A PBPK-QSP PLATFORM MODEL FOR T-CELL-DEPENDENT BISPECIFIC ANTIBODIES

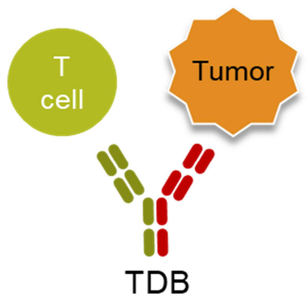
Susilo M[1], Jimenez L[2], Chen C[1], Gadkar K[1], Mandikian D[1], Boswell A[1], Schaller S[2] , Li C[1]

[1] Genentech Inc, California, USA [2] esqLABS GmbH, Saterland, Germany

Introduction

- T-cell-dependent bispecific (TDB) antibody is a promising therapeutic modality in drug development for both hematologic and solid malignancies. The TDB antibody allows the formation of a tri-molecular immune synapse between the CD3 in the T-cells and the target antigen in the tumor cells, which triggers tumor cell killing by T-cell activation.
- In vivo biodistribution of TDB, and hence its tumoricidal effect depends on the relative affinity of each TDB binding arm to their respective targets [1].
- TDB drug development challenges include drug-specific parameters identification, dose regimen optimization and combination with other mAb therapies
- This complexity prompts the development of a quantitative platform model for TDBs that captures the inter-relationship of binding affinities, biodistribution, and target engagement to assist in the discovery (e.g., understanding proof of concept) and development of TDBs.

Fig. 1 - TDB synapse

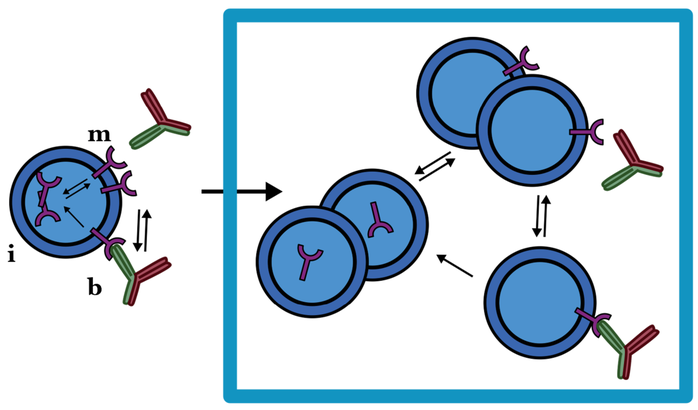


- **Aim:** To develop a PBPK-QSP platform for TDBs using the open-source software OSP Suite (PK-Sim® and MoBi®) [2, 3] and corresponding R interfaces at the example of a HER2/CD3 TDB.

Methods

- Platform development by stages:
  1. Development of a dynamic T-cell distribution model in PK-Sim® as a whole-body PBPK model, including tumor and lymph node as additional organs and adapting animal physiological parameters with in-house data [4]. T-cell kinetic parameters were calibrated and validated using tissue time-concentration data from exogenously administered activated T-cells in mice [5]. The T-cell kinetics model considered tissue-specific transmigration rates and tissue retention as well as the internalization and recycling kinetics of the T-cell receptor CD3. Naïve T-cells were assumed to have 10% the transmigration rates of activated T-cells [6].

Fig. 2 - Modelling of T-cell/CD3 receptor kinetics



m = free CD3 receptor on membrane

b = CD3 receptor bound to TDB

i = internalized CD3 receptor

Initial ratio between membrane and internalized CD3 was set to 2

Internalization leads to TDB clearance

T-cell elimination only in the lung interstitial space

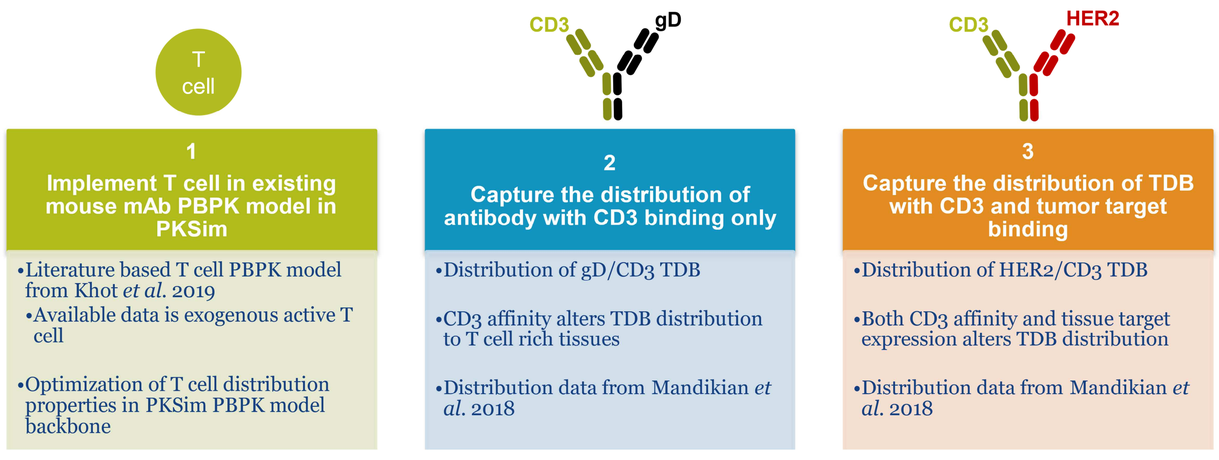
No T-cell proliferation (short time scale)

  2. Expansion of the platform to include a PBPK model describing the binding kinetics of gD/CD3 monospecific antibody, which binds only to T cells. Four binding scenarios were evaluated:
     - No T-cell binding: mAb targeting glycoprotein D (gD)
     - CD3 binding: mAbs with KD = 446 nM (CD3L), 14.4 nM (CD3H) and 1.44 nM (CD3VH, assumed)

     The CD3 turnover and internalization rate were calibrated using the gD/CD3 mouse biodistribution data with the three levels of CD3 binding affinities [1].

  3. Further expansion of the platform to include a PBPK model describing the binding kinetics of HER2/CD3 TDB, which binds to T-cells and HER2 expressing target cells. HER2 target receptor turnover was calibrated using HER2/CD3 antibody mouse biodistribution data with different levels of CD3 affinities: KD = 446 nM (HER2-CD3L) and 14.4 nM (HER2-CD3H) [1].

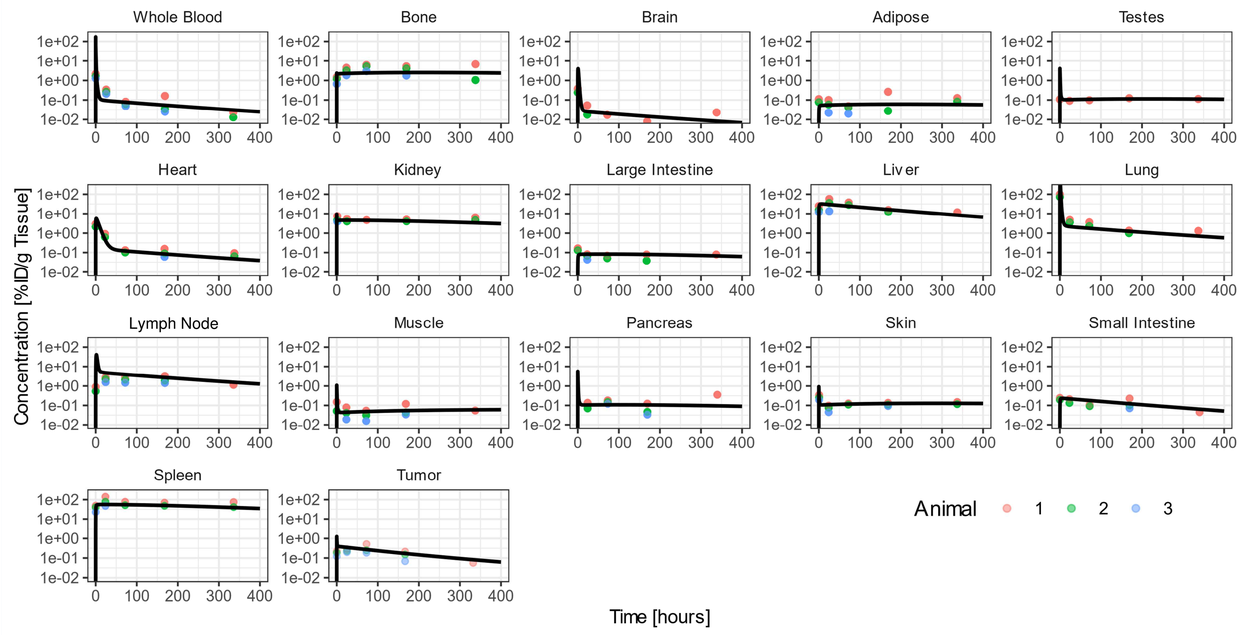
Fig. 3 - Workflow for the development of a PB-QSP platform for TDBs in PK-Sim® and MoBi®



Results and Discussion

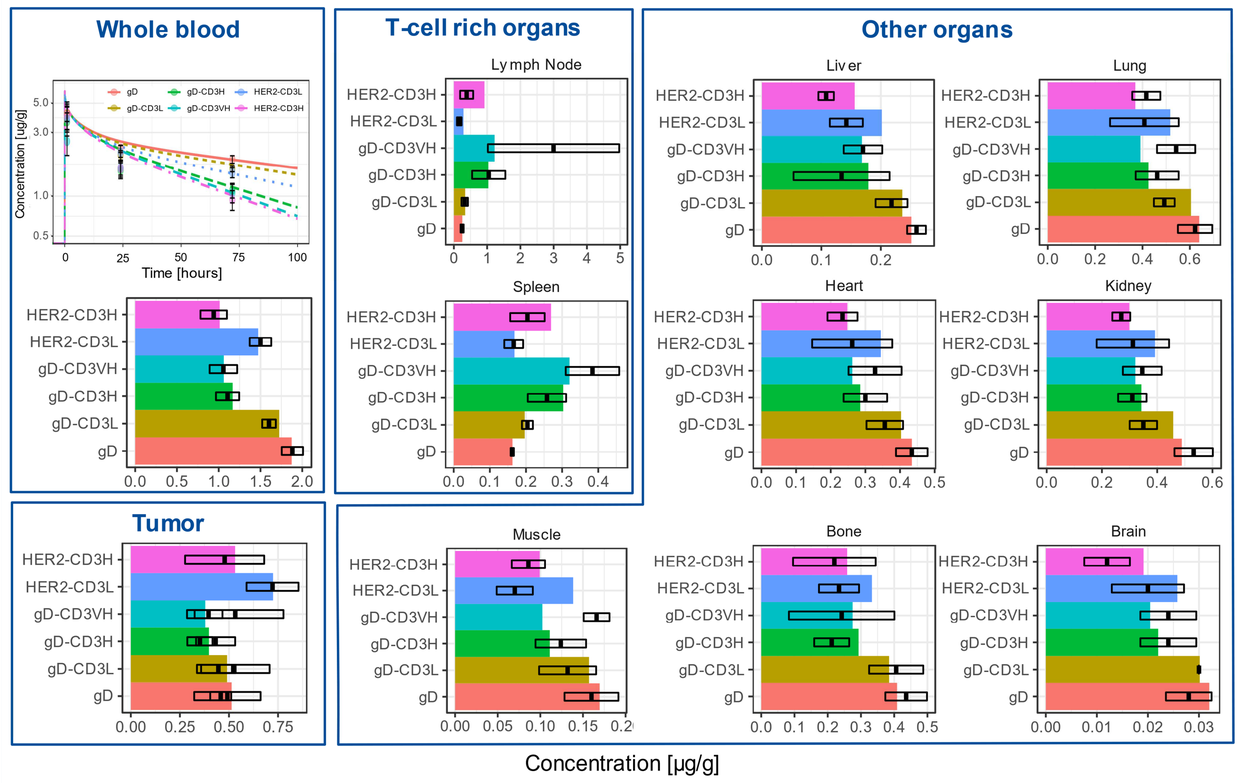
- The TDB/T-cell PB-QSP platform qualitatively and quantitatively captures the observed tissue distributions at the site of action, on-target/off-tumor, and off-target.

Fig. 4 - PB-QSP platform parametrized to capture distribution of exogenously administered T-cells [5]



- To account for the interspecies variability between datasets (male C57BL/6 vs female huCD3e-TG), transmigration rates and retention factors for naïve T-cells (derived from Khot et al. 2019 [5]) were allowed to vary up to 2-fold for all tissues, except for the tumor (5-fold) and the lymph node organ (15-fold), to fit the TDB data from Mandikian et al. 2018 [1]. Higher variations for the tumor and lymph node were allowed considering the data differences for tumor type (melanoma vs CT26-HER2) and acquisition of lymph node data (inguinal lymph node vs lumped location agnostic lymph node).
- The model adequately described the unique “push-and-pull” distribution patterns between T-cell-rich organs and tumor tissue as a function of relative binding affinities of the TDB to HER2 and CD3 [1].

Fig. 5 - PB-QSP platform parametrized for TDBs with different T-cell affinities. Total TDB at 72h p.a. [1]



- Antibodies with high CD3 affinity have reduced half-life and exposure in blood and higher distribution to T-cell-rich tissues. Compared to the gD/CD3 monospecific antibody, the HER2/TDB bispecific antibody have lower plasma and lymph node distribution, but higher distribution to the HER2+ tumor.
- Inclusion of a saturation effect on internalization (i.e., reduced CD3 internalization rate) may improve the fitting to the data for the TDB with very high CD3 affinity (gD-CD3VH; KD = 1.44 nM).

Conclusions and future work

- The TDB/T-cell PBPK-QSP platform can be applied to evaluate the tri-molecular immune synapse formation of TDBs at the tissue/organ of interest and site of action with varying binding effector and target affinities in mouse xenografts.
- The platform allows convenient extension with effect models for assessing the impact of TDB binding properties on TDB tissue distribution and T-cell tumor-killing efficacy.
- Future extensions of this platform include the integration of the downstream pharmacodynamics and target cell killing by the TDB [7] and translating the model to other nonclinical species and humans.

References

1. Mandikian et al. Mol. Cancer Ther. 2018;17(4):776–785. doi: 10.1158/1535-7163.MCT-17-0657
2. Willmann et al. Biosilico 2003;1(4):121-124. doi: 10.1016/S1478-5382(03)02342-4
3. Lippert et al. CPT Pharmacomet. Syst. Pharmacol. 2019;8:878-882. doi: 10.1002/psp4.12473
4. Mandikian et al. AAPS J. 2018;20(6):107. doi: 10.1208/s12248-018-0264-z
5. Khot et al. J. Pharmacol. Exp. Ther. 2019;368(3):503-513
6. Zhu et al. Cancer Res. 1996;56(16):3771-81. PMID: 8706023
7. Hosseini et al. NPJ Syst Biol Appl. 2020;6(1):28. doi: 10.1038/s41540-020-00145-7