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Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies

Yanguang Cao and William J. Jusko

Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY 14214, USA

William J. Jusko: wj Jusko@buffalo.edu

Abstract

Target-mediated drug disposition (TMDD) usually accounts for nonlinear pharmacokinetics (PK) of drugs whose distribution and/or clearance are affected by their targets owing to high affinity and limited capacity. TMDD is frequently reported for monoclonal antibodies (mAb) for such reason. Minimal physiologically-based pharmacokinetic models (mPBPK), which accommodate the unique PK behaviors of mAb, provide a general approach for analyzing mAbs PK and predicting mAb interstitial concentrations in two groups of tissues. This study assessed the feasibility of incorporating TMDD into mPBPK models to consider target-binding in either plasma (cTMDD) or interstitial fluid (*ISF*) (pTMDD). The dose-related signature profiles of the pTMDD model reveal a parallel early decay phase, in contrast with the cTMDD model that exhibits a faster initial decline for low doses. The parallel early phase in the pTMDD model is associated with the slow perivascular extravasation of mAb, which restricts the initial decline regardless of interstitial target-mediated elimination. The cTMDD and pTMDD models both preserve the long terminal phase that is typically perceived in conventional two-compartment (2CM) and TMDD models. Having TMDD in *ISF* impacts the typical relationships between plasma concentrations and receptor occupancy, and between saturation of apparent nonlinear clearance and saturation of receptors. The vascular reflection coefficient (σ_v) was found to affect receptor occupancy in *ISF*. In the cTMDD model, saturation of nonlinear clearance is equivalent to saturation of receptors. However, in the pTMDD model, they are no longer equal and all parameters pertaining to receptors or receptor binding (R_{total} , K_D , K_{ss} , k_{int}) shifts such relationships. Different TMDD models were utilized in analyzing PK for seven mAbs from digitized literature data. When the target is in plasma, the cTMDD model performed similarly to the 2CM and TMDD models, but with one less system parameter. When the target exists in *ISF*, the pTMDD functioned well in analyzing only plasma data to reflect interstitial target binding properties. Assigning TMDD consistent with target-expressing tissues is important to obtain reliable characterizations of receptors and receptor binding. The mPBPK model exhibits excellent feasibility in integrating TMDD not only in plasma but also in *ISF*.

Keywords

Minimal PBPK; Monoclonal antibody; Target-mediated drug disposition; PBPK

Introduction

Monoclonal antibodies (mAb) have emerged as effective therapeutic agents for a variety of diseases and the mAb market is expected to continue witnessing rapid growth over the next decade [1]. More than 30 antibodies have been approved by the U.S. Food and Drug Administration, and hundreds of candidates are under clinical investigation [2]. The pharmacokinetic (PK) behaviors of mAb are different from small molecules in aspects such as limited vascular permeability, neonatal Fc receptor recycling, and more frequent receptor-mediated nonlinearity [3]. Accommodation of their unique PK properties can assist in better understanding and assessing factors that determine mAb PK and pharmacodynamics (PD). Minimal physiologically-based pharmacokinetic models (mPBPK) offer a simple modeling approach that incorporates physiological elements into PK analysis when only plasma data are available [4]. Our second-generation mPBPK model was developed for mAbs with this modeling concept [5]. We applied this model to extensively survey mAb PK for humans in the literature and demonstrated the feasibility of this model as a general approach in analysis of mAbs with linear PK [6].

The term “target-mediated drug disposition” (TMDD) was introduced by Levy [7] and the modeling framework was established by Mager and Jusko [8]. Drugs exhibiting TMDD often bind with high affinity and to a significant extent (relative to dose) to their target. Such drug-target interaction can be reflected in their PK profiles. TMDD is frequently reported for mAbs with strong target binding affinity and high target abundance [9]. Applying TMDD models in mAb PK analysis can reveal more insights about their targets and target binding dynamics. Although the reductionist feature of mPBPK was emphasized previously [4, 5], the model has flexibility for integrating TMDD mechanisms. The present study demonstrates this feasibility.

Most of the previous TMDD models utilized compartmental models [8–12], and considered target binding in the central compartment (2CM + TMDD) under an assumption that the target is in either blood or tissues that are at rapid equilibrium with blood. For PK analysis of mAbs, this assumption usually yields better parameter identifiability but sometimes gives inconsistent parameter estimates, particularly relating to receptor binding and dynamics [12]. One possible reason is that many mAbs have targets in extravascular space where rapid distributional equilibrium does not occur due to their limited vascular permeability. The “rapid equilibrium” assumption that is commonly applied for small molecules in TMDD models likely causes model misspecifications and yields biased parameters for mAbs when their targets are in extravascular space. Therefore, for these mAbs, building TMDD in the interstitial fluid (*ISF*) may appropriately reflect and characterize target binding properties. The second-generation mPBPK model provides a simple approach to predict interstitial concentrations of mAbs in two groups of lumped tissues. Thereby, mPBPK models can implement peripheral (interstitial) TMDD features. The present study evaluates this

feasibility and further compares model properties where TMDD is present in plasma or *ISF*. Related issues to be addressed are the influences of perivascular extravasation or vascular reflection coefficients on the interstitial target dynamics and target occupancy, how the interstitial target-mediated elimination affects the apparent nonlinear clearance, and how the perivascular extravasation restricts interstitial target-mediated elimination.

Theoretical

Model structure and simulation

The proposed model structures with TMDD in either plasma (Model A, cTMDD) or *ISF* (Model B, pTMDD) compartments in the mPBPK model are shown in Fig. 1. The mPBPK model has the same structure and symbol designations as our previous one [5]. Plasma clearance (CL_p) is the only nonspecific clearance in this model because CL_p appears to reflect the most common nonspecific clearance mechanism as found in our recent assessment [6]. In principle, the location of TMDD should be chosen consistent with target-expressing tissues. Here, for the case studies, we considered TMDD in both V_{tight} and V_{leaky} , two groups of lumped tissues defined according their endothelium structure [5], as most of the interstitial targets assessed in this study are ubiquitously expressed in various tissues. The same target dynamics and antibody-target binding properties are assumed in two groups of tissues. The target-binding process is approximated by a quasi-steady-state model, where the binding rate is balanced by the sum of the dissociation and internalization rates [13].

The differential equations for Model B are:

$$\frac{dC_p}{dt} = \frac{Input}{V_p} + [C_{lymph} \cdot L - C_p \cdot L_1 \cdot (1 - \sigma_1) - C_p \cdot L_2 \cdot (1 - \sigma_2) - CL_p \cdot C_p] / V_p \quad (1)$$

$$IC=0$$

$$\frac{dA_{tight_total}}{dt} = [L_1 \cdot (1 - \sigma_1) \cdot C_p - L_1 \cdot (1 - \sigma_L) \cdot C_{tight_free}] - AR_{tight} \cdot k_{int} \cdot V_{tight} \quad (2)$$

$$IC=0$$

$$\frac{dR_{tight_total}}{dt} = k_{syn} - (R_{tight_total} - AR_{tight}) \cdot k_{deg} - AR_{tight} \cdot k_{int} \quad (3)$$

$$IC = k_{syn} / k_{deg}$$

$$\frac{dA_{leaky_total}}{dt} = [L_2 \cdot (1 - \sigma_2) \cdot C_p - L_2 \cdot (1 - \sigma_L) \cdot C_{leaky_free}] - AR_{leaky} \cdot k_{int} \cdot V_{leaky} \quad (4)$$

$$IC=0$$

$$\frac{dR_{leaky_total}}{dt} = k_{syn} - (R_{leaky_total} - AR_{leaky}) \cdot k_{deg} - AR_{leaky} \cdot k_{int} \quad (5)$$

$$IC = k_{syn} / k_{deg}$$

$$\frac{dC_{lymph}}{dt} = [L_1 \cdot (1 - \sigma_L) \cdot C_{tight_free} + L_2 \cdot (1 - \sigma_L) \cdot C_{leaky_free} - C_{lymph} \cdot L] / V_{lymph} \quad (6)$$

$$IC=0$$

where A_{tight_total} and A_{leaky_total} represent total mass of mAb, C_{tight_free} and C_{leaky_free} indicate free concentrations of mAb, R_{tight_total} and R_{leaky_total} refer to total concentrations of target, and AR_{tight} and AR_{leaky} are concentrations of drug-target complex in the two groups of lumped tissues V_{tight} and V_{leaky} . The IC is the Initial Condition. The V_p is plasma volume, C_{lymph} is mAb concentrations in lymph, and L_1 and L_2 are lymph flows in two lumped tissues. The σ_1 and σ_2 are vascular reflection coefficients for V_{tight} and V_{leaky} , and σ_L is lymphatic reflection coefficient, predefined as 0.2 in this model, as in several previous PBPK models [14]. Rate constants are k_{syn} for target biosynthesis, k_{deg} for target degradation, and k_{int} for antibody-target complex internalization. Considering that TMDD is mostly associated with antibodies that bind with cell membrane receptors, only free mAb is assumed to be collected in lymph and further recycled back to plasma, and the drug-receptor complex is immobile in ISF . The free antibody concentrations are:

$$C_{tight_free} = 0.5 \cdot ((C_{tight_total} - K_{ss} - R_{tight_total}) + \sqrt{(C_{tight_total} - K_{ss} - R_{tight_total})^2 + 4 \cdot C_{tight_total} \cdot K_{ss}}) \quad (7)$$

$$C_{leaky_free} = 0.5 \cdot ((C_{leaky_total} - K_{ss} - R_{leaky_total}) + \sqrt{(C_{leaky_total} - K_{ss} - R_{leaky_total})^2 + 4 \cdot C_{leaky_total} \cdot K_{ss}}) \quad (8)$$

The K_{ss} is a steady-state constant defined by Gibiansky et al. [13] as:

$$K_{ss} = \frac{k_{int} + k_{off}}{k_{on}} \quad (9)$$

The k_{on} and k_{off} are antibody-receptor association and antibody-receptor dissociation rate constants. The antibody- target complex concentrations are:

$$AR_{tight} = \frac{R_{tight_total} \cdot C_{tight_free}}{K_{ss} + C_{tight_free}} \quad (10)$$

$$AR_{leaky} = \frac{R_{leaky_total} \cdot C_{leaky_free}}{K_{ss} + C_{leaky_free}} \quad (11)$$

The physiological restrictions are: V_p is actual plasma volume and V_{lymph} is total lymph volume, and:

$$\sigma_1 < 1 \quad \text{and} \quad \sigma_2 < 1 \quad (12)$$

$$V_{tight} = 0.65 \cdot ISF \cdot K_p \quad \text{and} \quad V_{leaky} = 0.35 \cdot ISF \cdot K_p, \quad (13)$$

where ISF is total volume of system interstitial fluid, and K_p is available fraction of ISF for antibody distribution. The relative fractions of V_{tight} (0.65) and V_{leaky} (0.35) to total ISF were calculated based upon the values used in full-PBPK models, as were the fractions of L_1 (0.33) and L_2 (0.67) to L [14, 15]. The physiologic parameters [14, 15] for a 70 kg body

weight person are: $L = 2.9$ L/day, $ISF = 15.6$ L, $V_{lymph} = 5.2$ L, and $V_p = 2.6$ L. The physiologic parameters for a 2.6 kg body weight monkey are: $L = 0.275$ L/day, $ISF = 0.579$ L, $V_{lymph} = 0.193$ L, and $V_p = 0.0966$ L. The physiologic parameters for a 20 g body weight mouse are: $L = 0.12$ mL/h, $ISF = 4.35$ mL, $V_{lymph} = 1.7$ mL, and $V_p = 0.85$ mL. Also, $K_p = 0.8$ for native IgG₁ and 0.4 for native IgG₄. Given the similar isoelectric point (pI) values (in the range of 8–9) of the currently assessed antibodies with native IgG₁ (8.6 for human IgG₁) [16], K_p was set to 0.8 for the following analysis.

Typical plasma concentration versus time profiles were simulated for three conditions when target-binding is assumed present in either plasma or V_{leaky} or V_{tight} . A full TMDD model (with k_{on} and k_{off}) was applied in the simulations and the differential equations are provided in the Supplementary materials. The parameters used for this simulation are listed in Table 1.

Receptor occupancy (RO) as a function of σ_v

When targets are in interstitial space, the relationship between plasma concentrations and RO is expected to differ from that when targets in blood. Their relationship would be affected by distribution rate and extent. A simulation was performed to evaluate how interstitial distribution alters the relationship between plasma concentrations and RO. Combining Eqs. (10) and (2) produces:

$$\frac{dA_{ISF_total}}{dt} = L \cdot (1 - \sigma_v) \cdot C_p - L \cdot (1 - \sigma_L) \cdot C_{ISF} - \frac{R_{total} \cdot k_{int} \cdot C_{ISF} \cdot V_{ISF}}{K_{ss} + C_{ISF}} \quad (14)$$

In Eq. (14), σ_1 , L_1 , and V_{tight} were replaced with σ_v , L , and V_{ISF} to represent a general situation. The A_{ISF_total} is total amount of antibody in ISF that could be either $A_{leaky-total}$ or $A_{tight-total}$, or antibody mass in any other tissue ISF. An equilibrium state is obtained when $dA_{ISF_total}/dt = 0$. This could approximate the situation where antibody concentrations reach steady-state in both plasma and ISF after infusion or multiple-dosing. This approximation factors out “ t ” (time) to produce an explicit equation evaluating the relationships of other factors. Then,

$$L \cdot (1 - \sigma_v) \cdot C_p - L \cdot (1 - \sigma_L) \cdot C_{ISF} - \frac{R_{total} \cdot k_{int} \cdot C_{ISF} \cdot V_{ISF}}{K_{ss} + C_{ISF}} = 0 \quad (15)$$

From $RO = \frac{C_{ISF}}{K_{ss} + C_{ISF}}$, yields $C_{ISF} = \frac{RO \cdot K_{ss}}{1 - RO}$, and substituting C_{ISF} in Eq. (15), after rearrangement, generates:

$$RO = \frac{[(1 - \sigma_v) \cdot C_p + \omega + v] - \sqrt{[(1 - \sigma_v) \cdot C_p + \omega + v]^2 - 4v \cdot (1 - \sigma_v) \cdot C_p}}{2v}, \quad (16)$$

where $v = R_{total} \cdot k_{int} \cdot \frac{V_{ISF}}{L}$ and $\omega = K_{ss} \cdot (1 - \sigma_L)$.

The relationship between RO and σ_V was then simulated according to Eq. (16) with a changing value of C_p from 500 to 4,000 nM. The other parameters used in this simulation and for the following analysis of human PK data are: $L = 2.9$ L/day and $V_{ISF} = 15.6$ L for a 70 kg person, $\sigma_L = 0.2$, $R_{total} = 10$ nM, $K_{ss} = 20$ nM, and $k_{int} = 2$ h⁻¹.

Saturation of nonlinear clearance versus saturation of receptor

In Model B, the apparent target-mediated nonlinear clearance (CL_{TM}) can be derived in a similar manner as the well-stirred hepatic clearance model where plasma apparent clearance is a function of blood flow and hepatic intrinsic clearance [17]. The well-stirred distribution of antibody in interstitial space was based on the fact that antibody has much higher diffusivity in ISF than for perivascular extravasation [18, 19]. The apparent CL_{TM} is,

$$CL_{TM} = \frac{L \cdot (1 - \sigma_V) \cdot \frac{R_{total} \cdot k_{int} \cdot V_{ISF}}{K_{ss} + C_{ISF}}}{L \cdot (1 - \sigma_L) + \frac{R_{total} \cdot k_{int} \cdot V_{ISF}}{K_{ss} + C_{ISF}}} \quad (17)$$

This derivation was made assuming a constant R_{total} , which entails an assumption of $k_{deg} = k_{int}$. This assumption allows a simple derivation of CL_{TM} , which otherwise may not be easily solved explicitly. The CL_{TM} will reach its maximum value (CL_{TM_max}) when $C_{ISF} \rightarrow 0$, then,

$$CL_{TM_max} = \frac{L \cdot (1 - \sigma_V) \cdot \frac{R_{total} \cdot k_{int} \cdot V_{ISF}}{K_{ss}}}{L \cdot (1 - \sigma_L) + \frac{R_{total} \cdot k_{int} \cdot V_{ISF}}{K_{ss}}} \quad (18)$$

For a mAb with nonlinear clearance, the clearance usually increases with a decrease of plasma concentration and a maximum clearance is expected when concentration approaches to zero. The clearance saturation ($1 - CL_{TM}/CL_{TM_max}$) is defined to reflect the remaining fraction of nonlinear clearance at a given concentration. When the target is present in plasma, clearance saturation is equivalent to target saturation (RO) given that antibody concentrations are usually much higher than target concentrations. If the target exists in ISF , the two are no longer equal. Combining Eqs. (17) and (18), their relationship is:

$$1 - \frac{CL_{TM}}{CL_{TM_max}} = \frac{\omega \cdot RO}{\omega + \nu \cdot (1 - RO)} \quad (19)$$

where the parameters relating to ν and ω are the same as in Eq. (16). The association between clearance saturation and target saturation was simulated and the factors that influence their relationship were also assessed. The parameters used in this simulation are the same as used for Eq. (16): $L = 2.9$ L/day and $V_{ISF} = 15.6$ L for a 70 kg person, $\sigma_L = 0.2$, $R_{total} = 10$ nM, $K_{ss} = 20$ nM, and $k_{int} = 2$ h⁻¹.

Data analysis

The proposed models were applied to nonlinear PK data for seven mAbs that were found in the literature: zalutumumab [20], transzusumab [21], onartuzumab [22], MEDH7945A [23], romosozumab [24], mavrilimumab [25], and efalizumab [26]. Plasma concentrations versus

time data for these antibodies were extracted using Digitizer software [27]. Where possible, a wide range of doses were utilized with all data for each mAb fitted jointly. Different models (2CM + TMDD, pTMDD, cTMDD) were compared in analyzing these data. The model structure of 2CM + TMDD is identical as previously proposed [8]. The differential equations for the 2CM + TMDD and cTMDD and all model codes are provided in the Supplementary Materials.

Computer simulations were performed using ADAPT 5 and fittings utilized the maximum likelihood method in ADAPT 5 with naïve pooling data modeling [28]. The variance model was:

$$V_i = (\text{intercept} + \text{slope} \cdot Y(t_i))^2 \quad (20)$$

where V_i is the variance of the response at the i th time point, t_i is the actual time at the i th time point, and $Y(t_i)$ is the predicted response at time t_i from the model. Variance parameters *intercept* and *slope* were estimated together with system parameters.

Model performance was evaluated by goodness-of-fits, visual inspection, sum of square residuals, Akaike Information Criterion (AIC), Schwarz Criterion (SC), and Coefficient of Variation (CV) of the estimated parameters. Joint fittings were performed for all dose levels of each mAb.

Results

General simulations and evaluations

The simulated plasma concentration versus time profiles with target-binding in either plasma (cTMDD), or V_{leaky} (pTMDD- V_{leaky}), or V_{tight} (pTMDD- V_{tight}) are shown in Fig. 2. The first two cases exhibit typical nonlinear profiles (concentration-dependent decline slopes) while the last one does not. The PK profiles of the cTMDD model reveal a rapid initial decline phase for low doses, which is similar to the 2CM + TMDD model [8]. In contrast, the plasma concentrations in the pTMDD- V_{leaky} model decline in parallel for all doses in the early phase. The cTMDD and pTMDD- V_{leaky} models both exhibit a prolonged terminal phase.

Additional simulations, assuming extremely high target densities and fast complex internalization rates, indicate that no matter how high the target-mediated clearance, the PK profiles of the pTMDD- V_{leaky} model never declined at a slope greater than that in the early phase (α -phase) of relatively high doses. This is in contrast with the cTMDD and TMDD + 2CM models where an extremely high decline slope is usually seen for low doses [8]. The early parallel decay phase, as seen in the signature profiles of the pTMDD model, is associated with the slow perivascular extravasation of mAb, which restricts the initial decline regardless of interstitial target-mediated elimination. This is the reason why there was no noticeable nonlinearity when target-binding is in V_{tight} , as the limited extravasation rate to V_{tight} ($L_1 \times (1 - \sigma_1)$) cannot support a significant CL_{TM} . Based on estimations of average σ_1 and σ_2 values for V_{tight} and V_{leaky} [6], the CL_{TM_max} are expected to be around 3.4 mL/kg for V_{tight} and 54 mL/kg for V_{leaky} in a 70 kg person. The CL_{TM_max} is expected to

be even smaller if targets are exclusively expressed within a limited interstitial space (such as a small solid tumor).

In the mPBPK model, vascular reflection (σ_v) is the major factor governing the extravasation process. A higher value of σ_v generally produces lesser interstitial distribution. As shown by the simulated relationship between RO and σ_v at an equilibrium state ($dA_{ISF_total}/dt = 0$) in Fig. 3, the σ_v negatively influences RO at a given plasma concentration. Zone I indicates the range of σ_v for tissues with fenestrated or discontinuous vascular endothelium (V_{leaky}) and Zone II represents σ_v range for tissues with continuous vascular endothelium (V_{tight}). Interestingly, there appears to be a stronger plasma concentration-(or dose-) dependency for lower σ_v values (Zone I) than for the relatively high σ_v values (Zone II) in increasing RO (efficacy). In other words, an improvement of RO (efficacy) may be easier achieved by increasing administered mAb doses for tissues with low σ_v than those with relatively high σ_v . In contrast, tissues with high σ_v exhibit a greater σ -dependency and enhancing extravasation (or reducing σ_v), such as modulating epithelial junctions [29, 30], seems to be a more efficient strategy than increasing doses to make an improvement of RO .

With an assumption of constant R_{total} , Fig. 4 displays the relationship between saturation of nonlinear clearance ($1 - CL_{TM}/CL_{TM_max}$) and saturation of receptors (RO) with different values of parameters pertaining to receptors and receptor binding properties. When TMDD exists in blood (solid line, Fig. 4), the saturation of nonlinear clearance is equivalent to saturation of targets if one considers that mAb concentrations are normally much higher than their targets. However, as shown in Fig. 4, their relationship is significantly shifted when the target is present in extravascular space and missing the target location in plasma for the TMDD model would lead to a biased inference of RO . Saturation of the apparent nonlinear clearance does not directly imply RO in the pTMDD model. Any parameter pertaining to v and ω (Eq. (19)) is expected to contribute to the degree of shift. The higher values of R_{total} and k_{int} and higher binding affinity (K_{ss} , K_D) would predict a larger shift. Although σ_v considerably affects interstitial receptor saturation (Fig. 3), it does not seem to contribute to this relationship shift. In general, the higher clearance saturation ($1 - CL_{TM}/CL_{TM_max}$) requires higher plasma drug concentrations. The steep rise (on the right of Fig. 4) indicates that a further improvement of RO needs a large escalation of plasma concentrations (or doses). In other words, when the target is in *ISF*, further improvement of RO by increasing doses appears to be more challenging for high RO , even though it is important for effective therapeutics. In any case, because of the lower concentrations of mAb in *ISF* than in plasma, a higher concentration (or dose) of mAb is warranted to achieve the same level of RO as that in plasma.

Case studies

Zalutumumab—Zalutumumab is a human IgG₁ that targets the epidermal growth factor receptor (EGFR). Lammerts van Bueren et al. [20] conducted a PK study of zalutumumab in monkeys. Their analysis revealed nonlinear PK that was attributed to extensive interstitial EGFR binding. The authors successfully applied a two-compartment model with a linear plasma clearance and an EGFR-mediated nonlinear clearance in *ISF* to simulate the plasma

PK profiles. The model simulations showed good agreement with measurements. We extracted the data and applied two models to re-analyze the data: cTMDD and pTMDD (Fig. 1). In both models, k_{deg} was assumed equal to k_{int} due to a close estimate of the two parameters in initial fittings. Both models well-captured the PK profiles (Fig. 5) and the estimated parameters are listed in Table 2. However, as discussed in the original paper, EGFR are prevalent in the *ISF* and the pTMDD model should represent the system more mechanistically. This is reflected by more robust parameter estimates (lower CV%) and slight improvement of fittings (smaller *Obj*, 233 vs 236) for the pTMDD than for the cTMDD model.

Trasuzumab—Tukoda et al. [21] evaluated the PK of trasuzumab, another humanized IgG₁ targeting HER2 after ascending doses were given to patients with metastatic breast cancer. The plasma PK profiles showed nonlinear behavior with dose-dependent terminal half-lives. The mean plasma data were analyzed with the pTMDD model. The value of k_{deg} was assumed equal to k_{int} . The model captured the PK profile well (Fig. 6) with reasonable parameter estimates (Table 2).

Onartuzumab—Onartuzumab is a monovalent (one-armed) humanized IgG₁ directed against the hepatocyte growth factor receptor (c-Met) with potential antineoplastic activity. Xiang et al. [22] found nonlinear PK of onartuzumab over a dose range of 0.5–30 mg/kg in monkeys. Onartuzumab exhibited a parallel early decline phase for all doses followed by concentration-dependent elimination. The data were fitted with the pTMDD model. The model nicely captured the PK profiles (Fig. 7) and resulted in parameters with reasonable precision (Table 2).

MEHD7945A—MEHD7945A is a human IgG₁ with dual binding specificity that is designed to target both HER3 and EGFR. Kamath et al. [23] assessed its PK in SCID beige mice and monkeys and described the PK using a two-compartment model with linear and nonlinear plasma clearances. In principle, a two-target-mediated drug disposition model is mechanistically preferred for MEHD7945A PK analysis. However, the separate contribution of each target to the nonlinear plasma profile could not be successfully identified in our initial analysis, particularly when only based on the mean plasma data. The pTMDD model with one target was then applied and the model captured the PK profiles well in both species (Fig. 8). The parameter estimates are listed in Table 2. According to our analysis, monkeys seem to have higher binding affinity than mice, suggested by a much lower K_{ss} value (0.094 vs 206 nM).

Romozumab—Romozumab is a humanized IgG₂ that binds to sclerostin, a protein secreted by bone cells, which inhibits bone formation. A first-in-human study by Padhi et al. [24] investigated the PK of romozumab in healthy men and postmenopausal women. Nonlinear PK was observed, which is likely due to sclerostin-mediated disposition and elimination. The cTMDD model was tested first. Even though this model captured the profile well, it predicted a plasma basal sclerostin concentration ($k_{syn}/k_{deg} = 19.4$ nM) much higher than experimental measurements (~0.05 nM) [31]. Such low plasma sclerostin concentrations cannot adequately support a large nonlinear clearance if sclerostin-mediated

elimination is the reason for non-linear PK, suggesting that sclerostin-mediated elimination may primarily occur in extravascular space, a relatively large pool and/or a pool with high sclerostin expression. The pTMDD model seems to be a reasonable option. The pTMDD model captured the profile well (Fig. 9) and yielded reasonable parameter estimates (Table 2). The estimated basal sclerostin concentration in interstitial fluid was about 14.2 nM, which is lower than the plasma predicted value, but still much higher than plasma measurement values. Given that sclerostin is primarily produced and secreted in tissues, it is likely that tissue concentrations are higher than in plasma. With more data, it might be possible to include joint plasma and *ISF* TMDD models.

Mavrilimumab—Mavrilimumab is full human IgG₁ targeting granulocyte–macrophage colony-stimulating factor receptor. A first-in-human study by Bemester et al. [25] assessed the PK of mavrilimumab in subjects with rheumatoid arthritis. Profound nonlinearity was observed over a wide dose range of 0.01–10 mg/kg. Wang et al. further analyzed the data with a model consisting of a 2CM model with both linear and nonlinear clearance (target-mediated) in the central compartment (2CM + TMDD). The mean PK data were digitized and reanalyzed in our study with the cTMDD as well as 2CM models. Both models captured the profiles well and produced comparable parameter values (Table 2). The cTMDD model adequately describes the plasma data (Fig. 10) with one less systemic parameter than the 2CM + TMDD model ($\text{Obj} < 0.1$).

Efalizumab—Efalizumab is a humanized IgG₁ that binds to the α -subunit of LFA-1 (lymphocyte function-associated antigen-1). Efalizumab was approved for use in psoriasis but was later withdrawn from the market due to fatal brain infections. The PK data of efalizumab from a number of clinical studies was reviewed and analyzed by Joshi et al. [26] with a 2CM + TMDD model. We re-analyzed the PK data with both cTMDD and pTMDD models. As shown in Fig. 11, the cTMDD model well-captured all of the plasma profiles, but the pTMDD model failed to account for the profiles at low doses. This example further demonstrated that the apparent CL_{TM} cannot go larger than distribution clearance for the pTMDD model and the slope of plasma profiles at any time cannot be higher than that in the early decline phase (α -phase) at relatively high doses. This model preference is consistent with LFA-1 having expression sites on lymphocytes that are largely circulated in blood.

Discussion

A minimal PBPK model has been developed specifically for mAb PK analysis utilizing only plasma data to characterize mAb disposition and predict *ISF* concentrations in two groups of lumped tissues. The feasibility of incorporating TMDD mechanisms into mPBPK models was assessed in this study to consider target-binding in either plasma (cTMDD) or *ISF* (pTMDD). The simulated signature profiles reveal a parallel early decline phase for the pTMDD model, in contrast with the cTMDD and TMDD + 2CM models where an extremely rapid initial decline is usually observed for low doses [8]. The cTMDD and pTMDD models both preserve the prolonged terminal phase that is typically found in 2CM + TMDD models. The case studies further demonstrated that the mPBPK model has feasibility in enacting TMDD in either plasma or *ISF*, in accordance with where targets are

primarily expressed. This extends the traditional TMDD modeling framework to consider target-binding not only in vascular space, but also in extravascular space.

The TMDD models depict the drug-target binding process as the key component for the nonlinear PK analysis. When only plasma data are available, the convention is to integrate TMDD with the 2CM model with target-binding in the central compartment [8]. Parameter identifiability has been the major concern for the conventional 2CM + TMDD model if TMDD is assigned to a peripheral compartment when only plasma data are available. The mPBPK model accommodates the unique distribution features of mAb, such as distribution limited to *ISF*, vascular reflection coefficients (σ_1 and σ_2) governing the initial distribution, and the lymph reflection coefficient ($\sigma_L = 0.2$) predefined. These physiological assignments and constraints allow mPBPK models to give reasonable predictions of mAb concentrations in *ISF* and appear to support an identifiable pTMDD model (Cases 1–5). The appropriate assignment of target binding sites would anticipate more realistic characterizations of target dynamics and target binding properties. When the target is in plasma, the cTMDD model showed similar model performance to the conventional 2CM + TMDD model, but with one less system parameter (Case 6). The pTMDD model gave more precise and reliable estimations than the cTMDD model when targets are primarily in *ISF* (Cases 1 and 5). In contrast, the cTMDD model performed better than the pTMDD model when targets are mostly in plasma (Case 7). The study only assessed TMDD in either plasma or *ISF*. But other situations, such as TMDD in V_{tight} or V_{leaky} alone, or in both plasma and *ISF*, are also feasible in mPBPK models. Thus, the mPBPK model appears to be able to handle TMDD in accordance with the target-expressing tissues. It is important to assign TMDD at suitable sites, as it anticipates more reasonable evaluations of receptor binding properties and makes more reliable predictions of *RO* and the related pharmacodynamics.

When targets are present in plasma (Model A, cTMDD), the mAb in plasma are directly associated with target binding. Characterization of target-mediated clearance is independent of mAb interstitial distribution. The higher target density and faster mAb-target complex internalization usually predict greater target-mediated plasma clearance, irrespective of distribution rate. However, when targets are in *ISF* (Model B, pTMDD), the mAb in *ISF* rather than that in plasma are related to target binding. The plasma concentrations, upon which our model-fitting is usually based, no longer directly and faithfully reflect target binding processes. In this case, the apparent CL_{TM} is greatly restricted by extravasation and the value of CL_{TM} will become a function of extravasation rate and target-mediated interstitial clearance (Eq. (17)). The statement that higher target density and faster complex internalization lead to larger plasma clearance will no longer hold particularly when the target-mediated elimination rate is faster than the extravasation rate, wherein the apparent nonlinear clearance will be mainly defined by extravasation rate ($L \times (1 - \sigma_v)$). Thus, an important feature of the pTMDD model is that the apparent nonlinear clearance (CL_{TM}) (Eq. (17)) is always smaller than distribution clearance ($\Sigma L \cdot (1 - \sigma_v)$). This is reflected in plasma profiles as the slope of plasma decline is always lower than that in the early phase (α -phase) no matter how low are the concentrations (or dose) and how large is the interstitial target-mediated elimination (Figs. 2, 5, 6, 7, 8, 9). This is in contrast to the cTMDD model where

an extreme high decline slope is usually observed at low concentrations (or dose) (Figs. 2, 10, 11).

In the pTMDD model, the extravasation-limited CL_{TM} will shift the traditional relationships between plasma concentrations and RO (Fig. 3), and between saturation of CL_{TM} and RO (Fig. 4). The extravasation properties, such as σ_v , play essential roles in shaping these relationships. It is generally anticipated that the larger σ_v predicts lower ISF concentrations, and subsequently produces smaller RO . For mAbs with limited accessibility (high σ_v) to target tissues, improving extravasation (or reducing σ_v) seems to be more efficient than increasing doses to achieve a higher RO (Fig. 3, Zone II). This conclusion may assist decision-making in mAb development. In addition, in the pTMDD model, saturation of clearance ($1 - CL_{TM}/CL_{TM-max}$) does not directly imply the saturation of target (RO). The larger target-mediated elimination in ISF would create greater deviations between the clearance saturation and target saturation, and make it more difficult to enhance RO by simply increasing doses (Fig. 4).

Selection between pTMDD and cTMDD models should be made according to target expression sites. The model performance in comparing pTMDD and cTMDD models in analyzing the same data set sometimes implies the location where the targets primarily mediate the nonlinear clearance. In considering and comparing the extravasation rates of many mAbs [6], the maximal nonlinear clearance ($CL_{total, low\ dose} - CL_{linear, high\ dose}$) that is obtained in Noncompartmental Analysis may also infer the target sites and imply the degree of antibody accessibility to such target sites. If a target is exclusively expressed in a certain tissue (such as a solid tumor), then the limited accessibility to this tissue may not produce a sufficiently high plasma CL_{TM} and the CL_{TM-max} in this situation may somewhat reflect the degree of antibody accessibility into this tissue. Therefore, higher nonlinear clearances are frequently associated with targets in either plasma (Case 6 and 7) or tissues with high vascular permeability.

Comparisons between 2CM + TMDD and Michaelis–Menten (M–M) models have been made [32]. The 2CM + TMDD model approximates to the M–M model when total target concentrations are constant ($dR_{total}/dt = 0$) and free drug concentrations are relatively higher than target concentrations ($R_{total} \cdot K_D/(K_D + C)^2 \ll 1$). To satisfy the second condition, the plasma concentration should be high enough to obscure the early rapid decline at low doses, which is typically seen in 2CM + TMDD signature profiles [8]. Then, the M–M model would emerge as a comparable approach in describing the data at relatively high plasma concentrations. When the target is in ISF (pTMDD), the early rapid decline phase does not exist at low doses due to the restricted extravasation, but the feature of a relatively long terminal phase is preserved. Therefore, when the PK data does not reveal a long terminal phase (Cases 2, 4, 5), the M–M model may provide comparable curve fittings as the pTMDD model, but the parameter interpretation is complicated (results not included). Most importantly, a chance to explore the interstitial target and target binding properties will be wasted if a M–M model is chosen for this type of PK data analysis. The M–M model cannot capture a long terminal phase as shown in Cases 1 and 3. Systematic comparisons between the pTMDD, cTMDD, and M–M models may be helpful for further model selection of new mAbs.

When targets are primarily in plasma, antibodies are directly exposed to targeted antigens. However, when targets are in *ISF*, the extravasated antibody has limited presentation to antigens. Only part of the interstitial space is actually accessible for antibody distribution [33, 34]. The limited accessibility is associated with size and steric exclusion [35], irregular vascularization [36], and target-mediated elimination [37, 38]. These factors may also cause spatial heterogeneity in distribution [39]. The limited accessibility and spatial heterogeneity in *ISF* distribution would affect the actual fraction of targets presented to antibody. Of note, this would challenge the pTMDD model which simply assumes an instantaneous and homogenous distribution in *ISF*. Such assumption may create a virtual dilution of the receptor pool and result in a relatively lower estimate of target concentrations and probably slower complex internalization. Thus, the parameters derived from this pTMDD model should be considered with respect to the target accessibility and distribution heterogeneity of antibody in *ISF*. When tissue data and/or more prior knowledge are available, the pTMDD model may be able to accommodate these distribution complexities. However, when analyzing only plasma data, defining target-expressing tissues (total *ISF*) and the accessible fraction in *ISF* become imperative for the pTMDD model to obtain reasonable characterization of receptor binding and dynamics. Any bias in defining the available *ISF* volume would result in the deviation of parameter estimates pertaining to receptor and receptor binding.

In conclusion, the mPBPK models show flexibility in handling TMDD models in either plasma (cTMDD) or *ISF* (pTMDD). The simulated profiles of the pTMDD model reveal a parallel early decline phase due to the restricted extravasation, which is in contrast with typical signature profiles of the cTMDD model with a rapid early decline for low doses. Both models preserve the feature of the long terminal phase as seen with the conventional TMDD + 2CM model. Although more investigations are warranted, the mPBPK model seems to support a pTMDD model without parameter identifiability issues. Having TMDD in *ISF* would shift the typical relationships between plasma concentration and *RO* and saturation of nonlinear clearance and *RO*. The importance of finding the target-expressing tissues and accessible fraction in the tissues is important for the pTMDD model to obtain reasonable characterizations of receptors and receptor binding properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Model structures of second-generation minimal PBPK models with target-mediated drug disposition in either plasma (cTMDD, Model A) or interstitial fluid (pTMDD, Model B). Symbols and physiological restrictions are defined in Eqs. (1)–(12). The plasma compartment in the *left box* represents the venous plasma as in full PBPK models but is not applied in this model

Fig. 2.

Plasma concentration versus time profiles for increasing doses from 2.6 to 1,300 nmol based on target-mediated drug disposition in either plasma (*top*), V_{leaky} (*middle*), or V_{tight} (*bottom*) in the mPBPK modeling framework. Differential equations for the simulations are shown in Supplementary Materials and parameter values are listed in Table 1

Fig. 3.

Simulated relationships between interstitial receptor occupancy (RO) and vascular reflection coefficient (σ_v) at given plasma antibody concentrations. The simulation is based on Eq. (16) and parameters listed in Table 1. Zone I indicates the range of σ_v for tissues with fenestrated or discontinuous vascular endothelium (V_{leaky}) and Zone II reflects the range for tissues with continuous vascular endothelium (V_{tight})

Fig. 4.

Simulated relationships between saturation of plasma nonlinear clearance ($1 - CL_{TM}/CL_{TM-max}$) and saturation of targets (RO). When the target is in *ISF*, any parameters that are related to target and target binding contribute to the deviation of their relationship from that with target in blood. The simulation is based on Eq. (19) and parameters listed in Table 1

Fig. 5.

Pharmacokinetic profiles of zalutumumab in monkeys. *Symbols* are observations for the indicated doses and curves are model fittings based on the pTMDD model (*solid line*) or the cTMDD model (*dashed line*). Fitted parameters are listed in Table 2

Fig. 6. Pharmacokinetic profiles of traszsumab in patients with metastatic breast cancer. *Symbols* are observations for the listed doses and curves are model fittings using the pTMDD model. Fitted parameters are listed in Table 2

Fig. 7. Pharmacokinetic profiles of onartuzumab in monkey. *Symbols* are observations for the listed doses and curves are model fittings using the pTMDD model. Fitted parameters are listed in Table 2

Fig. 8.

Pharmacokinetic profiles of MEHD7945A in mice (*top*) and monkeys (*bottom*). Symbols are observations for the listed doses and curves are model fittings using the pTMDD model.

Fitted parameters are listed in Table 2

Fig. 9.
Pharmacokinetic profiles of romosozumab in healthy men and postmenopausal women.
Symbols are observations for the listed doses and curves are model fittings using the pTMDD model. Fitted parameters are listed in Table 2

Fig. 10. Pharmacokinetic profiles of mavrilimumab in human subjects with rheumatoid arthritis. *Symbols* are observations for the listed doses and curves are model fittings using the cTMDD model. Fitted parameters are listed in Table 2

Fig. 11.

Pharmacokinetic profiles of efalizumab in humans. *Symbols* are observations for the listed doses and curves are model fittings based on the cTMDD model (*top*) or the pTMDD model (*bottom*). The inadequate prediction of the low dose profiles using the pTMDD model is associated with an important feature of the model that the apparent nonlinear clearance (CL_{TM}) (Eq. (17)) is always smaller than distribution clearance ($\Sigma L \cdot (1 - \sigma_v)$). Fitted parameters are listed in Table 2

Table 1

Parameter values employed for model simulations

Parameter	Definition	Value	Unit
σ_1	Vascular reflection coefficient for V_{iight}	0.945	–
σ_2	Vascular reflection coefficient for V_{leaky}	0.687	–
CL_p	Systemic clearance	0.001	L/h/kg
k_{on}	Drug receptor association rate	0.100	1/(nM h)
k_{off}	Complex dissociation rate	0.001	1/h
k_{syn}	Target biosynthesis rate	0.100	nM/h
k_{deg}	Free target degradation rate	0.010	1/h
k_{int}	Complex internalization rate	0.030	1/h

Table 2

Pharmacokinetic parameters (CV%, coefficient of variation) estimated using minimal PBPK models with target-mediated drug disposition

Case [Reference]	1 [20]	2 [21]	3 [22]	4 [23]	5 [24]	6 [25]	7 [26]
Antibody	Zalutumumab	Trasuzumab	Onartuzumab	MEHD7945A	Romsozumab	Mavrilimumab	Efalizumab
Model	pTMDD	cTMDD	pTMDD	pTMDD	pTMDD	cTMDD	cTMDD
Parameter/units	Monkey	Man	Monkey	Mouse	Monkey	Man	Man
σ_1	–	0.952 (1.11)	0.843 (182)	0.95 (<0.01)	0.823 (7.11)	0.95 (–)	0.95 (–)
σ_2	–	0.546 (2.91)	0.709 (112)	0.260 (27.3)	0.718 (5.75)	0.769 (0.473)	0.870 (5.26)
CL_p	ml/h/kg	0.298 (6.75)	0.333 (5.46)	0.170 (38.4)	0.438 (11.3)	0.141 (2.49)	0.254 (10.2)
K_{ss}	nM	0.376 (74.3)	1.79 (74.5)	206 (48.6)	0.094 (620)	0.930 (18.0)	25.5 (653)
k_{syn}	nM/h	0.310 (36.1)	0.973 (21.9)	3.47 (46.2)	0.679 (24.0)	0.094 (2.47)	0.160 (56.8)
k_{deg}	10^{-2} /h	0.243 (39.2)	0.754 (22.7)	1.51 (34.2)	1.45 (91.2)	8.16 (4.71)	0.535 (66.5)
k_{int}	10^{-2} /h	0.243 (39.2)	0.754 (22.7)	1.51 (34.2)	1.45 (91.2)	1.18×10^2 (–)	0.312 (464)
V_c	L					2.43 (0.246)	
V_p	L					4.20 (9.94)	
CL_d	L/h/70kg					0.052 (2.52)	