PREDICTION OF HUMAN CLINICAL PHARMACOKINETICS BASED ON *EX VIVO* MODELS OF THE INTESTINE, LIVER AND KIDNEY COMBINED WITH PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING

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INTRODUCTION

Accurate prediction of absorption, distribution, metabolism and excretion (ADME) is essential during preclinical drug development but remains challenged by inadequate translational models and poor *in vitro-in vivo* extrapolation. *Ex vivo* models, particularly when combined with physiologically-based pharmacokinetic (PBPK) modelling, offer a promising approach by recapitulating *in vivo* tissue composition and transporter functionality.

AIM

Predict clinically relevant ADME parameters of four model drugs (digoxin, rosuvastatin, furosemide and metformin) using data from *ex vivo* porcine intestine, liver and kidney models integrated into a whole-body PBPK model.

METHODS

1) InTESTine™

- Various regions of porcine gastrointestinal mucosal tissue explants were incorporated into the InTESTine™ system, creating an intestinal barrier model ([1], Figure 1).
- Apical to basolateral transport (apparent permeability (P_{app})) of digoxin, rosuvastatin, furosemide and metformin was determined.

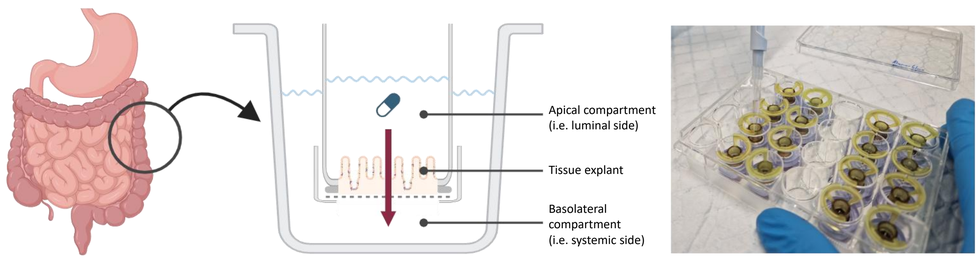

Figure 1. *Graphical representation and image of the InTESTine™ model.*

2) Combined *ex vivo* liver-kidney normothermic machine perfusion (NMP)

- Porcine liver and kidney were perfused through the portal vein, hepatic and renal artery with red blood cell-based perfusate, thereby facilitating production and collection of bile and urine ([2], Figure 2).
- Digoxin, rosuvastatin, furosemide and metformin were administered as a cocktail via a slow portal bolus to mimic oral absorption
- Compound uptake from perfusate, as well as biliary and urinary excretion, were quantified using liquid chromatography–mass spectrometry (LC-MS).

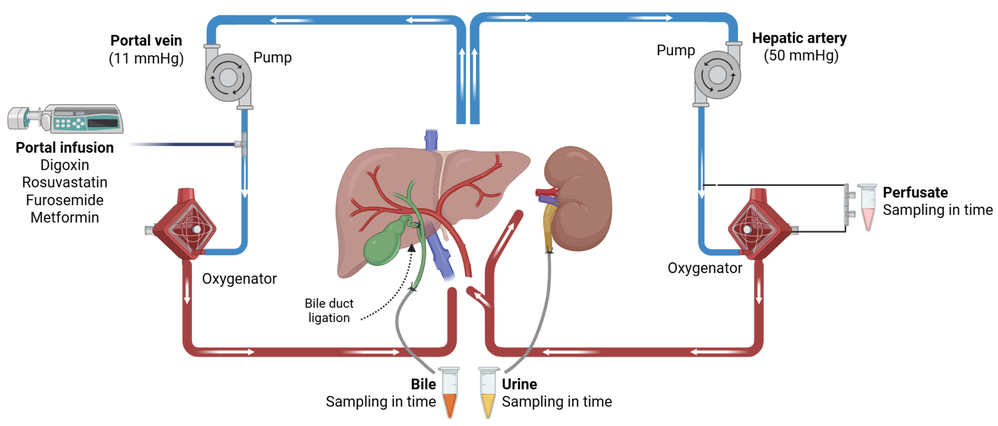

Figure 2. *Schematic representation of the combined liver-kidney perfusion setup using the LiverAssist™ device.*

3) PBPK model

- Intestinal P_{app} values together with biliary and urinary clearances, extrapolated from combined *ex vivo* liver-kidney NMP, were integrated into a PBPK model to predict plasma pharmacokinetics (AUC, C_{max}, T_{max}, Figure 3).

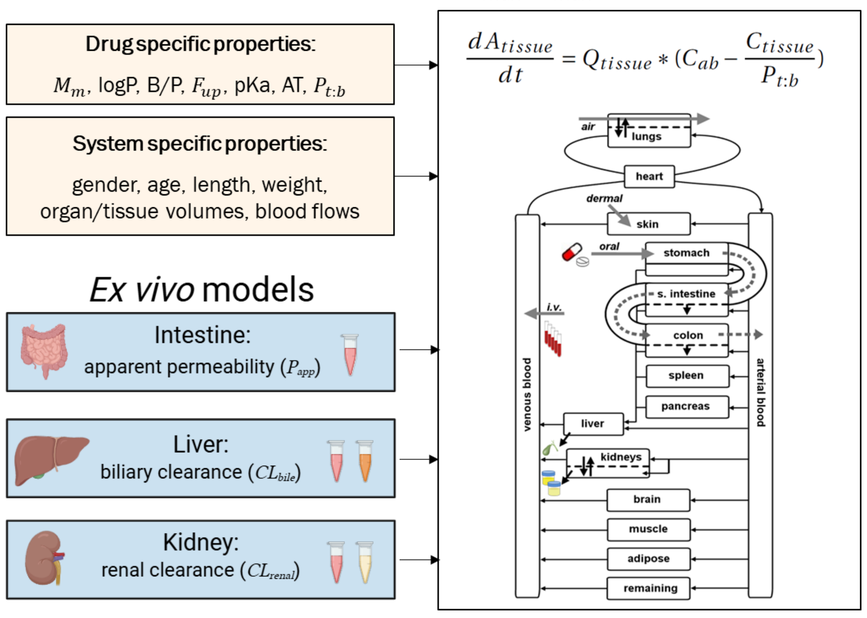

Figure 3. *Schematic representation of the PBPK model.*

References

[1] Stevens LJ et al., Eur J Pharm Sci. (2019) 1(137):104989
[2] Stevens LJ et al., Drug Metab Dispos. (2021) 49(9): 780-789

RESULTS

1) InTESTine™

- Observed P_{app} values ranged from 0.2 to 11*10^{-6} cm/s depending on compound and gastrointestinal region (Figure 4).

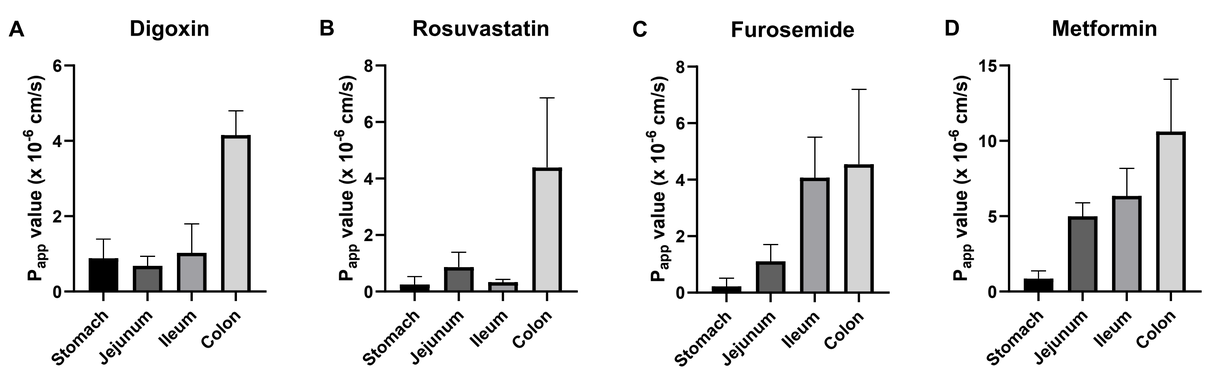

Figure 4: *Intestinal absorption presented as apparent permeability (P_{app}) of digoxin (10 µM, A), rosuvastatin (10 µM, B), furosemide (10 µM, C) and metformin (100 µM, D) across different regions of the gastrointestinal tract. Data represent mean ± SD (n=2).*

2) Combined *ex vivo* liver-kidney NMP

- Functional uptake from the perfusate observed for all model drugs (Figure 5).
- Digoxin and rosuvastatin showed predominant biliary excretion while furosemide and metformin were primarily excreted into urine.

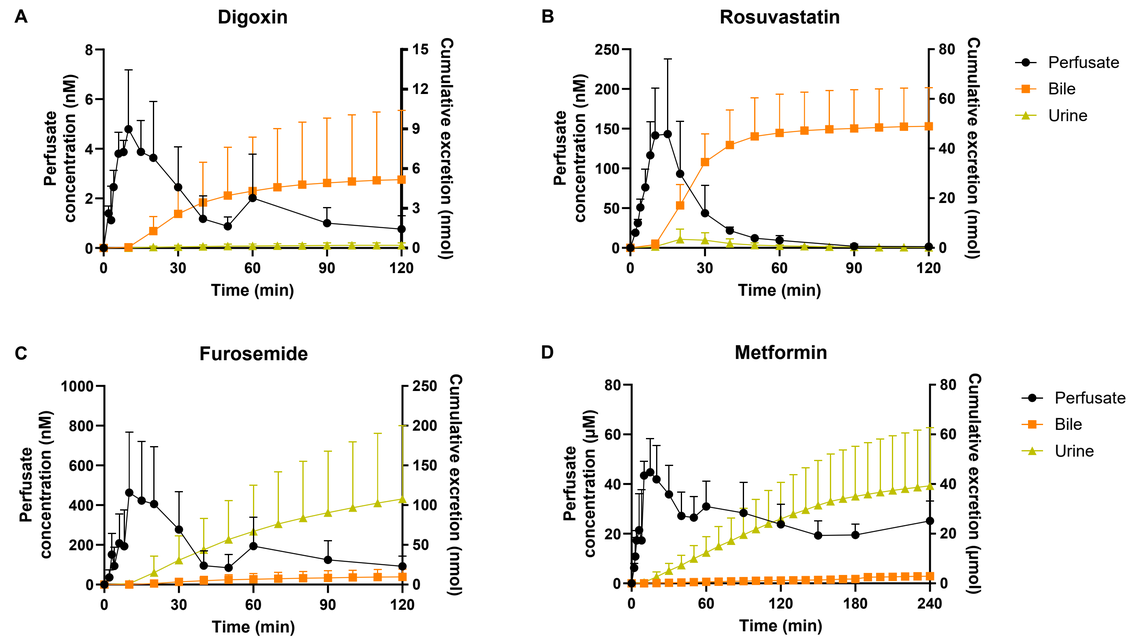

Figure 5: *Hepatic and renal clearance in combined ex vivo liver-kidney NMP following portal dosing of digoxin (0.056 mg, A), rosuvastatin (1.4 mg, B), furosemide (0.74 mg, C) and metformin (74.2 mg, D). Black lines represent perfusate concentrations, while orange and yellow lines represent cumulative biliary and urinary excretion, respectively. Data represent mean ± SD (n=4).*

3) PBPK model

- Incorporation of *ex vivo* ADME data from InTESTine™ and combined liver-kidney NMP enabled prediction of plasma pharmacokinetics (AUC, C_{max}, T_{max}, Figure 6).
- Preliminary results show reasonable agreement with reference clinical studies.

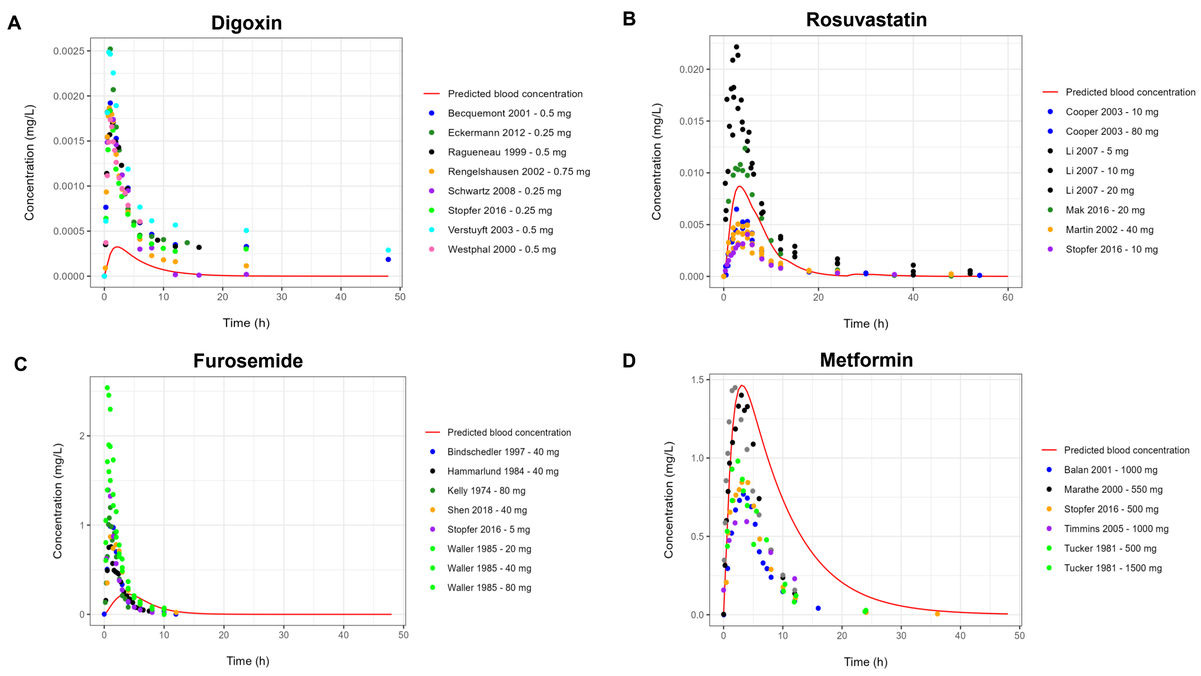

Figure 6: *Model-based predictions of concentration-time profiles for digoxin (A), rosuvastatin (B), furosemide (C), and metformin (D) generated using ex vivo-derived ADME data integrated into a PBPK model. Predicted curves (red line) were compared to human clinical observations (multi-coloured dots).*

CONCLUSIONS AND FUTURE PERSPECTIVES

- Integration of physiologically relevant *ex vivo* InTESTine™ and combined liver-kidney NMP within a generic PBPK framework provides a unique and powerful translational approach to predict ADME profiles.
- Next steps focus on advancing renal elimination (both experimental and computational) and expanding the platform to include intestinal microbial metabolism, drug-drug interactions and the impact of disease processes.