DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODEL OF AN ANTI-HER2 ANTIBODY-DRUG CONJUGUATE WITH REZETECAN PAYLOAD IN MICE

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Introduction

A quantitative understanding of the whole-body pharmacokinetics (PK) of antibody-drug conjugates (ADCs) is essential for establishing the exposure-response relationship and evaluating the safety profile of ADCs [1]. Several preclinical, clinical or translational PBPK and QSP models have been published in recent years, especially for first-generation ADCs targeting HER2 [2-5]. In addition, a human PBPK model was published for an ADC with a new payload, Rezetecan [6]. Here, we build on these approaches to derive a mice PBPK model of an anti-HER2 ADC with Rezetecan payload [7] in the Open Systems Pharmacology Suite [8].

Objectives

- Predict and verify the whole-body PK of the different ADC analytes in tumor-bearing mice with detailed biodistribution data
- Identify the most sensitive parameters that can affect tumor exposure of the different ADC analytes

Material & Methods

- **Drug:** ADC (Trastuzumab Rezetecan)
- **Species:** Rat, Mouse
- **Administration:** IV bolus of Payload in rat, IV bolus of ADC in mouse
- **Target:** HER2
- **Observations:** 1 analyte at 3 doses in rat; 3 analytes at 2 doses in tumor-bearing mouse (NCI-N87, human gastric cell-derived xenograft).
- **Model structure:** See Fig. 1.
- **Model calibration:** See Figs. 2-3 in rat and Fig. 4 in mouse. Tables 1-3.
- **Free target concentration, drug-target receptor occupancy and sensitivity in healthy and tumor tissues:** see Fig. 5 & Table 4.

Model structure

- **ADC plasma deconjugation**
- **Drug-target binding** in healthy tissues and tumor compartment
- **Competition** between the ADC and the naked antibody for binding to the target.
- **Intracellular processing of ADC and payload** within the endosomal compartment leading to **ADC degradation/recycling, payload release, and target recycling**.

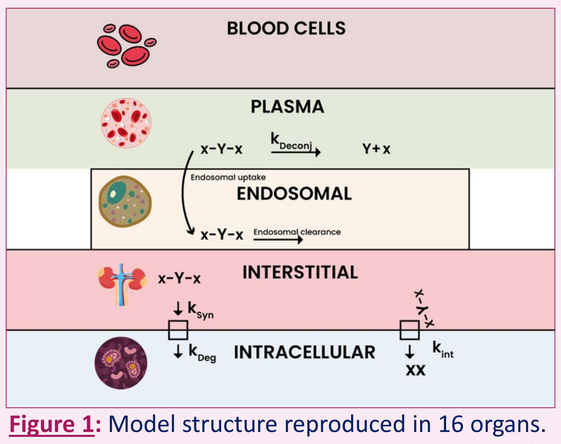
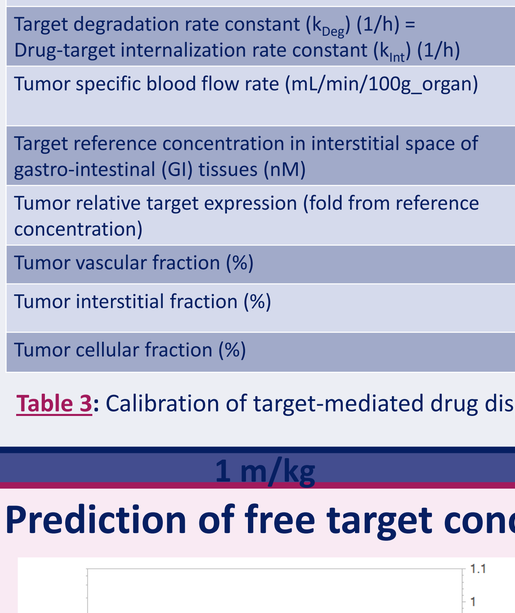


Figure 1: Model structure reproduced in 16 organs. **Y**: antibody. **x**: payload. **x-Y-x**: ADC. Quasi-steady state with $k_{syn} = k_{int} = k_{deg}$.

Calibration of ADC properties in mouse



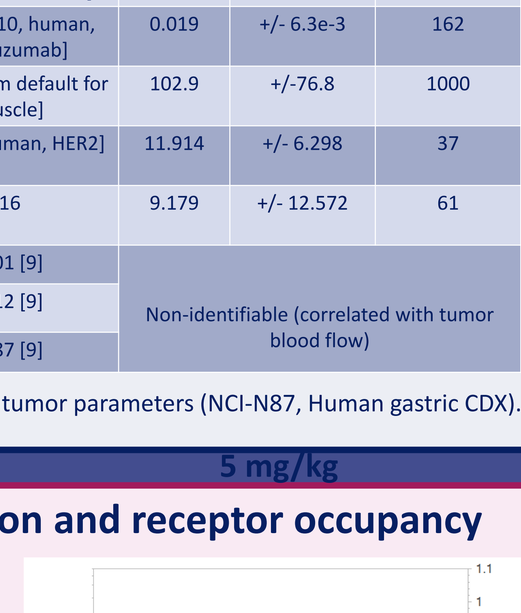


Figure 4: Visual predictive check of calibration of plasma concentrations for 3 analytes and whole tumor exposure to Payload. **Left:** Plasma ADC (purple) and Total antibody (yellow) concentrations at 1 mg/kg (dots, solid lines) and 5 mg/kg (diamonds, dotted lines). **Right:** Payload concentration in plasma (blue) and in whole CDX tumor (pink) at 1 mg/kg (dots, solid lines) and 5 mg/kg (diamonds, dotted lines).

Parameter	Start value [ref]	Final value	95% CI	% change
Deconjugation rate constant (k_{Dec}) (1/h)	3.06e-3 [4, mouse, Trastuzumab DM1]	7e-3	+/- 5.9e-3	228
Target degradation rate constant (k_{Deg}) (1/h) = Drug-target internalization rate constant (k_{int}) (1/h)	0.0117 [10, human, trastuzumab]	0.019	+/- 6.3e-3	162
Tumor specific blood flow rate (mL/min/100g_organ)	9.1 [PK-Sim default for muscle]	102.9	+/-76.8	1000
Target reference concentration in interstitial space of gastro-intestinal (GI) tissues (nM)	32 [10, human, HER2]	11.914	+/- 6.298	37
Tumor relative target expression (fold from reference concentration)	16	9.179	+/- 12.572	61
Tumor vascular fraction (%)	0.01 [9]	Non-identifiable (correlated with tumor blood flow)		
Tumor interstitial fraction (%)	0.12 [9]			
Tumor cellular fraction (%)	0.87 [9]			

Table 3: Calibration of target-mediated drug disposition and tumor parameters (NCI-N87, Human gastric CDX).

Calibration of Payload properties in rat

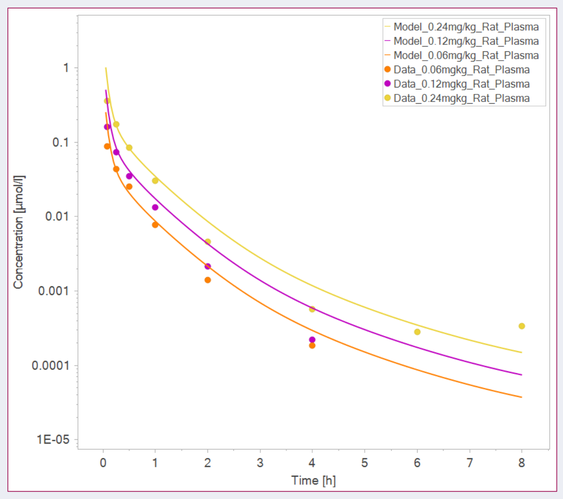


Figure 2: Calibration versus observations in rat at 3 doses. **Lines:** simulations. **Dots:** observations.

Parameter	Initial value [ref]	Final value	95% CI
Lipophilicity (log units)	1.89 [7, logD]	2.72	+/- 0.17

Table 1: Calibration of Rezetecan lipophilicity since the input parameter corresponds to logD. Other parameters come from in-house experiments of Hengrui.

Prediction of Payload PK in mouse

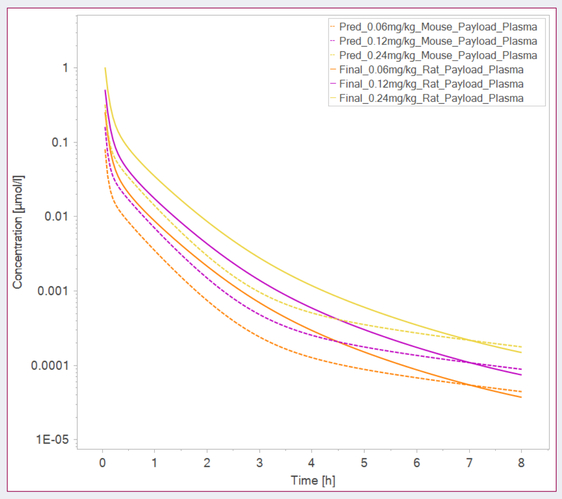


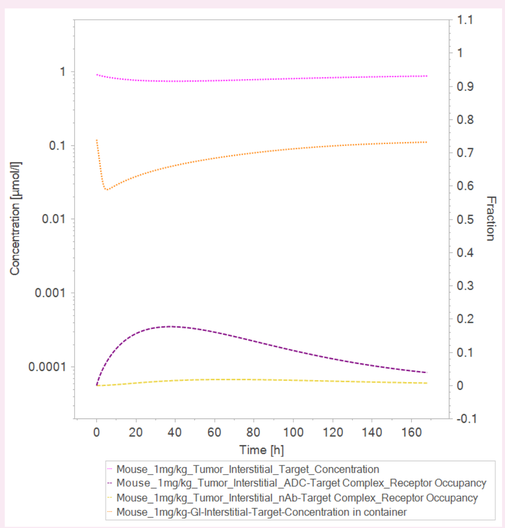
Figure 3: Translation from rat to mouse. Dotted lines: prediction in mouse.

Parameter	Rat	Mouse
Body weight (BW, kg)	0.23 [Default PK-Sim]	0.02 [Default PK-Sim]
Non-specific hepatic clearance mL/min/kg)	45 [Sponsor popPK model]	100 [Allometrized]
Fraction unbound (Fu, dimensionless)	0.052 [Sponsor experiment]	0.15 [Sponsor experiment]
Blood/Plasma ratio (dimensionless)	0.71 [calculated*]	1.03 [calculated*]

Table 2: Translational assumptions. * calculated in PK-Sim from BW and Fu.

Prediction of free target concentration and receptor occupancy

1 m/kg



5 mg/kg

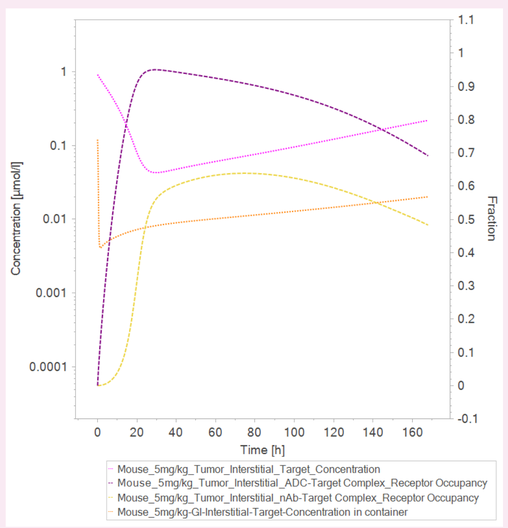


Figure 5: Left axis: Free target concentration in gastro-intestinal tissues (orange) and tumor (pink). **Right axis:** Receptor occupancy for ADC-target (purple) and antibody-target (yellow) complexes in the interstitial space of the tumor. **Left: 1 mg/kg: max 20% RO. Right: 5 mg/kg: max 95% RO.**

Sensitivity	ADC Plasma	ADC Tumor-Interstitial	ADC GI-Interstitial	Payload Plasma	Payload Tumor-intracellular	Payload GI-interstitial
Positive on AUC_{tend}	kon_{FcRn}	Tumor relative target expression, target synthesis factor, kD_{FcRn}, k_{Int}, k_{Dec}	kon_{FcRn}	k_{Dec}, target synthesis factor, k_{Int}, kon_{FcRn}, Tumor relative target expression	Lipophilicity, tumor relative target expression, target synthesis factor	Target synthesis factor, k_{Int}
Negative on AUC_{tend}	Target synthesis factor, k_{Dec}, kD_{FcRn}, tumor relative target expression	Tumor volume, kon_{FcRn}	target synthesis factor, k_{Dec}, kD_{FcRn}	Lipophilicity, Fraction unbound, GFR fraction, kD_{FcRn}	Tumor vascular fraction	Lipophilicity, Fraction unbound, k_{Dec}

Table 4: Most sensitive parameters affecting exposure (AUC_{tend}) to different ADC analytes in plasma, tumor and healthy organs such as GI tissues (100% variation range around the calibrated values of Table 3).

Conclusions

- The PBPK model was able to capture the PK of all three ADC analytes in plasma, tissues, and tumor reasonably well and will be further assessed on different xenografted mice administered with the same ADC and other ADCs with the same payload.
- This model can serve as a platform for translational and clinical investigations of safety and efficacy of ADCs with Rezetecan payload.

References

[1] Singh, A.P. and Shah, D.K. (2017) *The AAPS Journal*, 19(4), pp. 1054–1070. **[2]** Khot, A. *et al.* (2017) *The AAPS Journal*, 19(6), pp. 1715–1734. **[3]** Chang, H.-P., Li, Z. and Shah, D.K. (2022) *Pharmaceutical Research*, 39(1), pp. 1–24. **[4]** Scheuher, B. *et al.* (2023) *Journal of Pharmacokinetics and Pharmacodynamics,* 51, pp. 429-447. **[5]** Chang, H.-P. and Shah, D.K. (2025) *Journal of Pharmacokinetics and Pharmacodynamics*, 52(3), p. 27. **[6]** Zunino, C. *et al.* (2025) *CPT: Pharmacometrics & Systems Pharmacology*, 14(9), pp.1494-1503. **[7]** Yao H, Yan M, Tong Z, et al. (2024) J Clin Oncol 2024; 42: 3453–65. **[8]** Dallmann, A. *et al.* (2025) *CPT: Pharmacometrics & Systems Pharmacology*, 14(5), pp. 822–827. **[9]** Boswell, C.A. *et al.* (2010) *Molecular Pharmaceutics*, 7(5), pp. 1848–1857. **[10]** Zasedateleva, T. *et al.* (2024) *CPT: Pharmacometrics & Systems Pharmacology*, 13(12), pp. 2068–2086.