



Introduction

- CD3 bispecifics are engineered antibodies that bind CD3 on T cells and target antigens on cancer cells (TAAs), activating T cells to kill cancerous cells.
- However, they may induce adverse effects such as CRS (Cytokine Release Syndrome) from on-target off-tumor toxicity, prompting ongoing research to define the optimal therapeutic balance.
- Research aimed at optimizing CD3 bispecifics for cancer therapy involves integrating mechanistic modeling with experimental data to comprehensively elucidate the drug's mechanism of action (effected via the CD3-mAb-TAA trimers) in tumor and normal tissues, emphasizing CD3 receptor occupancy as pivotal in determining both efficacy and potential adverse events like cytokine release syndrome (CRS).

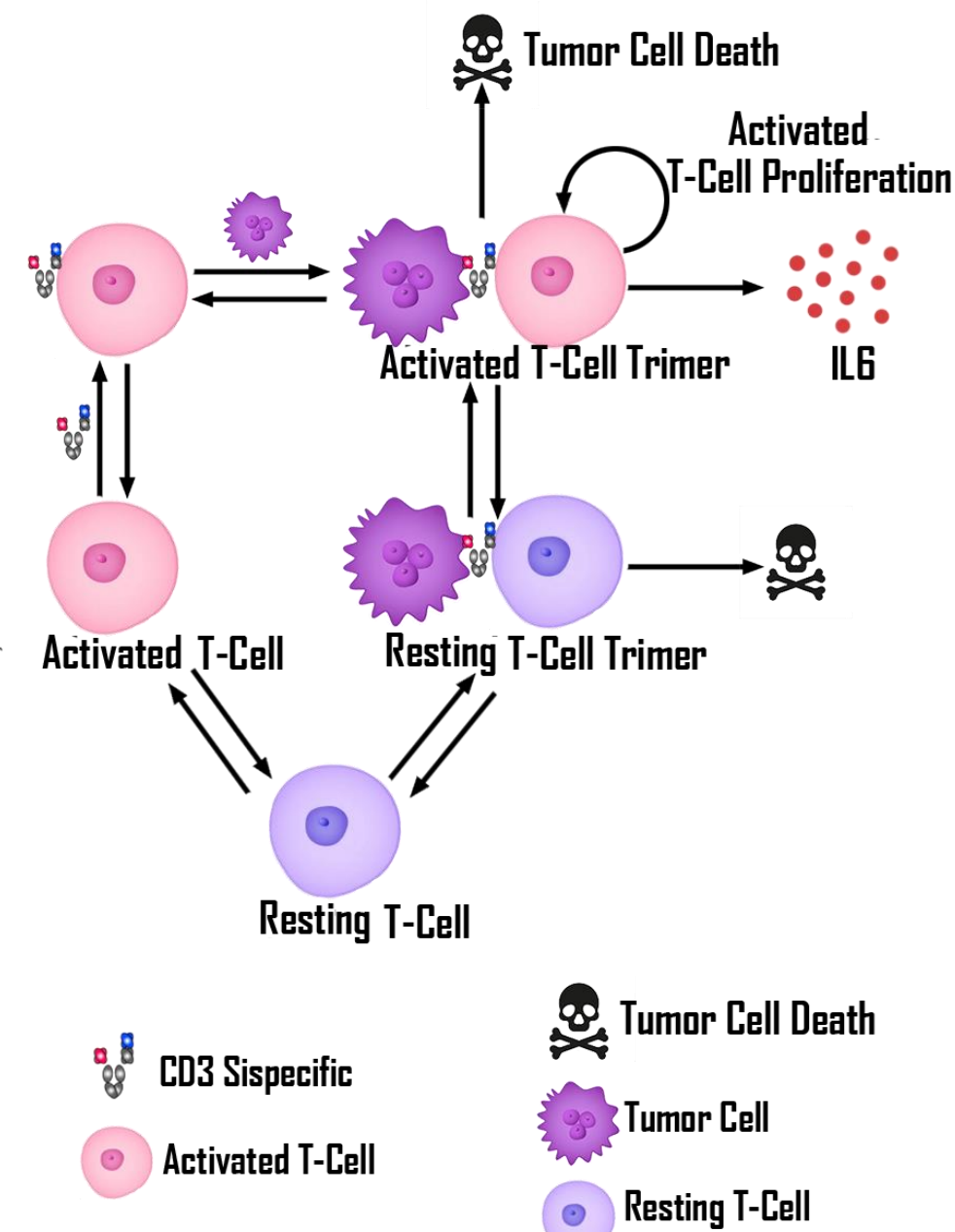


Figure 1: CD3 Bispecific T-Cell Engager – Mechanism of Action

Objectives

The primary goal of developing QSP models for CD3 BiSpecifics is to simulate alternative dose fractionation techniques in the patient population by varying T-Cell numbers and TAA expression levels, thereby facilitating their potential applications in early clinical stages. We focus on Xaluritamig (a STEAP TDB for prostate cancer). In particular, we simulate the following scenarios:

- To simulate normal tissue CD3-mAb-TAA complex formation (surrogate for safety) for different doses of Xaluritamig.
- Recommend an alternate dosing regimen and incremental dose for Xaluritamig based on optimal trimer formation by calibrating the platform model to capture (PK/PD) properties, and safety profiles obtained from previous studies or clinical trials.
- Explore alternate dose priming strategies to mitigate CRS/adverse events.

Approach

Mathematical models to capture:

- A minimal Physiological model to capture the T-cell trafficking, Human PK, and IL6 release and to predict an alternate dose priming strategy in clinical settings

Table 1: Model and Parameter Output

Data type	Model	Output
In-vivo (Clinical)	Repurpose the model published by Hosseini et al[1] to a mPBPK model to capture the PK, STEAP1 expression, and T-Cell dynamics	- Bispecific plasma clearance - T-Cell desensitization parameters - T-Cell margination parameters - IL6 production parameters

Model Diagram

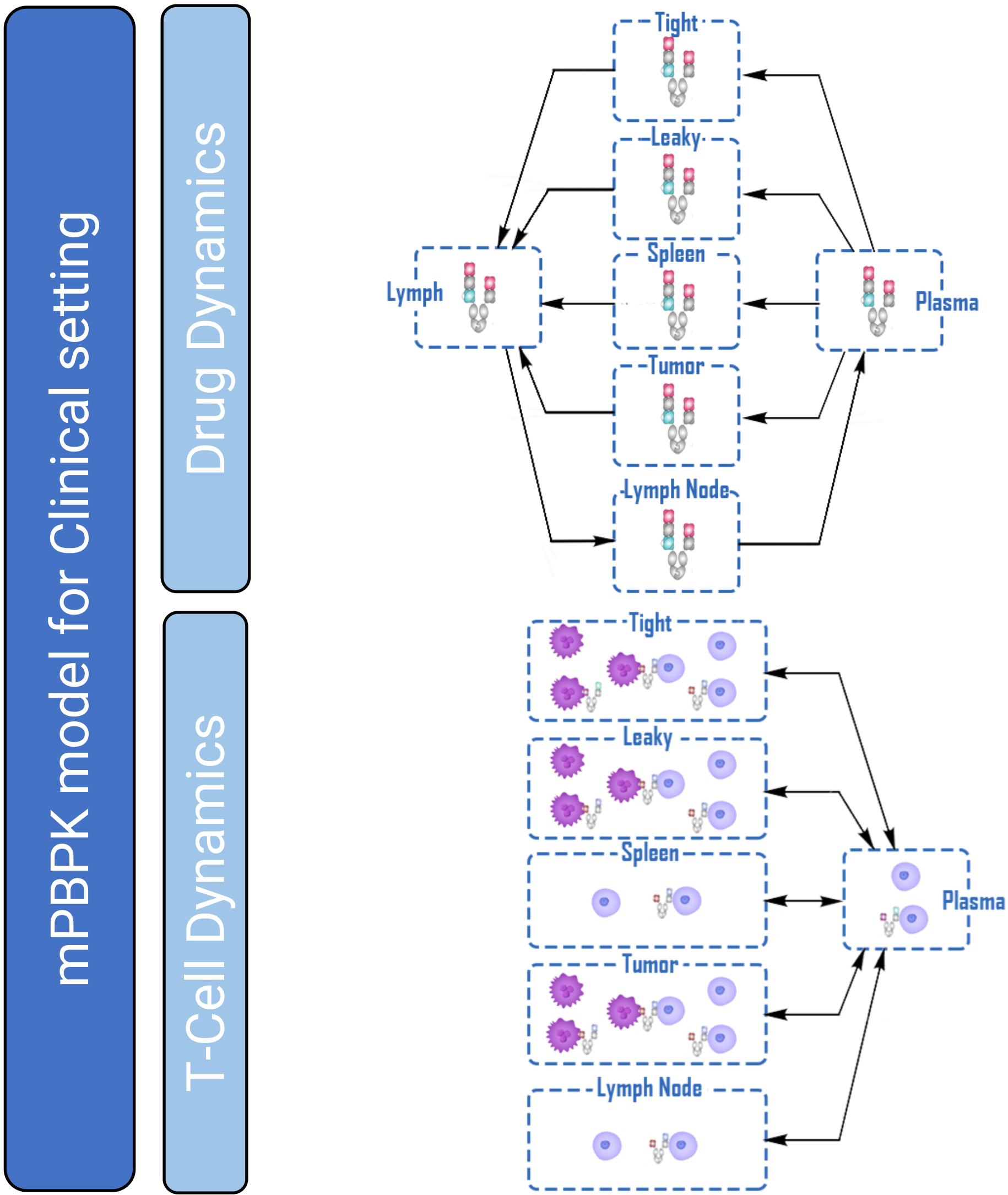


Figure 2: In vivo model setup for pre-clinical and Clinical settings capturing T-Cell dynamics and Bispecific distribution.

Results

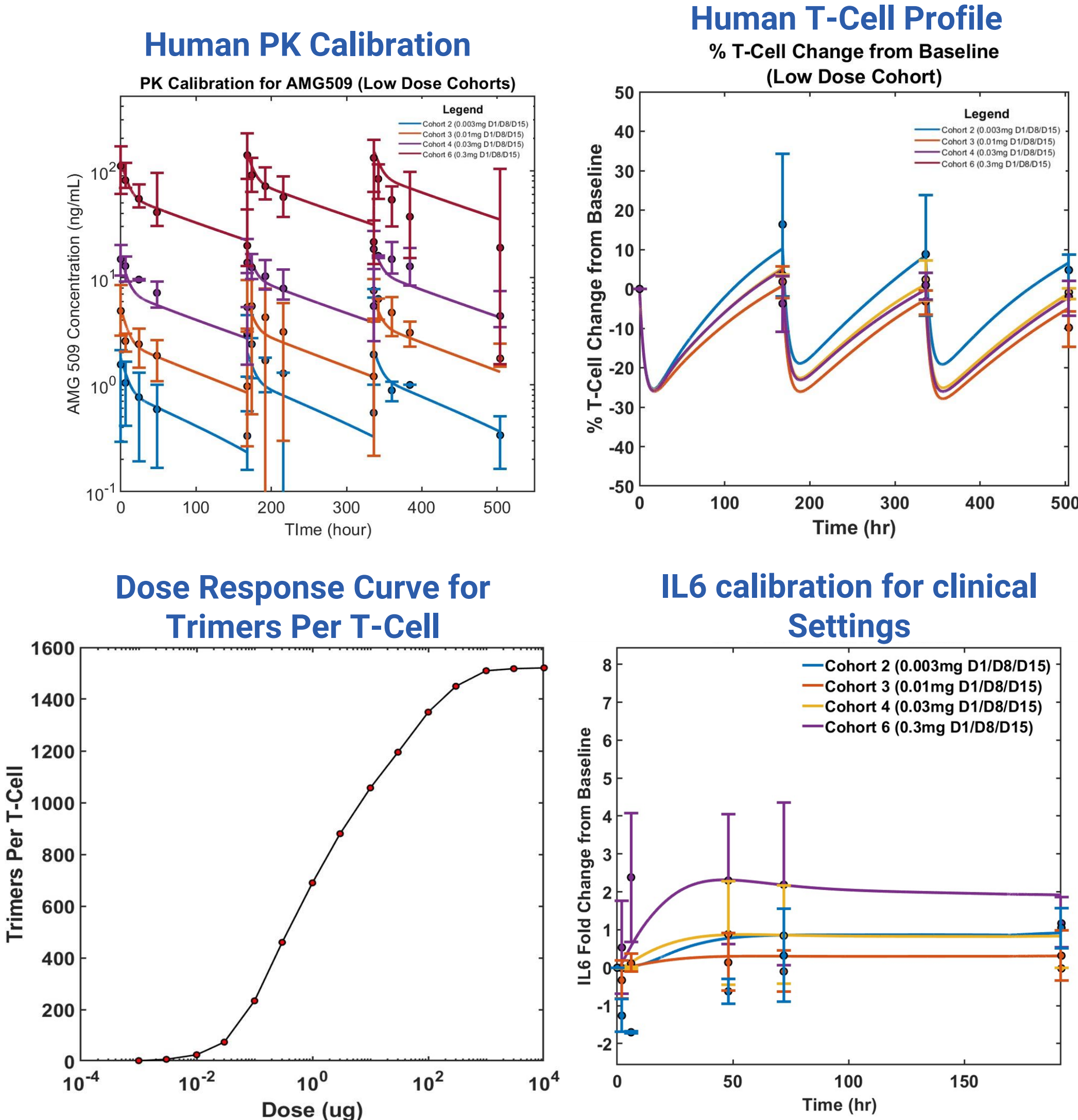


Table 2 : Parameter table for In vivo calibration exercise

Parameter	Description	Estimate (%CV)	Unit
CLp	Plasma Clearance of BiSpecific	0.022 (12.5%)	L/hr
sigma2	Vascular Reflection coefficient to Leaky Tissue	0.687	---
Chi_Trans	Trans Avidity Factor	1e5	---
Chi_Cis	Cis Avidity Factor	15	---
Vm_prolif	Proliferation Rate for Non-Exhausted T-Cells	3.08e-2 (3.35)	hr ⁻¹
Km_prolif	Trimers per T-Cell needed for 50% of Max rate	415 (120)	Trimers/T-Cell
K_margin	Margination Intensity	1	---
Vm_IL6	IL6 production rate per cell per hour	5E-11 (30.17)	pg/hr/T Cell
Km_IL6 [†]	Trimers Per T-Cell needed for 50% max IL6 Production	728	Trimers/T-Cell

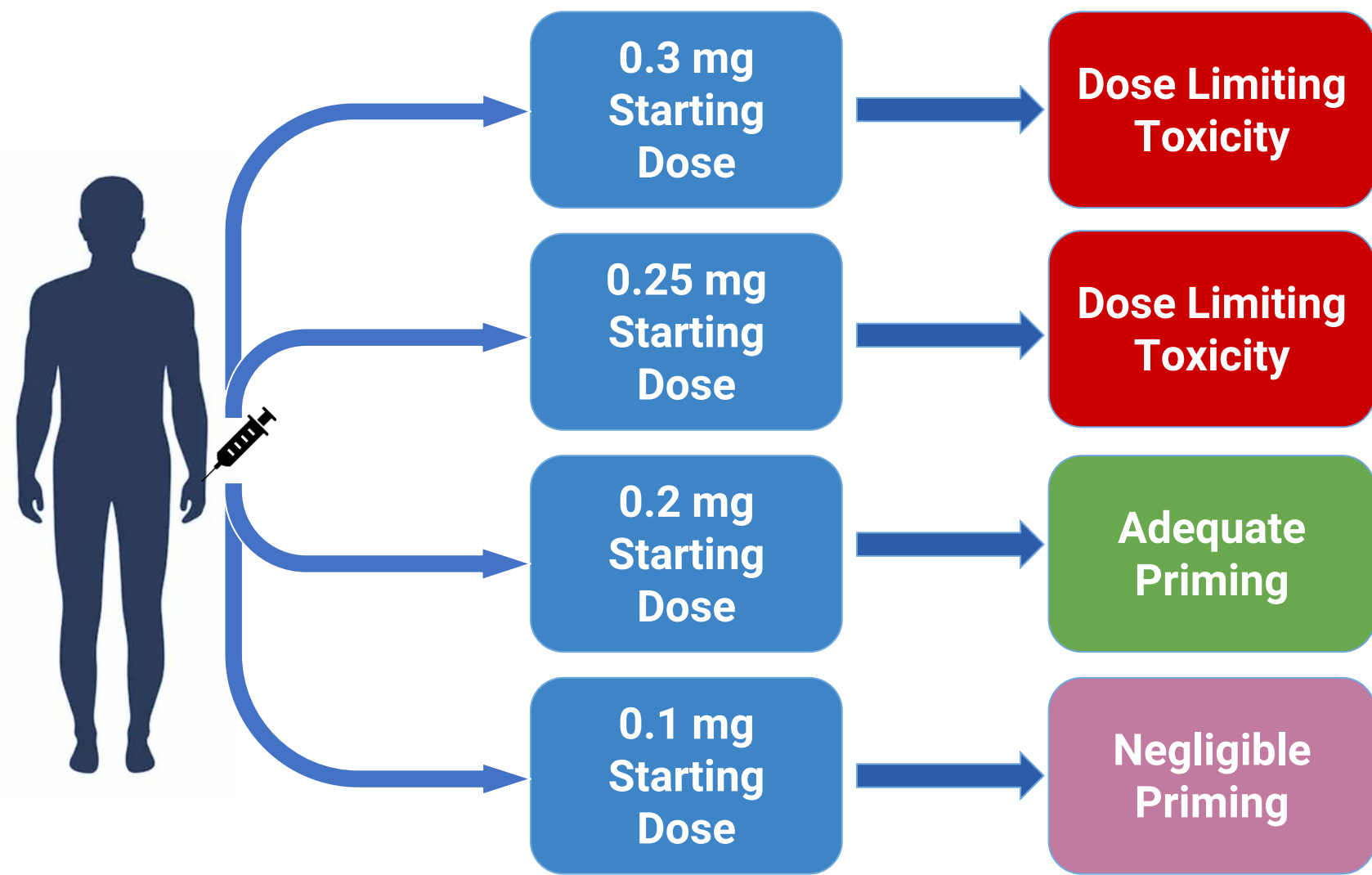
[†]: Trimers Per T-Cell needed for the EC50 value of 1.55 mg (estimated from the Trimers Per T-Cell Dose response curve.)

Figure 3:Virtual Population analysis in human for IL6 Priming

Conclusions

In the clinical trials, administering an initial dose of 0.3 mg of the therapeutic agent led to DLT in most patients, while a 0.1 mg dose did not reach DLT but was insufficient to induce T-cell exhaustion.

After calibrating our model with the low dose clinical trial data for Xaluritamig, a 0.2 mg starting dose was identified as optimal starting dose.



Hence, we recommend a **dosing regimen of 0.2mg/0.3mg/1mg in a QW manner**, to have most efficient priming with minimal risk of CRS.

Next Steps

- Incorporate the high-dose data into the model training process to refine the Dose priming and IL6 production rate in clinical settings.
- Addition of the efficacy module and translate the studies from preclinical mice TGI data and predict the minimum efficacious dose in clinical settings.

Limitations

- The current model considers only IL6 is the major contributor of CRS and therefore other cytokines are not taken into account.
- The model was trained based only on the low dose cohort to inform the priming dose selection.

References

[1]Mitigating the Risk of Cytokine Release Syndrome in a Phase I Trial of CD20/CD3 Bispecific Antibody Mosunetuzumab in NHL: Impact of Translational System Modelling.

[2] Xaluritamig, a STEAP1 × CD3 XmAb 2+1 Immune Therapy for Metastatic Castration- Resistant Prostate Cancer: Results from Dose Exploration in a First-in-Human Study