Biomarker consideration & translational modelling

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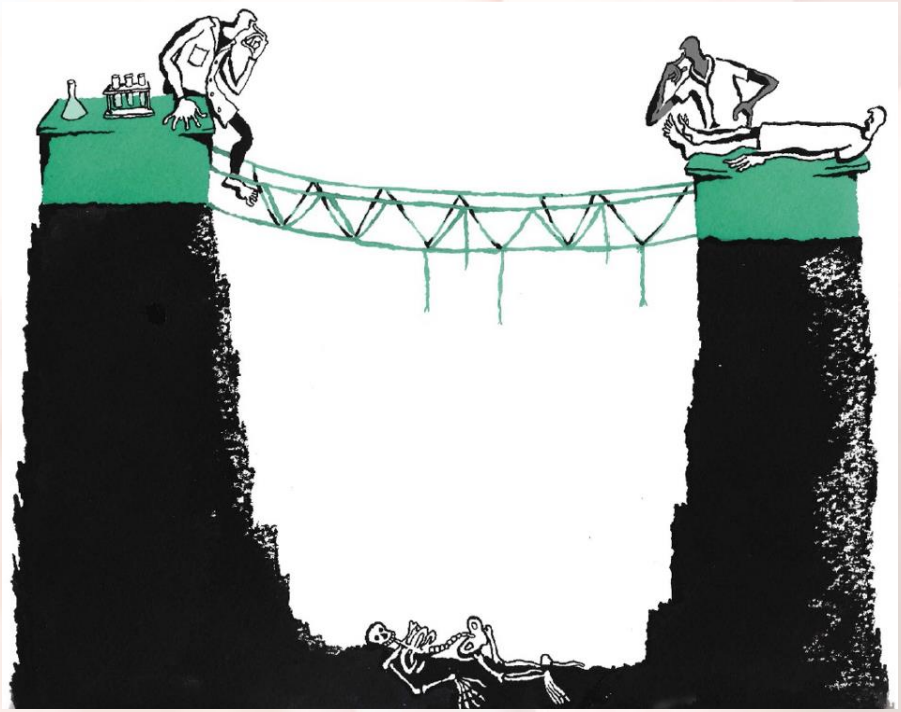
Challenges in Translational Research

- About 15 years ago, Declan Butler first used the term “Valley of Death” to describe the gap between basic biomedical research and clinical applications
- Today, translation remains a main challenge during drug development



Butler, D. Translational research: Crossing the valley of death. *Nature* 453, 840–842 (2008).

Crossing the "Valley of Death"

Biomarkers
- Target engagement (TE)
- Receptor occupancy (RO)

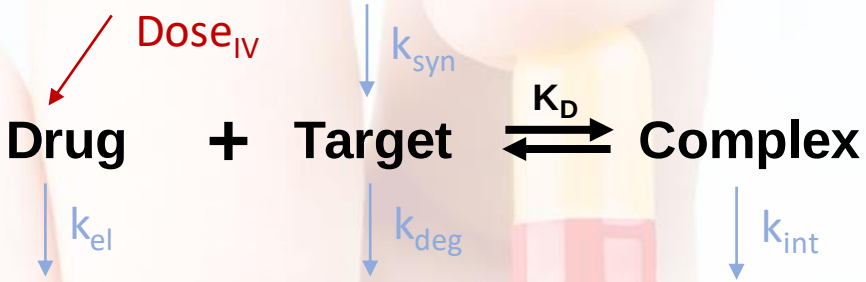
Mechanism-based PK/PD modeling
- Drug-specific and system-specific parameters

TE and RO Based Translational Modeling Strategy

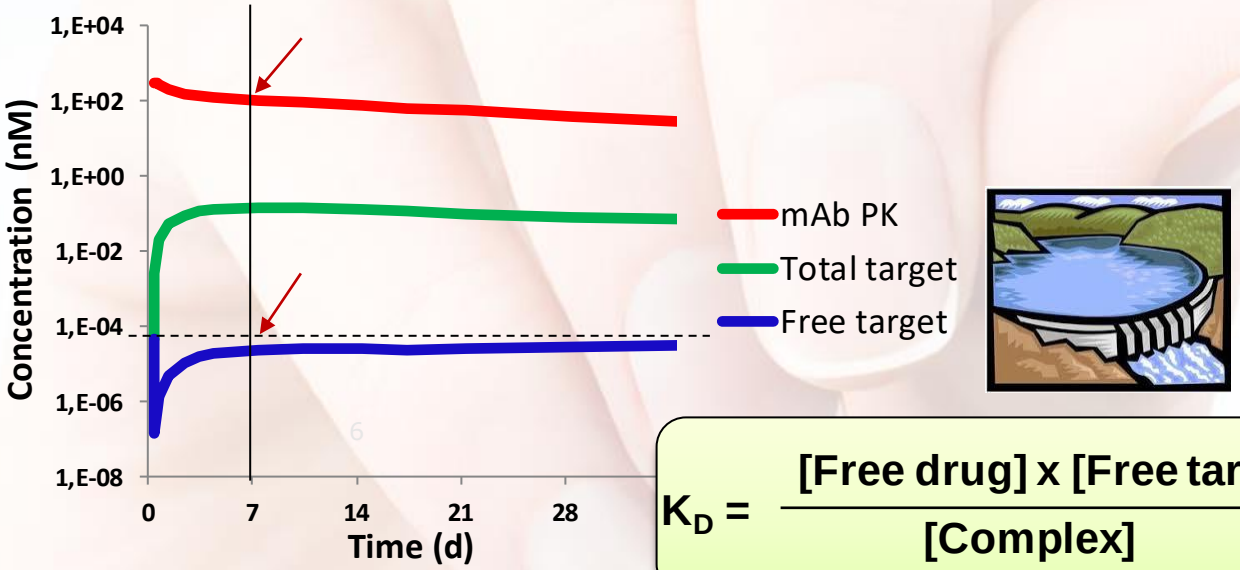
- The pharmacodynamic effect of all targeted therapeutics is driven by its interaction with the therapeutic target
  - **Target engagement (TE),** when the target is a soluble protein
  - **Receptor occupancy (RO),** when the target is a cell surface receptor

- TE/RO assessments play a central role in translational pharmacology
  - Although TE or RO does not guarantee efficacy, it is a quantifiable drug/target associated readout that can be used to model optimal doses related to downstream PD effects
  - Provide a mechanism to extrapolate the drug effect between preclinical species and humans, and between healthy and disease populations

Assess TE and RO In Vivo

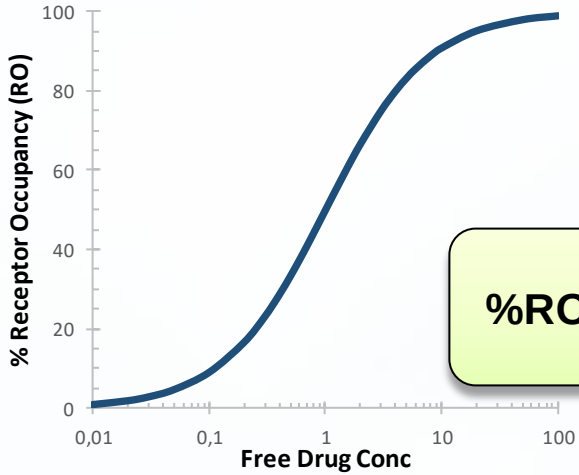


TE



$$K_D = \frac{[\text{Free drug}] \times [\text{Free target}]}{[\text{Complex}]}$$

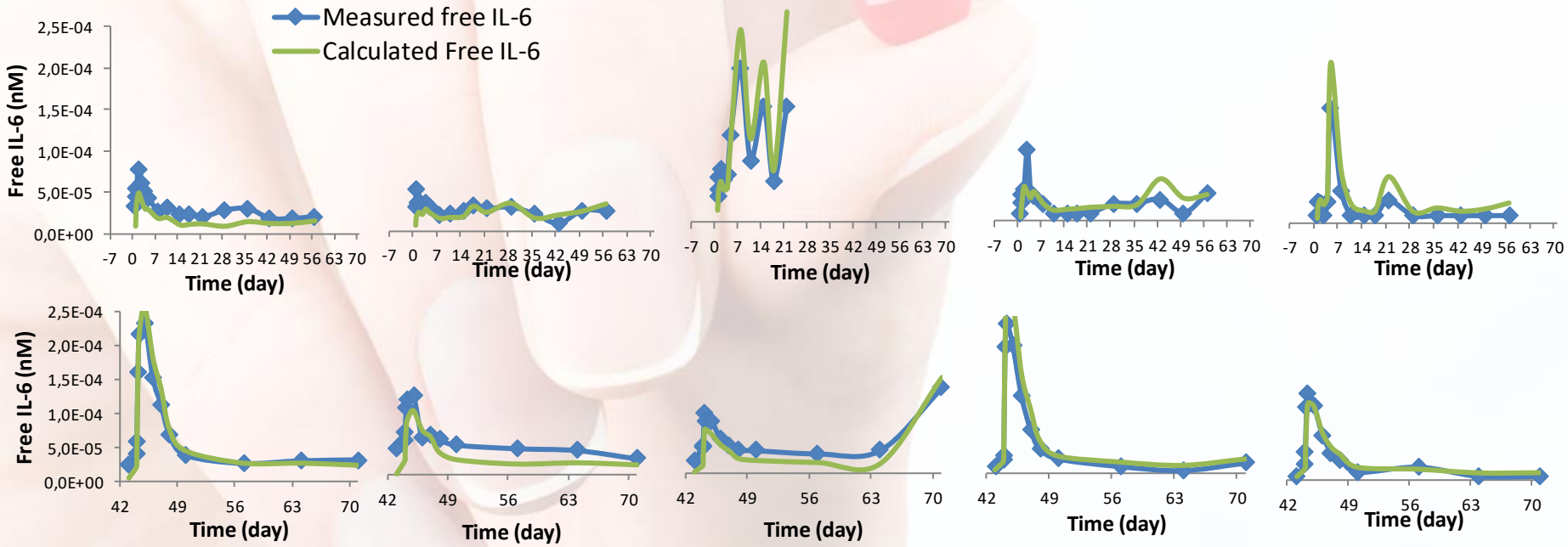
RO



$$\%RO = \frac{[\text{Free drug}]}{[\text{Free drug}] + K_D}$$

We Can Trust Maths

- The Free IL-6 values calculated from measured Total Drug, Total IL-6 and a single fitted in vivo K_D agreed well with the measured data
- Under quasi-equilibrium conditions, free target level is a function of total drug, total target and *in vivo* K_D



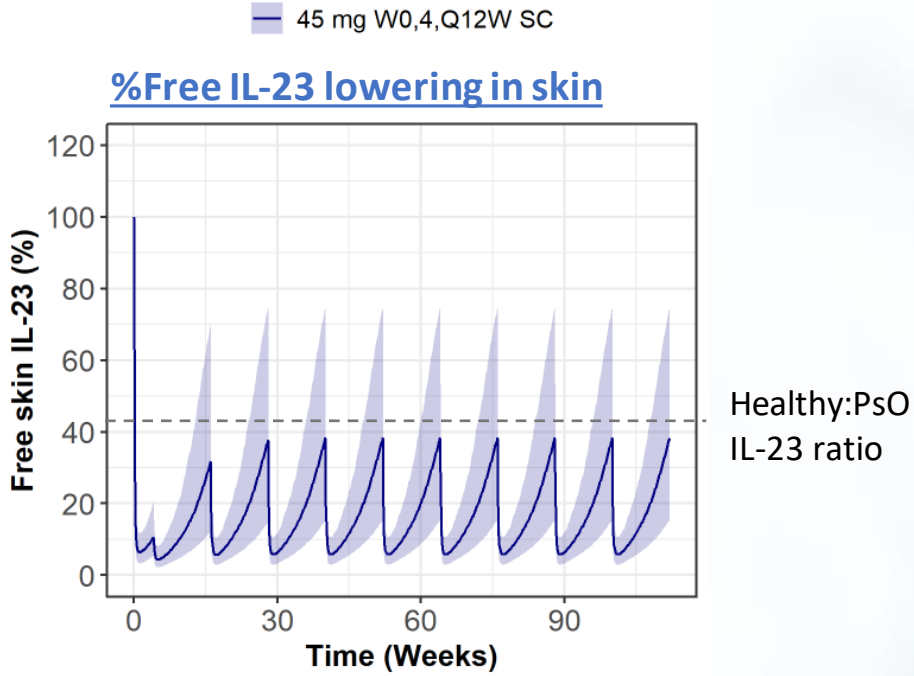
Wang W et al., (2014) AAPS J. 16:129-39.

Target Engagement-Based Dose Prediction

- A preclinical study was conducted to assess skin IL-23 TE following anti-IL-23 mAb dosing in an IL-23-induced mouse psoriasis-like model
- A mechanistic PK/PD model was developed based on PK/TE data from preclinical models and human physiological parameters, and it was used to characterize skin IL-23 suppression following ustekinumab dosing

- The elimination of biologics from the tissue sites is largely driven by the lymph flow

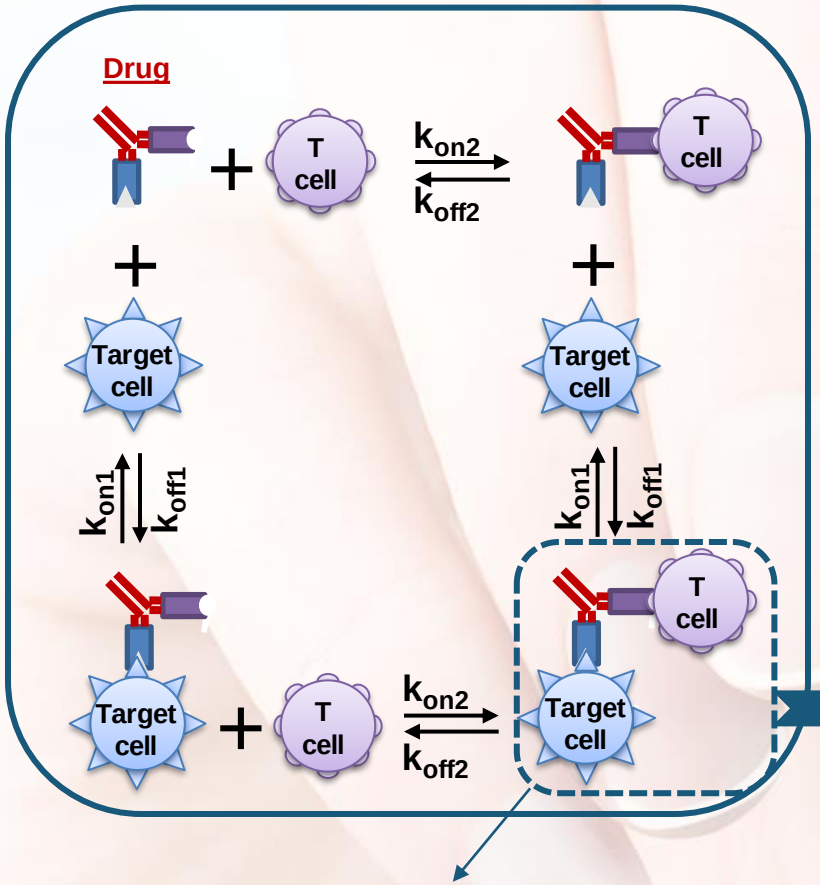
Wang W et al., (2016) Pharm Res. 33:1040-1049.



Chen X et al., (2018) JPET. 365(1):140-155

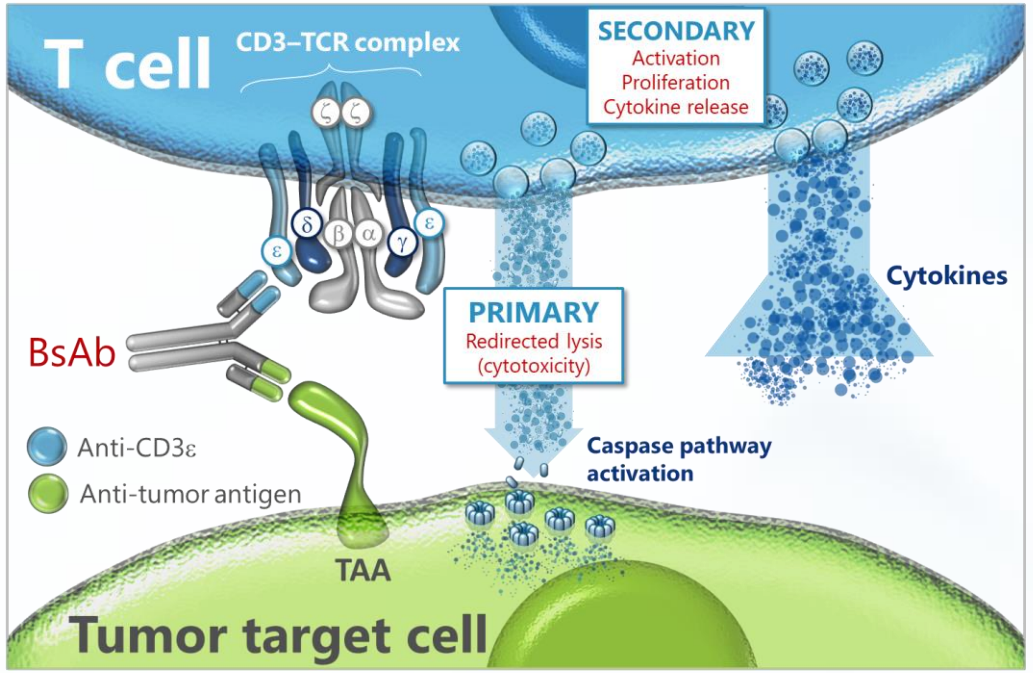
Mechanism-Based PK/PD Model for T-Cell Redirecting Bispecific Antibodies

TBE Model Schematic



- T cell activation
- Cytokine release
- Target cell depletion

TBE = Target Cell-Biologics-Effector Cell

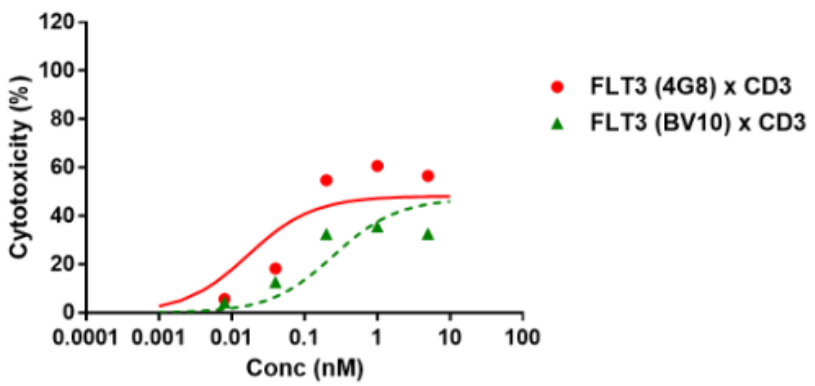


CD3 = cluster of differentiation 3;
TCR = T cell receptor;
BsAb = bispecific antibody

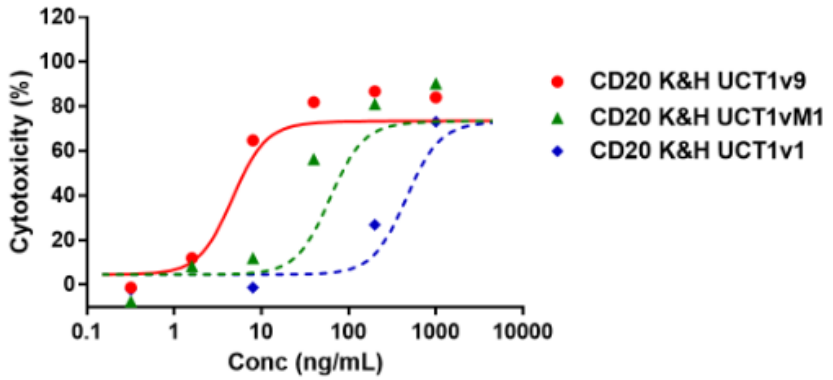
Jiang X et al., mAbs (2018)

Using Mechanism-Based Model to Dissect Drug-Specific and System-Specific Factors

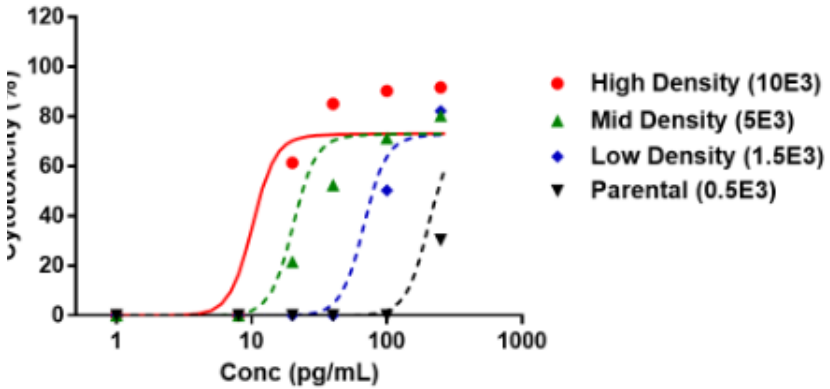
Target Receptor Binding Affinity



CD3 Binding Affinity



Target Density



Jiang X et al., mAbs (2018)

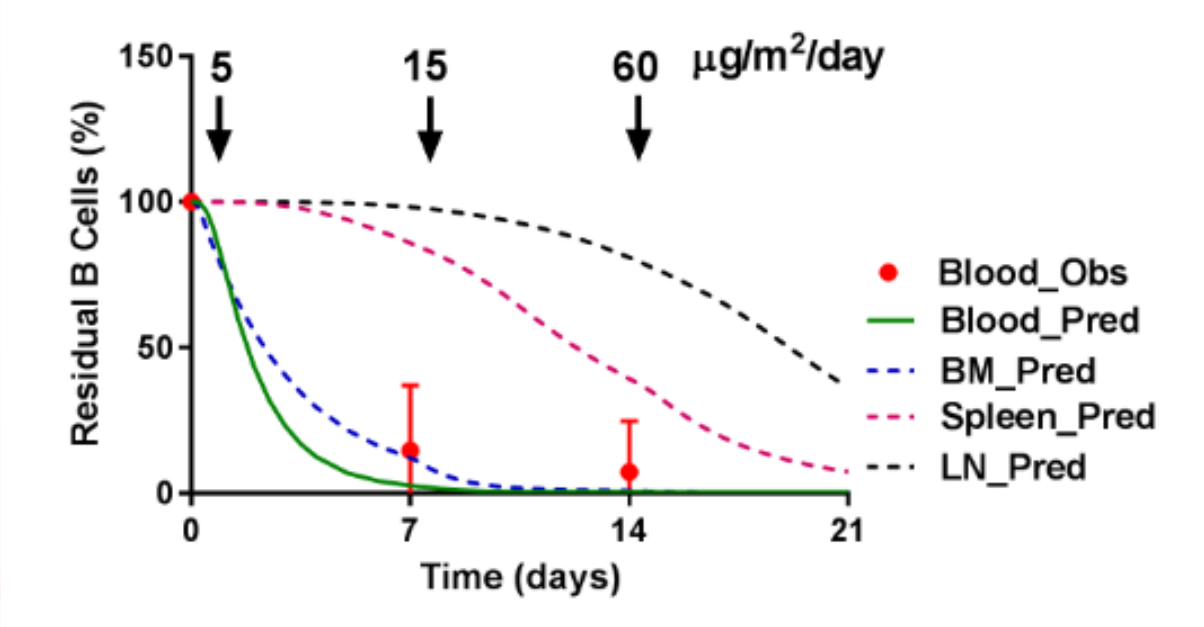
Drug-specific factors

- Affinity to CD3
- Affinity to target receptor
- Potency (scaffold, epitope)

System-specific factors

- Drug conc (PK)
- T cell abundance and dynamics
- Target cell abundance and tumor growth rate
- Potency (T cell activity)

Model Predicted B Cell Depletion and Blinatumomab Efficacious Dose in ALL and NHL Patients



- The model predicted tissue site B cell depletions are in-line with the blinatumomab efficacious doses:
  - Acute lymphoblastic leukemia (ALL)-- BM, @15ug/m^2/day
  - Non-Hodgkin's lymphoma (NHL)– LN, @60ug/m^2/day

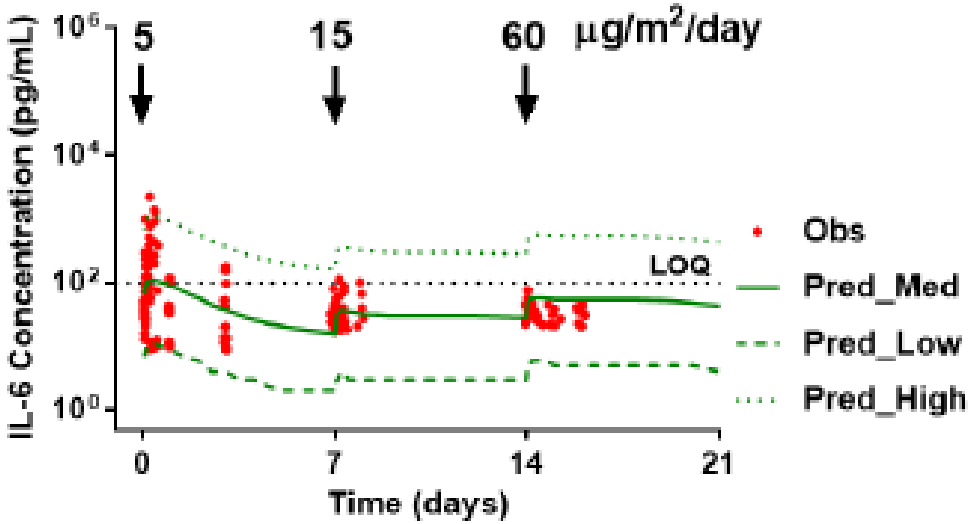
Jiang X, et al. Eur J Pharm Sci. 2020;146:105260.

Dosing information & raw data obtained from Hijazi Y, et al., (2018) Curr. Clin. Pharmacol. 13, 55–64.

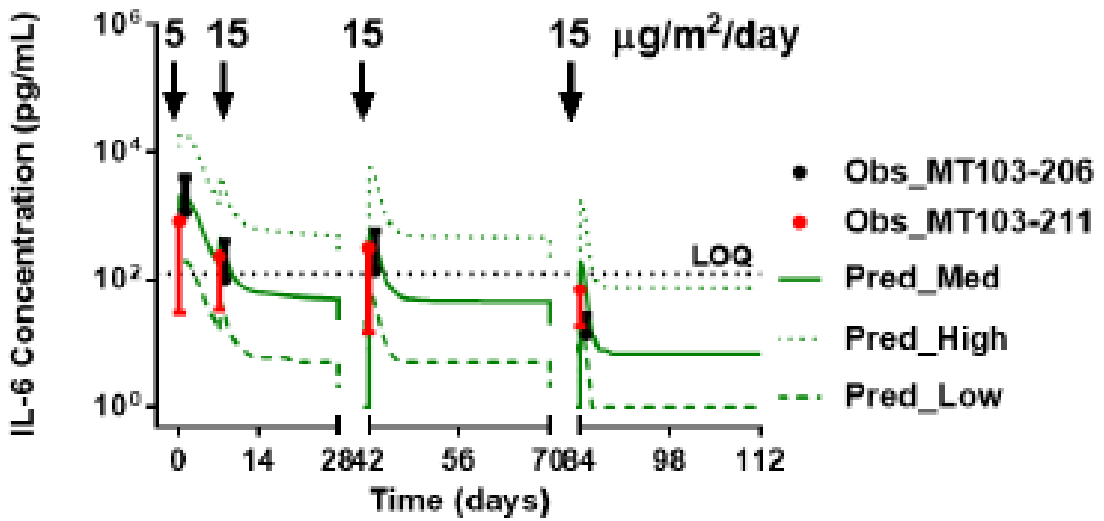
Extrapolation Among Different Patient Subpopulations

- By modifying disease-specific parameters, the model developed with cytokine data of blinatumomab in NHL patients successfully predicted the increase in cytokine release in ALL patients

Model development (NHL)



Model prediction (ALL)



Jiang X, et al. Eur J Pharm Sci. 2020;146:105260.

Conclusions

- Biomarkers and mechanism-based models are powerful tools to bridge the gaps during translational research
- Although TE or RO does not guarantee efficacy, it is a quantifiable drug/target associated readout that can be used to facilitate rational dose selection
- Mechanism-based PK/PD model differentiates “drug-specific” vs. “system-specific” parameters and provides a way to extrapolate between systems and predict

Backups