Integrating in silico epitope prediction and mechanistic QSP modeling for benchmarking immunogenicity risk

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Objective

To develop a standardized framework for comparative immunogenicity risk assessment by integrating in silico epitope prediction and mechanistic QSP modeling. The framework is benchmarked against monoclonal antibodies with known anti-drug antibody incidences:

Tocilizumab	Trastuzumab
(negative control, <1% ADA)[1]	(positive control, ~10% ADA)[1]

Conclusions

We have established a predictive, systematic, and mechanistic approach for comparative ADA risk assessment of therapeutic proteins. The framework quantifies the progressive reduction in mAb exposure as ADAs emerge within a virtual population. Furthermore, this standardized workflow allows for the introduction of other mAbs to partition the response into multiple quantitative levels of immunogenicity, significantly enhancing the classification power for new drug candidates.

Background

The formation of Anti-Drug Antibodies (ADA) is a critical determinant of patient safety, pharmacokinetics, and therapeutic efficacy for monoclonal antibodies (mAb). To predict these risks, we utilized a Quantitative Systems Pharmacology (QSP) model of immunogenicity[2,3], implemented in MoBi. The model includes description of ADA response after either IV or SC administration, enabling a data-driven methodology for identifying critical T-cell epitopes and conducting virtual population simulations.

Methods

The multiscale QSP model simulates immune dynamics and ADA generation by integrating drug-specific factors (MHC-II epitope properties) with patient-specific factors (HLA genotypes and PK parameters).

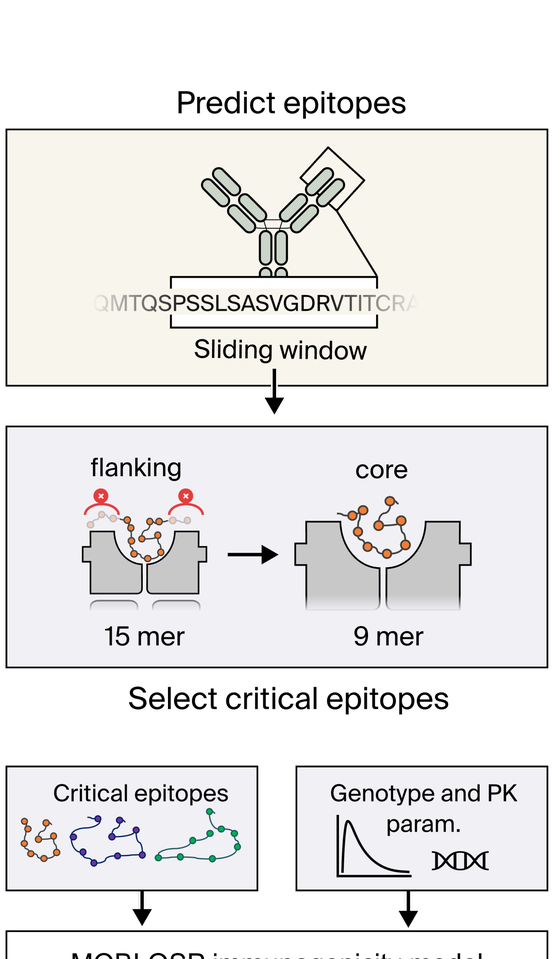
Epitope identification & selection

Identification

mAb sequences analyzed with NetMHCIIpan v4.3[4] to identify potential T-cell epitopes (9-mer binding cores + flanking regions).

Prioritization

Clustering by shared cores; selection based on binding affinity (BA) and HLA promiscuity across target populations.



Virtual population generation

Genotypes

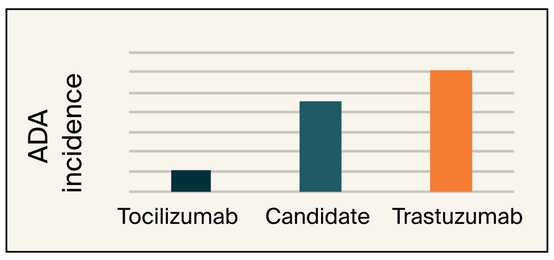
MHC-II receptor distributions sampled from donor databases to reflect HLA diversity.

Pharmacokinetics

Subject-specific PK parameters integrated from literature models to account for exposure variability[5,6].

Immunogenicity assessment

Quantitative prediction of immunogenicity incidence and magnitude within the virtual cohort.



Results

Tocilizumab (TCZ) and Trastuzumab (TSZ) sequences were analyzed according to the strategy outlined in Methods, and the two core sequence with highest MHC frequencies were used as epitopes for ADA predictions (Figure 1).

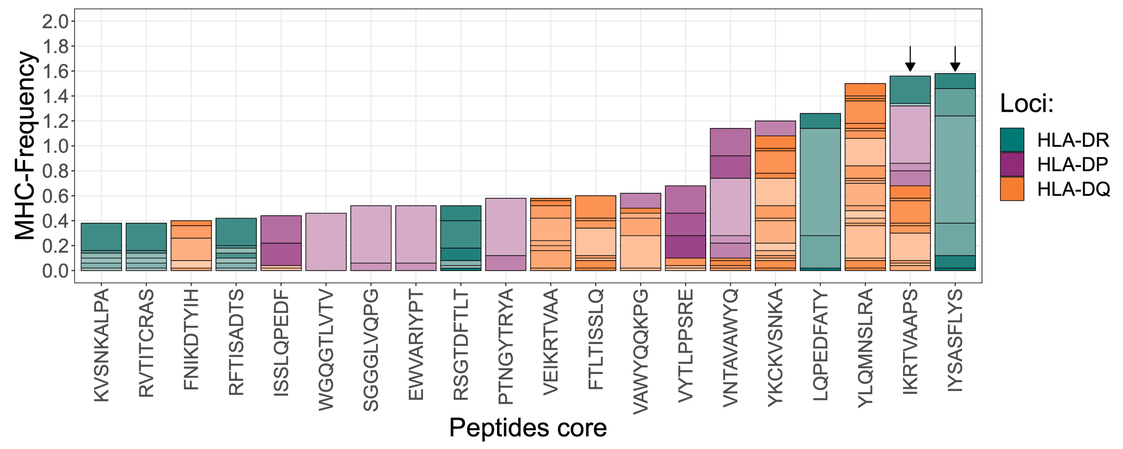


Figure 1. Distribution of TSZ epitopes by core sequence and their frequency in the donor population. The color coding of the bars indicates the MHC-II class to which each epitope binds, highlighting the promiscuity of binding across different MHC-II molecules. Only the top 20 epitopes are shown.

Simulations of a chronic intravenous dosing regimen (Figure 2) showed a clear differential immunogenic response, with TSZ exhibiting a higher incidence of ADAs and greater ADA-mediated clearance compared to TCZ, aligning with the observed clinical data.

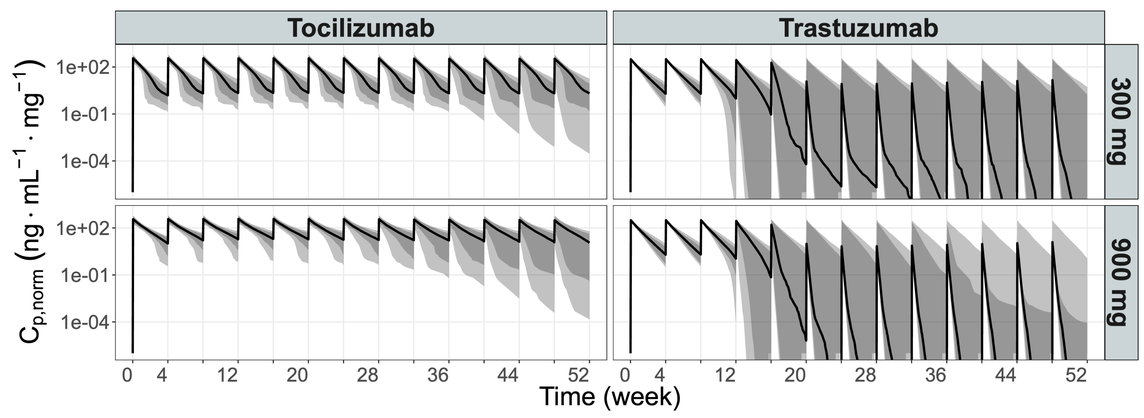


Figure 2. Predicted dose-normalized plasma concentration-time profiles over 52 weeks period of TSZ and TCZ IV administration. The solid line, dark shaded area and light shaded area represent the simulated median, the 10-90% quantiles and the 2.5-97.5% quantiles of the QSP model for a virtual population (n=200).

The C_{trough} fold reduction showed different ADA⁺ subpopulations (Figure 3).

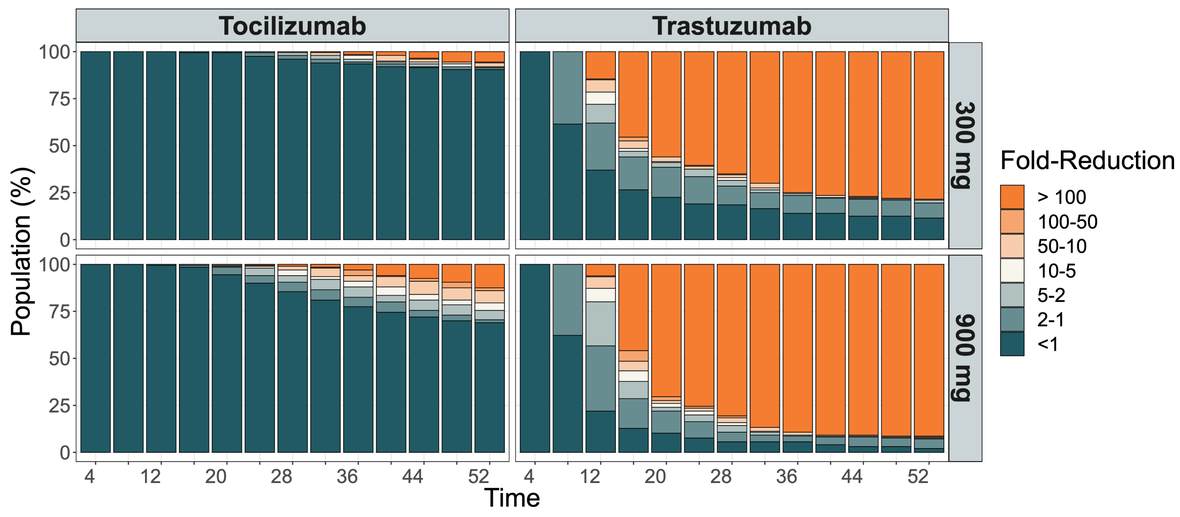


Figure 3. Percentage of virtual population showing varying degrees of C_{trough} reduction due to ADA following 300 mg or 900 mg q4w IV dosing over 52 weeks.

References

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