A Whole-Body PBPK Model to Quantify Organ-Specific Biodistribution and Systemic Clearance of Bacteriophages

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Introduction

- **Bacteriophages(phages)** are promising antibacterial agents with unique host-dependent replication.
- Plasma PK alone may not reflect organ-level phage exposure, because phages can be rapidly cleared from blood while accumulating unevenly across tissues.
- **Physiologically Based Pharmacokinetic (PBPK)** modeling provides a mechanistic framework to quantify organ-specific phage biodistribution and systemic clearance.

Aims

- Develop a whole-body PBPK model for phage following IV administration in rats.
- Compare organ-specific biodistribution across structurally distinct phages.
- Identify key physiological processes driving heterogeneous tissue exposure.

Methods

- **Data**: Plasma and tissue plaque-forming units (PFU) data after low- (5 x 10^9 PFU/kg) and high-dose (5 x 10^{10} PFU/kg) intravenous phage administration [1].

Table1. Phage information.

Phages	Capsid size	Tail size
SE_SZW1	73.6 nm	138.6 nm
PA_LZ7	70.2 nm	158.6 nm
AB_SZ6	54.2 nm	none

- **Model structure**: Whole-body PBPK framework including plasma, liver, spleen, lung, kidney, brain, and other major organs [2]. MPS uptake was included in vascular space for liver and spleen because of sinusoidal capillary.

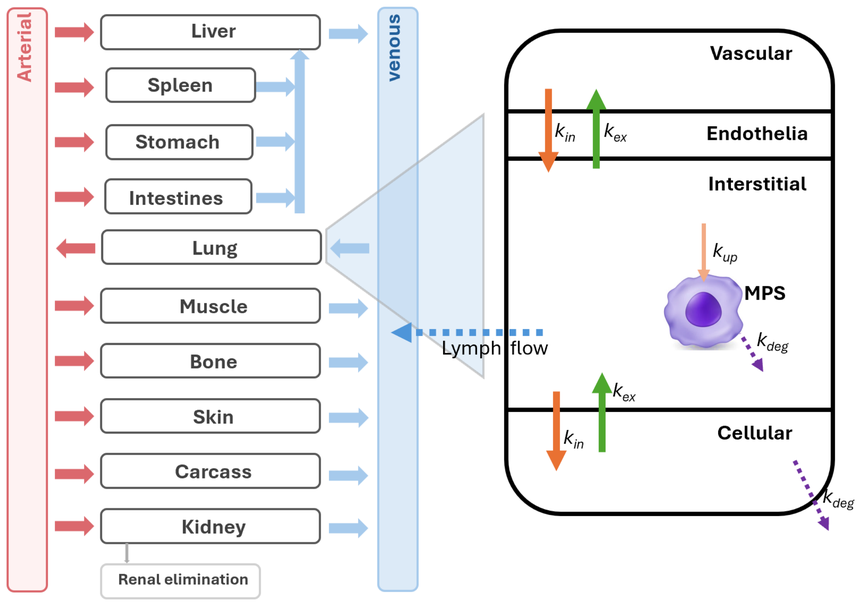

Fig.1 Whole-body PBPK model structure.

- Each organ is represented by vascular, interstitial, cellular, and MPS.
- Endothelial exchange(k_{in}, k_{ex}) and lymph flow control tissue penetration.
- k_{up} describes MPS uptake and k_{deg} describes intracellular/MPS degradation.

- **Sensitivity-informed parameter selection:** Sobol sensitivity analysis was used to identify parameters with the strongest influence on plasma and tissue phage exposure.
- **Modeling and estimation:** R-based model solved with deSolve and selected sensitive parameters were then estimated.

Results

Model fitting performance

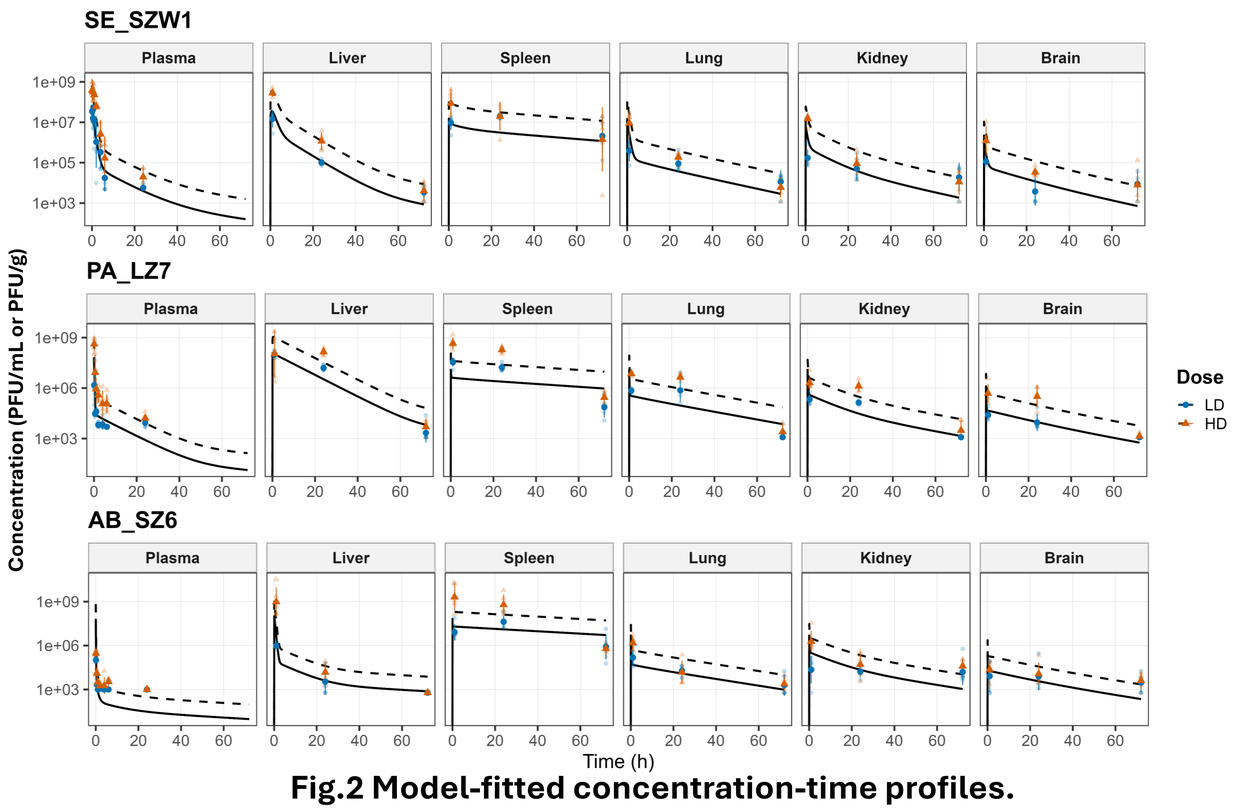

Fig.2 Model-fitted concentration-time profiles.

- The model captured the plasma and tissue concentration-time profiles across LD and HD groups.
- Liver and spleen accumulation was reproduced by MPS-mediated uptake, supporting their dominant role in systemic phage sequestration (**Fig.2**).

Fitted model parameter estimates

Table 2. Model estimations. low value medium value High value

Parameter	Definition	SE_SZW1	PA_LZ7	AB_SZ6
k_up_Spn	MPS uptake rate	0.918	4.60	80.71
k_up_Lvr		12.3	189.97	1216.47
k_deg_Lvr	Degradation rate	0.822	0.149	3.376
k_endo_Lun	Endocytosis rate	1.63	26.93	12.17
k_endo_Kid		5.95	29.39	70.69
k_endo_brain		0.401	2.05	2.49
sigma	Residual error	0.732	0.812	0.964

- **AB_SZ6** showed the highest fitted MPS uptake and tissue exchange parameters with smallest size **(Table 2)**.
- **PA_LZ7** showed higher lung uptake than **SE_SZW1**, indicating that tissue distribution cannot be explained by particle size alone **(Table 2)**.

Model evaluation

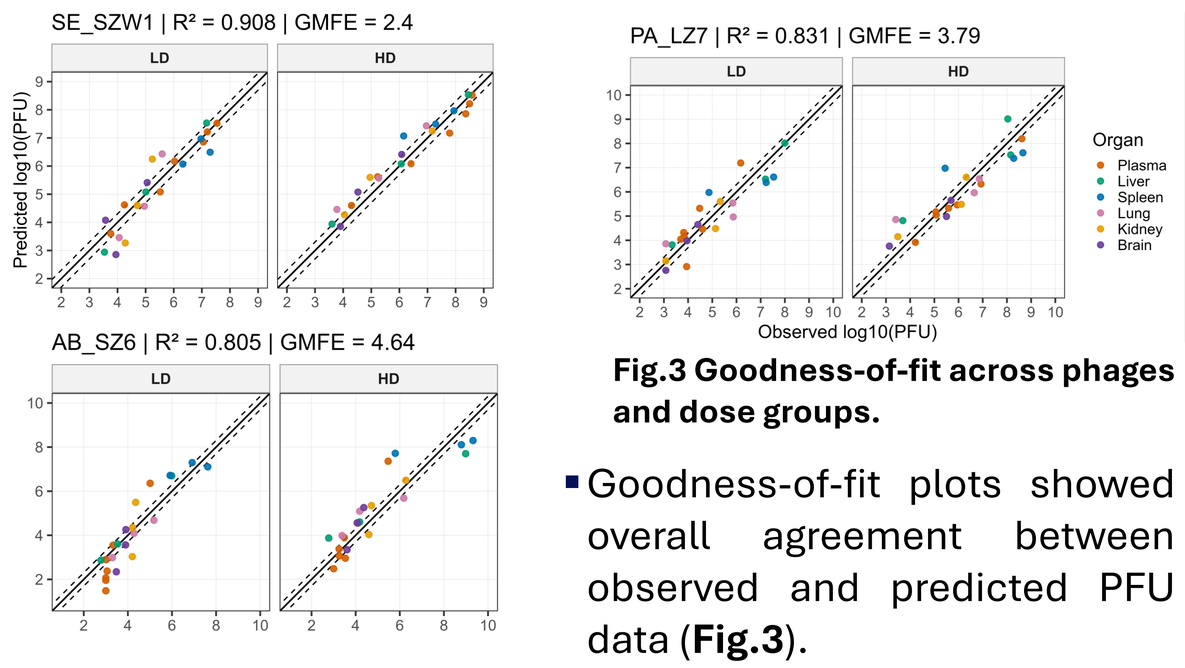

Fig.3 Goodness-of-fit across phages and dose groups.

- Goodness-of-fit plots showed overall agreement between observed and predicted PFU data (**Fig.3**).

Conclusions

A **whole-body PBPK framework** captured phage plasma clearance and organ-specific biodistribution, suggesting that tissue exposure is jointly governed by **MPS-mediated sequestration, endothelial exchange, and phage-specific properties** beyond particle size alone.

1. Tan X, et.,al. 2024. J Virol 98:e01359-23.
2. Echterhof A, et.al. 2026. Antimicrob Agents Chemother 70:e01506-25

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