A predictive human oral bioavailability assay

Utilizing integrated Gut + Liver Microphysiological System (MPS)

The current challenge

1. Musther *et al*. (2014). Animal versus human oral drug bioavailability: Do they correlate?

> ***Oral bioavailability (F = Fa × Fg × Fh) is driven by absorption and first-pass effects that are hard to capture with isolated in vitro models***

> ***Human bioavailability estimations from in vivo animal models weakly correlate with human-derived data (R^2=0.34)[1]***

Isolated *in vitro* assays

Permeability/transport readouts in isolation

Caco-2 cells lack the metabolic functionality to estimate Fg

Hepatic clearance measured separately

Incomplete first-pass effect requires assumptions to reconstruct F

Animal *in vivo*

Oral and IV dosing to define species–specific F (but not individual Fa, Fg, Fh parameters)

Human relevance of absorption & metabolism can differ across species

Does not distinguish poor absorption vs extensive first-pass metabolism

Hard to separate gut-wall vs hepatic contribution to low F

Why improving predictions matters to decision-making?

Prioritise candidates with optimal bioavailability and inform formulation strategy

Reduce reliance on animals through early human-relevant iteration, or resolve uncertainty where species predictions differ

Replace isolated estimates with integrated biological system data to improve confidence in *in silico* predictions

Differentiate gut and liver DDI risk to support more informed development decisions

Overcome your limitations

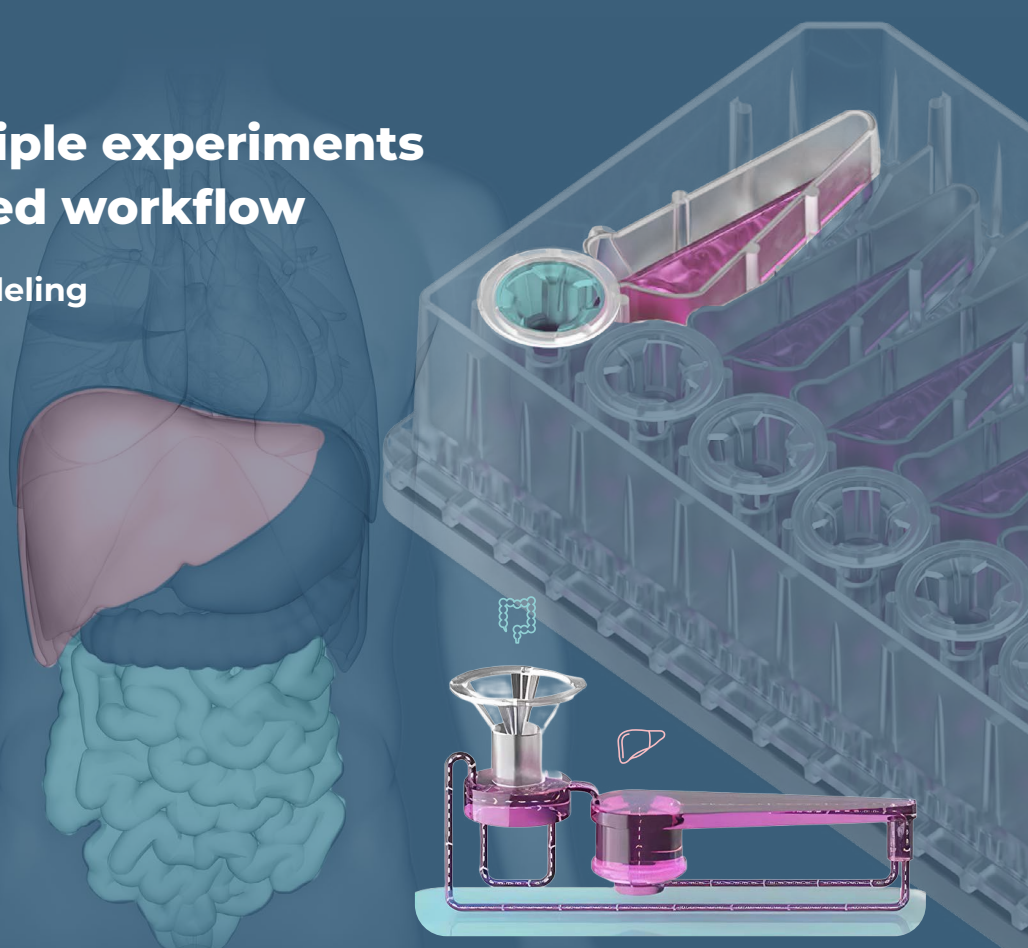
Consolidate multiple experiments into one integrated workflow

Bioavailability assay + modeling

Primary human Gut/Liver MPS provides

- Relevant gut and liver metabolic functionality
- Physiological gut transporter profile
- Oral + IV dosing in a single experiment

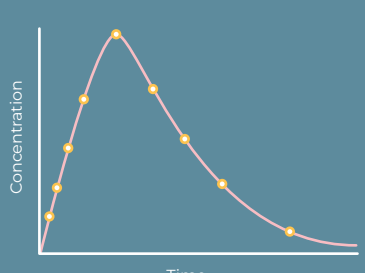
Linked computational modeling tools provide the mechanistic parameters to estimate F



Experimental workflow

In-house or outsource

Data



Computational modeling

ADME parameters

Fa
Fg
Efflux ratio

→ Gut intrinsic clearance

Fh
Liver intrinsic clearance
Metabolite profiling

→ F

PBPK

Drug chemistry
Other *in vitro* data
Physiological based data

Human PK prediction

> ***Integrating MPS data with mechanistic modeling enables deeper biological insights with greater precision. It allows us to address critical questions like: "When does saturation occur?" or "At what concentration does the system show non-linear behavior***

Dr Yassen Abbas - Biology Group Leader, CN Bio

Read publication
cn-bio.com/R1627

Where is the PhysioMimix® Bioavailability assay most beneficial?

- Target validation
- Screening
- Lead optimization
- Preclinical
- Clinical trials

1. Inform lead candidate selection and *in vivo* study design to reduce animal use
2. Explore formulation strategies
3. Inform FIH dose and dosing schedules

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Contact us to discuss how to incorporate into your workflows, or outsource to our Contact Research Services

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