University at Buffalo
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PBPK State of the Science: An Academic Perspective on Modeling Biologics

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FDA Workshop on PBPK

November 18, 2019

Best Practices for PBPK Modeling

- How valid is the model?
  - To what extent should a model be considered adequate?
  - What are the confidence measures of the adequacy of the model?
- Essential content needed for clinical pharmacology review
  - Clearly stated goals and objectives
  - Workflow of model construction and verification of software
  - Information on input parameters and software information
  - Details of the experimental design of simulations and sensitivity analysis
- Question-oriented evaluation and assessment of results
  - For example, “Can PBPK simulations predict the magnitude of DDI in subjects with varying degrees of renal impairment?”
  - “Are the model and its parameters consistent with accepted physiology?”

Zhao et al. CPT. 92:17-20 (2012); Kuemmel et al. CPT:PSP. (Epub ahead of print)

Scientific Challenges for PBPK Modeling

- How valid is the model?
  - To what extent should a model be considered adequate?
  - What are the confidence measures of the adequacy of the model?
- Integration of genomics, proteomics, metabolomics for transporters and enzymes
- Increasing detail of organ, tissue, and cellular disposition
- Refinement of models and system parameters for special populations
- Integration of experimental micro-physiological systems (MPS)
- Modeling complex biological therapeutics
- Need for **models of collaboration** to enable **decision making**

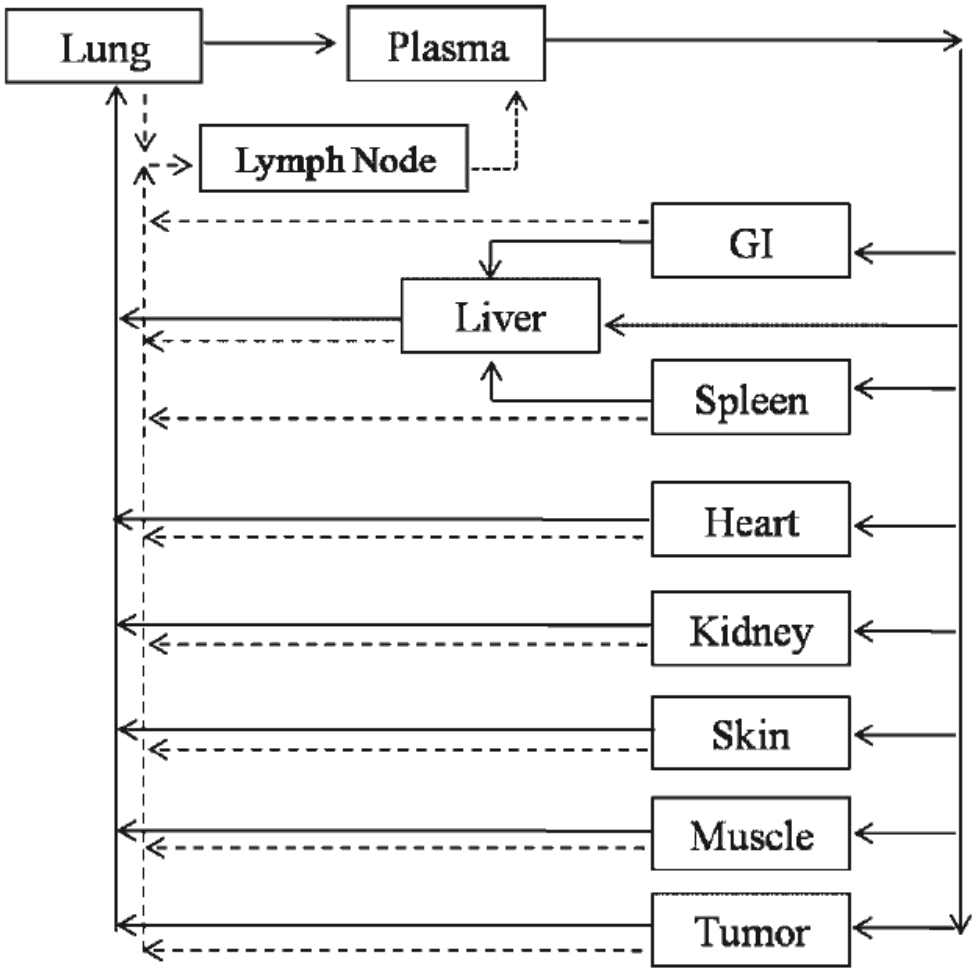
Zhao et al. CPT. 92:17-20 (2012); Kuemmel et al. CPT:PSP. (Epub ahead of print)

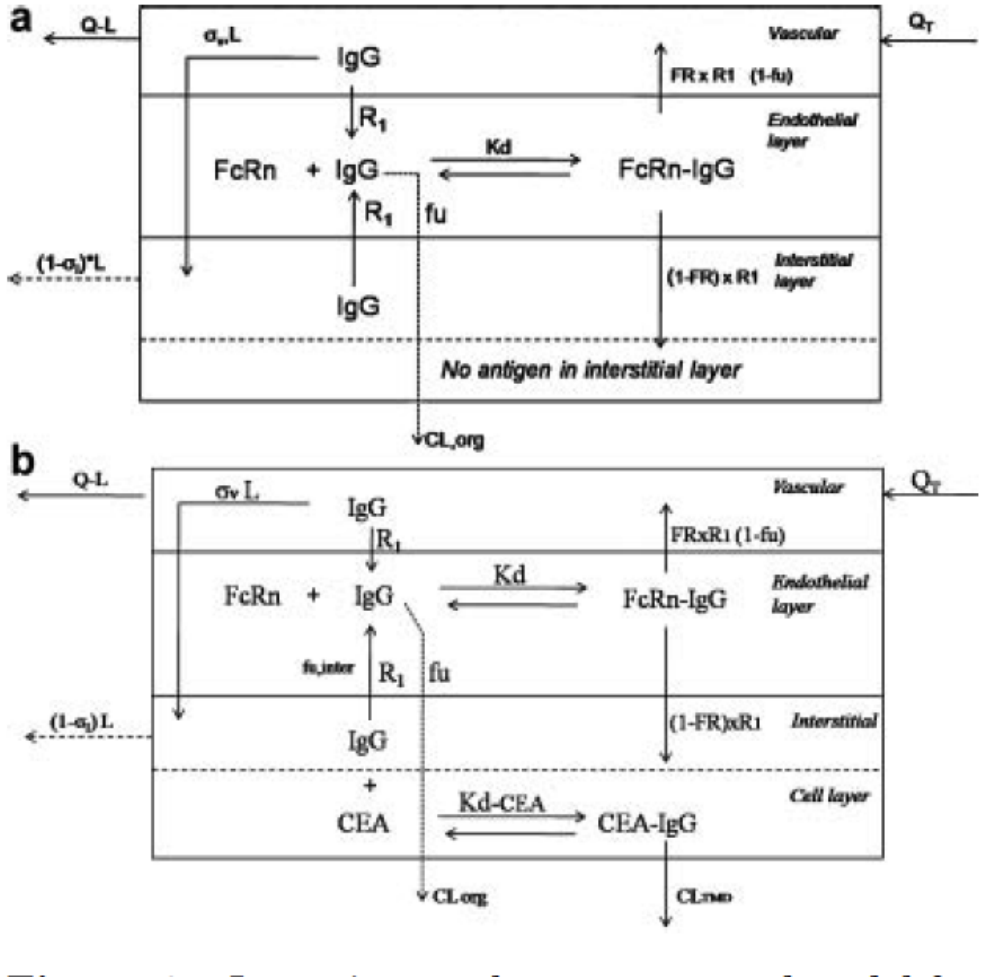
Macromolecules vs. Small Molecule Drugs

Adapted from Mahmood and Green. *J Clin Pharmacol*. 47:1540 (2007)

Properties	Protein Drugs	Small Molecule Drugs
Molecular weight	**>1000 Dalton**	**<1000 Dalton**
Route of administration	**Parenteral (IV, IM, SC)**	**All routes**
Plasma protein binding	**Negligible importance**	**May be important**
Volume of distribution	**0.04 – 0.2 L/kg**	**Hydrophobicity and plasma and tissue protein binding**
Half-life	**Long (days to weeks)***	**Short (hours)**
Cell-surface receptor interactions	**Play a significant role in distribution and elimination**	**May be important in limited cases**
Elimination	**Phagocytosis, endocytosis, proteolysis, and renal**	**Biotransformation, biliary, and renal**
Immunogenicity	**May play a role**	**Not applicable**

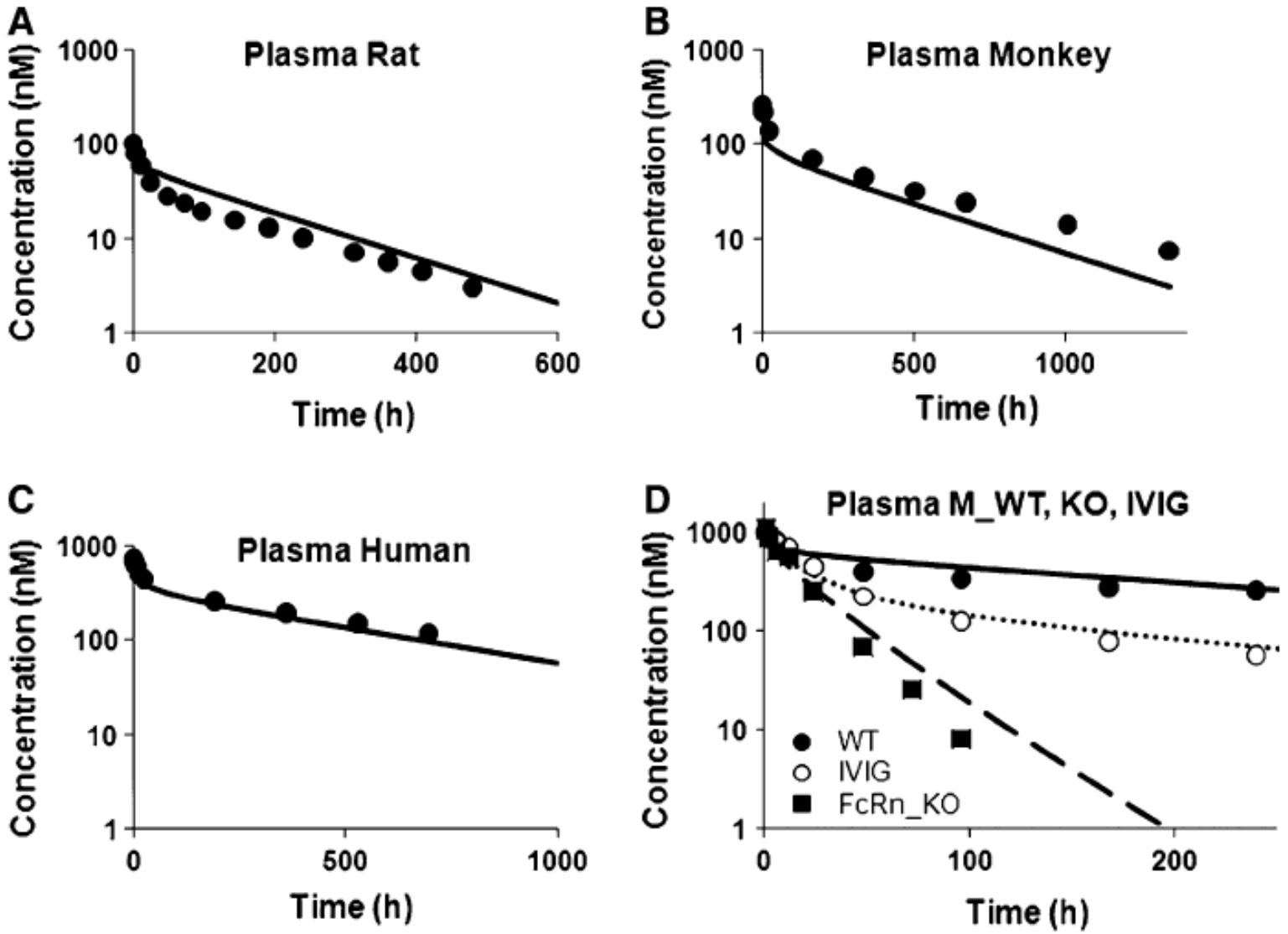
IgG PBPK Model with Target-Mediated Drug Disposition





Urva et al. J Pharm Sci. 99:1582 (2010)

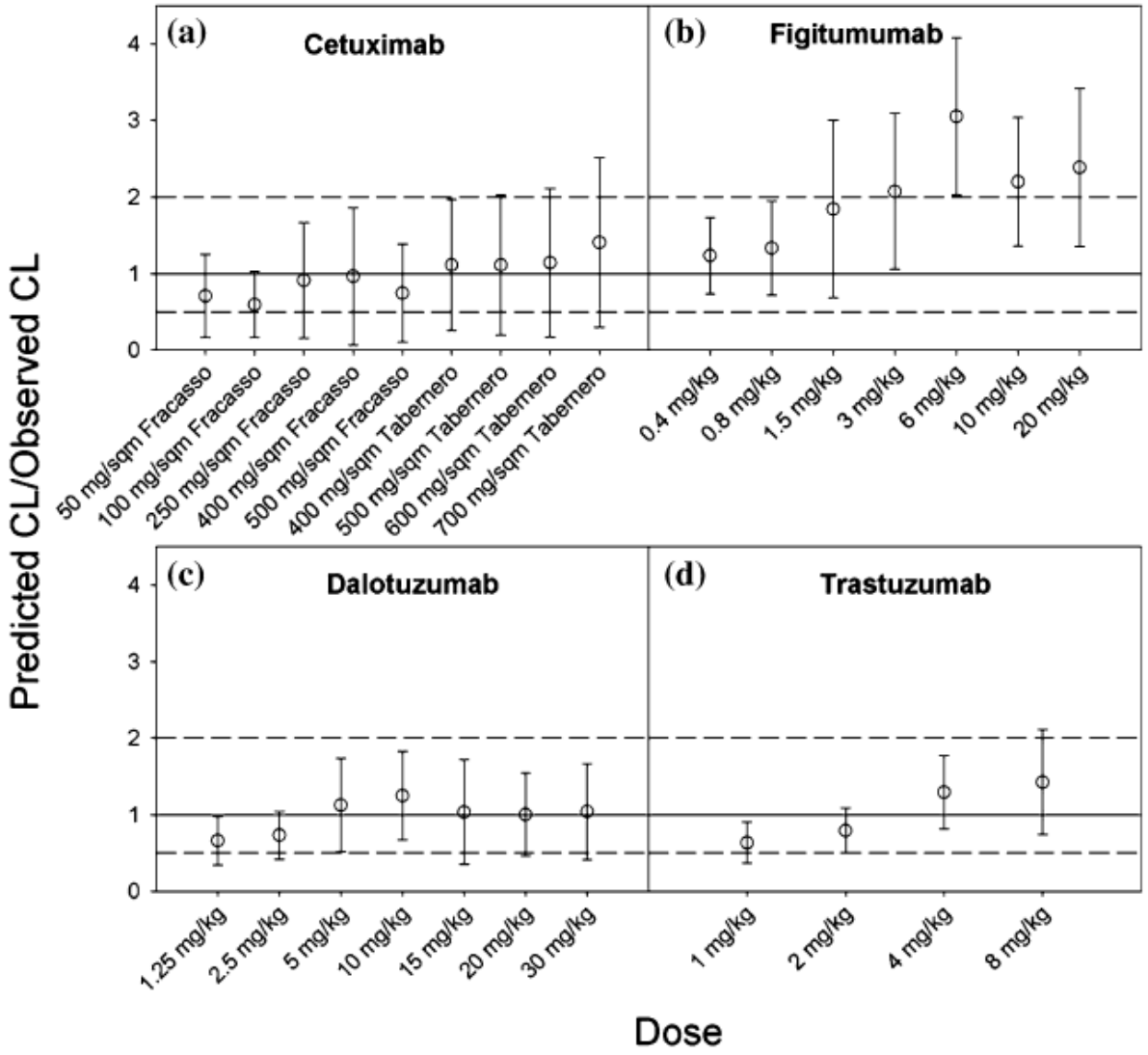
Toward a Platform PBPK Model for Monoclonal Antibodies

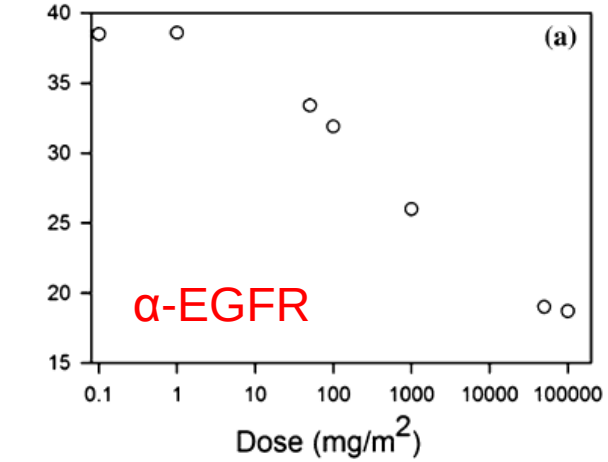


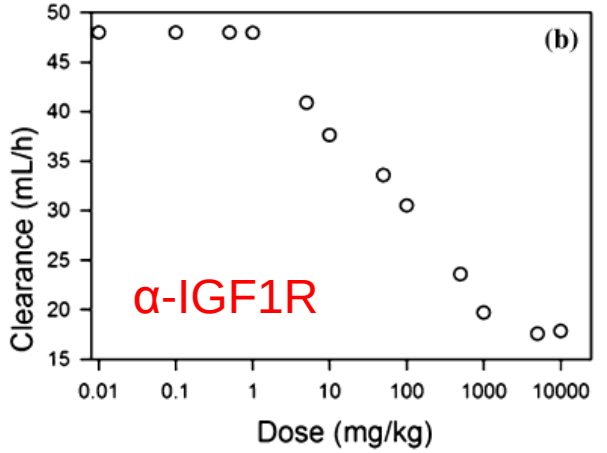
Shah and Betts. JPKPD. 39:67-86 (2012)

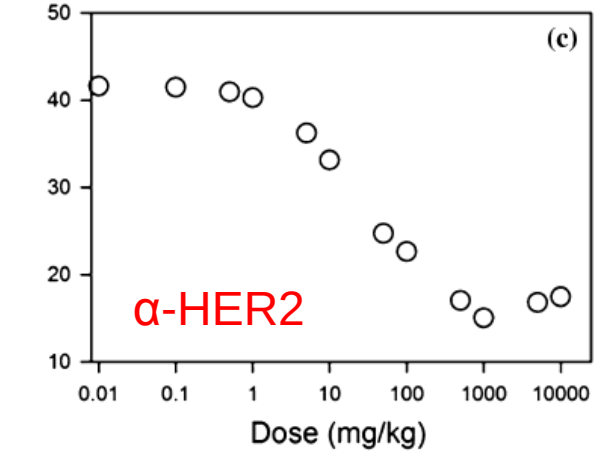
PBPK Prediction of Human mAb PK

Glassman and Balthasar. *JPKPD*. 43:427-46 (2016)



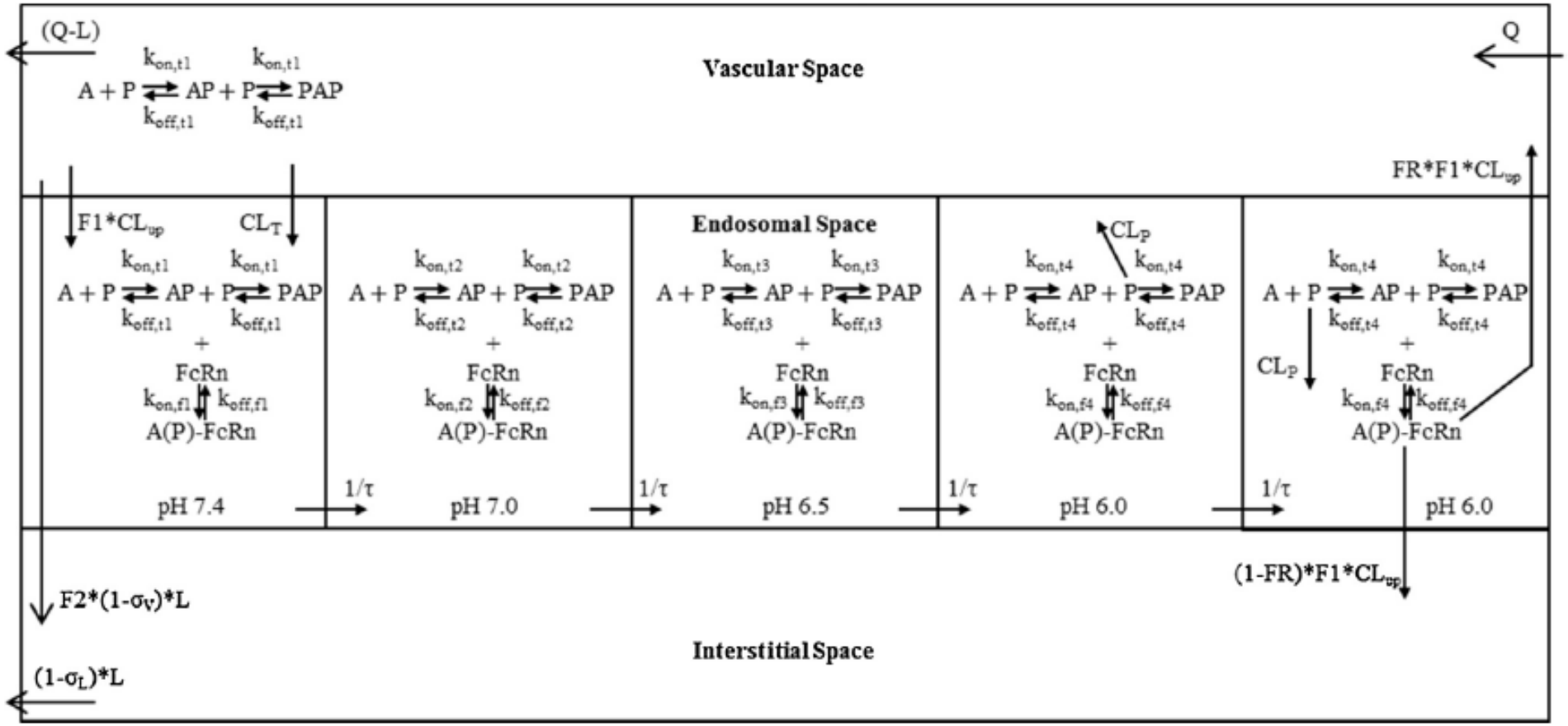






Catenary PBPK Model for “Catch and Release” Anti-PCSK9

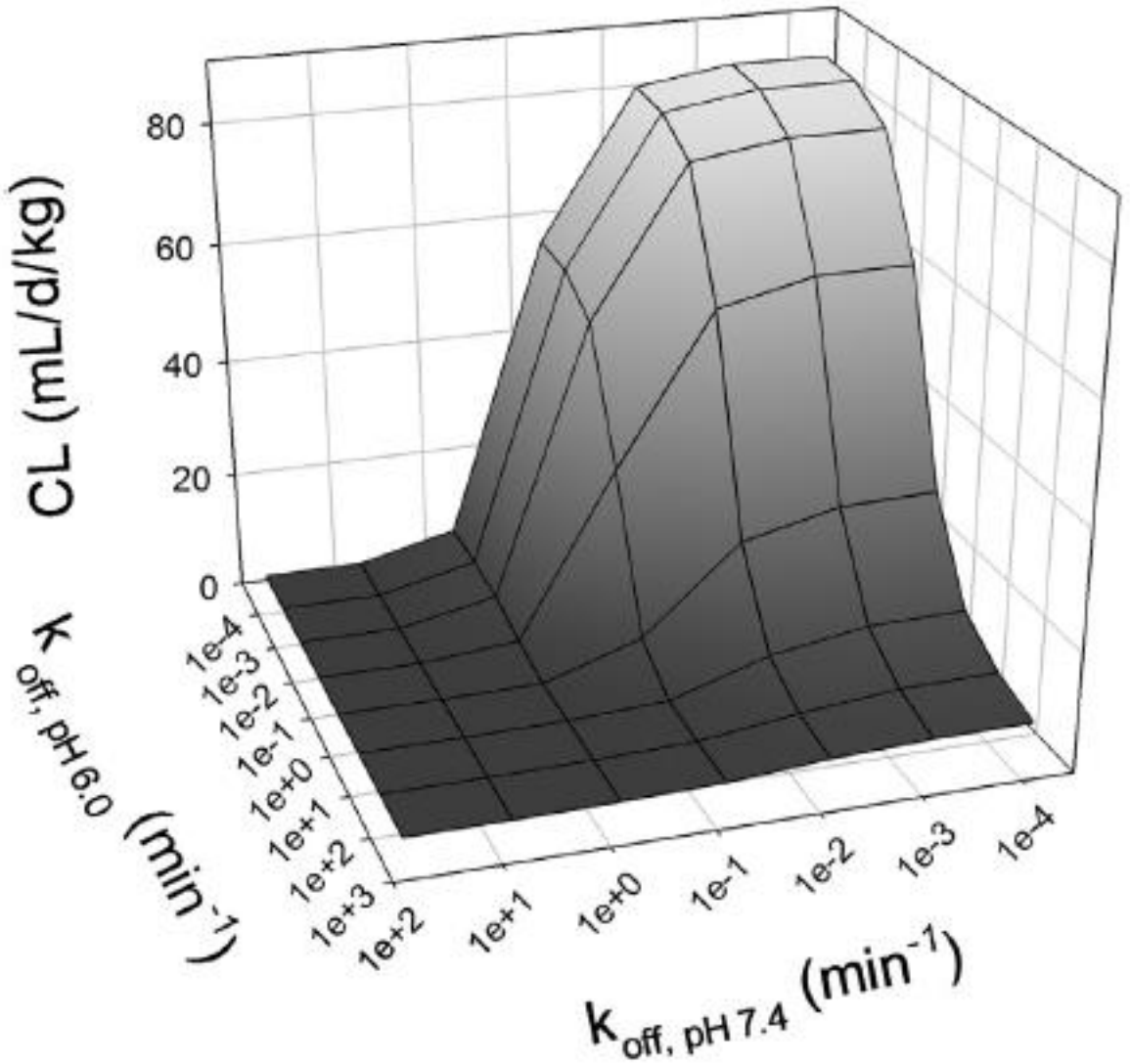
Glassman and Balthasar. *Int J Pharm*. 505:69-78 (2016)



A (free mAb), P (free PCSK9), AP (single-arm bound mAb), PAP (two-arm bound mAb), FcRn, and A(P)-FcRn (mAb or single-arm bound mAb in complex with FcRn)

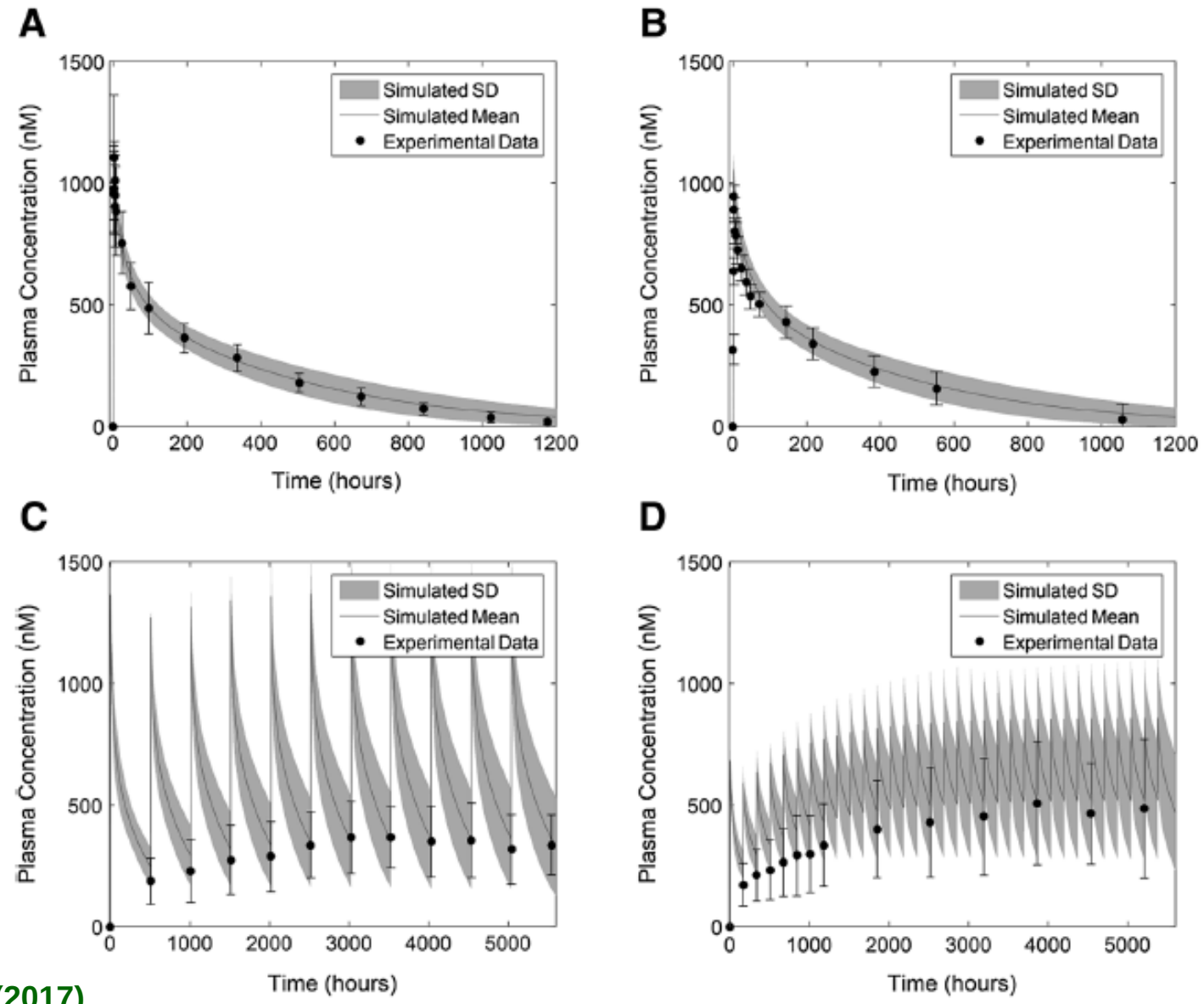
Catenary PBPK Model for “Catch and Release” Anti-PCSK9

Glassman and Balthasar. *Int J Pharm*. 505:69-78 (2016)



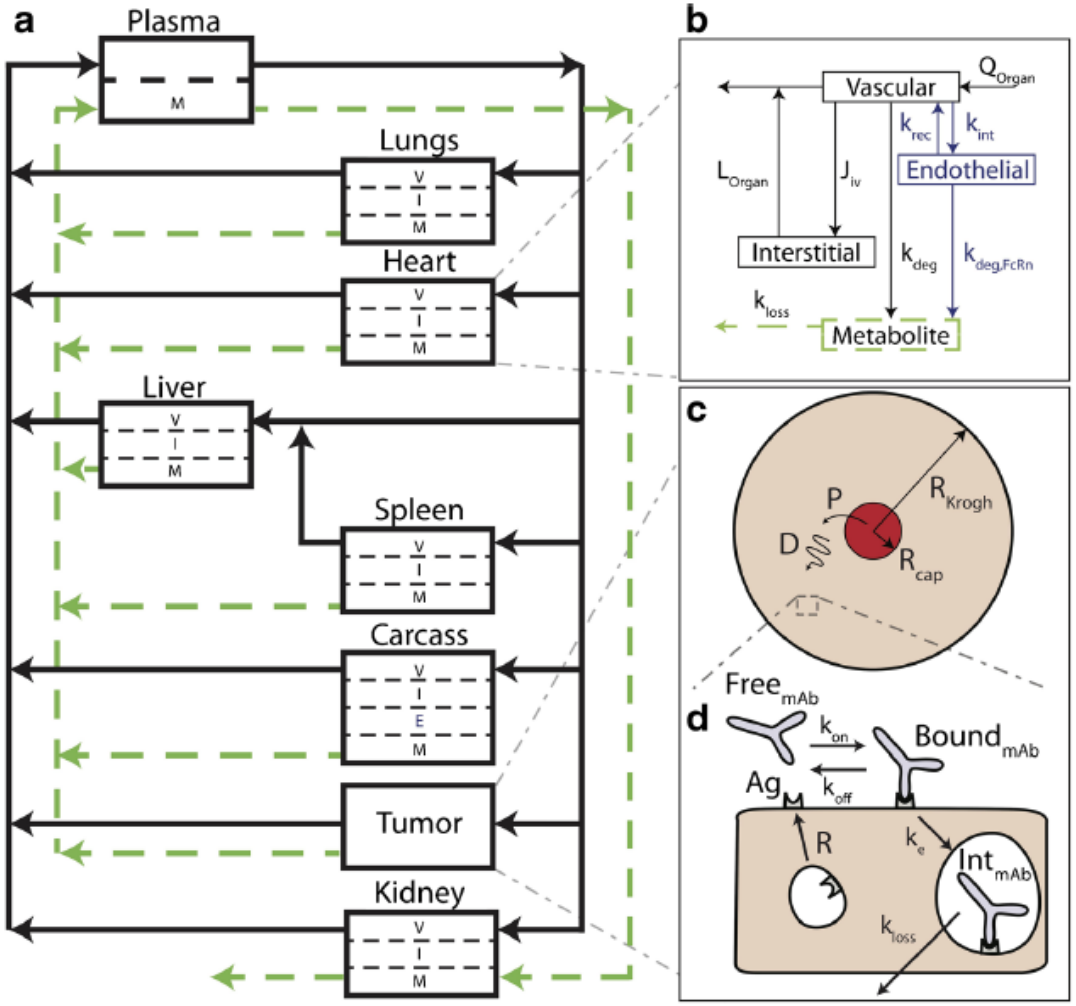
“Overall, the model suggests that when the mAb-target dissociation rate constant at pH 6.0 is rapid relative to the time-course of endosomal transit (t1/2 = 7.5 min), then ‘catch and release’ mAbs would be expected to have CL values in line with mAb in the absence of TMDD.”

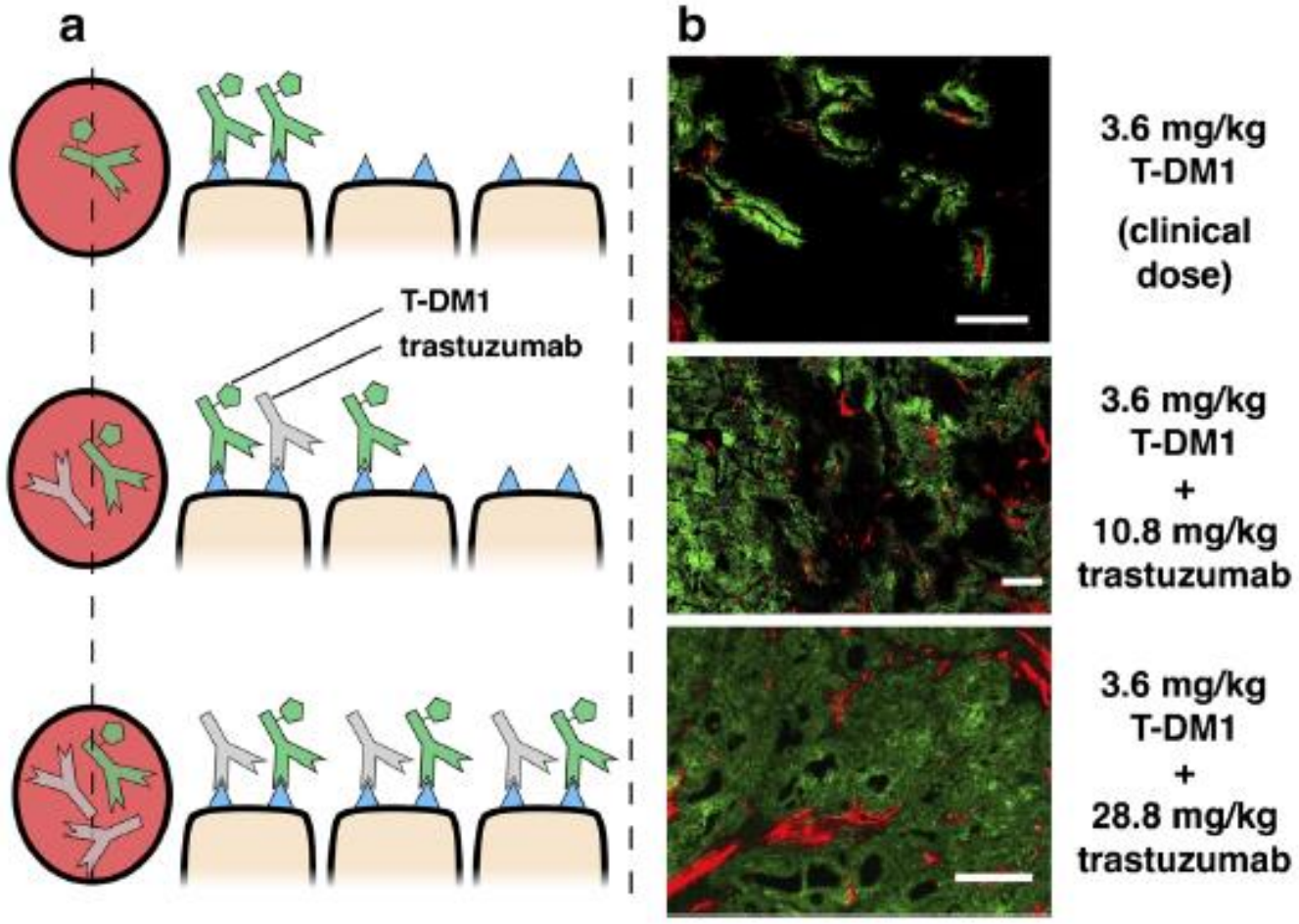
Population-PBPK Simulations of Trastuzumab PK



Malik et al. JPKPD. 44:277-90 (2017)

PBPK Model of Antibody-Drug Conjugates (ADCs)





Cilliers et al. AAPSJ. 18:1117 (2016)

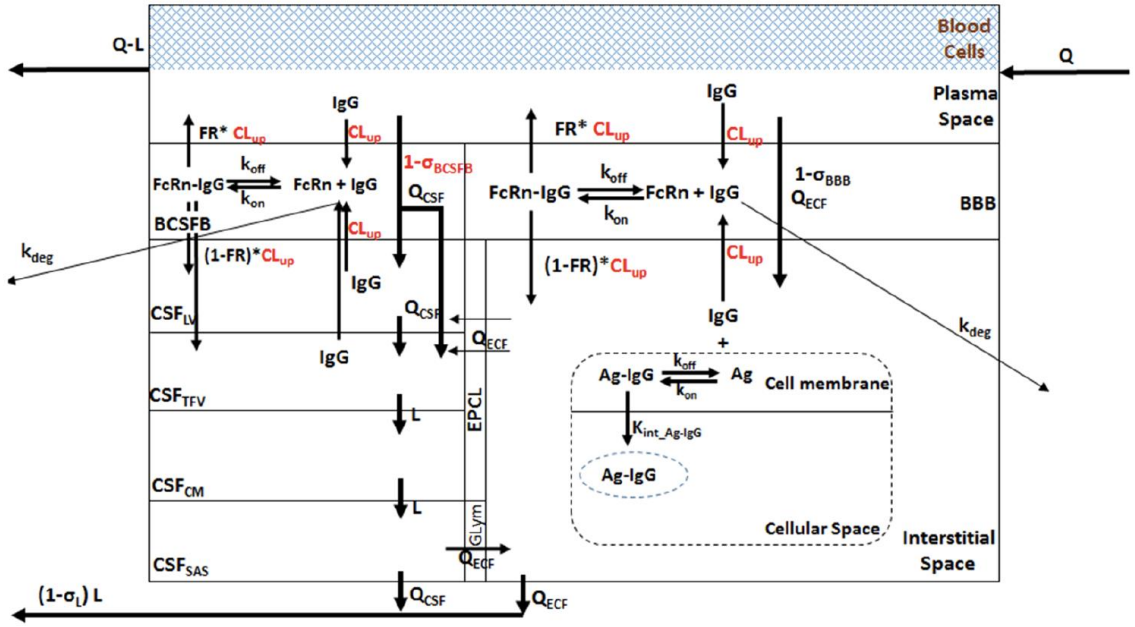
PBPK Prediction of Disease-Mediated TP-Drug Interactions

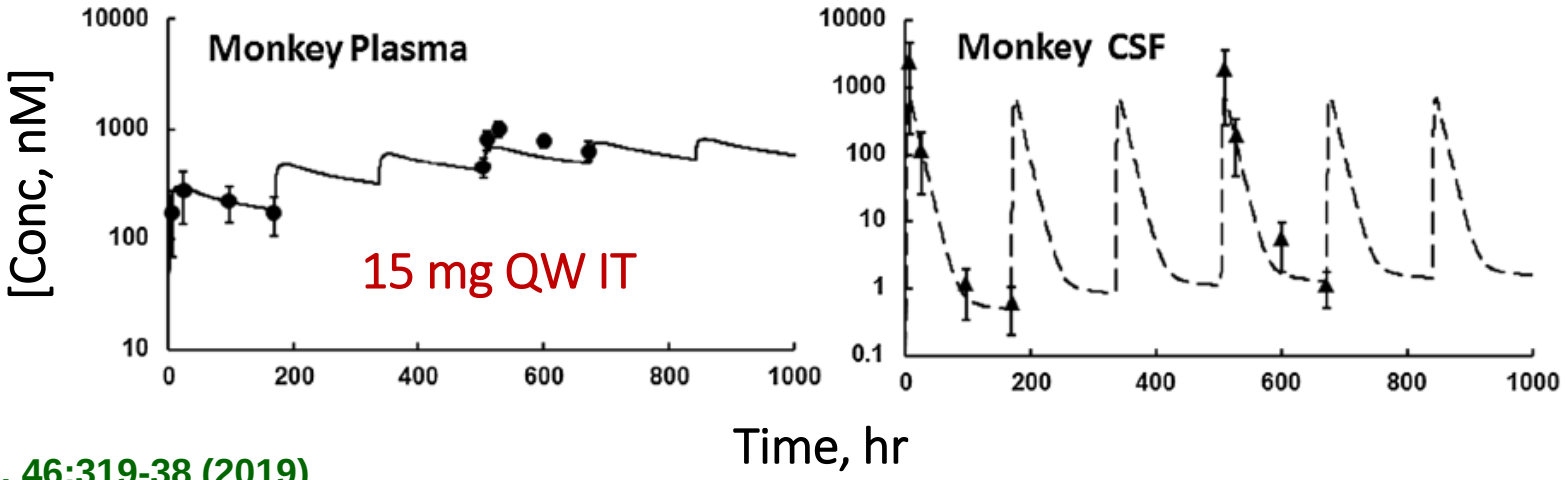
Drug AUC Ratios Before and After Sirukumab (anti-IL-6 mAb)

	Observations	Predictions
CYP Substrates	AUC_{D29}/AUC_{D1} (post/pre sirukumab)	AUC_{D29}/AUC_{D1} (post/pre sirukumab)
Midazolam	0.65 (0.47–0.89)	0.57 (0.44–0.69)
Omeprazole	0.59 (0.34–1.02)	0.66 (0.54–0.77)
S-Warfarin	0.82 (0.73–0.92)	0.75 (0.63–0.87)
Caffeine	1.34 (0.84–2.15)	1.34 (0.99–2.08)

Jiang et al. AAPSJ. 18:767-76 (2016)

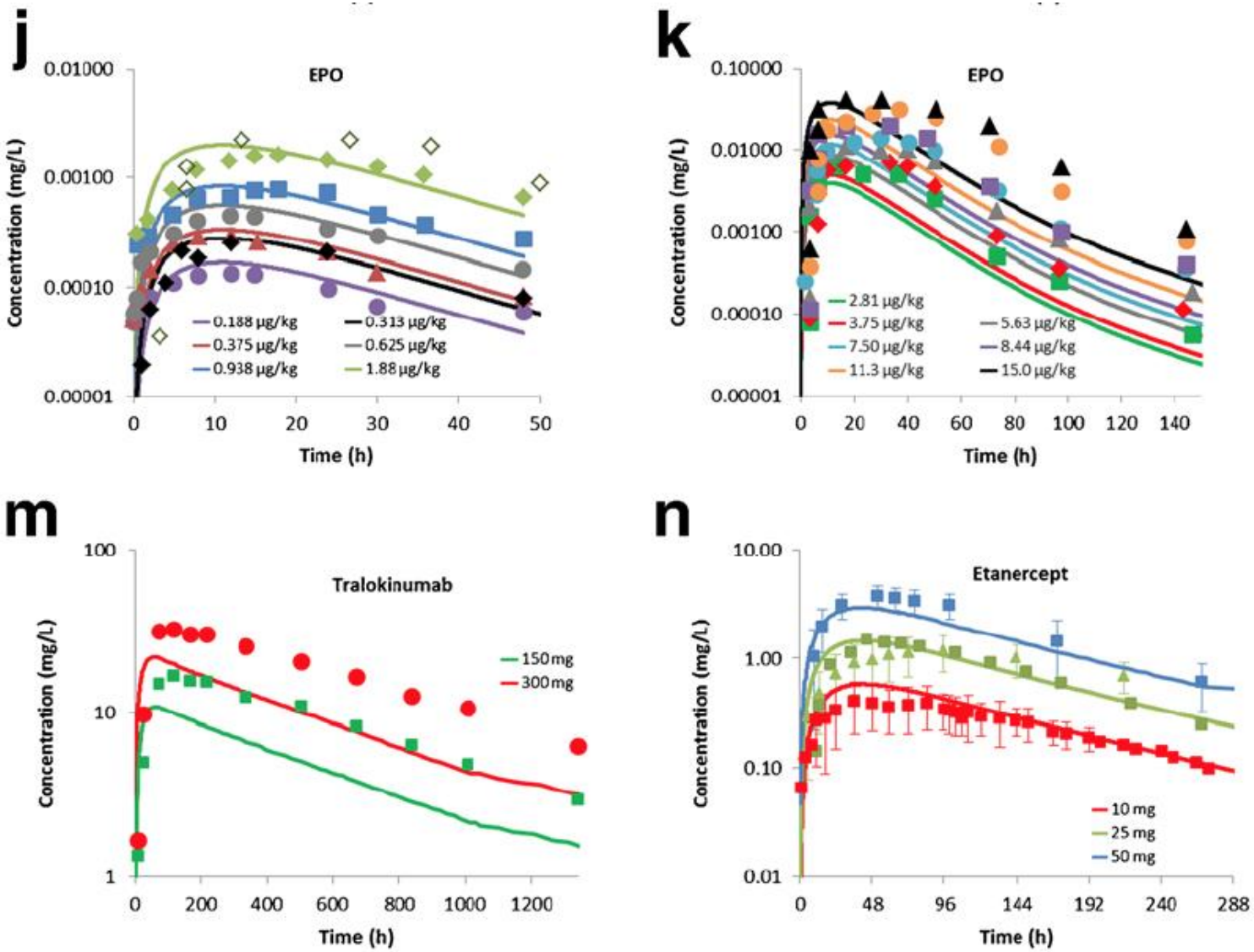
Translational PBPK of mAb PK in Brain





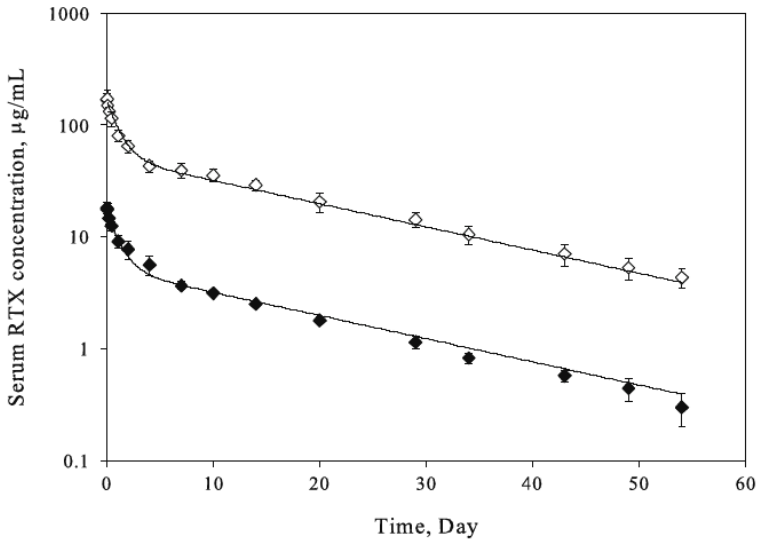
Chang et al. JPKPD. 46:319-38 (2019)

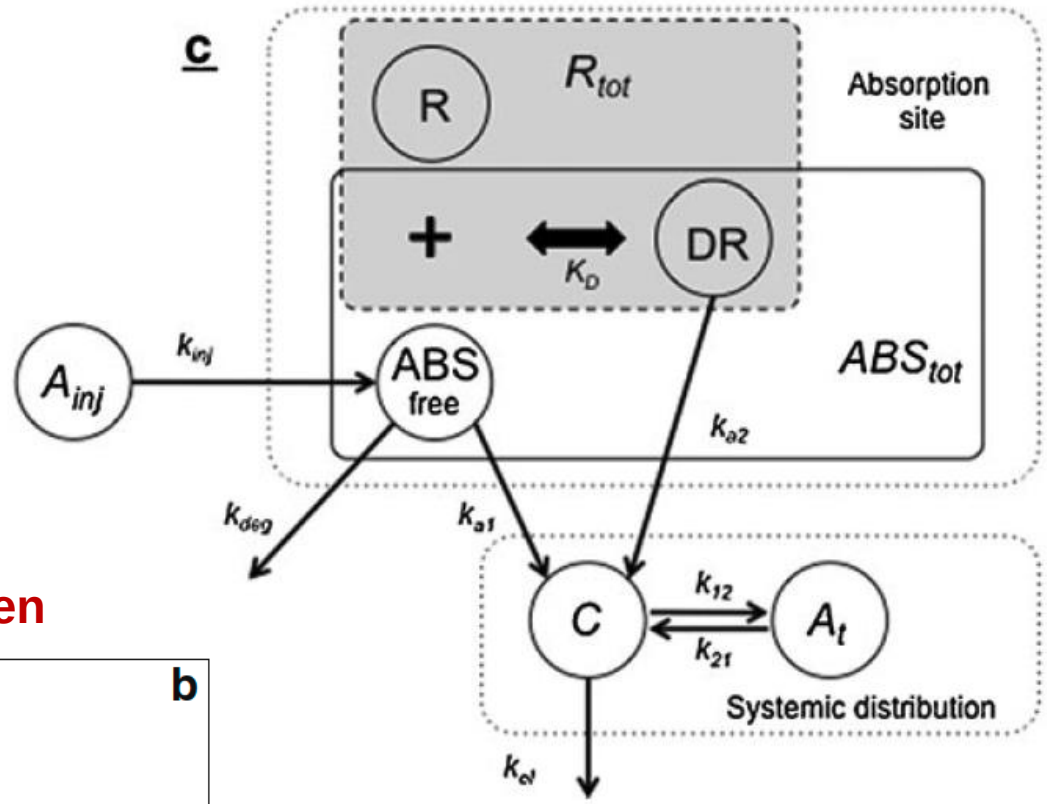
PBPK Model to Predict SC Absorption of Therapeutic Proteins



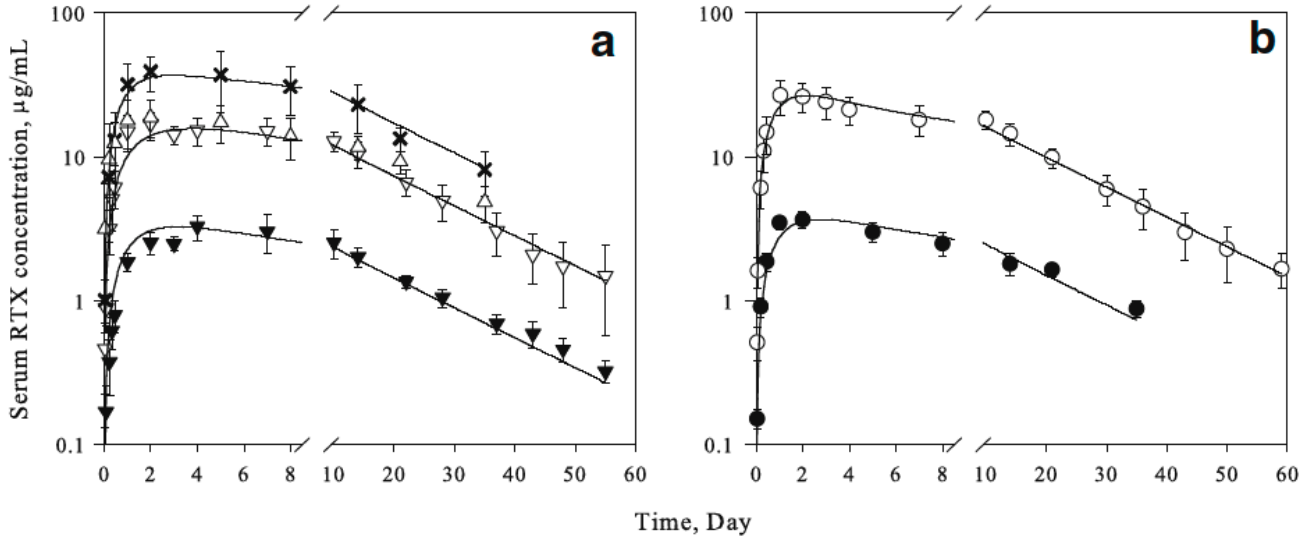
Gill et al. AAPSJ. 18:156-70 (2016)

Absorption Model for Rituximab in Rats





Back **Abdomen**



F
HD: 31% ± 7%
LD: 69% ± 12%

Kagan et al. *Pharm Res* 29:490 (2012)

Population Absorption Model for Trastuzumab in Rats

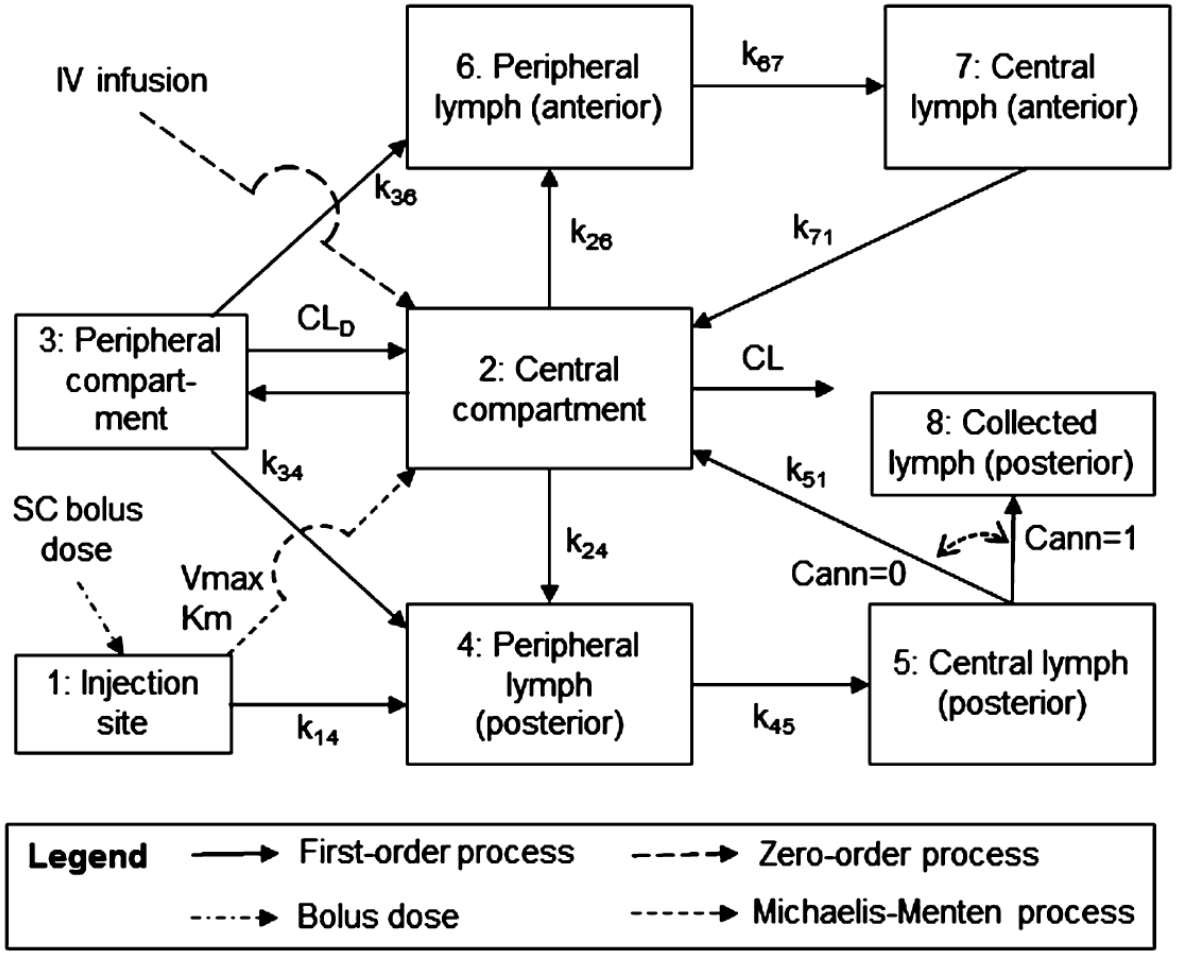
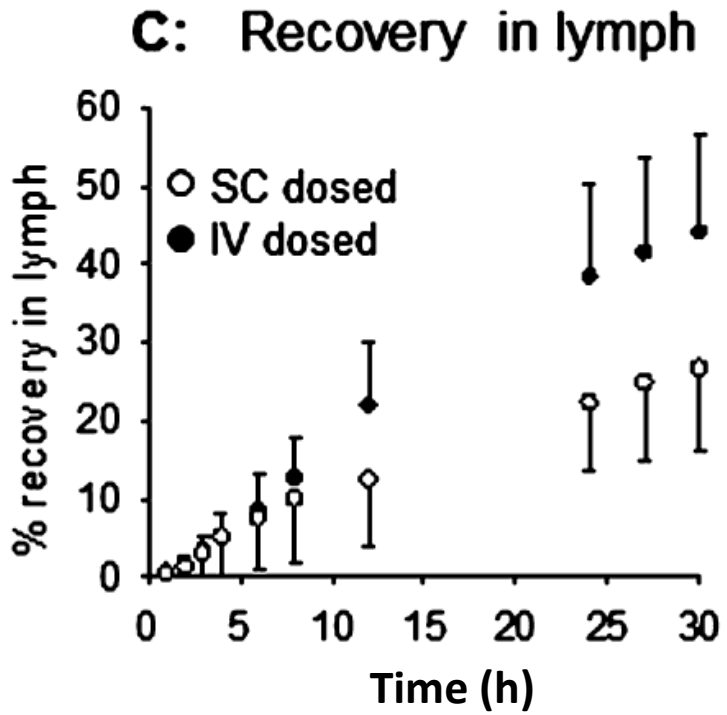


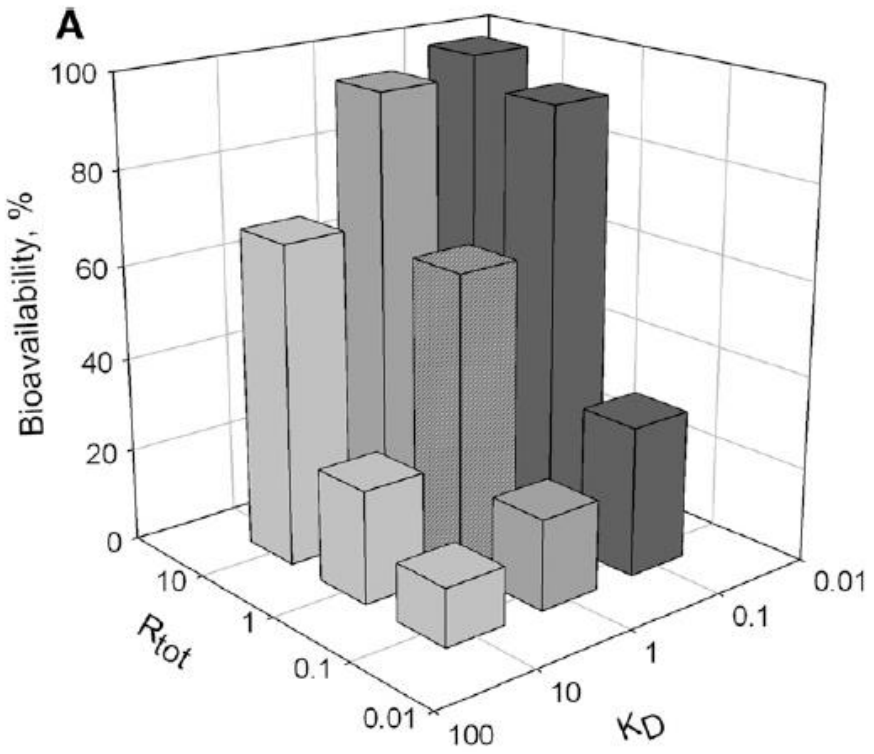
Figure 1. Structure of the population pharmacokinetic model that simultaneously described the plasma concentration and lymph profiles of trastuzumab in rats.

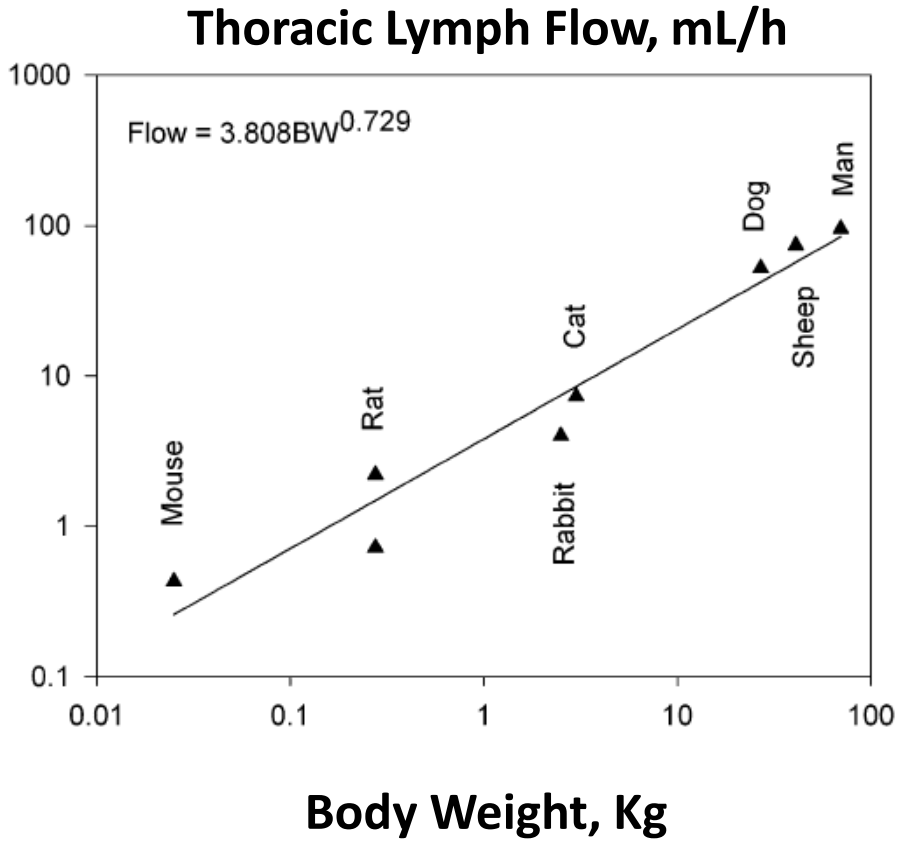


"…the lymphatic system is an integral part of the absorption profile of trastuzumab from interstitial injection sites and is a conduit for the continued circulation of proteins with prolonged plasma exposure profiles in rats."

Dahlberg et al. *Mol Pharmaceutics Res* 11:496 (2013)

FcRn Binding and Interspecies Differences in Lymph Flow

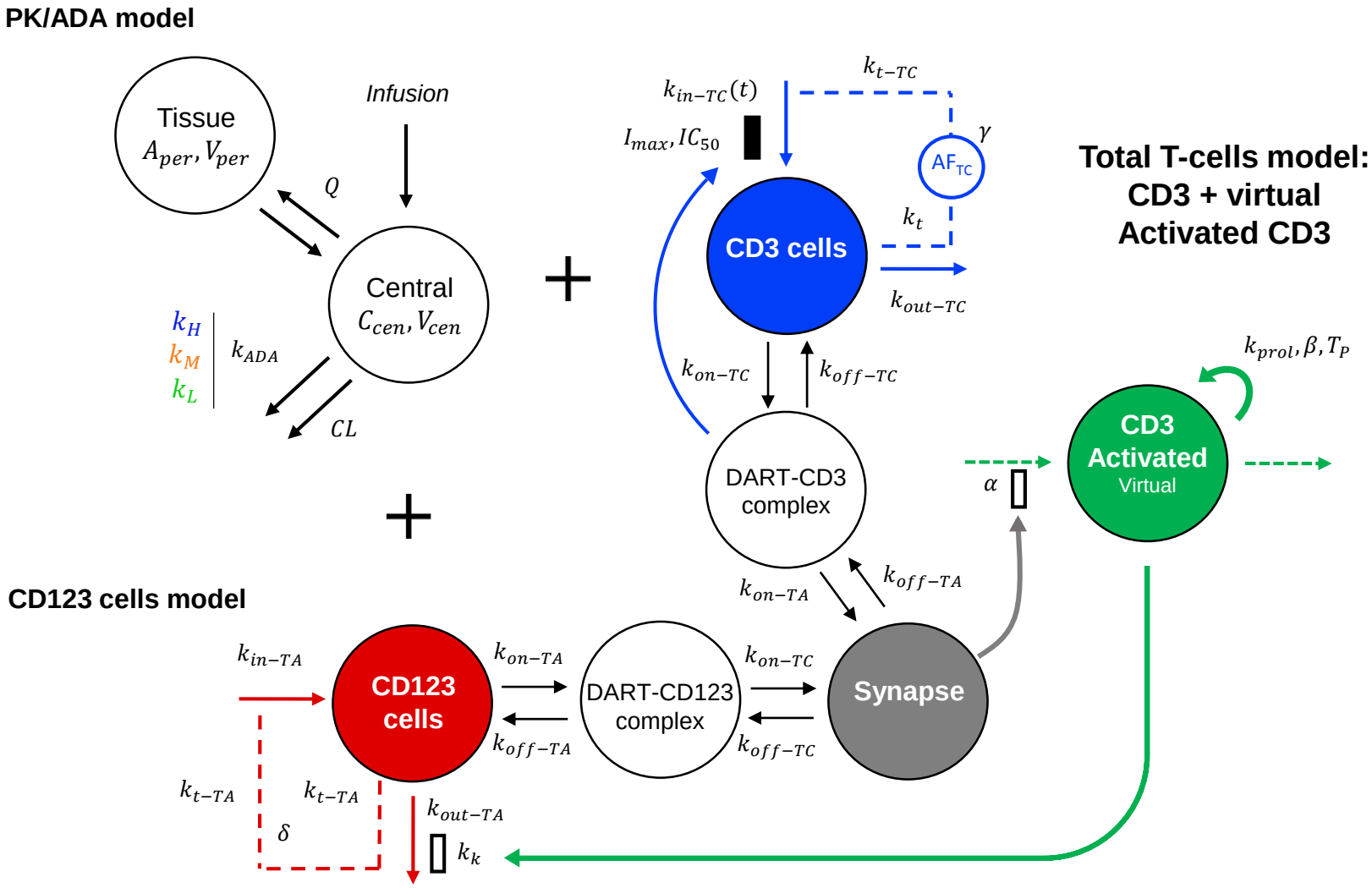




Kagan et al. *Drug Metab Dispos*. 42:1890 (2014); Lindena et al. *J Clin Chem Clin Biochem* 24:19 (1986); Porter et al. *Adv Drug Deliv Rev* 50:157 (2001)

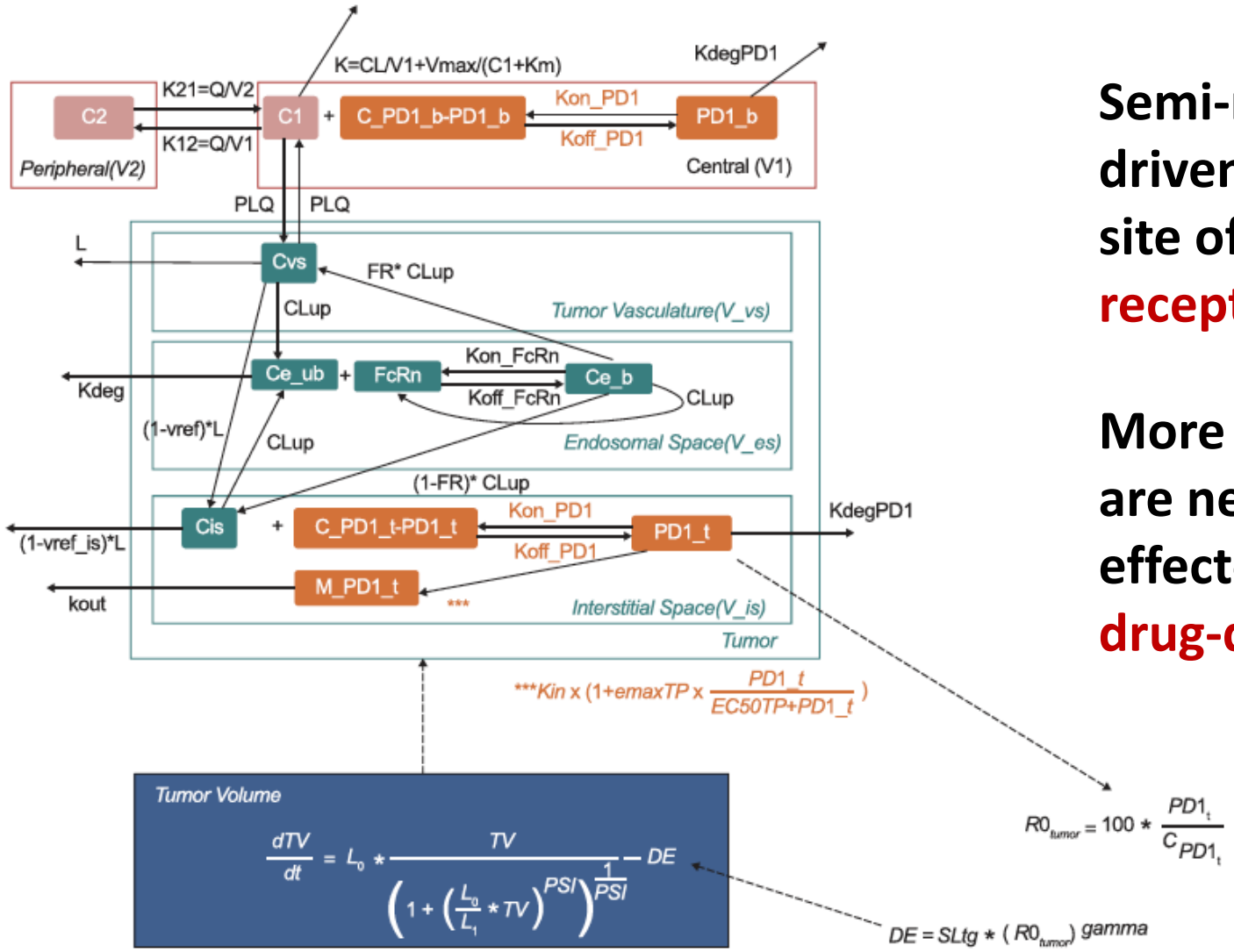
Mechanistic PK/PD Model of CD3 x CD123 DART®

Campagne et al. *Clin Cancer Res.* 24:2631-41 (2018)



- **Need to include circulating and tissue associated immune cells and ligands**

Translational PK/PD Model of anti-PD1

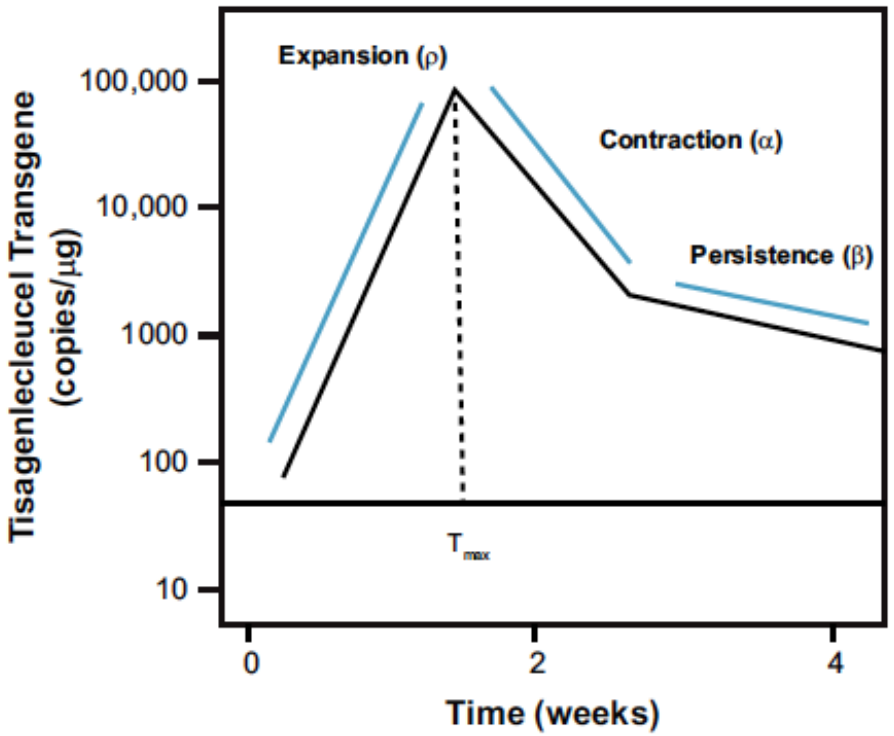


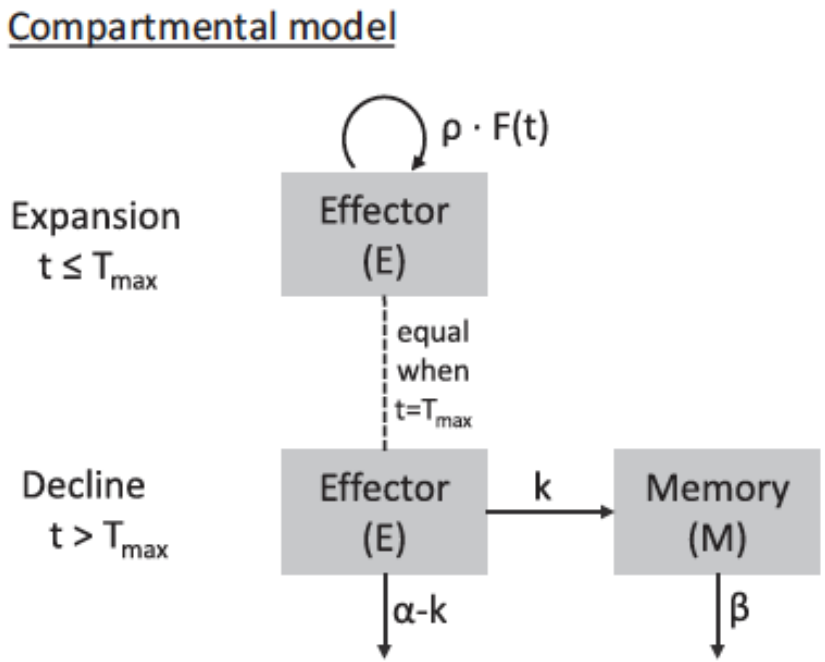
Semi-mechanistic model driven by distribution to site of action and receptor occupancy

More mechanistic models are needed to incorporate effector cell dynamics and drug-drug interactions

Lindauer et al. *CPT:PSP.* 6:11 (2017)

Cellular Kinetic Analysis of CAR-T Cell Therapy





Definitions

$\rho = \log(fold_x)/T_{max}$

$k = F_B \cdot (\alpha - \beta)$

Equations

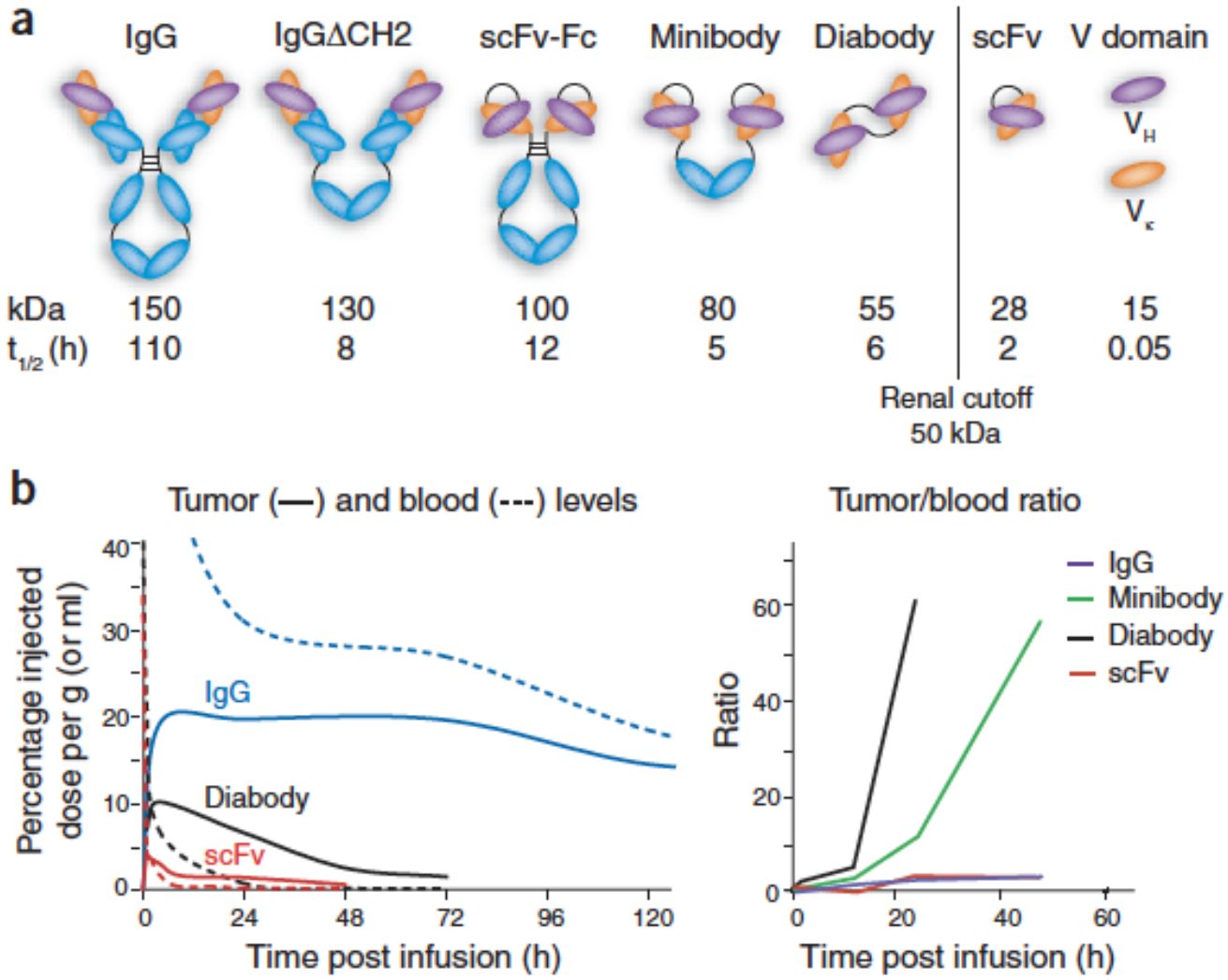
$$\frac{dE}{dt} = \rho \cdot F(t) \cdot E$$

$$\frac{dE}{dt} = -\alpha \cdot E$$

$$\frac{dM}{dt} = k \cdot E - \beta \cdot M$$

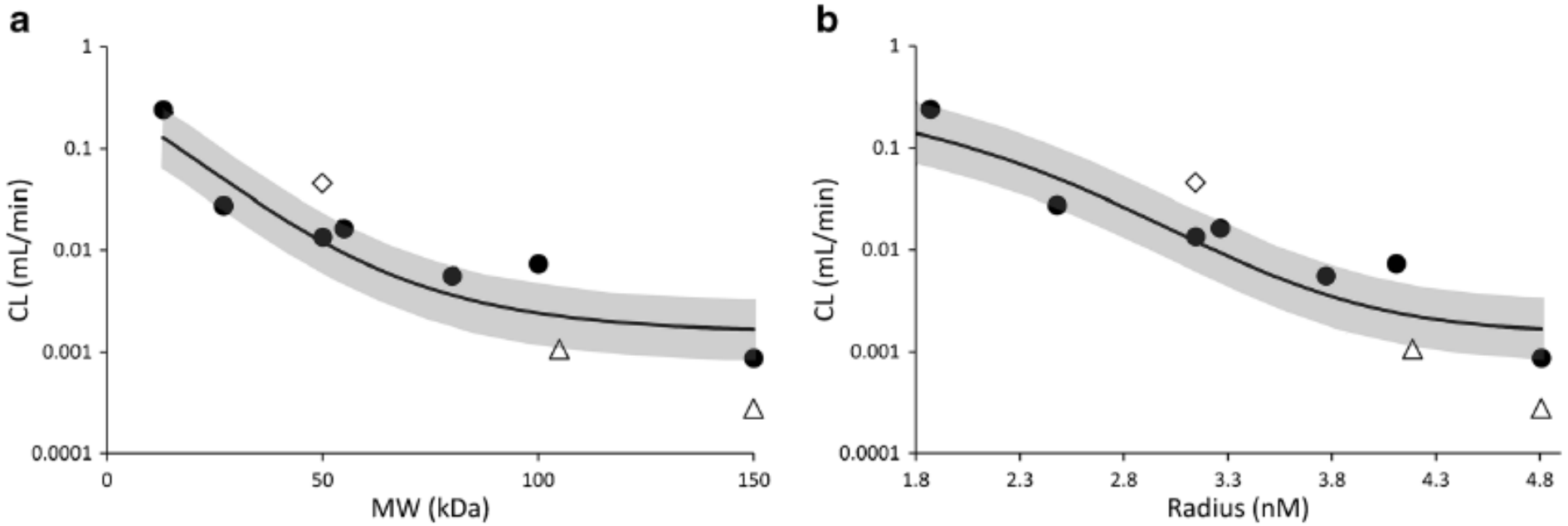
Stein et al. CPT:PSP 8:285-95 (2019)

Diverse PK of Engineered Antibody Fragments



Holliger and Hudson. *Nature Biotech.* 23:1126 (2005)

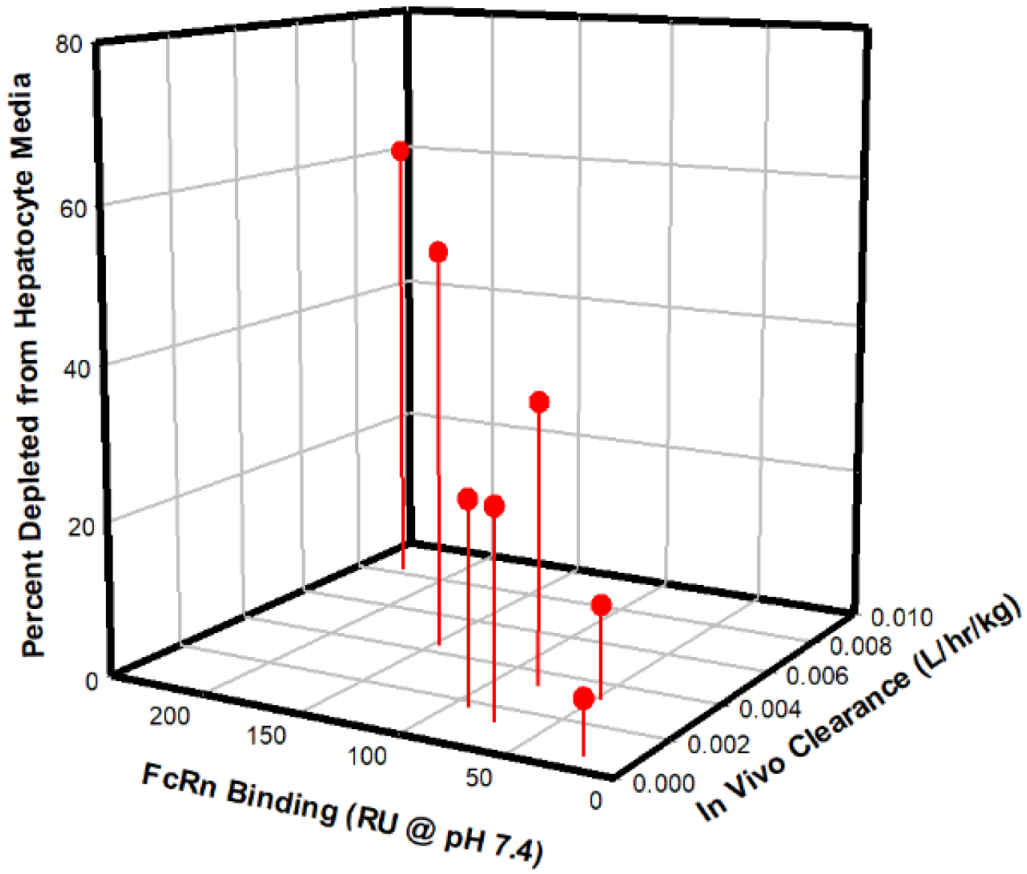
Role of Molecular Size in Antibody Fragment CL in Mice

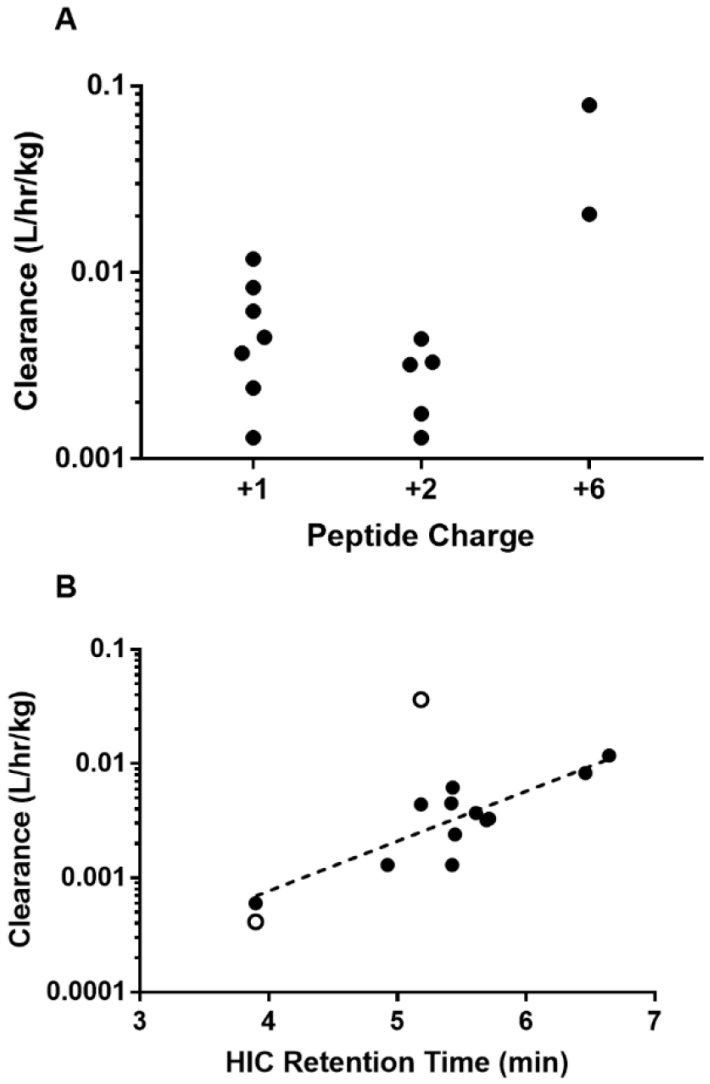


In contrast to QSAR, multiple pathways driven by biophysical properties will be needed to derive a general platform for characterizing the PK of diverse antibody-based constructs

Li et al. *Pharm Res.* 34:2131 (2017)

Use of Cryopreserved Hepatocytes to Characterize in vivo CL for Peptide-Antibody Conjugates





Foti et al. *Drug Metab Dispos.* 47:1111 (2019)

SUMMARY

- There is a strong need for risk-informed credibility assessments to address verification and validation needs for PBPK use in decision making.
- New biologics may present with unique pharmacokinetic features that extend beyond TMDD and its implications.
- New immunotherapy or immuno-oncology drugs are complex, including: checkpoint inhibitors, bispecifics (e.g., BiTEs), fusion proteins, and cell-based therapies (e.g., T-cells and dendritic cells).
- Modeling by interdisciplinary collaborations are needed, and this field may usher in a wave of QSP models for regulatory purposes (e.g., PB models of cells and ligands).
- There may be a need for including more biophysical properties of biologics. for example: formulation effects on SC absorption, pH-dependent binding, binding-site barriers, incorporating hepatocyte bioassays, and predicting immunogenicity.