Marie Sklodowska-Curie Doctoral Network (MSCA-DN)

Training for Organoids modelling Physiology and Pathology in the human gastrointestinal tract

TOP GUT Call for applications for 11 Doctoral (PhD) Training Positions in the field of innovative preclinical model for advancing personalized medicine.

Offer Description

TOP-GUT is a highly interdisciplinary and intersectoral training network focused on **training 11 doctoral candidates (DCs) (of which, one is recruited by the Swiss partner) in the field of innovative preclinical model for advancing personalized medicine**.

TOP-GUT aims at providing to **11 DCs** the skills to

- develop new human organ models mimicking cellular compositions of organs
- advance organ-on-chip technology
- improve tools and protocols for more complex gastrointestinal (GI) models
- develop new models for personalized medicine using patient-derived organoids
- manage **ethical, regulatory and legal aspects** together with innovation management of implementation of GI models and to prepare the DCs for the **European job market**

Participating in TOP-GUT offers doctoral candidates many unique opportunities, including:

- A project as Marie Skłodowska Curie trainee in one of the participating institutions with the objective of receiving a doctoral degree (PhD).
- State-of-the art, exciting research in an international consortium with highly integrated research projects.
- At 5 months of research training in the lab of another consortium member, mostly in a different EU country than the country where most of the project will take place.
- Training in both academic and commercial research environments.
- Salary according to EU guidelines for Marie Skłodowska Curie trainees, including mobility payments and family allowances where applicable.

Application Process

TOP-GUT will select Doctoral Candidates through a 2-step recruitment process.
The selection procedure will be open, transparent, and merit-based, fully aligned with the Code of Conduct for the Recruitment of Researchers. Although the selection will be based on the quality of applications, gender balance will also be considered.

Candidates can apply for **maximum three PhD projects** and the applications need to be submitted separately. Applications (in English) must include:

1) a **cover letter** which will also include the motivation for the position, emphasizing the candidate's strengthregarding the project and the requirements (max 3 pages)
2) a **CV** (max 2 pages),
3) a scanned **copy of all relevant diplomas or certificates** that formally entitle the candidate to embark on a doctorate. Typically, these documents will include Batchelor's and Master's Degree certificates. In case the Master Degree has not been obtained yet at the closing date for application, the candidate has to submit adeclaration signed by their supervisor or University official stating that the degree will be obtained by the time of PhD enrolment.
4) **Letter of Recommendation** from two appropriate referees or two contact details of referees.

Application documents in **a single pdf file** should be sent by email to the relevant project supervisors (**see email address in individual project descriptions**). The subject line of the email must be in the following format: "exTra: application for Project# _Title of PhD project".

The closing date for applications is 15th December, 2023

Applicants are advised to familiarise themselves thoroughly with the projects, for which they apply and be ready to answer questions on their chosen topics. After reviewing all project applications, supervisors of individual projects will contact selected applicants to organise an initial screening interview by telephone or videoconferencing. The most promising candidates might then be invited to a personal interview at the host institution or a further videoconference, potentially with several other project supervisors.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Research projects offered by TOP-GUT

ESR	Project Title	Primary Supervisor	Institution	EU State
1	Characterization of carbohydrate complexity along the GI tract	Hans Wandall hhw@sund.ku.dk	University of Copenhagen (UCPH)	DK
2	The impact of carbohydrate complexity on host-microbe interaction	Sina Bartfeld s.bartfeld@tu-berlin.de	Technische Universitat Berlin(TUB)	DE
3	Cross-tissue organoid immune cell integration and function	Birgit Sawitzki birgit.sawitzki@bih-charite.de	Charité Universitaetsmedizin Berlin (CHAR)	DE
4	Automation of PDO models in microphysiological systems	Eva Dehne career@tissuse.com	TissUse (TissUse)	DE
5	Building gut architecture	Silvia Mihăilă s.mihaila@uu.nl	Universiteit Utrecht (UU)	NL
6	An 3D platform to model gut-stroma interactions	Cristina Barrias ccbarrias@i3s.up.pt topgut_doc6@i3s.up.pt	Instituto de Investigação e Inovação em Saúde da Universidade do Porto (i3S)	PT
7	Gut on a chip for IBD research	Dorota Kurek d.kurek@mimetas.com	Mimetas (MIM)	NL
8	Gastric cancer PDOs as model for personalized T-cell targeted immune cell therapy	Hans Wandall hhw@sund.ku.dk	University of Copenhagen (UCPH)	DK
9	Gastric cancer organoids as model for personalized cancer therapy	Celso Reis celsor@ipatimup.pt topgut_doc9@i3s.up.pt	Instituto de Investigação e Inovação em Saúde da Universidade do Porto (i3S)	PT
10	The ethics and law of GI models Position not yet open	Søren Holm Heidi Beate Bentzen This position will be published separately	University of Oslo (UiO)	NO
11	ECP preconditioning to reverse trained immunity in kidney transplantation	Roger Geiger roger.geiger@irb.usi.ch	Università della Svizzera italiana (IRB)	CH

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

DoC1	Characterization of carbohydrate complexity along the GI tract
Host Institution	University of Copenhagen (UCPH)
Primary Supervisor	Hans Wandall
Email address	hhw@sund.ku.dk
Planned duration	36 months
Subject Area	Organoid technology, glycobiology, mass spectrometry, genetic engineering, glycobiology. infection biology

Introduction: The GI tract is not one homogeneous tissue. Gene expression, including innate immunity genes, greatly varies between the segments, and pathogens and probiotics affect different segments in different ways. Each segment features specific mucin expression and glycan profiles, and it can be expected that each segment will have their specific local stromal/immune cell interactions. In this project we will analyse and compare the glycan and mucin complexity along the GI tract to learn about commonalities and differences. We will define the compositional and spatial heterogeneity of the immune cell landscape in the tissue and decipher the mucin and glycocode along the cephalocaudal axis. We will study the impact of specific mucins and glycans for interactions with probiotics or pathogens of the stomach and intestine.

Aims: A1) Characterization of the carbohydrates and mucins using mass spectrometry-based glycoprofiling of both O- and N-linked glycans of tissue and PDOs of stomach, small intestine, and large intestine. **A2)** The functional implications of mucins and specific glycoconjugates on cellular differentiation and regeneration will be examined by genetically glycol-engineered human gastric and intestinal PDOs.

Expected Results: PDOs and GI epithelial cells from patient tissues will be fully characterized regarding expressed complex N-linked and O-linked glycans using MS/MS. This will provide information on the expression of specific glycans in the different segments of the GI tract involved in differentiation, transformation, and interactions with probiotics and pathogen and test to what degree future GI-models reflect the normal human glyco-environment. The generated knock out PDO will allow us to define the role of mucin and in tissue homeostasis, and (in cooperation with DC2 and DC8 and DC9) cancer biology, targeted treatments, and host pathogen interactions

Secondments: 1) TUB (S. Bartfeld) for training in PDO culture (M13, duration 2 month); 2) BIO (C.Clausen) for the characterization of models (M24; duration 3 months), and 3) i3S (C. Barrias) for training in histological evaluation of the created models focusing on mucin expression (M34, 1 months).

Enrolment in Doctoral degree(s): UCPH**.** Promoter: Hans Wandall (UCPH)

Project-specific selection criteria We are looking for a highly motivated and enthusiastic scientist with a strong background in biochemistry and cell biology. The candidate must have a master's degree in biochemistry, molecular biology, (bio)medicine, biology, or similar. Knowledge in 2D and 3D cell culture, and familiarity with mass spectrometry, glycobiology, microscopy, and flow cytometry an advantage. Familiarity with host-pathogen interactions is desired. You have a curious mindset and an active interest in glycosylation and cell biology. Proficient communication skills and ability to work in teams. Excellent written and spoken English skills. Applicants should be highly organized and motivated to carry out research related to the topics described above.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Recommended reading:

1. Ye Z, Kilic G, Dabelsteen S, …. Olsen JV, Wandall HH. Characterization of TGF-β signaling in a human organotypic skin model reveals that loss of TGF-βRII induces invasive tissue growth. Science Signaling. 2022 Nov 22
2. Nielsen MI, de Haan N, ……Wandall HH. Global mapping of GalNAc-T isoform-specificities and O-glycosylation site-occupancy in a tissue-forming human cell line. Nat Commun. 2022 Oct 21
3. de Haan N, …Wandall HH. In-Depth Profiling of O-Glycan isomers in Human Cells Using C18 Nanoliquid Chromatography-Mass Spectrometry and Glycogenomics. Anal Chem. 2022 Mar 15
4. Ieva Bagdonaite‡….Carolyn R. Bertozzi, Hans H. Wandall….Morten Thaysen-Andersen, and Nichollas E. Scott. Glycoproteomics. Nature Reviews Methods Primers. 2022, 2 (1): 1-29.
5. Dabelsteen S, …Wandall HH. Essential Functions of Glycans in Human Epithelia Dissected by a CRISPR-Cas9-Engineered Human Organotypic Skin Model. Dev Cell. 2020 Sep 14;54(5)

Funded by the European Union under Grant Agreement 101119911

DoC2	The impact of carbohydrate complexity on host-microbe interaction
Host Institution	Technische Universitat Berlin (TUB)
Primary Supervisor	Sina Bartfeld
Email address	s.bartfeld@tu-berlin.de
Planned duration	36 months
Subject Area	organoid technology, microbiology, infection biology, microscopy

Introduction: The mucosal barrier of the gastrointestinal tract and its carbohydrate composition has a central role in infections, inflammatory and neoplastic conditions. PDOs from the different segments of the GI tract recapitulate the specific mucins expression and mimic the mucus barrier in vitro. This barrier is specifically targeted by pathogens and probiotics across the GI tract. The aim of this project is to study the impact of specific mucins and glycans on interactions with probiotics and pathogens of the stomach and intestine. For that, the carbohydrate complexity of stomach and intestine PDOs will be analysed and characterized, and in vitro models will be adapted to study the impact of carbohydrate complexity in homeostasis and infection scenarios.

Aims: A1) Establish infection condition for selected bacteria in the intestine and stomach. **A2**) Defining the impact of specific glycosyltransferases and mucins on host-pathogen interactions in the stomach or intestine

Expected Results: We will use genetically engineered PDO either present in the lab (*MUC5AC* KO) or generated by DC1 (other mucins and glycosyltransferases) for infection with gastric or intestinal pathogens and probiotics. DC will use the gastric pathogen *Helicobacter pylori* versus the commercially available probiotic *Lactobacillus reuteri* for the stomach, and enteropathogenic *Escherichia coli* (EPEC) versus commercially available probiotic *E. coli* Nissle in the intestine to study the effect of mucus barrier protection of the epithelial cells, attachment of bacteria and development of hallmarks of pathology (such as A/E lesion formation in the case of EPEC). Using knowledge from the other projects, we can implement differentiation conditions (3D, perfusion, stroma) to further enhance secretory cell differentiation and mucus secretion. This will accelerate the use of PDO as model for infectious diseases and probiotics treatment.

Secondments: 1) UCPH (H. Wandall) for training in glycoproteomics, and genetic targeting of key glycosyltransferase genes (M9, duration 1 month). 2) NZB (K.Tykwinska) for training in probiotics such as *L. reuteri* ("Pylopass") and their impact on PDO (M18, duration 3 months). 3) BAC3GEL (D. Pacheco): for training in mucus production (M30, duration 1 month).

Enrolment in Doctoral degree(s): TUB. Promoter: Sina Bartfeld (TUB). Co-Promoters: Hans Wandall (UCPH).

Project-specific selection criteria We are looking for an excellent and highly motivated student with a strong background in cell biology and infection biology. Candidate must have a master degree in Biology, Microbiology, Biomedicine or similar. Candidate should have laboratory experience in cell culture, ideally with organoids and be familiar with microscopy, flow cytometry, and transcriptomic techniques. Prior experience working with pathogens in BSL2 is desired. Very good communication skills, ability to work in a team and willingness to cooperate intensively with projects partners are expected. Very good English skills are required.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Recommended reading:

1. Kayisoglu O, ..., Bartfeld S. Location-specific cell identity rather than exposure to GI microbiota defines many innate immune signalling cascades in the gut epithelium. Gut. 2021 Apr;70(4) PMID 32571970
2. Aguilar C, ..., Bartfeld S. Helicobacter pylori shows tropism to gastric differentiated pit cells dependent on urea chemotaxis. Nat Commun. 2022 Oct 5;13(1) PMID 36198679
3. Dabelsteen S, ..., Wandall HH. Essential Functions of Glycans in Human Epithelia Dissected by a CRISPRCas9-
4. Engineered Human Organotypic Skin Model. Dev Cell. 2020 Sep 14;54(5) PMID 32710848

Funded by the European Union under Grant Agreement 101119911

DoC3	Cross-tissue organoid immune cell integration and function
Host Institution	Charité Universitaetsmedizin Berlin (CHAR)
Primary Supervisor	Birgit Sawitzki
Email address	birgit.sawitzki@bih-charite.de
Planned duration	36 months
Subject Area	Immunology, multiplex technologies, multiplex data analysis including AI

Introduction: The gastrointestinal tract is a heterogeneous organ system broadly subdivided into stomach, small and large intestine. Gene expression, including innate immunity genes, greatly varies between the segments. Population by pathogens and commensals varies across different segments. Thus it can be expected that each segment will have their specific local stromal/immune cell compositional and spatial organization, Interestingly, cancers of the stomach and the colon are abundant and deadly, while cancers of the small intestine are rare. The local immune cell and especially T cell composition could be decisive for the lower potential of cancer development. The basic understanding of this is important to be develop new healthy and diseased human gut organ models mimicking the cellular heterogeneity. Applying spatial transcriptomics and proteomics technologies the student the group seeks to understand whether the homeostatic immune cell composition is linked to the formation of an inhibitory tumour growth-promoting environment.

Aims: A1) Map differences in immune cell composition, functional states and inflammatory signals across different human GI tissues (stomach, small and large intestine from cancer and non-affected patients); **A2)** Integrate immune cells into 2-organ-chip and gastric cancer organoids for improved modelling of host-pathogen interactions and CAR-T-cell responses

Expected Results: We will substantially advance the design and functionality of gastric PDOs by embedding the tissue and clinical state-specific immune cell compartment. This will improve the power of PDO to model human diseases and predict treatment responses. To do so we will make use of our established human tissue procurement pipeline and broad consent embedded into the Charité 3R initiative. Applying state of the art multiplex technologies (cytometry, imaging, single cell and spatial transcriptomics) and artificial intelligence (AI) tools we will create and utilise a database linking data on intra-tissue immune cells to clinical information. We will also incorporate existing data from open access platforms. Once established we will test strategies to embed tissue-specific immune cell features into 2-organ-chip and gastric cancer PDO.

Secondments: 1) HSA (S. Biniaminov) to develop AI software tool to analyse and share intra-tissue immune cell data at (M20 for 3 months; 2) TUB/UU (S. Bartfeld, S. Mihăilă) to try protocols for immune cell embedding (M26 for 3 months)

Enrolment in Doctoral degree(s): CHAR (BSRT graduate school https://bsrt.cloud.opencampus.net/), Promoter: Birgit Sawitzki (CHAR); Co-promoters: Sina Bartfeld (TUB), Matthias Barone (CHAR)

Project-specific selection criteria background in immunology, interest in translational research:

- M.Sc. or equivalent degree in Biochemistry, Bioinformatics, Biology, Cell/Molecular Biology, Bioengineering, Genetics, Medical Biology, or a related field
- Strong academic background and dedication to translational research especially in immune-mediated diseases

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

- Interest and/or expertise in working with biological systems
- Prior experience with at least one of the following methods is highly desirable: multi-parameter (flow) cytometry, single cell RNAseq, computational biology or data analysis of multiplex datasets
- Scientific curiosity and motivation to perform scientifically rigorous experimental work
- Appreciation for interdisciplinary work and proactive drive to collaborate across disciplines
- Ability to work independently as well as part of a team, excellent organizational skills and high reliability
- Strong verbal and written communication skills in English (i.e. German not required)

Recommended reading:

Multiplex technologies (cytometry, imaging, single cell and spatial transcriptomics) on patient tissue samples:

1. Georg P, Astaburuaga-García R, Bonaguro L, et al. Complement activation induces excessive T cell cytotoxicity in severe COVID-19. Cell. 2022;185(3):493-512.e25. doi:10.1016/j.cell.2021.12.04026.
2. Schulte-Schrepping J, Reusch N, Paclik D, et al. Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment. Cell. 2020;182(6):1419-1440.e23. doi:10.1016/j.cell.2020.08.001
3. Lin, JR., Chen, YA., Campton, D. *et al.* High-plex immunofluorescence imaging and traditional histology of the same tissue section for discovering image-based biomarkers. *Nat Cancer* **4**, 1036–1052 (2023). https://doi.org/10.1038/s43018-023-00576-1

Funded by the European Union under Grant Agreement 101119911

DoC4	Automation of PDO models in microphysiological systems
Host Institution	TissUse GmbH (TissUse)
Primary Supervisor	Eva-Maria Dehne
Email address	eva.dehne@tissuse.com
Planned duration	36 months
Subject Area	Microphysiological multi-organ system / automation / human (patho)physiology / organoids

Introduction: TissUse is a Berlin, Germany-based, biotechnology company, which has developed a unique "Multi-Organ-Chip" platform that provides unparalleled preclinical insight on a systemic level using human tissues. This enabling technology platform consists of a miniaturized construct that closely simulates the activity of multiple human organs in their true physiological context. The chips provide a new approach to predict, for example, toxicity, ADME profiles and efficacy *in vitro*, reducing and replacing laboratory animal testing and streamlining human clinical trials.

Aims: **A1)** Emulating both the physiology and the pathophysiology of GI-liver connection. **A2)** Establish highly standardized culture conditions and assays for high throughput applications.

Expected Results: We will establish one or two selected cancer PDO models along the gastrointestinal tract using our microfluidic 2-organ platform. The new assay combining cancer and liver models in a dynamically perfused on-chip co-culture will be leading towards enhanced culture stability and physiological relevance. Physiological local microenvironments like tissue architecture, pH and pO2 gradients, and aspects of the microbiome will be taken into consideration. Pathophysiological local microenvironments will encompass cancer embedment (surrounding tissue composition, vasculature, pO2 gradients, connective tissue …) and invasive and dormant cancer behaviour microenvironment. The assays will be subjected to standardized culture conditions on the HUMIMIC Autolab, furthermore allowing for high content data acquisition and KI-assisted monitoring of culture behaviour.

Secondments: 1) TUB (S. Bartfeld) for learning about PDO culture (M12, duration 3 months). 2) UCPH (H. Wandall) for glycobiology and genetic engineering of the models (M18, duration 1 month), 3) CHAR (B. Sawitzki) for immune cell PDO interaction (M30, duration 1 month).

Enrolment in Doctoral degree(s): TUB. Promoter: Sina Bartfeld (TUB)

Project-specific selection criteria: MSc in Biotechnology, Biology or a comparable qualification

- Hands-on experience in cell culture, preferably human primary cells or iPSC; ideally experience in 3D tissue engineering
- Sound knowledge in molecular biology techniques and imaging
- Interest in working with microfluidic systems and promoting automated handling of the chips

Ability to work in a team, commitment and sense of responsibility

1. **Recommended reading:**
2. www.tissuse.com
3. https://www.youtube.com/watch?v=RRUtxMXwKws

Marx U, et al. An Individual Patient's "Body" on Chips – How Organismoid Theory Can Translate Into Your Personal Precision Therapy Approach. Front. Med. (2021) doi: 10.3389/fmed.2021.728866

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

DoC5	Building gut architecture
Host Institution	Universiteit Utrecht (UU)
Primary Supervisor	Silvia Mihăilă
Email address	s.mihaila@uu.nl
Planned duration	36 months
Subject Area	Bioengineering

Introduction: In vitro gut models currently lack physiological relevance, prompting innovative approaches for enhanced cell culture. Incorporating a collagen scaffold mimicking human intestinal villi architecture into a microfluidic device offers a 3D tissue structure and fluidic shear, improving cell differentiation and physiological function. In this '3D gut chip' we aim to demonstrate enhanced absorptive permeability and biotransformation and enzyme activity.

Aims: A1) Reproduce the crypt-villus features of the intestinal lumen on hydrogels; **A2)** culture of intestinal PDO on these patterns; **A3)** Integrate the topographies into a perfusable devices; **A4)** address barrier and biotransformation activities in static and dynamic (flow) conditions

Expected Results: We will develop a perfusable chip in which physiological functions of the intestinal lumen are replicated. The chip will consist of an epithelial compartment with crypt-villi-like patterned hydrogels seeded with intestinal PDOs, on top of a porous membrane. The other side of the membrane, the second compartment, representing the blood side, will allow for fluid perfusion. We will investigate the role of the stroma (stromal cells embedded in the hydrogels) to support tissue maturation and barrier function and assess absorption and biotransformation of (e.g., bacterial, diet-derived and drug) molecules from the gut compartment, through the stroma (hydrogel) and then into the blood compartment. We expect to identify the relation between topography-shear stress and absorption, and map the biotransformation profiles of gut-derived nutrients, metabolites, and drugs.

Secondments: 1) Bac3Gel (D. Pacheco): mucus permeability studies (M20, duration 3 months), 2) CHAR (B. Sawitzki): culture of immune cells in the patterned hydrogels (M30, duration 3 months) 3) TUB (S. Bartfeld): in vitro infection with bacteria cultures (M40, duration 3 months);

Enrolment in Doctoral degree(s): UU promoter: Roos Masereeuw (UU), Co-promoter Silvia Mihăilă (UU), Yvonne Vercoulen (UMCU)

Project-specific selection criteria:

A Master's degree in a related field (e.g., Biomedical Engineering, Regenerative Medicine, Molecular Biology, or a similar discipline).
Strong laboratory skills and experience in cell culture (organoids) and biofabrication (3D printing)
Excellent communication and teamwork skills.
The ability to work independently and drive a research project forward.
Prior experience in microfluidics, organ-on-a-chip systems, or similar technologies is a plus.

Recommended reading:

1. Nikolaev M, et al, Homeostatic mini-intestines through scaffold-guided organoid morphogenesis. Nature. 2020 PMID: 32939089.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

2. Creff J, et al, Fabrication of 3D scaffolds reproducing intestinal epithelium topography by high-resolution 3D stereolithography. Biomaterials. 2019 PMID: 31419651.
3. Valiei A, et al, Gut-on-a-chip models for dissecting the gut microbiology and physiology. *APL bioengineering*, *7*(1), 011502. https://doi.org/10.1063/5.0126541

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

DoC6	An 3D platform to model gut-stroma interactions
Host Institution	Instituto de Investigação e Inovação em Saúde da Universidade do Porto (i3S)
Primary Supervisor	Cristina Barrias
Email address	ccbarrias@i3s.up.pt; topgut_doc6@i3s.up.pt
Planned duration	36 months
Subject Area	Bioengineering/ Health Sciences

Introduction: Epithelial cells in vivo are supported by a matrix of stroma, produced by fibroblasts, and perfused by the vascular system. This microenvironment influences specific tissue functions, builds tissue niches, and balances the outcome of pathologies. We aim to replicate the intestinal stroma by co-culturing intestinal organoids with stromal fibroblasts in chemically controlled hydrogels with perfusable vessel-like channels. By varying the source of fibroblasts (tissue origin and/or healthy/disease state), we will be able to unveil their role in the development and function of GI epithelia, using different technologies.

Aims: A1) Build a 3D platform that combines human gastric/intestinal organoids with a stromal compartment integrating hydrogel-embedded fibroblasts and perfusable microvessels. **A2**) We will use the model to unveil the role of fibroblasts in the development and function of GI epithelia

Expected Results: We will build an advanced in vitro platform to emulate gut-stroma interactions, including heterotypic cell-cell and cell-matrix interactions supported by perfused microvessels. We will engineer a vascularized stroma from the bottom-up, by embedding spheroids (with fibroblasts and endothelial cells) in a customized hydrogel. We will use test different types of fibroblasts (tissue-specific vs. different location, and/or healthy vs. cancer-associated) to understand bidirectional interactions between GI epithelia and fibroblasts, which are central for proper organ development and function being also implicated in disease

Secondments: 1) MIM (D. Kurek) for training on OoC cultures (M9, duration 3 months), 2) UU (S. Mihăilă) to build the chip (M12, duration 3 months), and 3) CHAR (B. Sawitzki) for training on multiplex technologies (M24, duration 1 month).

Enrolment in Doctoral degree(s): University of Porto (ICBAS). Promoter: Cristina Barrias (i3S); Co-promoter: Silvia Mihăilă (UU) and Marta Silva (i3S)

Project-specific selection criteria Candidate must have a master´s degree in Bioengineering, Biotechnology, Biochemistry, Biology, or related Health Sciences fields. The candidate should have laboratory experience in biomaterials and 3D cell culture. Candidate must be familiar with cell and molecular biology techniques, including but not limited to: immunolabeling analysis, confocal imaging, and gene expression analysis. Preferred candidates will have experience in organoid cultures, microfluidic devices, and omics approaches.

Recommended reading:

DOI: 10.2139/ssrn.4592224; DOI: 10.3389/fbioe.2020.00494; DOI: 10.1016/B978-0-323-50878-0.00020-3; DOI: 10.1016/j.carbpol.2023.121226

Funded by the European Union under Grant Agreement 101119911

DoC7	Gut on a chip for IBD research
Host Institution	Mimetas (MIM)
Primary Supervisor	Dorota Kurek
Email address	d.kurek@mimetas.com
Planned duration	36 months
Subject Area	Organ-on-a-chip, human tissue and disease models, automation, phenotypic screening, AI-driven image analysis

Introduction: Understanding how different intestinal cells contribute to the progression and maintenance of Inflammatory Bowel Disease (IBD) is crucial for the development of new therapies. Leveraging the capabilities of microfluidic platform, OrganoPlate, we intend to construct a complex, patient-specific model that faithfully replicates the intricate interactions between intestinal fibroblasts, endothelial, epithelial, and immune cells within the context of the diseased gut. We aim to develop novel phenotypic assays that mimic certain aspects of IBD pathophysiology and, significantly, open avenues for finding new targets and personalized therapies. We hope not only to advance our fundamental comprehension of IBD but also to pioneer innovative therapeutic strategies through the establishment of robust, reproducible, high throughput phenotypic assays suitable for screening.

Aims: A1) Develop 3D human (patient specific) models in the microfluidic platform OrganoPlate to mimic intestinal architecture and the IBD environment **A2)** Develop a gut-on-a-chip model-based readouts for inflammatory phenotypes suitable for high-throughput screening. **A3**) Validate the model with tool compounds

Expected Results: We will develop a gut on-a-chip model using the Organoplate setup. In this plate, two channels are separated by a hydrogel. One channel is populated with cells from intestinal PDOs, the second channel will be infused with immune cells, initially from cell lines and ultimately with matching immune cells from PDO donors. Both channels are perfused. Using this setup, we will identify IBD patient-specific phenotypes, identify and optimize high-throughput assay(s) suitable for the identification of compounds correcting IBD phenotype.

Secondments: 1) UCPH (H. Wandall) to characterize mucins in the OrganoPlate gut model (M18, 1 month); 2) CHAR (B. Sawitzki) for immune cell integration) (M30, 2 months).

Enrolment in Doctoral degree(s): UU. Promoter: Roos Masereeuw (UU), co-promoter Silvia Mihăilă (UU)

Project-specific selection criteria:

-MSc in a Biology/Bioengineering or a related discipline with preference given to those candidates with experience in Stem cell/3D cell culture/immunology.
-You are highly experienced in tissue culture with a hands-on mentality;
-You are experienced in (confocal) microscopy and image analysis software;
-You have experience with live cell assays and standard molecular analysis techniques;
-You have affinity with novel technologies and are willing to contribute to the development thereof;
-Your work is of high quality, precise, and safe;
-You have a motivated and flexible work attitude and enjoy working in a dynamic environment;
-Proficiency in the English language.
-Experience with in vitro tissue modelling as well as omics data analysis and bioinformatics is a plus.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Recommended reading:

1. https://doi.org/10.1007/s10456-023-09888-3,

2. https://doi.org/10.3390/ijms20225661

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

DoC8	Gastric cancer PDOs as model for personalized T-cell targeted immune cell therapy
Host Institution	University of Copenhagen (UCPH)
Primary Supervisor	Hans Wandall
Email address	hhw@sund.ku.dk
Planned duration	36 months
Subject Area	Organoids, oncology, immunology, monoclonal mAbs, CARTsimmunotherapy, antibodies, glycobiology

Introduction: In the aging society, disease burden, such as cancer, is rising. At the same time, drug development successes are limited partly due to high drug failure rates in the transition from animal experimentation to human patients. This project aims to build human stem cell-based gastrointestinal models to mimic solid human cancers and use them as models for personalized cancer treatments. We have generated several monoclonal antibodies that target exquisite cancer-specific carbohydrate-based targets expressed in GI cancers. The developed monoclonal antibodies can be formulated as antibody-drug conjugates (ADCs), bispecifics, and CAR-T-cells. In this project, we will establish co-culture conditions with immune cells T-cells to allow evaluation of the specific targeting approach and evaluate the specificity and safety of the developed molecules.

Aims: Establish gastric cancer organoids as a model to test therapeutic interventions with biologicals, ADCs, bispecifics, and CAR-T-cells. **A2**) Establish co-culture conditions with targeted T-cells to allow evaluation of the specific targeting of cancer cells by live imaging.

Expected Results: We will take advantage of our developed monoclonal antibodies and established bispecifics, ADCs, and CAR-Ts that target cancer-specific short O-glycan structures, now in preclinical and clinical development. The effect of the bispecifics, ADCs, and CAR-Ts will be monitored using our established genetically engineered cells, our array of cancer cell lines, and 3D tumor-tissue models that recapitulate solid tumor growth ex vivo. We expect that the established model with clinically relevant organoids will allow us to develop robust systems for personalized and preclinical testing of the safety of bispecifics, ADCs, and CAR-Ts. In addition, the generation of a genetically engineered 3D co-culture system that reflects solid tumors will provide a flexible and scalable system that can be adapted to any potential target and ease optimization of future targeted therapeutics.

Secondments: 1) Roche-Gly (C. Klein, M18, 3 months) for training in co-culture with bispecific mAbs and relevant T-cells and 2) IRB (R. Geiger, M30, 1 month) for training in characterization and immunoprofiling of CAR-Ts co-cultured with cancer organoids.

Enrolment in Doctoral degree(s): UCPH, Promoter: Hans Wandall (UCPH)

Project-specific selection criteria: We are looking for a highly motivated and enthusiastic scientist with a strong background in biochemistry, immunology, or cell biology. The candidate must have a master's degree in biochemistry, molecular biology, (bio)medicine, biology, immunology, or similar. Knowledge of 2D and 3D cell culture and familiarity with immunology, cancer biology, glycobiology, microscopy, and flow cytometry is an advantage. You have a curious mindset and an active interest in cancer and cell biology, immunology, and personalized medicine. Proficient communication skills and ability to work in teams. Excellent written and spoken English skills. Applicants should be highly organized and motivated to carry out research related to the topics described above.

Recommended reading:

1. Aasted MKM, Groen AC, Keane JT, Dabelsteen S, Tan E, Schnabel J, Liu F, Lewis HS, Theodoropulos C, Posey AD, Wandall HH. Targeting Solid Cancers with a Cancer-Specific Monoclonal Antibody to Surface Expressed Aberrantly O-glycosylated Proteins. Mol Cancer Ther. 2023 Oct 2;22

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

2. Ye Z, Kilic G, Dabelsteen S, …. Olsen JV, Wandall HH. Characterization of TGF-β signaling in a human organotypic skin model reveals that loss of TGF-βRII induces invasive tissue growth. Science Signaling. 2022 Nov 22

3. Dabelsteen S, …Wandall HH. Essential Functions of Glycans in Human Epithelia Dissected by a CRISPR-Cas9-Engineered Human Organotypic Skin Model. Dev Cell. 2020 Sep 14;54(5)

4. Wandall HH, Nielsen MAI, King-Smith S, de Haan N, Bagdonaite I. Global functions of O-glycosylation: promises and challenges in O-glycobiology. FEBS J. 2021 Dec;288(24)

Funded by the European Union under Grant Agreement 101119911

DoC9	Gastric cancer organoids as model for personalized cancer therapy
Host Institution	i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto (i3S)
Primary Supervisor	Celso Reis
Email address	celsor@i3s.up.pt; topgut_doc9@i3s.up.pt
Planned duration	36 months
Subject Area	Health Sciences / Cell Biology / Oncobiology

Introduction: Gastrointestinal tumours are major heterogenous diseases that presents several molecular, cellular and extracellular components. This biological heterogeneity illustrates the underlying complexity driven by genetic, epigenetic, metabolic and environmental alterations acquired during the carcinogenesis process and tumour progression. Such heterogeneity allows the currently implemented tumour molecular classifications and is the basis for patient therapeutic stratification systems. Human gastrointestinal organoids represent innovative models to study the various biological components in cancer development and tumour progression. Focus on key oncogenic targets, such as tyrosine kinase receptors, immune checkpoints and the glycosylation impact will be developed in order to understand their biological role and their application in therapeutic studies applying Organoids in the context of personalized medicine.

Aims: A1) To expand the gastric PDO biobank and characterize the molecular features of the PDOs as a model to evaluate cancer therapy response to novel and currently approved therapeutic drugs. **A2**) To evaluate the model robustness to predict tumor resistance and patient therapy response. **A3**) To evaluate the impact of glycosylation in therapeutic targets by generation of genetic modified models.

Expected Results: We expect that the established PDOs which will be fully characterized for the molecular features comparing the approved and novel putative therapeutic targets, such as those targeting tyrosine kinase receptors, immune checkpoints and evaluate glycosylation impact in these targets. Approaches include transcriptomic, proteomics, glycomic studies, IHC, IF, Proximity Ligation Assay and MS/MS analysis. We expect to evaluate the molecular features of these PDOs in comparison with their respective primary tumors in order to evaluate and validate their potential application as models for personalized medicine.

Secondments: 1) UCPH (H. Wandall) for training in glycoproteomics, and genetic targeting of key glycosyltransferase genes. (M12, duration 3 months), 2) MIM (D. Kurek) for training in on Organ-on-chip cancer applications (M30 duration 3 month)

Enrolment in Doctoral degree(s): University of Porto UP-ICBAS. Promoter: Celso Reis (i3S); Co-promoter: Filipe Pinto (i3S).

Project-specific selection criteria: Candidate must have a master´s degree in Biology, Bioengineering, Biotechnology, Biochemistry, or related Health Sciences fields. The candidate should have laboratory experience in cell biology and biochemistry. Candidate must be familiar with cell and molecular biology. Preferred candidates will have experience in techniques to study patient-derived organoids and their applications in cancer research, cell culture, molecular biology, omics approaches, immunolabeling analysis, imaging approaches and drug screen assays.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Recommended reading:

1. Mereiter S, Balmaña M, Campos D, Gomes J, Reis CA. Glycosylation in the Era of Cancer-Targeted Therapy: Where Are We Heading? Cancer Cell. 2019 Jul 8;36(1):6-16.
2. Duarte HO, … Reis CA. ST6Gal1 targets the ectodomain of ErbB2 in a site-specific manner and regulates gastric cancer cell sensitivity to trastuzumab. Oncogene. 2021 May;40(21):3719-3733
3. Costa AF, Campos D, Reis CA, Gomes C. Targeting Glycosylation: A New Road for Cancer Drug Discovery. Trends Cancer. 2020 Sep;6(9):757-766.
4. Balmaña M, Mereiter S, Diniz F, Feijão T, Barrias CC, Reis CA. Multicellular Human Gastric-Cancer Spheroids Mimic the Glycosylation Phenotype of Gastric Carcinomas. Molecules. 2018 Oct 30;23(11):2815.
5. Yan HHN, …, Bartfeld S, …, Leung SY. A Comprehensive Human Gastric Cancer Organoid Biobank Captures Tumor Subtype Heterogeneity and Enables Therapeutic Screening. Cell Stem Cell. 2018 Dec 6;23(6):882-897.e11.
6. Yan HHN, .. Leung SY. A Comprehensive Human Gastric Cancer Organoid Biobank Captures Tumor Subtype Heterogeneity and Enables Therapeutic Screening. Cell Stem Cell. 2018 Dec 6;23(6):882-897.e11.

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

DoC11	Metabolic modulation of cancer PDOs with engineered probiotic bacteria for immunotherapy
Host Institution	Università della Svizzera italiana (IRB)
Primary Supervisor	Roger Geiger
Email address	roger.geiger@irb.usi.ch
Planned duration	36 months
Subject Area	Immunology / Cancer Immunotherapy / Engineered Bacteria / Organoids

Introduction: Bacteria colonizing tumors can be engineered to deliver therapeutic payloads directly to the tumor microenvironment. Given the capability to genetically modify these bacteria to produce various therapeutics, there is a need for high-throughput experimental platforms. These platforms are essential for screening bacterial candidates and assessing their effects on cancer and immune cells. Such platforms will assist in prioritizing bacterial strains for in vivo testing using mouse tumor models.

Aims: Develop a preclinical human model to test the impact of engineered probiotic bacteria on the T cell response to tumors. We will colonize colorectal cancer PDOs with engineered probiotic bacteria (*E. coli* Nissle) that either produce immunostimulatory metabolites or degrade immunosuppressive metabolites to enhance T cell responses to tumors. Then, cancer PDOs colonized with bacteria will be exposed to tumor antigen-specific T cells that target tumor cells. The cytotoxic effect of T cells will be monitored by time-lapse imaging.

Expected Results: We expect to establish a preclinical human model system to test the impact of genetically engineered, probiotic bacteria on the immune response to tumoroids. This model system will be tremendously useful to test and optimize new bacterial strains for their potential use as living biomedicines.

Secondments: 1) TUB (S. Bartfeld) for training on PDOs (M9, duration 1 month), i3S (C. Reis) for training on organoids and cancer (M10, duration 1 month), 2) Roche ITB (M. Lutolf) for training on organoid-on-a-chip models (M30, duration 3 months)

Enrolment in Doctoral degree(s): Università della Svizzera italiana (USI). Promoter: Roger Geiger (USI) Co-promoter: Matteo Pecoraro (IRB)

Project-specific selection criteria: Applicants are required to hold a master's degree in Immunology, Biology, Bioengineering, or a related field within the Health Sciences domain. We seek candidates that are curious and passionate about science and integrate well into our team. Laboratory experience, in particular with work related to immunology, bacterial engineering or culturing of organoids is an advantage.

Recommended reading:

DOI: 10.1126/science.add9667,

DOI: 10.1038/s41586-021-04003-2

Funded by the European Union under Grant Agreement 101119911
Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.