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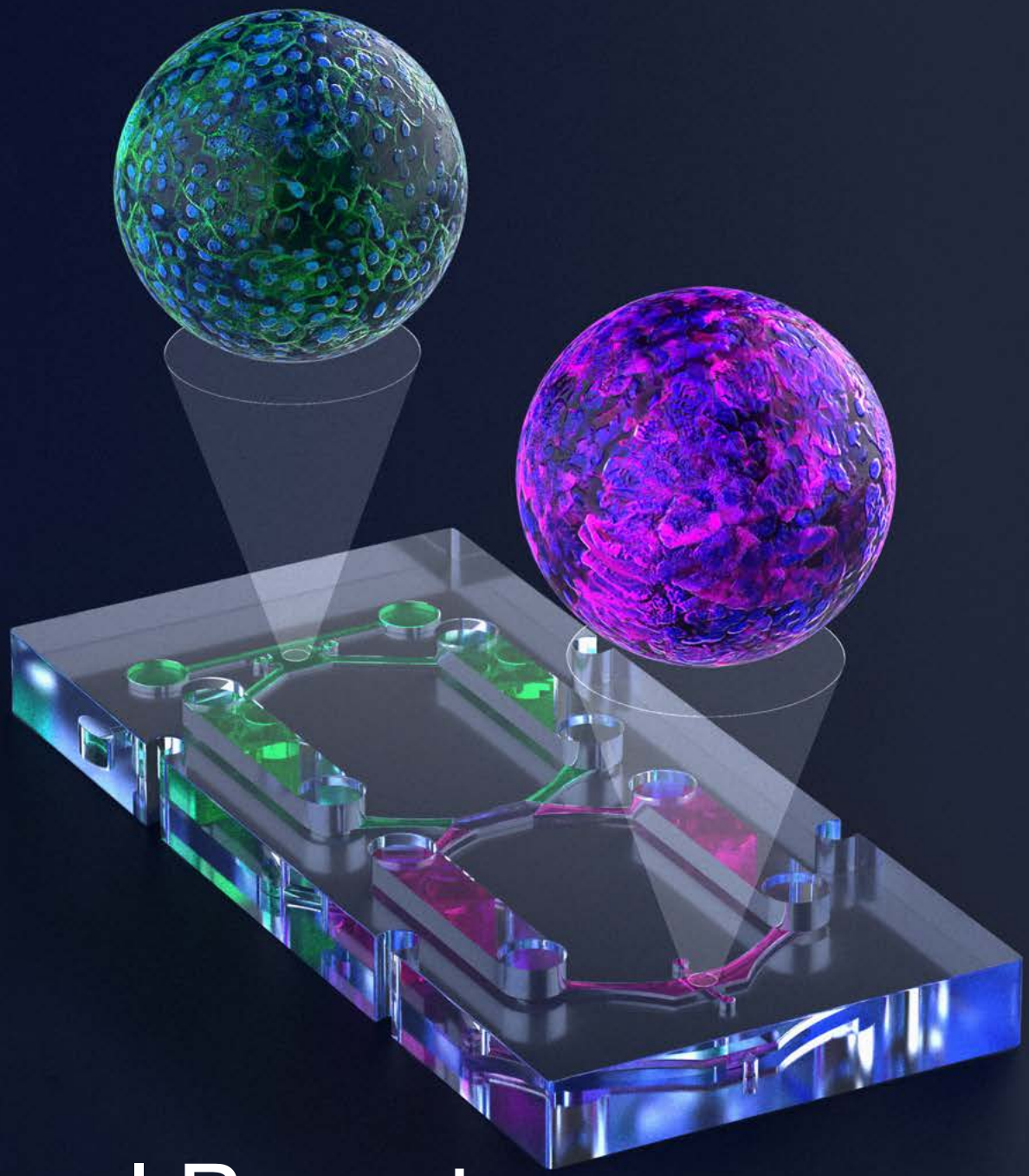
Hybrid Technology Hub - Centre for Organ on a Chip Technology



Annual Report 2023

Oslo University Hospital

University of Glasgow

Imperial College London

The Research Council of Norway

UNIVERSITAS OSLOENSIS MDCCCXI

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From the director

Complex *in vitro* models are often needed to recapitulate higher-level anatomical, physiological or pathological aspects of tissues and organs. Organoids and organ-on-a-chip technology are such emerging *in vitro* models.

Organoids are defined as self-organizing, three-dimensional (3D) tissue cultures, typically grown from stem cells, that model aspects of organ development, composition and function. Organ-on-chip (OoC) technology combines microfabrication and *in vitro* cell cultivation techniques to grow cells in an engineered environment under in vivo-like conditions to recapitulate organotypic cellular architecture and functionality. Over the past decade, organoids and OoCs have emerged as physiologically relevant model systems that are complementary, and sometimes superior, to two-dimensional tissue cultures and animal models. Accordingly, organoids and OoCs are increasingly used for modeling organ physiology and disease conditions. Moreover, they are proving valuable models for drug development and personalized medicine, evidence by the recent "FDA Modernization Act 2.0" bill passed in the US Senate that specifically mentions these models as potential replacements for animal testing. Beyond that, the technology has an outlook towards developing human organ representations for transplantations. However, current organoid technology only fragmentary represent the histology and physiology of adult organs and is hampered by inconsistent production/ characterization procedures – resulting in significant variability.

The Hybrid Technology Hub (HTH) Centre of Excellence is working towards stem cell derived representations of organs that are central in controlling energy homeostasis with a focus on liver, adipose tissue, pancreas islets and muscle cells. This requires an interplay of supervised differentiation protocols, microfluidics, imaging and tracking technologies, integrated bioinformatics, and – as the technology matures – ethical supervision.

In 2023 the Centre entered the second 5 year funding period where work will focus on further improving the organoid systems and the OoC platform. The Centre will work towards standardization, scaling and robotization of the developed assays, and – importantly – towards clinical translation. Hitherto, the Centre published 142 peer reviewed scientific articles, filed 3 patents, was involved in establishing the Research School for Training the Next Generation of Micro- and Nanotechnology Researchers in Norway (TNNN), and raised 282 million NOK in complementary external funding, including grants from the Research Council of Norway, from the Health Region East (HSØ), from the Norwegian Cancer Society. Centre staff obtained three Oslo Life Science convergence environment grants and five SPARK innovation grants. Importantly, PIs at the Centre were awarded two European Research Council (ERC) advanced grant, a EU "Science With and For Society" (SwafS) project, and a European Innovation Council (EIC) grant and a Wellcome Leap grant. The Centre is grateful for the substantial funding that enables us to deepen and expand our research portfolio.

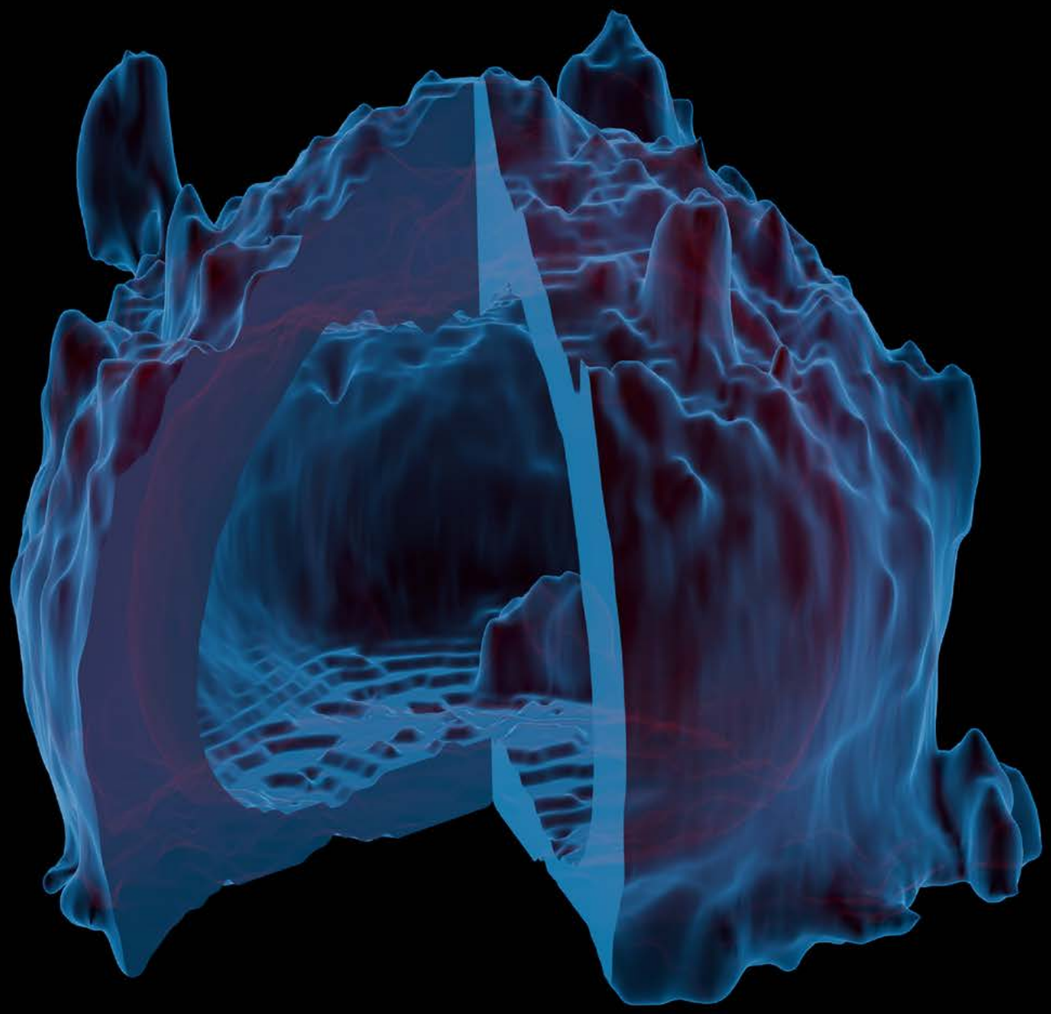
Hence, in 2023, the Centre has added further capacity by establishing collaborations with Novartis, with Oncosyne AS and by deepening the collaboration with Symeres Inc. The Centre has made further process in its liver, islet, bile duct and heart organoids and started to integrate the organoids into the rOoC microfluidic platform that was developed in the Centre and that allows integrating organ representations with endothelial cells and components of the immune system. The Centre has started to develop a bile duct-on-chip platform that draws on a significant biobank of healthy and diseased human material. Furthermore, the Centre has established a sub-group that works on gastruloid technology that should boost our understanding of early steps in organogenesis in a move towards more complex organ representation. This project received substantial funding from the European Innovation Council. The ethic aspects of this work are addressed by an EU funded program on the ethics of organoids that embraces prominent European scholars including the head of the International Society for Stem Cell Research (ISSCR) Prof. Christine Mummery and Dr. Heidi B. Bentzen.

On the analytical side, the Centre has advanced mass spectrometry to deliver metabolic measurements from a dual Organ-on-chip platform, allowing measuring metabolic interactions between liver and islet organoids. The Centre has established a Raman confocal spectroscopy platform in Oslo that is compatible with the partner laboratory at Imperial, and that allows direct chemometric measurement on organoids and gastruloids. Recently, the Centre has also added a Tomocube holotomographic imaging system that allows enhanced label free life tracking of cells and organoids. Furthermore, the Centre is advancing spatial transcriptomics and single cell RNA sequencing technologies. In the Bioinformatics program, the Centre has completed a globally accessible distributed data sharing (GADDS) platform based in parts on block-chain technology to facilitate FAIR-like data-sharing.

HTH Centre Director Prof. Stefan Krauss on hiking trip in Nepal.

I want to thank the PIs, researchers and staff in the Centre for their hard work and unmatched collaborative spirit – without their dedication, the Centre would not be possible. I also want to thank our host, the Institute of Basic Medical Sciences at the University of Oslo, as well as the Department of Immunology at the Oslo University Hospital, the University of Glasgow and Imperial College London for their dedication and support. We are grateful to the Scientific Advisory Board headed by Prof. Bengt Norden for excellent scientific advice as well as to the board of the Centre headed by Prof. Jan G. Bjålie for professional supervision. Finally, I want to thank for the significant resources that we received to be able to work towards advancing biomedical science. What could be a more fulfilling task?

Stefan Krauss
Centre Director



3D rendering of a living bile duct (cholangiocyte) organoid imaged by label-free holotomographic imaging and segmented using machine learning. Organoid diameter: approx. 100 μm (credit: Thomas Combriat, Henry Hoyle).

Research groups

Krauss group

Microphysiological systems and developmental pathways

Stefan Krauss
Centre Director

Coming from a developmental biology background we apply principles of self-organization to improve hiPSC derived organ representations that are compatible with scalable drug interrogation.

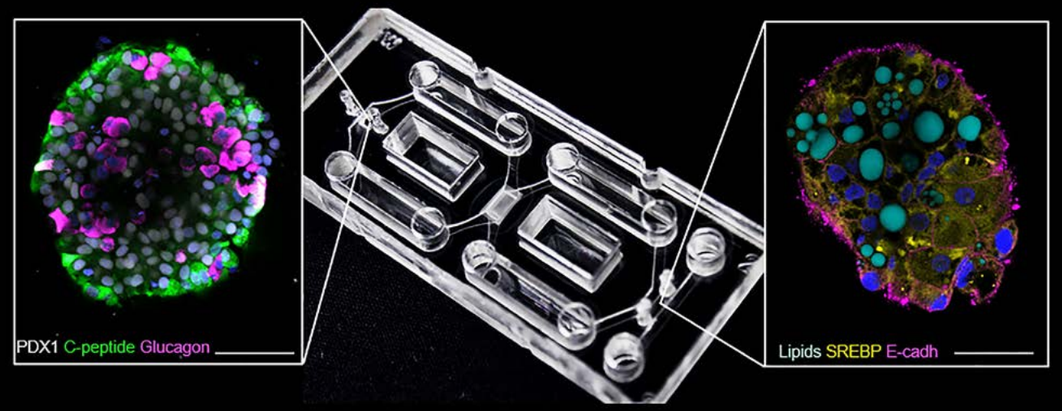


Illustration of the innovative HTH developed recirculating organ-on-chip (rOoC) platform functioning without the need for a pump. Within the rOoC, there are distinct compartments for organoids, each equipped with their own channels for perfusion, ensuring autonomous support. As illustrated the platform can effectively mimic metabolic interactions between the liver (located on the right) and pancreatic islets (found on the left). Thus, by utilizing human stem cell-derived organoids, this platform enables enhanced disease modelling and more accurate drug testing.

A novel organ-on-a-chip platform

We developed a novel, scalable directional flow organ-on-chip (rOoC) platform that creates controlled unidirectional gravity-driven flow by a combination of a 3D-tilting system and an optimized microfluidic layout. The platform allows integrating organoids with endothelialized microfluidic channels and components of the immune system. The platform is currently used for i) combining stem cell derived islets and liver organoids to reconstitute the metabolic cross talk between the two organ representations and ii) for integrating and analyzing the interactions between monocytes and healthy/diseased liver organoids. Work on the rOoC platform has been published in *Advanced Healthcare Materials*, DOI: *10.1002/adhm.202303785*, a patent is pending. In addition, we have received Wellcome Leap (Dynamic Resilience) funding to use the rOoC platform for modelling resilience upon stressors using liver spheroids “on chip”. This project is coordinated by P. Loskill (U. Tubingen) with partners at the Sanger Institute (R. Vento). We also have received funding from the Norwegian Cancer Society for exploring intravasation/extravasation in a tumor-on-chip model and have recently entered a collaboration with the Norwegian startup Oncosyne AS to develop tumor models using the rOoC platform.

Raman based chemometric imaging on liver organoids

Quantitative chemometric imaging tools for validating the composition of organoids, their functional maturity, disease state and response to therapeutic interventions are of significant interest in the rapidly expanding organoid arena. Raman spectral imaging (RSI) allows high-content, label-free detection of tell-tale biomolecules, but requires reliable quantification of deconvoluted spectra to unfold its full potential. Using qRamanomics, developed in the laboratory of Centre partner M. Stevens, we first tested liver organoid maturity and variation. We then used the method to identify biomolecular response signatures to a panel of liver altering drugs, probing drug-induced compositional changes in the organoids. We also were able to follow for the first time *in situ* monitoring of drug metabolism and accumulation in liver organoids. The work is published in Cell Rep Methods (2023 Mar 31;3(4):100440).

Liver organoids

Coming from a developmental biology background, the laboratory works towards an improved structure and functionality of liver organoids, and hence a better physiological representation of the human liver. The liver is shaped by morphogenetic signals from the central vein and the portal triade. Identifying these signals, and applying them for directing organoid development has been a major challenge. Using hESC and hiPSC derived hepatocyte lineages, endothelial lineages and stellate cells we have achieved stable features of zonation in liver organoids and differential response to fibrotic challenges. As a next step, we have integrated liver organoids in a directional flow platform that has been developed in our laboratory. We are now working towards using the liver organoids for i) testing immune responses to drug induced liver injury, ii) for testing the toxicity of PFOS, iii) for probing the impact of nutritional supplements and iv) for testing the age and individualized response to stressors. Collaborative (S. Wilson, M. Stevens, H. Scholz) published work on liver organoids includes *Journal of Chromatography A* in press JCA-23-1589R1; *J Steroid Biochem Mol Biol. (2023 Sep: 232:106355)*; *LCGC Europe. 2023 May; 36 (s5)* DOI: *10.56530/lcgc.eu.st2089i6*; *Cell Rep Methods (2023 Mar 31;3(4): 100440).*; *Advanced Healthcare Materials*, DOI: *10.1002/adhm.202303785*; Frontiers in Bioengineering and Biotechnology *in press.* Collaborative work with E. Melum is ongoing to model the bile duct in a microphysiological system.

Gastruloid development

Common organoid technology is based on individual hiPSC derived lineages that are combined to 3D structures. However, despite significant progress in organoid and organ-on-a-chip technology, it remains challenging to achieve the high physiological and histological complexity of mature organs. A potential alley to reach higher tissue complexity is to develop organs in their naïve embryonic 3D tissue context. Towards this goal we have established a gastruloid sub-group that develops anteriorized mouse and human gastruloids with the aim of reaching organ induction. The group is supported by two Marie Skłodowska Curie fellowships and a European Innovation Council (EIC) pathfinder project “supervised morphogenesis” that is coordinated by S. Krauss and comprises partners at U. Glasgow, Imperial College, MPG Dresden and others. The projects enters the EIC portfolio “Engineered Living Materials (ELM)".

WNT inhibitor development

The laboratory has a long track record on morphogenetic signals and chemical biology. In this context we have developed a WNT inhibitor program centered around the central tankyrase (TNKS) biotarget. For this program we are now establishing a startup with the aim of bringing the lead inhibitor in this program to IND with lung fibrosis as the primary indication. The work is a collaboration with Centre partner Jo Waaler and Symeres Inc. Publications include *Cancer Research Communications* 2 (4), 233-245; *Biomedicines* (2023 Oct 7;11(10):2719).

Meta-analysis of the Organoid and OoC field

In the context of mapping the Organoid and OoC field we have published a comprehensive review that categorizes the field by organs/tissues modeled by organoid/OoCs, diseases modeled in organoid/OoCs and geographic distribution of the research. The work was published in *Advanced Healthcare Materials*, (2023 Jul 21:e2301067).

Aims: The Krauss lab. works towards advanced organoids/OoC models and on methods for interrogating them.

Scholz group
Islets

Hanne Scholz
Vice Director

The Scholz group works on developing new cell-based therapies to treat diabetes in a pre-clinical and clinical setting. The group focuses on developing and cultivating organoids from pluripotent stem cells and pancreatic progenitor cells, aiming to obtain true metabolic regulation through the investigation of their metabolism and maturation process. This year highlight has been the successfully development of a new organ-on-chip platform combining liver and pancreatic islet organoids (HTH SPARK project with the Krauss group).

Beta cell replacement therapy

Beta cell replacement therapy by clinical allogenic islet transplantation is a minimally invasive procedure that has evolved as a safe and efficient treatment option for type 1 diabetic patients with poor glycemic control. The islet transplantation performed at the Department of Transplantation Medicine, OUS (H. Scholz) has recently been shown to be more efficient than intensive insulin treatment and has improved health-related quality of life for patients. The Scholz group works actively through international networks (IPITA, ESOT, EPITA, NNCIT) to improve and broaden this therapy worldwide.

Highlights from the research projects conducted in the UiO: Life Science Convergence ABINO (led by Hanne Scholz)

On November 24th 2023 ABINO PhD candidate Dongho Kwak, Department of Musicology, RITMO defended his thesis “Music for cells? Rhythmic mechanical stimulations of cell cultures”. In July 2023 ABINO PhD candidate Chencheng Wang was honored with the "Chinese Government Award for Outstanding Self-financed Students Abroad”. The ABINO researchers Thomas Combriat, Petter A. Olsen and Stefan Krauss developed a new imaging technique based on acoustic wave-induced stroboscopic optical mechanotyping of adherent cells (Advanced Science. DOI: *10.1002/advs.202307929*). Together with HTH researcher Dag Kristian Dysthe and part of the CompSci: Training in Computational Science PhD Candidate Franziska Schoeb works on develop a deep learning-based analysis of stem cell differentiation pathways.

Generation of beta cells from pluripotent stem cells (PSCs)

Through the ABINO project we have established state of art protocol for direct in vitro differentiation of human PSCs to insulin-producing cells at the HTH core facility. However, differentiated cells do not fully recapitulate the defining feature of mature human islets. In our recent study we showed the influence of high glucose concentrations on the PSCs differentiation. We found a beneficial effect on the K_{ATP} activity, but on the cost of the mitochondrial respiration ability (Figure). To follow up, we now do a systematic study on the different nutrients that control insulin secretion in these stem cell-derived islets.

Determination of insulin secretion from islet organoids

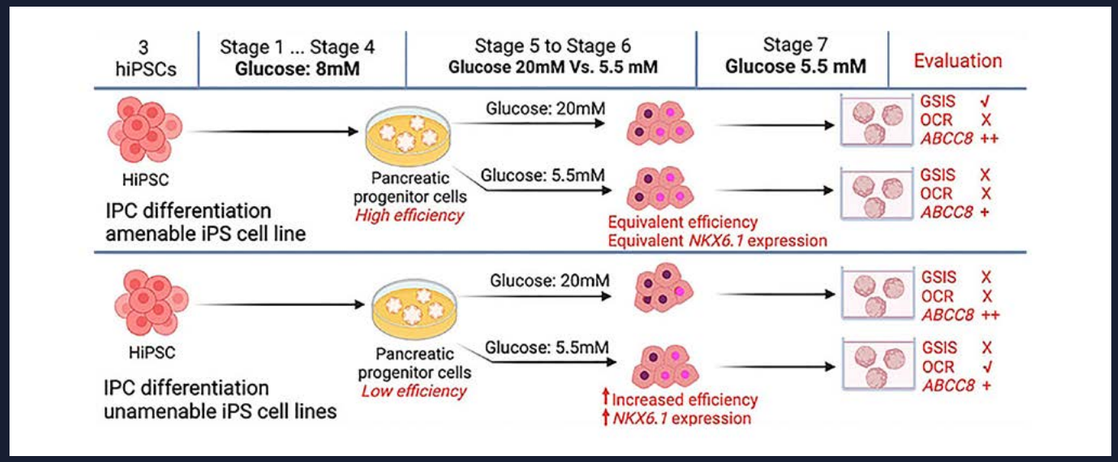
Human pluripotent stem cells (PSC) can generate islet organoids that can be used for drug screening and regenerative medicine. In a joint project with Steven R. Wilson's group, we continue to develop the method for quantification of insulin production from islet organoids based on liquid chromatography mass spectrometry (LC-MS). We found that implementation of preparative agarose gel electrophoresis-electrodialysis (PGE-ED) reduce the interference from the islet organoids cell culture medium allowing for better outcome on LC-MS analysis of human insulin.

Generation of insulin-producing cells from cholangiocyte organoids (CO)

In collaboration with HTH researcher E. Melum and Prof. Sampaziotis, University of Cambridge, UK we intend to develop differentiation protocols for CO organoids to the pancreatic progenitor stage. Currently, we investigate the phenotype of CO after over expression of beta cell specific transcription factors using lentivirus vector. We believe that this approach lays the foundation for creating a new cell source capable of transforming into insulin producing cells.

The group also collaborates within HTH with Molly Stevens group on imaging and sensor development, and Simon Rayner Group on bioinformatics.

Glucose concentration in regulating induced stem cells differentiation toward insulin-producing cells



Conclusion: High glucose concentration (20mM) used during insulin-producing cell differentiation is necessary to generate functional cells. However, high glucose could worsen the outcome in cell lines unamenable to induced IPC differentiation.

Chencheng Wang, et al. *Transpl. Int.* 2023
doi: *10.3389/ti.2024.11900*

↑ **Figure:** Illustration of the impact of glucose levels on stem cell differentiation of human pluripotent stem cells towards insulin producing beta cells. Credit: Chencheng Wang. Created with Biorender.com

Rayner group
Computational Biology

Simon Rayner
Principal Investigator

The primary research focus of the group is understanding how systems evolve in response to external influences. This is why we call ourselves a Computational Biology group instead of a Bioinformatics group – rather than developing tools to analyze biological data, we are developing software to understand biological function.

The most obvious example of evolution in a biological system is when a pathogen, such as a coronavirus, mutates to evade a vaccine. However, such evolutionary mechanisms are present in other systems too. For example, there is clear evidence the human genome has evolved in response to environment, with specific populations showing distinct genetic traits associated with geographical location. A third example is how scientific publications are influenced by measures such as Impact Factor. For example, researchers can publish research that will be rated higher if they focus on viruses such as HIV or influenza, rather than neglected pathogens which tend to be published in lower impact factor journals. We are investigating each of these systems by developing a suite of software tools and algorithms and defining metrics to identify and quantify changes.

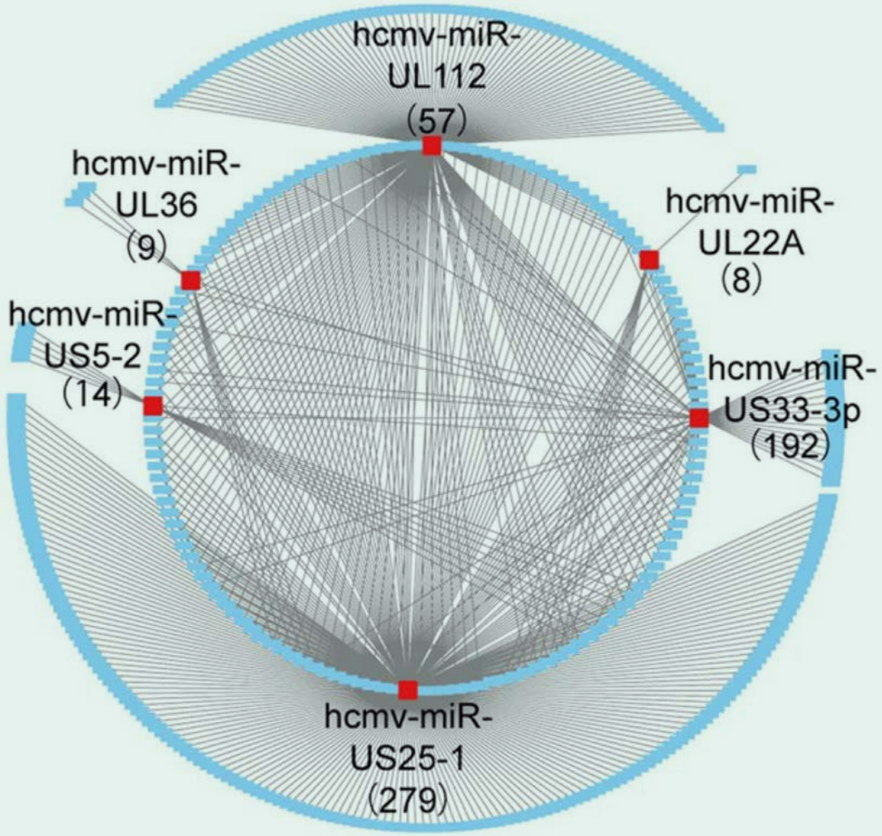
For our studies of the evolution of human genome, we are focusing on the non-coding regions of the genome and investigating how genetic and epigenetic changes impact regulatory control. One of our specific interests is the regulatory role of microRNAs (miRNAs). These are short RNA segments that regulate gene expression by binding to the 3'UTR of their gene targets. However, rather than performing standard miRNA studies which identify single miRNAs associated with a specific condition (such as cancer), we are interested in the role of miRNAs in providing stability in biological systems.

While we use publicly available data in this work, this doesn't always meet our needs and we also carry out our own experimental studies. This includes standard experiments such as Next Generation Sequence to profile miRNA and mRNA expression and their associated regulatory networks, but also more advanced technologies such as Single Cell Spatial Sequencing. For example, we have been using the technique to characterize brain organoids to profile the impact of Human Cytomegaloviruses infection of brain development in newborns.

These works are particularly relevant to the research that is carried out in the HTH as we can use these tools to study organoids at the genetic level and identify differences with human organs. For example, liver organoids have been developed that exhibit core structural features and express key genes, but their regulatory profiles have not been characterized. Similarly, Single Cell sequencing yield deeper characterization of organoids to help understand how well they approximate living systems.

Another area where we contribute to the HTH is in data standardization and integration. The Findable, Accessible, Interoperable and Reusable (FAIR) principles provide a framework to define the basic elements required to support effective data management but implementing the FAIR principles remains a challenge. We have developed the Globally Accessible Distributed Data Sharing (GADDS) platform to facilitate FAIR like data sharing in cross-disciplinary research collaborations. The platform consists of (i) a blockchain based metadata quality control system, (ii) a private cloud-like storage system and (iii) a version control system. GADDS uses containerized technologies, providing minimal hardware standards and easing scalability, and offers decentralized trust via transparency of metadata, facilitating data exchange and collaboration.

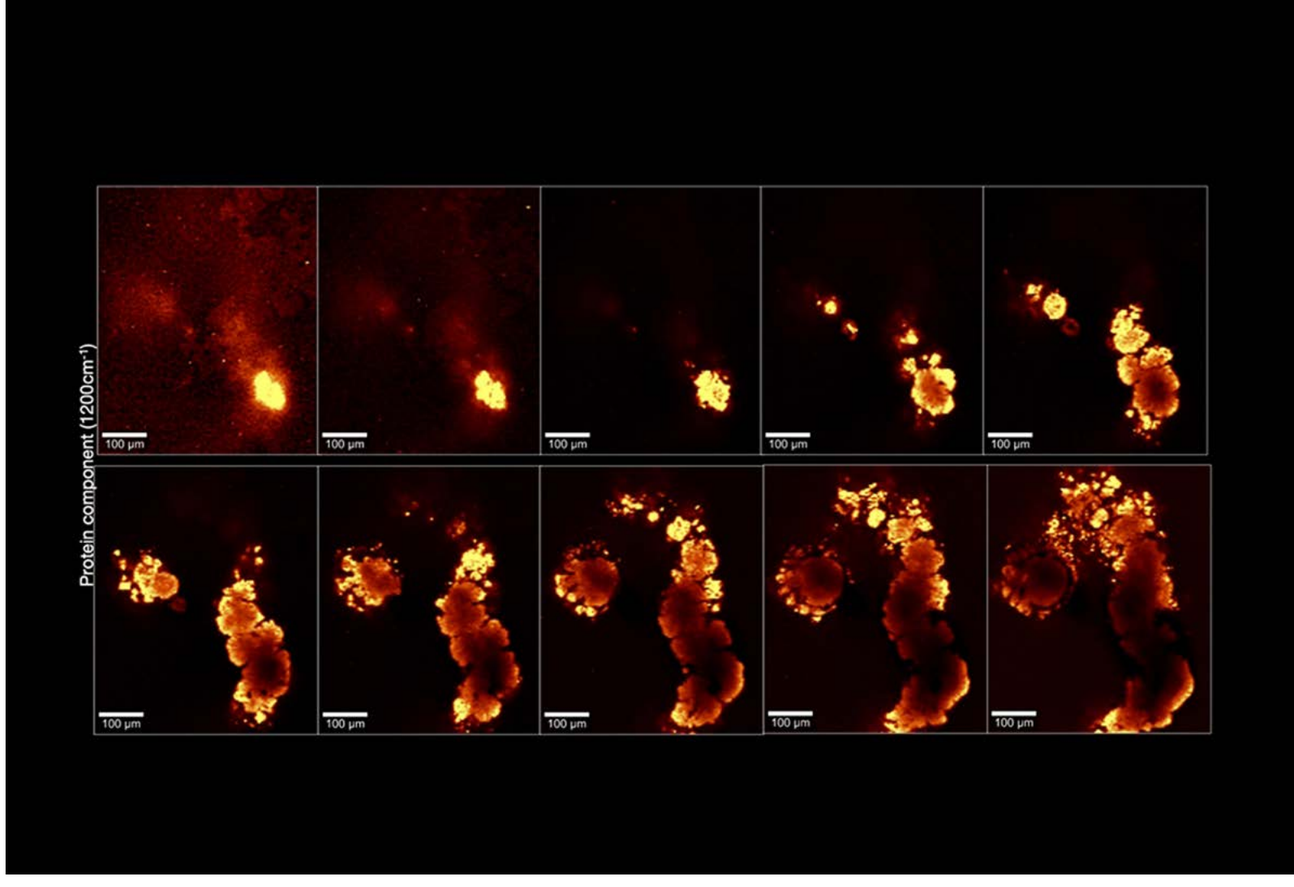
We are working with all groups in the HTH to integrate the different generated data types (for example microscopy data, sequencing data and metadata for experimental protocols) to allow the application of advanced statistical learning approaches to analyze the data.



↑
Target interaction network of highly expressed human cytomegalovirus (HCMV) viral miRNAs and their predicted cellular target host genes during infection of host cells with HCMV. Red squares represent HCMV miRNAs, blue rectangles represent predicted host target genes, and gray lines connect miRNAs with their predicted target genes. Numbers of predicted target genes for each miRNA are indicated below in parentheses. perturbation of the host genes disrupts the maturation of neuroprogenitor cells, highlighting a central role of miRNAs in development

Stevens group
Imaging and sensor technology

Molly Stevens
Principal Investigator



Raman spectroscopic imaging of gastruloids showing the distribution of amide III.

We are developing advanced imaging and sensing technologies to be able to analyze organoids and biological material on-chip.

Volumetric quantitative Ramanomics

The stevens group has previously developed methodology to perform volumetric quantitative chemometric imaging (quantitative volumetric Raman imaging (qVRI). qVRI can be used to quantitatively investigate the biomolecular spatial distribution of (bio)molecules in three-dimensional tissues. In the last year, efforts have been focused on the development of a Raman reference atlas for tissues, which aims to record the Raman signatures of mature organ tissues (such as heart, brain, kidney) and identify unique features of these tissues. We plan to use these signatures and apply them onto the developmental trajectory of organ development, using both human as well as mouse derived tissues and novel organoid and gastruloid methodology (work, which is embedded in the SUMO consortium).

Sensor systems

We have been developing the Localized Surface Plasmon Resonance (LSPR) insulin sensor to explore the fundamental biology of insulin secretion and organoid response to drug treatment. Last year, we optimised the LSPR chip design and built it on biocompatible PMMA to embed it into organ-on-chip microfluidic systems. The LSPR sensor's pumping system improved reproducibility and sensing stability. Besides, we implemented computational methods to evaluate the performance of the optimised LSPR sensor on insulin solutions, reaching a limit of detection of 2.5 μM. Although the lowest limit of detection achieved using insulin solutions is 0.5 μM, experiments with secretion from pancreatic islets indicated that the sensor could detect lower detection limits. We tested that this detection was not because of changes in the solution and confirmed a shift in the spectra with these secretions. Future work should focus on developing the sensor with the affibody that achieved the lowest limit of detection to be embedded in the microfluidic chip with organoids and perform real-time measurements.

Optogenetics

We have been working on the optogenetic stimulation of human induced pluripotent stem cells (hiPSC) derived cells and organoids for their spatiotemporal control. An hiPSCs line with light-sensitive ion channels has been established using lentiviral transduction, and it has been confirmed that optogenetic hiPSCs-derived cardiomyocytes could be manipulated by light. This work was published in Advanced Science. Following up on this work, we developed an additional hiPSCs line including both excitatory and inhibitory optogenetic channels to provide enhanced spaciotemporal control of their activity. This was confirmed again using hiPSCs-derived cardiomyocytes that could be stimulated or inhibited used different light wavelengths. Due to silencing problems derived from lentiviral transduction we are now moving towards CRISPR/Cas9 transduction strategies to selectively introduce genetic modifications into the AAVS1 locus also known as "safe harbour". This would enhance optogenetic protein expression and we expect to see enhanced control in both cardiomyocytes and motor neuron organoids.

SPARTA®

With the improved system, we have further demonstrated the use of SPARTA for distinguishing EVs in complex samples, such as plasma EV samples (unpublished), in addition to label-free chemical characterisation of cargo loading and release, nanocarrier composition and surface interactions in various nanotherapeutic delivery vectors, such as lipid nanoparticles, polymersomes, liposomes and polyplexes. We have also presented an analytical framework to use SPARTA data for the label-free determination of cargo loading location. This framework was developed by analysing the relationship between carrier and cargo peaks across the particle population spectra data obtained from SPARTA, and can be used to distinguish core and membrane loading behaviour.

Related papers

C. Saunders, J. E. J. Foote, J. P. Wojciechoswski, A. Cammack, S. V. Pedersen, J. J. Doutch, H. M. G. Barriga, M. N. Holme, J. Penders, M. Chami, A. Najer, M. M. Stevens. “Revealing Population Heterogeneity in Vesicle-Based Nanomedicines Using Automated, Single Particle Raman Analysis.” ACS Nano. 2023

A. Fernandez-Galiana, O. Bibikova, S. Vilms Pedersen, M. M. Stevens. “Fundamentals and applications of Raman-based techniques for the design and development of active biomedical materials.” Advanced Materials. 2023.

C. Saunders, C.A. de Villiers, M. M. Stevens. “Single Particle Chemical Characterisation of Nanoformulations for Cargo Delivery.” AAPS Journal. 2023.

Gadegaard group
Chip design

Nikolaj Gadegaard
Principal Investigator

The Biomedical Interfaces at Glasgow (BIG) focuses on research and development of novel techniques for the design and manufacturing of Organ-on-Chip (OoC) technology.

During the past year, work revolved around two major subjects: 1) the simulation of microfluidic environments, focusing on the prediction of shear stress, modelling of perfusion methods, and the design implications of porous membranes fluidics and transport; and 2) the manufacturing of microfluidic devices, using 3D printed tooling for injection moulding.

Finite element modelling is a powerful tool, well-established in the simulation and research of a wide variety of biomedical applications and microfluidic environments. In the lab, such tool has been extensively used by Duarte Menezes (PhD Student, University of Glasgow) to support the design of microfluidic devices by providing extensive knowledge on the resulting fluidics and dynamics of molecular transport. It has also been used as a means of performing in silico research, with a particular focus towards the integration of porous membrane and its respective design implications. Three major projects were completed based on the respective modelling work. First, the prediction of shear stress as a function of flow rate and design parameters, to sustain the experimental results obtained in vitro for a human placental barrier model developed by the group at HTH in Oslo. Second, extensive research on the implications of porous membrane barriers in microfluidic devices, by investigating the effects of both membrane, channel and experimental parameters in the resulting flow rate, shear stress, transient transport and steady state concentration of diluted molecules. This data was further corroborated by in vitro experiments performed in the lab with MDCK cells and published in the *Chemical Engineering* Journal [1]. Finally, the respective model was adapted to contemplate various perfusion methods, including asynchronous, pulsatile, circulatory flow. Such work was critical in providing in-depth knowledge on the particular dynamics of microfluidic devices developed by the group at HTH, in Oslo, and contributing for a publication in the *Advanced Healthcare Materials* Journal [2].

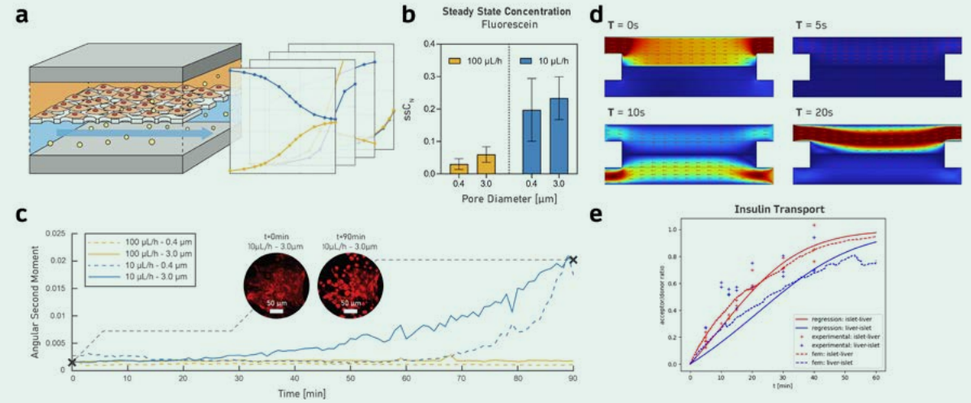
Driven chiefly by consumer need, 3D printing has taken sizeable leaps in the past few years, becoming an increasingly accessible, cheap, and consumer friendly technology, capable of progressively higher feature resolution. Work in the lab, conducted by Duarte Menezes (PhD Student, University of Glasgow), has been focused on adapting the referring technology to the development of soft tooling for injection moulding and the creation of polymeric microfluidic chips. A wide range of parameters have been investigated, towards ensuring the compatibility, quality and reproducibility of such a manufacturing procedure. Resin selection was investigated as a function of mould release success rate and verified to be greatly dependant on channel side-wall waviness and interlocking angle. In turn, interfacial stress was studied as a function of surface deflection and seen to compromise mould durability. Slicing parameters, and especially layer exposure, was seen to widely reduce surface roughness and, by doing so, importantly increase the optical transparency of chips, an essential feature for any microfluidic application. Finally, feature durability was investigated in injection moulding as a function of post processing parameters, such as UV exposure and curing time, as well as design properties, such as feature orientation and draft angle. Ultimately, it is described a rapid prototyping technology, where injection moulding tooling can be produced in under 2 hours for a small batch production with features <50 μm.

References:

[1] Menezes, P.D., et al., *A membrane's blueprint: In silico investigation of fluid flow and molecular transport as a function of membrane design parameters in organ-on-a-chip*. Chemical Engineering Journal, 2024. **481**: p. 148189.

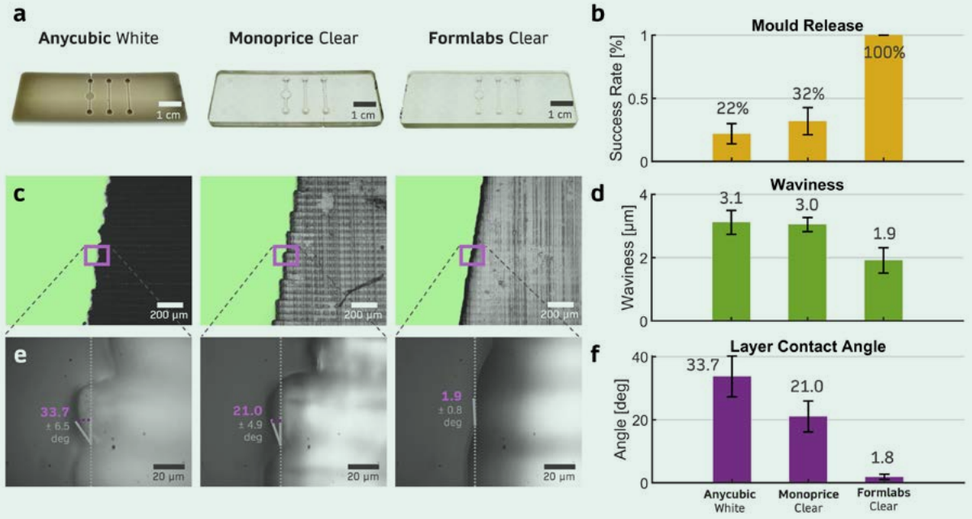
[2] Aizenshtadt, A., et al., *Pump-Less, Recirculating Organ-on-Chip (rOoC) Platform to Model the Metabolic Crosstalk between Islets and Liver*. Advanced Healthcare Materials. 2024 Jan 14:e2303785.

Figure 1:



a) Illustration of a bilayer microfluidic design with integrated porous membranes and cells cultured on top, on the left of membrane modelling results describing both the fluidics and transport dynamics implied by changes in design parameters. **b)** Permeability of porous membranes measured as a function of the steady state concentration of fluorescein, corroborating the data from the finite element model developed. **c)** The importance of controlling design parameters while developing tissue barrier models is expressed as a function of the transport of cytochalasin D and its resulting effect on cultures of MDCK cells. **d)** A membrane model with asynchronous, pulsatile, circulatory flow is shown. **e)** Permeability of Glucose, as measured experimentally and numerically, evidencing very good affinity between both the in vitro and in silico data.

Figure 2:



a) Moulds corresponding to three of the resins tested for the investigation of mould release are shown, whose success rate is plotted in **b)**. A close-up of the channel's sidewall is observed in **c)**, highlighting their respective wall waviness, whose average values are plotted in **d)**. **e)** The profile of the laminated layers is observed under higher magnification, evidencing the layer contact angles, whose values are plotted in **f)**.

Louch group
Cardiomyocyte function

William Edward Louch
Principal Investigator

Employing stem-cell derived cardiomyocytes to investigate cellular structure and function in health and disease.

Our research is focused on examining the subcellular structure of cardiac muscle cells, known as cardiomyocytes, and elucidating the role these structures play in orchestrating the heartbeat. The initiation of cell contraction occurs through the release of calcium at specialized sites called "dyads", where cell membrane invaginations known as t-tubules closely interact with release channels (Ryanodine Receptors) in the Sarcoplasmic Reticulum. The dyadic cleft measures only approximately 9 nm across, making examination of these structures difficult. To address this challenge, we employ emerging techniques for super-resolution microscopy. For example, in our recent work we have used live-cell variants of these techniques to show how unitary calcium release elements (calcium sparks) are sourced from finely-tuned collaborations between Ryanodine Receptors (see **Figure 1**; Hou *et al., Nat Cardiovasc Res*, 2023).

Importantly, dyadic structure is highly malleable. Our observations indicate that dyads undergo gradual assembly during cardiac development, contributing to the progressive strengthening of the heartbeat. Unfortunately, these structures are dismantled during the progression of diseases such as heart failure (Frisk *et al., J Am College Cardiol*, 2021). The resurgence of a fetal phenotype during disease progression underscores the critical importance of comprehending the mechanisms governing dyadic formation and stability. These structures hold promise as pivotal therapeutic targets for cardiac patients.

Animal models have traditionally played a crucial role in our field. However, recent investigations of human cardiac tissue have revealed significant differences in dyadic structure and function compared to model species, especially rodents (Frisk et al., J Am Coll Cardiol, 2021). Access to healthy human tissue is limited, particularly in the developing heart where we are keen to unravel the signals responsible for cardiomyocyte assembly. Fortunately, the emergence of induced pluripotent stem cell (iPSC)-derived cardiomyocytes and cardiac organoids has allowed our group to gain fresh insights into these processes in human cells. However, collaborative efforts with members of the Hybrid Technology Hub have revealed that the differentiation of these cardiomyocytes is still incomplete.

To enhance the differentiation of cardiomyocytes from iPSCs and within organoids, our research team has recently delved into the role of various proteins involved in assembling cellular substructures. Postdoctoral researcher Harmonie Perdreau-Dahl has discovered the crucial role of the membrane-bending protein BIN1. Her findings suggest that overexpression of BIN1 in iPSCs facilitates t-tubule formation, as illustrated in **Figure 2** (Perdreau-Dahl *et al., Circ Res*, 2023). Moreover, her research indicates that BIN1 collaborates with partner proteins myotubularin and dynamin-2 to accomplish this role.

We are also employing iPSC-derived cardiomyocytes to investigate how human mutations affect cellular contractile function. Postdoctoral fellow Jia Li and PhD student Magnhild Sekse Erdal are specifically investigating the giant elastic protein titin (Li *et al., Circ Res*, 2023). They have observed that this protein coordinates contraction across the cell in an isoform-dependent manner, and that truncating mutations desynchronize intracellular contraction. By employing strategies to normalize titin expression, we aim to prevent heart failure development in individuals with these mutations.

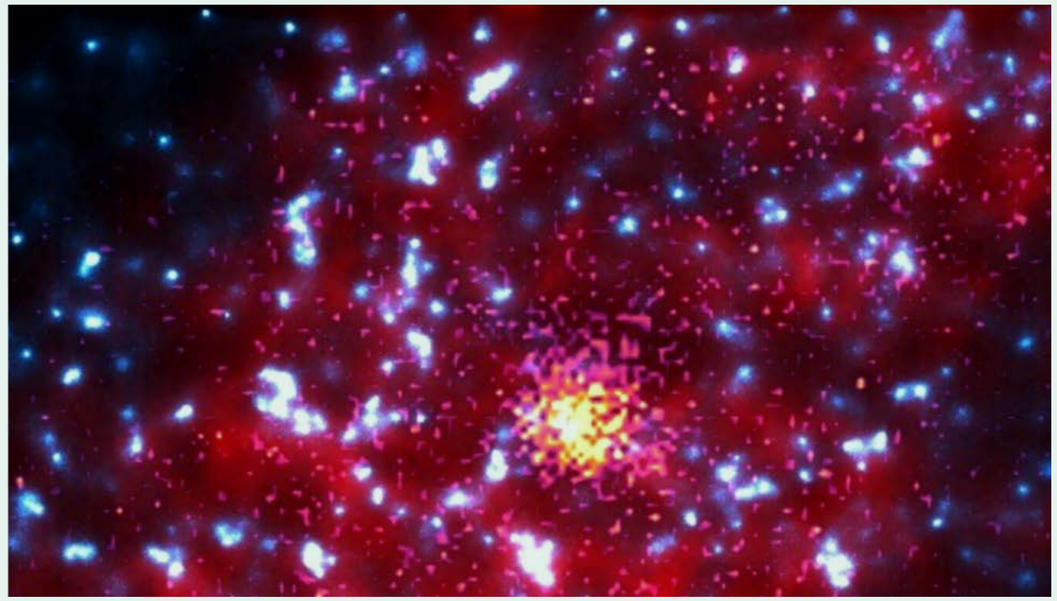


Figure 1: A calcium spark superimposed over localized Ryanodine Receptors (white) and Sarcoplasmic Reticulum (red).

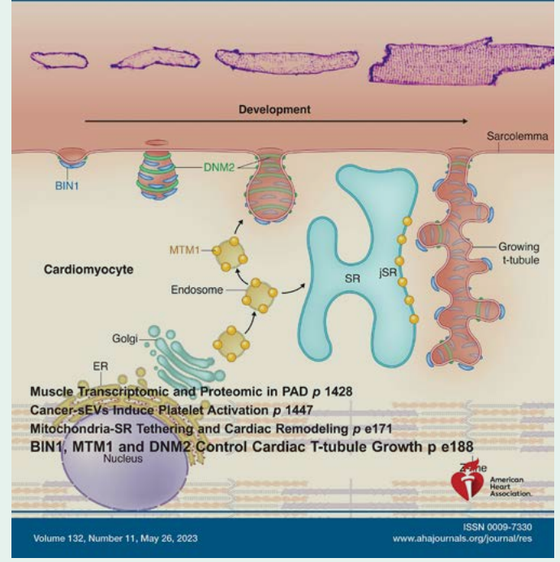


Figure 2: BIN1 controls t-tubule growth in collaboration with its partner proteins.

Solbakk group
Ethic of organoids

Jan Helge Solbakk
Principal Investigator

The ethics group focuses on the law and ethics of organoids. In 2023, this included contributions to three EU funded projects.

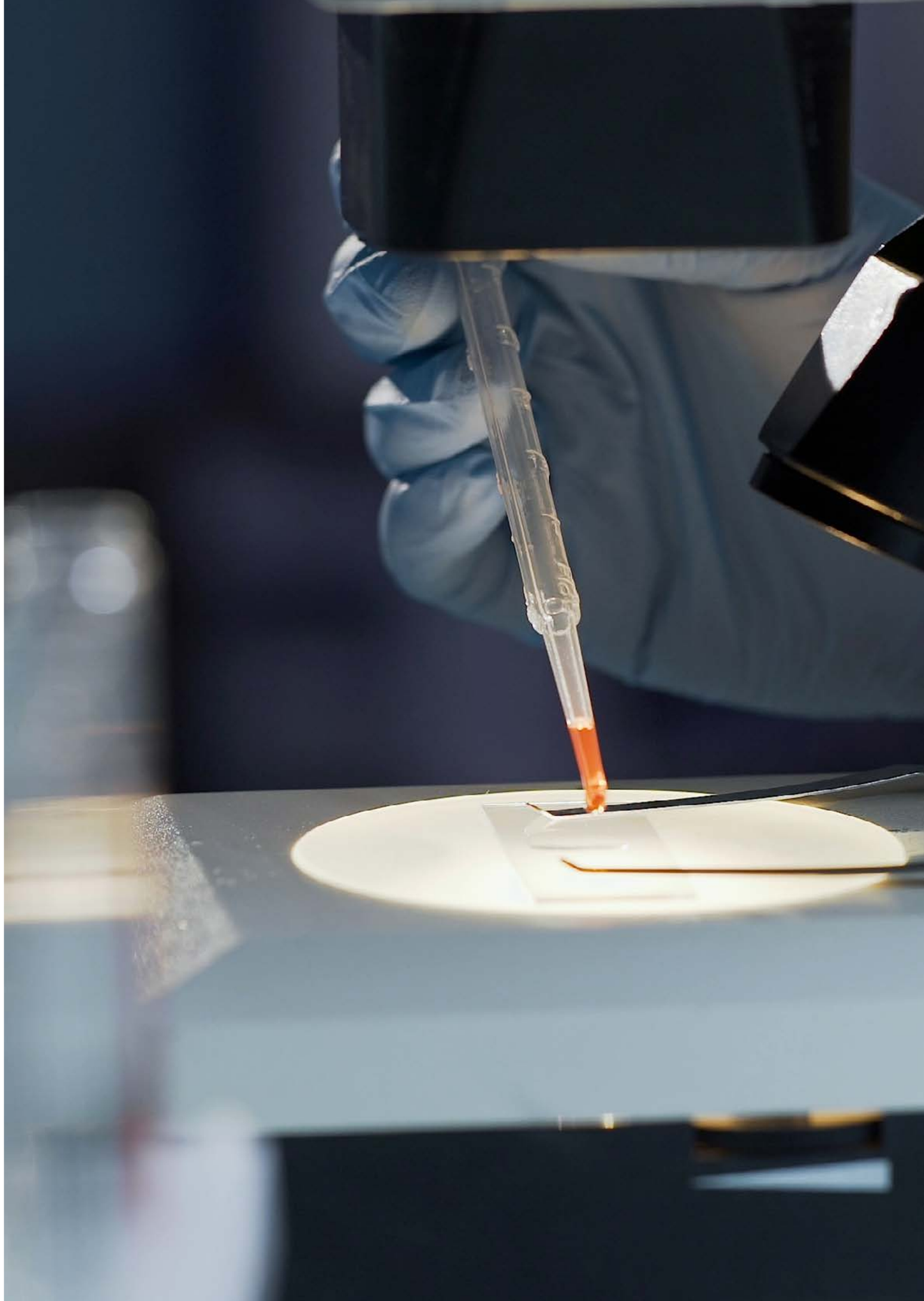
The Horizon 2020 Science with and for Society funded HYBRIDA project (Embedding a comprehensive ethical dimension to organoïd-based research and resulting technologies) continued with Heidi Beate Bentzen and Maxence Gaillard as two of the researchers, and Stefan Krauss as a member of the Advisory Board. A consortium meeting in the Pontifical Academy for Life in the Vatican was attended, where organoid ethics was discussed.

The European Innovation Council Pathfinder Challenges funded SUMO project (Supervised morphogenesis in gastruloids) coordinated by HTH with Stefan Krauss as PI, started in November 2022 at which time Heidi Beate Bentzen came onboard to address the ethics requirements and conduct tasks related to creating best practice guidelines for the gastruloid research field, a role she continued throughout 2023. An embedded ethics approach is used, where the ethics is interwoven with the science and best ethics practices are developed in tandem with the scientific advancements. To achieve this, quarterly ethics review meetings chaired by Bentzen are attended by the entire consortium, and ethics issues are discussed collaboratively. Maxence Gaillard joined the project as a HYBRIDA representative, and both Bentzen and Gaillard conducted lab visits to further strengthen the ethics deliberations. Professor Megan Munsie joined SUMO as a member of the Ethics Advisory Board. Consortium meetings in Germany were attended.

The Marie Skłodowska-Curie Actions Doctoral Network funded TOP-GUT project (Training for Organoids modelling Physiology and Pathology in the human gastrointestinal tract) started in November 2023. One of the network's 11 PhD Candidates will be based in Oslo, and will be supervised by Heidi Beate Bentzen, who alongside two colleagues will also provide the legal and ethical training for all the PhD Candidates in the network. Stefan Krauss is on the TOP-GUT Advisory Board. A call for applicants for the PhD position in the law and ethics of organoids was posted for a candidate to start in mid 2024.

Further networking in the field was achieved by Bentzen and Håkon Høgseth participating in the Nordic Committee on Bioethics and NordForsk workshop and symposium in Reykjavik on the moral status of stem-cell derived human embryo models, and Bentzen participating in a COST Action CA21151 Generation of hiPSCs from haplo-selected cord blood samples meeting in Sofia.

Bentzen published a paper related to HYBRIDA and SUMO with colleagues in 2023; Public Preferences for Digital Health Data Sharing: Discrete Choice Experiment Study in 12 European Countries (J Med Internet Res 2023;25:e47066, doi: *10.2196/47066*). Krauss was interviewed by the Norwegian Biotechnology Advisory Board's magazine GENialt. Krauss and Bentzen also gave presentations on organoid ethics for representatives from three medical schools in Thailand and from The Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP).



Bioanalytical chemistry team

Steven Wilson
Principal Investigator

Hanne Røberg-Larsen
Associated Parter

The bioanalytical chemistry team specializes in employing mass spectrometry for analyzing organoids and organ-on-a-chip systems.

The bioanalytical chemistry team (Wilson and Røberg-Larsen) focuses on using mass spectrometry- based systems for studying organoids and organ-on-a-chip systems. Approaches includes using various sample preparation techniques for organoids and organoid medium samples, separation science and imaging.

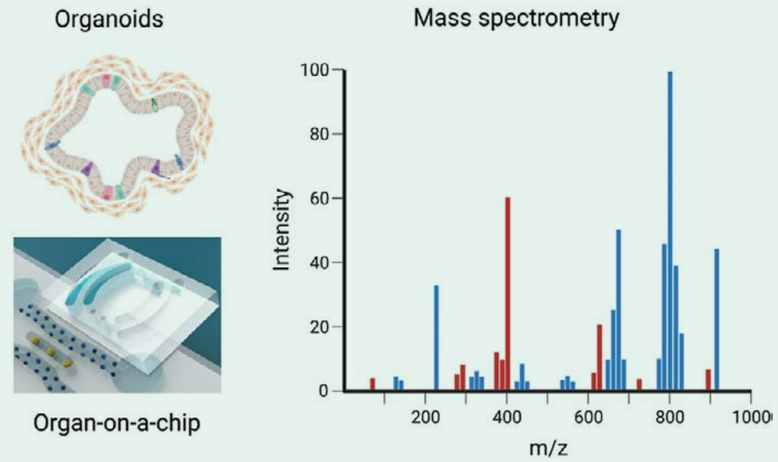
Islets organoids have been studied using liquid chromatography- mass spectrometry (LC-MS) with regards to hormones such as insulin (*Olsen et al.* Journal of Chromatography B 2023 and *Olsen et al.* Electrophoresis 2023), with an extended look at sample preparation of small organoid and organ-on-a-chip samples (*Hruskova et al.* Journal of Chromatography A, accepted 2023).

Method for biomarker discovery related to non-alcoholic fatty liver disease model, with focus on sterol analysis has been developed (*Kømurcu et al.* The journal of Steroid Biochemistry and Molecular Biology 2023), showing that steatotic liver organoids secrete more bioactive cholesterol metabolites compared to healthy. This path will be explored further in 2024, with a focus on persistent organic pollutions and their health effects, using organoids as model system. The project is funded through a Norwegian Research Council Young Researcher Talent grant.

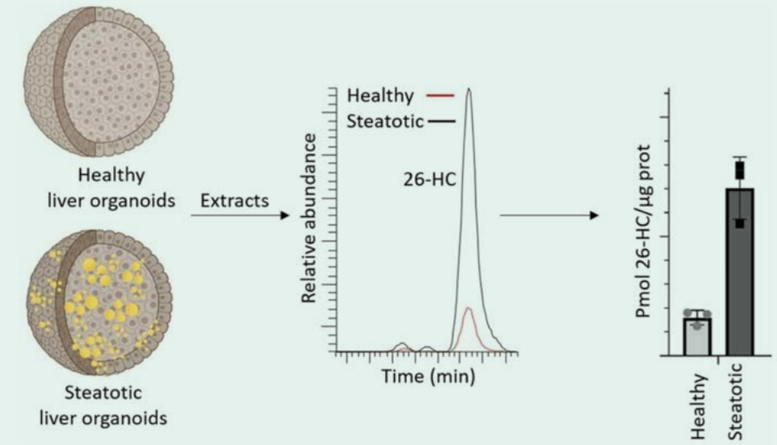
In addition to hormones and lipids, the group has also contributed with proteomics studies of organoids, e.g. *Aizenshtadt et al* LCGC 2023, and in co-publications with other HTH PIs, e.g. *LaLonde et al*, Cell Reports Methods, 2023. The group has in total (co)authored 12 peer reviewed publications, and has held keynote talks from major conferences to workshops, e.g. HPLC 2023 (Dusseldorf) and the EuroOCs summer school (Tubingen)

The group has also had an increased focus on innovation and is teaming up with Merck Life Science and Sintef Digital, developing novel sample preparation tools in chip format that will be used for drug analysis of organoids and OoC systems. The projects have in 2023 received qualification funding from the NRC. Additionally, Wilson and Røberg-Larsen are teaming with Waters Inc. for performing mass spectrometric imaging of organoids and will soon be analyzing gastruloids with the same approach.

The team´s students have also been very visible through their science. Notably, Stian Kogler was highlighted as a “young leading star” in Dagens Næringsliv.



Mass spectrometry (MS) is a technique that is used to "weigh" molecules, and through this process, create a spectrum that serves as a unique "fingerprint" of the molecule. MS can be used to identify and measure molecules and we apply MS for analyzing samples from organoids and organ-on-a-chip systems.

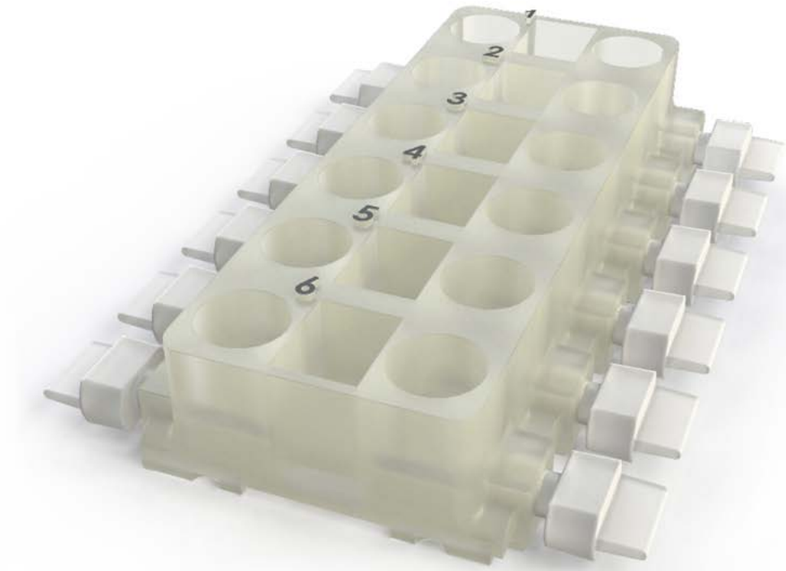


Mass spectrometry is applied by the group to study the biochemistry of steatotic liver organoids. Such efforts can results in biomarker discovery.

Research groups

Melum group
Experimental liver research

Espen Melum
Principal Investigator



↑
A computer image of a DUCT chip, an organ-on-a-chip platform for recreating the bile duct microenvironment *in vitro* (credit: Henry Hole).

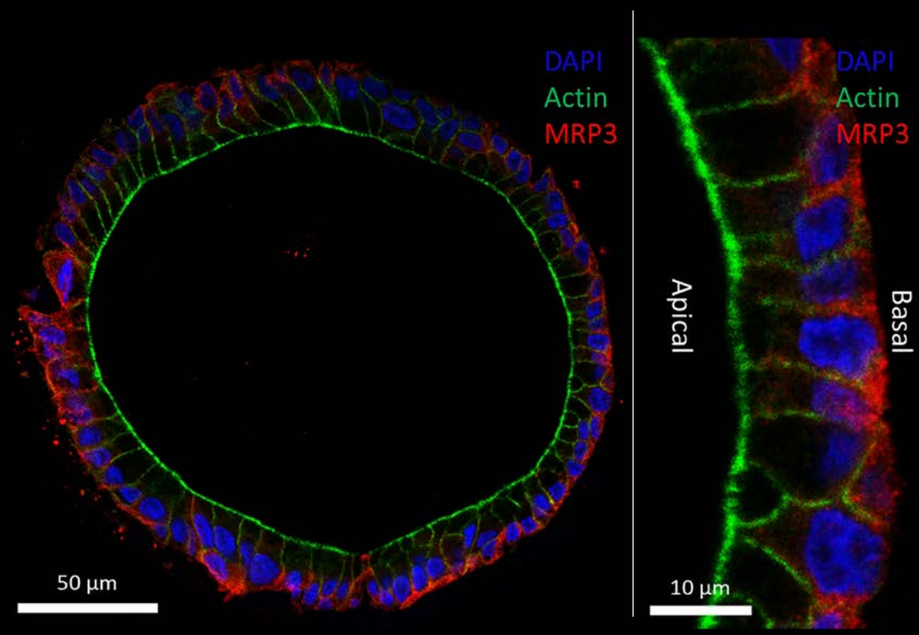
The group's primary focus is understanding the mechanisms behind cholangitis, with an emphasis on immunology, the immune system's interaction with the microbiome, and the role of cholangiocytes in inflammatory processes.

The experimental liver research focuses on understanding bile duct inflammation and is part of the Norwegian PSC research center (NoPSC). Our laboratory activities take place at both the Research Institute of Internal Medicine and the Hybrid Technology Hub (HTH). In 2023 the group consisted of the group leader, four senior researchers, two postdocs, four PhD students, the lab manager, one researcher and two technicians. The overarching topic in the group is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and what role the cholangiocytes play in propagation of inflammatory processes. Together with HTH we are addressing these questions using organoid and bile-duct-on-a-chip technology.

In 2023 our bile-duct-on-a-chip project moved from the prototype stage into a system that is useable in a range of experimental conditions. Seeding organoids in the chip now leads to a tight barrier allowing flow of relevant compounds through the duct. We have also tested how this barrier respond to pharmacological substances. The bile-duct-on-a-chip system was also in 2023 accepted into the University of Oslo's SPARK program for commercialization. This project will be led by Dr. Henry W. Hoyle and Dr. Anne Frank from the group. Being admitted to the SPARK program allows us to follow up on the commercial potential of the system and to get a dedicated mentor from the industry. In 2023 we also used our experience with organoids coming out of the collaboration with HTH in a large project with Novartis in Basel where we use their automated systems to examine the impact of various pharmacological substances on an induced inflammatory phenotype in the organoids.

The group also has large projects related to single-cell sequencing and spatial transcriptomics using both human and murine material. The laboratory work and sequencing in several of these projects were finished in 2023 and bioinformatics analysis is currently ongoing. Together with other researchers at HTH we initiated projects in 2023 where we will use this technology to understand development in gastruloids.

↓
Immunostained sections of a bile duct grown in the DUCT chip demonstrating well-defined apical-basal polarization. Actin filaments are stained red and the basally-expressed transporter protein MRP3 is stained green (credit: Henry Hole).



Corthay group
Tumor immunology

Alexandre Corthay
Principal Investigator

We are developing methods to visualize in vitro how immune cells fight cancer cells in a complex tumor microenvironment

Tumor on a chip

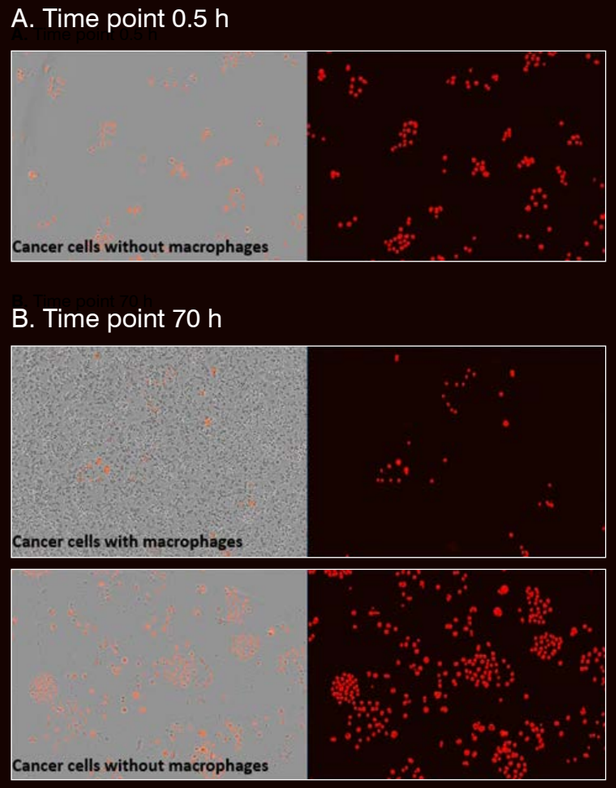
Although more chaotic in nature, solid tumors resemble normal organs by possessing a complex microenvironment consisting of multiple cell types. Malignant cells inside tumors are typically located in a disorganized epithelium that is embedded in a stroma consisting of non-malignant cells such as fibroblasts, endothelial cells, and various types of immune cells. To better understand how the immune system fights cancer, our group is working on recreating an immunocompetent tumor microenvironment on a chip. It allows us to investigate *in vitro* the complex cellular and molecular interactions that take place in either mouse or human tumors with the goal of developing novel immunotherapies for cancer. We have been able to recreate a basic tumor microenvironment that includes cancer cells, tumor-specific T cells, and tumor-associated macrophages, in microfluidic devices (chips) as 3D co-cultures in biomimetic hydrogel. Cell interactions and key processes such as cell division and death are being visualized over several days by high-content video-microscopy. Tumor on a chip technology has an enormous potential to explore the complex interactions between immune cells and cancer cells in a tumor microenvironment as a basis for the development of novel immunotherapies for cancer.

Cancer cell killing by macrophages

Historically, the development of cancer immunotherapy has been mostly focused on the ability of cytotoxic CD8 T cells to kill cancer cells. However, many cancer cells mutate to evade immune recognition by T cells. Previous work by our lab has revealed that another type of immune cells called macrophages may be very efficient at eliminating cancer cells, and we are therefore working on developing a novel cancer immunotherapy based on the optimized activation of tumor-associated macrophages. Tumor on a chip technology is a central tool for this enterprise because the cellular and molecular mechanisms how activated macrophages kill cancer cells remain poorly characterized. In 2023, we have managed to establish a microscopy-based, live imaging assay to visualize *in vitro* the killing of cancer cells by activated mouse and human macrophages, which we consider a breakthrough for our research. This assay will allow us to test *in vitro* various conditions and delivery techniques to optimize the induction of cytotoxic activity of tumor-associated macrophages towards cancer cells *in situ* in tumors.

Fungal polysaccharides trigger macrophage anti-cancer activity

Fungal polysaccharides can exert immunomodulating activity by triggering pattern recognition receptors on innate immune cells. In collaboration with Kari Inngjerdingen at the Department of Pharmacy, University of Oslo, we identified two water-soluble polysaccharides, AcF1 and AcF3, from the medicinal fungus Inonotus obliquus being able to trigger several critical antitumor functions of macrophages. AcF1 and AcF3 were shown to activate macrophages to secrete nitric oxide and pro-inflammatory cytokines, and to induce macrophage-mediated inhibition of cancer cell growth in vitro and in vivo. The water-soluble polysaccharides AcF1 and AcF3 were found to be agonists for Toll-like receptors and to have a strong potential for cancer immunotherapy by triggering multiple pattern recognition receptors and thereby inducing potent anti-cancer activity of macrophages.



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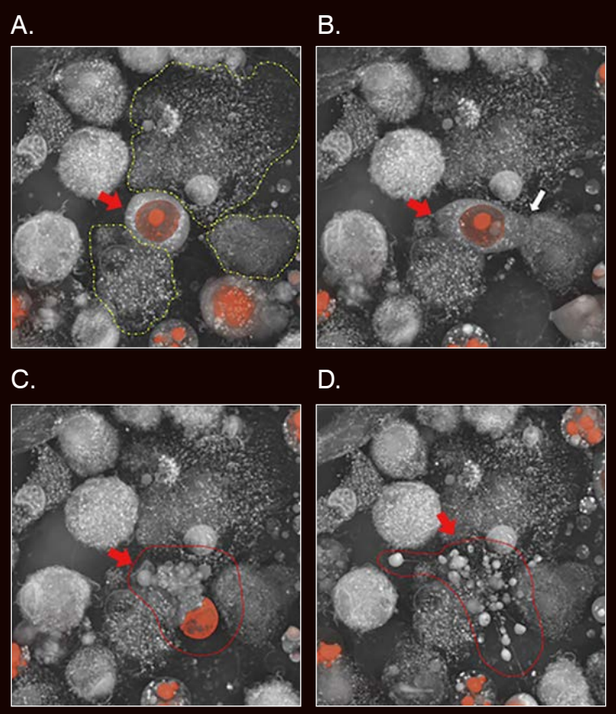
Macrophages eliminate cancer cells. (A) Cancer cells imaged 0.5 h after they were seeded out. (B) Cancer cells in co-culture with macrophages are eliminated whereas cancer cells alone proliferate. Left panel: Cancer cells express a red fluorescent protein; non-fluorescent macrophages are imaged by phase contrast microscopy. Right panel: Individual cancer cells are annotated and presented as red dots. The images were acquired by Incucyte S3 (credit: Inger Øybråten).



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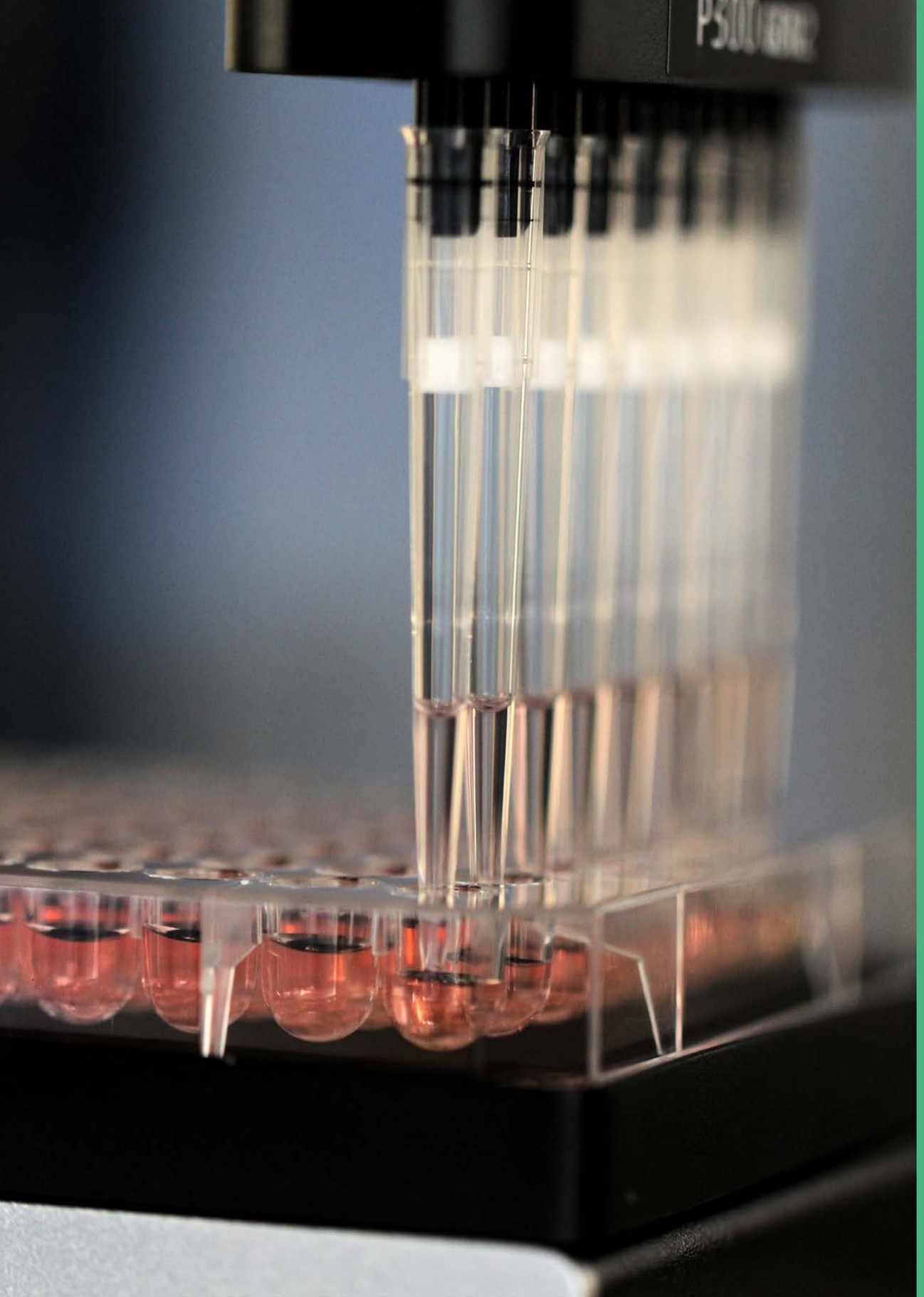
Cancer cells cultured together with macrophages are killed. (A) A cancer cell (red nucleus; red arrow) is situated between macrophages encircled by yellow dashed lines. (B) The cancer cell appears to be in contact with three macrophages. (C, D) The cancer cell forms blebs and disintegrate. The process in A-D is completed within 3 hours. The images were acquired by Tomocube HT-X1 (credit: Inger Øybråten).



Medium exchange of 3D gastruloid cultures by an automated pipetting robot (credit: Thomas Combriat).

Associated groups

Waaler group
Cell Signaling and Drug Discovery

Jo Waaler
Associated partner

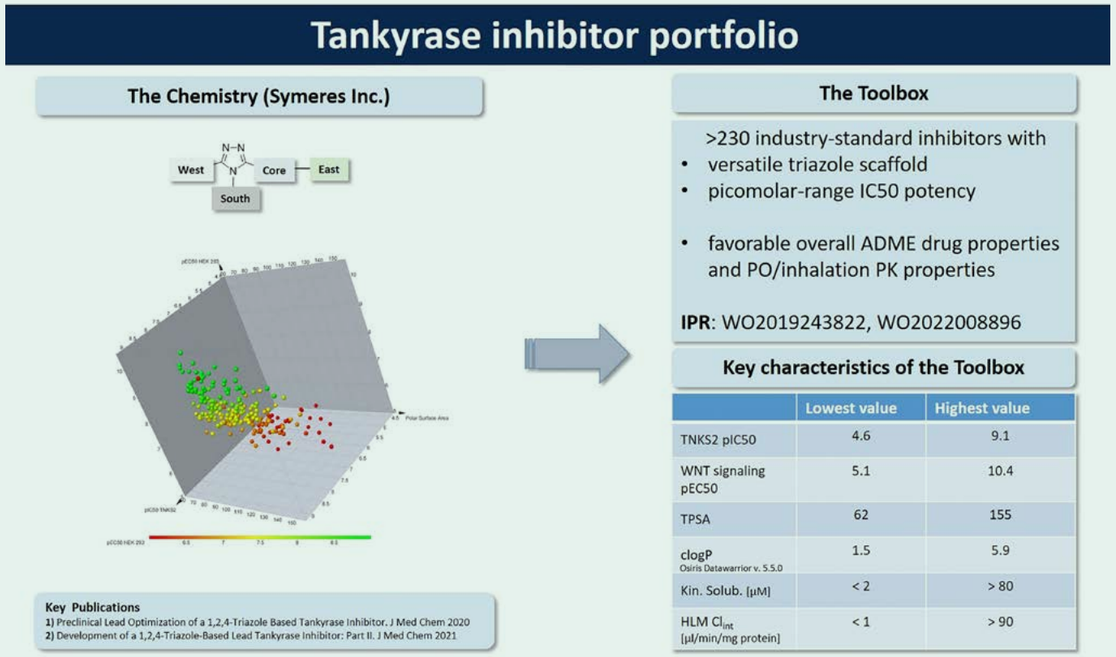
The objective for the research group is to translate the experience from work with cell signaling pathways and drug discovery to the work in the Centre.

Cell Signaling and Drug Development

The key scientific expertise of the research group is within molecular and mechanistic studies of central developmental and cancer-promoting cell signaling pathways. The research in particular focus on detailed molecular and mechanistic studies of WNT/β-catenin and YAP signaling pathways in control of tumor development/progression and microenvironment tumor-immune cell interplay, as well as sensitivity to immunotherapy. Drug development Although dysregulation of WNT/β-catenin and YAP signaling are hallmarks in a major fraction of cancers and diseases including fibrosis, therapy targeting these pathways is currently not available in clinical practice. Since 2006, Jo Waaler and Stefan Krauss have been central in a drug development program that has identified TNKS1 and 2 as key targets controling these pathways that have hitherto not been therapeutically addressed. Our program aiming towards clinical studies is executed together with Symeres Inc., an acknowledged Dutch chemistry company acting as our close scientific and business partner as well as Inven2, the TTO for Oslo University Hospital. The project has obtained extensive innovation funding in the recent years and at current we are supported by the Norwegian Research Council, UiO innovation and SPARK Norway. To our knowledge, our drug development program is leading the field for the biotarget and for a therapeutic TNKS-WNT/β-catenin-YAP signaling inhibitor.

TNKS inhibitor drug discovery

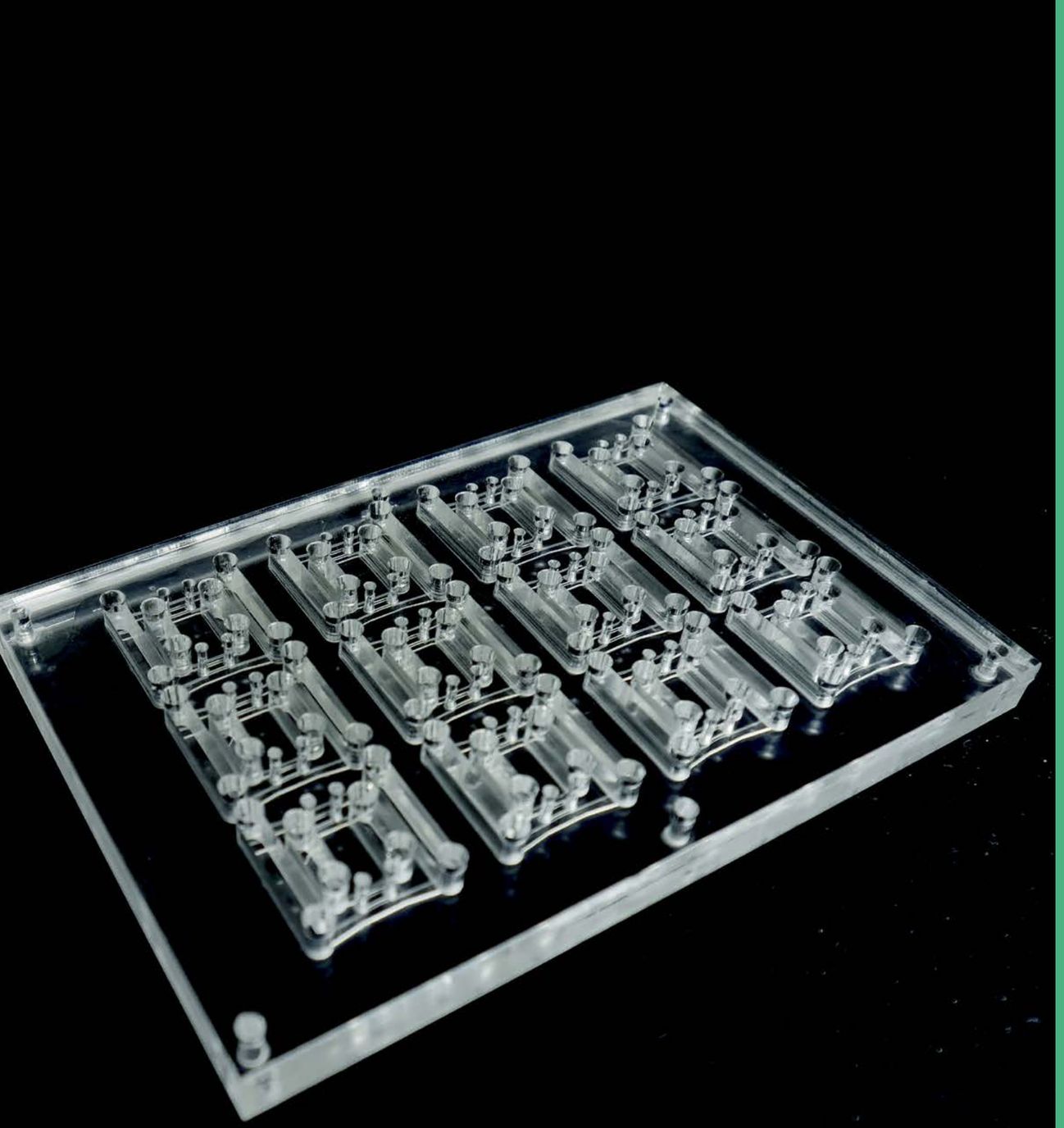
In 2021 and 2022 we published two closely related papers. The first paper (Journal of Medicinal Chemistry), described the development of the novel TNKS inhibitor OM-153. OM-153 showed picomolar IC50 inhibition in a cellular WNT/β-catenin signaling reporter assay (630 pM), no off-target liabilities, overall favorable absorption, distribution, metabolism, and excretion (ADME) properties, and an improved pharmacokinetic profile in mice. In the paper further addressing the biological properties of OM-153 (Cancer Research Communications, new AACR journal), we could show a robust anti-tumor effect in a colon carcinoma and immune oncology model, and importantly, with a significant therapeutic window (0.33 mg/kg - ≥10 mg/kg, dosed twice daily). This is remarkable, since the field was restricted by worries regarding intestinal toxicity mediated by TNKS inhibitors since 2013. In December 2023, Odin Therapeutics was created together with Stefan Krauss with the basis in a portfolio of TNKS inhibitors with the aim to develop drugs for use in the clinic (see figure).



	Lowest value	Highest value
TNKS2 pIC50	4.6	9.1
WNT signaling pEC50	5.1	10.4
TPSA	62	155
clogP Osiris Datawarrior v. 5.5.0	1.5	5.9
Kin. Solub. [µM]	< 2	> 80
HLM Cl_{int} [µl/min/mg protein]	< 1	> 90

Ongoing Projects

The current objective is to evaluate the effect and mechanism of action for TNKS inhibitor monotherapy and combination therapies in the regulation of signaling pathways in cancer and disease using cell culture as well as *ex vivo* and rodent models. The objective also includes testing of drugs in Organ on-chip-based platforms and models. The first sub-objective for the research group is to assess the effect of and mechanism of action behind TNKS/immune checkpoint inhibitor anti-cancer combination therapy against melanoma, as well as the involvement of the adaptive and innate immune system using isogenic mouse models. The second sub-objective is to evaluate the efficacy of TNKS inhibitor therapy against pulmonary fibrosis, including idiopathic pulmonary fibrosis (IPF), a disease with an in particular high medical unmet need.



Pumpless recirculating Organ-on-Chip (rOoC) platform in the well-plate format featuring 12 independent rOoCs in the popular 96-well grid for medium throughput Organ-on-Chip experimentation (credit: Mikel A. Martinez and Mathias Busek).

HTH associated research projects

ITOM

Integrated technologies for tracking organoid morphogenesis 2022–2026

About the project

There is a significant need for developing reliable human organ representations (termed organoids) for drug development, personalized drug testing, and on the longer run for organ transplantations. The advent of human induced pluripotent cell (hiPSC) technology has allowed developing *in vitro* human organoids that show features of the organs they represent, but are significantly less structured and less mature than their human counterparts. The field therefore requires high-content tracking tools and algorithms to guide organoid development. Developing such technologies will represent a leap towards reliable personalized organoids with organ-like histology and functionality.

In this project we will work on three technological platforms to track organoid morphology.

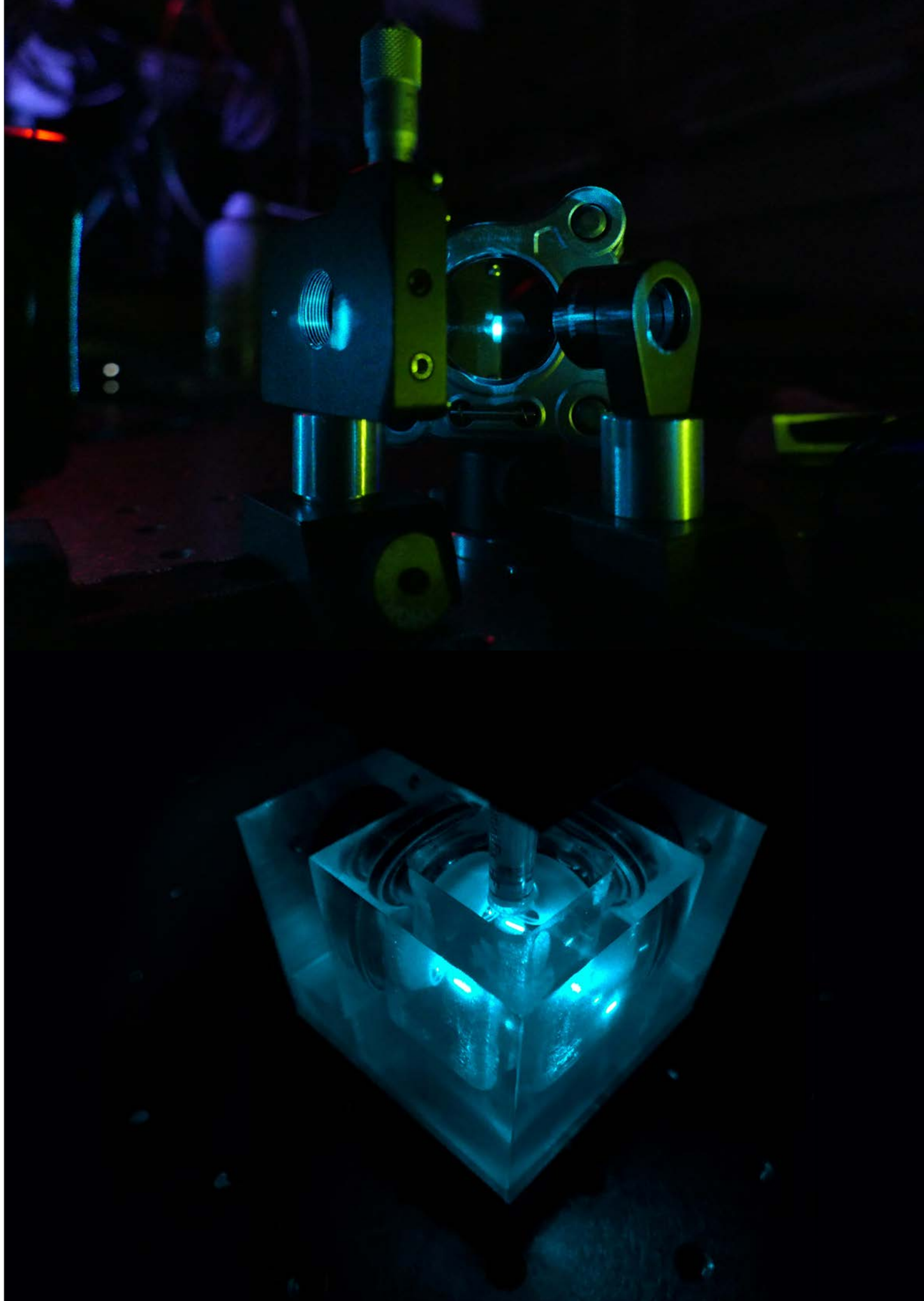
1. Confocal Raman microscopy that allows label-free visualization of Raman active molecules in fixed and living specimens.

2. High-resolution spatial transcriptomics and desorption electrospray ionization-mass spectrometry (DESI-MS).

3. Lightsheet microscopy for fast and slow time-lapse imaging of cells in the organoids.

Based on the imaging data, we will develop statistical physics models for organ/organoid pattern formation *in vitro*. The information will be used to tailor statistical models to improve organoid formation *in vitro*.

→
Images of a custom built lightsheet microscope tailored for analyzing the 3D shape changes in developing gastruloids. The top image highlights a close-up of the optics, while the bottom image showcases the gastruloid incubation/imaging chamber (credit: Joachim Mossige).



PROJECT LEADER

Prof. Stefan Krauss
Hybrid Technology Hub – Centre of Excellence, Institute of Basic Medical Sciences, University of Oslo (UiO) and Oslo University Hospital

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Prof. Joachim Mathiesen
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Dr. Hanne Røberg-Larsen
Department of Chemistry, UiO

Dr. Håkon Høgset
Institute of Basic Medical Sciences, UiO

FUNDING

The 4 year project is funded by the UiO: Life Science convergence environment program with 16,9 million NOK

FURTHER INFORMATION

https://www.uio.no/english/research/strategic-research-areas/life-science/research/convergence-environments/itom/

SUMO

Supervised morphogenesis in gastruloids

About the project

The lack of realistic *in vitro* organ models that can faithfully represent *in vivo* physiological processes is a major obstacle affecting the biological and medical sciences. The emergence of stem cell engineered organ models called organoids represents a viable alternative to animal research. However, current organoid technology has yet to produce larger histological and physiological faithful organ models. Specifically, current organoids are too small, not vascularized and lack the 3-dimensional organization found *in vivo*. In this interdisciplinary project we aim to challenge all these limitations by using the emerging gastruloid technology guided by cutting edge bioengineering and artificial intelligence.

The work of the consortium focuses on:

1. Developing mouse gastruloid technology to achieve reproducible heart and gut development.
2. Vascularization of gastruloids to produce 1 cm^3 ELM.
3. Advancing human gastruloid technology within ethical boundaries
4. Developing correlative live imaging technologies and Raman spectroscopy as a benchmarking and tracking tool for gastruloids.
5. Developing machine learning (ML) based tracking algorithms in 3D.
6. Establishing a standardized close-loop system and DBTL platform for upscaling.
7. Implementing a DBTL platform to establish a PoC environmental toxicology pipeline.
8. Providing an ethical, safety and regulatory framework for advanced human gastruloid technology.
9. Engageing in a social dialogue with the public advanced human gastruloid technology.
10. Strengthening gastruloid/organoid community; Disseminate technology to the European biotech industry.

The SUMO project enters a thematic “Engineered Living Matter” portfolio that comprises 7 projects.

PROJECT LEADER

Prof. Stefan Krauss
Hybrid Technology Hub - Centre of Excellence, Institute of Basic Medical Sciences, University of Oslo (UiO) and Oslo University Hospital

PARTICIPANTS

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Centre for Medical Ethics, Institute of Health and Society, University of Oslo

Prof. Molly Stevens
Imperial College of Science, Technolgy and Medicine, London

Prof. Nikolaj Gadegaard
University of Glasgow

Dr. Jesse Veenvliet
Max-Planck-Gesellschaft Dresden

Dr. Jens v Kries
Forschungsverbund Berlin

Dr. Iftach Nachmann
Tel Aviv University

FUNDING

The 5 year project is funded by the EU program: HORIZON.3.1 - The European Innovation Council (EIC) with 4,95 million Euro

FURTHER INFORMATION

https://cordis.europa.eu/project/id/101071203

https://supervised-morphogenesis.eu

→
Immunostaining of a cardiogenic mouse gastruloid 168 hours after aggregation using an improved differentiation protocol. Magenta represents Cardiac Troponin T (cTnT), which is a marker for the heart field located in the anterior part of the gastruloid. Green represents Sox2, which marks a neural tube-like structure. Yellow represents FoxA2, which marks the developing gut tube and blue represents DAPI which stains DNA (credit: Sergei Ponomartcev and Natalia Smirnova).

→
Immunostaining of a mouse gastruloid (aggegoid) generated by co-culture of embryonic stem cells with extra embryonic endoderm-like cells. White represents cell membranes stained with WGA. Green represents the Flk1 reporter, which marks blood vessel precursors. Magenta represents Sox17, which marks the extraembryonic endoderm cells included in the embryonic gut tube (credit: Sergei Ponomartcev and Natalia Smirnova).

HYBRIDA

Embedding a comprehensive ethical dimension to organoid-based research and related technologies

About the project

The main objective of the project is to develop a comprehensive regulatory framework for organoid research and organoid-related technologies. The work in the consortium focuses on:

1. Identify different forms of conceptual uncertainty by exploring the ontological, moral and legal status of organoids present in different cultures and knowledge traditions.
2. Reducing epistemological uncertainty in organoid research and produce improvements in impact assessment of organoïd-related technologies.
3. Exploring regulatory uncertainty prevalent in existing normative and ethical frameworks pertaining to technologies similar to organoid-related technologies.
4. Understanding the worries, fears and expectations of the general public, vulnerable groups, patients, donors and civil society organisations with respect to organoids.
5. Engaging relevant stakeholders, in order to co-create and validate the 4 main products of HYBRIDA.
6. Producing a set of operational guidelines for the field of organoid research.
7. Producing a Code of responsible conduct for organoid researchers and, if needed, suggest a supplement to the ECoC.
8. Enhancing existing ethics and normative frameworks with a focus on organoid research and organoid-related technologies.

PROJECT LEADER

Søren Holm
Department of Law, School of Social Sciences, University of Manchester / University of Oslo

PARTICIPANTS

The University of Manchester;
Universite Catholique de Louvain;
Aarhus University;
University Leiden;
Technical University Athens;
Insubria University
University of Oslo

FUNDING

The 3 year project is funded by the EU program: H2020-EU.5. – SCIENCE WITH AND FOR SOCIETY with 26,5 million NOK

FURTHER INFORMATION

https://hybrida-project.eu

https://cordis.europa.eu/project/id/101006012

Wellcome LEAP

Female resilience on-chip: Monitoring dynamic resilience using Multi-Organ-Chips linking metabolic state and immune response in pre- and postmenopausal women.

Group photo from the annual meeting with principle investigators from all participating groups of the Wellcome Leap Dynamic Resilience program.

About the project

Current research on dynamic resilience has been limited to observational clinical settings and simplified *in vitro* assays. However, in order to investigate the mechanisms that control and alter resilience and to identify associated biomarkers, advanced *in vitro* models that can be subjected to stressors in defined ways are urgently needed. Organ-on-Chip (OoC) technology has the potential to address these limitations by enabling the connection of multiple tissue models and the integration of immune components, allowing for studies on human physiological processes with a granularity that current models do not provide.

In this project we unite experts in OoC platform design, organoid development, immunology, genomics, bioinformatics/ artificial intelligence, and clinical research to create a resilience-on-chip platform. We believe that metabolic changes during aging contribute to an inflammatory environment, impacting resilience and having immune metabolic effects. We hypothesize that dynamic resilience mechanisms are centrally impacted by metabolic changes during aging that create an overall inflammatory environment which leads to loss of resilience and hence are of immune metabolic nature.

To explore this hypothesis with high granularity, we propose:

1. Leveraging a three-organ Multi-Organ-Chip (MOoC) connecting hormone, metabolic and immune sensitive organs (WAT, liver and lymphoid tissue).

2. Applying a series of readouts that allow the dynamic monitoring of immune metabolic changes in an integrated approach.

3. Interrogating the platform with a battery of stressors.

4. Benchmarking the in vitro data set with the human in vivo situation on a patient-specific level.

PROJECT LEADER

Prof. Peter Loskill
Natural and Medical Sciences Institute at the University of Tübingen (NMI), Germany.

PARTICIPANTS

NMI-μOrgano team
Prof. Dr. Peter Loskill
Dr. Claudia Teufel
Dr. Madalena Cipriano

NMI-MIA team
Dr. Nicole Schneiderhan-Marra
Dr. Alex Dulovic NMA

Wellcome Sanger Institute team
Dr. Roser VentoTormo

University of Oslo team
Prof. Stefan Krauss
Prof. Dr. Espen Melum
Dr. Aleksandra Aizenshtadt
Dr. Mathias Busek

Clinical and Regulatory Advisory Board
Prof. Dr. Sara Y. Brucker, EKUT University Women's Hospital, Tubingen.

Prof. Dr. Espen Melum, Research Institute of Internal Medicine (RIIM), UiO.

Dr. Heidi Beate Berntzen, UiO.

FUNDING

The 3-year project is funded by the Wellcome Leap Dynamic Resilience program with 6,3 million USD.

FURTHER INFORMATION

https://wellcomeleap.org/dr/program/

Research and engagement

Innovation

SPARK teams

SPARK is a two-year UiO:Life Science innovation program to further develop ideas within health-related life sciences for the benefit of patients and society.

rOoC (revolving Organ-on-chip platform)

Project leader

Dr. Aleksandra Aizenshtadt, HTH, UiO.

Team members

Dr. Shadab Abadpour, Dr. Mathias Busek, Chencheng Wang, Prof. Steven Ray Haakon Wilson, Prof. Stefan Krauss, Dr. Hanne Scholz.

Tankyrase inhibition for therapy of fibrotic diseases

Project leader

Shoshy Alam Brinch, Hybrid Technology Hub, UiO and Department of Immunology and Transfusion Medicine, Oslo University Hospital.

Team members

Jo Waaler (OUS/UiO) and Stefan Krauss (UiO/OUS)

DUCT chip – An artificial bile duct on a chip recapitulating immune functions

Project leader

Henry Hoyle, Division of Surgery, Inflammatory Diseases and Transplantation, OUS.

Team members

Anna Katharina Frank, Espen Melum, Stefan Krauss, Mathias Busek, Aleksandra Aizenshtadt and Kayoko Shoji

Patents

Krauss S, Nazare M, Lehtio L, Waaler J, Wegert A, Leenders R.G.G "compounds". Application submitted 19. June 2018 IPO patent application number 1810071.9. Published 29.12.2019 WO2019/243822

Krauss S, Waler J, Lehtio L, Leenders R.G.G. Wegert A. “compounds” application submitted 6. July 2020 IPO patent application number 2010359.4

Krauss S, Aizhenshtadt A, Mikel Martinez, Busek M “Cell Culture Device”. Application submitted 19 July 2021 UK patent application (Appl. 2110366.8)

DOFI

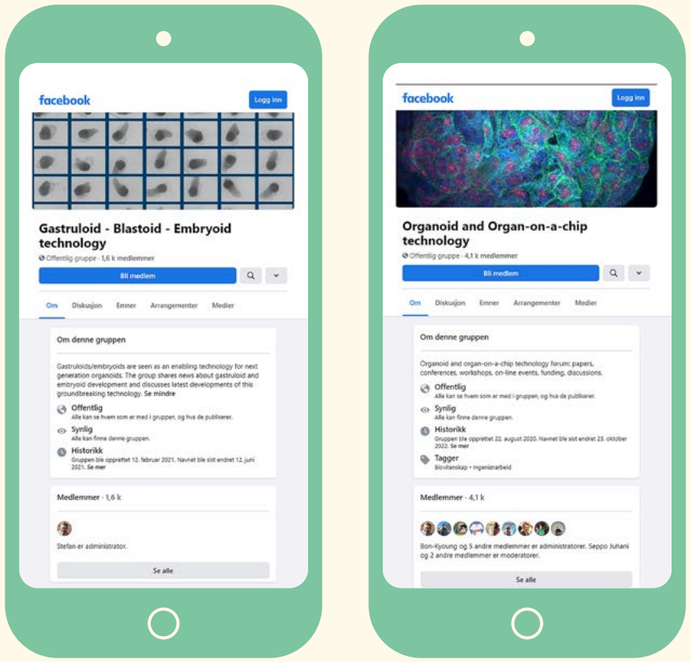
14/09/2020 DUCT chip – An artificial bile duct on a chip recapitulating immune functions; Espen Melum, Anna Frank, Stefan Krauss

13/08/2021 Human iPS derived zone specific hepatocytes; Aleksandra Aizenshtadt and Stefan Krauss

10/01/2023 Devise for analytical Electromembrane Extraction from 3D cell culture, Organoids and organ-on-a-chip platforms; Frøydis Sved Skottvoll, Steven Ray Wilson, Stig Pedersen Bjergaard, Jörg P. Kutter, Michal Mielnik, Aleksandra Aizenshtadt, Stefan Krauss

Outreach

Media / Social media



Facebook

HTH manages two public Facebook groups focused on gastruloids and organoids, with 1700 and 4300 followers, respectively.

https://www.facebook.com/groups/143900280909369

https://www.facebook.com/groups/304082784189295

Linkedin

HTH managed group

https://www.linkedin.com/groups/12584551/

1700 + 4300
followers

Popular science presentations / Articles in media

Han kan redde millioner av dyr fra medisinsk forskning

HTH PhD student Stian Kogler was highlighted as a “young leading star” in Dagens Næringsliv. May 5th, 2023.

https://www.dn.no/d2/ledestjerner/ledestjerner-2023/ledestjerner/persontilpasset-medisin/han-kan-redde-millioner-av-dyr-fra-medisinsk-forskning/2-1-1445483

Laboratoriedyrkede organer – et alternativ til dyreforsøk?

Steven Wilson presented at the Tekna seminar on «Diagnostikk og analytisk kjemi» June 1st, 2023.

https://www.tekna.no/fag-og-nettverk/miljo-og-biovitenskap/bio-og-klimabloggen/diagnostikk-og-analytisk-kjemi/

Can stem cell treatment cure type1 diabetes?

Hanne Scholz presented at Oslo Diabetes Research Centre, «Folkemøte om diabetes» August 24th, 2023.

https://www.oslodiabetes.no/news/2023/8/24/folkemte-om-diabetes

Bereder grunnen for kunstige organer

Presentation of ITOM convergence environment in the APOLLON research magazine. August 24th, 2023.

https://www.apollon.uio.no/artikler/2023/3_kunstige_organer.html

Eit vindauge til menneskets tilbliing

Presentation of HTH research on stem cell derived embryo models in the Genialt magazine published by The Norwegian Biotechnology Advisory Board. 4-2023.

https://www.bioteknologiradet.no/tidsskriftet-genialt/genialt-4-2023/

Education

RESEARCH SCHOOL FOR TRAINING THE NEXT GENERATION OF MICRO- AND NANO-TECHNOLOGY RESEARCHERS IN NORWAY

TNNN – Research School for Training the Next Generation of Micro- and Nanotechnology Researchers in Norway

About the project

The Hybrid Technology Hub CoE participates in the Research School for Training the Next Generation of Micro- and Nanotechnology Researchers in Norway (TNNN). Micro and Nano Science and Technology is a highly cross disciplinary field that covers many areas of science including physics, chemistry, material technology, biology and medicine. It is the driving force behind a large part of modern science and technology, with numerous applications that span photovoltaics, batteries, fuel cells, opto-electronics, sensors, medical diagnostics, biomedical research, quantum computing and many others.

The Research School for Training the Next Generation of Micro- and Nanotechnology Researchers in Norway (TNNN) will address current gaps in PhD-level education in this field. In particular, it will establish a vibrant national network of junior scientists working in this area of science and technology development, provide training in transferable skills and facilitate collaboration with industry.

The Research School focuses on:

1. National Junior Scientist Research Conference: This conference will be organized every year and will include plenary and invited talks from leaders in various areas of nanotechnology, contributed talks from PhD candidates and postdoctoral researchers, presentations from industry, workshops and networking events
2. Workshops in generic/transferable skills
3. Problem solving workshops organized together with partners from the Norwegian industry
4. Innovation, entrepreneurship and commercialization courses and workshops

The TNNN research school held its 2nd annual national conference at the University of South-Eastern Norway (USN) on June 21st–23rd, 2023. The program included international invited speakers, industry talks, student talks and posters, university and industry lab visits and social activities.

HTH contact point

Dr. Hanne Scholz, Hybrid Technology Hub – Centre of Excellence, Institute of Basic Medical Sciences, University of Oslo (UiO) and Oslo University Hospital.

Further information

Research School for Training the Next Generation of Micro- and Nanotechnology Researchers in Norway (TNNN) – NTNU.

https://www.ntnu.edu/tnnn

Education

The NoOC (The Nordic organ-on-chip Network) networking event March 9th, 2023

The NoOC networking event was held as a virtual meeting lasting half a day. The program included keynote talks from experienced researchers and pitches by PhD and postdoctoral students from across the Nordic region. Lotta Isosaari (Tampere University, Finland) was honored with the best pitch award, earning a travel grant to visit a fellow Nordic laboratory.

Graduated PhD students

On October 20th, 2023, Christine Olsen defended her dissertation: “Multifaceted challenges with liquid chromatography mass spectrometry determination of bioactive hormones secreted from stem cell-derived islet organoid”.

Frøydis Sved Skottvold warmly congratulates Christine Olsen (on the right). Photo: Steven Wilson.

On November 24th, 2023, Dongho Kwak defended his dissertation “Music for cells? Rhythmic mechanical stimulations of cell cultures”

In the center stands Dongho Kwak, flanked by supervisors Prof. Alexander Refsum Jensenius and Prof. Anne Danielsen (RITMO, UiO) on the left, and Dr. Hanne Scholz and Dr. Petter Angell Olsen (HTH) on the right. Photo: David Burke.

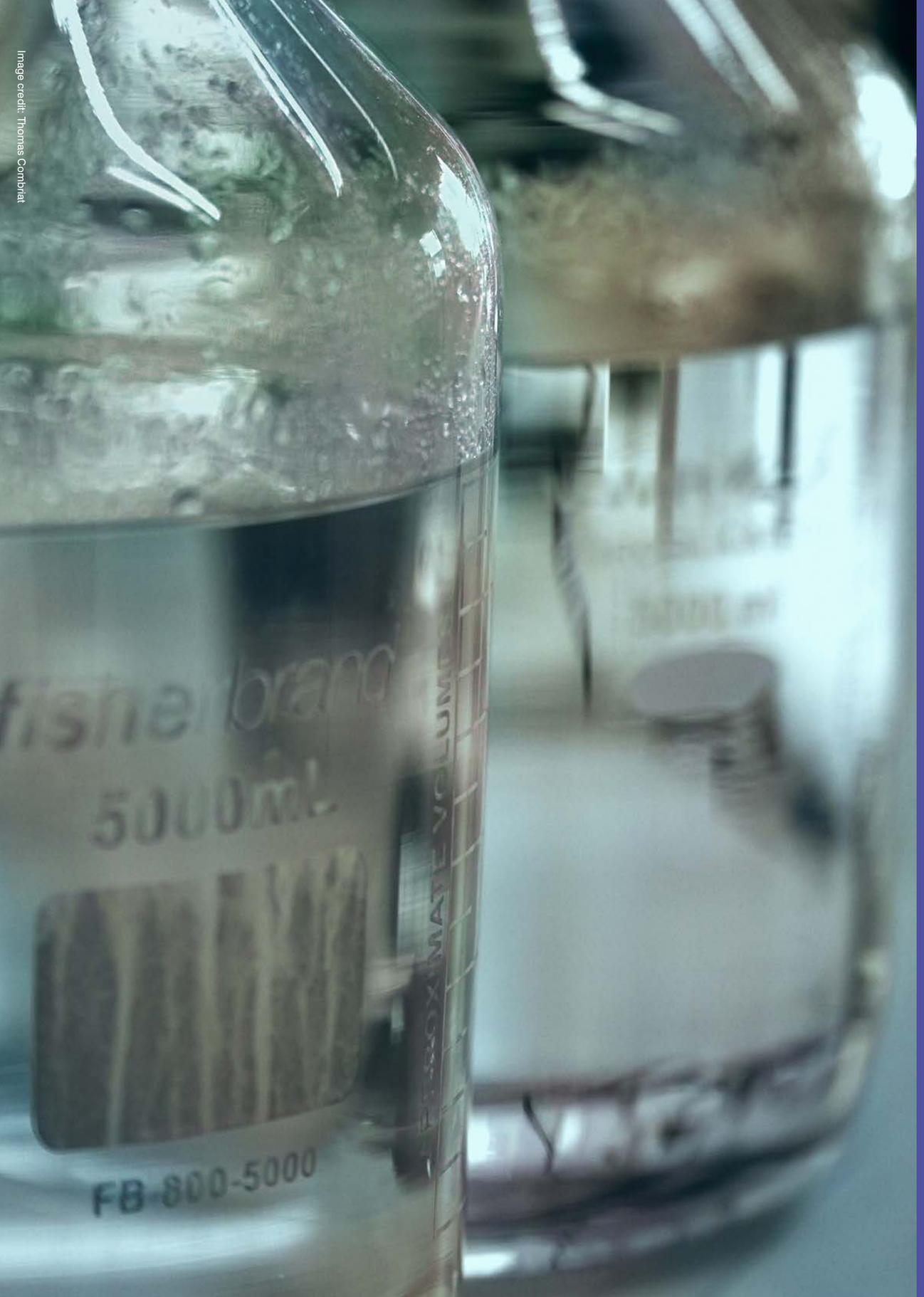


Image credit: Thomas Combriat

About the centre

Organizational chart

- 1 man-year
- 1/2 man-year

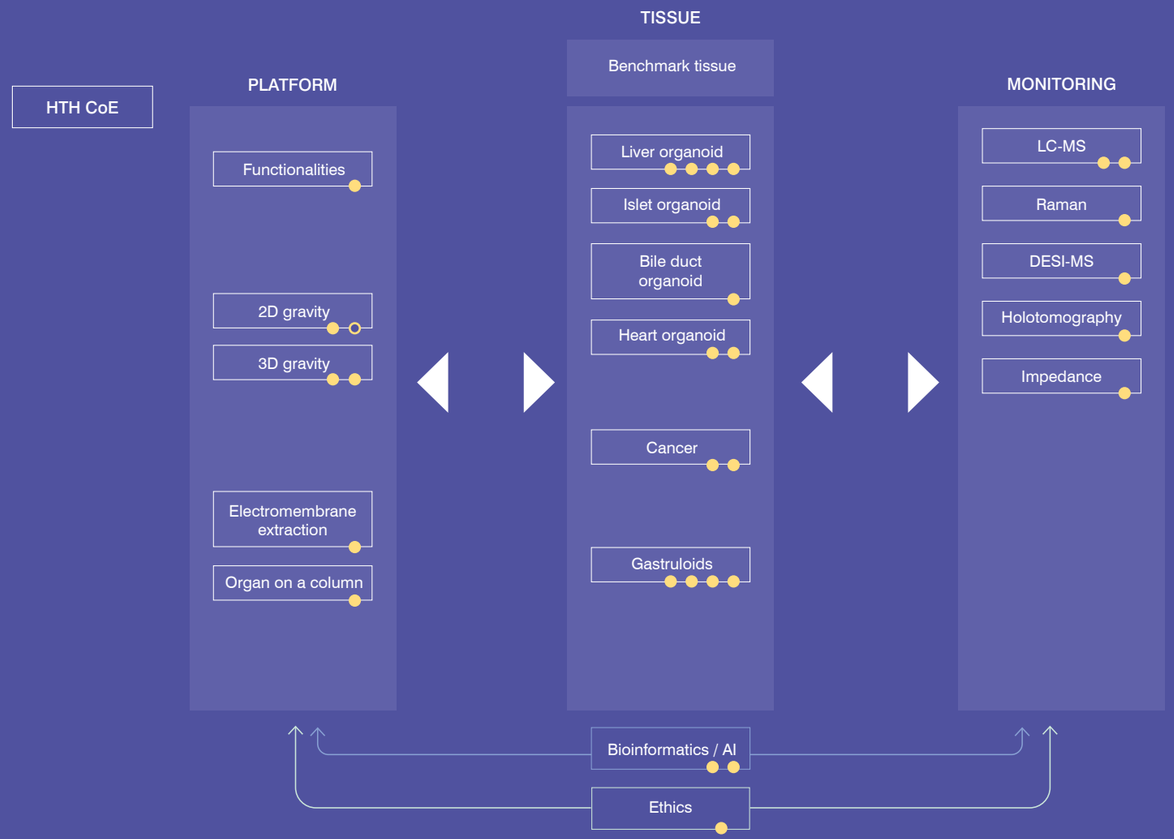


Image credit: Thomas Combriat

About the centre

Team members 2023

Management

Stefan Krauss
Centre Director

Hanne Scholz
Vice Director

Petter Angell Olsen
Administrative coordinator
and Facility manager

Principal investigators

Nikolaj Gadegaard

Molly Stevens

Simon Rayner

Steven Wilson

Jan Helge Solbakk

Stefan Krauss

Hanne Scholz

William Edward Louch

Espen Melum

Alexandre Corthay

Associated Partners

Jo Waaler

Hanne Røberg-Larsen

Team members 2023

Postdoctoral fellows and researchers


Alexandra Aizenshtadt
Lab. manager


Kayoko Shoji


Anna Frank


Shadab Abadpour


Mathias Busek


Thomas Combriat


Olga Bibikova


Ludivine Delon


Sergei Ponomartcev


Håkon Høgset


Junya Shoji


Igor Meszka


Inger Øybråten


Sean Harrison


Andrea Dalmao-Fernandez


Jonas Aakre Wik


Henry Hoyle


Jia Li


Heidi Beate Bentzen

PhD candidates


Steffen Nøvik


Mikel Amirola Martinez


Chencheng Wang


Dongho Daniel Kwak


Stian Kogler


Shoshy Alam Brinch


Ingrid Wilhelmsen


Malgorzata Elzbieta Zawadzka


Franziska Schoeb


Duarte Menezes


Natalia Smirnova

Head technician


Justyna Stokowiec

Technicians


Ida Johnsen


Lydia Busek


Alexey Golovin


Yuliia Boichuk


Emilie Gasparini


Dilara Lal, Lal


Jeanette Konstanse Steen

Board 2023

Professor Jan G. Bjålie
Pro-Dean for Research and Innovation Faculty of Medicine, University of Oslo

Chairman of the board

Board members

Professor Lene Frost Andersen
Head of department, Institute of Basic Medical Sciences, University of Oslo

Professor Lars Eide
Institute of Clinical Medicine, University of Oslo

Professor Steve Beaumont
University of Glasgow

Professor Raoul Charles Coombes
Imperial College, London

Professor Stefan Krauss
Centre Director, Hybrid Technology Hub, University of Oslo

Scientific Advisory Board (SAB) 2023

Professor Bengt Norden
Chalmers University of Technology, Sweden

Professor Anna Herland
KTH Royal Institute of Technology, Sweden

Professor Peter Loskill
Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Germany

Professor Thomas Laurell
Department of Biomedical Engineering, Lund University

About the centre

International collaborations

ACADEMIC COLLABORATIONS

- Aarhus University
- Armauer Hansen Research Institute
- Chalmers University of Technology
- Chinese Academy of Sciences-Max Planck Gesellschaft Partner Institute for Computational Biology
- Forschungsverbund Berlin
- Harvard Medical School
- Institut Cochin
- Italian National Research Council
- Juntendo University School of Medicine
- Karolinska Institutet
- KTH Royal Institute of Technology
- Leiden University Medical Center
- Maastricht University
- Max-Planck-Gesellschaft zur Förderung der Wissenschaften
- RMIT University
- Technical University of Denmark
- Tel Aviv University
- The University of Texas Medical Branch
- Université d'Artois
- University of Arizona
- University of Bergen
- University of California
- University of Cambridge
- University of Copenhagen
- University of Helsinki
- University of Illinois at Urbana-Champaign
- University of Natural Resources and Life Sciences
- University of Oulu
- University of Turku
- Univesity of Oslo / Oslo university hospital
- Uppsala University Hospital
- Wuhan Institute of Virology
- Wyss Institute at Harvard University
- Yale School of Medicine / Yale Stem Cell Center

INDUSTRIAL COLLABORATIONS

- AstraZeneca R&D
- CVMD iMed Bioscience
- NOVARTIS
- Symeres Inc
- Waters

Best pitch award ceremony at the annual retreat.

Retreats

Quality Hotel Leangkollen (35-minute drive from Oslo centrum).

HTH annual retreat

November 2nd–3rd 2023

The 2023 HTH annual retreat was held at Leangkollen Hotell and had 50 participants. The schedule spanned two days and featured virtual presentations by two renowned international speakers (Jacob Hanna and Dmitriy Krepkiy). Moreover, representatives from UiO covered topics related to proposal writing, ethics, and innovation. To enhance collaboration and teamwork, the agenda also included group work sessions and team-building activities.

HTH participating in Holmenkoll-stafetten.

HTH minigolf tournament.

Publications 2023

Abadpour, Shadab; Niemi, Essi Maria; Strid Orrhult, Linnea; Hermanns, Carolin; de Vries, Rick; Parreiras Nogueira, Liebert; Haugen, Håvard Jostein; Josefsen, Dag; Krauss, Stefan Johannes Karl; Gatenholm, Paul; van Apeldoorn, Aart & Scholz, Hanne.

Adipose-Derived Stromal Cells Preserve Pancreatic Islet Function in a Transplantable 3D Bioprinted Scaffold.

Adv Healthc Mater. 2023 Dec;12(32):e2300640.

Doi: *10.1002/adhm.202300640*

Aizenshtadt, Aleksandra; Midtøy, Lise; Thiede, Bernd; Krauss, Stefan; Røberg-Larsen, Hanne; Wilson, Steven Ray.

Micro-Pillar Array Column Separations for Proteomics of Liver Organoids.

LCGC Europe. 2023 May; 36 (s5).

Doi: *10.56530/lcgc.eu.st2089i6*

Anderson, Colin C.; Bonney, Elizabeth A.; Mueller, Thomas F.; Corthay, Alexandre Benoit; Havele, Calliopi; Singh, Nevil J.; Øynebråten, Inger & Bretscher, Peter A.

On antigen-specific signals, immune class regulation and energetics: Report III from the workshops on foundational concepts of immune regulation.

Scand J Immunol. 2023 Sep;98(3):e13311.

Doi: *10.1111/sji.13311*

Boix Lemonche, Gerard; Nagymihaly, Richard; Niemi, Essi Maria; Josifovska, Natasha; Johansen, Stian; Moe, Morten Carsten; Scholz, Hanne & Petrovski, Goran.

Intracorneal Implantation of 3D Bioprinted Scaffolds Containing Mesenchymal Stromal Cells Using Femtosecond-Laser-Assisted Intrastromal Keratoplasty.

Macromol Biosci. 2023 Jul;23(7):e2200422.

Doi: *10.1002/mabi.202200422*

Dalmao-Fernandez, Andrea; Aizenshtadt, Aleksandra; Bakke, Hege Gilbø; Krauss, Stefan Johannes Karl; Rustan, Arild Christian; Thoresen, G. Hege & Kase, Eili Tranheim.

Development of three-dimensional primary human myospheres as culture model of skeletal muscle cells for metabolic studies.

Front Bioeng Biotechnol. 2023 Mar 23:11:1130693.

Doi: *10.3389/fbioe.2023.1130693*

Fernández-Galiana, Álvaro; Bibikova, Olga; Vilms Pedersen, Simon; Stevens, Molly M.

Fundamentals and Applications of Raman-Based Techniques for the Design and Development of Active Biomedical Materials.

Adv Mater. 2023 Mar 31.

Doi: *10.1002/adma.202210807*

Greguš, Michal; Ivanov, Alexander R, Wilson, Steven Ray.

Ultralow flow liquid chromatography and related approaches: A focus on recent bioanalytical applications.

Review J Sep Sci. 2023 Sep;46(18).

Doi: *10.1002/jssc.202300440*

Harrison, Sean Philip; Siller, Richard; Tanaka, Yoshiaki; Chollet Dugarte, Maria Eugenia; de la Morena-Barrio, María Eugenia; Xiang, Yangfei; Patterson, Benjamin; Andersen, Elisabeth; Bravo-Pérez, Carlos; Kempf, Henning; Åsrud, Kathrine S.; Lunov, Oleg; Dejneka, Alexandr; Mowinckel, Marie-Christine; Stavik, Benedicte; Sandset, Per Morten; Melum, Espen; Baumgarten, Saphira Felicitas; Bonanini, Flavio; Kurek, Dorota; Mathapati, Santosh Sadashiv; Almaas, Runar; Sharma, Kulbhushan; Wilson, Steven Ray Haakon; Skottvoll, Frøydis Sved; Boger, Ida Caroline Sneis; Bogen, Inger Lise; Nyman, Tuula Anneli; Wu, Jun Jie; Bezrouk, Ales; Cizkova, Dana; Corral, Javier; Mokry, Jaroslav; Zweigerdt, Robert; Park, In-Hyun & Sullivan, Gareth John.

Scalable production of tissue-like vascularized liver organoids from human PSCs.

Exp Mol Med. 2023 Sep;55(9):2005-2024.

Doi: *10.1038/s12276-023-01074-1*

Hou, Yufeng; Laasmaa, Martin; Li, Jia; Shen, Xin; Manfra, Ornella; Nordén, Einar S; Le, Christopher; Zhang, Lili; Sjaastad, Ivar; Jones, Peter P; Soeller, Christian & Louch, William E.

Live-cell photoactivated localization microscopy correlates nanoscale ryanodine receptor configuration to calcium sparks in cardiomyocytes.

Nat Cardiovasc Res. 2023; 2, 251–267.

Doi: *10.1038/s44161-022-00199-2*

Kogler, Stian; Kømurcu, Kristina Sæterdal; Olsen, Christine Sandsnes; Shoji, Jun-ya; Skottvoll, Frøydis Sved; Krauss, Stefan Johannes Karl; Wilson, Steven Ray Haakon & Røberg-Larsen, Hanne.

Organoids, organ-on-a-chip, separation science and mass spectrometry: An update.

TrAC Trends in Analytical Chemistry. 2023 April 161(116996).

Doi: *10.1016/j.trac.2023.116996*

Kwak, Dongho; Combriat, Thomas Michel Daniel; Jensenius, Alexander Refsum & Olsen, Petter Angell.

Characterization of Mechanical and Cellular Effects of Rhythmic Vertical Vibrations on Adherent Cell Cultures.

Bioengineering (Basel). 2023 Jul 6;10(7):811.

Doi: *10.3390/bioengineering10070811*

Kømurcu, Kristina Sæterdal; Wilhelmsen, Ingrid; Thorne, James L.; Krauss, Stefan Johannes Karl; Wilson, Steven Ray Haakon; Aizenshtadt, Aleksandra & Røberg-Larsen, Hanne.

Mass spectrometry reveals that oxysterols are secreted from non-alcoholic fatty liver disease induced organoids.

J Steroid Biochem Mol Biol. 2023 Sep:232:106355.

Doi: *10.1016/j.jsbmb.2023.106355*

LaLone, Vernon; Aizenshtadt, Aleksandra; Goertz, John; Skottvoll, Frøydis Sved; Mota, Marco Barbero; You, Junji; Zhao, Xiaoyu; Berg, Henriette Engen; Stokowiec, Justyna; Yu, Minzhi; Schwendeman, Anna; Scholz, Hanne; Wilson, Steven Ray Haakon; Krauss, Stefan Johannes Karl & Stevens, Molly M.

Quantitative chemometric phenotyping of three-dimensional liver organoids by Raman spectral imaging.

Cell Rep Methods.
2023 Mar 31;3(4):100440.
Doi: *10.1016/j.crmeth.2023.100440*

Mathisen, Andreas Frøslev; Abadpour, Shadab; Legøy, Thomas Aga; Paulo, Joao A.; Ghila, Luiza Mihaela; Scholz, Hanne & Chera, Simona.

Global proteomics reveals insulin abundance as a marker of human islet homeostasis alterations.

Acta Physiol (Oxf). 2023
Oct;239(2):e14037.
Doi: *10.1111/apha.14037*

Olsen, Christine; Wang, Chencheng; Abadpour, Shadab; Lundanes, Elsa; Hansen, Audun Skau; Skottvoll, Frøydis Sved; Scholz, Hanne; Wilson, Steven Ray.

Determination of insulin secretion from stem cell-derived islet organoids with liquid chromatography-tandem mass spectrometry.

J Chromatogr B Analyt Technol Biomed Life Sci. 2023 Jan 15:1215:123577.
Doi: *10.1016/j.jchromb.2022.123577*

Olsen, Christine; Wang, Chencheng; Aizenshtadt, Aleksandra; Abadpour, Shadab; Lundanes, Elsa; Skottvoll, Frøydis Sved; Golovin, Alexey; Busek, Mathias; Krauss, Stefan Johannes Karl; Scholz, Hanne & Wilson, Steven Ray Haakon.

Simultaneous LC-MS determination of glucose regulatory peptides secreted by stem cell-derived islet organoids.

Electrophoresis. 2023
Nov;44(21-22):1682-1697.
Doi: *10.1002/elps.202300095*

Oskarsdotter, Kristin; Säljö, Karin; Sämfors, Sanna; Niemi, Essi Maria; Li, Susann; Simonsson, Stina; Apelgren, Peter; Scholz, Hanne; Gatenholm, Paul & Kölby, Lars.

Autologous endothelialisation by the stromal vascular fraction on laminin-bioconjugated nanocellulose-alginate scaffolds.

Biomed Mater. 2023 Jun 26;18(4).
Doi: *10.1088/1748-605X/acdebb*

Perdreau-Dahl, Harmonie; Lipsett, David B; Frisk, Michael; Kermani, Fatemeh; Carlson, Cathrine R; Brech, Andreas; Shen, Xin; Bergan-Dahl, Anna; Hou, Yufeng; Tuomainen, Tomi; Tavi, Pasi; Jones, Peter P; Lunde, Marianne; Wasserstrom, Andrew J; Laporte, Jocelyn; Ullrich, Nina D; Christensen, Geir; Morth, Preben J & Louch, William E.

BIN1, Myotubularin, and Dynamin-2 Coordinate T-Tubule Growth in Cardiomyocytes.

Circ Res. 2023 May
26;132(11):e188-e205.
Doi: *10.1161/CIRCRESAHA.122.321732*

Saunders, Catherine; Foote, James E J,; Wojciechoswski, Jonathan P; Cammack, Ana; Pedersen, Simon V, Doutch, James J; Barriga, Hanna M G; Holme, Margaret N; Penders, Jelle; Chami, Mohamed; Najer, Adrian; Stevens, Molly M.

Revealing Population Heterogeneity in Vesicle-Based Nanomedicines Using Automated, Single Particle Raman Analysis.

ACS Nano. 2023
Jun 27;17(12):11713-11728.
Doi: *10.1021/acsnano.3c02452*

Shoji, Jun-ya; Davis, Richard P.; Mummery, Christine L. & Krauss, Stefan Johannes Karl.

Global Meta-Analysis of Organoid and Organ-on-Chip Research.

Adv Healthc Mater. 2023 Jul 21.
Doi: *10.1002/adhm.202301067*

Skogvold, Hanne Bendiksen; Rootwelt, Helge; Reubsaet, Léon; Katja Benedikte Prestø Elgstøen, Katja Benedikte Prestø; Wilson, Steven Ray.

Dried blood spot analysis with liquid chromatography and mass spectrometry: Trends in clinical chemistry.

J Sep Sci. 2023 Aug;46(15).
Doi: *10.1002/jssc.202300210*

Skogvold, Hanne Bendiksen; Wilson, Steven Ray; Rønning, Per Ola; Ferrante, Linda; Opdal, Siri Hauge; Rognum, Torleiv Ole; Rootwelt, Helge; Elgstøen, Katja Benedikte Prestø.

A global metabolomics minefield: Confounding effects of preanalytical factors when studying rare disorders.

Analytical Science Advances.
2023 July;4(7-8).
Doi: *10.1002/ansa.202300010*

Sorokina, Liudmila; Matic, Josipa; Rieder, Anne; Koga, Shiori; Afseth, Nils Kristian; Wilson, Steven Ray; Wubshet, Sileshi Gizachew.

Low Molecular Weight Peptide Fraction from Poultry Byproduct Hydrolysate Features Dual ACE-1 and DPP4 Inhibition.

ACS Food Sci. Technol. 2023 Nov; 3(12).
Doi: *10.1021/acsfoodscitech.3c00417*

Tse, Janson; O'Keefe, Ryan; Rigopolous, Angela; Carli, Annalisa L. E.; Waaler, Jo; Krauss, Stefan Johannes Karl; Ernst, Matthias & Buchert, Michael.

A Mouse Model for the Rapid and Binomial Assessment of Putative WNT/βCatenin Signalling Inhibitors.

Biomedicines. 2023 Oct 7;11(10):2719.
Doi: *10.3390/biomedicines11102719*

Wilhelmsen, Ingrid; Amirola Martinez, Mikel; Stokowiec, Justyna; Wang, Chencheng; Aizenshtadt, Aleksandra & Krauss, Stefan Johannes Karl.

Characterization of human stem cell-derived hepatic stellate cells and liver sinusoidal endothelial cells during extended *in vitro* culture.

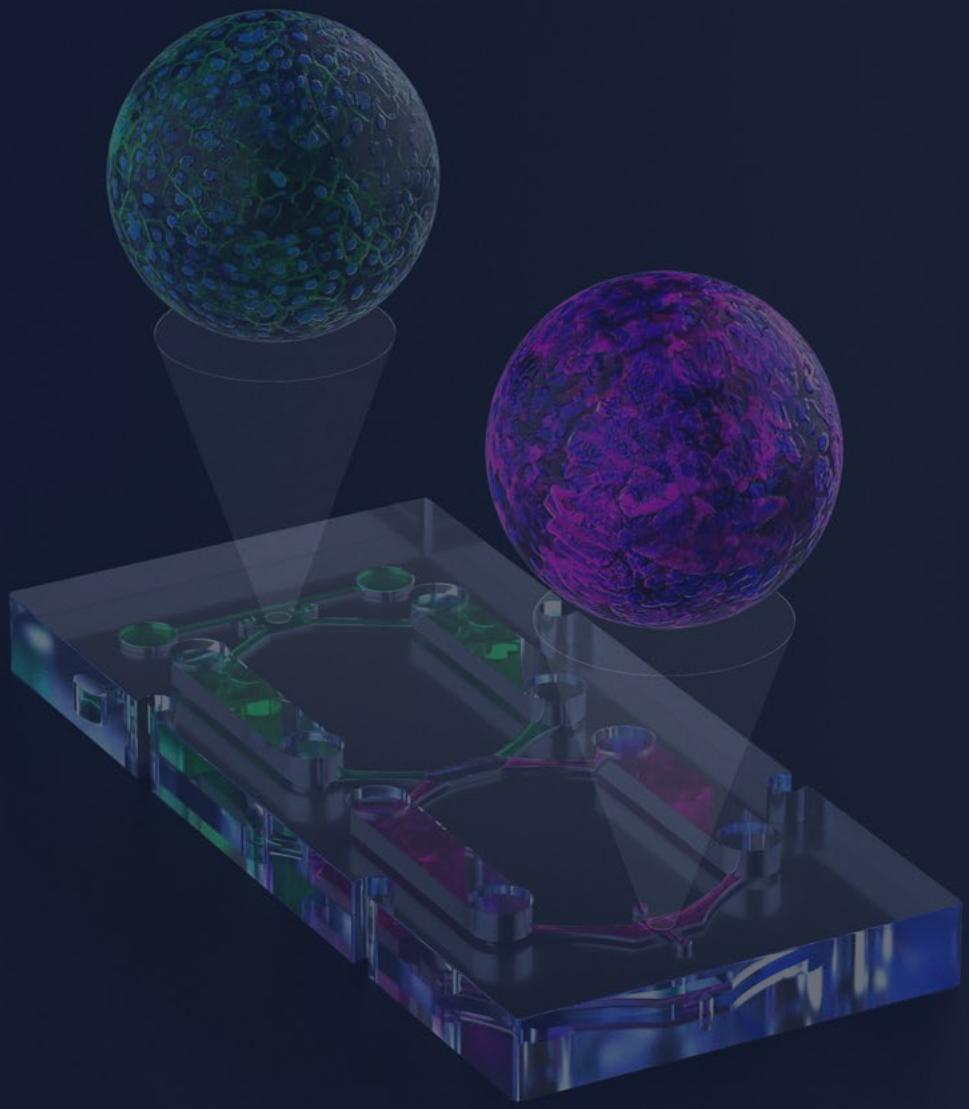
Front Bioeng Biotechnol.
2023 Jul 25:11:1223737.
Doi: *10.3389/fbioe.2023.1223737*

Funding 2023

Project name	Funding scheme	Project leader	Sum	Period
NATIONAL				
Tankyrase Inhibition in Cancer Immunotherapy	HSØ – Forskerstipend	Jo Waaler	4.4 M NOK	2019–2022
Scalable directional pump-less perfusion (dpp) organ-on-a-chip platform	FORNY20–2020	Stefan Krauss	0.5 M NOK	2021–2022
Scientia Fellows II	H2020-MSCA-COFUND	Stefan Krauss and Espen Melum	1.6 M NOK	2021–2022
Virus induced Acute Respiratory Distress Syndrome (ARDS): testing WNT inhibition as a novel therapeutic principle on a Lung-on–a-Chip platform	HSØ – Åpen prosjektstøtte	Stefan Krauss	9 M NOK	2021–2023
Tankyrase Inhibition in Cancer Immunotherapy	HSØ – Karrierestipend	Jo Waaler	9 M NOK	2021–2024
DUCT chip – Immune studies using a bile duct on a chip	NFR – FRIMED2-FRIPRO	Espen Melum	12 M NOK	2021–2027
Tankyrase inhibition as a therapeutic principle in idiopathic lung fibrosis	NFR – FORNY20	Stefan Krauss	5 M NOK	2022–2023
Unleashing the full antitumor potential of macrophages for next-generation cancer immunotherapy	HSØ – Åpen prosjektstøtte	Alexandre Corthay	9 M NOK	2022–2025
Integrated technologies for tracking organoid morphogenesis (ITOM)	UiO:Lifescience-Convergence	Stefan Krauss	16.9 M NOK	2022–2026
Pharmacokinetics-on-chip	NFR – FORNY20	Steven Wilson	0.5 M NOK	2023–2024
KVAL: A neural network-based image denoising software	NFR – FORNY20	Hao Wu (Louch Group)	0.5 M NOK	2023
New hope for heart failure with preserved ejection fraction (HFpEF)	HSØ – Postdoktorstipend	William E. Louch	2.6 M NOK	2023–2025
Pump-less recirculation Organ-on-Chip platform	NFR – FORNY20	Mathias Busek (Krauss group)	5.0 M NOK	2023 - 2025
TumorChip – development of a tumor-on-a-chip platform for testing WNT signaling inhibition as an enabling factor in melanoma immune oncology"	DNK	Stefan Krauss	8.0 M NOK	2023–2025

Funding 2023

Project name	Funding scheme	Project leader	Sum	Period
PRIVATE				
PSC Studies using a Bile-Duct-on-a-Chip	PSC partners	Tom H. Karlsen/Anna Frank/Stefan Krauss	0.6 M NOK	2021–2022
Generation of insulin-producing cells from bile duct cells (cholangiocyte organoids)	Novo Nordisk Foundation	Hanne Scholz	1.3 M NOK	2021–2023
Endocrinology & Metabolism 2022	Novo Nordisk Foundation	Hanne Scholz	1.3 M NOK	2022–2023
EMGUT: Energy Materials for the Gut	Novo Nordisk Foundation	Anja Boisen DTU/Nikolaj Gadegaard	5.5 M NOK	2022–2027
Testing av legemidler med lab-dyrkede organer, som alternativ til dyreforsøk	Dyrevernsalliansen	Steven Wilson and Stian Kogler	0.1 M NOK	2023
Wellcome LEAP: Female resilience on-chip: Monitoring dynamic resilience using Multi-Organ-Chips linking metabolic state and immune response in pre- and post-menopausal women.	Wellcome Trust	Peter Loskill (Co-PI: Stefan Krauss)	9.6 M NOK	2023–2027
INTERNATIONAL				
Hybrida – Ethics of Organoids	EU H2020 – SwafS	Søren Holm (HTH participants: Jan H. Solbakk, Stefan Krauss, Heidi B. Bentzen)	26.5 M NOK	2021–2024
Moral residue – epistemological ramifications, ethical implications, and didactic opportunities (MORE)	ERC Advanced Grants	Jan Helge Solbakk	27.4 M NOK	2022–2027
Supervised morphogenesis in gastruloids (SUMO)	EIC Pathfinder	Stefan Krauss	51.3 M NOK	2022–2027
EUropean network to tackle METAbolic alterations in HEART failure” (EU-METAHEART)	EU COST action	Christoph Maack (HTH participant: William E. Louch)	5.6 M NOK	2023–2027



Hybrid Technology Hub

– Centre for Organ-on-chip Technology

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Layout

Anagram Design

Cover image

Illustration of the HTH developed recirculating organ-on-chip (rOoC) platform that operates without a pump. The rOoC includes separated organoid compartments each with its own perfusion channels to provide independent support.

Credit: Mathias Busek