A Modular PBPK–QSP Platform for Translational Modeling of Bispecific T-Cell Engagers

Carmine Schiavone(1), Wilbert De Witte (1), Alexander Kulesza (1), Stephan Schaller (1)

(1) esqLABS GmbH, Saterland, Germany

Presenter:
Carmine Schiavone

camine.schiavone@esqlabs.com

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Use of PKSim / MoBi for new biologics modality "first-in-human" trial design

Introduction

Bispecific T-cell engagers are being developed for oncology and other indications, but early-stage development is challenging because of large design spaces, non-linear pharmacodynamics, and limited translatability from animal models [1,2]. Our aim is to provide a modular PBPK–QSP platform implemented in the Open Systems Pharmacology suite to support translational decisions for programs targetin CD3 expressing cells. This work builds on a previously published whole-body PBPK–QSP framework that represents antibody and T-cell biodistribution and trimer (CD3–drug–target) formation [3], adapted here for rapid assembly and reuse.

Methods

We first built a baseline whole-body PBPK model in PK-Sim, defining drug properties, antibody format, system physiology, and explicit targets in relevant tissues such as CD3 on T cells and the specific target. This baseline captures distribution, blood and lymph flows, and nonspecific clearance. We then exported that model to MoBi and migrated selected physiological processes and extended the model to obtain four reusable modules: Renal Clearance, Trimer Formation, Cytokine Response, and Target-mediated Internalization. The modules share a common interface that reads concentrations and receptor levels and returns occupancies, internalization fluxes, and cytokine trajectories. This enables rapid assembly of new scenarios without changing the PBPK core provided by PKSim. Figure 1 shows the workflow from PK-Sim to the MoBi module library. Figure 2 provides the mechanistic view of the Trimer and Cytokine modules.

The Trimer Formation module builds bivalent binding on each cell and then the ternary complex between a CD3-positive T cell and a target-positive cell. The Cytokine Response module converts the engagement signal into cytokine production with zero-order synthesis and first-order decay, and includes a receptor-limitation term and a feedback inhibition term driven by cytokine exposure. Together these modules turn target engagement into a time course of cytokines that feeds dose and regimen design.

Scenario simulations are created by selecting modules and parameter sets suited to the question at hand such as tumor or autoimmune indication, affinity variants, or step-up dosing. We then calibrate to clinical pharmacokinetics and pharmacodynamic markers, validate against held-out endpoints, and run virtual populations to explore variability. Outputs include tissue exposure, trimer occupancy, internalization rates, and cytokine time courses, which we use for dose selection and regimen design.

Results

The framework predicts plasma concentrations across species and dosing regimens using parameters set a priori from literature and platform defaults, with no fitting. In chimpanzee simulations of blinatumomab given as scaled IV bolus doses 0.06, 0.10, 0.12 µg/kg, the predicted time courses align with observed profiles over multiple cycles and capture the rapid distribution phase and the steep decline between infusions. The configuration uses the modules Renal Clearance, Trimer Formation, Cytokine Response, and Internalization. In mice, a 150 kDa IgG-like molecule given as a 1 mg/kg IV bolus is reproduced by modifying FcRn binding while leaving the PBPK core unchanged. The predicted profile matches the observed magnitude and slope over the first 72 hours. Together these examples show that the module library transfers across species and formats and that small mechanistic changes enable forward prediction without recalibration. Figure 3 summarizes these results.

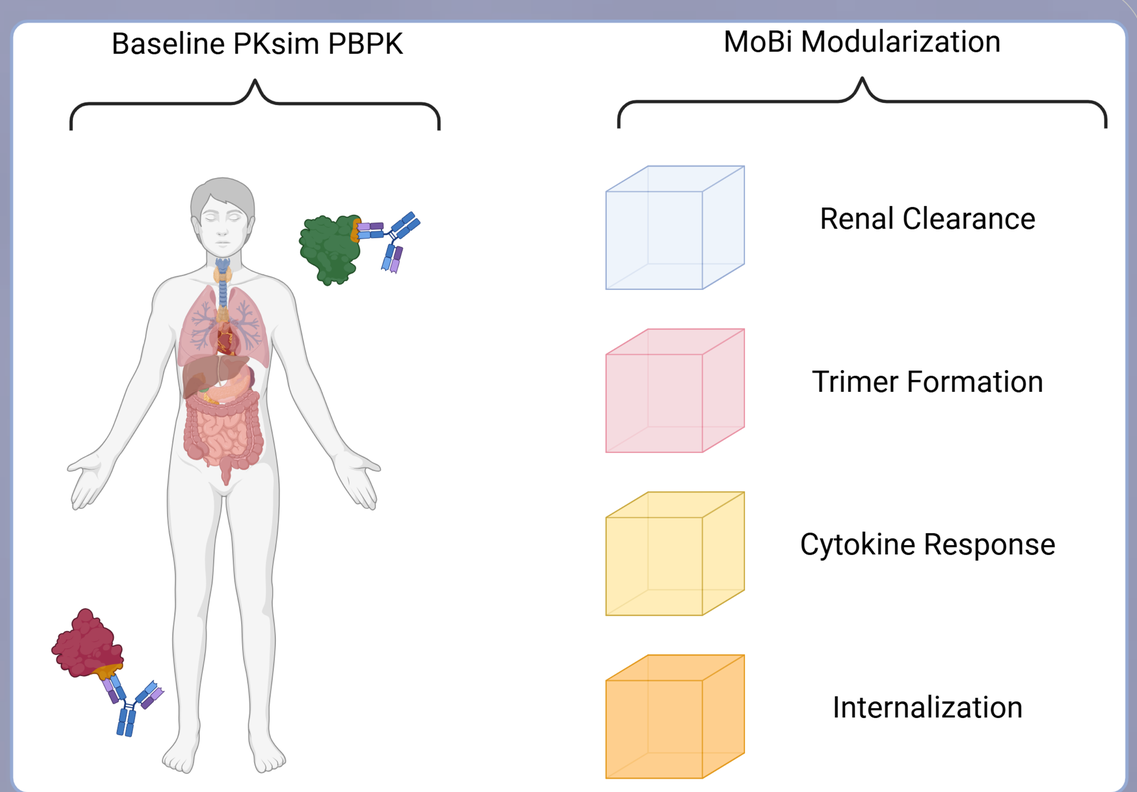
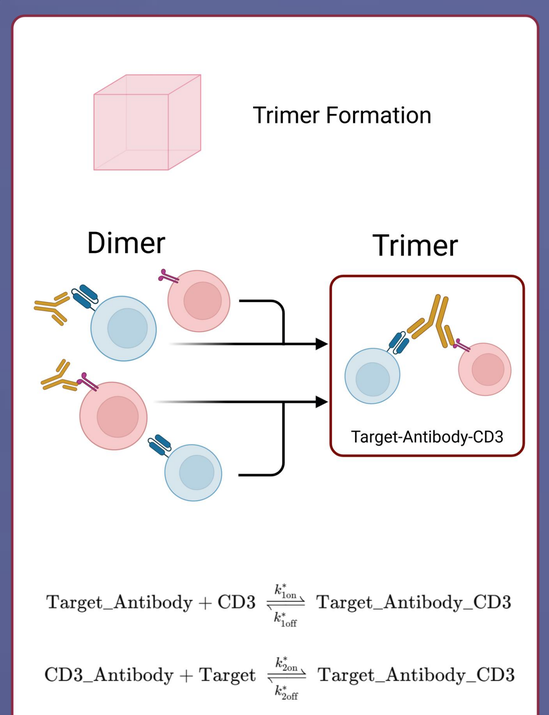


Figure 1: Baseline PBPK in PK-Sim on the left shows the human system with drug and targets. On the right the MoBi view shows four reusable modules named Renal Clearance, Trimer Formation, Cytokine Response, and Internalization. The figure conveys export from PK-Sim to MoBi and reuse of the same PBPK core while switching pharmacology modules to build scenarios.



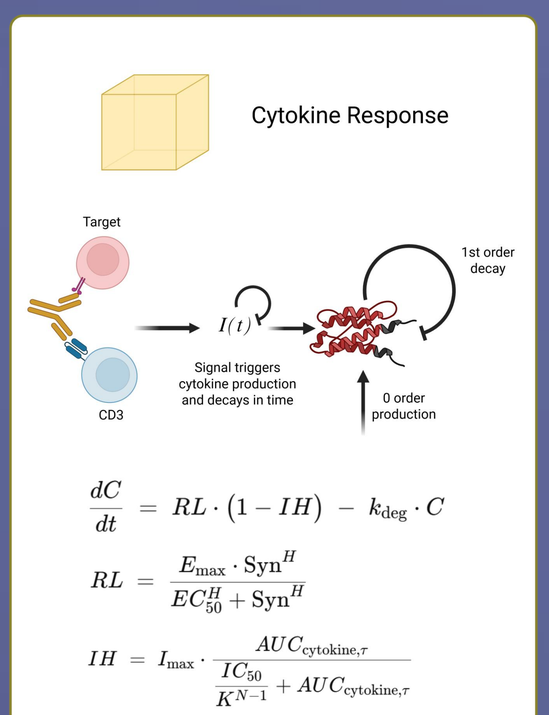


Figure 2: The left panel illustrates dimer formation on each cell followed by creation of the ternary complex between a CD3-positive T cell and a target-positive cell. The right panel shows how target engagement drives a time-varying input that triggers cytokine synthesis at zero order with first-order decay, with a receptor-limitation term and a feedback inhibition term linked to cytokine exposure. Together the panels summarize how engagement is translated into a cytokine time course.

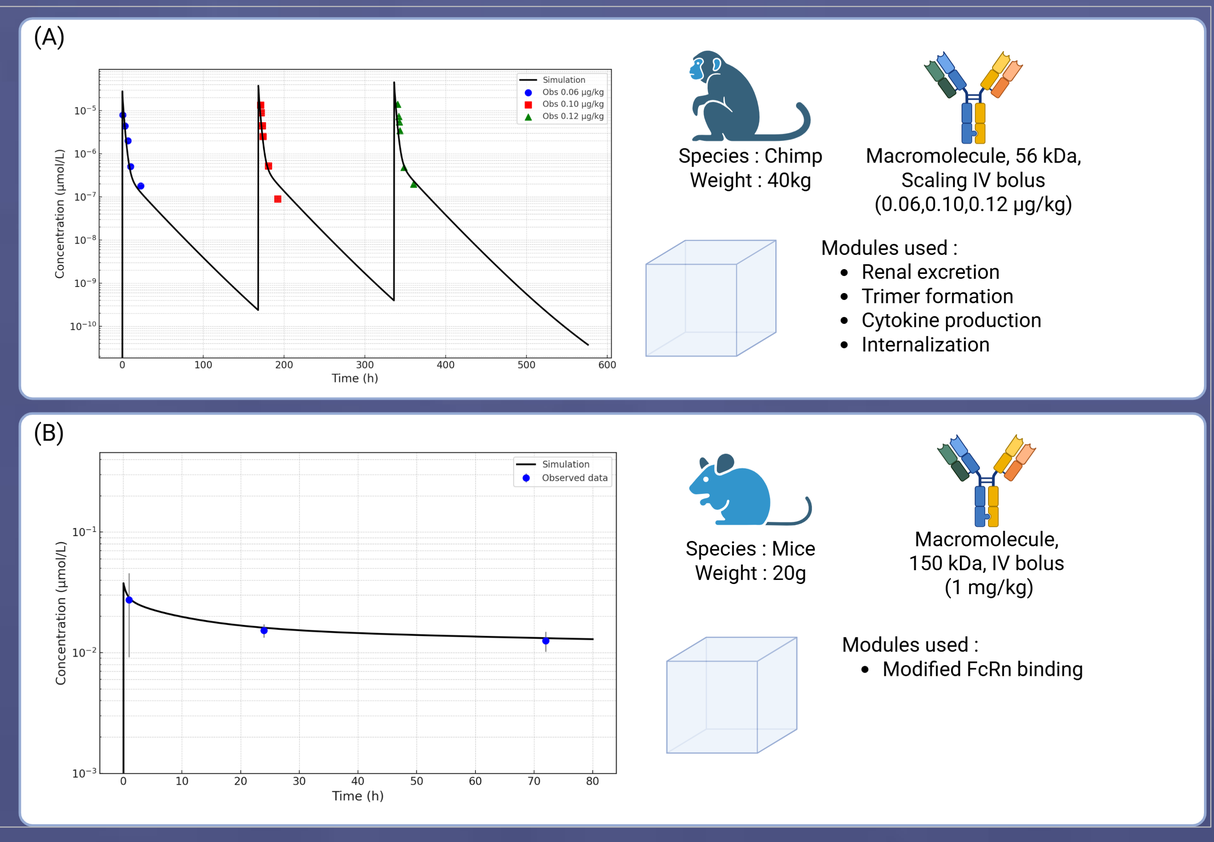


Figure 3: Predictions of plasma concentration. Panel A shows chimpanzee blinatumomab after scaled IV bolus doses with close agreement to observed data using the four core modules. Panel B shows the reproduction of Susilo's et al. paper using a 150 kDa IgG-like molecule in mice after a 1 mg/kg IV bolus. These examples highlight cross-species transfer and module utility

Conclusion

A modular PBPK–QSP platform in the OSP environment enables forward prediction across species and formats without ad hoc fitting and supports rapid scenario building by reusing a common PBPK core with switchable pharmacology modules. The results show that literature-based parameters and minimal mechanistic changes are sufficient to reproduce observed kinetics, which provides a practical path to dose selection and regimen design early in development. Ongoing work will extend the library and link cytokine dynamics more tightly to exposure and clinical readouts.

References

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Modeling Scaling Coding

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