Generic PBPK model to predict preclinical and clinical PK of antibodies

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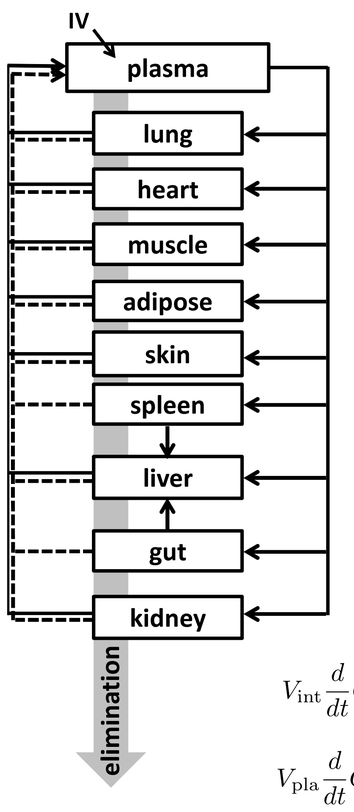
Motivation & Objectives

One of the primary applications of PBPK modelling is to predict efficacious and non-toxic clinical dose and human PK for new chemical and biological entities (NCEs, NBEs). *In silico* methods to predict tissue-to-plasma partition coefficients have significantly advanced the use of PBPK models for NCEs. The routine application of PBPK models to predict PK of NBEs, in particular monoclonal antibodies (mAbs), however is still challenging [1]. Antibody biodistribution coefficients (ABCs) [2] strongly support extrapolation of mAb PK between species.

Objective:

Evaluation of the feasibility of a generic PBPK modelling approach based on ABC values to study mAb PK in different preclinical species and humans

Generic PBPK model [3,5]



Parameterisation in terms of:

- Plasma V_{pla} and interstitial tissue volumes V_{int}
- lymph flows L_{org} (convection; dashed lines) and tissue-specific vascular reflection coefficients σ_{vas} (constant across species)
- interstitial-to-accessible plasma concentration partition coefficients K_{int} (related to ABCs)

$$\mathrm{ABC_{int}} = \mathrm{C_{int}}/\mathrm{C_{pla}} = (1-\sigma_{\mathrm{vas}})\cdot \mathrm{K_{int}}$$

species-specific clearance processes:

- linear, target-unspecific plasma clearance CLpla
  assumption: mAb << endogenous IgG
  (not suitable for IVIG therapy)
- to account for target-mediated clearance: parallel linear and nonlinear clearance from plasma

Tissue model: extravasation rate-limited tissue distribution

$$V_{\mathrm{int}}\frac{d}{dt}C_{\mathrm{int}} = L_{\mathrm{org}}\cdot\left((1-\sigma_{\mathrm{vas}})C_{pla} - \frac{C_{\mathrm{int}}}{K_{\mathrm{int}}}\right)$$

$$V_{\mathrm{pla}}\frac{d}{dt}C_{\mathrm{pla}} = \sum_{\mathrm{org}} L_{\mathrm{org}}\cdot\left(\frac{C_{\mathrm{int}}}{K_{\mathrm{int}}} - (1-\sigma_{\mathrm{vas}})C_{\mathrm{pla}}\right) - \mathrm{CL_{pla}}\cdot C_{\mathrm{pla}} - \frac{V_{\max}\cdot C_{\mathrm{pla}}}{\mathrm{Km}+C_{\mathrm{pla}}}$$

Interstitial-to-plasma concentration ratios $ABC_{int} = C_{int} / C_{pla}$ derived from ABC_{tis} in [2] and interstitial volume fractions $f_{int} = V_{int}/V_{tis}$ from [6]: $ABC_{int} = ABC_{tis}/f_{int}$

tissue	adipose	bone	gut	heart	kidney	lung	muscle	skin	spleen	liver
ABC_{int}	0.35	0.70	0.53	0.75	0.61	0.58	0.32	0.51	0.61	0.66

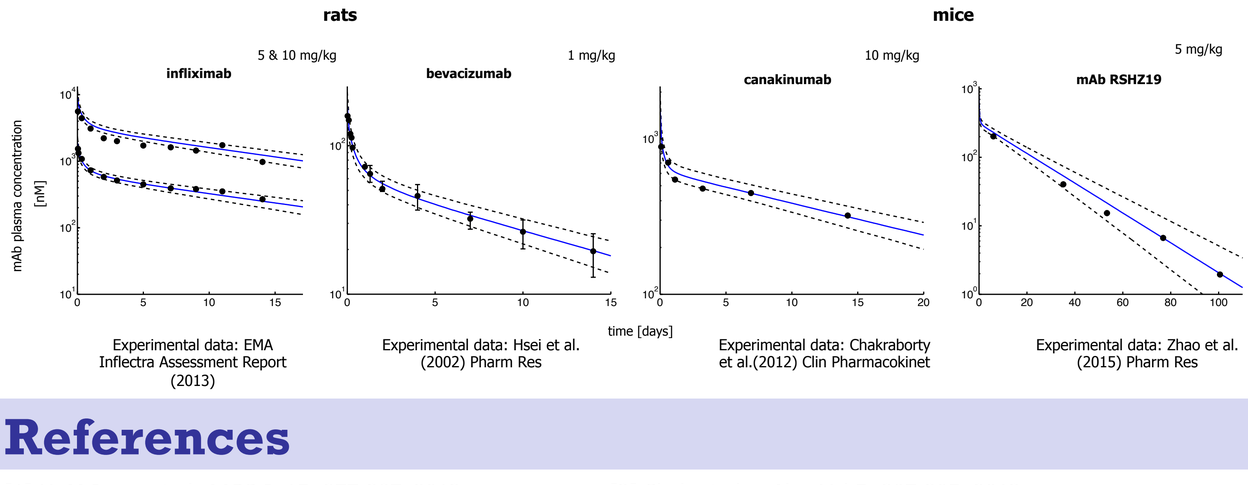
ABC_{tis} values constant across different species [2]

Methods & Data

- Plasma PK data of 24 different intact mAbs of IgG isotype from mice, rats and humans were obtained from literature.
- PK data was analysed with the generic PBPK model parameterised by ABC values.
  - Only unknown parameters refer to species-specific clearance processes (joint fitting for entire dose range)
- Percentiles for simulated data are based on predictions with variability in blood flow (±20%) and blood volume (±20%), hematocrit (±10%) and mAb dose (±10%), ABCs, vascular reflection coefficients (±10%), lymph flow (±20%) and plasma clearance (±20%) for preclinical species; and with linear plasma clearance (±30%) and Vmax (±30%) for humans.

Results: ABCs are suitable to model diverse preclinical data

- **The generic PBPK model parameterised by ABCs with total linear clearance from plasma was successfully applied to plasma mAb PK profiles of different antibodies in mice and rats (without target).**
- Dots are observations (±SD) and curves are model fittings. (solid blue lines-median for predictions, dashed dotted lines - 5th and 95th percentiles for predictions)



Experimental data: EMA Inflectra Assessment Report (2013)

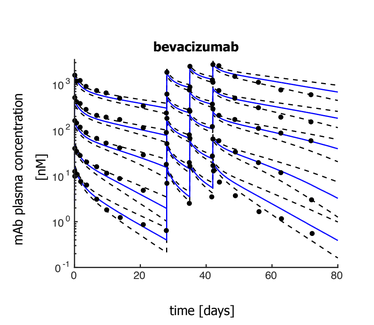
Experimental data: Hsei et al. (2002) Pharm Res

Experimental data: Chakraborty et al.(2012) Clin Pharmacokinet

Experimental data: Zhao et al. (2015) Pharm Res

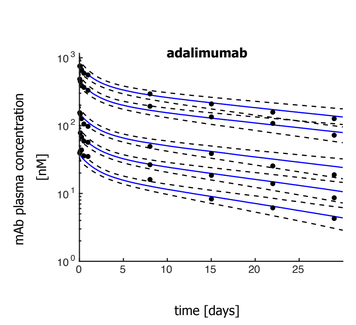
Modelling human mAb PK

- **The generic PBPK model with parallel linear and nonlinear clearance was successfully applied to plasma PK data of different mAbs in humans.**
- Dots are observations (± SD) and curves are model fittings. (solid blue lines-median for predictions, dashed dotted lines - 5th and 95th percentiles for predictions)



CL_{pla} =0.1680 l/d
Km =13 nM
Vmax =7.6464 nmol/d

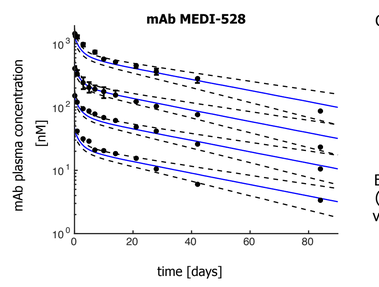
Experimental data: Gordon et al. (2001) J Clin Oncol: cancer patients following mAb doses 0.1, 0.3, 1, 3 and 10 mg/kg



CL_{pla} =0.1992 l/d
Km =4.457 nM
Vmax =1.2552 nmol/d

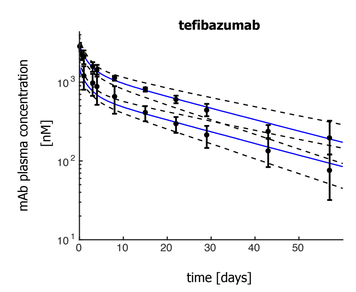
Experimental data: Weisman et al. (2003) Clin Ther: RA patients following mAb doses 0.25, 0.5, 1, 3 and 5 mg/kg

- In most cases, also in the presence of target, linear PK for mAbs was observed - depending on dose range and target concentrations. In the dose-linear range, only linear total clearance was estimated.



CL_{pla} =0.1320 l/d

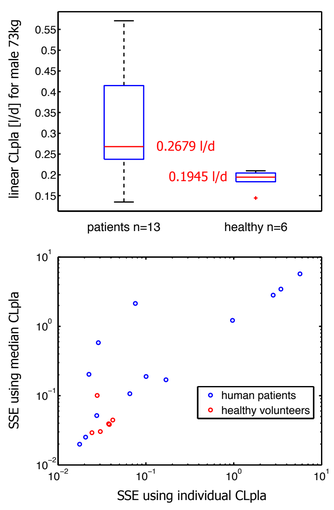
Experimental data: White et al. (2009) Clin Ther: healthy adult volunteers following mAb doses 0.3, 1, 3 and 9 mg/kg



CL_{pla} =0.2232 l/d

Experimental data: Hetherington et al. (2006) AAC: patients with end-stage renal disease following mAb doses 10 and 20 mg/kg

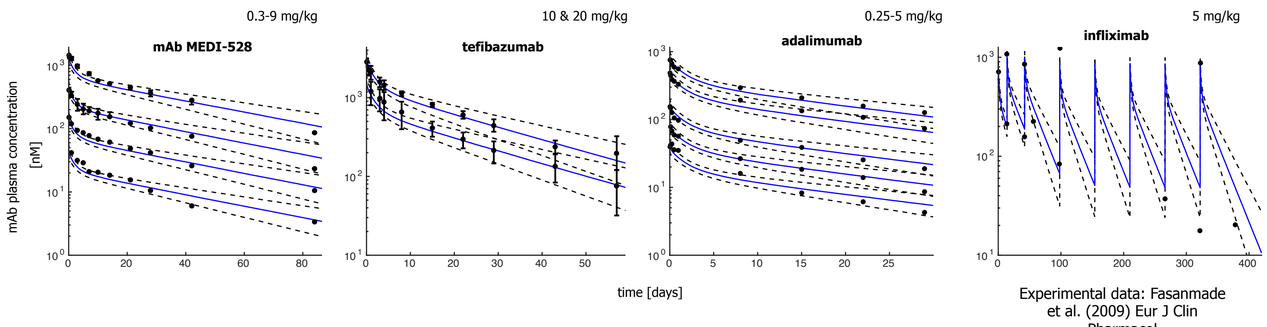
PBPK-based prediction in case of mAb in excess of target



Plasma clearance of healthy volunteers (median CLpla= 1.1096 l/h/kg for male 73 kg, CV 12.5%) is comparable to clearance of endogenous IgG (1.2e-04 l/h/kg for BW 73 kg) [4]. Variability of plasma clearance is higher between human patients (median CLpla= 1.5342e-04 l/h/kg for male 73 kg, CV 41%) and within the reported range for mAbs [4].

Sum of squared errors (SSE) are similar for predictions using individual fitted plasma clearance and median plasma clearance of healthy volunteers or human patients.

- **The median plasma clearance for healthy volunteers and patients serves as a starting value for linear total clearance to obtain good predictions for PK of mAbs in excess of target.** Dots are observations (±SD) and curves are model predictions.



Experimental data: Fasanmade et al. (2009) Eur J Clin Pharmacol

Challenges when predicting (human) mAb PK

- **Observability of nonlinear PK:** influenced by
  - Target type (soluble vs. membrane-bound target; degree of shedding)
  - Bioanalytics: mAb form measured in biological fluid; target inference in mAb assay; presence of anti-drug antibodies
  - Range of available mAb doses
- **Antibody-to-antibody variability** (mAb charge, glycosylation, mAb dose, concomitant administration, immunogenicity, differences in target density esp. between healthy volunteers and patients, differences in FcRn binding between species)

Conclusion

- Scale-Up confirms statement in Shah/Betts [2] that ABCs are suitable to model diverse data
- Generic PBPK approach parameterised by ABC values allows to study mAb PK across species with only clearance as unknown parameter
- Median linear plasma clearance in humans provides prediction in case of mAb in excess of target

References

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[3] L. Fronton et al. J Pharmacokinet Pharmacodyn, 41: 87-107, 2014.

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[6] Kawai et al. J Pharmacokinet Pharmacodyn, 22:327-65, 1994.

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