Poster : T-041

Incorporating target shedding into a minimal PBPK-TMDD model for mAbs

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OBJECTIVE

- The impact of target-mediated drug disposition (TMDD) on PKPD of therapeutic proteins has been well appreciated in recent years.
- However, target dynamics are more complex than published TMDD models currently account for. For instance, virtually all structural and functional categories of membrane proteins have been found to be shed from cells [1], and for a large percentage of marketed monoclonal antibody therapeutics (mAb), target shedding has been shown to exist and several clinical studies have also indicated a significant effect of target shedding on mAb PKPD [2].
- The objective of this study is to extend existing TMDD models to take into account the dynamic interaction between a drug and its targets in the physiological or pathophysiological condition, where the target is present as both a membrane bound and a shed, soluble form.

METHODS

Membrane bound targets can exist in the tissues or on circulating cells in blood, and they are subject to ectodomain shedding to generate soluble target, both of which may coexist in the blood, interstitial space, or both. Furthermore, drugs may modulate the shedding, resulting in a high concentration of soluble target. In order to mechanistically model both target-mediated drug disposition as well as drug-mediated target disposition, we first generalized the existing TMDD models to take account of the ectodomain shedding and the interconnection between membrane bound and soluble forms of targets in addition to TMDD at both forms of the target.

The left diagram in Figure 1 schematically shows the shedding model used in this study, where the distribution of shed target from tissue to plasma is characterized by the first-order rate constant λ, and the membrane target shedding is represented by first-order rate constant (k_{shed}). Assuming the system is at equilibrium when there is no drug present, we can derive the steady state solutions, as shown in the bottom right panel of figure 1, which serve as the initial conditions of the governing equations for drug-target dynamic interactions, as shown below. Furthermore, we allow the drug to modify the shedding rate by incorporating inhibitory or stimulatory effect into parameter k_{shed}.

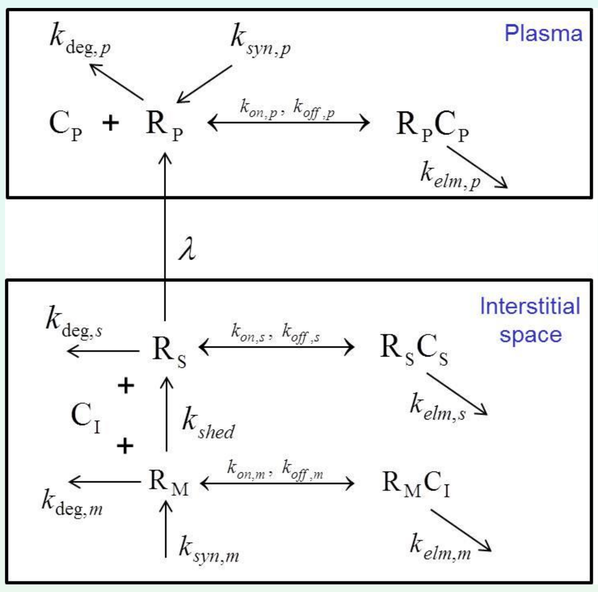

Figure 1. Schematic representation of ectodomain shedding model.

- R_M -- membrane target receptor in interstitial space
- R_S--shed soluble target in interstitial space
- R_P -- soluble target in plasma
- C_I -- drug in interstitial space
- C_P -- drug in plasma
- V_P -- plasma volume
- V_I -- interstitial volume

$$[R_M]_{SS} = \frac{k_{syn,i}}{k_{shed} + k_{deg,i}}$$

$$[R_S]_{SS} = \frac{k_{syn,s} + k_{shed}[R_M]_{SS}}{\lambda + k_{deg,s}}$$

$$[R_P]_{SS} = \frac{1}{k_{deg,p}}\left(k_{syn,p} + \lambda \frac{V_I}{V_P}[R_S]_{SS}\right)$$

Plasma :

$$\frac{d[R_P]}{dt} = k_{syn,p} + \frac{V_I}{V_P}\lambda[R_S] - k_{deg,p}[R_P] - k_{on,p}C_P[R_P] + k_{off,p}[R_PC_P],\ [R_P](0) = [R_P]_{SS}.$$

$$\frac{d[R_PC_P]}{dt} = k_{on,p}C_P[R_P] - (k_{elm,p} + k_{off,p})[R_PC_P],\quad [R_PC_P](0) = 0.$$

Interstitial Space :

$$\frac{d[R_M]}{dt} = k_{syn,m} - k_{shed}[R_M] - k_{deg,m}[R_M] - k_{on,m}C_I[R_M] + k_{off,m}[R_MC_I],\ [R_M](0) = [R_M]_{SS}.$$

$$\frac{d[R_MC_I]}{dt} = k_{on,m}C_I[R_M] - (k_{elm,m} + k_{off,m})[R_MC_I],\ [R_MC_I](0) = 0.$$

$$\frac{d[R_S]}{dt} = k_{shed}[R_M] - \lambda[R_S] - k_{deg,s}[R_S] - k_{on,s}C_I[R_S] + k_{off,s}[R_SC_I],\ [R_S](0) = [R_S]_{SS}.$$

$$\frac{d[R_SC_I]}{dt} = k_{on,s}C_I[R_S] - (k_{elm,s} + k_{off,s})[R_SC_I],\ [R_SC_I](0) = 0.$$

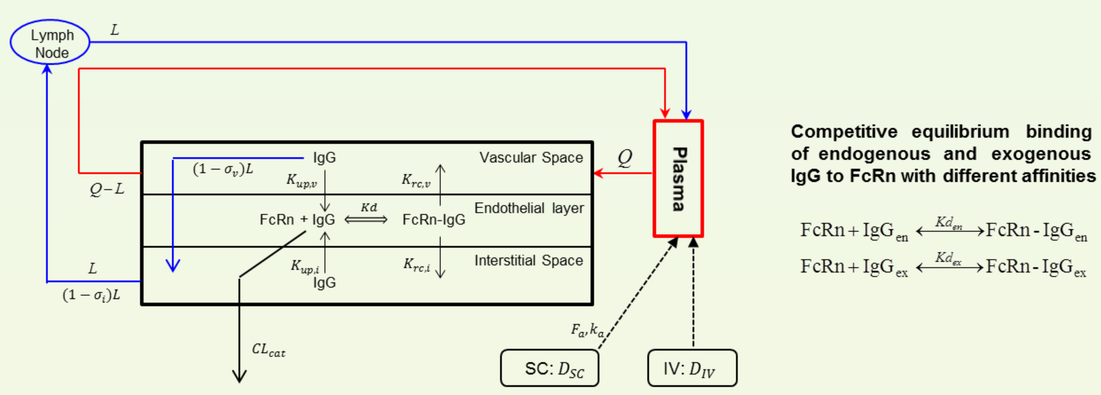

Figure 2. Minimal PBPK model structure for mAbs[3].

Competitive equilibrium binding of endogenous and exogenous IgG to FcRn with different affinities

$$FcRn + IgG_{en} \overset{Kd_{en}}{\longleftrightarrow} FcRn\text{-}IgG_{en}$$

$$FcRn + IgG_{ex} \overset{Kd_{ex}}{\longleftrightarrow} FcRn\text{-}IgG_{ex}$$

A general simulation algorithm was developed in Matlab, incorporating TMDD models with and without shedding into a minimal PBPK model for mAb developed previously [3] (see Figure 2 for model structure). In general, the integrated model described considers a number of different target properties, including

(1) membrane bound targets in tissues or on circulating cells in blood without shedding;

(2) soluble targets in the circulation

(3) membrane bound targets in tissue interstitial space with shedding and the shed target as a soluble form existing in the interstitial space as well as in the circulation (as shown in figure 1)

(4) both membrane bound and soluble forms of targets coexist due to differential splicing.

Simulations were run assuming that in the absence of binding to the target the mAb has typical IgG kinetics (21 day half-life).

Simulations were then conducted with the TMDD model with and without shedding occurring. The parameters used for the PBPK model are defined in Table 1 and for the shedding model in Table 2

RESULTS

Figures 2, 3 and 4 demonstrate the simulated effect of target shedding on the plasma levels and receptor occupancy of a mAb as well as free target level following multiple dosing of the mAb.

- When no shedding of target occurs then multiple dosing with a dosing interval of 20 days is sufficient to suppress the level of membrane bound target (Figure 2; Left panel)
- When target shedding is considered, then the same dosing interval is not able to suppress both the membrane-bound and free soluble target levels in the interstitial space (Figure 2; right panel)
- When target shedding is considered a dosing interval of 10 days is needed to block the membrane-bound target (Figure 3).
- When the potency of binding to the membrane bound receptor is assumed to be 100-fold higher (lower K_D) than that to the soluble receptor, then receptor occupancy of the membrane bound receptor is increased and the levels of free membrane bound receptor decreased (Figure 4) compared to the previous situations where equal potency for the membrane bound and soluble receptor was assumed.

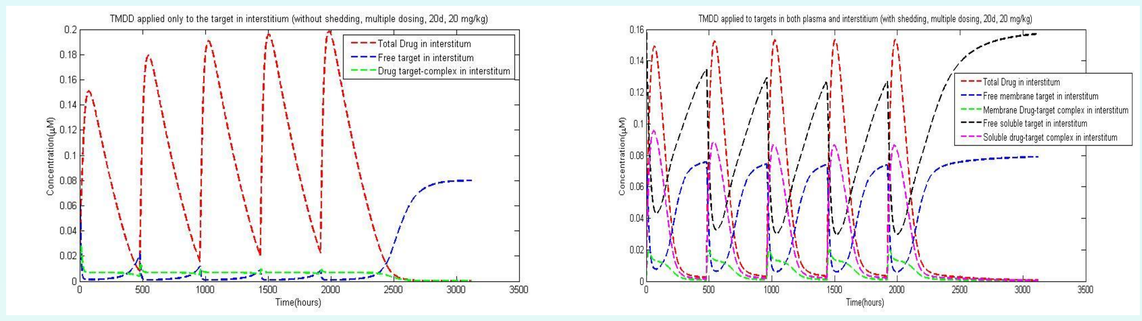

Figure 2 *Left:* Simulation of a mAb with 20 days of doing interval, assuming no target shedding. *Right:* Simulation of a mAb with 20 days of doing interval, assuming target shedding.

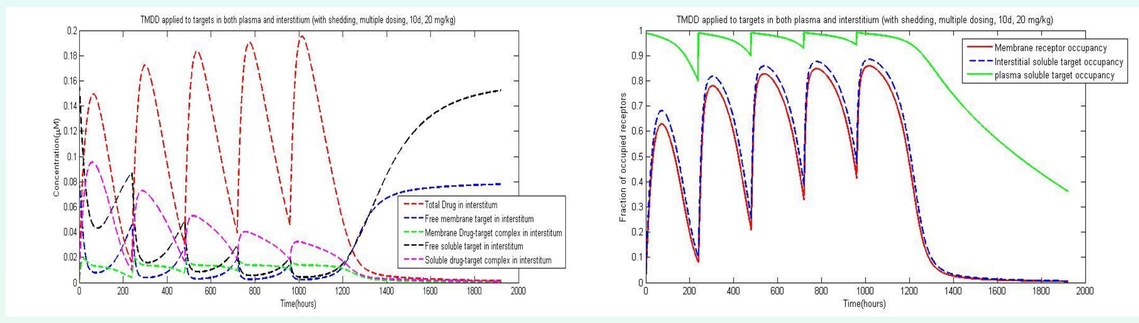

Figure 3 Simulation of a mAb with equal affinity toward both membrane-bound and soluble targets, with 10 days of doing interval, assuming target shedding

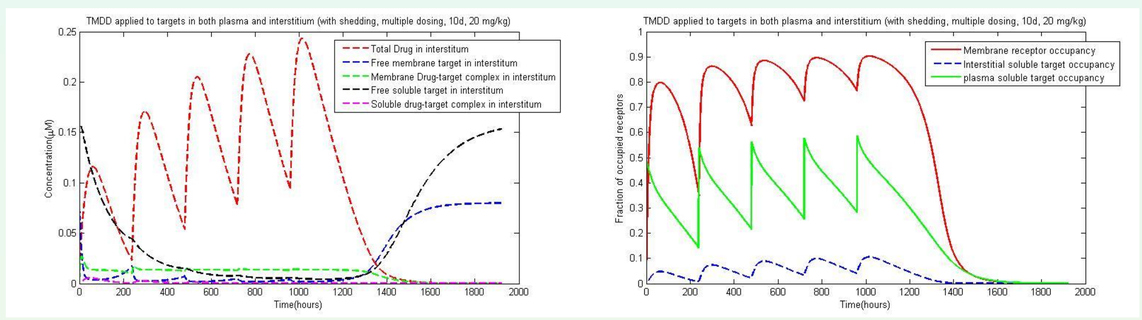

Figure 4 Simulation of a mAb with 100 fold higher affinity to the membrane-bound target than that of soluble targets, with 10 days of doing interval, assuming target shedding.

CONCLUSION

Published TMDD models have been extended to take into account the effect of target shedding on the behavior of a typical monoclonal antibody in a minimal PBPK model. This simulation study shows that when a high concentration of soluble target exists due to membrane target shedding, using a TMDD without consideration of the shedding process could be misleading in determining dosing regimen.

REFERENCES

[1] Zang Y, Pastan I. High shed antigen levels within tumors: an additional barrier to immunoconjugated therapy. *Clin. Cancer Res*. 14(24), 7981-7986(2008).

[2] Kuang B, King L, Wang H. Therapeutic monoclonal antibody concentration monitoring: free or total? *Bioanalysis*. 2010; 2(6): 1125-40.

[3] Li L, Chetty M, Gardner I, Dostalek M, Grist E, Machavaram K. development of a minimal-PBPK model for simulating monoclonal antibody pharmacokinetics in human. Poster presentation at *AAPS National Biotechnology Conference* 2012 (21st—23rd May).

Table 1. Model parameters of the minimal PBPK models

Parameters	Values	Parameters	Values
$K_{up,v}$	0.02979 (1/h)	*Lymph Flow*	120 (mL/h)
$K_{up,i}$	0.02979 (1/h)	*FcRn abundance*	40 (μM)
CL_{cat}	0.0175 (L/h)	*Plasma flow (L/h)*	190 (L/h)
$K_{rc,v}$	0.2999 (1/h)	*Binding affinity of mAb to FcRn (K_D pH 6)*	0.728 (μM)
$K_{rc,i}$	0.1196 (1/h)		

Table 2. Model parameters for the simulation studies.

Parameters	Values	Parameters	Parameters
$k_{on,m}$	31.375 (1/μM/h)	$k_{on,p} = k_{on,m}$	$k_{on,s} = k_{on,m}$
$k_{off,m}$	0.6083 (1/h)	$k_{off,p} = k_{off,m}$	$k_{off,s} = k_{off,m}$
$K_{d,m}$	0.0194 (μM)	$K_{d,p} = K_{d,m}$	$K_{d,s} = K_{d,m}$
$k_{deg,m}$	0.0145 (L/h)	$k_{deg,p} = k_{deg,m}$	$k_{deg,s} = 0$
$k_{syn,m}$	0.0023 12(μM/h)	$k_{syn,p} = k_{syn,m}$	$k_{syn,s} = 0$
$k_{elm,m}$	0.16375 (1/h)	$k_{elm,p} = 0.01k_{elm,m}$	$k_{elm,s} = 0.01k_{elm,m}$
k_{shed}	0.0145 (L/h)		
λ	0.00725 (L/h)		

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