QST Modeling Using BIOLOGXsym Informed by Liver Microphysiology Data Predicts Biologics Induced Liver Injury and Enhanced Susceptibility in MASLD

J.J. Beaudoin[1,*], L. Clemens[1], L.A. Vernetti[2], M.T. Miedel[2], M.W. Castiglione[2], D.L. Taylor[2], F. Huizar[1], C. Vallejo[1], C.I. Sandefur[1], M. Kelley[1], V.V. Lakhani[1], C. Battista[1], S.Q. Siler[1], K. Yang[1], L.K.M. Shoda[1]

[1]Strategic Consulting Services, QSP Solutions, Simulations Plus Inc., Research Triangle Park, NC, United States; [2]Organ Pathobiology and Therapeutics Institute, University of Pittsburgh, Pittsburgh, PA, United States

***CONTACT INFORMATION:** james.beaudoin@simulations-plus.com

SimulationsPlus

BACKGROUND

Drug development has grown to include biologic treatments that address a range of unmet medical needs. However, biologics may induce liver injury, particularly in contexts such as metabolic dysfunction-associated steatotic liver disease (MASLD), which has been associated with increased susceptibility to drug-induced liver injury (DILI)[1,2]. While quantitative systems toxicology (QST) modeling integrating mechanistic in vitro data has been successfully applied to mitigate small molecule DILI[3-5], biologic-induced liver injury (BILI) presents distinct challenges due to extracellular target engagement and involvement of non-hepatocyte cell types. Microphysiological systems offer a means to capture these complexities. Here, mechanistic outputs from a microphysiological system are leveraged in a QST model to predict BILI risk in healthy and MASLD patients for a range of biologics.

METHODS

- BIOLOGXsym is a QST model developed in MATLAB 2021a to simulate BILI liabilities by mathematically representing relevant hepatic biochemistry, physiology, and biologics-specific mechanisms (e.g., inhibition of IL-6 signaling by tocilizumab)[6] (**Figure 1**)
- Mechanistic toxicity readouts from 10-day experiments using the Liver Acinus MicroPhysiology System (LAMPS, **Figure 2**)[7] were generated following treatment with biologics with and without known BILI liabilities (glial growth factor 2 (GGF2), tocilizumab, ipilimumab, nivolumab, infliximab, bevacizumab[8,9]) and used as BIOLOGXsym inputs
- Physiologically based pharmacokinetic models developed in GastroPlus v9.8 were used to simulate hepatic interstitial exposures at clinically relevant dosing[6,10]
- Simulations were conducted using virtual populations of normal healthy volunteers (NHV SimPops, n=285) and MASLD patients (MASLD SimPops, n=263)

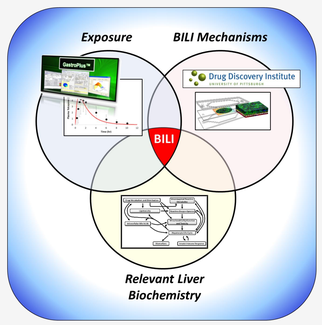

Figure 1. BIOLOGXsym modeling integrates liver exposure predictions, hepatotoxicity mechanisms, and a mathematical representation of liver biochemistry and physiology.

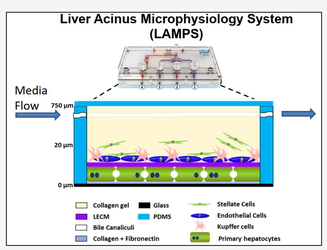

Figure 2. The LAMPS is an experimental platform to assess drug efficacy and safety. Schematic diagram of the LAMPS showing the 4 liver cell types (hepatocytes, Liver Sinusoidal Endothelial Cells [LSECs], stellate and Kupffer cells) organized into a complex, 3D biomimetic of the human liver.

RESULTS

- BIOLOGXsym simulations integrating LAMPS-derived toxicity mechanisms (**Table 1**), liver exposure, and the NHV SimPops predicted plasma alanine aminotransferase (ALT) >3 × upper limit of normal (ULN) in a percentage of patients for biologics with known clinical BILI liabilities, including GGF2 (Sim: 0.7%, Data: 4.6%), tocilizumab (Sim: 8.8%, Data: 0.7-33.8%), ipilimumab (Sim: 15.1%, Data: 10.9%), nivolumab (Sim: 0.7%, Data: 1.4-1.5%), and infliximab (Sim: 0.7%, Data: 0.7%) (**Figure 3A**)
- For the negative control bevacizumab, no mechanistic LAMPS signal was observed, and no ALT elevations were simulated
- While 19.4% of the MASLD SimPops exhibited baseline ALT >3 × ULN (no drug treatment), higher frequencies of ALT elevations were predicted following treatment with most BILI-associated biologics, including tocilizumab (71.5%), ipilimumab (67.7%), nivolumab (76.0%), and infliximab (30.8%), supporting the hypothesis that MASLD increases susceptibility to BILI (**Figure 3B**)

Biologic (Exposure in LAMPS Assays)	Oxidative Stress	Mitochondrial Dysfunction	Bile Efflux	Secretome GCDCA	BSEP Protein
GGF2 (10, 100, 382 ng/mL)	**, †††	·, †	*, ††	***, ‡	N/A
Tocilizumab (1.6, 5 µM)	***, †††	—	—	—	N/A
Ipilimumab (0.557, 2.06 µM)	—	***, †††	**, ††	—	—
Nivolumab (0.92, 3.30 µM)	***, †††	*, †	·, †	**, †	—
Infliximab (30, 147 µg/mL)	**, ††	**, ††	***, †††	**, †	—
Bevacizumab (165, 426 µg/mL)	—	—	—	—	—

Table 1. Summary of key mechanistic assay data from experiments with the LAMPS model. Significance levels of Bonferroni-adjusted *p*-values are denoted by asterisks (regression: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$) and obelisks (Dunn's test: † $p < 0.05$, †† $p < 0.01$, and ††† $p < 0.001$). Pink and red represent a significant decrease in one test and two tested concentrations, respectively. Light and dark green represent a significant increase in one test and two tested concentrations, respectively. White boxes with a dash indicate no statistically significant change. N/A: not available. Data accessible at https://eveanalytics.com.

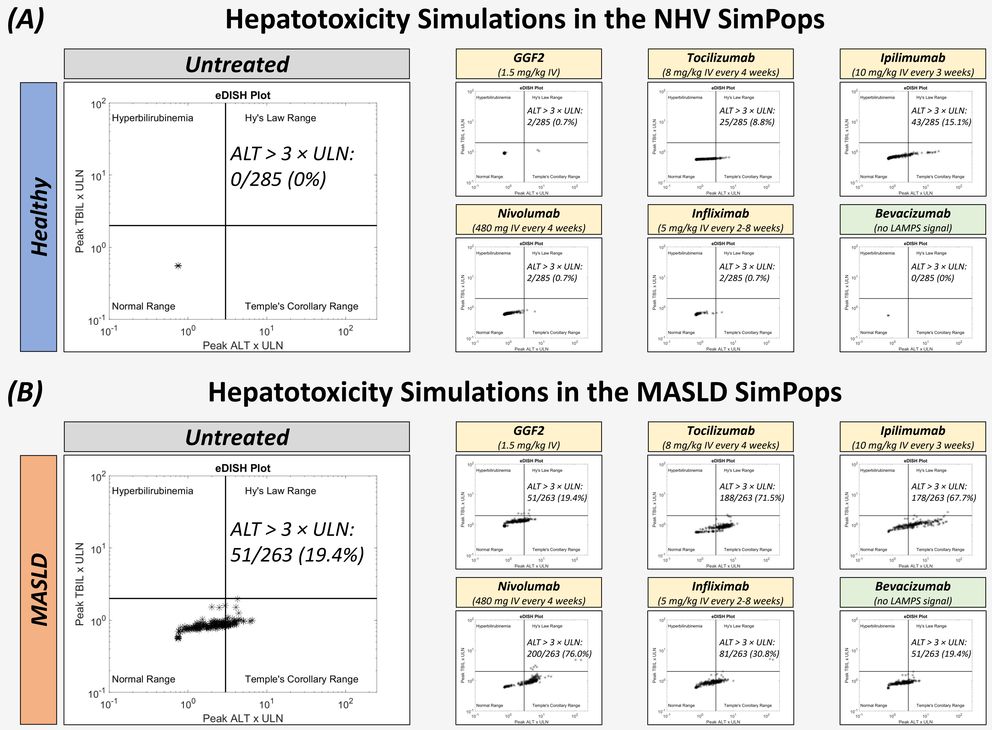

Figure 3. Simulated evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots for clinical protocols of biologics in the NHV SimPops (A) and MASLD SimPops (B)

CONCLUSION

These results demonstrate that QST modeling using BIOLOGXsym, informed by mechanistic LAMPS data, can predict clinically observed BILI liabilities for large molecules and identify increased risk in MASLD patients.

REFERENCES

[1]Fromenty. J Hepatol. (2013) 58 (4); [2]Sawada et al. J Gastroenterol Hepatol. (2020) 35 (6); [3]Woodhead et al. Xenobiotica. (2024) 54 (7); [4]Shi et al. Clin Pharmacol Ther. (2026) 119 (1); [5]Nielsen et al. Clin Pharmacol Ther. (2026) Online ahead of print.; [6]Beaudoin et al. Int J Mol Sci. (2023) 24 (11); [7]Taylor et al. Handb Exp Pharmacol. (2019) 260; [8]Vernetti et al. SOT 63rd Annual Meeting & ToxExpo, Salt Lake City, UT (2024); [9]Huizar et al. SOT 63rd Annual Meeting & ToxExpo, Salt Lake City, UT (2024); [10]Vallejo et al. Pharmaceutics (2025) 17 (3)

CONFLICT OF INTEREST

J.J. Beaudoin, L. Clemens, F. Huizar, C. Vallejo, C.I. Sandefur, M. Kelley, V.V. Lakhani, C. Battista, S.Q. Siler, K. Yang and L.K.M. Shoda are or were employees of Simulations Plus Inc., which received a National Institutes of Health Small Business Innovation Research Award in collaboration with the University of Pittsburgh Organ Pathobiology and Therapeutics Institute to develop a QST platform for the evaluation of liver injury induced by biologics.

ACKNOWLEDGEMENTS

This work was supported by NIH Award R44TR003535.

www.simulations-plus.com