Using a Gut/Liver Microphysiological System to Predict Drug-Drug Interactions in Humans

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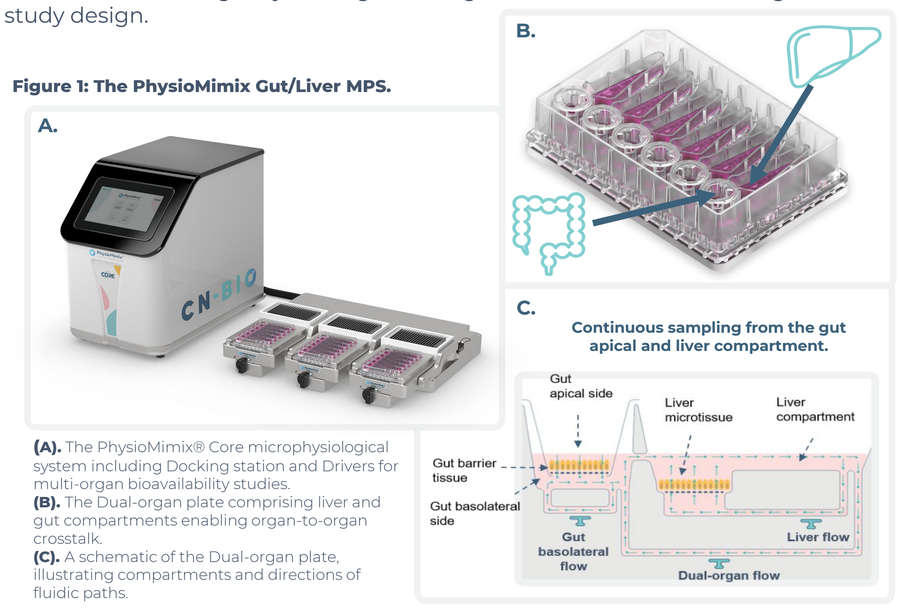
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Introduction

Drug-drug interactions (DDIs) are a major concern in patients with comorbidities who are treated with multiple medicines. Not only can this reduce therapeutic efficacy and cause toxicity issues, but interactions between different medicinal drugs can also affect metabolising enzyme or transporter activity. This in turn can then alter oral bioavailability, systemic exposure, and ultimately clinical outcomes[1].

Predicting DDIs before first-in-human studies remains challenging, particularly when both intestinal absorption and hepatic metabolism influence drug disposition[2]. Human-relevant microphysiological systems (MPS) enable the mechanistic study of gut and liver DDIs in a single interconnected fluidic system. Here, we present a Gut/Liver MPS combining primary jejunal epithelial cells (RepliGut® Planar) with human hepatocyte-derived liver microtissues (Figure 1) to investigate a broad range of enzyme and transporter DDIs across a range of compounds. This in vitro dual-organ approach resolves gut and liver DDI mechanisms in a single system, generating human-relevant data to guide dose selection and clinical study design.

Figure 1: The PhysioMimix Gut/Liver MPS.



(A). The PhysioMimix® Core microphysiological system including Docking station and Drivers for multi-organ bioavailability studies.
(B). The Dual-organ plate comprising liver and gut compartments enabling organ-to-organ crosstalk.
(C). A schematic of the Dual-organ plate, illustrating compartments and directions of fluidic paths.

Objectives

- Investigate P-gp transporter inhibition by studying the interaction between dabigatran etexilate and zosuquidar.
- Investigate CYP3A4 metabolic enzyme inhibition by studying the interaction between darunavir and ritonavir.
- Investigate CYP3A4 metabolic enzyme induction by studying the interaction between dabrafenib and rifampicin

Methods

Establishment of the Gut/Liver MPS: The primary Gut/Liver MPS was established by first seeding jejunum crypt epithelial stem cells (RepliGut®) onto Transwell® inserts in static conditions. Primary human hepatocytes (PHH) were seeded on collagen coated scaffolds within the Dual-organ plate for formation of 3D liver microtissues. Following 4 days post PHH seeding, Transwell® inserts were added into the gut compartments of the Dual-organ plates and fluidically connected to their respective liver compartment.

Drug dosing: Victim and perpetrator compounds (Table 1) were dosed in combination to either the gut apical (to stimulate oral dosing) or liver compartment (to stimulate IV dosing) immediately after establishment of the Gut/Liver MPS on day 4. Preparator drugs were additionally pre-dosed 24 hours before this, allowing time for the preparator to stabilise and take effect. Media samples were taken from each compartment at 0, 2, 6, 24, 48, and 72 hours before being sent to LC-MS/MS to generate time-course concentration data.

***In silico* modeling**: Time-course concentration data were used to support an *in silico* compartmental model predicting key ADME parameters, including hepatic clearance, intestinal absorption, and oral bioavailability with and without DDI.

Table 1 Drug concentrations used in the Gut/Liver MPS DDI study

Victim compound	Oral dosing concentration	IV dosing concentration	Perpetrator compound	Oral dosing concentration	IV dosing concentration	Perpetrator compound clinical significance
Dabigatran etexilate	10 µM	5 µM	Zosuquidar	2 µM	No IV dosing	Increase in victim drug bioavailability through P-pg efflux transporter inhibition.
Darunavir	50 µM	5 µM	Ritonavir	10 µM	10 µM	Increase in victim drug bioavailability through metabolic enzyme inhibition preventing breakdown.
Dabrafenib	10 µM	5 µM	Rifampicin	10 µM	10 µM	Reduction in victim drug bioavailability through metabolic enzyme induction.

Conclusions

- Dabigatran etexilate metabolite profiles and dabigatran formation showed prodrug metabolism consistent with human CES1 and CES2 distribution, giving a mechanistic insight into metabolic drug pathways with the Gut/Liver MPS.
- P-gp inhibition by zosuquidar altered dabigatran etexilate transport and absorption in the primary gut model.
- Ritonavir inhibition of CYP3A4 increased darunavir oral bioavailability, consistent with its known *in vivo* boosting effect[3].
- Rifampicin accelerated dabrafenib metabolism and reduced bioavailability, capturing induction-driven clearance, in agreement with *in silico* predictions and in murine data.
- Combining human primary tissues with computational modeling, this Gut/Liver MPS gives mechanistic insights into oral drug disposition and improves prediction of clinical DDI outcomes — informing dose selection, reducing adverse interactions, and reducing reliance on animal studies.

References

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Results

Figure 2: Mechanistic profiling of dabigatran etexilate DDI with a P-gp inhibitor

CES1 = Carboxylesterase 1 | CES2 = Carboxylesterase 2
M1 = BIBR 0951 | M2 = BIBR 1087

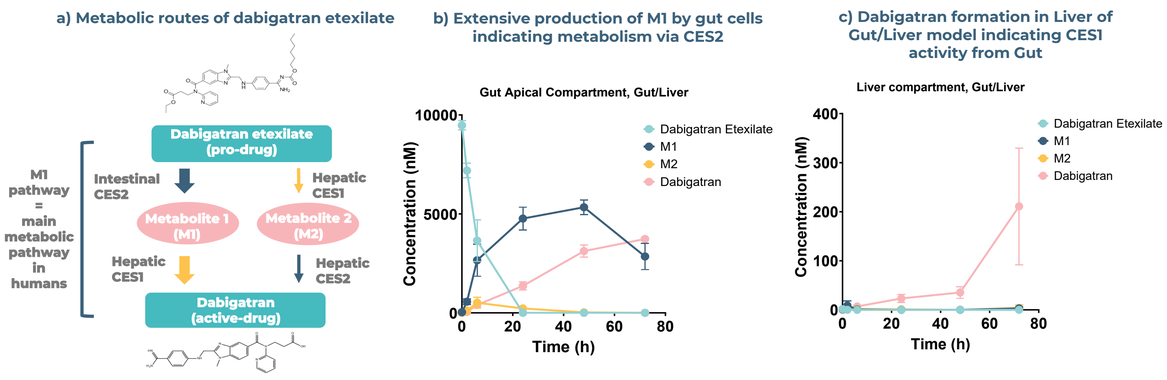


Figure 3: Co-administration of darunavir and ritonavir inhibits CYP3A4 metabolism increasing drug bioavailability

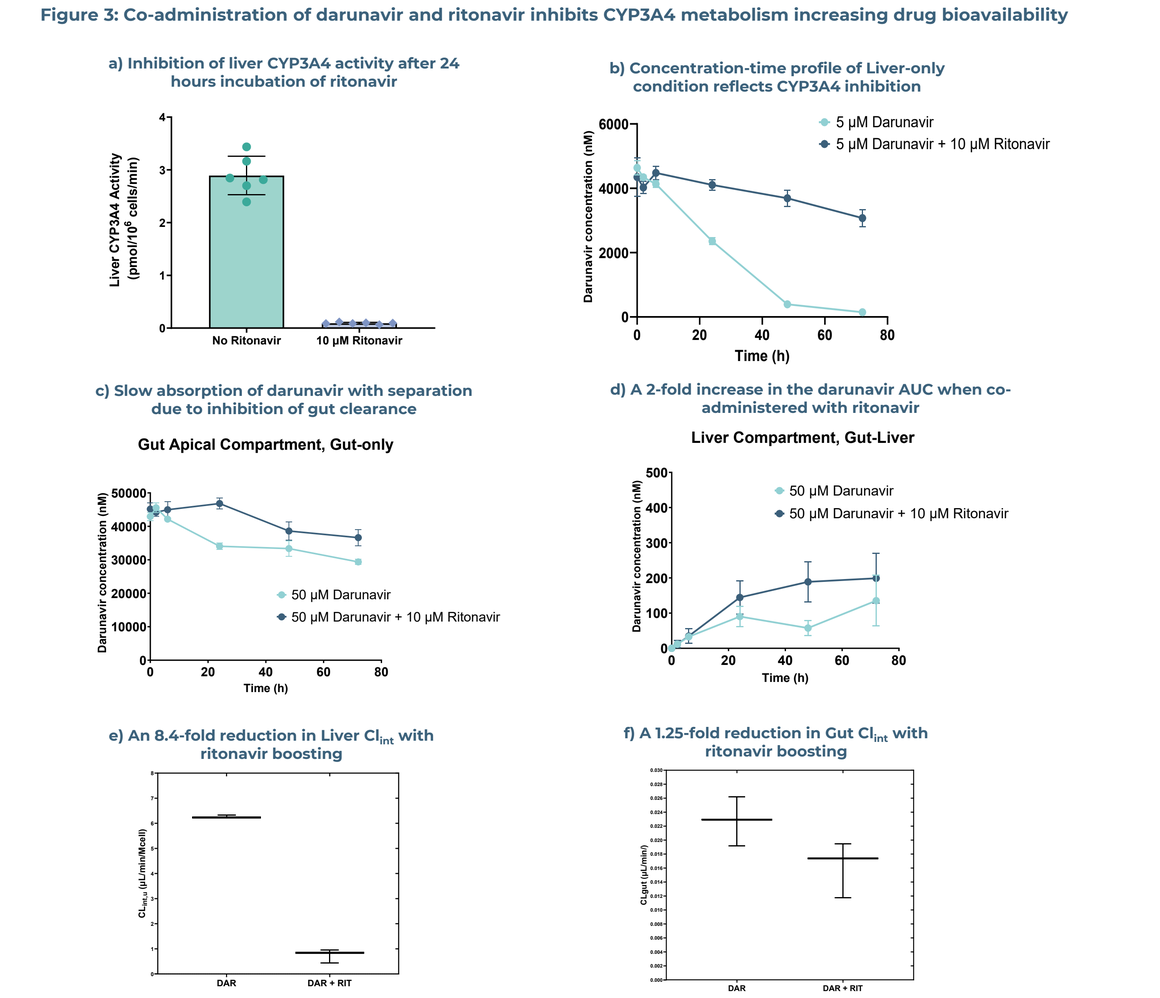
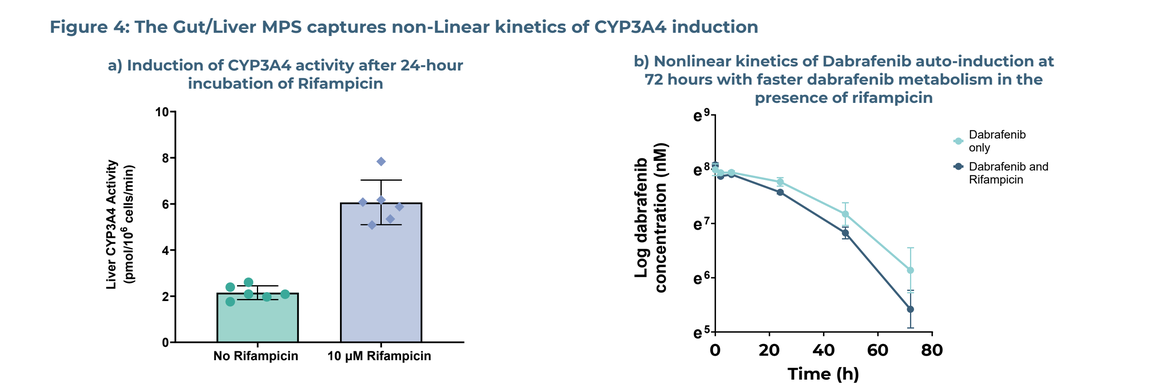


Figure 4: The Gut/Liver MPS captures non-Linear kinetics of CYP3A4 induction



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