

Antibody drug conjugates targeting solid tumors: Understanding the link between plasma trough concentration and their tumour distribution

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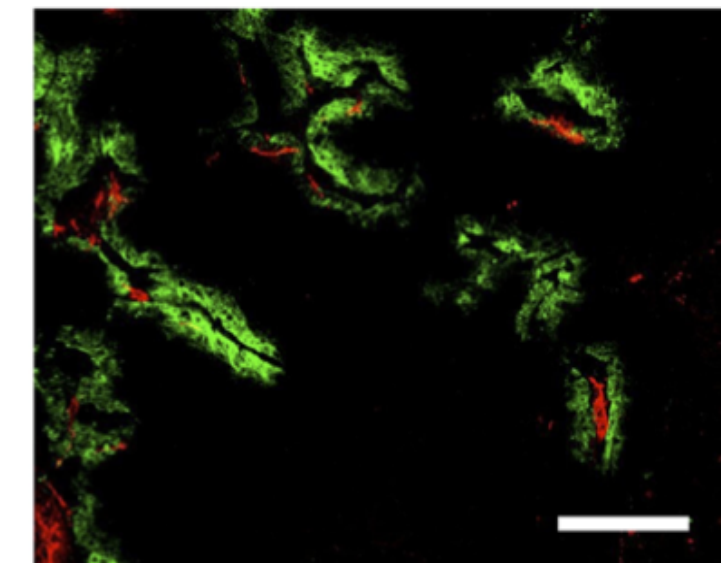
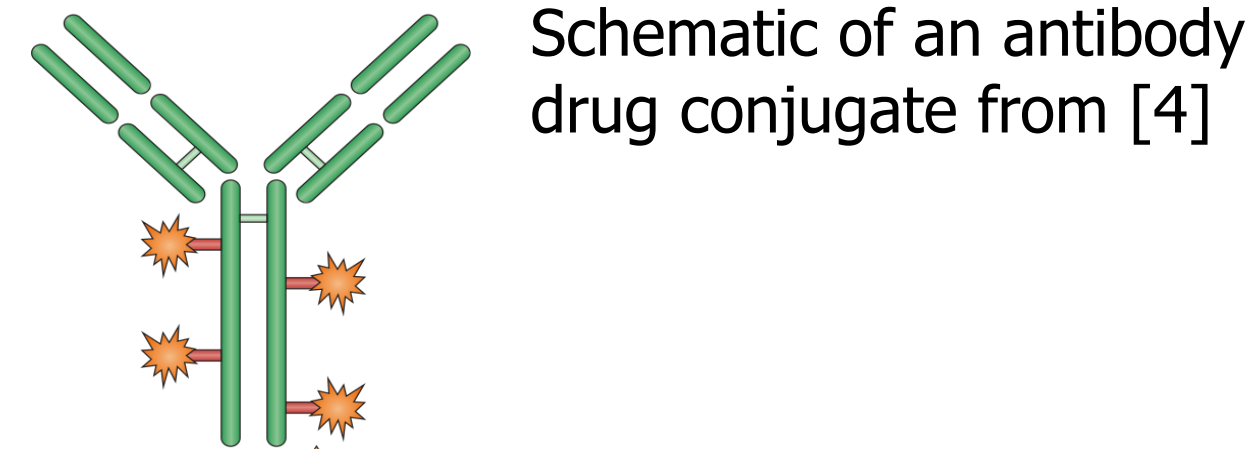
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Motivation & Objectives

Heterogeneous distribution of antibody drug conjugates (ADC) within solid tumors due to limitation of dose and dosing frequency is discussed as a factor limiting the therapeutic efficacy of ADCs [1]. Heterogeneity is suspected to arise from the so-called '**binding site barrier**' phenomenon, where the penetration of antibody into tumour tissue is retarded due to high-affinity binding to overexpressed receptors within solid tumors.



Perivascular distribution of the ADC trastuzumab emtansine within tumour tissue in xenograft mice [1]

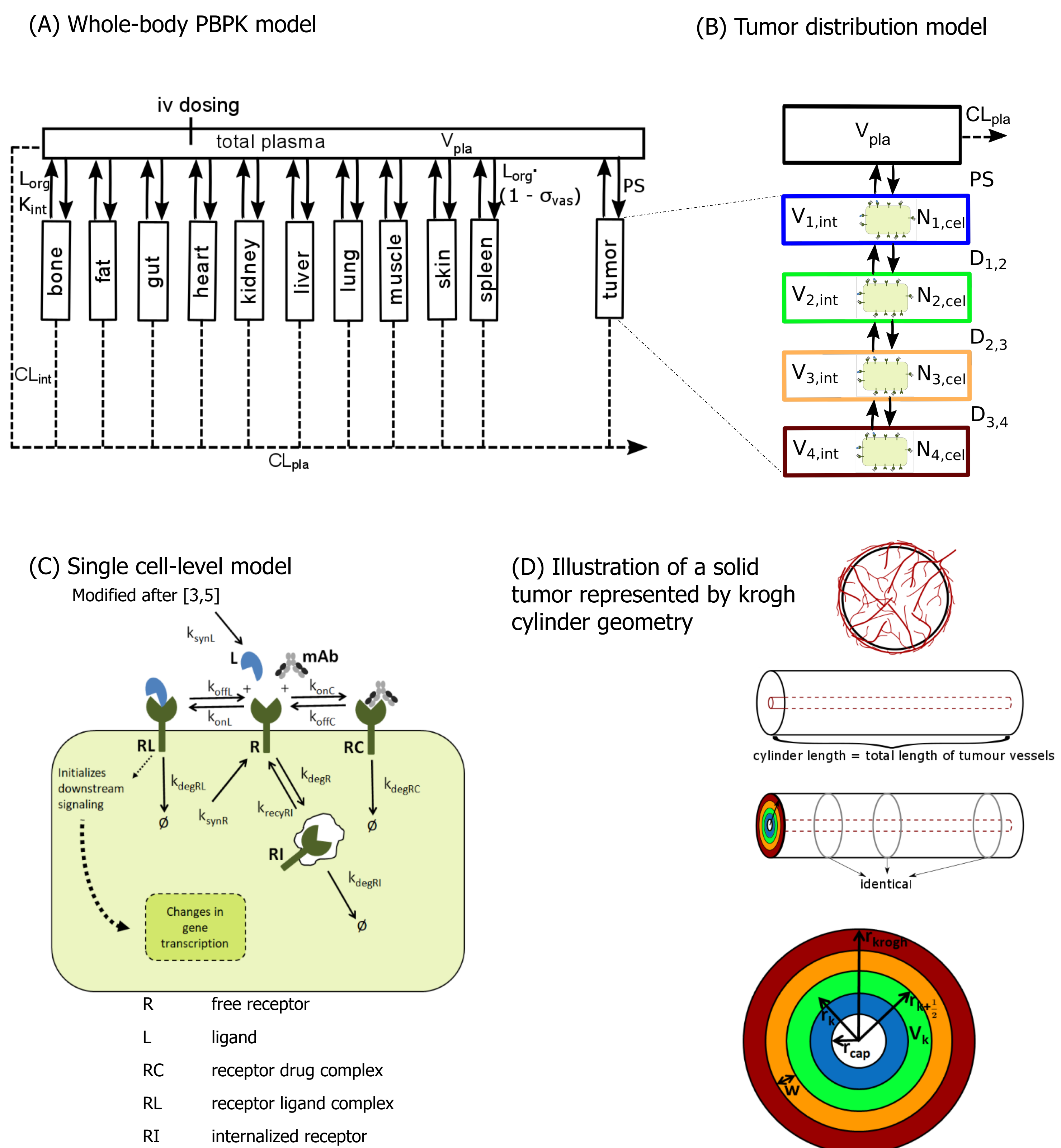
Objective:

Comprehensive investigation of antibody tumor distribution and its implications on therapeutic efficacy

- following clinical dosing regimens of ADCs
- in a mechanistic pharmacometric modelling framework allowing to study in detail receptor saturation in human patients

Methods

We used a physiologically-based pharmacokinetic (PBPK) modelling approach [2] with a tumor distribution model extended by a detailed single cell-level to account for antibody-receptor interactions as well as receptor dynamics [3].



A) Structure of the PBPK model for antibody PK including tumor compartment (CMT)

- Organs except tumor are interconnected via extravasation and the lymph flow (solid arrows)
- Total plasma comprises total arterial and venous plasma, including the vascular space of the organs
- mAb can potentially be unspecifically cleared from plasma as well as any other CMT except tumor (dashed arrows)

B) Tumour distribution model

- Tumor CMT is divided into 4 layers that consist of interstitial and cellular space
- mAb can distribute between tumor and plasma (permeability surface area product)
- in each tumor layer, mAb can bind to its receptor or distribute to any adjacent layer (diffusion exchange rates)

C) Single cell-level model

- Considers receptor dynamics and receptor-mAb interaction
- Receptor saturation, i.e., $RC/(RC+R)$ as measure of therapeutic efficacy

References

[1] Cilliers et al. AAPS J 2016.

[2] Fuhrmann et al. J Pharmacokinet Pharmacodyn 2017.

[3] Krippendorff et al. J Pharmacokinet Pharmacodyn 2012

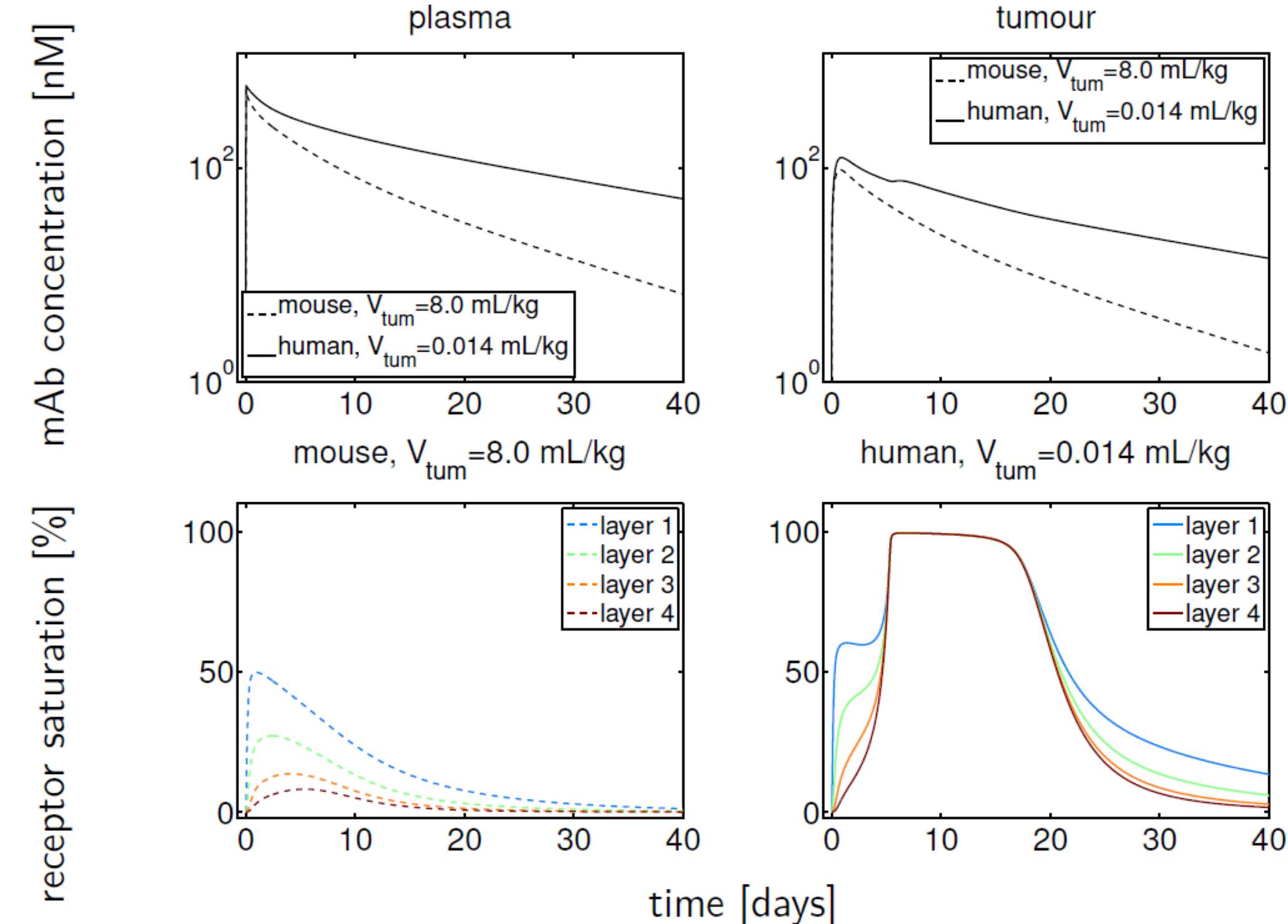
[4] Zolot et al. Nat Rev Drug Discov 2013

[5] Yarden & Shilo 'Snapshot: EGFR Signalling Pathway' 2007 Cell

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Results

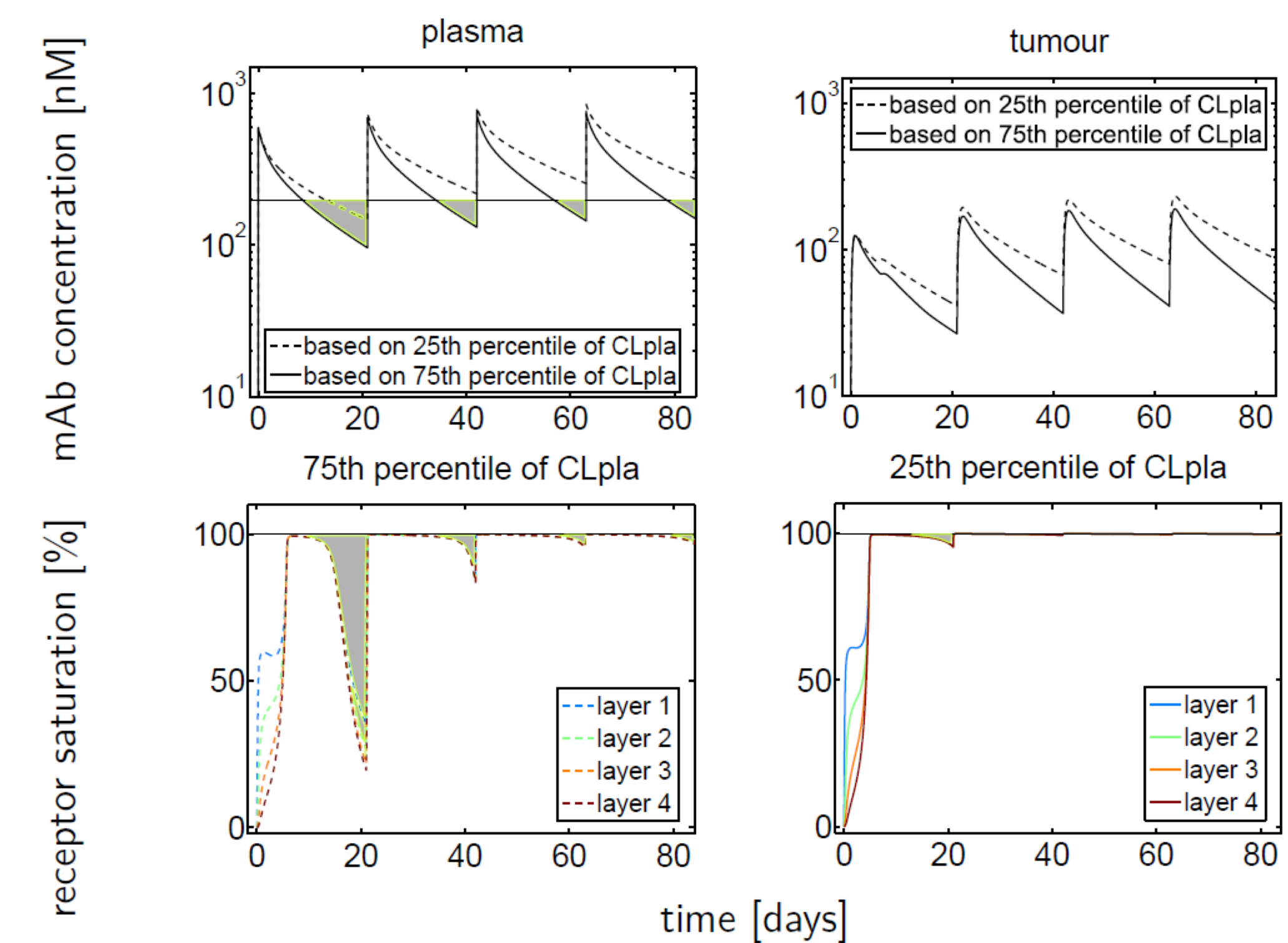
Tumor distribution following clinical dosing regimens of ADCs can be homogeneous



- Predicted plasma and tumor concentration-time profile
 - following T-DM1 dose: 3.6 mg/kg BW
 - at clinically detectable tumor volume in a human male patient as well as typical xenograft tumor volume in mice

Duration of receptor saturation is markedly influenced by plasma clearance (CL_{pl})

- In case of saturated target-mediated CL, the duration of receptor saturation is markedly influenced by the unspecific (target-independent) CL.
- This is of relevance in cancer therapy, since unspecific immunoglobulin CL can be increased, e.g. in the case of hypoalbuminemia as biomarker for cachexia or immunogenicity.



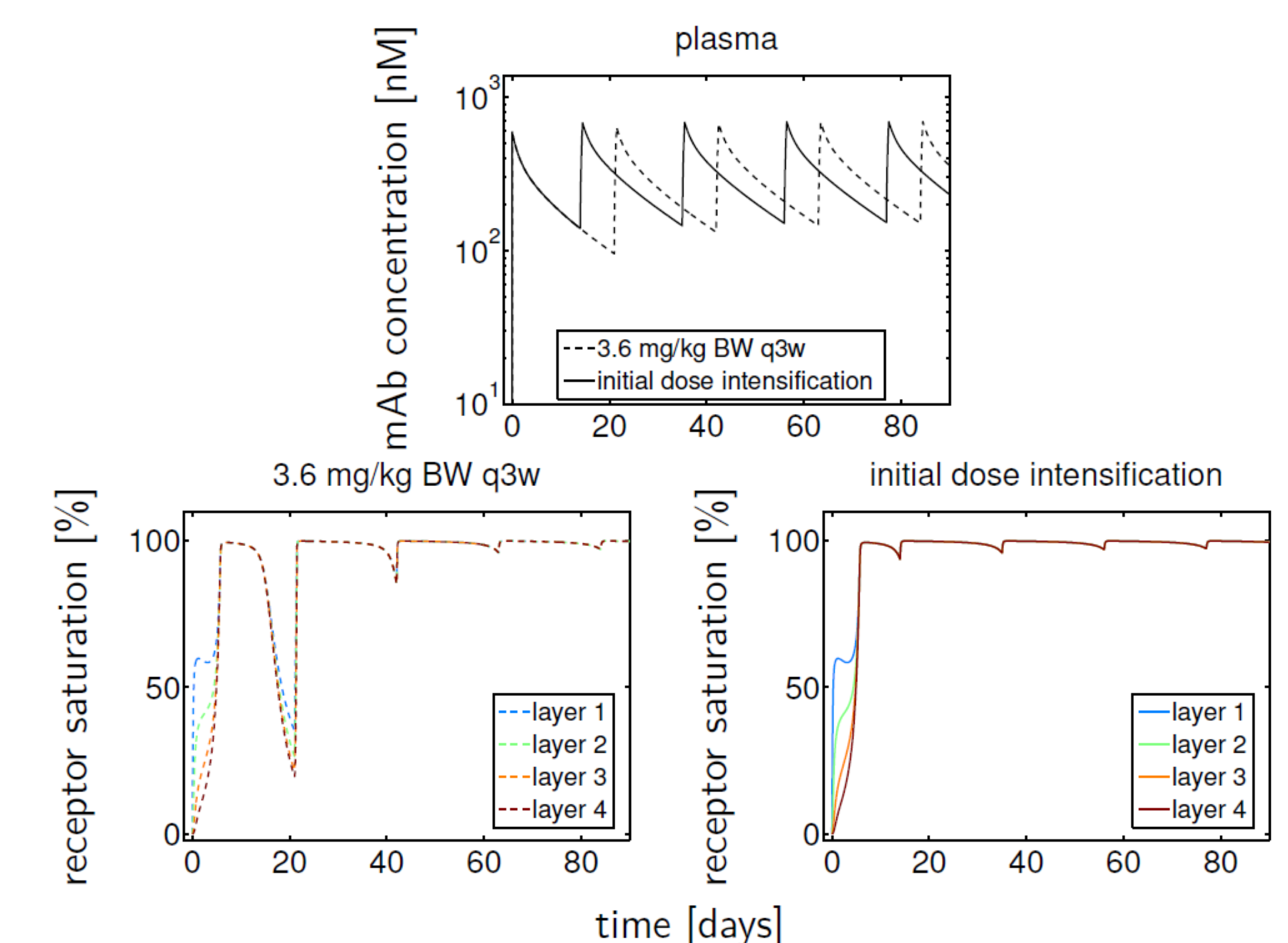
- Predicted impact of variation in CL_{pl} on plasma and tumor PK
 - following approved T-DM1 dose in human patients: 3.6 mg/kg BW q3w

- Predicted impact of variation in CL_{pl} on receptor saturation
 - Only first treatment cycle is influenced

How can we prevent the decrease in receptor saturation after first dose?

Dose intensification within the first treatment period to guarantee receptor saturation

- Strong relationship between plasma ADC trough concentration and receptor saturation.
- In the context of multiple dosing and if receptor saturation is required for efficacy, this finding has important implications for (i) the first treatment cycle and (ii) increased unspecific CL.
- Dose intensification within the initial treatment period of ADCs targeting solid tumors can be mechanistically supported using our pharmacometric modelling approach.



- Predicted plasma PK following
 - 3.6 mg/kg q3w (dashed line)
 - Dose intensification within the initial treatment period

- Predicted impact of dose intensification on receptor saturation

Conclusion & Discussion

- Our pharmacometric modelling approach offers a mechanistic framework to study in detail tumor distribution and its implications for therapeutic effects.
- Our analysis demonstrated that the binding site barrier phenomena is strongly species dependent. This raises the question to what extent the binding site barrier phenomena is relevant for the human situation.