

A vascularized gut–pancreas multiorgan-on-a-chip model to study diet-dependent metabolic crosstalk

I Context

Obesity and Type 2 Diabetes (T2D) represent major global health challenges, arising from systemic metabolic dysfunction and impaired communication among key organs—the gut, pancreas, liver, adipose tissue, and brain. T2D progression typically involves insulin resistance followed by pancreatic β -cell failure, yet substantial inter-individual variability limits the predictive value of current experimental models. A pivotal clinical observation is that bariatric surgery, such as gastric bypass, rapidly improves glycemic control and insulin secretion, before significant weight loss occurs [1]. This suggests that anatomical and functional remodeling of gut signaling directly influences pancreatic endocrine function. Furthermore, recent studies have revealed altered jejunal endocrine cell lineages in T2D, which potentially drive impaired glycemic control and reduced intestinal metabolic flexibility [2]. Although increased secretion of incretin hormones such as glucagon-like peptide-1 (GLP-1) partly explains post-surgical metabolic improvement, emerging evidence points to additional, yet unidentified, non-incretin gut-derived mediators that promote pancreatic re-sensitization [3]. **Dissecting how diet shapes intestinal secretomes and their downstream impact on insulin secretion is therefore critical for advancing therapeutic strategies in T2D.**

Addressing this challenge requires *in vitro* models that are both physiologically relevant and mechanistically tractable. Organ-on-a-chip (OoC), recognized by the FDA as promising alternatives to animal models, enable controlled reconstruction of tissue architecture, dynamic flow, and biochemical gradients. However, the study of complex systemic diseases requires moving beyond single-organ systems. The next-generation approach focuses on creating microvascularized, interconnected multi-organ models that emulate systemic circulation and molecular exchange between key tissues. Incorporation of endothelialized, vessel-like channels has been shown to enhance the maturation of individual organ modules and *in vivo*-like inter-organ signaling [4]. By enabling dynamic, vascular-mediated gut–pancreas communication within a controlled microfluidic environment, such platforms provide a unique opportunity to causally dissect diet-dependent metabolic pathways that are inaccessible *in vivo* and insufficiently resolved in existing *in vitro* systems, thereby accelerating the development of predictive and precision therapies for metabolic disease.

II Hypothesis & Objectives

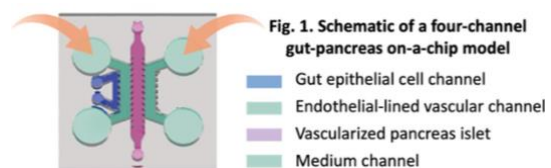
We hypothesize that diet-dependent gut–pancreas metabolic communication involves not only classical incretin hormones (GLP-1, GIP) but also a broader repertoire of gut-derived metabolites and cytokine-like mediators whose imbalance contributes to β -cell dysfunction in obesity and T2D. Restoring this inter-organ dialogue—such as after bariatric surgery—triggers pancreatic re-sensitization and improved insulin secretion. We further postulate that these complex interactions can be mechanistically reconstructed and quantified using a vascularized Gut–Pancreas OoC (GP-oC).

The project aims to develop and validate a vascularized multi-organ microphysiological platform that enables dynamic modeling of gut–pancreas communication under healthy, diabetic, and remission-like conditions. This integrative system will constitute a powerful preclinical tool to identify molecular mediators of metabolic crosstalk and to support precision-medicine approaches in metabolic disease.

III Methodology & Plan

(i) Development of a vascularized pancreatic islet-on-a-chip model (Year 1):

A murine pancreatic islet-on-a-chip (PI-oC) model is under development in Dr. Amouyal's team using a multiwell chip design from Dr. Bello and Dr. Xiao's team. Substrate stiffness and flow will be precisely controlled to ensure long-term islet viability and preserve β -cell functionality. A microvascularization strategy will be implemented to enable interconnection with a vascular transport system. A modular, four-channel microfluidic platform has been designed by Dr. Bello and Dr. Xiao's team (Fig. 1), to incorporate murine pancreatic islets into an engineered vascular network, establishing a vascularized PI-oC model.



(ii) Development of a vascularized gut-on-a-chip model (Year 1): A multicellular murine gut-on-a-chip model (Gut-oC) will be developed by Dr. Amouyal's team using the four-channel microfluidic chip. The system will integrate a gut epithelial channel separated from an endothelial channel by micropillars, allowing efficient molecular exchange (Fig. 1).

(iii) Development of the functional gut-pancreas inter-organ connection (Year 2): Isolated pancreatic and gut modules will be integrated to the four-channel microfluidic device to establish a functional vascularized multiorgan-on-a-chip (VMOoC) system (Fig. 1). Gut-oC and PI-oC modules will be connected via a vascular transport channel that mimics systemic circulation. This vessel will enable selective inter-organ molecular exchange while maintaining barrier integrity to keep organ-specific media separate. Integration will be performed stepwise, with the Gut-oC positioned upstream to replicate portal flow toward the PI-oC, enabling dynamic analysis of gut-derived metabolic signals affecting pancreatic function. Precise flow control will harmonize perfusion across modules. Functional validation will track gut hormone transfer (e.g., GLP-1) and the resulting glucose-stimulated insulin secretion (GSIS) in the PI-oC, demonstrating physiologically relevant inter-organ communication. This proof-of-concept confirmation ensures that the system is functionally integrated and capable of physiological inter-organ communication before disease modeling starts.

(iv) Mechanistic validation (Year 3): The VMOoC system will be used to test the hypothesis that non-incretin intestinal metabolites are key modulators of pancreatic function following metabolic intervention. Standardized secretome media will be generated from murine models representing key metabolic phenotypes (e.g., healthy controls on chow diet vs. obese/diabetic mice on high-fat diet). Secretomes will be collected under high-glucose (20 mM) stimulation to mimic the postprandial state. Comprehensive molecular profiling will combine untargeted metabolomics and multiplexed Luminex assays quantifying major entero-hormones (GLP-1, GIP, PYY) and cytokines. These secretomes will be perfused through the VMOoC to measure real-time insulin and glucagon secretion. Correlation analyses will link metabolite shifts to insulinogenic responses while controlling for incretin effects, to reveal novel non-hormonal mediators of metabolic gut-pancreas metabolic crosstalk.

IV. Suitability to IUIS

This project aligns closely with the mission of the IUIS by integrating system biology, translational bioengineering, and advanced *in vitro* modeling to address major health challenges such as obesity and T2D. Its interdisciplinary approach—combining microfluidic engineering, metabolism biology, and clinical insights—contributes to the development of predictive and human-relevant health technologies, making it particularly well suited for the IUIS doctoral program.

V. Supervisors, feasibility & interdisciplinary collaboration

The two teams of this project have collaborated for the past three years with promising preliminary results. Dr. Valérie Bello is a MCU at Dev2A, who will bring her expertise in matrix remodeling, hydrogels, and biomechanics, and morphogenesis of tissue and organs, as the thesis director [5]. Dr. Wenjin Xiao is a team leader at Dev2A, and will bring her expertise in vessel engineering and on-demand vascularized OoC development, as a co-supervisor [6]. Dr. Chloé Amouyal is a clinical endocrinologist leading a sub-group at NutriOmics, and will bring her expertise in metabolic disease related to obesity, as well as *in vitro* intestine and pancreas models using animal cells and *in vivo* validation, as a co-supervisor [3, 7]. All technical and scientific expertise from both SU teams will support the PhD student's progress. Dr. Bello and Dr. Xiao's team is fully equipped with cutting-edge tools for biofabrication and microfluidics, while the host laboratory Dev2A provides comprehensive cellular and molecular biology infrastructure. All primary cells are routinely obtained with appropriate ethical approvals by Dr. Amouyal's team. All the equipment required for islet isolation and gut organoid development is fully operational and available. Funding for the project will be supported by existing team resources (e.g., pre-valorization project), and ongoing grant applications, including the ANR JCJC proposal submitted by Dr. Amouyal, which has been selected to phase II.

References: [1]. Umeda et al., *Obes Surg.* 2011. [2]. Osinski et al., *Int J Obes.* 2021. [3]. Amouyal et al., *EBioMedicine.* 2020. [4]. Ronaldson-Bouchard et al., *Nat Biomed Eng.* 2022. [5]. Buisson et al., *Cells Dev.* 2025. [6]. Monroy-Romero et al., *ACS Biomater Sci Eng.* 2024. [7]. Gaujoux S et al., *Gland Surg.* 2026.