Bioconvergence: A ONE Merck initiative to advance Organ-on-Chip technology with organoid models for biomedical research

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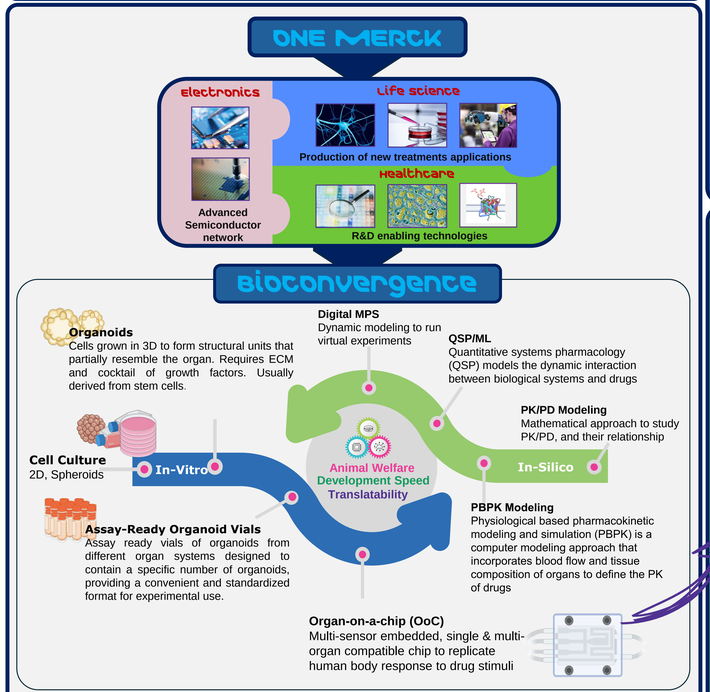
Abstract

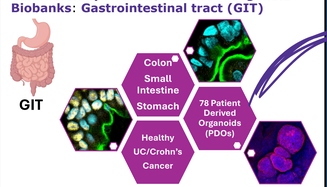
Here, bioconvergence integrates organoid biology with semiconductor-enabled microphysiological systems (MPS) to improve translational drug discovery. We are merging human 3D gut and liver organoids (iPSC- and patient-derived), validated for lineage identity, barrier function, and Phase I/II metabolism, with a customizable silicon microfluidic chip developed with imec. The platform will support single and modular multi-organ configurations with on-board sensing (enzymatic lactate, glucose, H2O2; electrical TEER), integrated top-and-bottom microscopy, and a roadmap to photonic sensing for low-volume, longitudinal readouts with CMOS-compatible scalability. Current work has established single-organ feasibility under perfusion and sensor characterization using Caco-2 and iPSC-derived colon organoids. Planned studies will extend this to iPSC small intestine, patient derived Organoid (PDO) duodenum, and iPSC liver, followed by modular multi-organ use cases and compound response profiling. This ONE Merck initiative aims to deliver more clinically translatable *in vitro* and *in silico* models, advancing toxicology, DMPK, and disease modeling while reducing animal use.



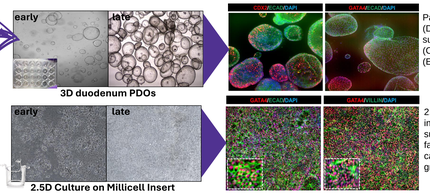
Development of unique assay ready organoid biology

Development and Characterization of Human Duodenum PDOs for Preclinical Drug Testing

Commercially Available 3dGRO® Organoid Biobanks: Gastrointestinal tract (GIT)



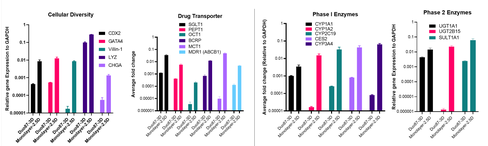
Characterization of intestinal PDOs in 3D vs 2.5D culture



Patient-derived duodenum Organoid (Duo87) express key cellular markers such small intestine transcription factors (CDX2, GATA4, Red) and Epithelial cells (E-cadherin, green).

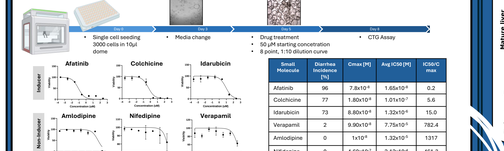
2.5D monolayer culture on 24-well Millicell insert also express key cellular markers such as small intestine transcription factors (GATA4, red), Epithelial cells (E-cadherin, green), and brush-border (Villin, green) cells.

Gene Expression profile in 3D vs 2.5D culture



qRT-PCR for comparison of gene expression analysis in proliferative (3D) *vs* differentiated (2.5D Monolayer) duodenum organoid culture: Differentiated duodenum organoids (2.5D, Monolayer) express higher level of cellular diversity genes (LYZ, CHGA), Phase I & II enzymes (CYP3A4, UGT1A1, UGT2B15) and drug transporters genes (SGLT1, PEPT1, BCRP) compared to proliferative 3D organoids.

Gut-Tox prediction in 3D Duodenum organoids

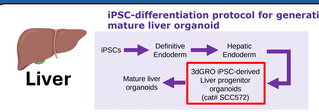


Small Molecule	Diarrhea Incidence [%]	Cmax [M]	Avg IC50 [M]	IC50/C max
Afatinib	96	$7.8x10^{-6}$	$1.65x10^{-5}$	0.2
Colchicine	77	$1.80x10^{-9}$	$1.01x10^{-7}$	5.6
Idarubicin	73	$8.80x10^{-9}$	$1.32x10^{-6}$	15.0
Verapamil	2	$9.90x10^{-8}$	$7.75x10^{-5}$	782.4
Amlodipine	0	$1x10^{-8}$	$1.32x10^{-5}$	1317
Nifedipine	0	$4.60x10^{-7}$	$2.12x10^{-4}$	461.3

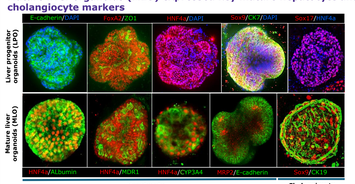
3D duodenum PDO drug screen for gut-toxicity prediction. Patient-derived duodenum organoids (Duo87) were cultured in 3D in a 96-well plate format and screened to assess their ability to predict gut toxicity using a reference set of known diarrheagenic and non-diarrheagenic compounds. shown are representative results for six compounds (subset of the full dataset); in total, 30 diarrheagenic and 30 non-diarrheagenic compounds were evaluated and benchmarked against reported literature values.

Development and Characterization of Human induced pluripotent stem cells (iPSC) derived liver organoids for Preclinical Drug Testing

iPSC-differentiation protocol for generating mature liver organoid

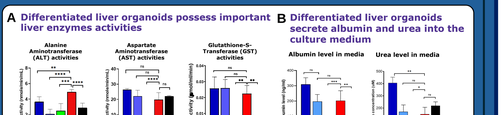


Mature liver organoids (MLO) expressed key mature hepatocyte and cholangiocyte markers



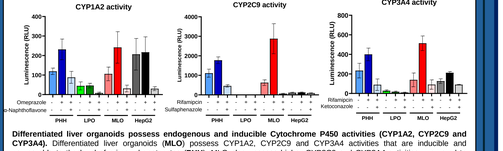
Upper panel: Liver progenitor organoids (LPO) are polarized and can be differentiated to mature liver organoids (MLO) expressing key maturation and functional markers (lower panel). Immunofluorescence data showed the liver progenitor organoids (LPO) are polarized and expressing liver progenitor markers. Differentiated mature liver organoids (MLO) expressed mature functional hepatocyte and cholangiocyte markers.

A Differentiated liver organoids possess important liver enzymes activities **B Differentiated liver organoids secrete albumin and urea into the culture medium**



A: Differentiated liver organoids possess important liver enzymes (ALT, AST and GST) activities. Enzyme activities were detected in differentiated liver organoids (**MLO**) at the level comparable to primary hepatocytes (**PHH**). **B: Differentiated liver organoids secrete albumin and urea into the culture medium.** Albumin and Urea secretion were detected in the media from differentiated liver organoids (**MLO**) at the level comparable to primary hepatocytes (**PHH**) and HepG2 cells.

Mature liver organoids possess functional and inducible Cytochrome P450 activities



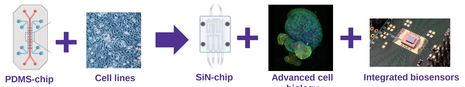
Differentiated liver organoids possess endogenous and inducible Cytochrome P450 activities (CYP1A2, CYP2C9 and CYP3A4). Differentiated liver organoids (**MLO**) possess CYP1A2, CYP2C9 and CYP3A4 activities that are inducible and comparable to the level of primary hepatocytes (**PHH**). MLO also possess higher CYP2C9 and CYP3A4 activities compared to HepG2 cells. Liver Progenitor Organoids (LPO) possess very low to no CYP450 activities.

Development of an MPS platform with on-board biosensing- A Merck-imec collaboration

Why Microphysiological Systems (MPS) and why now?

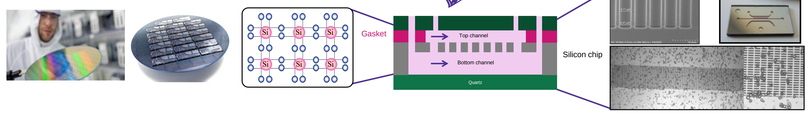
Animals remain a cornerstone of drug discovery and development. However, animals should only be used where unavoidable, and no alternative exists. Beyond ethics, regulators are increasing pressure to reduce and ultimately replace animal use (e.g., FDA roadmaps and EU 3Rs guidance). Is this feasible? Advances in human 3D biology and semiconductor-enabled microfluidics now make it increasingly practical to model key human organ functions, ex vivo, before first-in-animal or first-in-human studies. While existing platforms frequently fall short on physiological complexity, with multi-organ coupling and continuous time-resolved sensing, our bioconvergence strategy addresses these gaps by merging validated human organoids with a semiconductor-enabled silicon microfluidic chip.

Current MPS-platforms **Next generation MPS-platform**



Strategic collaboration between Merck and imec

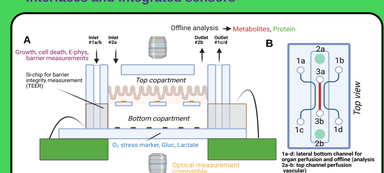
Silicon (SiN) as the Cornerstone of the next-generation MPS



Silicon as the cornerstone of the new MPS. Schematic cross section of the Merck–imec single organ-on-chip module built around a silicon membrane consisting of two compartments able to accommodate distinct biology. Right panel shows an electron microscopic image revealing the high precision lithography can reach. Upper right panel: size comparison of Merck-imec chip

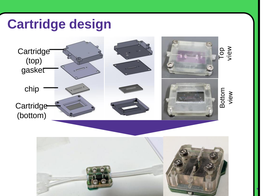
Merck-imec scalable single Organ-on-Chip module:

Modular system design enables easy expansion from single to multi-organ, featuring standardized interfaces and integrated sensors



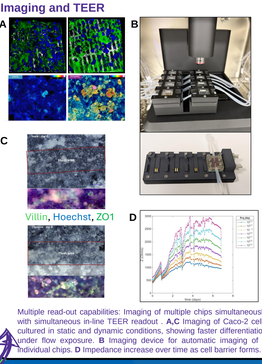
Schematic of the Merck–imec single organ-on-chip module. A silicon membrane separates two compartments, allowing high-resolution imaging, real-time biosensing, fluid sampling for offline measurements, and in situ, continuous, label-free readouts of cell adhesion, viability, and barrier integrity. **A:** Cross Section; **B:** Top view.

Cartridge design



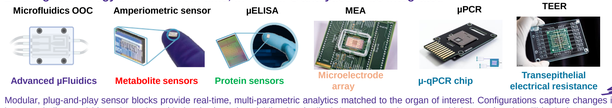
Upper panel: Initial cartridge design showing the integration of the silicon chip into the fluidic chamber. **Lower Panel** showing updated cartridge with integrated TEER capability.

Multiplexed time-resolved read-out capabilities: Imaging and TEER



Multiple read-out capabilities: Imaging of multiple chips simultaneously with simultaneous in-line TEER readout . **A,C** Imaging of Caco-2 cells cultured in static and dynamic conditions, showing faster differentiation under flow exposure. **B** Imaging device for automatic imaging of 8 individual chips. **D** Impedance increase over time as cell barrier forms.

Existing technology blocks for real-time, in-line MPS analytics to be integrated



Modular, plug-and-play sensor blocks provide real-time, multi-parametric analytics matched to the organ of interest. Configurations capture changes in key metabolites and biomarkers alongside barrier integrity, yielding longitudinal data streams that connect biology to function. This design supports flexible study setups and seamless expansion to multi-organ circuits.

MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany.