compartment where the majority of binding to FcRn takes place. Physiologically these 2 processes (transfer and binding) might interfere with each other. However, since these 2 assumptions (*i.e.*, fast endosomal transfer and rapid binding) are applied sequentially, the 2 assumptions do not contradict each other, at least from a theoretical aspect.

Assumption: Endosomal transfer of mAb/IgG between endosomal compartments is very fast relative to the time scale of other processes:

$$\tau \rightarrow 0 \quad (22)$$

$$\frac{1}{\tau} \times A_{\text{END Organ-4}} \rightarrow \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}} + \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}} \text{ as } \tau \rightarrow 0 \quad (23)$$

Thus, equation for free mAb/IgG in the terminal compartment can be expressed as:

$$\begin{aligned} \frac{dA_{\text{END Organ-5}}^{\text{exo}}}{dt} = & \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^{\text{exo}} + \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^{\text{exo}} - \frac{k_{\text{on-5}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{exo}} \\ & \times (R_{\text{totalOrgan-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}}) + k_{\text{off-5}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} - \frac{CL_{\text{Proteolysis}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{exo}} \end{aligned} \quad (24)$$

and the equation for complex mAb/IgG in the terminal compartment can be expressed as:

$$\begin{aligned} \frac{d\text{ARCPX}_{\text{Organ-5}}^{\text{exo}}}{dt} = & \frac{k_{\text{on-5}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{exo}} \times (R_{\text{totalOrgan-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}}) - k_{\text{off-5}} \\ & \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} - \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} \end{aligned} \quad (25)$$

Assumption: Free drug, the target and the complex are at rapid equilibrium meaning that the binding and

It can be shown that input in to the first endosomal compartment will be transferred to the terminal compartment as $\tau \rightarrow 0$ (Please refer to Appendix 9),

dissociation rates are much faster than other processes (18).

Thus,

$$\frac{k_{\text{on-5}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{exo}} \times (R_{\text{totalOrgan-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}}) - k_{\text{off-5}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{exo}} = 0 \quad (26)$$

And

Similarly,

$$k_{\text{off-5}} / \frac{k_{\text{on-5}}}{V_{\text{END}}^{\text{Organ}}} = \text{KD}_{\text{END}} \quad (27)$$

Solve for $\text{ARCPX}_{\text{Organ-5}}^{\text{exo}}$

$$\text{ARCPX}_{\text{Organ-5}}^{\text{endo}} = \frac{A_{\text{END Organ-5}}^{\text{endo}} \times (R_{\text{totalOrgan-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{exo}})}{\text{KD}_{\text{END}} + A_{\text{END Organ-5}}^{\text{endo}}} \quad (29)$$

$$\text{ARCPX}_{\text{Organ-5}}^{\text{exo}} = \frac{A_{\text{END Organ-5}}^{\text{exo}} \times (R_{\text{totalOrgan-5}} - \text{ARCPX}_{\text{Organ-5}}^{\text{endo}})}{\text{KD}_{\text{END}} + A_{\text{END Organ-5}}^{\text{exo}}} \quad (28)$$

Substitute $\text{ARCPX}_{\text{Organ-5}}^{\text{endo}}$ in Eq. 27 to solve for $\text{ARCPX}_{\text{Organ-5}}^{\text{exo}}$ in terms of the free amounts of

endogenous ($A_{\text{END Organ-5}}^{\text{endo}}$) IgG and exogenous mAb ($A_{\text{END Organ-5}}^{\text{exo}}$)

$$\text{ARCPX}_{\text{Organ-5}}^{\text{exo}} = \frac{A_{\text{END Organ-5}}^{\text{exo}} \times \text{Rtotal}_{\text{Organ-5}} \times \text{KD}_{\text{END}}}{\left[\text{KD}_{\text{END}} + A_{\text{END Organ-5}}^{\text{exo}} \right] \times \left[\text{KD}_{\text{END}} + A_{\text{END Organ-5}}^{\text{endo}} \right] - A_{\text{END Organ-5}}^{\text{exo}} \times A_{\text{END Organ-5}}^{\text{endo}}} \quad (30)$$

and $A_{\text{END Organ-5}}^{\text{endo}}$ and $A_{\text{END Organ-5}}^{\text{exo}}$ are negligible compared to KD_{END} ($A_{\text{END Organ-5}}^{\text{exo}} \ll \text{KD}_{\text{END}}$ and $A_{\text{END Organ-5}}^{\text{endo}} \ll \text{KD}_{\text{END}}$) (Please refer to Supplementary Figure 2)

Thus, Eq. 29 for $\text{ARCPX}_{\text{Organ-5}}^{\text{J}}$ can be simplified to

$$\text{ARCPX}_{\text{Organ-5}}^{\text{J}} = \frac{A_{\text{END Organ-5}}^{\text{J}} \times \text{Rtotal}_{\text{Organ-5}}}{\text{KD}_{\text{END}}} \quad (31)$$

Equations derived for $\text{ARCPX}_{\text{Organ-5}}^{\text{J}}$ showed that the IgG/mAb-FcRn complex is proportional to the free IgG/mAb. In the following section, equations for free IgG/mAb (Eq. 27) and complex (Eq. 28) are added to get $A_{\text{Total END Organ-5}}^{\text{J}}$

$$\text{ARCPX}_{\text{Total END Organ-5}}^{\text{J}} = A_{\text{END Organ-5}}^{\text{J}} + \text{ARCPX}_{\text{Organ-5}}^{\text{J}} \quad (32)$$

$$\frac{dA_{\text{Total END Organ-5}}^{\text{J}}}{dt} = \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^{\text{J}} + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^{\text{J}} - \frac{\text{CL}_{\text{Proteolysis}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{J}} - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{J}} \quad (33)$$

Assumption: total mAb/IgG in compartment 5 is in equilibrium, *i.e.*

$$\frac{dA_{\text{Total END Organ-5}}^{\text{J}}}{dt} = 0 \quad (34)$$

Consequently,

$$\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^{\text{J}} + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^{\text{J}} - \frac{\text{CL}_{\text{Proteolysis}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times A_{\text{END Organ-5}}^{\text{J}} - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{END}}^{\text{Organ}}} \times \text{ARCPX}_{\text{Organ-5}}^{\text{J}} = 0 \quad (35)$$

Substituting $ARCPX_{Organ-5}^J$ by Eq. 31 allows one to solve Eq. 43 for $A_{END\ Organ-5}^J$

$$A_{END\ Organ-5}^J = \frac{\left(\frac{CL_{Uptake}^{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J + \frac{CL_{Uptake}^{Organ}}{V_{ISF}^{Organ}} \times A_{ISF\ Organ}^J \right)}{\left(\frac{CL_{Proteolysis}^{Organ}}{V_{END}^{Organ}} + \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times \frac{R_{totalOrgan-5}}{KD_{END}} \right)} \quad (36)$$

Substituting $A_{END\ Organ-5}^J$ from Eqs. 38 and 34 allows solving for $ARCPX_{Organ-5}^J$ in terms of vascular and interstitial amounts

$$ARCPX_{Organ-5}^J = A_{VAS\ Organ}^J \times \frac{\frac{R_{totalOrgan-5}}{KD_{END}} \times \frac{CL_{Uptake}^{Organ}}{V_{VAS}^{Organ}}}{\frac{CL_{Proteolysis}^{Organ}}{V_{END}^{Organ}} + \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times \frac{R_{totalOrgan-5}}{KD_{END}}} \quad (37)$$

$$+ A_{ISF\ Organ}^J \times \frac{\frac{R_{totalOrgan-5}}{KD_{END}} \times \frac{CL_{Uptake}^{Organ}}{V_{ISF}^{Organ}}}{\frac{CL_{Proteolysis}^{Organ}}{V_{END}^{Organ}} + \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times \frac{R_{totalOrgan-5}}{KD_{END}}}$$

Let the terms multiplying $A_{VAS\ Organ}^J$ and $A_{ISF\ Organ}^J$ be k_1 and k_2 , respectively. Thus,

$$ARCPX_{Organ-5}^J = A_{VAS\ Organ}^J \times k_1 + A_{ISF\ Organ}^J \times k_2 \quad (38)$$

Substitute $ARCPX_{Organ-5}^J$ in the equation for vascular and interstitial compartments (Please refer to Fig. 3):

$$\begin{aligned} \frac{dA_{VAS\ Organ}^J}{dt} &= \frac{Q_{Organ}}{V_{Plasma}} \times A_{Plasma}^J - \frac{Q_{Organ} - L_{Organ}}{V_{VAS}^{Organ}} \\ &\times A_{VAS\ Organ}^J - (1 - \sigma_{VAS}) \times \frac{L_{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J \\ &- \frac{CL_{Uptake}^{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \\ &\times k_1 \times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \\ &\times k_2 \times A_{ISF\ Organ}^J \end{aligned} \quad (39)$$

Introduce the input term from the vascular to the interstitial compartment: (This term appears in the interstitial compartment)

$$\begin{aligned} \frac{dA_{VAS\ Organ}^J}{dt} &= \frac{Q_{Organ}}{V_{Plasma}} \times A_{Plasma}^J - \frac{Q_{Organ} - L_{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J - (1 - \sigma_{VAS}) \times \frac{L_{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J \\ &- \frac{CL_{Uptake}^{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_1 \\ &\times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_2 \times A_{ISF\ Organ}^J - (1 - FR) \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_1 \times A_{VAS\ Organ}^J \\ &+ (1 - FR) \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_1 \times A_{VAS\ Organ}^J \end{aligned} \quad (40)$$

which can be simplified to:

$$\begin{aligned} \frac{dA_{VAS\ Organ}^J}{dt} &= \frac{Q_{Organ}}{V_{Plasma}} \times A_{Plasma}^J - \frac{Q_{Organ} - L_{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J - (1 - \sigma_{VAS}) \times \frac{L_{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J \\ &- \frac{CL_{Uptake}^{Organ}}{V_{VAS}^{Organ}} \times A_{VAS\ Organ}^J \\ &+ \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_1 \times A_{VAS\ Organ}^J + FR \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_2 \times A_{ISF\ Organ}^J - (1 - FR) \times \frac{CL_{Uptake}^{Organ}}{V_{END}^{Organ}} \times k_1 \times A_{VAS\ Organ}^J \end{aligned} \quad (41)$$

A similar substitution of $\text{ARCPX}_{\text{Organ-5}}^J$ in the equation for the interstitial compartment yields:

$$\begin{aligned} \frac{dA_{\text{ISF Organ}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J - (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J \\ & + (1-\text{FR}) \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_1 \times A_{\text{VAS Organ}}^J + (1-\text{FR}) \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \times A_{\text{ISF Organ}}^J \end{aligned} \quad (42)$$

Introduce the input term from the interstitial to the vascular compartment: (This term appears in the vascular compartment and should be accounted for)

$$\begin{aligned} \frac{dA_{\text{ISF Organ}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J - (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J + (1-\text{FR}) \\ & \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_1 \times A_{\text{VAS Organ}}^J + (1-\text{FR}) \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \times A_{\text{ISF Organ}}^J + \text{FR} \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \\ & \times A_{\text{ISF Organ}}^J - \text{FR} \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \times A_{\text{ISF Organ}}^J \end{aligned} \quad (43)$$

$$\begin{aligned} \frac{dA_{\text{ISF Organ}}}{dt} = & (1-\sigma_{\text{VAS}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J - (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{ISF}}} \times A_{\text{ISF Organ}}^J + (1-\text{FR}) \\ & \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_1 \times A_{\text{VAS Organ}}^J + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \times A_{\text{ISF Organ}}^J - \text{FR} \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2 \times A_{\text{ISF Organ}}^J \end{aligned} \quad (44)$$

Let $\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_1$ be a first-order input from the vascular compartment to itself ($k_{\text{VAS-VAS}}^{\text{Organ}}$)

Let $\text{FR} \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2$ be a first-order input from interstitial compartment to vascular compartment ($k_{\text{ISF-VAS}}^{\text{Organ}}$)

Let $(1-\text{FR}) \times \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_1$ be a first-order input from vascular compartment to interstitial compartment ($k_{\text{VAS-ISF}}^{\text{Organ}}$)

Let $\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{END}}} \times k_2$ be a first-order input from the interstitial compartment to itself ($k_{\text{ISF-ISF}}^{\text{Organ}}$).

The final equations for vascular and interstitial compartments can be written as:

A. Vascular Space

$$\begin{aligned} \frac{dA_{\text{VAS Organ}}^J}{dt} = & \frac{Q_{\text{Organ}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}} - \frac{Q_{\text{Organ}} - L_{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J - (1-\sigma_{\text{VAS}}) \\ & \times \frac{L_{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J - \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{Organ}}^{\text{VAS}}} \times A_{\text{VAS Organ}}^J + k_{\text{VAS-VAS}}^{\text{Organ}} \\ & \times A_{\text{VAS Organ}}^J + k_{\text{ISF-VAS}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J - k_{\text{VAS-ISF}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J \end{aligned} \quad (45)$$

B. Interstitial Space

$$\begin{aligned} \frac{dA_{\text{ISF Organ}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times \frac{L_{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J - (1-\sigma_{\text{LY}}) \times \frac{L_{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J - \frac{CL_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J + k_{\text{VAS-ISF}}^{\text{Organ}} \\ & \times A_{\text{VAS Organ}}^J + k_{\text{ISF-ISF}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J - k_{\text{ISF-VAS}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J \end{aligned} \quad (46)$$

Appendix 3: Simplified Model Equations After Rapid Binding and Fast Endosomal Transfer Assumptions (Step 1)

I. plasma
Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{plasma}}^{\text{endo}}}{dt} = & K_0 \times V_{\text{Plasma}} + k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{endo}} - \frac{L_{\text{GIT}} + L_{\text{Spleen}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{endo}} - \frac{Q_{\text{Liver}} + Q_{\text{Heart}} + Q_{\text{Kidney}} + Q_{\text{Skin}} + Q_{\text{Muscle}}}{V_{\text{Plasma}}} \\ & \times A_{\text{Plasma}}^{\text{endo}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^{\text{endo}} \times F_{\text{return}} \text{IC} = A_{\text{plasma}}^{\text{endo}} \text{SS} \end{aligned} \quad (47)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{\text{plasma}}}{dt} = & k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}} - \frac{L_{\text{GIT}} + L_{\text{Spleen}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}} - \frac{Q_{\text{Liver}} + Q_{\text{Heart}} + Q_{\text{Kidney}} + Q_{\text{Skin}} + Q_{\text{Muscle}}}{V_{\text{Plasma}}} \\ & \times A_{\text{Plasma}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}} \text{IC} = \text{Dose}_{\text{mAb}} \end{aligned} \quad (48)$$

II. Organs

A. Vascular Space

Equations for the vascular compartment in liver and lung are different from other organs.

i. lung

$$\begin{aligned} \frac{dA_{\text{VAS Lung}}^J}{dt} = & k_{\text{VAS-circul.}}^{\text{Liver}} \times A_{\text{VAS Liver}}^J + k_{\text{VAS-circul.}}^{\text{Heart}} \times A_{\text{VAS Heart}}^J + k_{\text{VAS-circul.}}^{\text{Kidney}} \times A_{\text{VAS Kidney}}^J + k_{\text{VAS-circul.}}^{\text{Skin}} \times A_{\text{VAS Skin}}^J \\ & + k_{\text{VAS-circul.}}^{\text{Muscle}} \times A_{\text{VAS Muscle}}^J - k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J - k_{\text{VAS-EL}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J - (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Lung}} \\ & \times A_{\text{VAS Lung}}^J + k_{\text{VAS-VAS}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J + k_{\text{ISF-VAS}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J - k_{\text{VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J \\ & A_{\text{VAS Lung}}^{\text{endo}} \text{IC} = A_{\text{VAS Lung}}^{\text{endo}} \text{SS}; A_{\text{VAS Lung}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (49)$$

ii. liver

$$\begin{aligned}
 \frac{dA_{\text{VAS Liver}}^J}{dt} = & k_{\text{VAS-circul.}}^{\text{GIT}} \times A_{\text{VAS GIT}}^J + k_{\text{VAS-circul.}}^{\text{Spleen}} \times A_{\text{VAS Spleen}}^J + \frac{L_{\text{GIT}} + L_{\text{Spleen}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^J + \frac{Q_{\text{Liver}} - (Q_{\text{GIT}} + Q_{\text{Spleen}})}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{endo}} \\
 & - k_{\text{VAS-circul.}}^{\text{Liver}} \times A_{\text{VAS Liver}}^J - k_{\text{VAS-EL}}^{\text{Liver}} \times A_{\text{VAS Liver}}^J - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Liver}} \times A_{\text{VAS Liver}}^J + k_{\text{VAS-VAS}}^{\text{Liver}} \\
 & \times A_{\text{VAS Liver}}^J + k_{\text{ISF-VAS}}^{\text{Liver}} \times A_{\text{ISF Liver}}^J - k_{\text{VAS-ISF}}^{\text{Liver}} \times A_{\text{VAS Liver}}^J \\
 & A_{\text{VAS Liver}}^{\text{endo}} \text{IC} = A_{\text{VAS Liver}}^{\text{endo}} \text{SS}; A_{\text{VAS Liver}}^{\text{exo}} \text{IC} = 0
 \end{aligned} \tag{50}$$

iii. Other Organs (heart, kidney, skin, muscle, GIT, spleen)

$$\begin{aligned}
 \frac{dA_{\text{VAS Organ}}^J}{dt} = & \frac{Q_{\text{Organ}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^J - k_{\text{VAS-circul.}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J - k_{\text{VAS-EL}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J \\
 & + k_{\text{VAS-VAS}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J + k_{\text{ISF-VAS}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J - k_{\text{VAS-ISF}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J \\
 & A_{\text{VAS Organ}}^{\text{endo}} \text{IC} = A_{\text{VAS Organ}}^{\text{endo}} \text{SS}; A_{\text{VAS Organ}}^{\text{exo}} \text{IC} = 0
 \end{aligned} \tag{51}$$

B. Interstitial Space (Applies for all organs including liver and lung, all termed “Organ”)

$$\begin{aligned}
 \frac{dA_{\text{ISF Organ}}^J}{dt} = & (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Organ}} \times A_{\text{VAS Organ}}^J - (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J - k_{\text{ISF-EL}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J + k_{\text{VAS-ISF}}^{\text{Organ}} \\
 & \times A_{\text{VAS Organ}}^J + k_{\text{ISF-ISF}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J - k_{\text{ISF-VAS}}^{\text{Organ}} \times A_{\text{ISF Organ}}^J \\
 & A_{\text{ISF Organ}}^{\text{endo}} \text{IC} = A_{\text{ISF Organ}}^{\text{endo}} \text{SS}; A_{\text{ISF Organ}}^{\text{exo}} \text{IC} = 0
 \end{aligned} \tag{52}$$

III. Lymph Node

$$\begin{aligned}
 \frac{dA_{\text{LN}}^J}{dt} = & (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J + (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Liver}} \times A_{\text{ISF Liver}}^J + (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{GIT}} \times A_{\text{ISF GIT}}^J + (1 - \sigma_{\text{LY}}) \\
 & \times k_{\text{LY ISF-LN}}^{\text{Spleen}} \times A_{\text{ISF Spleen}}^J + (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Heart}} \times A_{\text{ISF Heart}}^J + (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Kidney}} \times A_{\text{ISF Kidney}}^J + (1 - \sigma_{\text{LY}}) \\
 & \times k_{\text{LY ISF-LN}}^{\text{Skin}} \times A_{\text{ISF Skin}}^J + (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Muscle}} \times A_{\text{ISF Muscle}}^J - \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^J \\
 & A_{\text{LN}}^{\text{endo}} \text{IC} = A_{\text{LN}}^{\text{endo}} \text{SS}; A_{\text{LN}}^{\text{exo}} \text{IC} = 0
 \end{aligned} \tag{53}$$

Appendix 4: Model Equations for Lumping of GIT and Spleen (Splanchnic) and Heart, Kidney, Skin, and Muscle (Visceral)

This is Step #2 in the model development. Please refer to Fig. 3 for model structure and Table I for model parameters.

I. plasma

Endogenous IgG

For the lumped compartment, the lymphatic can be described as the sum of flow for each individual organ as:

$$L_{\text{Splanchnic}} = L_{\text{GIT}} + L_{\text{Spleen}}$$

$$L_{\text{Visceral}} = L_{\text{Heart}} + L_{\text{Kidney}} + L_{\text{Skin}} + L_{\text{Muscle}}$$

Similarly, the plasma flow for the lumped compartment can be described as:

Then the equation for endogenous IgG in plasma becomes:

$$Q_{\text{Splanchnic}} = Q_{\text{GIT}} + Q_{\text{Spleen}}$$

$$Q_{\text{Visceral}} = Q_{\text{Heart}} + Q_{\text{Kidney}} + Q_{\text{Skin}} + Q_{\text{Muscle}}$$

$$\frac{dA_{\text{plasma}}^{\text{endo}}}{dt} = K_0 \times V_{\text{Plasma}} + k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{endo}} - \frac{L_{\text{Splanchnic}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{endo}} - \frac{Q_{\text{Liver}} + Q_{\text{Visceral}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{endo}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^{\text{endo}} \times F_{\text{return}}$$

$$IC = A_{\text{plasma}}^{\text{endo}} \text{SS} \quad (54)$$

Exogenous mAb

$$\frac{dA_{\text{plasma}}}{dt} = k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}} - \frac{L_{\text{Splanchnic}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}} - \frac{Q_{\text{Liver}} + Q_{\text{Visceral}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}}$$

$$IC = \text{Dose}_{\text{mAb}} \quad (55)$$

II. Organs

A. Vascular Space

Equations for the vascular compartment in liver and lung are different from other organs.

i. lung

$$\frac{dA_{\text{VAS Lung}}^{\text{J}}}{dt} = k_{\text{VAS-circul.}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}} + k_{\text{VAS-circul.}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^{\text{J}} - k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{J}} - k_{\text{VAS-EL}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{J}}$$

$$- (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{J}} + k_{\text{VAS-VAS}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{J}} + k_{\text{ISF-VAS}}^{\text{Lung}} \times A_{\text{ISF Lung}}^{\text{J}} - k_{\text{VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{J}}$$

$$A_{\text{VAS Lung}}^{\text{endo}} IC = A_{\text{VAS Lung}}^{\text{endo}} \text{SS}; A_{\text{VAS Lung}}^{\text{exo}} IC = 0 \quad (56)$$

ii. Liver

$$\frac{dA_{\text{VAS Liver}}^{\text{J}}}{dt} = k_{\text{VAS-circul.}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}} + \frac{L_{\text{Splanchnic}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{J}} + \frac{Q_{\text{Liver}} - (Q_{\text{Splanchnic}})}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{J}} - k_{\text{VAS-circul.}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}}$$

$$- k_{\text{VAS-EL}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}} - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}} + k_{\text{VAS-VAS}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}} + k_{\text{ISF-VAS}}^{\text{Liver}} \times A_{\text{ISF Liver}}^{\text{J}}$$

$$- k_{\text{VAS-ISF}}^{\text{Liver}} \times A_{\text{VAS Liver}}^{\text{J}}$$

$$A_{\text{VAS Liver}}^{\text{endo}} IC = A_{\text{VAS Liver}}^{\text{endo}} \text{SS}; A_{\text{VAS Liver}}^{\text{exo}} IC = 0 \quad (57)$$

iii. splanchnic (GIT and spleen lumped)

$$\frac{dA_{\text{VAS Splanchnic}}^{\text{J}}}{dt} = \frac{Q_{\text{Splanchnic}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^{\text{J}} - k_{\text{VAS-circul.}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}} - k_{\text{VAS-EL}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}} - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}}$$

$$+ k_{\text{VAS-VAS}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}} + k_{\text{ISF-VAS}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^{\text{J}} - k_{\text{VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^{\text{J}}$$

$$A_{\text{VAS Splanchnic}}^{\text{endo}} IC = A_{\text{VAS Splanchnic}}^{\text{endo}} \text{SS}; A_{\text{VAS Splanchnic}}^{\text{exo}} IC = 0 \quad (58)$$

iv. visceral (heart, kidney, skin, muscle lumped)

$$\begin{aligned} \frac{dA_{VAS\ Visceral}^J}{dt} &= \frac{Q_{Visceral}}{V_{Plasma}} \times A_{Plasma}^J - k_{VAS-circul.}^{Visceral} \times A_{VAS\ Visceral}^J - k_{VAS-EL}^{Visceral} \times A_{VAS\ Visceral}^J - (1-\sigma_{VAS}) \\ &\times k_{LY\ VAS-ISF}^{Visceral} \times A_{VAS\ Visceral}^J + k_{VAS-VAS}^{Visceral} \times A_{VAS\ Visceral}^J + k_{ISF-VAS}^{Visceral} \times A_{ISF\ Visceral}^J - k_{VAS-ISF}^{Visceral} \times A_{VAS\ Visceral}^J \\ A_{VAS\ Visceral}^{endo} IC &= A_{VAS\ Visceral}^{endo} SS; A_{VAS\ Visceral}^{exo} IC = 0 \end{aligned} \quad (59)$$

B. Interstitial Space

i. lung, liver

(All organs but splanchnic and visceral)

$$\begin{aligned} \frac{dA_{ISF\ Organ}^J}{dt} &= (1-\sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Organ} \times A_{VAS\ Organ}^J - (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Organ} \times A_{ISF\ Organ}^J - k_{ISF-EL}^{Organ} \\ &\times A_{ISF\ Organ}^J + k_{VAS-ISF}^{Organ} \times A_{VAS\ Organ}^J + k_{ISF-ISF}^{Organ} \times A_{ISF\ Organ}^J - k_{ISF-VAS}^{Organ} \times A_{ISF\ Organ}^J \\ A_{ISF\ Organ}^{endo} IC &= A_{ISF\ Organ}^{endo} SS; A_{ISF\ Organ}^{exo} IC = 0 \end{aligned} \quad (60)$$

ii. splanchnic (GIT and spleen lumped)

$$\begin{aligned} \frac{dA_{ISF\ Splanchnic}^J}{dt} &= (1-\sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Splanchnic} \times A_{VAS\ Splanchnic}^J - (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Splanchnic} \times A_{ISF\ Splanchnic}^J \\ &- k_{ISF-EL}^{Splanchnic} \times A_{ISF\ Splanchnic}^J + k_{VAS-ISF}^{Splanchnic} \times A_{VAS\ Splanchnic}^J + k_{ISF-ISF}^{Splanchnic} \times A_{ISF\ Splanchnic}^J - k_{ISF-VAS}^{Splanchnic} \times A_{ISF\ Splanchnic}^J \\ A_{ISF\ Splanchnic}^{endo} IC &= A_{ISF\ Splanchnic}^{endo} SS; A_{ISF\ Splanchnic}^{exo} IC = 0 \end{aligned} \quad (61)$$

iii. visceral (heart, kidney, skin, muscle lumped)

$$\begin{aligned} \frac{dA_{ISF\ Visceral}^J}{dt} &= (1-\sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Visceral} \times A_{VAS\ Visceral}^J - (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Visceral} \times A_{ISF\ Visceral}^J - k_{ISF-EL}^{Visceral} \\ &\times A_{ISF\ Visceral}^J + k_{VAS-ISF}^{Visceral} \times A_{VAS\ Visceral}^J + k_{ISF-ISF}^{Visceral} \times A_{ISF\ Visceral}^J - k_{ISF-VAS}^{Visceral} \times A_{ISF\ Visceral}^J \\ A_{ISF\ Visceral}^{endo} IC &= A_{ISF\ Visceral}^{endo} SS; A_{ISF\ Visceral}^{exo} IC = 0 \end{aligned} \quad (62)$$

III. Lymph Node

$$\begin{aligned} \frac{dA_{LN}^J}{dt} &= (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Lung} \times A_{ISF\ Lung}^J + (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Liver} \times A_{ISF\ Liver}^J + (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Splanchnic} \\ &\times A_{ISF\ Splanchnic}^J + (1-\sigma_{LY}) \times k_{LY\ ISF-LN}^{Visceral} \times A_{ISF\ Visceral}^J - \frac{1}{\tau_{LN}} \times A_{LN}^J \\ A_{LN}^{endo} IC &= A_{LN}^{endo} SS; A_{LN}^{exo} IC = 0 \end{aligned} \quad (63)$$

Appendix 5: Model Equations after fast transfer from liver to lung (Step#3)

Liver compartment no longer exists and the appearance of $\frac{Q_{Liver}}{V_{Plasma}}$ is solely indicative of the transfer from plasma to lung. Finally, splanchnic is now positioned to be parallel to other organs, *i.e.*, visceral.

I. plasma
Endogenous IgG

$$\begin{aligned} \frac{dA_{plasma}^{endo}}{dt} &= K_0 \times V_{Plasma} + k_{VAS-circul.}^{Lung} \times A_{VAS\ Lung}^{endo} \\ &- \frac{Q_{Splanchnic} + Q_{Visceral} + Q_{Liver}}{V_{Plasma}} \times A_{plasma}^{endo} + \frac{1}{\tau_{LN}} \\ &\times A_{LN}^{endo} \times F_{return} IC = A_{plasma}^{endo} SS \end{aligned} \quad (64)$$

Exogenous mAb

$$\frac{dA_{\text{plasma}}}{dt} = k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}} - \frac{Q_{\text{Splanchnic}} + Q_{\text{Visceral}} + Q_{\text{Liver}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}} \quad (65)$$

IC = Dose_{mAb}

II. Organs

A. Vascular Space

Equations for the vascular compartment in lung are different from other organs.

i. lung

$$\begin{aligned} \frac{dA_{\text{VAS Lung}}^J}{dt} = & k_{\text{VAS-circul.}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J + k_{\text{VAS-circul.}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J + \frac{Q_{\text{Liver}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^J - k_{\text{VAS-circul.}}^{\text{Lung}} \\ & \times A_{\text{VAS Lung}}^J - k_{\text{VAS-EL}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J + k_{\text{VAS-VAS}}^{\text{Lung}} \\ & \times A_{\text{VAS Lung}}^J + k_{\text{ISF-VAS}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J - k_{\text{VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J A_{\text{VAS Lung}}^{\text{endo}} \text{IC} = A_{\text{VAS Lung}}^{\text{endo}} \text{SS}; A_{\text{VAS Lung}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (66)$$

ii. splanchnic (GIT and spleen lumped)

$$\begin{aligned} \frac{dA_{\text{VAS Splanchnic}}^{\text{endo}}}{dt} = & \frac{Q_{\text{Splanchnic}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^J - k_{\text{VAS-circul.}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J - k_{\text{VAS-EL}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J \\ & - (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J + k_{\text{VAS-VAS}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J + k_{\text{ISF-VAS}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^J \\ & - k_{\text{VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J A_{\text{VAS Splanchnic}}^{\text{endo}} \text{IC} = A_{\text{VAS Splanchnic}}^{\text{endo}} \text{SS}; A_{\text{VAS Splanchnic}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (67)$$

iii. visceral (heart, kidney, skin, muscle lumped)

$$\begin{aligned} \frac{dA_{\text{VAS Visceral}}^J}{dt} = & \frac{Q_{\text{Visceral}}}{V_{\text{Plasma}}} \times A_{\text{Plasma}}^J - k_{\text{VAS-circul.}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J - k_{\text{VAS-EL}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J - (1 - \sigma_{\text{VAS}}) \\ & \times k_{\text{LY VAS-ISF}}^{\text{Visceral}} \times A_{\text{VAS Organ}}^J + k_{\text{VAS-VAS}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J + k_{\text{ISF-VAS}}^{\text{Visceral}} \times A_{\text{ISF Visceral}}^J - k_{\text{VAS-ISF}}^{\text{Visceral}} \\ & \times A_{\text{VAS Visceral}}^J A_{\text{VAS Visceral}}^{\text{endo}} \text{IC} = A_{\text{VAS Visceral}}^{\text{endo}} \text{SS}; A_{\text{VAS Visceral}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (68)$$

B. Interstitial Space

i. lung

$$\begin{aligned} \frac{dA_{\text{ISF Lung}}^J}{dt} = & (1 - \sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J - (1 - \sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J - k_{\text{ISF-EL}}^{\text{Lung}} \\ & \times A_{\text{ISF Lung}}^J + k_{\text{VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J + k_{\text{ISF-ISF}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J - k_{\text{ISF-VAS}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J A_{\text{ISF Organ}}^{\text{endo}} \text{IC} \\ & \therefore A_{\text{ISF Organ}}^{\text{endo}} \text{SS}; A_{\text{ISF Organ}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (69)$$

ii. splanchnic (GIT and spleen lumped)

$$\begin{aligned} \frac{dA_{\text{ISF Splanchnic}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J - (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^J - \\ & k_{\text{ISF-EL}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^J + k_{\text{VAS-ISF}}^{\text{Splanchnic}} \times A_{\text{VAS Splanchnic}}^J + k_{\text{ISF-ISF}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^J - k_{\text{ISF-VAS}}^{\text{Splanchnic}} \\ & \times A_{\text{ISF Splanchnic}}^J A_{\text{ISF Splanchnic}}^{\text{endo}} \text{IC} = A_{\text{ISF Splanchnic}}^{\text{endo}} \text{SS}; A_{\text{ISF Splanchnic}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (70)$$

iii. visceral (heart, kidney, skin, muscle lumped)

$$\begin{aligned} \frac{dA_{\text{ISF Visceral}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J - (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Visceral}} \times A_{\text{ISF Visceral}}^J - k_{\text{ISF-EL}}^{\text{Visceral}} \\ & \times A_{\text{ISF Visceral}}^J + k_{\text{VAS-ISF}}^{\text{Visceral}} \times A_{\text{VAS Visceral}}^J + k_{\text{ISF-ISF}}^{\text{Visceral}} \times A_{\text{ISF Visceral}}^J - k_{\text{ISF-VAS}}^{\text{Visceral}} \times A_{\text{ISF Visceral}}^J A_{\text{ISF Visceral}}^{\text{endo}} \text{IC} \\ & = A_{\text{ISF Visceral}}^{\text{endo}} \text{SS}; A_{\text{ISF Visceral}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (71)$$

III. Lymph Node Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{LN}}^J}{dt} = & (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J + (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Splanchnic}} \times A_{\text{ISF Splanchnic}}^J + (1-\sigma_{\text{LY}}) \\ & \times k_{\text{LY ISF-LN}}^{\text{Visceral}} \times A_{\text{ISF Visceral}}^J - \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^J A_{\text{LN}}^{\text{endo}} \text{IC} = A_{\text{LN}}^{\text{endo}} \text{SS}; A_{\text{LN}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (72)$$

Appendix 6: Model Equations for Lumping Splanchnic and Visceral into Peripheral (Step#4)

I. plasma

Endogenous IgG

$$\begin{aligned} \frac{dA_{\text{plasma}}^{\text{endo}}}{dt} = & K_0 \times V_{\text{Plasma}} + k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^{\text{endo}} - \frac{Q_{\text{Peripheral}} + Q_{\text{Liver}}}{V_{\text{Plasma}}} \times A_{\text{plasma}}^{\text{endo}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^{\text{endo}} \times F_{\text{return}} \\ \text{IC} = & A_{\text{plasma}}^{\text{endo}} \text{SS} \end{aligned} \quad (73)$$

Exogenous mAb

$$\begin{aligned} \frac{dA_{\text{plasma}}}{dt} = & k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}} - \frac{Q_{\text{Peripheral}} + Q_{\text{Liver}}}{V_{\text{Plasma}}} \times A_{\text{plasma}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}} \\ \text{IC} = & \text{Dose}_{\text{mAb}} \end{aligned} \quad (74)$$

H. Organs

A. Vascular Space

Equations for the vascular compartment in lung are different from other organs.

i. lung

$$\begin{aligned} \frac{dA_{\text{VAS Lung}}^J}{dt} = & k_{\text{VAS-circul.}}^{\text{Peripheral}} \times A_{\text{VAS Peripheral}}^J + \frac{Q_{\text{Liver}}}{V_{\text{Plasma}}} \times A_{\text{plasma}}^J - k_{\text{VAS-circul.}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J - k_{\text{VAS-EL}}^{\text{Lung}} \\ & \times A_{\text{VAS Lung}}^J - (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J + k_{\text{VAS-VAS}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J + k_{\text{ISF-VAS}}^{\text{Lung}} \times A_{\text{ISF Lung}}^J \\ & - k_{\text{VAS-ISF}}^{\text{Lung}} \times A_{\text{VAS Lung}}^J A_{\text{VAS Lung}}^{\text{endo}} \text{IC} = A_{\text{VAS Lung}}^{\text{endo}} \text{SS}; A_{\text{VAS Lung}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (75)$$

ii. Peripheral (splanchnic and visceral lumped)

$$\begin{aligned}
\frac{dA_{VAS\ Peripheral}^J}{dt} = & \frac{Q_{Peripheral}}{V_{Plasma}} \times A_{Plasma}^J - k_{VAS-circul.}^{Peripheral} \times A_{VAS\ Peripheral}^J - k_{VAS-EL}^{Peripheral} \times A_{VAS\ Peripheral}^J \\
& - (1 - \sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J + k_{VAS-VAS}^{Peripheral} \times A_{VAS\ Peripheral}^J + k_{ISF-VAS}^{Peripheral} \\
& \times A_{ISF\ Peripheral}^J - k_{VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J A_{VAS\ Peripheral}^{endo} IC = A_{VAS\ Visceral}^{endo} SS; A_{VAS\ Visceral}^{exo} IC = 0
\end{aligned} \tag{76}$$

B. Interstitial Space
Peripheral

$$\begin{aligned}
\frac{dA_{ISF\ Peripheral}^J}{dt} = & (1 - \sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J - (1 - \sigma_{LY}) \times k_{LY\ ISF-LN}^{Peripheral} \times A_{ISF\ Peripheral}^J \\
& - k_{ISF-EL}^{Peripheral} \times A_{ISF\ Peripheral}^J + k_{VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J + k_{ISF-ISF}^{Peripheral} \times A_{ISF\ Peripheral}^J - k_{ISF-VAS}^{Peripheral} \\
& \times A_{ISF\ Peripheral}^J A_{ISF\ Peripheral}^{endo} IC = A_{ISF\ Visceral}^{endo} SS; A_{ISF\ Visceral}^{exo} IC = 0
\end{aligned} \tag{77}$$

III. Lymph Node
Endogenous IgG

$$\begin{aligned}
\frac{dA_{LN}^J}{dt} = & (1 - \sigma_{LY}) \times k_{LY\ ISF-LN}^{Lung} \times A_{ISF\ Lung}^J + (1 - \sigma_{LY}) \times k_{LY\ ISF-LN}^{Peripheral} \times A_{ISF\ Peripheral}^J - \frac{1}{\tau_{LN}} \times A_{LN}^J \\
& A_{LN}^{endo} IC = A_{LN}^{endo} SS; A_{LN}^{exo} IC = 0
\end{aligned} \tag{78}$$

Appendix 7: Model Equations for Fast Transfer from Lung to Plasma (Step#5)(Figure 4d)
I. plasma

Endogenous IgG

$$\begin{aligned}
\frac{dA_{plasma}^{endo}}{dt} = & K_0 \times V_{Plasma} + k_{VAS-circul.}^{Peripheral} \times A_{VAS\ Peripheral}^{endo} - \frac{Q_{Peripheral}}{V_{Plasma}} \times A_{Plasma}^{endo} + \frac{1}{\tau_{LN}} \times A_{LN}^{endo} \times F_{return} \\
& IC = A_{plasma}^{endo} SS
\end{aligned} \tag{79}$$

Exogenous mAb

$$\begin{aligned}
\frac{dA_{plasma}}{dt} = & k_{VAS-circul.}^{Peripheral} \times A_{VAS\ Peripheral} - \frac{Q_{Peripheral}}{V_{Plasma}} \times A_{Plasma} + \frac{1}{\tau_{LN}} \times A_{LN} \times F_{return} \\
& IC = Dose_{mAb}
\end{aligned} \tag{80}$$

II. Peripheral
A. Vascular Space

$$\begin{aligned}
\frac{dA_{VAS\ Peripheral}^J}{dt} = & \frac{Q_{Peripheral}}{V_{Plasma}} \times A_{Plasma}^J - k_{VAS-circul.}^{Peripheral} \times A_{VAS\ Peripheral}^J - k_{VAS-EL}^{Peripheral} \times A_{VAS\ Peripheral}^J \\
& - (1 - \sigma_{VAS}) \times k_{LY\ VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J + k_{VAS-VAS}^{Peripheral} \times A_{VAS\ Peripheral}^J + k_{ISF-VAS}^{Peripheral} \times A_{ISF\ Peripheral}^J \\
& - k_{VAS-ISF}^{Peripheral} \times A_{VAS\ Peripheral}^J A_{VAS\ Peripheral}^{endo} IC = A_{VAS\ Visceral}^{endo} SS; A_{VAS\ Visceral}^{exo} IC = 0
\end{aligned} \tag{81}$$

B. Interstitial Space Peripheral

$$\begin{aligned} \frac{dA_{\text{ISF Peripheral}}^J}{dt} = & (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Peripheral}} \times A_{\text{VAS Peripheral}}^J - (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}^J \\ & - k_{\text{ISF-EL}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}^J + k_{\text{VAS-ISF}}^{\text{Peripheral}} \times A_{\text{VAS Peripheral}}^J + k_{\text{ISF-ISF}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}^J \\ & - k_{\text{ISF-VAS}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}^J A_{\text{ISF Peripheral}}^{\text{endo}} \text{IC} = A_{\text{ISF Visceral}}^{\text{endo}} \text{ss}; A_{\text{ISF Visceral}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (82)$$

III. Lymph Node

$$\begin{aligned} \frac{dA_{\text{LN}}^J}{dt} = & (1-\sigma_{\text{LY}}) \times k_{\text{LY ISF-LN}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}^J - \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}}^J \\ & A_{\text{LN}}^{\text{endo}} \text{IC} = A_{\text{LN}}^{\text{endo}} \text{ss}; A_{\text{LN}}^{\text{exo}} \text{IC} = 0 \end{aligned} \quad (83)$$

Appendix 8: Rapid equilibrium between plasma and Vascular compartments forming Central compartment (Model Equations) (Step#6)

(Figure 5) (Supplementary Table 4)

In this step, rapid equilibrium from plasma to vascular compartment is assumed. The rate of transfer from plasma to vascular compartment of Peripheral organs ($\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}$) is of the same order as transfer rate from the vascular compartment of Peripheral organs to plasma ($k_{\text{VAS-circul.}}^{\text{Peripheral}}$). These two rates are assumed to be faster than rates governing transfer between vascular and interstitial spaces:

$$k_{\text{VAS-circul.}}^{\text{Peripheral}} \gg k_{\text{VAS-EL}}^{\text{Peripheral}}, k_{\text{LY VAS-ISF}}^{\text{Peripheral}}, k_{\text{VAS-VAS}}^{\text{Peripheral}}, k_{\text{ISF-VAS}}^{\text{Peripheral}}, k_{\text{VAS-ISF}}^{\text{Peripheral}} \quad \frac{1}{k_{\text{VAS-circul.}}^{\text{Peripheral}}} \sim 0$$

(Table III):

Further, we assume that the vascular compartment is in rapid equilibrium such that the rate of change is negligible (i.e., $\frac{dA_{\text{VAS Peripheral}}}{dt}$ is much smaller than the right hand side of the differential equation)

Dividing Eqs. 114/115 by $k_{\text{VAS-circul.}}^{\text{Peripheral}}$ leads to

$$0 = \frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}} * A_{\text{Plasma}} - A_{\text{VAS Peripheral}} - 0 - 0 + 0 + 0 - 0 \quad (84)$$

After rearrangement

$$A_{\text{Plasma}} = \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}} \times A_{\text{VAS Peripheral}} \quad (85)$$

Introduce a new variable for the total amount in vascular and plasma compartments (Central)

$$A_{\text{Central}} = A_{\text{Plasma}} + A_{\text{VAS Peripheral}} \quad (86)$$

Then

$$A_{\text{Plasma}} = \frac{A_{\text{Central}}}{\left(1 + \frac{Q_{\text{Peripheral}}}{k_{\text{VAS-circul.}}^{\text{Peripheral}} V_{\text{Plasma}}}\right)} \quad (87)$$

and

$$A_{\text{VAS Peripheral}} = \frac{A_{\text{Central}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)} \quad (88)$$

Adding differential equations for vascular and plasma compartments to get the differential equation for A_{Central} results in

$$\begin{aligned}
\frac{dA_{\text{Central}}}{dt} = & -k_{\text{VAS-EL}}^{\text{Peripheral}} \times \frac{A_{\text{Central}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)} - (1-\sigma_{\text{VAS}}) \times k_{\text{LY VAS-ISF}}^{\text{Peripheral}} \times \frac{A_{\text{Central}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)} + k_{\text{VAS-VAS}}^{\text{Peripheral}} \\
& \times \frac{A_{\text{Central}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)} + k_{\text{ISF-VAS}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}} - k_{\text{VAS-ISF}}^{\text{Peripheral}} \times \frac{A_{\text{Central}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}}
\end{aligned} \tag{89}$$

Regroup rates and change parameter names to reflect new model structure

Let

$$k_{\text{EL}}^{\text{Central}} = \frac{k_{\text{VAS-EL}}^{\text{Peripheral}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)}$$

be elimination rate from the central compartment

Let $\frac{k_{\text{LY VAS-ISF}}^{\text{Peripheral}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)}$ be transfer rate from the central to

interstitial (*i.e.*, peripheral) compartment *via* lymphatic flow

Let $\frac{k_{\text{VAS-VAS}}^{\text{Peripheral}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)}$ first-order input from central compart-

ment to itself which reflects the impact of recycled drug from endosomal compartment

Let $\frac{k_{\text{VAS-ISF}}^{\text{Peripheral}}}{\left(1 + \frac{k_{\text{VAS-circul.}}^{\text{Peripheral}}}{\frac{Q_{\text{Peripheral}}}{V_{\text{Plasma}}}}\right)}$ be first-order input from central to

interstitial compartment

Let $k_{\text{ISF-VAS}}^{\text{Peripheral}}$ be termed $k_{\text{ISF-Central}}^{\text{Peripheral}}$ to reflect the updated model structure

Thus equations for Central, Peripheral and lymph node compartments are provided as follows,

Central Compartment

$$\begin{aligned}
\frac{dA_{\text{Central}}}{dt} = & -k_{\text{EL}}^{\text{Central}} \times A_{\text{Central}} - (1-\sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} \times A_{\text{Central}} + k_{\text{Central}}^{\text{Central}} \times A_{\text{Central}} + k_{\text{ISF-Central}}^{\text{Peripheral}} \\
& \times A_{\text{ISF Peripheral}} - k_{\text{Central-ISF}}^{\text{Central}} \times A_{\text{Central}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}}
\end{aligned} \tag{90}$$

Peripheral Compartment

$$\begin{aligned}
\frac{dA_{\text{ISF Peripheral}}}{dt} = & (1-\sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} \times A_{\text{Central}} - (1-\sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}} - k_{\text{ISF-EL}}^{\text{Peripheral}} \\
& \times A_{\text{ISF Peripheral}} + k_{\text{Central-ISF}}^{\text{Central}} \times A_{\text{Central}} + k_{\text{ISF-ISF}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}} - k_{\text{ISF-Central}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}}
\end{aligned} \tag{91}$$

Lymph Node

$$\frac{dA_{\text{LN}}}{dt} = (1-\sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}} - \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \tag{92}$$

Rearrange equation for A_{Central} and $A_{\text{ISF Peripheral}}$

$$\frac{dA_{\text{Central}}}{dt} = -(k_{\text{EL}}^{\text{Central}} - k_{\text{Central}}^{\text{Central}}) \times A_{\text{Central}} - ((1 - \sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} + k_{\text{Central-ISF}}^{\text{Central}}) \times A_{\text{Central}} + k_{\text{ISF-Central}}^{\text{Peripheral}} \times A_{\text{ISF Peripheral}} + \frac{1}{\text{Tau}_{\text{LN}}} \times A_{\text{LN}} \times F_{\text{return}} \quad (93)$$

$$\frac{dA_{\text{ISF Peripheral}}}{dt} = ((1 - \sigma_{\text{VAS}}) \times k_{\text{LY-ISF}}^{\text{Central}} + k_{\text{Central-ISF}}^{\text{Central}}) \times A_{\text{Central}} - ((1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}} + k_{\text{ISF-Central}}^{\text{Peripheral}}) \times A_{\text{ISF Peripheral}} - (k_{\text{ISF-EL}}^{\text{Peripheral}} - k_{\text{ISF-ISF}}^{\text{Peripheral}}) \times A_{\text{ISF Peripheral}} \quad (94)$$

Subsequently, the following rearrangements and assumptions were made:

- 1- Rearrangement: Subtracting the rate of recycling of mAb from the endosomes back to the central compartment ($k_{\text{Central}}^{\text{Central}}$, $5.8\text{E-}06 \text{ h}^{-1}$) which acts as an input to the central compartment from the central compartment elimination, ($k_{\text{EL}}^{\text{Central}}$, $6.1\text{E-}06 \text{ h}^{-1}$) results in a slower elimination rate termed, k_{EL}^{C} ($3\text{E-}07 \text{ h}^{-1}$).

$$k_{\text{EL}}^{\text{Central}} - k_{\text{Central}}^{\text{Central}} = k_{\text{EL}}^{\text{C}} \quad (95)$$

Similarly, subtracting the rate of recycling of mAb from the endosomes back to the peripheral compartment ($k_{\text{Peripheral}}^{\text{Peripheral}}$, $2.73\text{E-}06 \text{ h}^{-1}$) from the peripheral compartment elimination, ($k_{\text{EL}}^{\text{Peripheral}}$, $2.85\text{E-}06 \text{ h}^{-1}$) results in a slower peripheral elimination rate termed, k_{EL}^{P} ($1.2\text{E-}07 \text{ h}^{-1}$).

$$k_{\text{EL}}^{\text{Peripheral}} - k_{\text{Peripheral}}^{\text{Peripheral}} = k_{\text{EL}}^{\text{P}} \quad (96)$$

- 2- Rearrangement: Transfer from central to peripheral compartments via lymphatic flow and the reflection of the fraction mAb-FcRn complex recycled are combined into one term that describes the sum of the two processes.

$$(1 - \sigma_{\text{V}}) \times k_{\text{LY Cen-Per}} + k_{\text{Cen-Per}} = k_{\text{C-P}} \quad (97)$$

- 3- Assumption: Rate of return of mAb to the lymph node via lymphatic flow ($(1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}}$, 0.39 h^{-1}) is faster than the reflection of the fraction mAb-FcRn complex recycled, ($k_{\text{ISF-Central}}^{\text{Peripheral}}$, $1.95\text{E-}06 \text{ h}^{-1}$)

$$(1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}} \gg k_{\text{ISF-Central}}^{\text{Peripheral}} \quad (98)$$

- 4- Assumption: Rate of return from peripheral compartment to lymph node ($(1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}}$, 0.39 h^{-1}) is comparable to rate of return from lymph node to central

compartment ($\frac{1}{\text{Tau}_{\text{LN}}}$, 0.11 h^{-1})

$$(1 - \sigma_{\text{LY}}) \times k_{\text{LY-ISF-LN}}^{\text{Peripheral}} \sim \frac{1}{\text{Tau}_{\text{LN}}} = k_{\text{LN}} \quad (99)$$

- 5- Assumption: 100% of the drug in the lymph node is subject to return to the central compartment (i.e., $F_{\text{return}} = 1$)
Rewrite Eqs. 93, and 94

$$\frac{dA_{\text{Central}}}{dt} = -k_{\text{EL}}^{\text{C}} \times A_{\text{Central}} - k_{\text{CP}} \times A_{\text{Central}} + k_{\text{LN}} \times A_{\text{LN}} \quad (100)$$

$$\frac{dA_{\text{ISF Peripheral}}}{dt} = k_{\text{CP}} \times A_{\text{Central}} - k_{\text{LN}} \times A_{\text{ISF Peripheral}} - k_{\text{EL}}^{\text{P}} \times A_{\text{ISF Peripheral}} \quad (101)$$

Further, $k_{\text{EL}}^{\text{C}} \sim k_{\text{EL}}^{\text{P}} = k_{\text{EL}}$. Thus, Final model equations can be written as:

A. Central Compartment

$$\frac{dA_{\text{Central}}}{dt} = -k_{\text{EL}} \times A_{\text{Central}} - k_{\text{CP}} \times A_{\text{Central}} + k_{\text{LN}} \times A_{\text{LN}} \text{IC} = \text{Dose}_{\text{mAb}} \quad (102)$$

B. Peripheral Compartment

$$\frac{dA_{\text{ISF Peripheral}}}{dt} = k_{\text{CP}} \times A_{\text{Central}} - k_{\text{LN}} \times A_{\text{ISF Peripheral}} - k_{\text{EL}} \times A_{\text{ISF Peripheral}} \text{IC} = 0 \quad (103)$$

C. Lymph node Compartment

$$\frac{dA_{\text{LN}}}{dt} = k_{\text{LN}} \times (A_{\text{ISF Peripheral}} - A_{\text{LN}}) \text{IC} = 0 \quad (104)$$

Appendix 9: Derivation of the Output Function in Transit Compartment System with Fast Transfer

In this appendix, we show that the output from the last of N transit compartments equals to the input, if the transfer

rate between transit compartments is fast compared to other processes. We assume that all model variables describing amounts are nonnegative. We also skip the proofs of the following statements:

$$0 \leq A_{\text{END Organ-}i}^{\text{endo}}, 0 \leq A_{\text{END Organ-}i}^{\text{exo}}, 0 \leq \text{ARCPX}_{\text{END Organ-}i}^{\text{endo}}, 0 \leq \text{ARCPX}_{\text{END Organ-}i}^{\text{exo}}, i = 1, 2, 3, 4 \quad (105)$$

and

$$\text{ARCPX}_{\text{Organ-}i}^{\text{endo}} + \text{ARCPX}_{\text{Organ-}i}^{\text{exo}} \leq \text{Rtotal}_{\text{Organ-}i}, i = 1, 2, 3, 4 \quad (106)$$

and there exist positive constants M^{endo} and M^{exo} such that

$$\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J \leq M^J, J = \text{endo or exo} \quad (107)$$

First we will show that for $i=1,2,3,4$, $J=\text{endo or exo}$

$$\frac{1}{\tau} \times A_{\text{END Organ-}i}^J \leq M^J + k_{\text{off-}1} \times \text{Rtotal}_{\text{Organ-}1} + \dots + k_{\text{off-}i} \times \text{Rtotal}_{\text{Organ-}i} \quad (108)$$

and

$$\frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-}i}^J \leq \tau \times \frac{k_{\text{on-}i}}{V_{\text{END}}^{\text{Organ}}} \times \text{Rtotal}_{\text{Organ-}i} \times (M^J + k_{\text{off-}1} \times \text{Rtotal}_{\text{Organ-}1} + \dots + k_{\text{off-}i} \times \text{Rtotal}_{\text{Organ-}i}) \quad (109)$$

Applying the integrating factor $e^{t/\tau}$ to (9) and (10) one can obtain the following solution for $A_{\text{END Organ-}1}^J$:

$$\begin{aligned} A_{\text{END Organ-}1}^J(t) = & \int_0^t \left(\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J(z) + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J(z) \right) \times e^{\frac{z-t}{\tau}} dz \\ & - \frac{k_{\text{on-}1}}{V_{\text{END}}^{\text{Organ}}} \times \int_0^t A_{\text{END Organ-}1}^J \times (\text{Rtotal}_{\text{Organ-}1} - \text{ARCPX}_{\text{Organ-}1}^J(z) - \text{ARCPX}_{\text{Organ-}1}^J(z)) \times e^{\frac{z-t}{\tau}} dz \\ & + k_{\text{off-}1} \times \int_0^t \text{ARCPX}_{\text{Organ-}1}^J(z) \times e^{(z-t)/\tau} dz \end{aligned} \quad (110)$$

and

$$\begin{aligned} \text{ARCPX}_{\text{Organ-}1}^J(t) = & \frac{k_{\text{on-}1}}{V_{\text{END}}^{\text{Organ}}} \times \int_0^t A_{\text{END Organ-}1}^J \times (\text{Rtotal}_{\text{Organ-}1} - \text{ARCPX}_{\text{Organ-}1}^J(z) - \text{ARCPX}_{\text{Organ-}1}^J(z)) \times e^{\frac{z-t}{\tau}} dz - k_{\text{off-}1} \\ & \times \int_0^t \text{ARCPX}_{\text{Organ-}1}^J(z) \times e^{(z-t)/\tau} dz \end{aligned} \quad (111)$$

(107) and (108) imply that

$$\begin{aligned} A_{\text{END Organ-}1}^J(t) \leq & M^J \times \int_0^t e^{\frac{z-t}{\tau}} dz + k_{\text{off-}1} \times \text{Rtotal}_{\text{Organ-}1} \\ & \times \int_0^t e^{\frac{z-t}{\tau}} dz \leq \tau \times (M^J + k_{\text{off-}1} \times \text{Rtotal}_{\text{Organ-}1}) \end{aligned} \quad (112)$$

and

$$\text{ARCPX}_{\text{Organ-}1}^J(t) \leq \frac{k_{\text{on-}1}}{V_{\text{END}}^{\text{Organ}}} \times \text{Rtotal}_{\text{Organ-}1} \times \int_0^t A_{\text{END Organ-}1}^J \times e^{\frac{z-t}{\tau}} dz \quad (113)$$

From (113) it follows

$$\text{ARCPX}_{\text{Organ-}1}^J(t) \leq \tau^2 \times (M^J + k_{\text{off-}1} \times \text{Rtotal}_{\text{Organ-}1}) \times \frac{k_{\text{on-}1}}{V_{\text{END}}^{\text{Organ}}} \times \text{Rtotal}_{\text{Organ-}1}$$

This proves (109) and (110) for $i=1$. The proof of cases $i=2,3,4$ is analogous.

In the next step we will show that for $i=1,2,3,4$, $J=\text{endo or exo}$

$$\frac{1}{\tau} \times A_{\text{END Organ-}i}^J \rightarrow \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J \text{ as } \tau \rightarrow 0 \quad (114)$$

That will yield (23) for $i=4$. Consider first the case $i=1$. Multiplying (110) by $1/\tau$ results in

$$\begin{aligned} \frac{1}{\tau} \times A_{\text{END Organ-1}}^J(t) = & \int_0^t \left(\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J(z) + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J(z) \right) \times \frac{1}{\tau} e^{\frac{z-t}{\tau}} dz \\ & - \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \times \int_0^t \frac{1}{\tau} \times A_{\text{END Organ-1}}^J \times \left(\text{Rtotal}_{\text{Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^J(z) - \text{ARCPX}_{\text{Organ-1}}^J(z) \right) \times e^{\frac{z-t}{\tau}} dz \\ & + k_{\text{off-1}} \times \int_0^t \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-1}}^J(z) \times e^{(z-t)/\tau} dz \end{aligned} \quad (115)$$

From (107) and (112) the following bound applies to the integral

$$\begin{aligned} \int_0^t \frac{1}{\tau} \times A_{\text{END Organ-1}}^J \times \left(\text{Rtotal}_{\text{Organ-1}} - \text{ARCPX}_{\text{Organ-1}}^J(z) - \text{ARCPX}_{\text{Organ-1}}^J(z) \right) \times e^{\frac{z-t}{\tau}} dz \leq & (M^J + k_{\text{off-1}} \times \text{Rtotal}_{\text{Organ-1}}) \\ & \times \text{Rtotal}_{\text{Organ-1}} \times \tau \end{aligned} \quad (116)$$

This means that the integral in (117) approaches 0 as $\tau \rightarrow 0$. Similarly, (110) implies that the last integral in (116) can be bound as follows:

$$\begin{aligned} \int_0^t \frac{1}{\tau} \times \text{ARCPX}_{\text{Organ-1}}^J(z) \times e^{(z-t)/\tau} dz \leq & \tau^2 \times \frac{k_{\text{on-1}}}{V_{\text{END}}^{\text{Organ}}} \\ & \times \text{Rtotal}_{\text{Organ-1}} \times (M^J + k_{\text{off-1}} \times \text{Rtotal}_{\text{Organ-1}}) \end{aligned} \quad (117)$$

which implies that this integral approaches 0 as $\tau \rightarrow 0$. To conclude that

$$\begin{aligned} \int_0^t \left(\frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J(z) + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J(z) \right) \\ \times \frac{1}{\tau} e^{\frac{z-t}{\tau}} dz \rightarrow \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \times A_{\text{VAS Organ}}^J(t) + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \\ \times A_{\text{ISF Organ}}^J(t) \end{aligned} \quad (118)$$

we observe that

$$\gamma(t) = \frac{1}{\tau} e^{\frac{-t}{\tau}}$$

is the gamma probability density function which possesses the approximate identity property (22,23)

$$\int_0^t f(z) \gamma(t-z) dz \rightarrow f(t) \text{ as } \tau \rightarrow 0 \quad (119)$$

for any continuous function $f(t)$. This completes proof of (114) for $i=1$. The proof of cases $i=2,3,4$ differs only in the part:

$$\begin{aligned} \int_0^t \frac{1}{\tau} \times A_{\text{END Organ-(i-1)}}^J(z) \times \frac{1}{\tau} e^{\frac{z-t}{\tau}} dz \rightarrow \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{VAS}}^{\text{Organ}}} \\ \times A_{\text{VAS Organ}}^J(t) + \frac{\text{CL}_{\text{Uptake}}^{\text{Organ}}}{V_{\text{ISF}}^{\text{Organ}}} \times A_{\text{ISF Organ}}^J(t) \text{ as } \tau \rightarrow 0 \end{aligned} \quad (120)$$

However, by induction, (107) implies (108) which concludes Appendix 9.

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