Development of mPBPK-target engagement model to support translation decision making for novel cell engagers for oncology

Anuraag Saini, Seshasai Pallikonda Chakravarthy, Goutam Nair, Kartikeya Raman, Bhairav Paleja, Mrittika Roy, *Rukmini Kumar

***rukmini@vantage-research.net**

Vantage Research Inc, USA

INTRODUCTION

Bispecific therapeutics, that engage immune cells, have emerged as a promising class of drugs due to their ability to target two distinct antigens simultaneously. Here the goal is to redirect immune cells towards cancer cells to have cytotoxic action (Fig.1).

This study focuses on 2 kinds of bispecific therapeutics based on the immune cells they targets (a) Tcells dependent bispecific (TDB) which bind to T cells and (b) NK cell engagers (NKE) which activate natural killer cells to kill cancer cells [1, 2, 3]. Further, plasma half-life of these therapeutics can be extended by introducing half-life extending (HLE) mutations in the Fc domain or other manipulations to the engager protein [4].

Mechanistic models have been proposed to describe the efficacy and safety for TDBs and NKEs independently [5,6]. In this study, mPBPK is designed to support decision-making in the development of three bispecific therapeutics. It has been calibrated to (a) Mosunetuzumab - TDB, (b) PSMAxCD3 – HLE-TDB and (c) anti CD30xCD16A – NKE.

OBJECTIVES

The objective of this study is to develop a mPBPK-target engagement model to predict clinical PK of novel bi-specifics based on available preclinical and invitro data using single virtual population. To do this

- Capture the pharmacokinetics (PK) properties like specific, receptor mediated clearance and binding affinity (KD) of three bispecific therapeutics: Mosunetuzumab-TDB, PSMAxCD3-HLE-TDB, and anti-CD30xCD16A-NKE
- Calibrate the model to plasma PK for non-human primates (NHPs) and humans and
- Predict plasma PK for these bispecific therapeutics in humans.

METHODS

An existing mPBPK model was extended to include the following features [2]:

- **Cell dynamics:** In addition to T cells, the model was extended to include the cell dynamics of NK cells, Monocytes, and B cells.
- **Receptor dynamics:** The model was also extended to include the receptor dynamics of CD3 on T cells, CD16A on NK cells and monocytes, and CD30 on B cells. This was done to track the binding of the drug to understand its effects on biodistribution and clearance due to TMDD. (Fig.2)
- **Endosomal compartment:** The model was further extended to include an endosomal compartment. This captures the long half life of PSMAxCD3 – HLE-TDB due to FcRn mediated endosomal recycling leading to prolonged circulation times [7] (Fig.3)

The model was recalibrated to plasma PK for TDB after incorporating receptor dynamics. It was validated using human PK data and adjusted if necessary.

For HLE-TDB, rhesus plasma PK was captured using endosomal recycling mechanism, and for NKE, direct calibration to human PK was done due to the lack of pre-clinical data. (Table. 1)

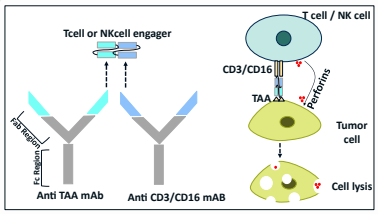


Figure 1

Effect diagram of the mPBPK model

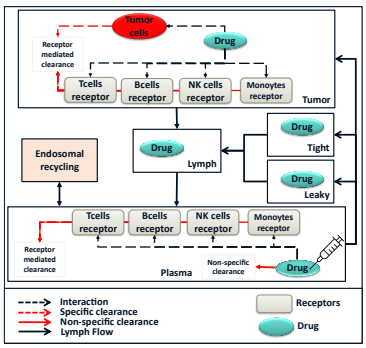


Figure 2

Endosomal Recycling

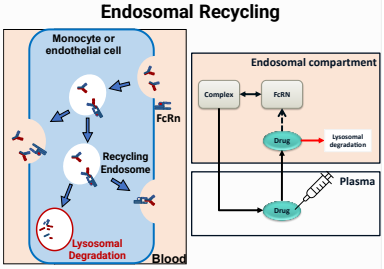


Figure 3

Workflow for model calibration and validation

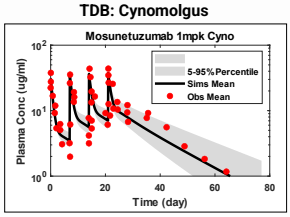
Cell Engagers	Cyno	Rhesus	Human
TDB	**Calibration** 1mpk **Validation** 0.1mpk **[1]**	-	**Validation** 2.4mpk **[2]**
HLE	-	**Calibration** 30upk **[4]**	**Prediction** 2.4mpk TDB
NKE	-	-	**Calibration** 7mpk **[3]**

Table 1

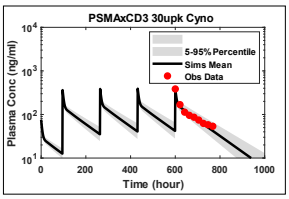
RESULTS

Calibration

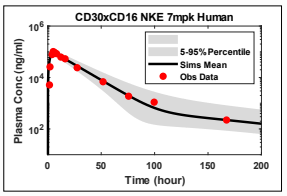
TDB: Cynomolgus



HLE-TDB: Rhesus

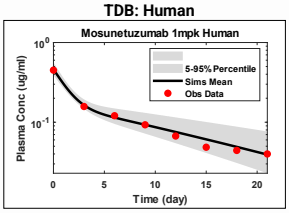


NKE: Human



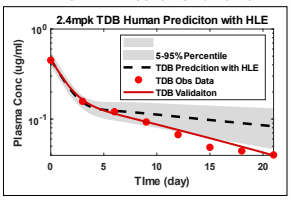
Validation

TDB: Human



Prediction

TDB with HLE mechanism: Human



Physiological PK Parameters [8]	Cyno	Rhesus	Human	Units
Vcentral	0.1	0.6	5.2	L
Vlymph	0.2	1.2	10.4	L
LymphFlow Rate	0.007	0.01	0.16	L/h
ISF	0.8	3.5	12	L

Drug Related Parameters	TDB	HLE-TDB	NKE	Units
Receptor-mediated clearance (estimated)	0.1	0.1	0.15	1/h
Non-specific clearance (estimated)	0.016	0.03	0.043	L/h
Sig1	0.9	0.95	0.8	-
Sig2	0.6	0.6	0.6	-
SigL	0.2	0.2	0.2	-
KD for effector cell antigen	470	230	130	nM

- **Observed data:** The red dots represent observed data from published literature.
- **Simulation output:** The black solid line represents the mean and gray shaded area depicts the variability in physiological and drug related parameters. To generate Vpop, Vcentral, Vlymph, and lymph flow were varied by 20%. Non-specific and receptor-mediated clearance were varied by 30%. Receptor densities were varied by 50%.

- **TDB calibration:** After adding receptor dynamics, the model was re-calibrated to cynomolgus PK for 1mpk dose to estimate receptor-mediated and non-specific clearance. The estimates are similar to the values reported in the published model.
- **TDB validation:** The translated human model was validated by capturing plasma PK for 2.4mpk dose without needing re-calibration i.e keeping the estimated drug-related parameters receptor-mediated and non-specific clearance un-modified. The receptor dynamic in tumor compartment impacts plasma PK.
- **HLE-TDB calibration:** The model was calibrated to rhesus PK for a 30upk dose and due to FcRN binding mediated endosomal recycling, the model captured the long terminal half life ~6 days.
- **Prediction for TDB with HLE mechanism:** The translated human model was used to predict the plasma PK of 2.5mpk dose of TDB. The impact of endosomal recycling can be seen in the lower clearance of the TDB from plasma. Human data from TDB validation study is used as a comparison.
- **NKE calibration:** The model was directly calibrated to the human PK for 7mpk dose since no public invivo pre-clinical data was available. Here two cell types were added since NKE binds to CD16A, and CD16A receptors are present on both NK cells and Monocytes.

CONCLUSIONS

- This mPBPK-target engagement model can be used to predict the pharmacokinetics (PK) of various bispecific therapeutics, whether they are T cell or NK cell dependent bispecifics.
- The endosomal recycling mechanism can explain the prolonged plasma half life of bispecifics to provide better efficacy at specific site of action like tumor compartment.
- In the case of NKE, where effector cell antigen is present on multiple cell types, the model can be used to obtain more accurate estimates of clearance and exposure.
- The model was able to capture the Plasma PK for NHPs and Human using a single virtual population by varying physiological parameters within the physiological limits.

FUTURE WORK

- This platform model of multispecifics will be calibrated to capture efficacy as tumor burden reduction.
- The model will be expanded to include cytokine secretion for estimating a safe and efficacious therapeutic window.
- This platform model will eventually be calibrated to similar data for existing and upcoming novel cell engagers to aid in the decision making for translational studies.

REFERENCES

1. Ferl GZ, et al., 2018, 10.1111/cts.12535
2. Hosseini I, et al. 2020, 10.1038/s41540-020-00145-7
3. Rothe A, et al. 2015, 10.1182/blood-2014-12-614636
4. Deegen P, et al., 2021, 10.1158/1078-0432.CCR-20-3725
5. Cao Y, et al. 2013, 10.1007/s10928-013-9332-2
6. Betts, A., et al. 2020, 10.1002/cpt.1961
7. Shah, D., et al. 2018, 10.1080/19420862.2018.1506648
8. Shah, D., et al. 2012, 10.1007/s10928-011-9232-2

ACKNOWLEDGEMENTS

We thank Khomveer Singh of Vantage Research for supporting model development.