

Development of a PBPK model of an anti-PD-L1 antibody to predict whole-body and tumor exposure in mice

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BACKGROUND

Immune checkpoint inhibitors targeting PD-1/PD-L1, such as atezolizumab, have significantly improved cancer treatment as monotherapy or combination [1]. However, combination strategies remain limited by an incomplete quantitative understanding of antibody biodistribution and target engagement within tissues and the tumor [2]. Preclinical data may support clinical development by improving the characterization of interspecies differences in antibody biodistribution.

OBJECTIVES

- Build a mouse PBPK model of an anti-PD-L1 monoclonal antibody.
- Predict and evaluate whole-body pharmacokinetics in tumor-bearing mice.
- Identify the parameters guiding biodistribution of the mAb in tumor.

MATERIAL & METHODS

- **Drug:** mAb (atezolizumab mouse surrogate)
- **Species:** mouse
- **Administration:** IV bolus
- **Target:** murine PD-L1
- **Observations** [3]: plasma concentrations at 3 doses (Fig. 1), receptor occupancy in plasma at 3 doses (Fig. 1), biodistribution by radio-labeling at 4 doses (Fig. 2).
- **Software:** PK-Sim® and MoBi® (OSP suite)
- **Model structure:** see Fig. 5.

VALIDATION

	1 mg/kg	10 mg/kg	30 mg/kg
	pred/obs	pred/obs	pred/obs
AUC _{inf} (μg·day/mL)	1,0	0,6	0,9
CL (mL/day/kg)	1,0	1,6	1,2
C _{max} (μg/mL)	1,0	0,9	0,7
Terminal t _{1/2} (day)	1,0	0,7	1,0
V _{ss} (mL/kg)	1,2	1,6	1,7

Table 1: Comparison of NCA results between model predictions and experimental data [3] in healthy mice.

In healthy mice, plasma PK was adequately described (Fig. 1), with NCA parameters within two-fold of observed values (Table 1). The model was then extended to tumor-bearing mice, assuming no substantial tumor effect on systemic PK.

Parameter (unit)	Start value	Final value	95% CI
Target reference concentration in the spleen (nM)	1 [4]	0.96	+/- 0.28
kD _{Drug-FcRn} in endosomes (nM)	931 [5]	989	+/- 257
kD _{Drug-Target} (nM)	1.16 [6]	4.49	+/- 2.2
kDeg target degradation rate constant (1/h)	1 [4]	0.59	+/- 0.69
kInt drug-target complex internalization rate constant (1/h)	0.1 [4]	2.09	+/- 12.5

Table 2: Optimization of the final model. Blue values were calibrated in healthy mouse model and reused in the tumor-bearing mice model. Pink values were calibrated using MC38 tumor-bearing mouse data.

These results support the model's ability to describe both healthy (Fig. 1) and tumor-bearing mice (Fig. 2), although TMDD-specific parameters remain less precisely characterized.

This approach enables the exploration of tissues and tumor biodistribution, which remains insufficiently characterized for immune checkpoint inhibitors.

Base PBPK model in PK-Sim for mAb

- Input PBPK parameters from the literature (in vitro data or calibrated values in QSP or PBPK models)
- Healthy mouse default from PK-Sim

Export to MoBi

Mechanistic model in MoBi – Healthy mouse

- Target mediated drug disposition
- Parameter identification of unknown or uncertain parameters

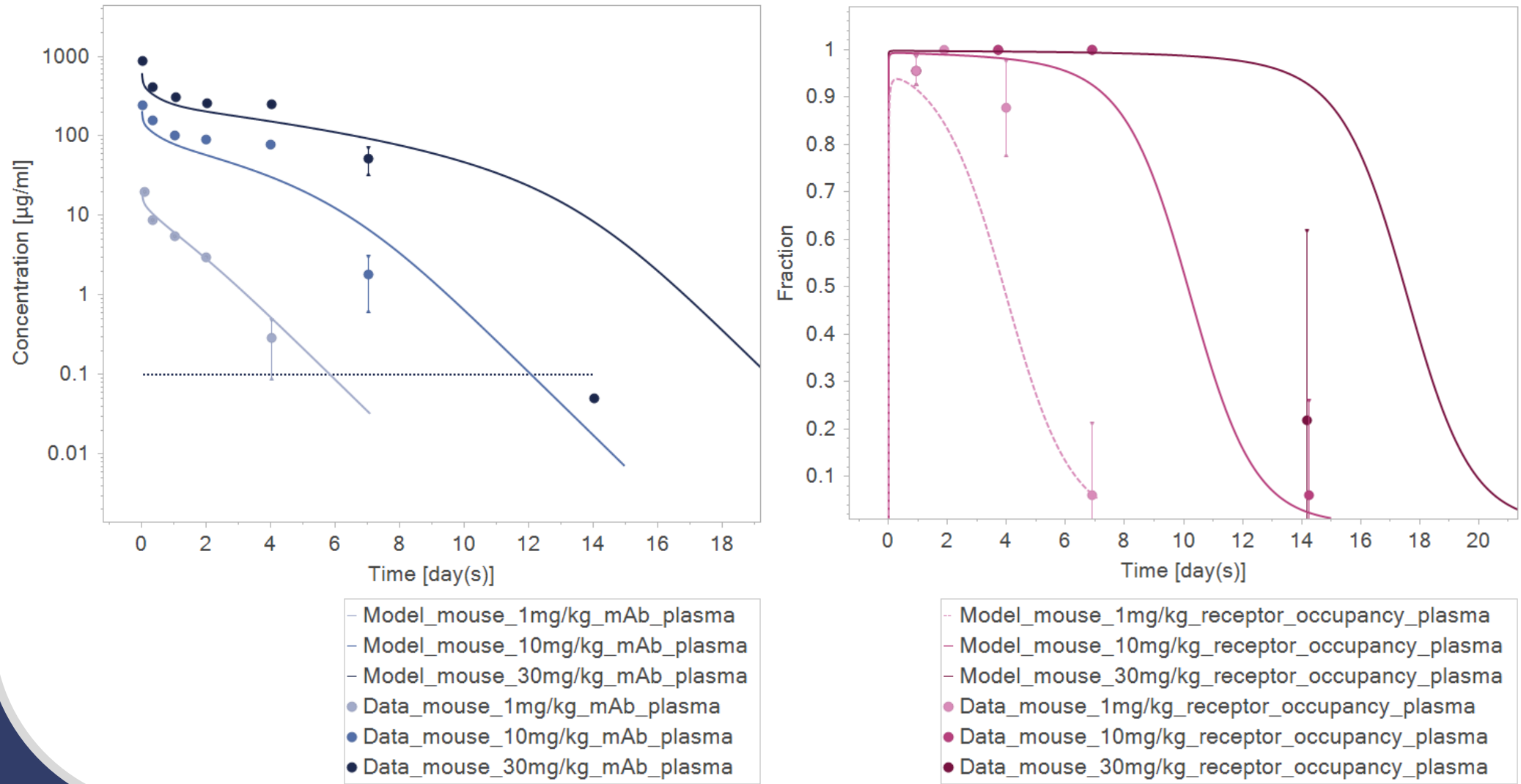


Figure 1: Observed [3] and simulated data with TMDD module for 3 doses. Left: Plasma concentrations. Right: Receptor occupancy in plasma.

Addition of a tumor compartment

Mechanistic model in MoBi – Tumor-bearing mice

- Tumor compartment: MC38 (colorectal carcinoma).
- New observed data leading to a new TMDD hypothesis: parameter identification of kDeg and kInt.
- Validation with another tumor: Cloudman (melanoma): change in tumor composition and tumor target expression according to the literature [3].

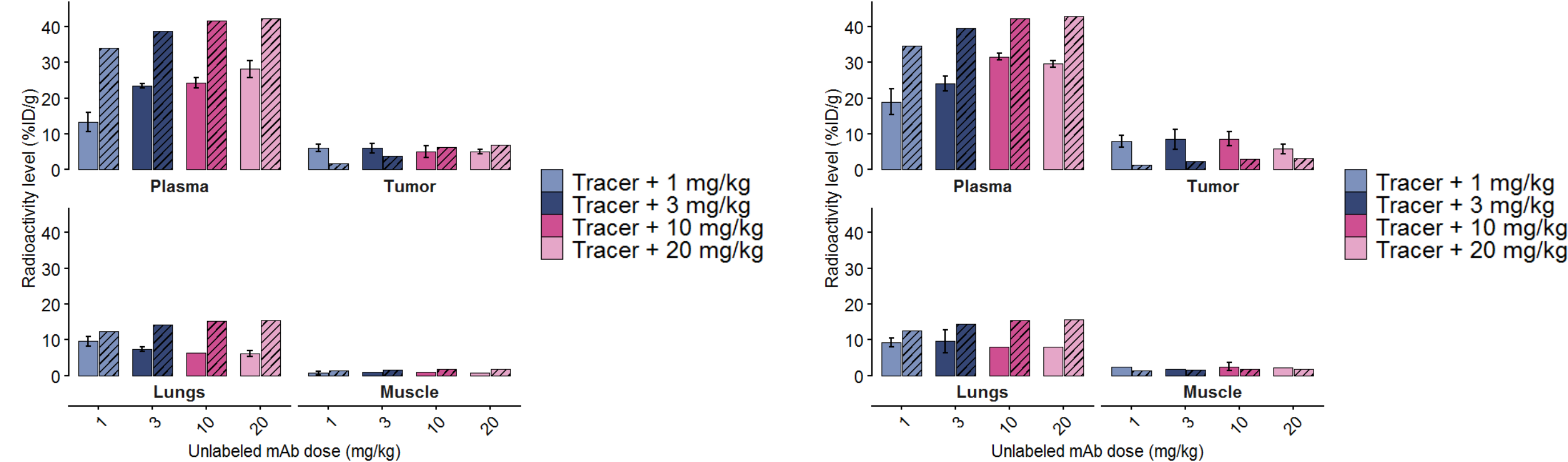
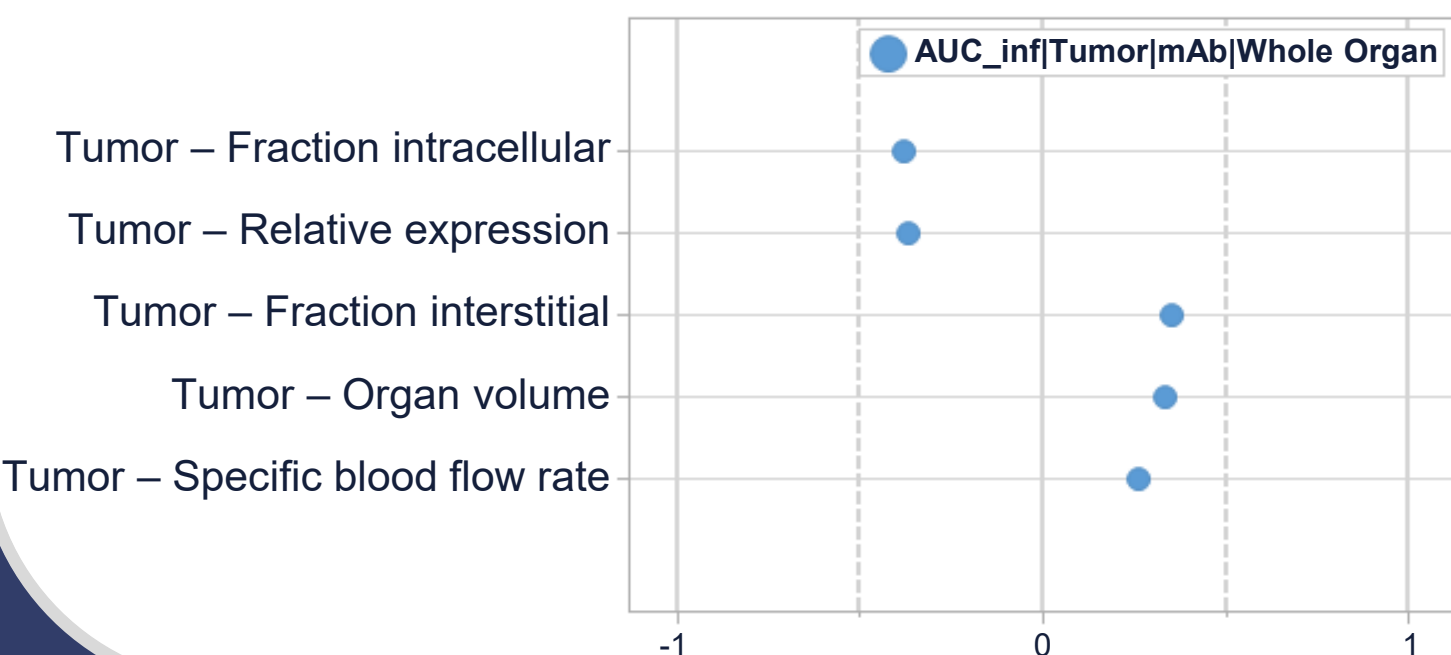


Figure 2: Observed [3] and predicted (hatched) radioactivity levels. Left: MC38 mouse. Right: Cloudman mouse.

Tumor exploration

Figure 3: Antibody biodistribution coefficients (ABCs) represent the linear relationship between plasma and tissue concentrations (expressed as %) [7]. They are estimated for both tumor-bearing mouse models.



Organ	ABC MC38 model (%)	ABC Cloudman model (%)
Lung	36	36
Spleen	28	28
Muscle	4	4
Liver	20	20
Tumor	9	6

Figure 4: Local sensitivity analysis of tumor-specific parameters on tumor exposure in the MC38 model. These parameters are often poorly characterized and influence predicted tumor exposure. Similar results were obtained with the Cloudman model.

MODEL STRUCTURE

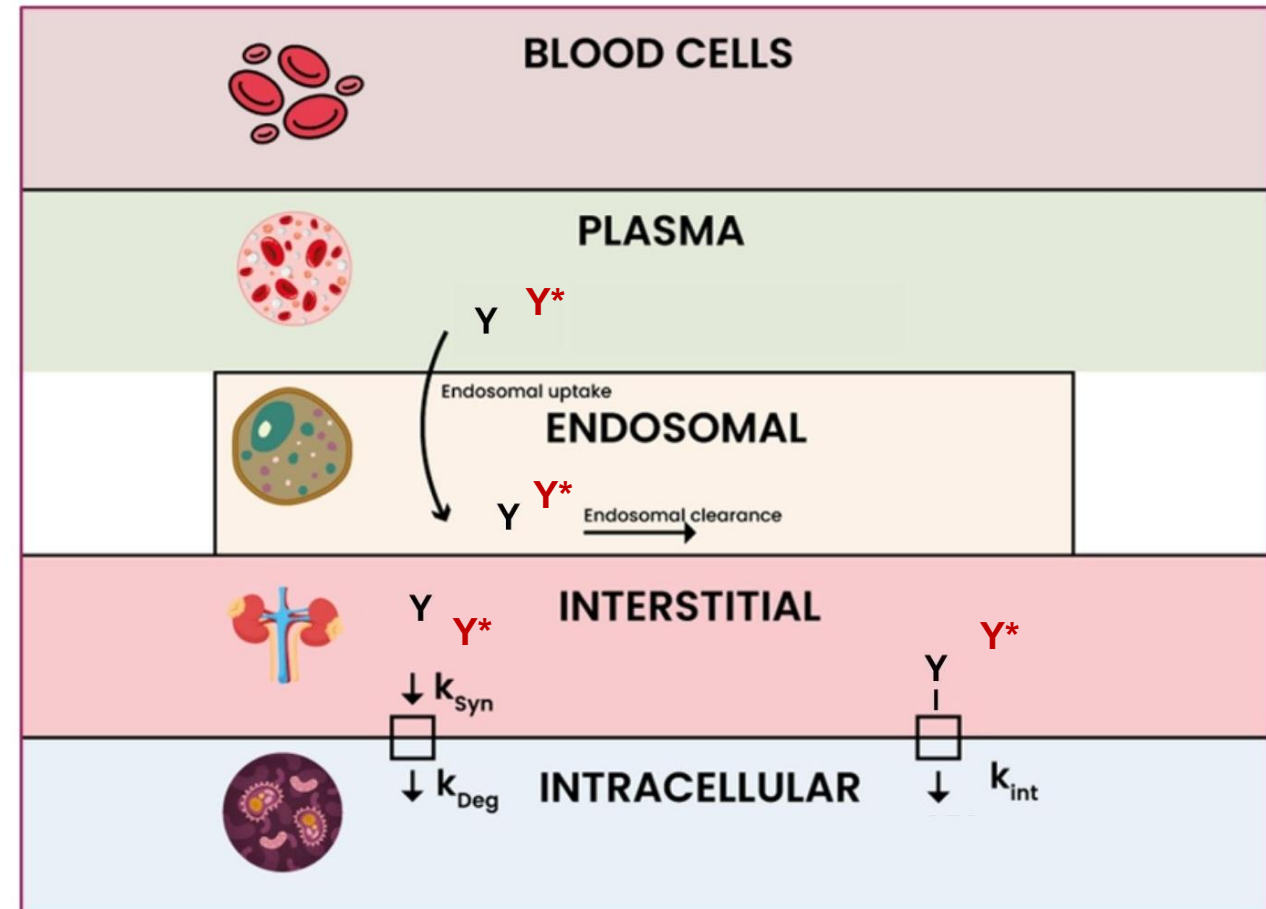
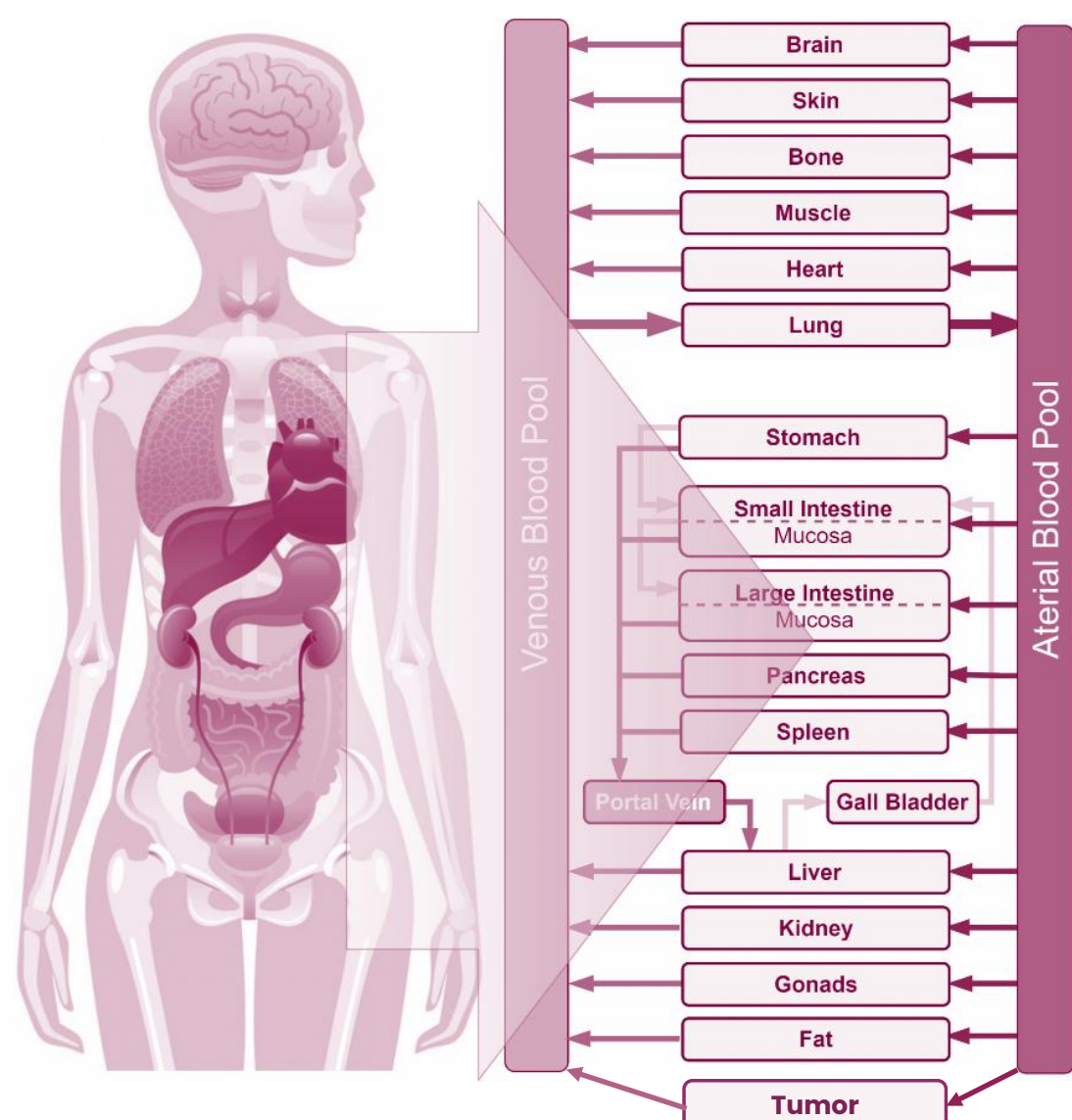


Figure 5: Model structure with 16 organs (top), each represented by five subcompartments (bottom), with an optional tumor compartment in MoBi. Y=antibody. Y*: radiolabeled antibody, included only for comparison with biodistribution data.

- Drug-target binding in interstitial compartment.
- FcRn recycling or degradation in endosomal compartment.
- Target recycling and internalization of drug-target complex.
- Competition between antibody and radiolabeled antibody for target binding to reproduce experimental biodistribution conditions (Fig. 2).

CONCLUSIONS

- Plasma data alone are insufficient to predict tumor exposure, highlighting the importance of biodistribution observed data (Fig. 2).
- Such mechanistic models may support translational strategies in human, guide preclinical-to-clinical extrapolation, and help optimize clinical trial design through improved understanding of tumor exposure factors (Fig. 3, 4).
- Integrating more robust tumor-specific data could improve PBPK translation across tumor types and species.

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