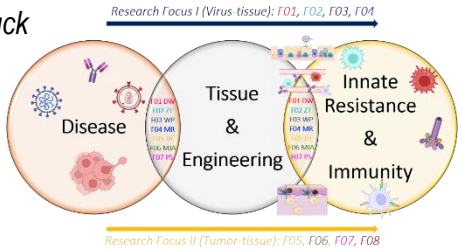
CONNECT

Call for Applications for the PhD program of the Medical University of Innsbruck

CrOsstalk in iNfection and cancer in disEase-on-Chip sysTems
(*CONNECT*)



Students motivated in unraveling the crosstalk of tissue and immune system upon viral infection and tumor development within human disease-on-chip models are invited to apply for a PhD position within the program CONNECT of the Medical University of Innsbruck (MUI), Austria (MUIDK-2022-1-2).

Research Context: Tissue cells crucially contribute to shaping immunity during infection, cancer and autoimmunity. Novel standardized and immune-competent human organ-on-a-chip models are urgently needed to unravel how different tissues affect inflammatory or de-regulated immune processes upon challenge with exogenous or endogenous triggers. .

Hypotheses/Research Questions/Objectives: During the projects within the *CONNECT* program, communication of skin, mucosa (lung, gut) and vascular barriers with immune regulatory mechanisms in infection, autoimmunity and cancer will be studied. We will advance our established organ-on-a-chip models to answer our research questions, how cells in barrier tissue communicate information across multiple disease states to the immune systems by integrating data from gene and protein expression with high content live cell imaging revealing cell-cell interactions in tissues. Using bioinformatics to model tissue/immune behavior and signal rewiring during disease at outer and inner barrier sites will complement the data obtained.

Approach/Methods: Implementing an educational program to investigate cross talk of tissue and immune system upon viral infection and tumor development in human disease-on-chip models will not only advance our understanding about differences and similarities in both fields regarding innate resistance and inflammation, but also accelerate the movement towards Replacement and Reduction of animal experiments. Research goals to decipher tissue-immune cross talk are centred around 3D bioprinting and bioinformatics, high content analyses (high content screening (HCS) & imaging platform, high content flow cytometry), luminex analyses and common immunologic and molecular biologic methods. PhD students will profit from the interdisciplinary and collaboration-driven environment within our program.

This PhD program offers:

- **4-year funded PhD position in the Innsbruck PhD School for Biomedical Sciences of the MUI with a salary according to the 'Kollektivvertrag' for PhD students at the Medical University of Innsbruck.**
- **Participation at one international meeting and two national meetings in the area of research.**
- **Up to 6 months stay abroad at a collaborating institution.**

Project-specific information and requirements:

PhD project 1: *Characterizing sex-dependent DC sensing mechanisms and immunometabolism at the tissue barrier during SARS-CoV-2 infection*

Supervisors:* *Doris Wilflingseder, Lukas A. Huber

The mechanism, by which the antigen-presentation capacity of DCs within respiratory tissues during COVID-19 is impaired, is largely unknown. The already in the Wilflingseder group established immune-competent respiratory barrier model will provide an exceptional opportunity to study in detail *molecular mechanisms, immunometabolism,*

and signal rewiring of DC functions during early SARS-CoV-2 infection under *in vivo*-like conditions in a primary cell model system. Immunometabolism reprogramming in DC subsets within tissues will be analysed in the Huber lab following infection with SARS-CoV-2. Thus, to provide insights on how PRR cross-talk, restriction factors, immunometabolism reprogramming, pyroptosis, inflammasome activation occur within the respiratory barrier and DCs within, we will study *re-programming of DCs in terms of maturation (DW), migration (DW), inflammation (DW), signaling (LAH) and metabolism (LAH) of SARS-CoV-2-specific immunity in both, female and male tissue models*.

Requirements:

- MSc in cell biology, molecular medicine, biology, medicine, immunology, or related
- Experience in cell culture techniques and ideally a background in immunology / DC biology are of advantage.

PhD project 2: ***Signaling rewiring in different lung epithelial cell subtypes following SARS-CoV-2 infection***

Supervisor: ***Zlatko Trajanoski***

The lung epithelium has a well-developed immunity to defend itself against respiratory challenges. However, during infection the precise rewiring of signaling pathways in epithelial cells and how this rewiring influences epithelial cell/immune cell interactions has not been elucidated so far. The organoid models and the cutting-edge molecular profiling methods will provide for the first time the opportunity to dissect *signaling rewiring in airway epithelial subsets*. We will use lung organoids derived from healthy tissue as well as from COPD patients and infect them with SARS-CoV 2 (collaboration with F01 DW and F03 WP), followed by single-cell RNA-sequencing. Additionally, we will use phosphoproteomic profiling of bulk epithelial cells. In parallel, we aim to adapt our bioinformatics method for reconstructing signaling rewiring using annotated cancer pathways to include immune pathways and pathways related to cell-cell interaction.

Requirements:

- MSc in bioinformatics, molecular medicine, biology, medicine, or related
- Experience in omic analyses

PhD project 3: ***Comparing dynamics of emerging and existing respiratory viral challenges within immune-competent lung-on-chip models***

Supervisor: ***Wilfried Posch***

Excessive inflammation triggered by a hitherto undescribed mechanism is a hallmark of SARS-CoV-2 infections and – without vaccination - is associated with enhanced pathogenicity and mortality. We now aim to decipher these inflammatory mechanisms in more detail within an immune-competent HAE model and *directly compare* downstream signaling cascades induced by the recently emerging SARS-CoV-2 or other respiratory challenges such as common human coronaviruses (HuCoV) or influenza A. The established immune/respiratory model (PubMed_WP) provides a good base for adding even more immune components for a more complex system and for performing a direct comparative analyses of various respiratory viral challenges (SARS-CoV-2 vs. HuCoV vs. Influenza) to determine *inflammatory signals, immune cell activation, infectivity and down-stream signaling events following viral challenge and its impact on the blood-brain-barrier (BBB)*. Analyses will be done in optimized human 3D models of upper and lower respiratory tract containing immune cells such as DCs, macrophages, T and B cells.

Requirements:

- MSc in cell biology, molecular medicine, biology, medicine, immunology, or related
- Experience in cell culture techniques and ideally a background in immunology are of advantage.

PhD project 4: ***Deciphering macrophage / dendritic cell functions in autoimmunity and infection in a model of the human blood-brain barrier***

Supervisor: ***Markus Reindl***

Autoimmune diseases affecting the central nervous system (CNS) are associated with autoantibodies and/or autoreactive T cells against neuronal or glial antigens. When activated by innate or adaptive immunological mechanisms, they can cross the otherwise tight blood-brain barrier (BBB) and cause CNS tissue damage. We developed a novel 3D bioprinted model of the BBB that has already provided first promising results and human macrophages / dendritic cells shall be added to this model to study their transmigration and their role in promoting tissue damage by antibody dependent cellular cytotoxocity together with human autoantibodies. Besides studying autoimmune reactions, our model will also be used to study the interaction of neurotropic viruses with endothelial, glial and neuronal cells (e.g. SARS-CoV-2). Analyses will be performed in 3D-bioprinted, immune-competent BBB models.

Requirements:

- MSc in molecular medicine, biology, medicine, immunology, neuroscience or related
- Experience in cell culture techniques and ideally a background in BBB functions are of advantage.

PhD project 5: ***Immune-modulatory effects on vessel barrier function and metastasis in 3D bioprinted, vascularized neuroblastoma-on-chip model***

Supervisor: ***Judith Hagenbuchner***

Solid tumors such as childhood neuroblastoma undergo hypoxic crisis when reaching a critical size and only the ability to re-organize the tumor environment and to induce tumor vascularization allows them to grow further and to metastasize to distant regions of the body. How immune cells in the tumor environment influence vessel barrier function and the ability of tumor cells to migrate during metastasis is a highly relevant clinical question, which cannot be studied using conventional 2D cell culture or tissue samples. This project will investigate in a perfused, 3Dbioprinted neuroblastoma-on-chip model, how immune cells (macrophages, dendritic cells) and cytokines in the tumor environment modulate vessel permeability and tumor cell migration. The methodology involves 3D bioprinting and fluidic chip design, iPSC differentiation, perfused culture of 3D tissue equivalents, confocal live cell fluorescence imaging and flow cytometry of cells isolated from bioprinted tissue. Transcriptomics of metastasizing cells will be analyzed by RNAseq.

Requirements:

- MSc in cell biology, molecular medicine, biology, medicine, immunology, or related
- Experience in cell culture techniques and ideally a background in tumor biology are of advantage.

PhD project 6: ***Studying signal rewiring in DC subsets in 3D bioprinted skin cancer-on- chip models***

Supervisors: ***Patrizia Stoitzner, Michael J. Ausserlechner***

Research in tumor immunology heavily relies on mouse cancer models, however translation of these findings into the patient situation is difficult. Therefore, there is an urgent need to develop skin cancer models that reflect most closely the human situation. Thus, we will use an established 3D bioprinted skin model and develop skin cancer-on-chip systems to study immune cell-tumor cell interactions. As our research focus is on dendritic cells (DC) we will investigate, how signaling pathways are rewired in 3D bioprinted skin cancer models to understand, how tumor development in the skin affects phenotype and function of various skin DC subsets. This knowledge is urgently needed to advance immunotherapy of cancer. By introducing LC and dermal DC into the epidermis and dermis,

respectively, we will investigate the interactions between these immune cells and tumor cells and subsequently, we will also try to use skin cancer organoids/spheroids generated from patient material for implementation into the 3D bioprinted skin model.

Requirements:

- MSc in cell biology, molecular medicine, biology, medicine, immunology, or related
- Experience in cell culture techniques and ideally a background in tumor biology/immunology are of advantage.

Your application:

We look forward to receiving your application until **March, 1st, 2023,** to the e-mail address ciit@i-med.ac.at. The application shall include:

(1) a cover letter (not longer than 1 page),

(2) a motivation statement (not longer than 1 page),

(3) a CV

(4) a short description of the master thesis and outcomes thereof

Please generate a single PDF with

the file name:

Application 2023_<YOUR NAME>.pdf

and send the e-mail with the Subject:

<PhD project_PROJECT SUPERVISOR NAME>_PhD Application CONNECT 2023

to ciit@i-med.ac.at