A Novel PBPK Approach for mAbs and its Implications for the Interpretation of Classical Compartment Models

Ludivine Fronton[1,2,3], Wilhelm Huisinga[2]

[1] Graduate Research Training Programm PharMetrX: Pharmacometrics & Computational Disease Modelling, Potsdam/Berlin;
[2] Institute of Mathematics / Institute of Biochemistry and Biology, Potsdam University, Potsdam, Germany;
[3] F. Hoffmann-La Roche Ltd, Basel, Switzerland (since June 2013).

Motivation

Despite detailed knowledge on the molecular processes involved in the disposition of monoclonal antibodies (mAbs), the structure, interpretation and parameterization of physiologically-based pharmacokinetic (PBPK) as well as classical compartment models is very diverse, with no apparent consensus.

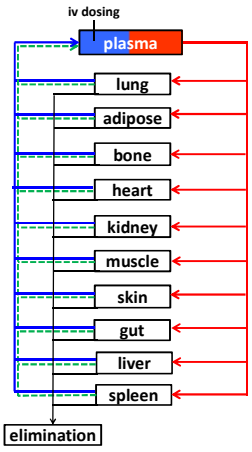
Objectives

To develop a simplified PBPK model, in mice, that

- **integrates the known relevant pharmacological processes to reliably describe mAbs disposition**
- **accounts for available plasma and tissue data including the correction for residual blood.**

To derive low-dimensional compartment models consistent with the simplified PBPK model which allow for a mechanistic interpretation.

Simplified PBPK model with extravasation rate-limited tissue distribution



Important assumptions underlying the derivation of the simplified PBPK model:

1) IgG_{endo} and mAb bind to FcRn with similar affinities:

$$KD_{IgG_{endo}} = KD_{mAb}$$

2) plasma mAb << plasma IgG_{endo}:

Linear intrinsic clearance potentially from any tissue

Rate of change of C_{pla} and C_{tis}:

$$V_{tis}\frac{d}{dt}C_{tis} = L_{tis}\cdot\left((1-\sigma_{tis})\cdot C_{pla} - \frac{C_{tis}}{K_{tis}}\right) - CLint_{tis}\cdot C_{tis}$$

$$V_{pla}\frac{d}{dt}C_{pla} = L_{pla}\cdot\left(C_{in} - (1-\sigma_{pla})\cdot C_{pla}\right)$$

PBPK parameters to be estimated:

1. elimination-corrected tissue partition coefficients, $\widehat{K_{tis}}$; in PBPK model C_{pla} replaced by $C_{pla,forced}$ predicted by an empirical 2-compartment model describing plasma data
2. tissue extraction ratio, E_{tis}, using the 'full' Simplified PBPK model .

Modelling and simulations performed in MATLAB R2010a.

Estimating mAb tissue biodistribution coefficients ABC_{tis} and total plasma clearance $CLpla_{tot}$

Estimated elimination-corrected tissue partition coefficients ($\widehat{K_{tis}}$) and resulting antibody biodistribution coefficients (ABC_{tis})

	$\widehat{K}_{tis}$	ABC_{tis}
Adipose	1.695	0.034
Bone	1.695	0.034
Gut	0.623	0.062
Heart	2.322	0.116
Kidney	2.576	0.129
Liver	1.324	0.132
Lung	2.152	0.108
Muscle	1.695	0.034
Skin	6.270	0.125
Spleen	0.303	0.030

$ABC_{tis} \ll 1$ reflects the flow-induced partitioning i.e. $Q_{inflow} << Q_{outflow}$.

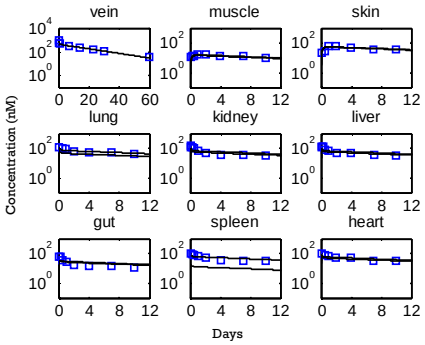
Estimated extraction ratios (E_{tis}) and total plasma clearance ($CLpla_{tot}$)

	sc. 2	sc. 3	sc. 4	sc. 5	sc. 6
Adipose	0.029	-	-	-	-
Bone	-	-	-	-	-
Gut	-	-	-	-	-
Heart	-	-	-	-	-
Kidney	<1e-8	-	-	-	-
Liver	0.029	-	-	-	0.042
Lung	-	-	-	-	-
Muscle	0.029	-	-	0.143	-
Skin	<1e-8	-	0.095	-	-
Spleen	0.029	0.920	-	-	-
$CLpla_{tot}$	1.326e-4	1.325e-4	1.326e-4	1.324e-4	1.326e-4

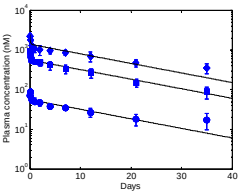
Only total plasma clearance can be reliably estimated, but not individual tissue contributions.

The simplified PBPK model describes the plasma and tissue data of 2 mAbs in mice

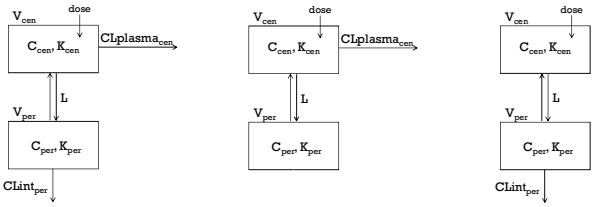
Plasma and tissue concentration predictions of sc. 2 for 7E3 (8mg/kg, IVb) in WT mice [1] (lower profiles: without residual blood contamination)



Plasma concentration predictions of sc. 2 for T84.66 at 3 dose levels (1, 10, 25 mg/kg, IVb), in nude mice [2]



Several classical compartment models are consistent with the simplified PBPK model



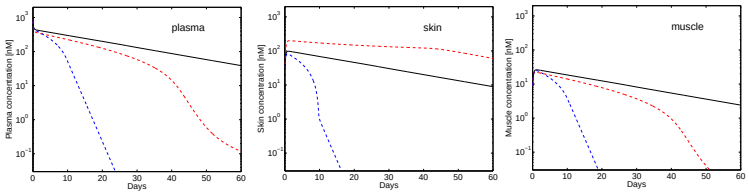
Different simple compartment models are consistent with the simplified PBPK model, depending on the definition of central and peripheral compartments and assumption on eliminating tissues.

Rate of change of C_{cen} and C_{per} when clearance from central compartment:

$$V_{cen}\frac{d}{dt}C_{cen} = L\cdot\left(\frac{C_{per}}{K_{per}} - (1-\sigma_{per})\cdot C_{pla}\right) - CLplasma_{cen}\cdot C_{pla}$$

$$V_{per}\frac{d}{dt}C_{per} = L\cdot\left((1-\sigma_{per})\cdot C_{pla} - \frac{C_{per}}{K_{per}}\right)$$

Prediction of plasma and tissue profiles in presence of a hypothetical membrane-bound target in skin



Typical profiles in presence of target-mediated drug disposition with

- high binding capacity and low elimination rate constant (red)
- low binding capacity and high elimination rate constant (blue)

in comparison to no target expression (black)

Conclusion

We developed a simplified PBPK model which allows for a better understanding of the disposition of mAbs, i.e. permeability-limited tissue distribution, linear total plasma clearance. Based on an extension of the lumping approach, we give a rational to the variety of empirical model successfully used to describe plasma data of mAbs. We moreover find that from commonly measured tissue data, it is not possible to identify which tissues are eliminating.

References

[1] Garg et al. J Pharmacokinetics Pharmacodynamics, Vol. 34:687–707 (2007)
[2] Urva et al. J. Pharm. Sc. Vol. 99(3):67–86 (2010)
[3] Krippendorf et al. J Pharmacokinetics Pharmacodynamics, Vol. 39:125-139 (2012)
[4] Shah and Betts mAbs, Vol. 5, 297-305 (2013)
[5] Pilari et al. J Pharmacokinetics Pharmacodynamics, Vol. 37, 365–405 (2010)