

# An r Shiny application for the projection of dose ranges in preclinical and first in human clinical studies during the early stages of drug development

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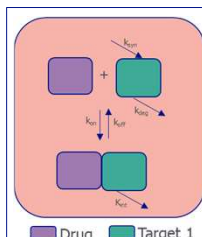
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## Introduction

Minimal physiology-based pharmacokinetic (mPBPK) models are a valuable tool in the earliest stages of therapeutic antibody (Ab) development, when only preliminary *in vitro* investigations and literature are available to project dose ranges required for *in vivo* and clinical studies. An estimate of clinical dose range in the preclinical stage is crucial for formulation development and design of toxicology studies [1]. Furthermore, an indication of uncertainty around the dose range projection is also vital to prevent foreseeable delays during development due to suboptimal formulation development.

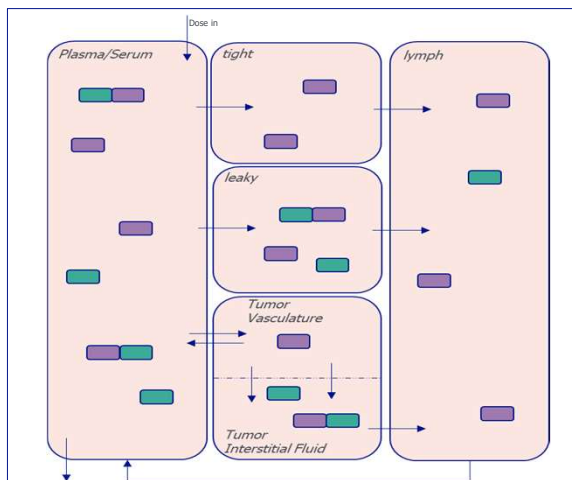
mPBPK models provide a framework that can characterize the disposition of Abs through plasma, lymph and tissues, including tumor, with high and low extravasation (leaky and tight tissues, respectively) and characterize target mediated drug disposition (TMDD) in relevant compartments [2]. We developed an r Shiny application that leverages the common properties of Abs combining drug and binding specific properties available from *in vitro* data to project dose ranges in preclinical species and in human based on target occupancy.



Target engagement characterization in given compartment

## Required parameters for input in rShiny application

| Parameter   | Description                                    | Units | Parameter          | Description                               |
|-------------|------------------------------------------------|-------|--------------------|-------------------------------------------|
| koff1       | Dissociation rate constant                     | 1/d   | Switch_multitarget | Turn on for multiple target engagement    |
| KD1         | Dissociation constant                          | nM    | Switch_tu          | Switch to turn on tumor compartment       |
| kint1       | Internalization rate of complex                | 1/d   | switch_bind_pl1    | Turn on TMDD in plasma compartment        |
| kdeg1       | Degradation rate of target                     | 1/d   | switch_bind_ti1    | Turn on TMDD in tight compartment         |
| plasma_R1bl | Baseline target concentration in plasma        | nM    | switch_bind_lk1    | Turn on TMDD in leaky compartment         |
| leaky_R1bl  | Baseline target concentration in leaky tissue  | nM    | switch_bind_ly1    | Turn on TMDD in lymph compartment         |
| tight_R1bl  | Baseline target concentration in tight tissues | nM    | Equalskdeg         | Assumption kdeg = kint in absence of data |
| tumor_R1bl  | Baseline target concentration in tumor         | nM    |                    |                                           |
| lymph_R1bl  | Baseline target concentration in lymph         | nM    |                    |                                           |
| bwsb        | Bodyweight range of subjects                   | kg    |                    |                                           |



mPBPK model structure describing drug disposition from plasma to lymph through tight, leaky and tumor tissues with the ability to characterize TMDD in compartments based on supplied parameters [2]



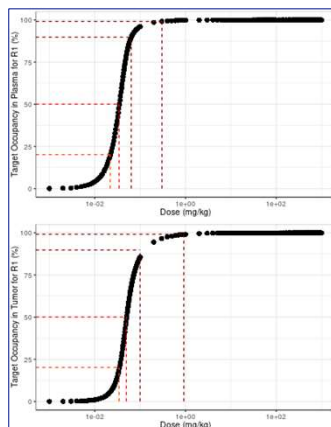
rShiny application with parameters inputted for pembrolizumab at a 0.05 mg/kg dose in a 70 kg human and the corresponding concentration time profiles projected for each compartment

## Methods

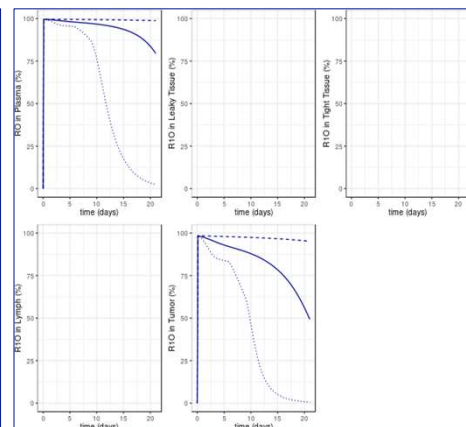
A mPBPK model framework as developed by Cao and Jusko was implemented in rShiny using mrgsolve [2]. The knobs function for sensitivity analysis was used to input typical ranges for Ab clearance and extravascular coefficients into tight and leaky tissues, lymphatic tissues and tumor [3]. A tumor compartment was incorporated such that distribution of Ab into tumor interstitial fluid via convection and diffusion through small and large pores from tumor vasculature governed target interaction [4]. Fixed structural parameters used in the mPBPK model for each species are summarized below. Required parameters to be inputted are summarized on the right. The model allows for characterizing target engagement to multiple targets based on antibody format.

## Results

As a model test case, pembrolizumab disposition was characterized using what would be *in vitro* data and compared to a published analysis [5]. In this scenario, minimal, mean and maximum target occupancy over 21 days was estimated over a dose range in a 70 kg human and the metrics of 20, 50, 90 and 99% were used to project potential relevant doses in human. Furthermore, drug disposition in all compartments was projected at a test dose of single dose 0.05 mg/kg with a shaded area highlighting the range of expected concentrations based on literature reported variability [3]. The corresponding target occupancy (R10) in each compartment was also projected. The resulting tabular output generated by the shiny app highlights a 0.9 mg/kg dose would be required to reach a minimum 99% TO in tumor, whereas 0.05 mg/kg achieves a minimum of 50% TO.



Minimum target occupancy over dose-range (mg/kg) of pembrolizumab in a 70 kg human for inputted parameters



Corresponding target occupancy at 0.05 mg/kg dose of pembrolizumab in a 70 kg human

## Fixed structural for mouse, cynomolgus monkey and human as implemented in the mPBPK model

| Parameter        | Description                                       | Units    | Mouse    | Monkey | Human |
|------------------|---------------------------------------------------|----------|----------|--------|-------|
| CLplasma_ref [3] | Flowrate: Typical linear clearance from plasma    | L/d      | 0.00027  | 0.022  | 0.42  |
| L_ref [2]        | Flowrate: from Lymph                              | L/d      | 0.0029   | 0.28   | 2.9   |
| sigma_ly [2]     | Reflection coefficient: Lymph                     | unitless | 0.2      | 0.20   | 0.20  |
| sigma_ti [3]     | Reflection coefficient: Tight tissue              | unitless | 0.95     | 0.95   | 0.95  |
| sigma_lk [3]     | Reflection coefficient: Leaky tissue              | unitless | 0.70     | 0.70   | 0.70  |
| Kp [2]           | Partition coefficient                             | unitless | 0.80     | 0.80   | 0.80  |
| Fracttight [2]   | Fraction: ISF in tight tissue                     | unitless | 0.65     | 0.65   | 0.65  |
| Fractleaky [2]   | Fraction: ISF in leaky tissue                     | unitless | 0.35     | 0.35   | 0.35  |
| FracLtight [2]   | Fraction: lymph flowrate to tight tissues         | unitless | 0.33     | 0.33   | 0.33  |
| FracLleaky [2]   | Fraction: lymph flowrate to leaky tissue          | unitless | 0.67     | 0.67   | 0.67  |
| ISF [2]          | Volume: Interstitial fluid                        | L        | 0.0044   | 0.58   | 15.6  |
| Vplasma_ref [2]  | Volume: plasma compartment                        | L        | 0.00085  | 0.097  | 2.6   |
| Vlymph_ref [2]   | Volume: Lymph Compartment                         | L        | 0.0017   | 0.19   | 5.2   |
| Bwref [2]        | Reference bodyweight                              | kg       | 0.02     | 2.6    | 70    |
| V_tumor [5]      | Volume: tumor                                     | L        | 0.00047  |        | 0.02  |
| Qt [5]           | Flowrate: plasma into tumor                       | L/d      | 0.14     |        | 0.81  |
| Lt [5]           | Flowrate: tumor into lymph                        | L/d      | 0.0010   |        | 0.043 |
| Jiso [5]         | Flowrate: Fluid recirculation                     | L/d      | 0.00029  |        | 0.13  |
| PS_LP [5]        | Permeability-surface area product for large pores | L/d      | 0.000077 |        | 0.035 |
| PS_SP [5]        | Permeability-surface area product for small pores | L/d      | 0.00022  |        | 0.10  |
| ftisf [5]        | Fraction: interstitial fluid in tumor             | unitless | 0.55     |        | 0.55  |
| ftvasc [5]       | Fraction: vasculature in tumor                    | unitless | 0.070    |        | 0.07  |
| alpha_LP [5]     | Fraction: Hydraulic conductivity large pores      | unitless | 0.10     |        | 0.1   |
| alpha_SP [5]     | Fraction: Hydraulic conductivity small pores      | unitless | 0.90     |        | 0.9   |
| sigma_LP [5]     | Reflection coefficient: Large pore                | unitless | 0.26     |        | 0.26  |
| sigma_SP [5]     | Reflection coefficient: Small pore                | unitless | 0.98     |        | 0.98  |

## Tabular output of dose (mg/kg) corresponding to a TO over 21 days (minimum, average and maximum) in plasma and tumor compartment for pembrolizumab in 70 kg human

| Dose Range          | Dose Range Table      | Concentration in Compartments | Receptor Occupancy in Compartments                                                         |
|---------------------|-----------------------|-------------------------------|--------------------------------------------------------------------------------------------|
| Target Occupancy... | DoseInPlasma.R10.Cmax | DoseInTumor.R10.Cmax          | DoseInPlasma.R10.Cmin, DoseInTumor.R10.Cmin, DoseInPlasma.R10.Cmean, DoseInTumor.R10.Cmean |
| 20                  | 0.00                  | 0.00                          | 0.02 0.04 0.00 0.01                                                                        |
| 50                  | 0.00                  | 0.00                          | 0.04 0.05 0.01 0.02                                                                        |
| 90                  | 0.00                  | 0.01                          | 0.06 0.06 0.04 0.07                                                                        |
| 99                  | 0.02                  | 0.08                          | 0.30 0.90 0.20 0.50                                                                        |

\*Cmax, Cmin and Cmean in this table refer to maximum, minimum and average target occupancy, respectively in plasma and tumor

## Conclusion

The rShiny application provides a user-friendly experience to adequately characterize drug disposition in relevant species for planning pre-clinical and clinical investigations at a time when only preliminary *in vitro* data and literature data is available.

## References

- [1] Maurer TS, Smith D, Beaumont K, Di L. Dose Predictions for Drug Design. J Med Chem. 2020 Jun 25;63(12):6423-6435. doi: 10.1021/acs.jmedchem.9b01365. Epub 2020 Jan 22. PMID: 31913040.
- [2] Cao Y, Jusko WJ. Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn. 2014 Aug;41(4):375-87. doi: 10.1007/s10928-014-9372-2. Epub 2014 Jul 31. PMID: 25077917; PMCID: PMC4167345.
- [3] Cao Y, Jusko WJ. Survey of monoclonal antibody disposition in man utilizing a minimal physiologically-based pharmacokinetic model. J Pharmacokinet Pharmacodyn. 2014 Dec;41(6):571-80. doi: 10.1007/s10928-014-9374-0. Epub 2014 Aug 22. PMID: 25146360; PMCID: PMC4226811.
- [4] Baxter LT, Zhu H, Mackensen DG, Jain RK. Physiologically based pharmacokinetic model for specific and nonspecific monoclonal antibodies and fragments in normal tissues and human tumor xenografts in nude mice. Cancer Res. 1994 Mar 15;54(6):1517-28. PMID: 8137258.
- [5] UTR, Chatterjee M, Lala M, Abraham AK, Freshwater T, Jain L, Sinha V, de Alwis DP, Mayawala K. Pivotal Dose of Pembrolizumab: A Dose-Finding Strategy for Immuno-Oncology. Clin Pharmacol Ther. 2021 Jul;110(1):200-209. doi: 10.1002/cpt.2170. Epub 2021 Mar 8. PMID: 33462831.
- [6] Baxter LT, Zhu H, Mackensen DG, Butler WF, Jain RK. Biodistribution of monoclonal antibodies: scale-up from mouse to human using a physiologically based pharmacokinetic model. Cancer Res. 1995 Oct 15;55(20):4611-22. PMID: 7533638.