Evaluation of human intestinal epithelium in MPS platform as an in vitro model for drug absorption

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October 11, 2023

DISCLAIMER

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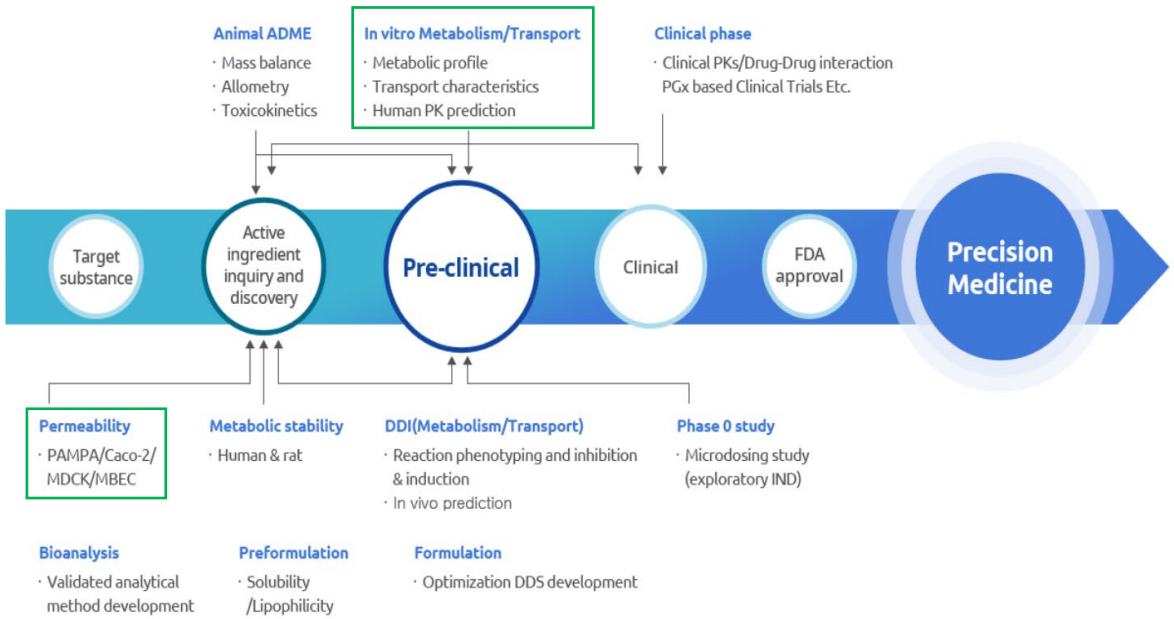
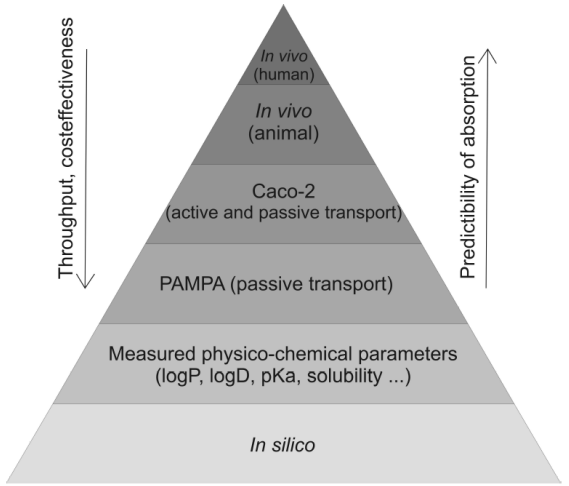
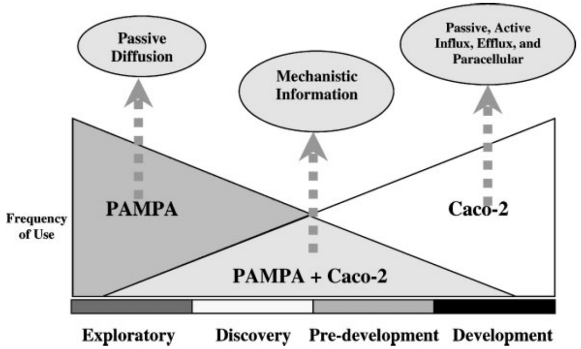
Outline

I. Introduction
II. Project aim
III. Project plan and progress
IV. Summary

I. Introduction







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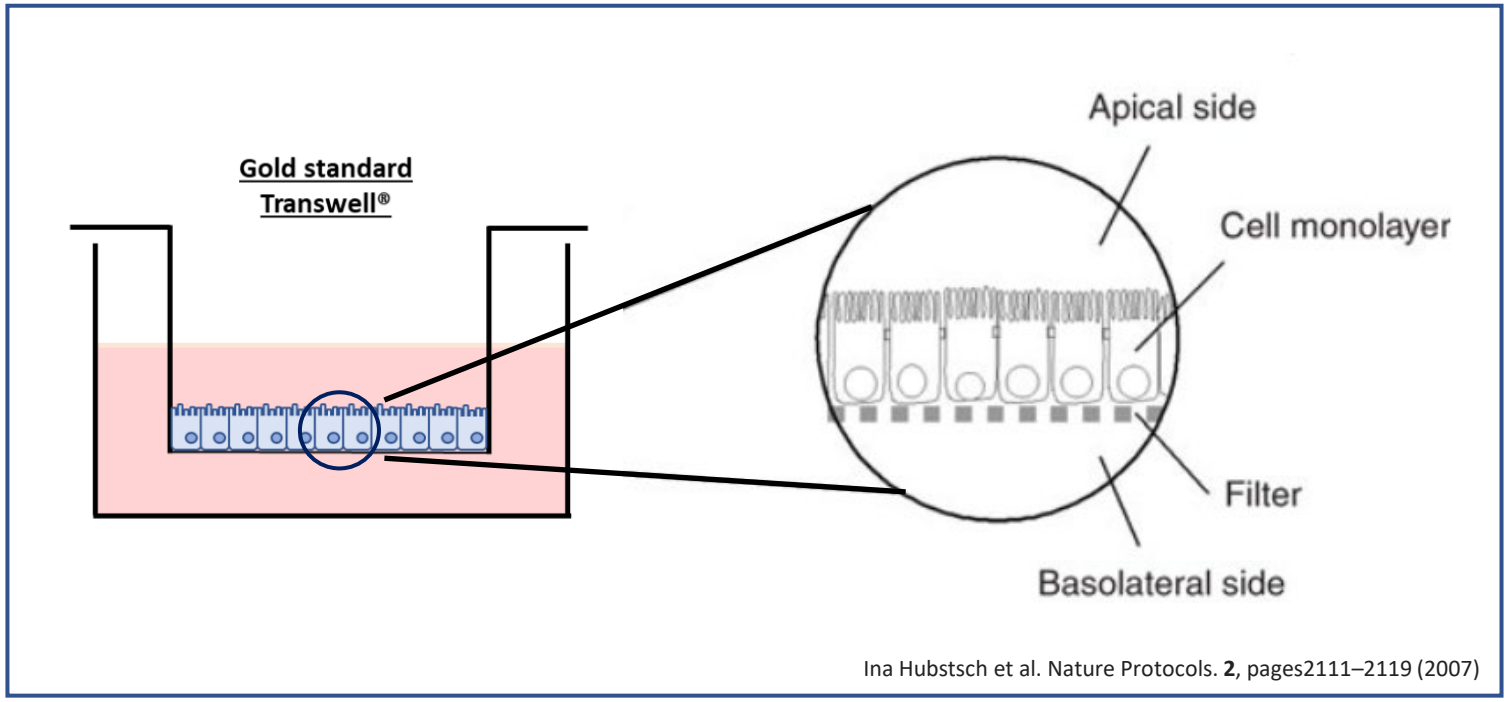
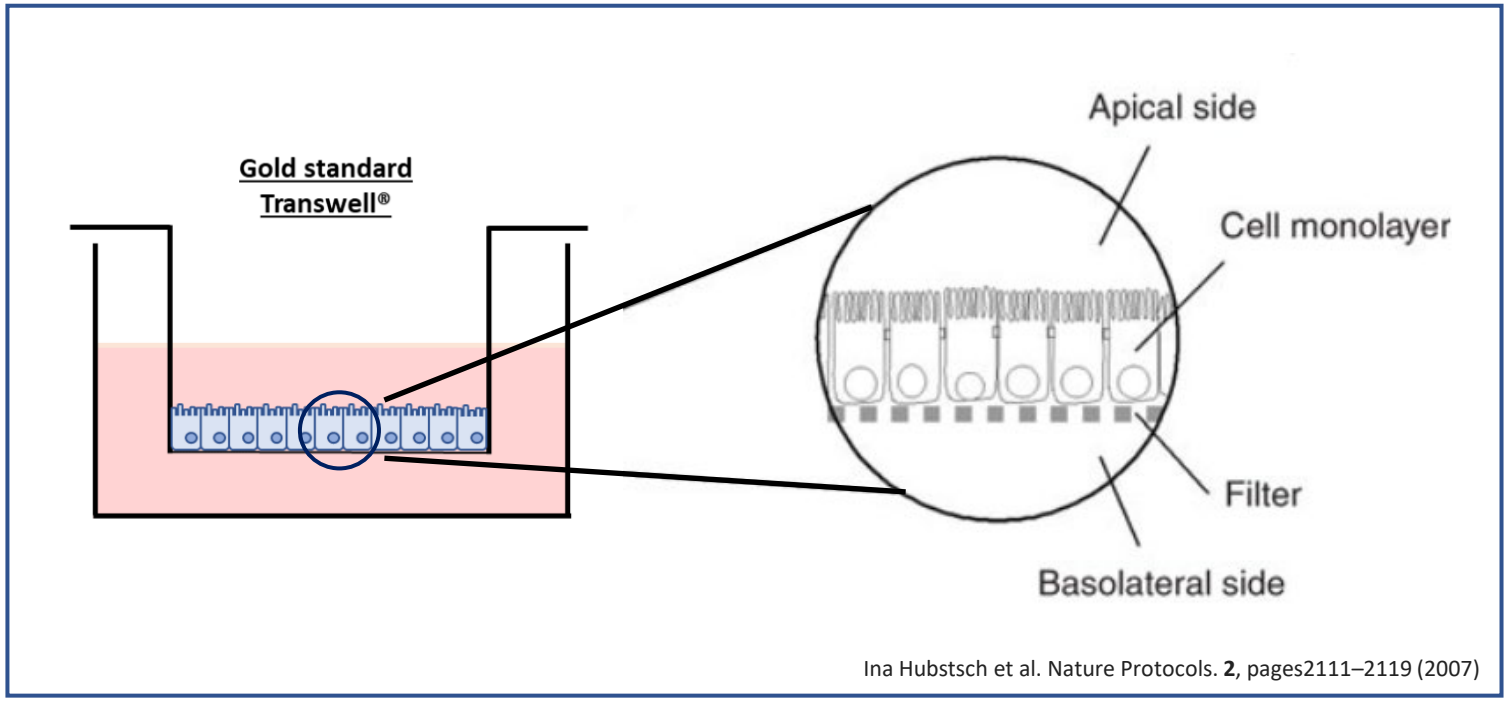
2D Caco-2 cell model



Ina Hubstsch et al. Nature Protocols. **2**, pages2111–2119 (2007)

- ✓ Tool for absorption screening of drug compounds during the early stage of drug discovery and development
- ✓ Screening potential drug-drug interactions and role of transporters
- ✓ Testing permeability enhancer
- ✓ In vitro model for Biowaiver application

2D Caco-2 cell model



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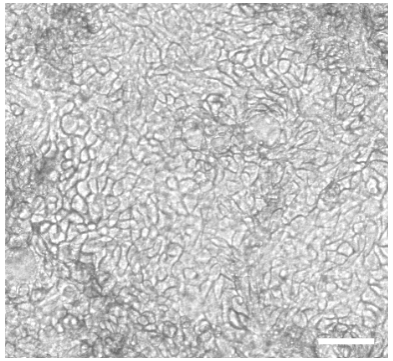
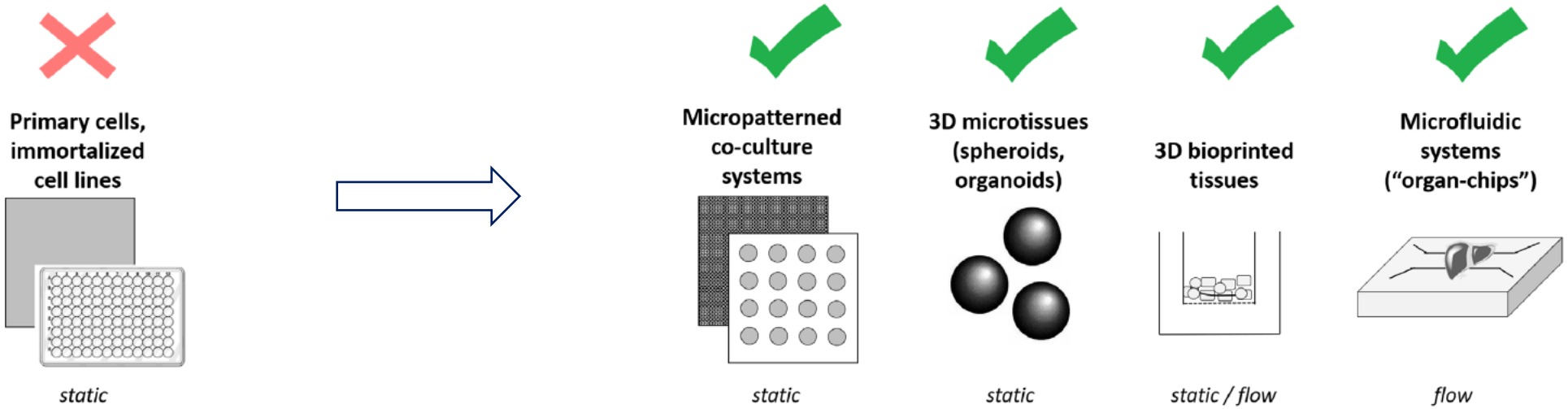


10X, Scale bar = 20 µm

- ⊕ Differentiation/polarization
- ⊕ Passive/active transport
  (e.g. MDR1 (P-gp), PEPT1)
- ⊕ P_{app} correlates with F_a in humans
- ⊕ Capability for rapid/high- throughput screening

- ⊖ High barrier integrity
- ⊖ Limited transporter/metabolizing enzyme expression and activity
- ⊖ Lack of interactions with mucous and microbiome
- ⊖ Lack of peristaltic movement and fluidic flow

Complex in vitro models (CIVM)



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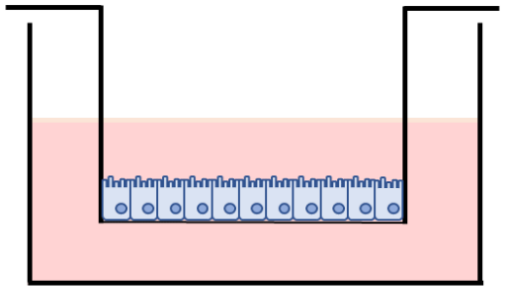
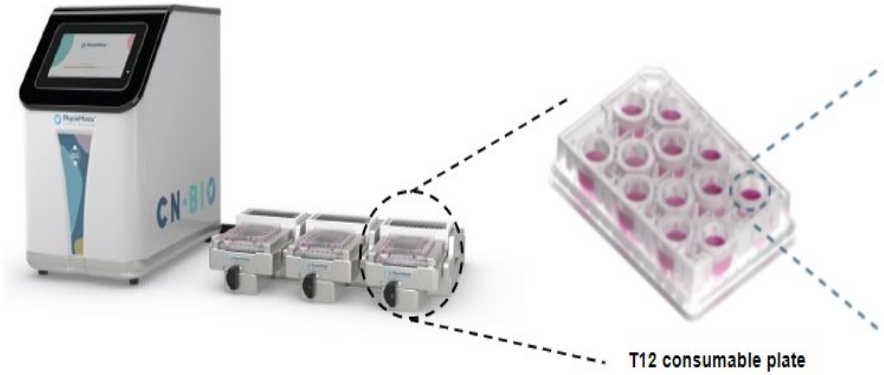
Gut-on-a-chip model

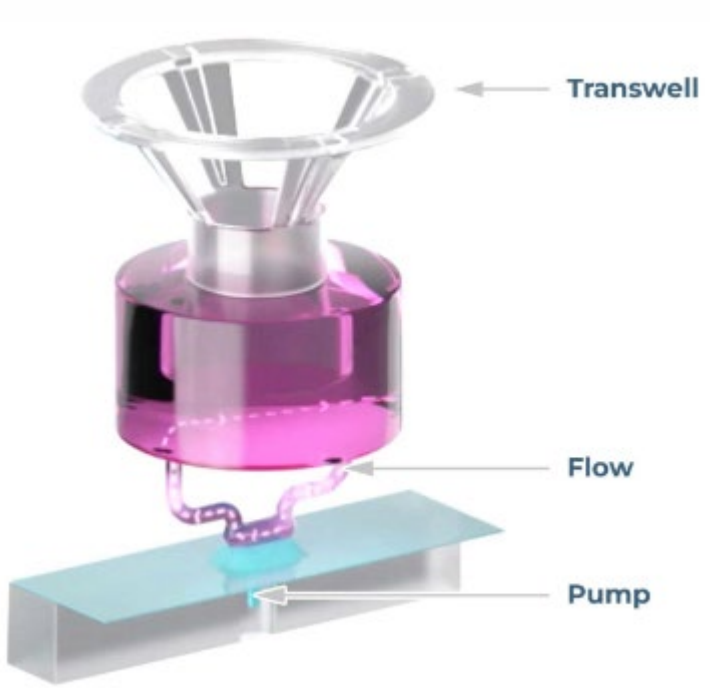
2D static Caco-2



Lack of Intestinal physiology

Microfluidics-based Caco-2





Perfused system providing fluidic flow

II. Project aim

Assess the gut MPS model as a superior substitute for the conventional 2D static model

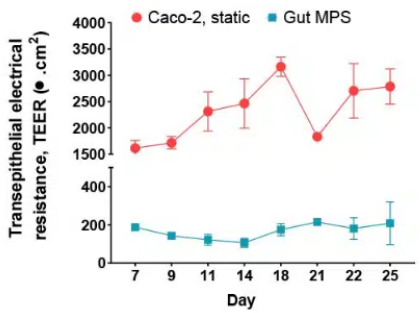
"Move new science into the FDA regulatory process"

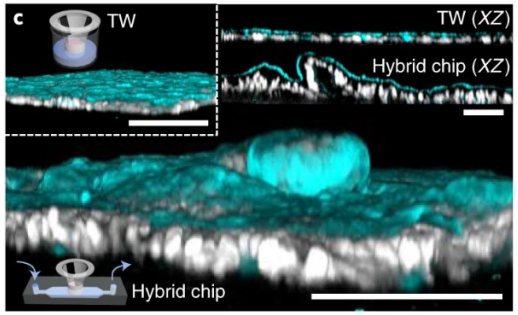
Tackle challenging scientific questions that impede the development and regulatory evaluation of CDER products

Develop and evaluate novel tools, standards, and approaches that increase the efficiency of regulatory review and drug development

III. Project Plan

Functional and phenotypical analysis





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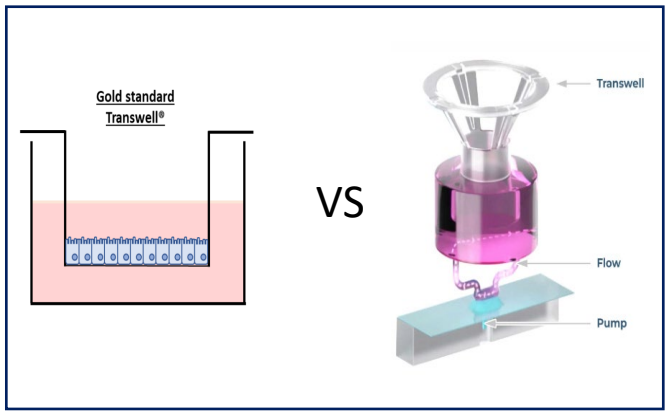
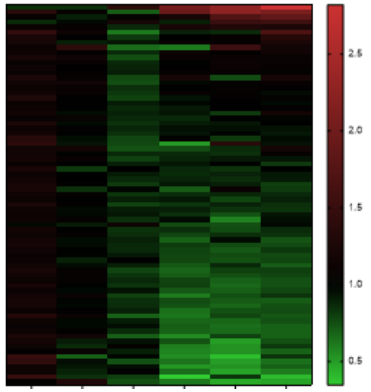
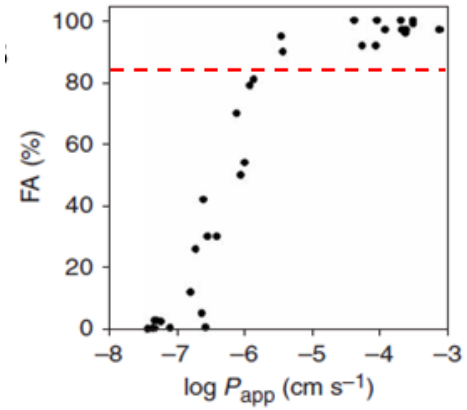


Human in vivo pharmacokinetics

Transcriptome profiling
& Activity assay

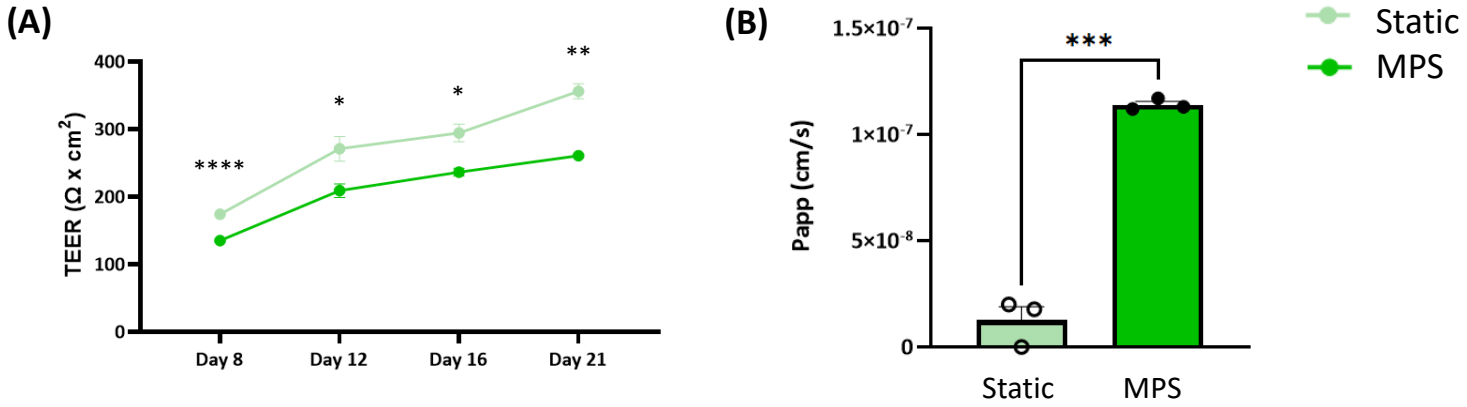


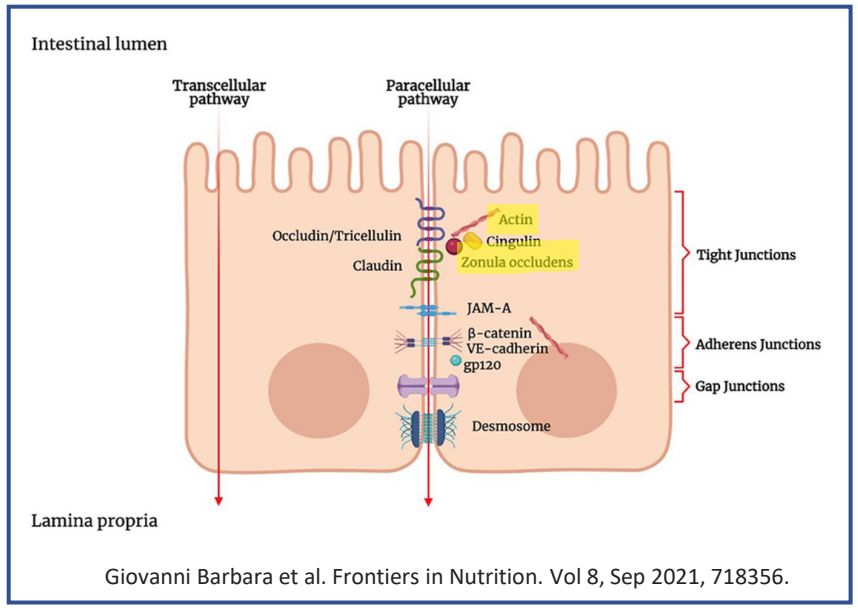


Drug permeability and
its correlation with F_a in humans
In silico modeling for absorption

Ina Hubstsch et al. Nature Protocols. **2**, pages2111–2119 (2007)

Barrier function and morphology





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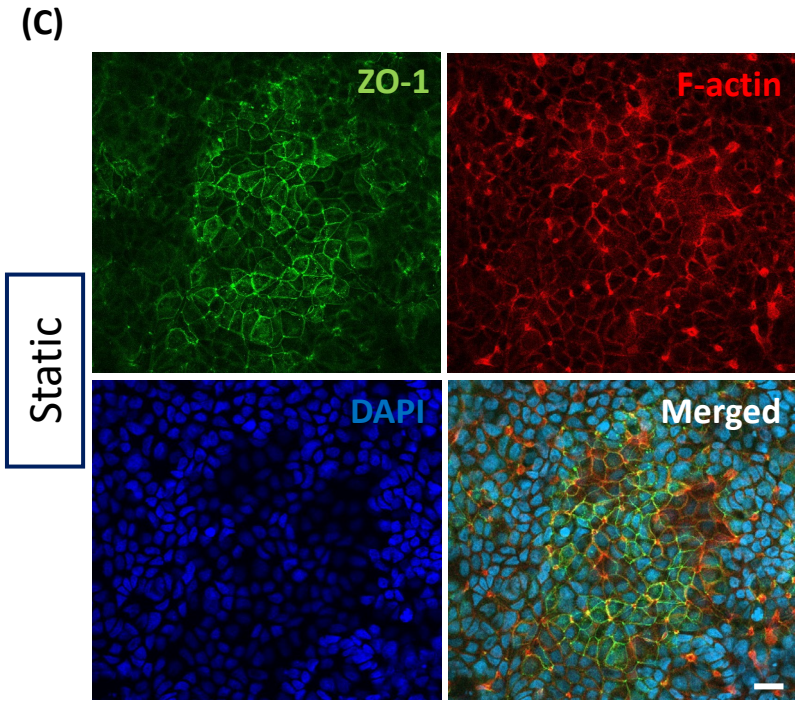
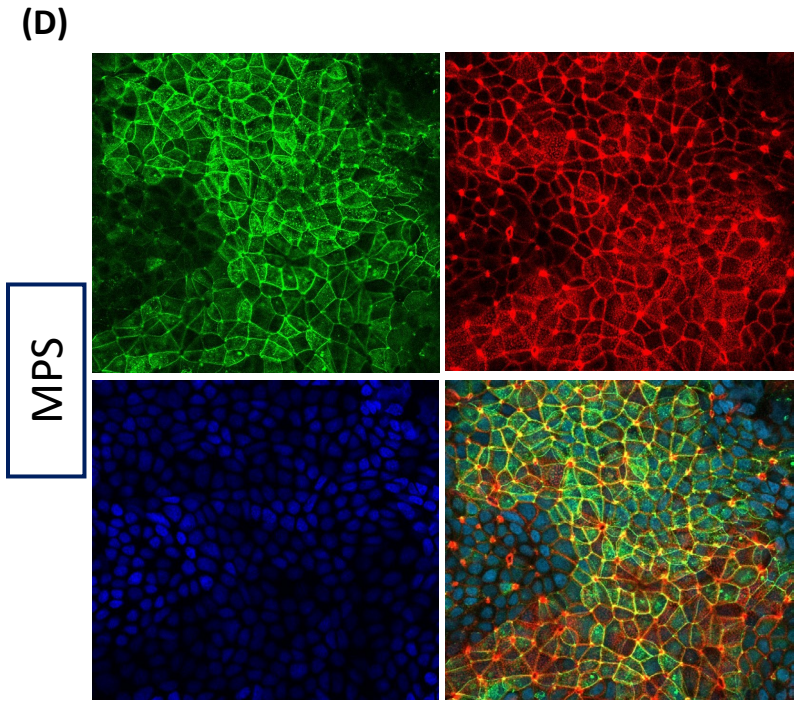
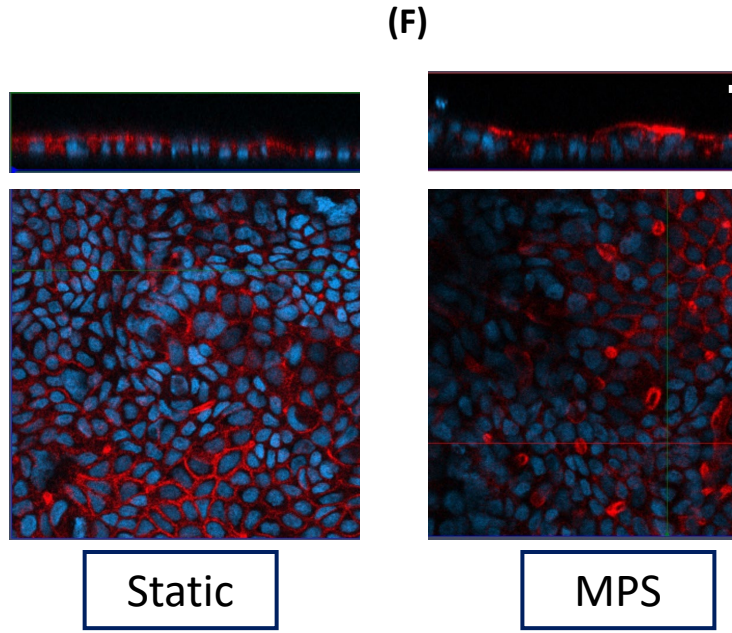
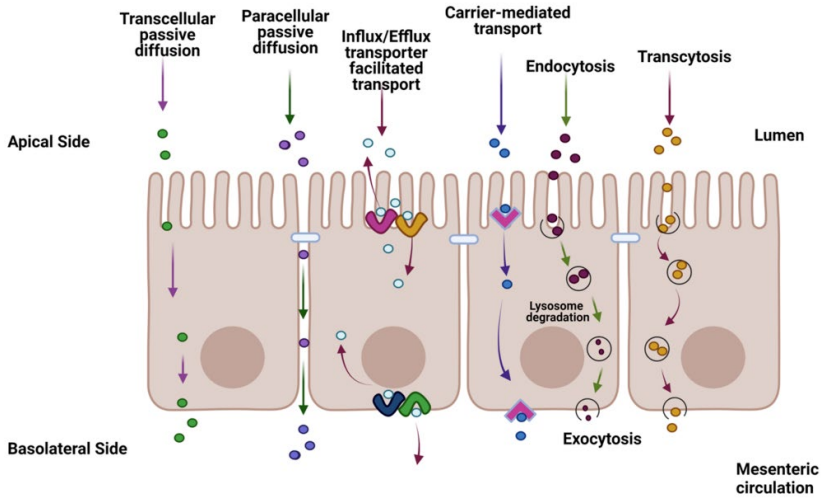




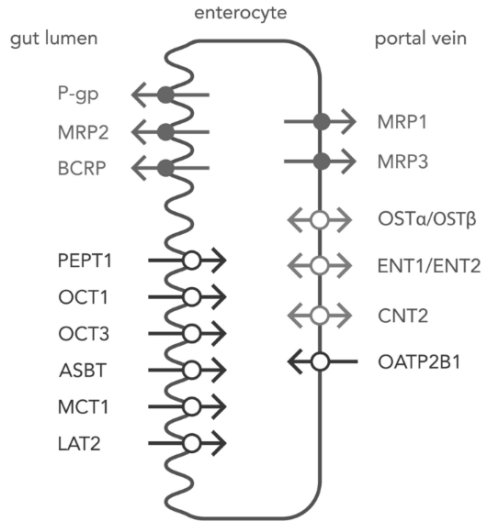


ZEISS LSM 900, 20X. Scale bar = 20 µm.
Same settings across samples.

Drug transporters and drug-metabolizing enzymes



Kiyohiko Sugano et al. Nature Reviews Drug Discovery. 9, pages597–614 (2010)



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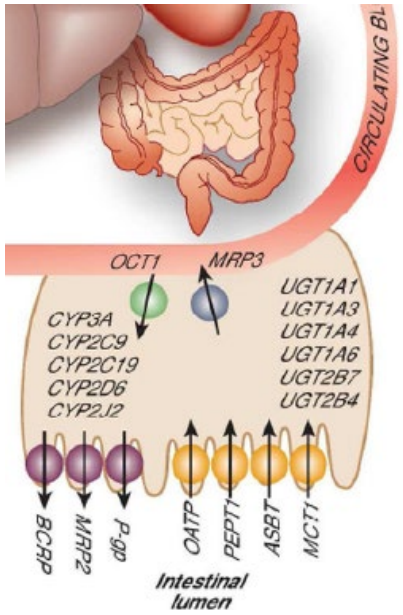

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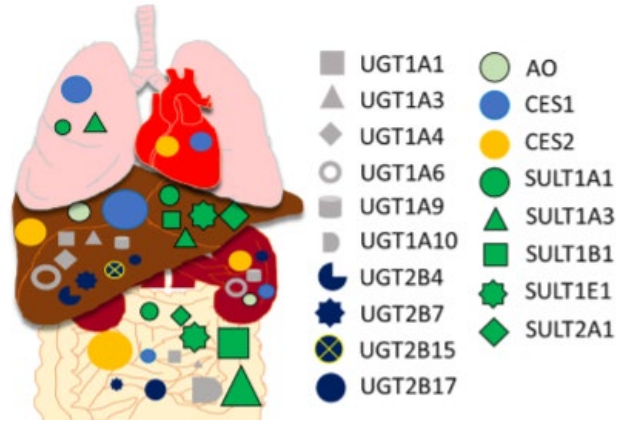

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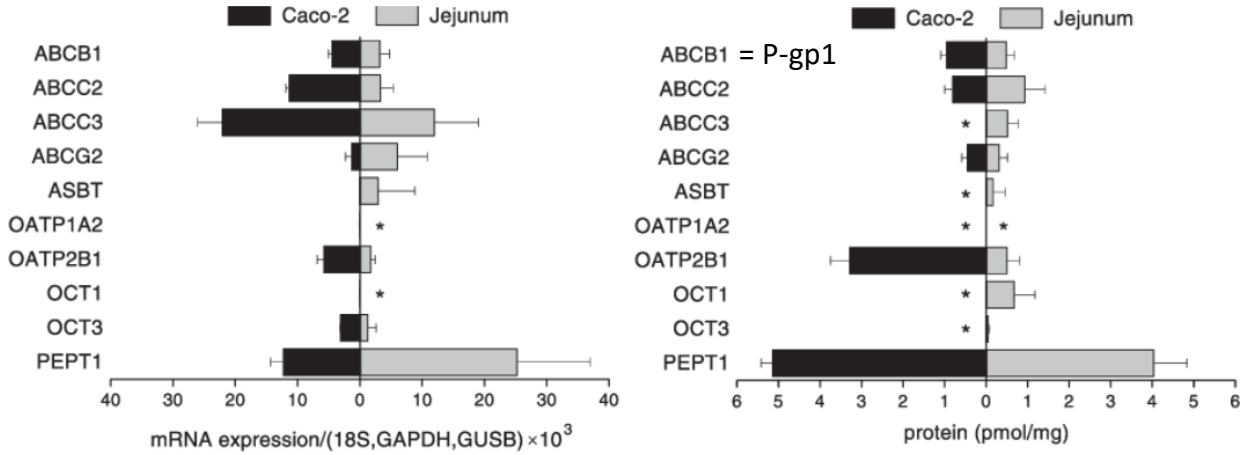
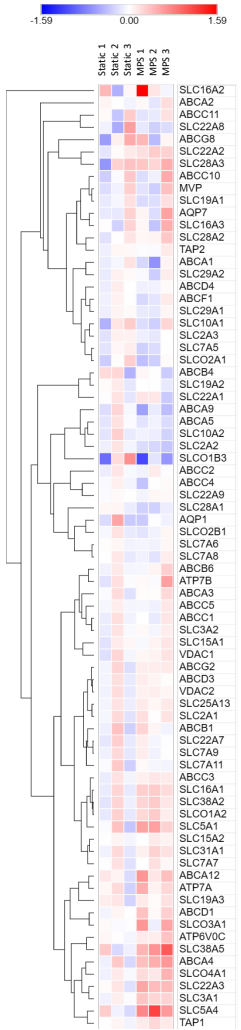


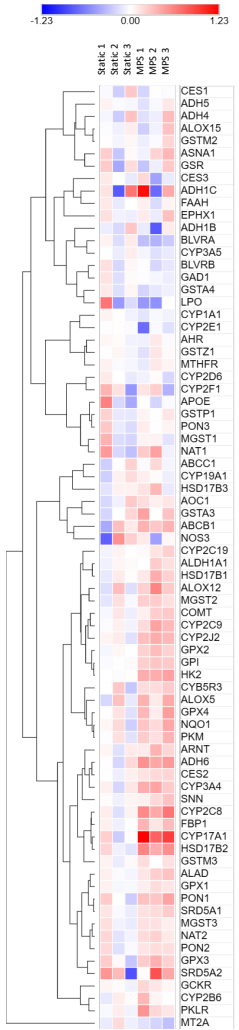
Marek Drozdzik et al. 72, 11

Transcriptomic profiling

Drug transporters



Drug-metabolizing enzymes



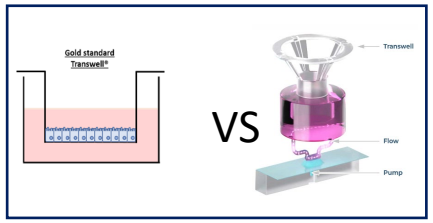
Upregulated expression of CYPs, SLC, OCT..

Functional analysis based on their protein quantities and activities

Heatmaps were generated using Broad Institute, Morpheus visualization and analysis software

IV. Summary

- ✓ Systemic characterization and evaluation of MPS model's capacity to recapitulate normal physiological functions of human intestine.
- ✓ Comprehensive grasp of the predictive capabilities of MPS model in establishing correlations between P_{app} and F_a in humans through drug absorption studies encompassing all four BCS drugs.



Human in vivo pharmacokinetics

Functional and phenotypical analysis

Transcriptome profiling

Protein quantification and activity assessment

Drug permeability
In silico modeling

Acknowledgements

Division of Applied Regulatory Science (DARS)

David Strauss, MD, Ph.D.
Rodney Rouse, DVM, MBA, Ph.D.
Kevin Ford, Ph.D.
Martha Iveth Garcia, Ph.D.
Robert Geiger, Ph.D.
Bhavya Bhardwaj, M.S.
Catherine Sullenberger, Ph.D.
Shekh Rahman, Ph.D.
Ashok Krishna, Ph.D.
Dylan Bruckner, Ph.D.

Collaborators

Bioanalytical and research team at DARS
Murali K. Matta, Ph.D.
Ryan De Palma, Ph.D.
Omnia Ismaiel, Ph.D.
Donna Volpe, Ph.D.
Mohammed Qusa, Ph.D.

PBPK modeling and simulation team at OCP
Jeffry Florian, Ph.D.
Yuching Yang, Ph.D.
John Mann, M.S.

CN Bio Innovations
Tomasz Kostrzewski, Ph.D.
Emily Richardson, Ph.D.
Yassen Abbas, Ph.D.
Hailey Sze, M.S.

Thank you for your attention