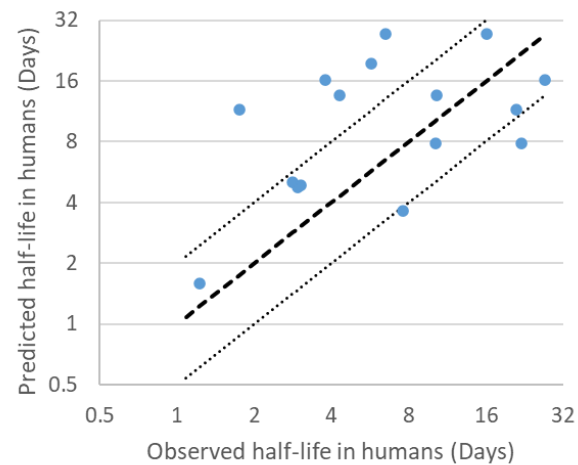


Predicting the pharmacokinetics of T-cell Engagers as a function of Target-Mediated Drug Disposition

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Introduction

The therapeutic modality of T-Cell Engagers (TCEs) represent a relatively novel and increasing part of pharmaceutical R&D portfolios, mainly in oncology. The pharmacokinetics of these molecules, a necessary precursor to any dose estimate, is complex. Despite typically being IgG-like molecules, the PK does not appear to follow the allometric principles of IgG monoclonal antibodies in that the half-lives in patients are often short, with no correlation between NHP and humans. An allometric scaling of TCE PK from the NHP to humans according to Deng et al. 2011 results in the following lack of correlation:

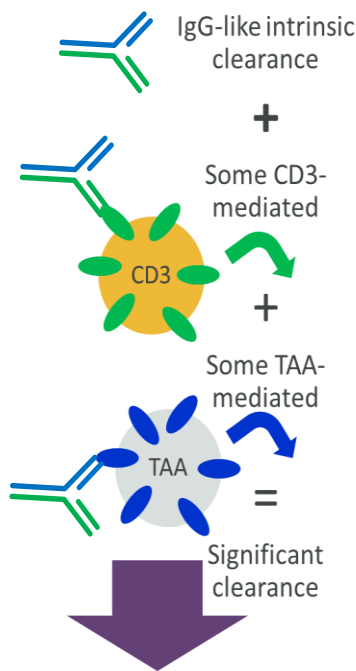


Here we propose workflow for the prediction and inter-species scaling of TCE PK, allowing for target-mediated drug disposition (TMDD), which explains inter-species observations and accurately estimates PK half-lives.

The Method in Principle

TCEs engage ≥two receptors and are often dosed at sub-saturating levels and so TMDD may be expected from both the receptor on the T-cell (CD3) and the TAA on the target cell. The half-life observed for a given TCE (at a given dose and dosing frequency) is the combination of:

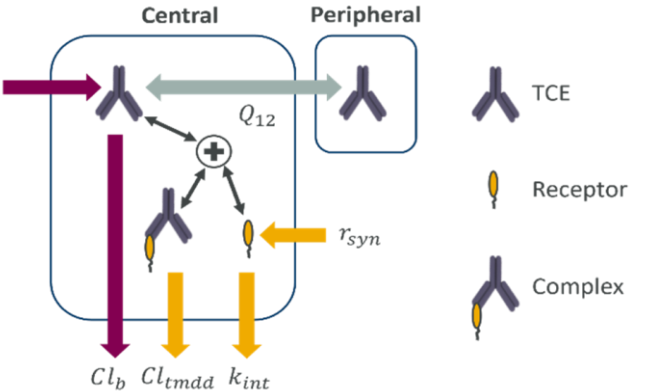
- the intrinsic, IgG-like, half-life of the molecule itself
- Due to binding CD3
- Due to binding the TAA



References

- Deng et al. 2011 DOI: 10.4161/mabs.3.1.13799
- Avery et al. 2016 DOI: 10.1080/19420862.2016.1193660
- Liu et al. 2000 Immunity, Vol. 13, 665–675,
- Chenard-Poirier et al. ASCO 2024
- Zhu et al. 2013. doi: 10.1158/1078-0432.CCR-12-2616
- Talquetamab FDA multi-disciplinary review BLA761342
- Teclistamab FDA multi-disciplinary review BLA761291

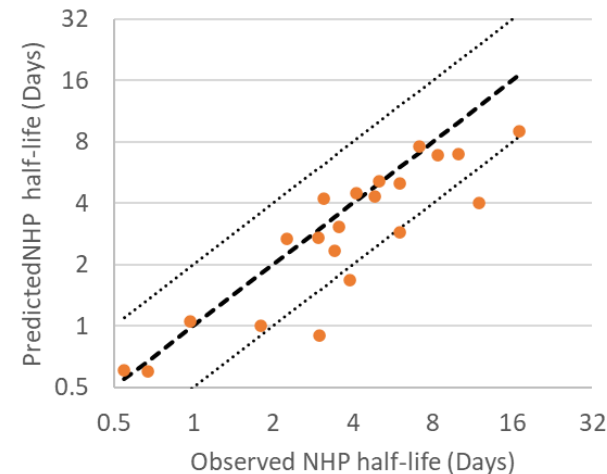
Model Schematic



A two compartmental model is used to simulate the PK of the TCE: a central compartment with iv infusion with linear clearance and two sources of TMDD, and a peripheral compartment.

Prediction Workflow - NHP

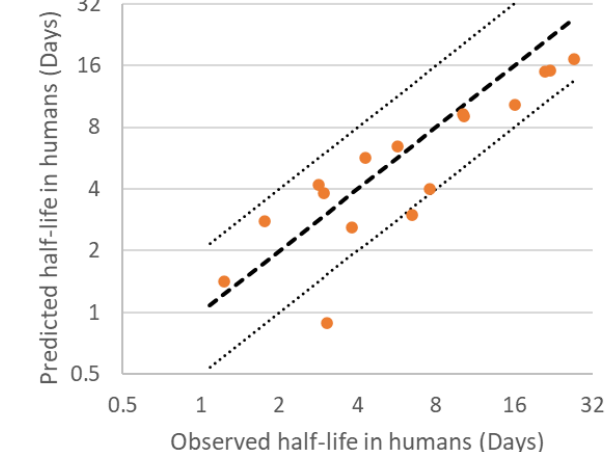
- Workflow for an *a priori* prediction of NHP PK
- Assumed intrinsic PK half-life of 9 days, or scaled from Tg32 mouse PK by Avery et al. 2016 if available
- 50k CD3 / T-cell, 1500 T-cells/ μ L; CD3 half-life of 36 mins from Liu et al. 2000; KD from SPR
- TAA-specific level & turnover from TMDD model fit to clinical PK data for anti-TAA mAb; KD by SPR
- Half-life calculated by model simulation for each dose and regimen



- Data from 21 TCEs was collected from the literature and compared to observed value.
- 17/21 within 2-fold of the observed half-life, mean absolute error of 43% and bias -24%**

Prediction Workflow - Humans

- Intrinsic half-life of the NHP re-estimated from the NHP data if identifiable and scaled to humans according to Deng et al. 2011.
- KDs replaced with human values
- Human half-life estimated from the model simulation for each clinical dosing regimen

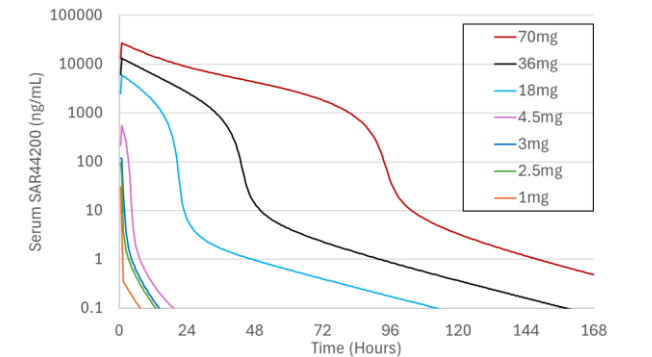


- Data from 17 TCEs collected from the literature
- 15/17 within 2-fold of the observed half-life, mean absolute error was 49% and bias -18%, compared to 10/17, 124% and +52% for allometry alone**

Example applications

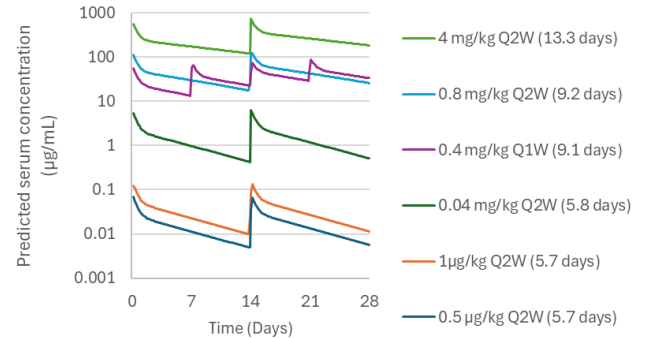
SAR-444200 (anti-GPC3)

- Affinities & PK from Chenard-Poirier et al. 2024
 - Model included the albumin binding explicitly as an extra TMDD term
 - Turnover of the TCR assumed to be similar to CD3
- GPC3 apparent level and turnover from GC33 in Zhu et al. 2013
- Simulation predicts the half-life at the higher doses of 21.5 hours compared to an observed average half-life of 26 hours
 - GPC3 binding drives fast clearance
- Correctly predicts the (very much) shorter half-lives below 18mg



Talquetamab (anti-GPRC5D)

- Affinities and clinical PK from the FDA review
- No TAA-specific TMDD-related data could be found: “CD3-only” simulation was performed
- Predicts a half-life of <6 days at the low FiH starting doses versus the observed 2-6 days
 - Shorter half-lives GPRC5D driven?
- Predicts 9 days for the RP2Ds of 0.4/0.8 mg/kg, compared to the 8-10 days observed
- 14 day half-life used in the clinical study design, from allometric scaling of NHP PK, only occurs at higher, saturating doses.



Conclusions

- The observed short half-lives of TCEs are due to TMDD mediated by both the T-cell (CD3) and TAA binding
- Lack of correlation between non-clinical species and humans is due to differences in cross-reactivity (KD) between those species, varying that TMDD
 - Differing doses and so target saturation can also be a factor
 - Allometric scaling alone of PK is incorrect
- TCE PK may be predicted accurately by modelling the CD3 and TAA-driven TMDD
 - CD3-driven effects determined from in vitro data
 - TAA-driven effects identifiable from anti-TAA mAb clinical PK
- Correctly accounts for species differences due to differing cross-reactivity
- Correctly accounts for dose-dependency due to variations in target saturation
- Provides estimates prior to *in vivo* studies, informing study design and limiting surprises