

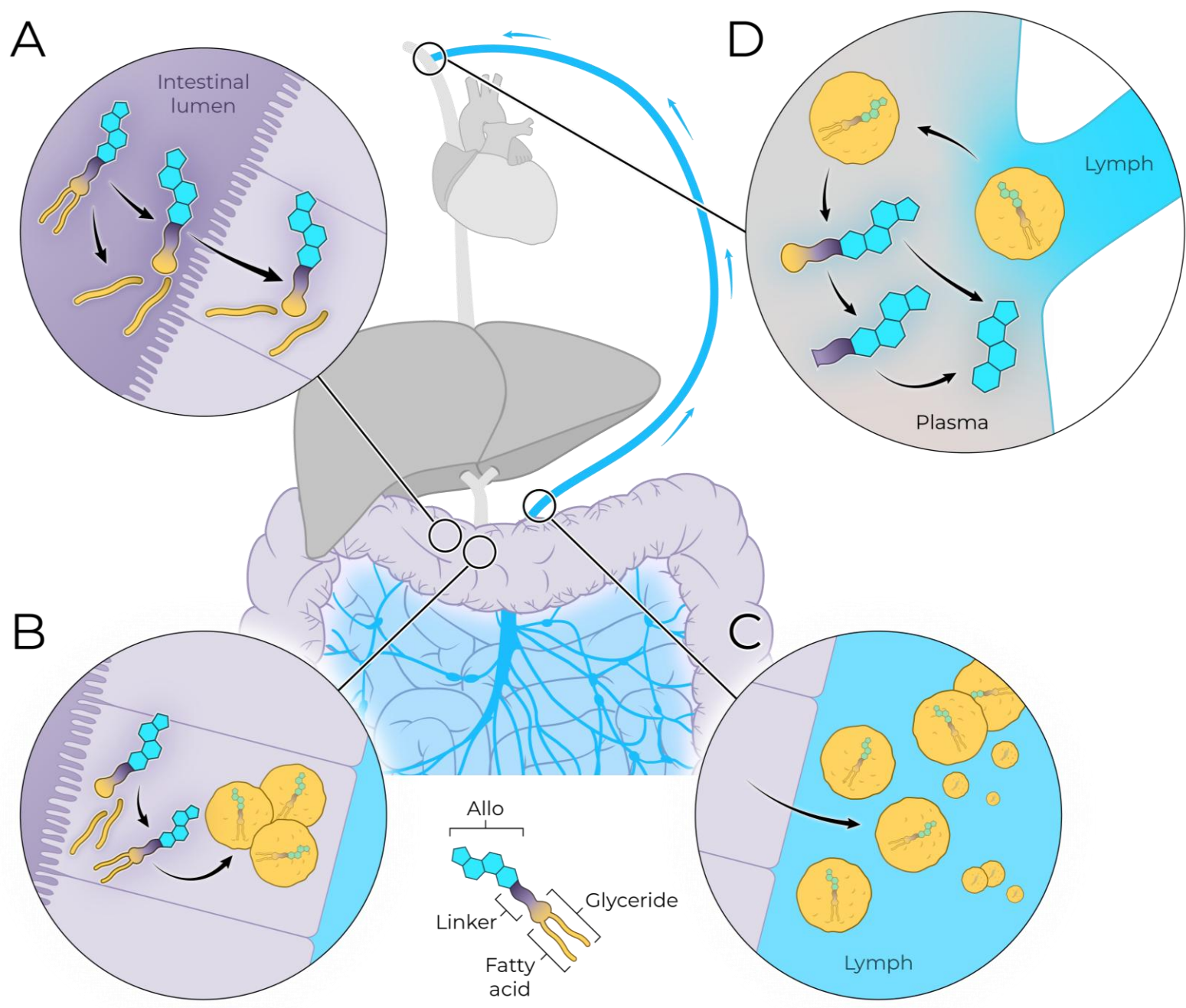
Development and Application of Physiologically Based Modeling of Lymphatic Absorption and Disposition of Allopregnanolone to Support of Model-Informed Drug Development of Lymphatic Glyph Prodrugs

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Introduction

- GlyphAllo™ (SPT-300 or Glyph Allopregnanolone) is an oral prodrug of allopregnanolone designed with the Glyph™ platform to overcome allopregnanolone's poor oral bioavailability due to substantial first-pass hepatic metabolism
 - Allopregnanolone is an endogenous neurosteroid that has been clinically validated as an antidepressant with anxiolytic and sleep-promoting effects
- The Glyph™ platform, a lymphatic-targeting prodrug technology, reversibly conjugates a drug of interest to a dietary fat molecule to shift absorption toward the intestinal lymphatics to address limitations of high first-pass hepatic metabolism, low oral bioavailability, and/or side effects
- Objective:** Here, we present the development of a physiologically based pharmacokinetic (PBPK) model to mechanistically describe intestinal absorption, lymphatic uptake, and the disposition of allopregnanolone following oral administration of GlyphAllo, and to use the model to enable translational and model-informed drug development applications

- (A) Glyph prodrug enters the intestinal lumen where it is hydrolyzed.
- (B) The hydrolyzed prodrug is re-esterified and assembled into chylomicrons.
- (C) The chylomicrons exit enterocytes and are taken up into the lymph for transport to the circulation.
- (D) The active moiety is released in plasma along with prodrug intermediates.



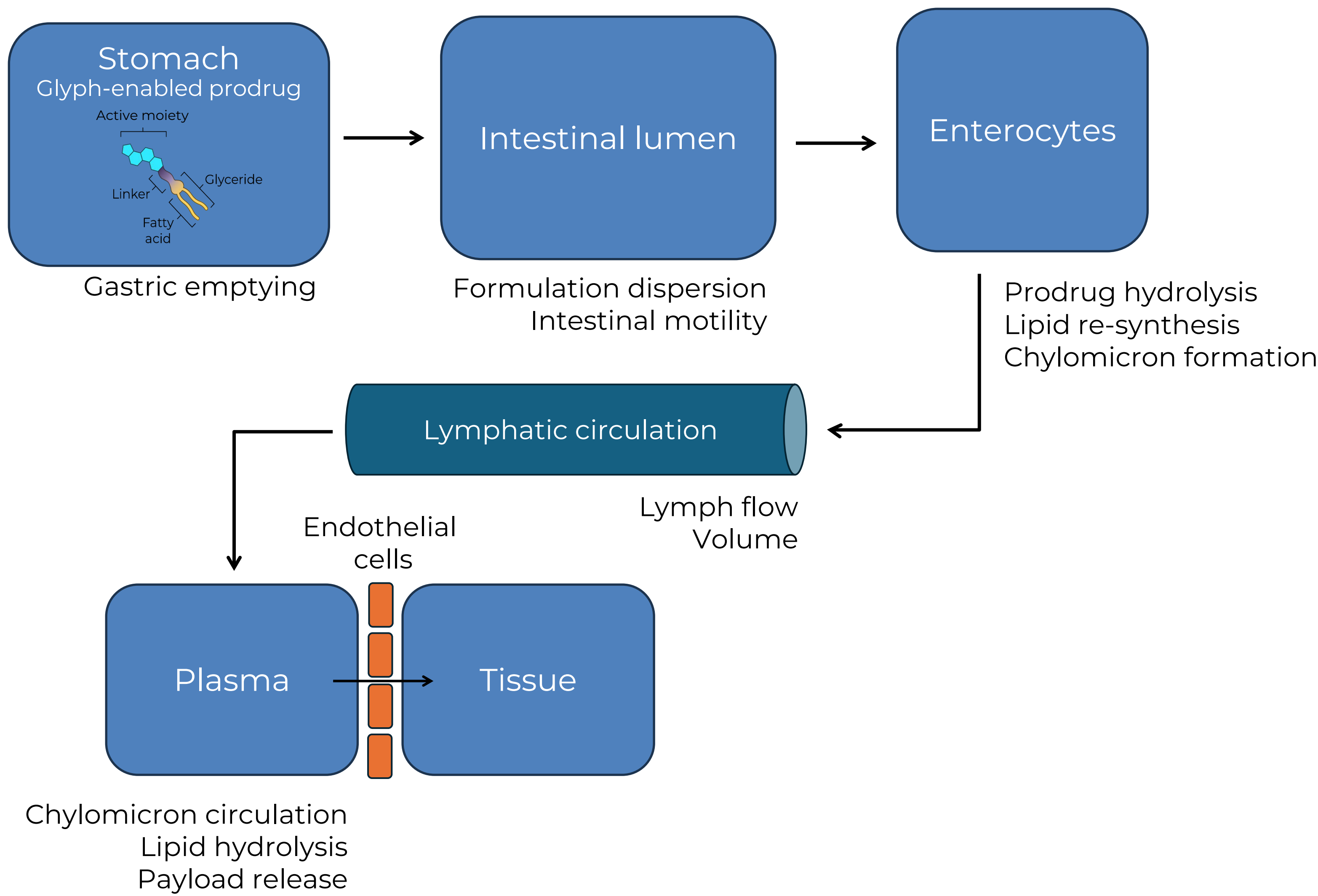
Methods

- A human PBPK model of lymphatic lipid handling was constructed with explicit representation of intestinal segments, mesenteric lymphatics, and thoracic duct transport
- To enable cross-species translation, rat and nonhuman primate physiology templates were also developed with species-specific intestinal and thoracic lymphatic trees
- Chylomicron formation and baseline transport into lymph were parameterized across intestinal regions and linked to oral absorption processes
- Recovery of drug mass from intestinal and thoracic lymphatic compartments was implemented using lymph flow and volume data from the literature¹⁻¹⁰ or allometrically scaled values
- All models were implemented, simulated, and verified in Mobi (Open Systems Pharmacology Suite)
- Model performance was evaluated using pharmacokinetic (PK) data from the phase 1 first-in-human trial of oral GlyphAllo in healthy volunteers (NCT05129865)¹¹ and previously published PK profiles of intravenous allopregnanolone¹²

Results

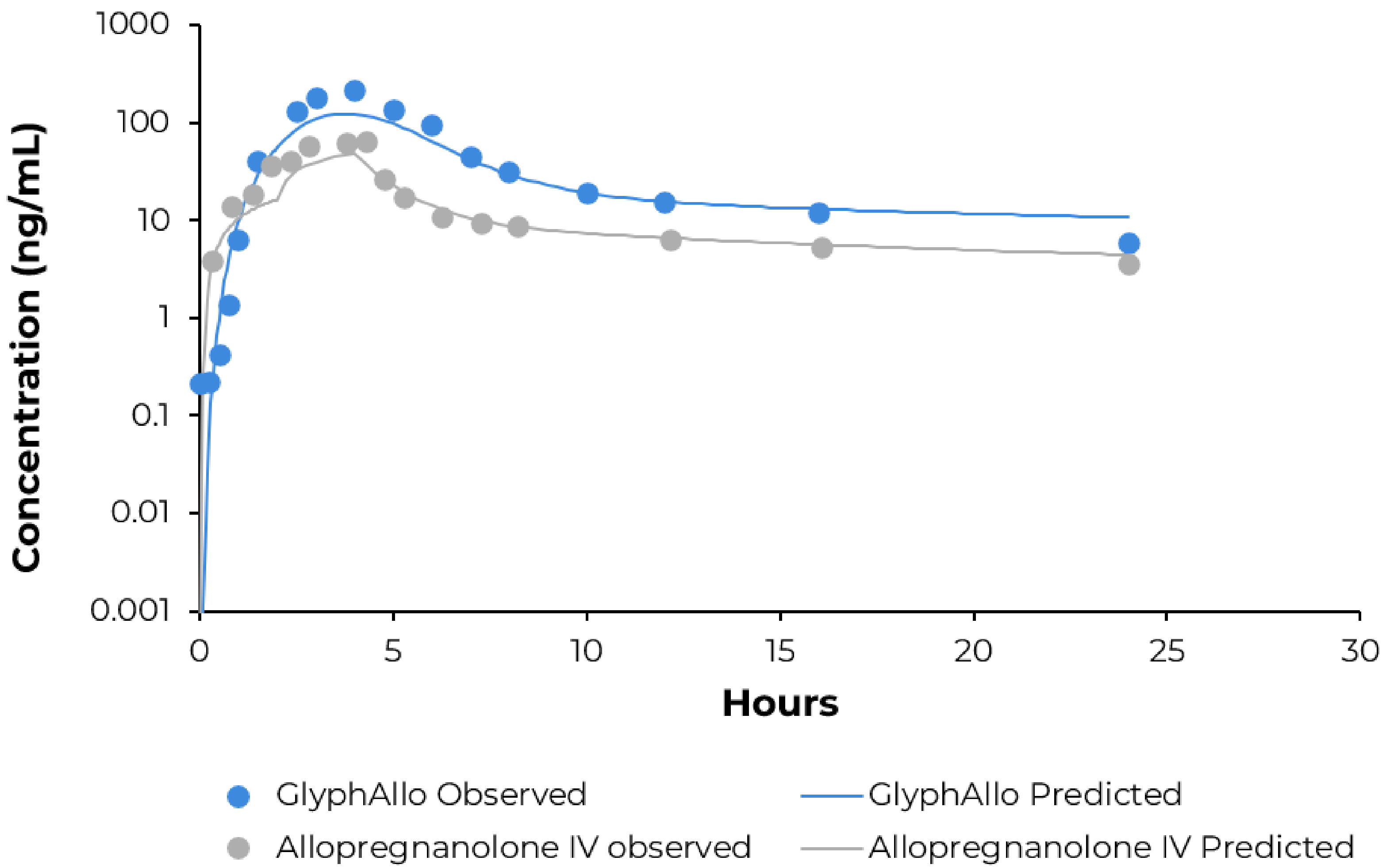
- A mechanistic whole body PBPK model was developed based on previously published literature and adapted to account for the lymphatic absorption of Glyph-enabled prodrugs (Figure 1) with the de-esterification and re-esterification of the prodrug occurring at the level of the enterocyte

Figure 1. PBPK Skeleton of lymphatic absorption for Glyph-enabled prodrugs.



- The PBPK model adequately predicted the plasma profiles for the observed data of allopregnanolone in all three species following oral administration of GlyphAllo and intravenous infusion of allopregnanolone, including the slow absorption process via the lymphatics (Figure 2)

Figure 2: Observed (dot) and PBPK model predicted (line) plasma allopregnanolone profiles following oral GlyphAllo administration (blue) and intravenous infusion of allopregnanolone (gray) in humans.



Conclusions

- The development of this PBPK model provided a mechanistic and translational framework for visualizing and quantifying lymphatic drug transport of allopregnanolone following oral administration of GlyphAllo
 - The results from this model are consistent with the ability of the Glyph platform to bypass first-pass metabolism through lymphatic absorption, addressing allopregnanolone's limitation of low oral bioavailability
- Results may support the interpretation of clinical PK, dose optimization, cross-species translation, and model-informed drug development of GlyphAllo and other Glyph-enabled prodrugs in development

Funding sources: This study was supported by Seaport Therapeutics. ClinicalTrials.gov Identifier: NCT05129865.

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Disclosures: KG, JSS, DKB, and MCC are employees of Seaport Therapeutics. CEG and GM are employees of Mammoth Preclinical.

Presented at the American Conference of Pharmacometrics; Oct 11-14, 2026; Oxon Hill, MD.

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