# Physiologically Based Pharmacokinetic Models for Infliximab, Ipilimumab, and Nivolumab Developed with GastroPlus® to Predict Hepatic Concentrations

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## OBJECTIVE

- Infliximab (IFX), ipilimumab (IPI), and nivolumab (NIVO) have been associated with hepatotoxicity.
- BIOLOGXsym™, a quantitative systems toxicology model, integrates hepatic interstitial concentrations with *in vitro* mechanistic toxicity data to predict the extent of liver toxicity.
- Physiologically based pharmacokinetic (PBPK) models can be used to make these exposure predictions.
- **The objective of this work was to use modeling and simulation to estimate liver concentrations after administration of three large molecules and validate in the absence of direct liver measurements.**

## METHODS

- Three separate PBPK models were developed in GastroPlus to simulate plasma and liver concentrations in healthy individuals and patients after administration of either IFX, IPI, or NIVO.
- **The models include distribution and clearance mechanisms specific to large molecules, FcRn binding dynamics, and target mediated drug disposition (TNF-α for IFX, CTLA-4 for IPI, PD-1 for NIVO). (Figure 1)**
- Observed plasma concentrations of each large molecule along with literature-informed parameter values were used to fit and validate the predicted plasma concentration from the PBPK models.
- Predicted liver concentrations of IFX, IPI, and NIVO were validated using previously reported data by Shah et al. [1]

## RESULTS

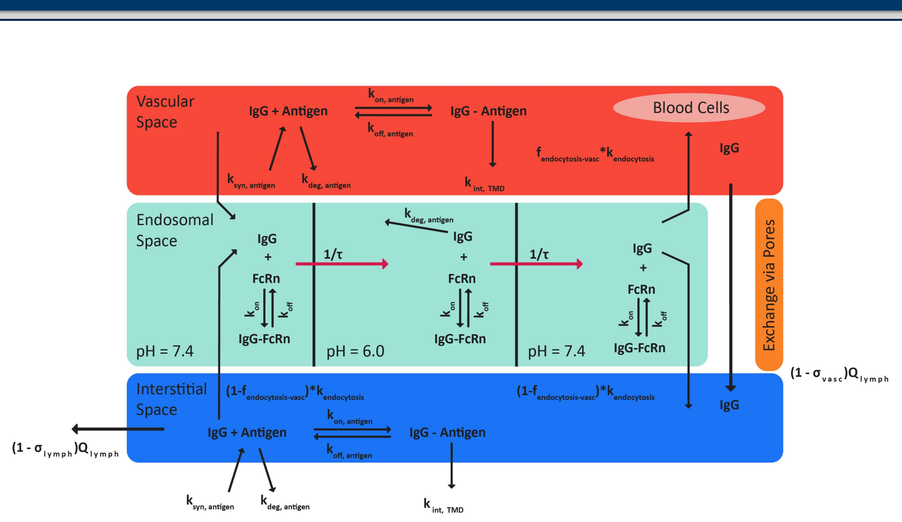


**Figure 1.** Schematic representation of processes impacting mAb distribution and clearance in GastroPlus PBPK model.

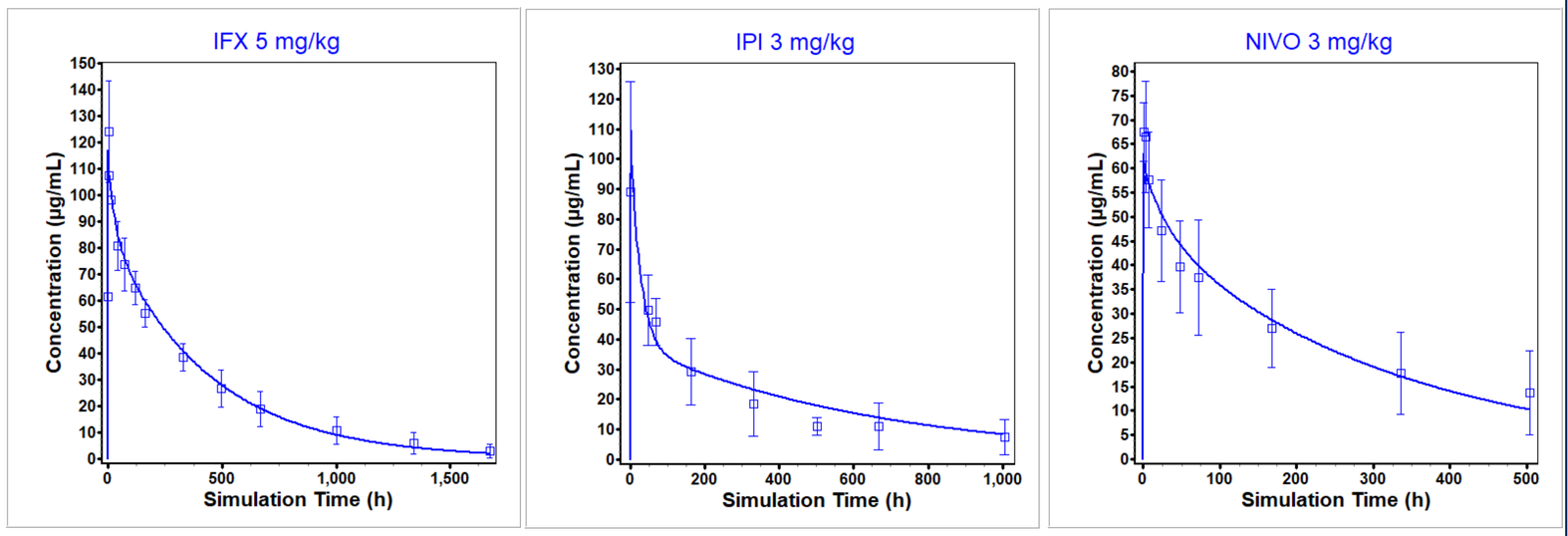


**Figure 2.** Examples of each model optimized to observed plasma concentration time profiles at clinical dosing levels for infliximab (left), ipilimumab (middle), and nivolumab (right). The observed data is given by the squares with variability bars and the mean model prediction is given by the solid line.

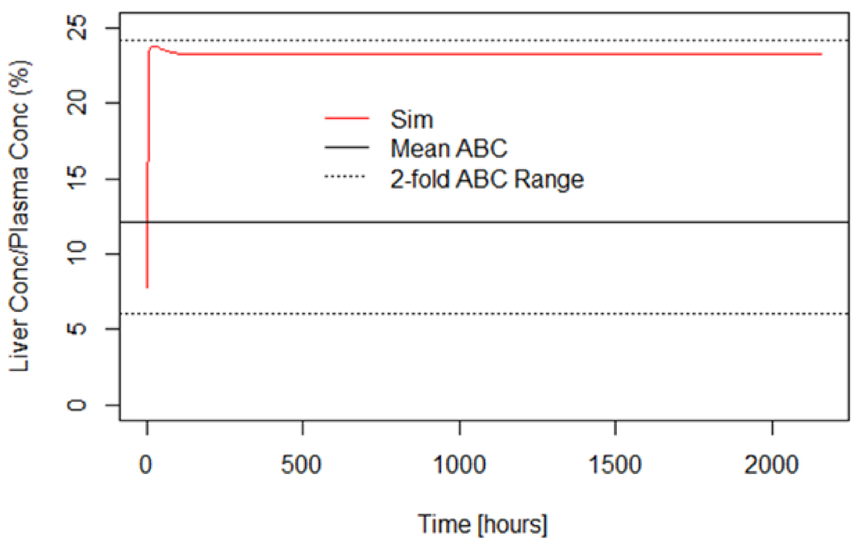


**Figure 4.** Simulated liver to plasma antibody biodistribution coefficient (ABC, red) falls within range of observed values across many species.

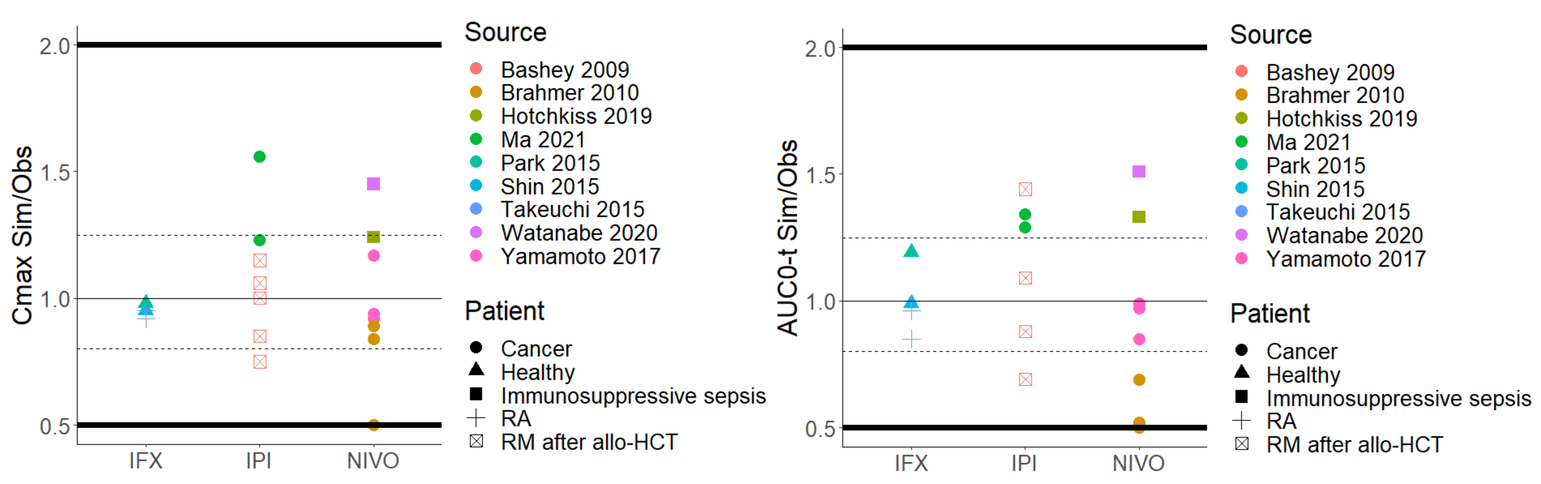


**Figure 3**. Ratio of simulated to observed for Cmax and AUC0-t for the optimization and validation data sets for each antibody. The solid line at 1 indicates no difference between simulated and observed exposure parameters. The dotted lines at 0.8 and 1.25 represent bioequivalence limits. The solid lines at 0.5 and 2 represent 2-fold change.

- The PBPK model for each large molecule was able to reproduce observed plasma concentration data in both healthy (when available) and patient populations including rheumatoid arthritis and patients with solid tumors (Figures 2 and 3).
  - Variation in health status (not explicitly represented in the PBPK models) may be a contributing factor to model discrepancies with the observed data.
- Liver concentrations were predicted to be between 10% (after Tmax) and 23% (at steady-state) of the plasma concentrations for each of the three drugs.
  - Results from Shah et al.[1] found that liver concentrations of monoclonal antibodies are linearly correlated with plasma concentrations and are estimated to be 12.1% of plasma concentrations (Figure 4).

## CONCLUSION

- Three separate PBPK models for IFX, IPI, and NIVO were developed using only plasma concentrations for optimization and validation.
- Not only were the models able to reproduce observed plasma concentration time profiles well within 2-fold of observed, but liver concentrations were also in line with expected estimations.
- These models will be useful for predicting hepatic exposure for use within BIOLOGXsym for making liver toxicity predictions.

## REFERENCES

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