Whole-body PBPK with tissue TMDD modelling to predict determining parameters of target occupancy in tissues

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Intro

Target occupancy can be determined by many different parameters related to target binding, target internalization, and pharmacokinetics. The potential impact of these parameters is widely acknowledged, but a common understanding of the most influential parameters for different pharmaceutically relevant scenarios is not available.[1]
In this simulation study, the aim was to answer the following question:
Is target-mediated drug disposition likely in single-tissue target binding for small and large molecules in tissue interstitial space?

Methods

Human PBPK models for a hypothetical small molecule and a large molecule including target binding were developed with PK-Sim® and MoBi® (part of the Open Systems Pharmacology Suite (OSPS)) version 11.0 [2]. Simulations were performed for a small molecule with the small molecule model and for a large molecule (mAb) with the large molecule model in PK-Sim. The default models were extended with target binding and target turnover.

For the small molecule simulations, PK and physicochemical parameters were chosen to represent a typical drug with fast plasma kinetics to allow a realistic impact of binding kinetics on receptor occupancy. For the large molecule, a typical mAb was chosen.

Parameter	Large molecule value	Small molecule value
Molecular weight (kDa)	150	0.5
Target affinity (nM)	1	1
Target koff (/h)	10	1
FcRn affinity endosomes (nM)	1000	99999999
Dose (mg/kg)	1	0.01 (daily)
Fraction unbound	1	0.5
Renal filtration (% of GFR)	0	100
Lipophilicity	NA	1
Target turnover (/h)	varied	0

Results

The large molecule simulations show that the distribution to tissue interstitial space can be slow enough to present a rate-limiting step, especially if the product of the target concentration and its degradation rate constant is high. This means that in such a situation, the tissue interstitial concentrations can be depleted, while the plasma concentrations do not reflect any TMDD.

Our small molecule simulations show that interstitially expressed targets are readily accessed by small molecules from plasma, which avoids target-mediated tissue retention, while intracellularly expressed targets can have enough of a distribution barrier from plasma to allow target-mediated tissue retention.

Conclusion

Our simulations indicate the importance of localized TMDD in tissues for small and large molecules. The target concentration and turnover are the driving factors for local TMDD similar to central TMDD.

1. For small molecules, target-mediated tissue retention is mostly relevant for intracellular target binding, as the interstitial space concentrations are in rapid equilibrium with plasma concentrations

2. Large molecules can be cleared in tissue interstitial space if the product of the target concentration and its degradation rate constant is high. These conditions are likely to be met for many targets expressed in tissue interstitial space

Distribution to the target site can be rate-limiting

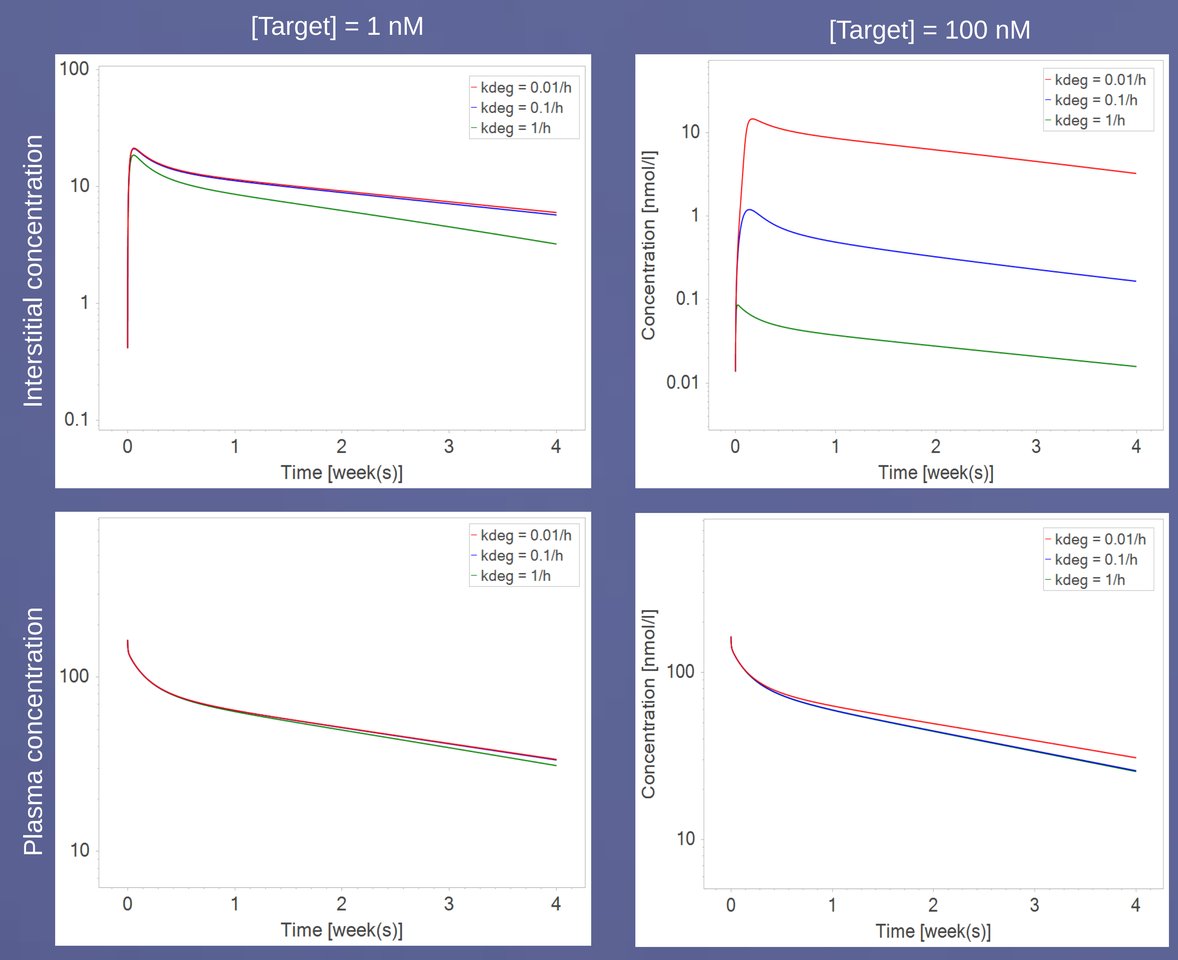

Figure 1: Predicted heart interstitial and plasma concentrations for a default IgG of 150 kDa binding a target selectively in the heart interstitial space with a 1 nM affinity and koff of 10/h

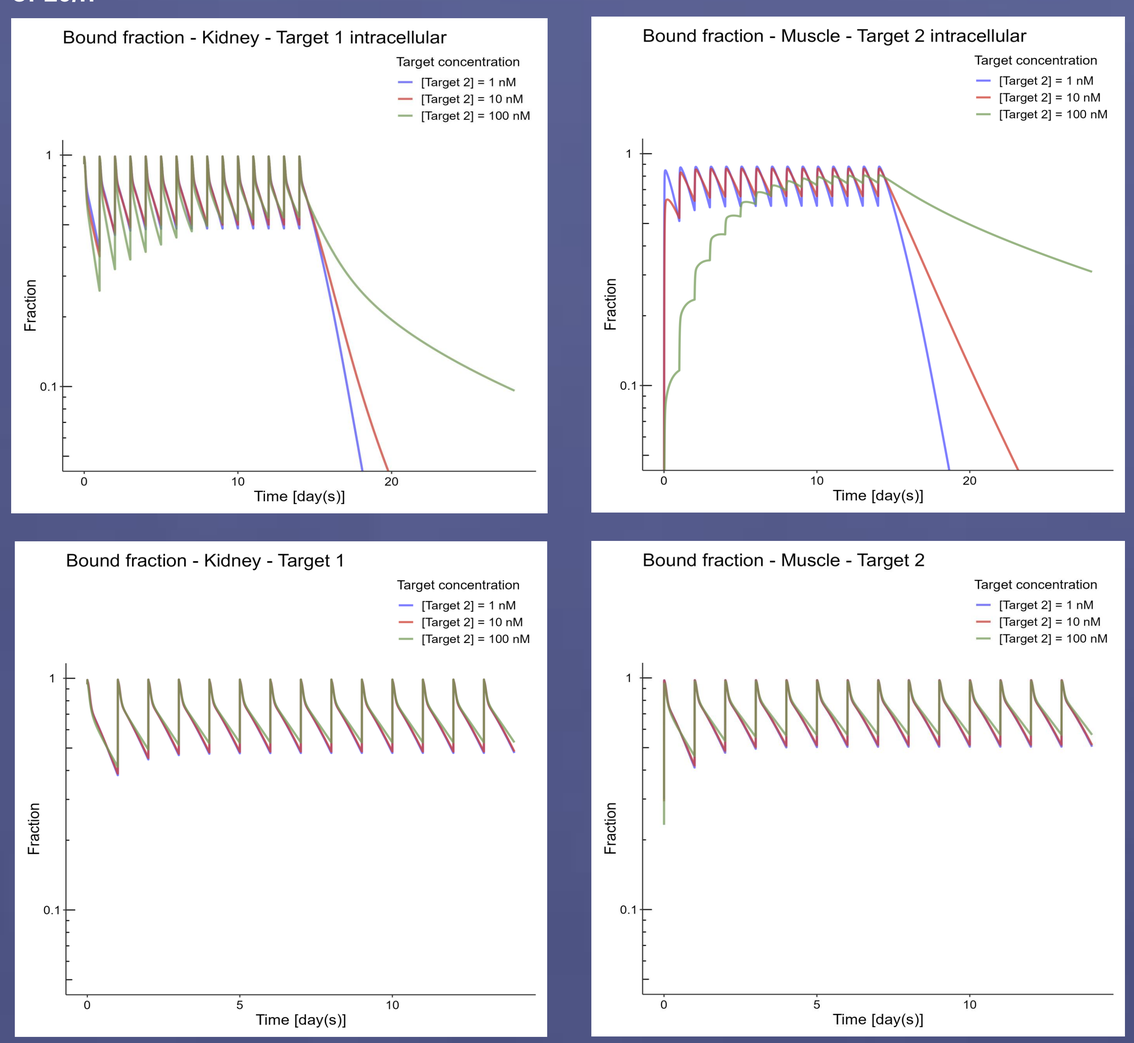

Figure 2 : Small molecule exploration of tissue selectivity for two identical targets located in kidney (Target 1) and muscle (Target 2). Top row: Exploration of tissue selectivity targets located in intracellular space. Target concentration is varied only for Target 2.
Bottom row: Exploration of tissue selectivity for targets located in interstitium. Target concentration is varied only for Target 2

References

[1] Pressly MA, Peletier LA, Zheng S, et al. The quest for balance between capturing data and model complexity: a quantitative clinical pharmacology approach applied to monoclonal antibodies. *CPT: Pharmacometrics & Systems Pharmacology*.

[2] Lippert J, Burghaus R, Edginton A, Frechen S, Karlsson M, Kovar A, et al. Open Systems Pharmacology community - an open access, open source, open science approach to modeling and simulation in pharmaceutical sciences. CPT Pharmacomet Syst Pharmacol. 2019;

Modeling Scaling Coding

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