Integrating Endogenous Ligand Competition into a Mechanistic Whole-Body PBPK Model of Therapeutic Monoclonal Antibodies

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Distribution of soluble endogenous ligands between plasma and tissues is critical for predicting tissue-level pharmacology.

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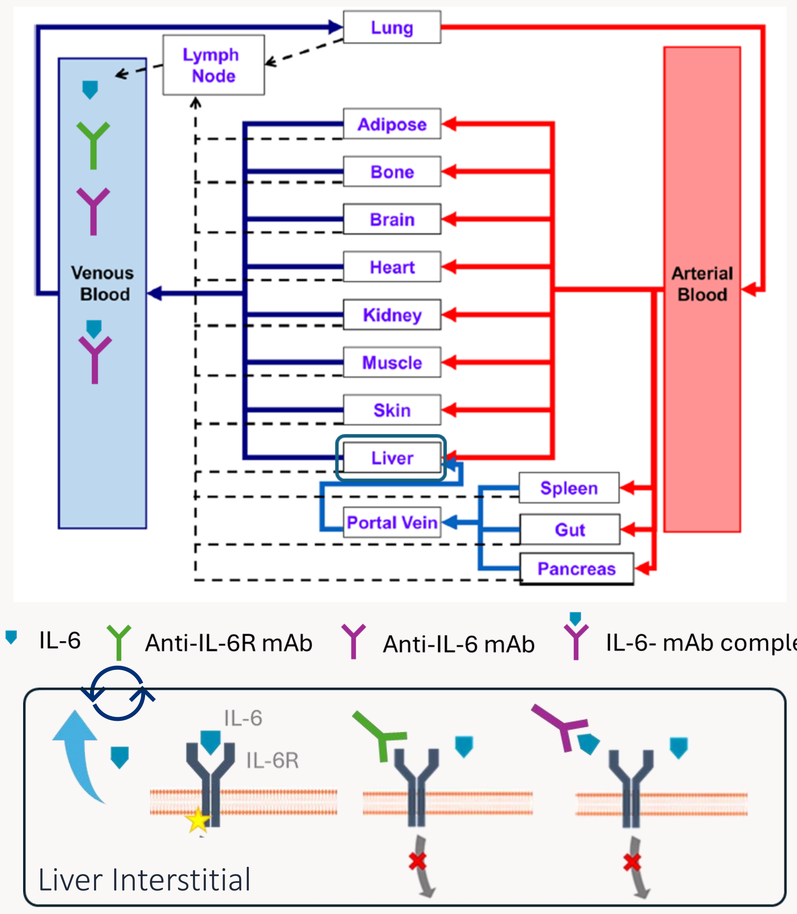
Background and Objective

Therapeutic monoclonal antibodies (mAbs) often modulate signalling by interfering with endogenous ligand–target interactions [1]. Although such competitive interactions may have minimal impact on systemic mAb PK, they can substantially influence tissue-level pharmacodynamic effect when soluble endogenous ligands distribute dynamically between plasma and tissues [2].

The objective of this work was to develop a mechanistic, whole-body PBPK framework that explicitly incorporates competitive binding between therapeutic mAbs and endogenous ligands, integrating mAb disposition, ligand turnover and distribution, and target engagement within a unified structure. The IL-6–IL-6R pathway was used as a representative example to predict hepatocyte IL-6–IL-6R complex dynamics following anti–IL-6 and anti–IL-6R therapy.

Methods

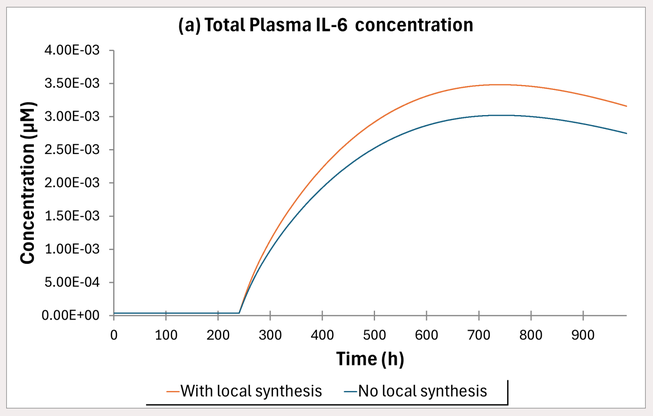
A mechanistic whole-body PBPK model was implemented in Simcyp Simulator V25 TP-Modulator, which is based on the full PBPK model of large molecules and designed to incorporate endogenous ligand-receptor interaction:

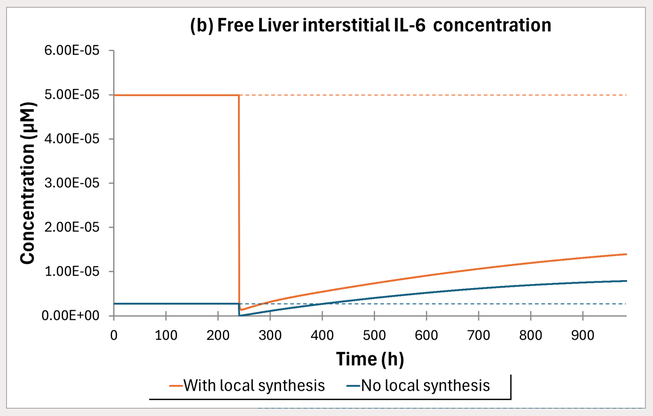


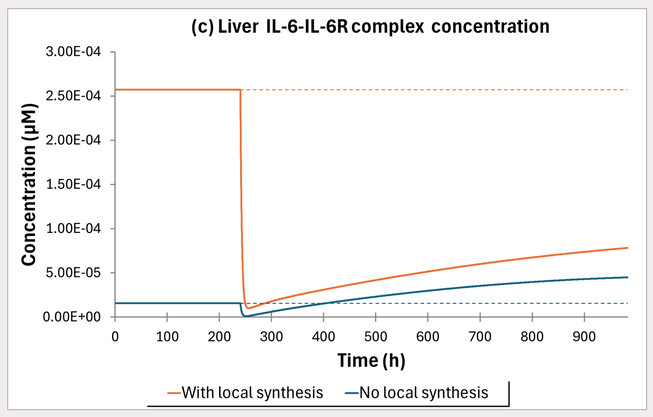
Steady-state tissue IL-6 and IL-6–IL-6R complex concentrations solved prior to mAb administration and used as initial conditions.

Results

ANTI-IL-6 mAb (soluble ligand targeting)

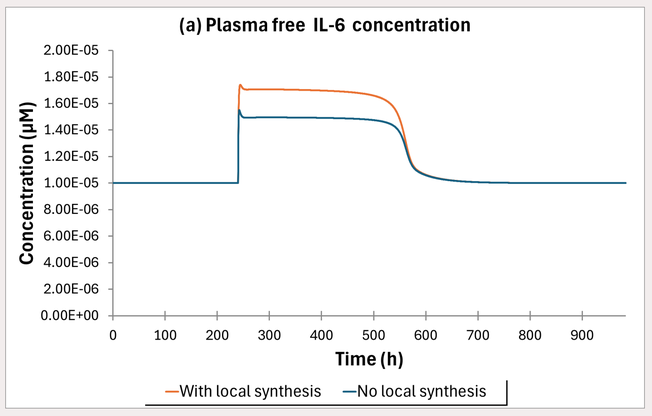


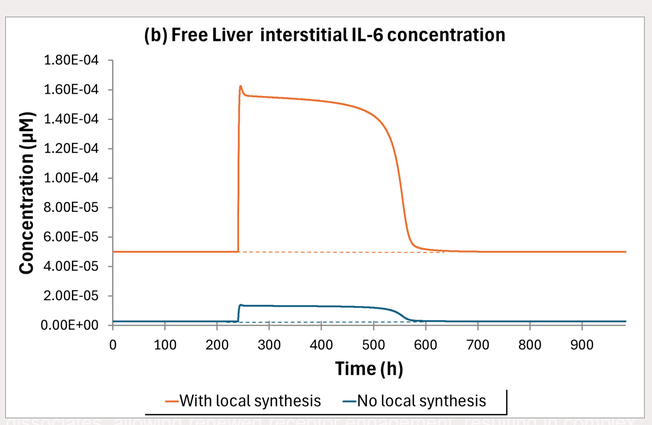


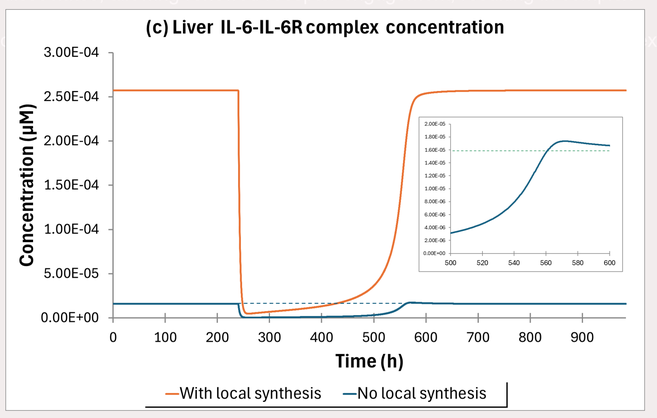


- System at steady state prior to mAb administration at Day 10
- Anti-IL-6 mAb prolongs IL-6 systemic persistence (a)
- Without local synthesis, accumulated IL-6 redistributes into tissues and dissociates, allowing renewed receptor engagement, resulting in complex rebound above the baseline (b) & (c)
- Local synthesis in liver drives redistribution to plasma and suppresses complex formation.

ANTI-IL-6R mAb (receptor targeting)







- Anti-IL-6R mAb displaces IL-6 from endogenous complexes, increasing circulating IL-6 (a) and (b)
- Without local synthesis, hepatic IL-6–IL-6R complex formation is initially suppressed, then recovered with a transient rebound, due to redistribution of systemic IL-6 (c)
- Locally synthesized IL-6 shows sustained suppression without rebound due to continued redistribution to plasma (c)

Discussion

This work demonstrates that explicit representation of endogenous ligand competition within a whole-body PBPK framework is critical for mechanistically predicting tissue-level target engagement. This work demonstrates that explicit representation of endogenous ligand competition within a whole-body PBPK framework is critical for mechanistically predicting tissue-level target engagement.

References

[1] Alaybeyoglu B et al. J Pharmacokinet Pharmacodyn (2021) 48(4):447-464.
[2] Wang W et al. AAPS J. (2014) 16(1):129-39.
[3] Wang L et al. Clin Transl Sci. (2022) 15(2):464-476.

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