Using physiologically-based pharmacokinetics-quantitative systems pharmacology model to optimize peptide-drug conjugates design (Poster #6846)

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Abstract

- Peptide-drug conjugates (PDCs) are being developed as new cancer treatments. The choice of peptide will impact both the pharmacokinetics and distribution to the tumor. Can the choice of peptide be optimized?
- A platform physiologically-based pharmacokinetics (PBPK)-quantitative systems pharmacology (QSP) model was developed to understand the complex interplay between the molecular weight (MW) of the peptide used in the PDC, its impact on pharmacokinetics (PK), tissue disposition, tumor penetration, and tumor drug exposure.
- A bell-shaped relationship is predicted between peptide size and PDC/ payload exposure. This is the result of two competing forces: smaller peptides result in better tumor penetration, but faster systemic clearance.
- Sensitivity analysis indicates this relationship is insensitive to tumor characteristics, such as TAA expression, or PDC binding affinity towards the TAA.

Methods

A platform PBPK–QSP model was developed by integrating a published PBPK model [1] with a genetic QSP model of ADC binding, internalization, and catabolism [2], using a molecular weight (MW)-based tumor penetration relationship [3] to couple the two models.
The model was parameterized using physiological organ volumes and blood flows for both human and mouse [4].

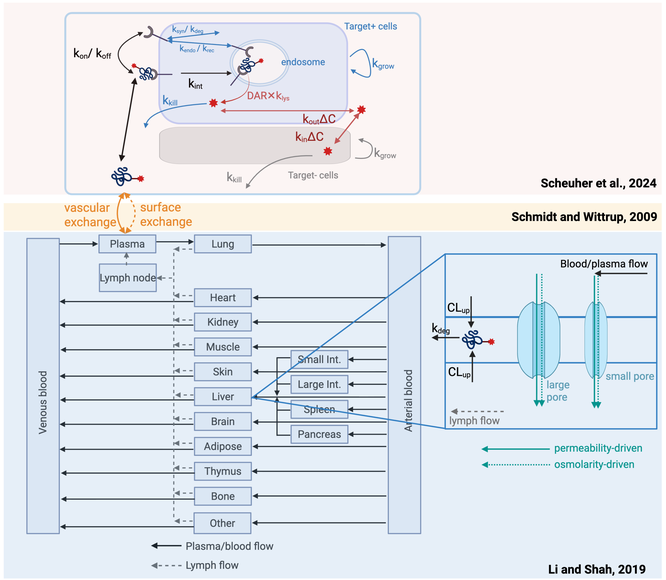

Figure 1. Diagram of the platform PBPK-QSP model.

Molecular weight-based renal clearance

The molecular weight-based renal clearance depends on the PDC concentration in kidney vasculature, glomerular filtration rate (GFR), and glomerular sieving coefficient (θ). The glomerular sieving coefficient is computed as

$$\theta = e^{1-\frac{8.7}{1+e^{0.028\times(-MW+72.3)}}}$$

where the MW is the molecular weight of peptide in kDa. The predicted θ is close to observed data [5].

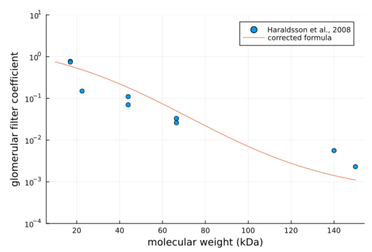

Figure 2. Validation of glomerular sieving coefficient.

Molecular weight-based tumor penetration The predicted relationship between peptide molecular weight and diffusivity (D_{pore}), acellular fraction of tumor volume available for peptide (ϵ), and permeability (P_{pore}) was verified by comparing to observed data [3].

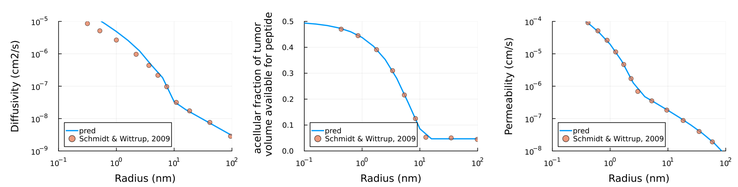

Figure 3. Validation of tumoral D_{pore} (left), ϵ (middle), and P_{pore} (right).

Predicted renal clearance and tumor penetration as a function of PDC peptide size

While PDCs with smaller peptides are predicted to have faster plasma clearance, higher tumoral Cmax, only a small fraction of the dose reaches the tumor. This results from the high percentage of renal clearance for small PDCs.

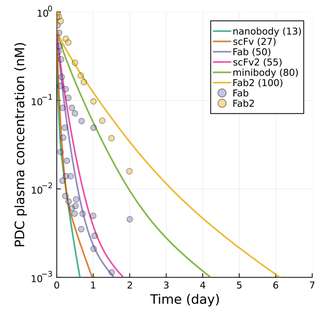

Figure 4A. Simulated plasma concentration of PDCs vs. data after 1 nM bolus intravenous (IV) dose.

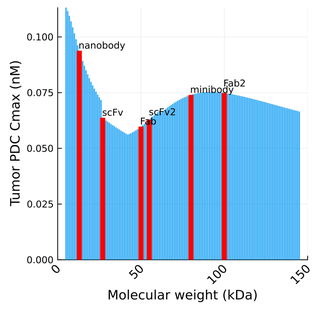

Figure 4B. Tumoral PDC Cmax vs. MW (1 nM bolus IV dose).

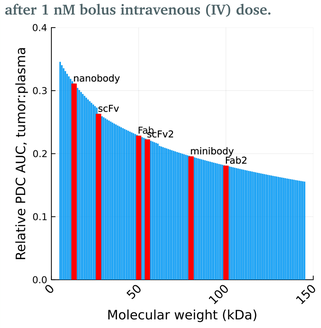

Figure 4C. Percent of the relative PDC AUC between tumor and plasma at week 9 vs. MW (1 nM bolus IV dose).

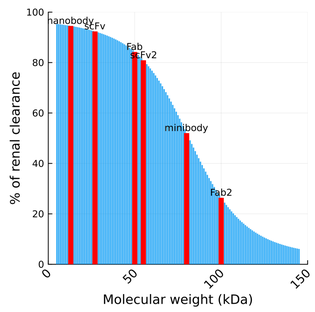

Figure 4D. Percent of the total PDC dose renally cleared at week 9 (1 nM bolus IV dose).

What properties have the biggest impact on tumor exposure?

- Tumoral free payload exposure is most impacted by peptide molecular weight and the payload decay rate (if radioactive).
- Tumoral free payload exposure is also impacted by tumor characteristics, such as tumor-associated antigen (TAA) expression level and internalization rate of TAA:PDC.

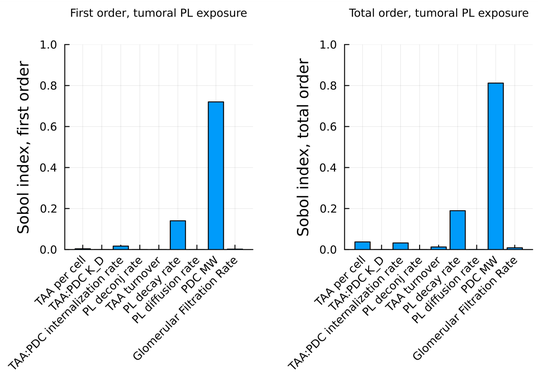

Figure 5A. Global sensitivity analysis of tumor-related parameters on tumoral free payload (PL) exposure.

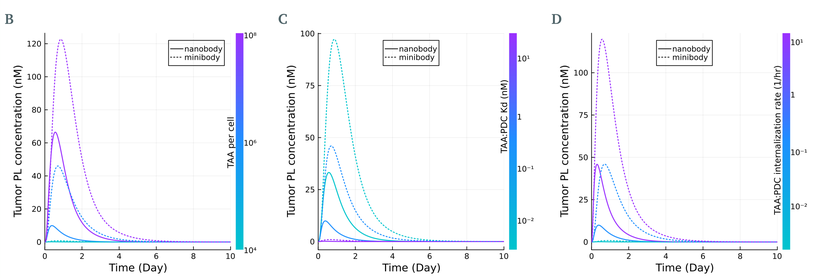

Figure 5B-D. Simulations of tumor PL for nanobodies (solid) and minibodies (dotted) with different tumor associated antigen (TAA) expression levels (B), PDC:TAA dissociation constants (Kd) (C), and internalization rates (Kint) (D).

Peptide size has a non-linear impact on tumor PDC & payload exposures when PDC doses are normalized by clearance

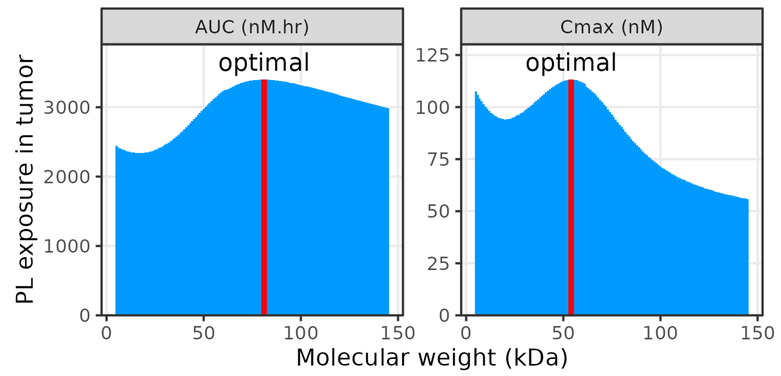

Figure 6. Impact of peptide molecular weight on the tumor exposure of PDC/PL. Exposure metrics explored here include the maximum concentration (Cmax) and the area under the curve of the concentration (AUC). Computation based on PK profile during 9 weeks after a single dose. Assumptions: DAR 8, tumor parameters comparable to 1 mL volume HER2+ tumors.

PDCs with smaller peptides produce higher, non-specific PDC exposure in other organs (e.g., liver, lung, skin).

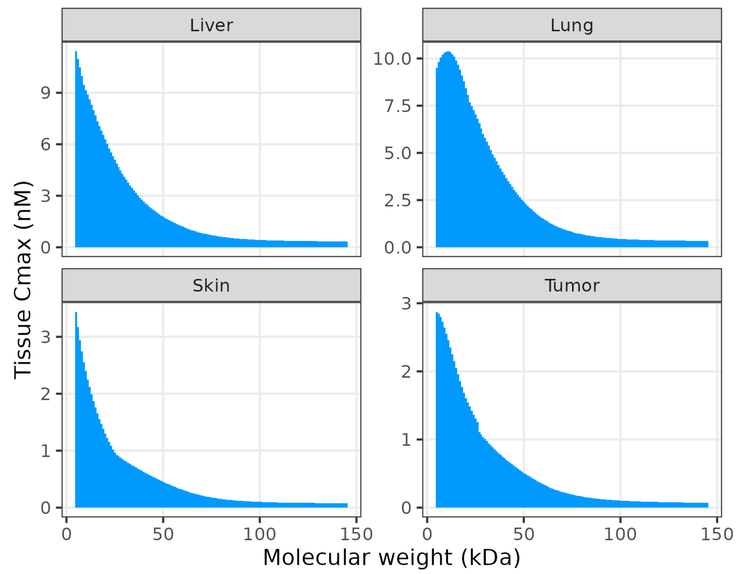

Figure 7. Impact of peptide molecular weight on the healthy tissue PDC Cmax. Computation based on PK profile during 9 weeks after a single dose.

Conclusion

- Selecting the optimal peptide and target is critical for PDCs, as these choices dictate exposure levels in both tumor and healthy tissues. The relationship between tumoral payload (PL) exposure (an efficacy driver) and systemic exposure (a safety driver) is nonlinear and influenced by a complex interplay of peptide molecular weight and tumor-specific characteristics.
- The PBPK-QSP model that was developed provides a deeper understanding of complex, intertwined dynamics.
- In the example context shown here (HER2-targetting PDC), peptides in the range of 50-100 kDa are predicted to optimize tumor-specific payload exposure.

References

[1] Li, Z. and Shah, D.K. *J. Pharmacokinet. Pharmacodyn.* **46** (2019):305–318.
[2] Scheuher, B., Ghusinga, K.R., McGirr, K., Nowak, M., Panday, S., Apgar, J., Subramanian, K. and Betts, A. *J. Pharmacokinet. Pharmacodyn.* **51** (2024):429–447.
[3] Schmidt, M.M. and Wittrup, K.D. *Mol. Cancer Ther.* **8** (2009):2861–2871.
[4] Shah, D.K. and Betts, A.M. *J. Pharmacokinet. Pharmacodyn.* **39** (2012):67–86.
[5] Haraldsson, B., Nyström, J. and Deen, W.M. *Physiol. Rev.* **88** (2008):451–487.