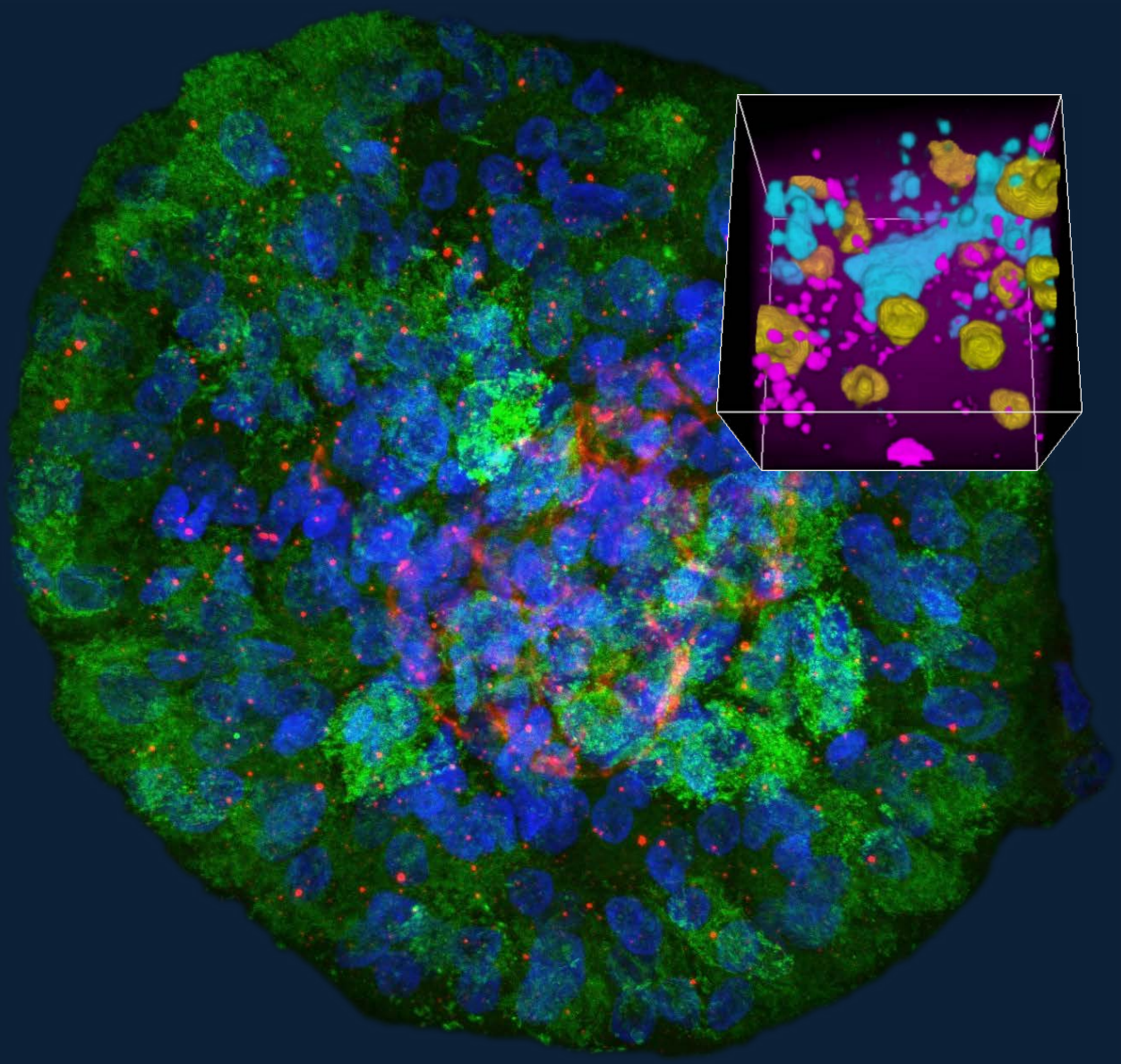
UiO : University of Oslo

CoE Hybrid Technology Hub

– for organ on a chip technology



ANNUAL REPORT 2020

Oslo University Hospital

University of Glasgow

Imperial College London

Norwegian Centre of Excellence
The Research Council of Norway

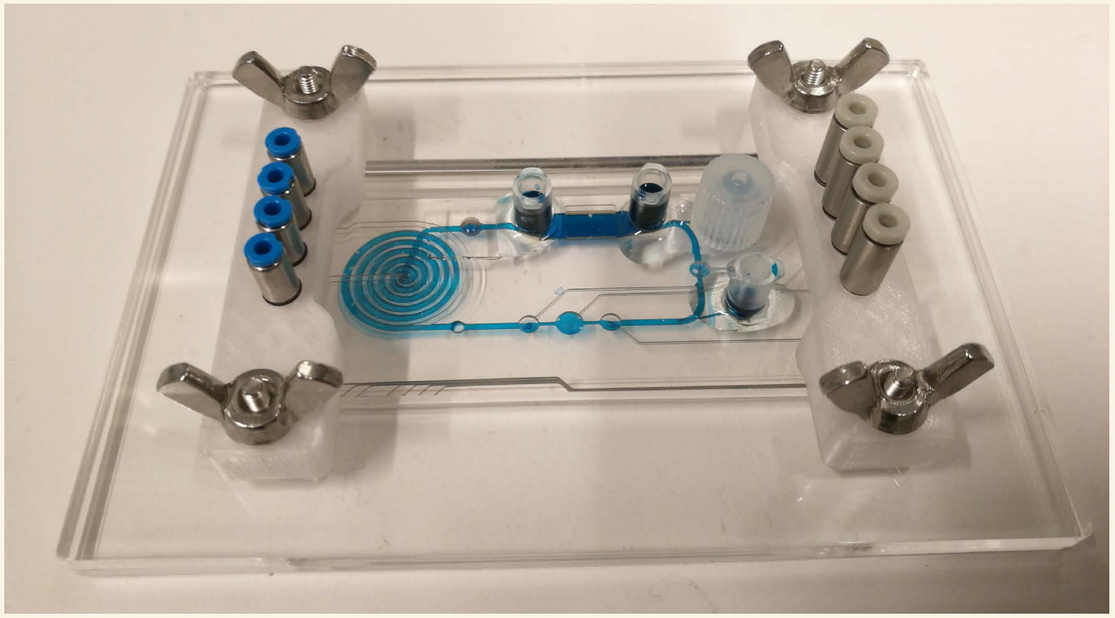
Contents

Developing organ on a chip technology

Complex in vitro models are necessary to recapitulate higher-level anatomical and physiological or pathological aspects of human biology.

Organ-on-a-chip (OoC) technology is quickly advancing as a platform for modelling complex organ representations and increasingly promises to reproduce human physiology in a way that enables predictive testing of medical interventions. This is key for preclinical testing of novel drugs, for personalization of drug testing and – importantly – for being able in future to respond far quicker to novel challenges such as the current COVID-19 outbreak. Due to rapid advances in the field, OoC technology is on the verge of widespread impact on academia and the pharmaceutical industry as much-needed physiological models and potential alternatives to animal testing.

To design predictive and reliable OoC technology, a significant number of issues need to be addressed and resolved. OoC development requires flexible integration of complex and rapidly advancing technologies, including sophisticated differentiation protocols of stem cells into the desired functional cell types, advanced microfluidics functionalities such as vascularization, inclusion of aspects of the immune system, imaging technologies, single cell RNA sequencing and spatial transcriptomics, sensor technology, data integration and benchmarking.

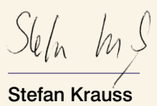


Active ”Organ-on-a-Chip” (OoC) platform with an integrated pneumatic micro pump (bottom, middle), a cell cultivation chamber (top, middle), in-/outlets (right) and a spiral oxygen exchanger (left). The platform is manufactured with a cost-efficient technology using laser-cut thermoplastic films thermally bonded together. For pneumatic pumping and oxygen exchange, a silicone or thermoplastic elastomer (TPE) film is sandwiched in the stack of thermoplastic films. Pumps and oxygenators are driven with customized controlling systems.

Organ-on-a-chip (OoC) technology is quickly advancing as a platform for modelling complex organ representations and increasingly promises to reproduce human physiology in a way that enables predictive testing of medical interventions.

Within the broad area of OoC development, the Centre of Excellence “Hybrid Technology Hub” works towards innovative OoC technology for modeling energy metabolism regulating organs. Here a particular focus is to get more sophisticated organ representations of liver, islets and adipose tissue by copying embryonic processes while keeping the processes scalable. In 2020, the Centre was able to substantially increase its activity, to hire extraordinary gifted PhD and post-doctoral fellows, to deepen the interactions with the partners at the University of Glasgow and at Imperial College London and to attract new associated members. This trajectory will continue in 2021.

I want to thank all the researchers and staff in the Centre for a remarkable dedication and work spirit despite the hassles and restrictions of the Covid-19 pandemic. Indeed, we managed to keep the Centre core facility operational throughout 2020 without a single case of Covid-19. I want to thank the Research Council of Norway for providing very significant long term funding. 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. Finally, I want to thank UiO:Life Science for very significant financial contributions to the Centre.

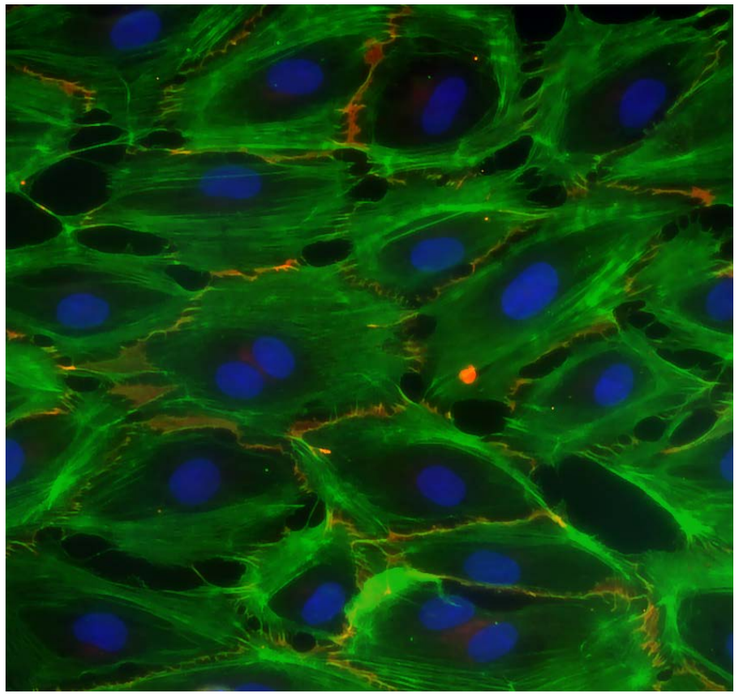


Stefan Krauss

Research groups

Krauss group
Developmental pathways and chemical biology

The Krauss group works on methods to improve the spatial-temporal development of organoids on an integrated microfluidic platform that is compatible with scalable drug testing.



Human endothelial cells oriented in the flow direction in a microfluidic OoC platform. Red: VE-Cadherin, green: actin filaments, blue: nuclei.

Stefan Krauss
Centre Director

Liver organoid development
Coming from a developmental biology background, the lab. works towards an improved structure and functionality of liver organoids, and hence better physiological representation of the human liver. The liver is shaped by morphogenetic signals from the central vein and the portal triade that shape and structure the parenchymal tissue. Identifying these signals, and applying them for directing organoid development has been a major challenge. Using iPS derived hepatocyte lineages, endothelial lineages and cholangiocytes A. Aizenshtadt, M. Amirola Martinez and A. Frank (Espen Melums group) have so far achieved basic features of zonation (manuscript in preparation). Using filament technology developed by K. Shoji, the lab is now working towards creating elongated and structured liver organoids - termed “lobuloids” - that allow central and peripheral perfusion and hence form a fundament for a histological structured scalable liver organoid. A further, recently initiated approach is gastruloid technology. H. Høgset is working towards advancing gastruloids to a stage where organ induction is initiated.

Platform development
A central goal of the Centre is to develop a scalable Organ-on-a-Chip platform that can be used for drug interrogation. In a first step, a PDMS free platform with an integrated pneumatic mini-pump system was developed by M. Busek (see image on page 5). As a next iteration, the platform was altered to allow endothelialized (arterial and venous) circulation independent of external support system, which is an important pre-requisit for standardization and scalability. The platform is currently extensively tested and will be published in 2021.

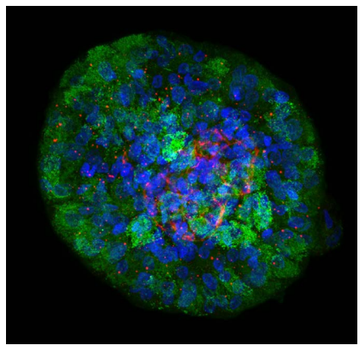
Raman Spectroscopy and LC/MS on organoids
Life tracking of maturation and metabolic activity of organoids is an important goal.

> A central goal of the Centre is to develop a scalable Organ-on-a-Chip platform that can be used for drug interrogation.
>
> ***Stefan Krauss***

In collaboration with the S. Wilson group we have identified phase I metabolism in iPS derived liver organoids (F.S. Skottvold manuscript in press). A. Aizenshtadt and V. Lalone have next mapped the organoids with Raman confocal spectroscopy directly identifying phase I metabolism. The work in an ongoing collaboration with the M. Stevens lab.

WNT inhibitor development
The laboratory has a long track record on morphogenetic signals, having discovered the ventralizing morphogen Shh and worked with the often spatially opposite Wnt signaling cascade which is also present in the liver lobes. Using chemical biology (collaboration Symeres Inc.) we have developed a leading WNT signaling inhibitor series that has currently reached a preclinical candidate stage (Waaler et al…Krauss 2020; 2 patents pending). In the frame of collaborations with S. Lehtonen, J. Distler and P. Morth respectively, a WNT/TNKS inhibitor from our program has shown efficacy in a mouse Db/Db model, identifying PGS-1a as a direct TNKS target (Wang et al., 2020), in a mouse graft-versus-host model (Zhang et al., 2021), in a Sjøgren autoantigen binding model (Perdreau-Dahl et al., 2020) and in a mouse immune oncology model (Waaler et al… Krauss 2020).

3D iPSC-derived hepatic organoids, consisting of endothelial cells (labelled with antibodies against CD31, red) and hepatocyte-like cells (labelled with antibodies against albumin, green).



Scholz group
Islets

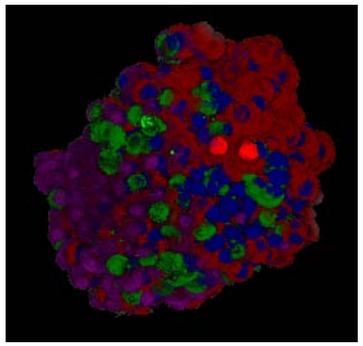
Hanne Scholz
Vice Director

Research in the Scholz group focuses on developing beta cell replacement therapy for type 1 diabetes and understanding human islet cell biology. Human islets consists mainly of insulin producing beta cells and glucagon producing alpha cells responsible for the fine-tune regulation of our blood glucose level in our body.

Human Islets
The group has contributed to several studies showing that human islets can be protected from diabetic micro-environmental stress such as inflammation and hyperglycemia. The group participates in a European network that investigate and improve the methodology for the isolation process of islets from deceased donor pancreases. In this context, the group works on innovative approaches using 3D bio-printing technology to deliver pancreatic islets with supporting cells that will allow to define alternative graft sites. In parallel, the studies work towards islet survival and long-term functionality on a chip platform.

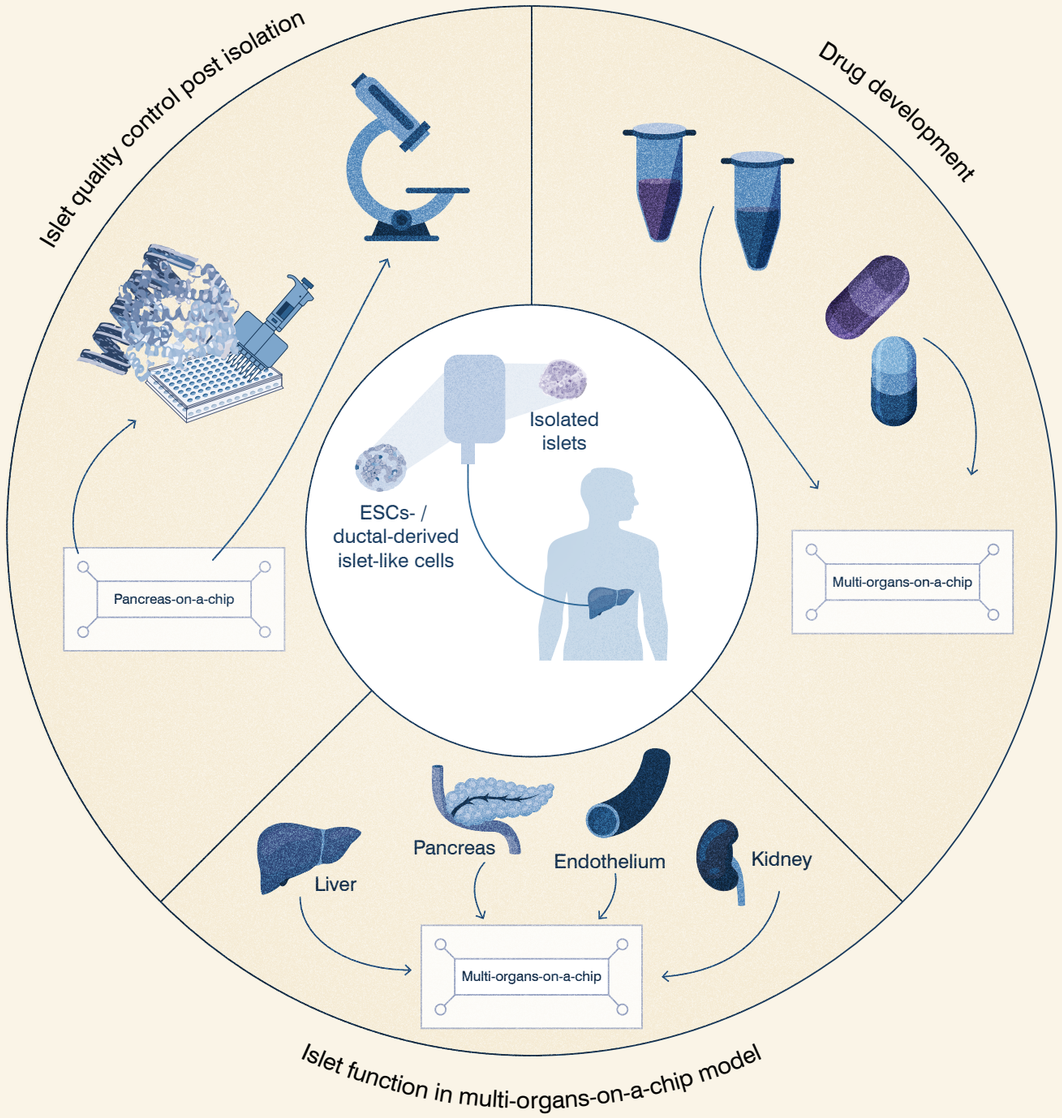
iPS derived Islets
The group collaborates with Prof. Helge Ræder and Assoc. Prof Simona Chera at the University of Bergen to develop human iPS derived insulin-producing beta cells. This work has led to several publications in the reporting year. In 2020, the project has been expanded by a new grant «Artificial Biomimetic systems – the Niche of Islet Organoids (ABINO)» funded by UiO:Life Science Convergence Environment II. The grant unites researchers from three Center of Excellence (CoE); RITMO (Anne Danielsen, Aleksander Refsum Jensenius, HTH-OoC (Stefan Krauss, Simon Rayner, Petter Angell Olsen, Hanne Scholz), and Depart Physics/CCSE (Anders Malthe-Sørenssen, Dag Kristian Dysthe) to investigate the impact of modulating signaling pathways for stem cell differentiation to develop functional islet organoids based on morphogenetic, mechanical and acoustic stimulation (see also page 38).

> Our work shows that human islets can be protected from diabetic micro-environmental stress such as inflammation and hyperglycemia.
>
> ***Hanne Scholz***



3D reconstruction of whole mount immunostaining of a human islet. Red: insulin in beta cells, green: glucagon in alpha cells, magenta: homeodomain transcription factor, blue: nuclei.
Image: PhD student Chencheng Wang

Pancreas-on-a-chip application for diabetes and islet transplantation research



Stevens group
Imaging and sensor technology

Molly Stevens
Principal Investigator

The Stevens group works on a broad panel of enabling diagnostic and imaging systems that are – amongst others - implemented on organoids.

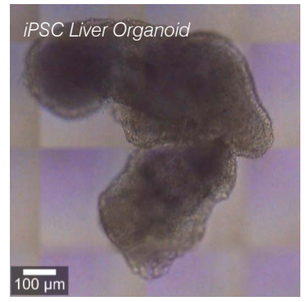
Sensor systems
Over the past year, the Stevens group at Imperial College London has been focusing on the development of tools and techniques to monitor the functionality of the organoids. The group is developing sensors and working towards their incorporation into organ-on-a-chip systems. They are taking advantage of two photophysical phenomena, Localized Surface Plasmon Resonance (LSPR) and Förster Resonance Energy Transfer (FRET). LSPR is generated when light interacts with conductive particles. When these particles are decorated with biorecognition elements, their resonant frequency can be monitored to quantify in real time soluble biomolecules of interest, e.g. small proteins secreted by the organoids on chip. Moreover, Stevens and collaborators have recently published in Advanced Materials a tumour-targeting DNA-inorganic hybrid nanocomposite aptasensor. The approach can be expanded across a diverse range of target system due to the design programmability of template DNA; therefore, it has the potential to be used to probe dynamic changes of specific biomarkers in a ratiometric and quantitative manner on the organ-on-a-chip platform.

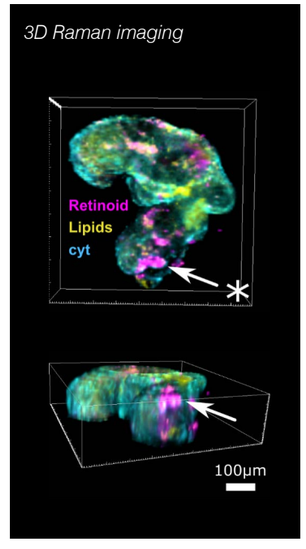
Nanoneedles
The Stevens group has extensive expertise in engineering biomaterials with nanotopographies that enable cell interfacing, and in studying cell-material interactions at the nanoscale. Of particular interest, the group has shown that nanoneedles can target mechanoresponsive elements within the intracellular domain and trigger intracellular signalling pathways. In the context of the Hybrid Technology Hub, nanoneedles are investigated to direct the fate of induced pluripotent stem cells.

Research groups

Raman microanalysis is used to assess drug metabolite distribution and accumulation in liver organoids.

Figure 1. 3D Raman chemical imaging reveals the heterogeneous distribution and stellate cell-mediated storage of retinoids: vitamin A metabolites with potent transcriptional activity known to serve as biomarkers of liver health.





Raman imaging
Stevens is also a leader in advanced imaging of biological processes by non-invasive Raman spectroscopy. Ongoing collaboration between Stevens and Krauss groups are working with a fatty liver disease model and using Raman to compare the compositional changes induced during lipid accumulation in the human iPS-derived liver organoids (see figure 1). Linear combination spectral modelling with pure component reference spectra revealed the distribution and relative amounts of material present within and throughout each sample analysed. Of particular interest, we are able to detect and identify retinoid compounds – sequestered as retinyl-palmitate – within iPSC liver organoids. This is particularly useful as multiple sources have reported retinoid content in stellate cells as a biomarker for liver health. In addition, Raman-based drug measurement feasibility in 3D liver spheroids derived from primary human hepatocytes has been verified. Raman microanalysis was used to assess drug metabolite distribution and accumulation in 3D liver spheroids exposed to Neratinib.

SERS reporters
To extend further the application of Raman imaging for healthy and steatotic liver organoids, Surface-enhanced Raman Spectroscopy (SERS) reporters are under development. The Stevens group is exploiting oligoyne molecules as extremely novel and attractive Raman reporters. A multiplex SERS-immunolabelling platform for stellate cells allows accessing of co-localisation of the stellate cells with retinoids.

Rayner group
Bioinformatics

Simon Rayner
Principal Investigator

The Rayner group with its track-record on data handling, is focusing on developing data sharing systems for the distributed large data sets at the Centre.

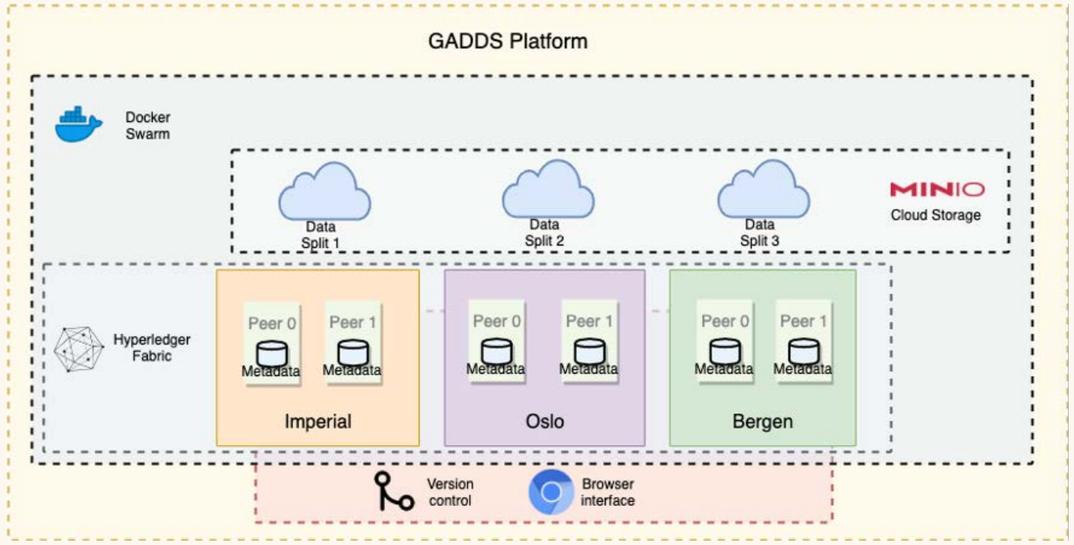
The GADDS data sharing platform
In 2020, the lab has completed development and first stage testing of our GADDS (Global Accessible Distribution Data Sharing) solution for integration and standardization of the data generated from the different groups and partners within the HTH. GADDS is scalable and designed to support an unlimited number of (physically) distributed participants and is based on three open-source technologies. The technology contains the following elements: i) Blockchain, (implemented with Hyperledger Fabric11) to provide a decentralized system to ensure adherence to metadata standards. ii) Cloud storage, (implemented with MinIO10) to provide fault tolerant distributed storage and ensure security and survivability of the data. iii) Version control (using a GitHub based solution developed in-house similar) to allow tracking of changes and recovery of different versions of (meta)data.

The platform is configured to be a Docker swarm cluster of a group of machines that can be either physical or virtual (which execute commands in form of applications) and nodes, which are machines configured to join in a network. In our current implementation, we have configured three organizations to participate in the test system that are located in three different locations: Imperial College London, Oslo University Hospital, and the University of Oslo computer cluster physically located in the city of Bergen. Finally, GADDS is a permissioned environment, so only users from the same consortium (i.e. project) can upload/download data (to provide necessary security and address sensitive data requirements).

As a first test application, we have incorporated a test data generated from the Tissue Engineering Group in the HTH and the Nano-electronic Systems Group at UiO. The Tissue Engineering Group are developing protocols to generate core-shell hydrogel fibres and the Nano-electric Systems Group is characterizing the final product. Data is stored using the Dublin core metadata14 standard and can only be uploaded when all metadata is provided and meets the specific standard. In this way, GADDS ensures data quality, allows data sharing among collaborators and ensures data privacy.

The work has been submitted as a research manuscript to Scientific Data and is currently under review. A preprint is available on the arxiv.org (P. Vazquez et al… Rayner).

> GADDS is scalable and designed to support an unlimited number of (physically) distributed participants and is based on three open-source technologies.
>
> ***Simon Rayner***



Gadegaard group
Chip design

Nikolaj Gadegaard
Principal Investigator

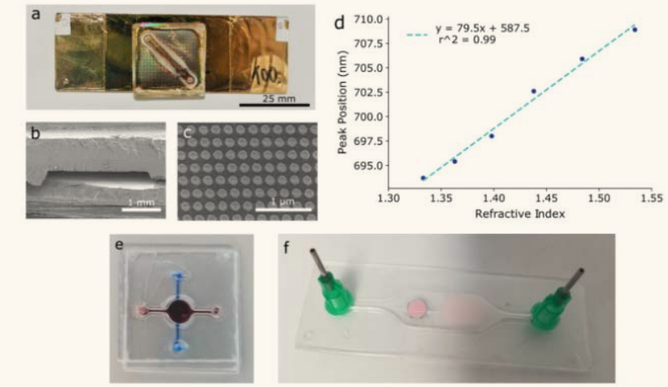
The Gadegaard group is focusing on scalable chip development and micro-patterning.

Over the past year, work in Glasgow has focused on expanding previous research in 3 main areas: i) simulation of microfluidic systems to further guide the design of devices; ii) increasing functionality of injection molded thermoplastic microfluidic chips through the integration of sensors and membranes; iii) and development of metabolism-on-a-chip models consisting of adipose, muscle and liver tissues.

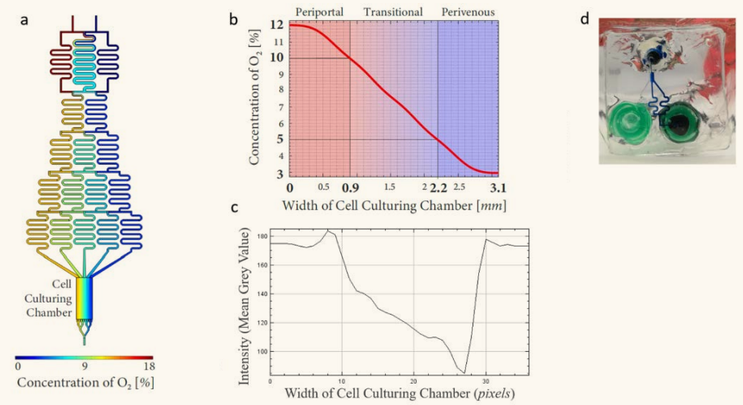
We have previously shown that 3D printed polymer tooling can be used to manufacture many identical devices in a pseudo-industrial process. In brief, 3D printed masters can be fabricated at a fraction of the cost, time, and expertise of conventional injection molding masters. From these masters, hundreds of identical devices can be manufactured quickly and at low cost. Over the past year, work carried out by Neil Convery (PhD Student, University of Glasgow) on the fabrication platform shows that the functionality of chips can be increased through the inclusion of sensors (surface plasmon resonance, and fluorescence) as well as membranes to simulate barriers in the body (Fig 1). While the 3D printed tooling is rapid and cheap, we have also developed computational models to further inform the design of devices thus streamlining the process further. Duarte Menzes (Masters Student, University of Glasgow/University of Porto) conducted finite element modelling of microfluidic devices to gain a further understanding of the behavior of the microfluidic systems and use these parameters to guide the design of future devices with the aim of designing a device capable of mimicking the oxygen gradient seen within a human liver. Once a design was shown to give the required parameters, it could easily be manufactured with our existing fabrication process (Fig 2). Finally, work undertaken by Maud Dirkx (Masters Student, University of Glasgow/Utrecht University) showed how different tissues could be cultured on injection molded chips. In this work, adipose, muscle, and liver tissue could be differentiated from stem cells on the chips and chips with different cell types could be connected to give an in-vitro metabolism-on-a-chip model capable of modelling insulin resistance.

> 3D printed masters can be fabricated at a fraction of the cost, time, and expertise of conventional injection molding masters.
>
> ***Nikolaj Gadegaard***

The designed devices can be modelled and a design settled upon before being printed and injection molded to produce a vast quantity of functional microfluidic chips. These chips can then be used to house cells of different tissue types and connected to mimic not just organs, but organ systems within the body providing a cheap, rapid, and robust basis for a drug testing platform. Furthermore, work has been coordinated between the University of Glasgow and the Hybrid Technology Hub in Oslo to develop further chips with novel functionalities and ensure that work can be easily shared digitally through 3D printing, or physically through the transport of biological material.



↑ *Figure 1*
a Photograph on an injection moulded SPR devices.
b and **c** show the channel and the nano-pattered surface respectively.
d illustrates how the resonance shifts with refractive index highlighting the use of such a device as a biosensor.
e shows a membrane chip with the upper red channel separated by a membrane form the lower blue one while **f** shows the oxygen sensor built into the chip.



↑ *Figure 2*
a FEM model of a microfluidic gradient generator with the gradient across the wide channel at the bottom shown in **b**.
Experimental data obtained from the device shown in **d** can be seen in **c** showing how a gradient can be achieved in reality.

Sullivan group
Organoids

Gareth Sullivan
Principal Investigator

The Sullivan laboratory interests are to gain a basic understanding of endoderm and mesoderm biology whilst developing novel methodologies.

The research areas that we have been exploring within the Centre include understanding differentiation, providing important insight into the derivation of mature functional cell types from human pluripotent stem cells (hPSCs). This is a requirement for the development of physiological organ-on-a-chip models that, in addition to tools allowing interrogation of disease/ toxicology, allows building tissue for testing potential therapies. To enable this we have been developing 3D hepatic and white fat organoid models.

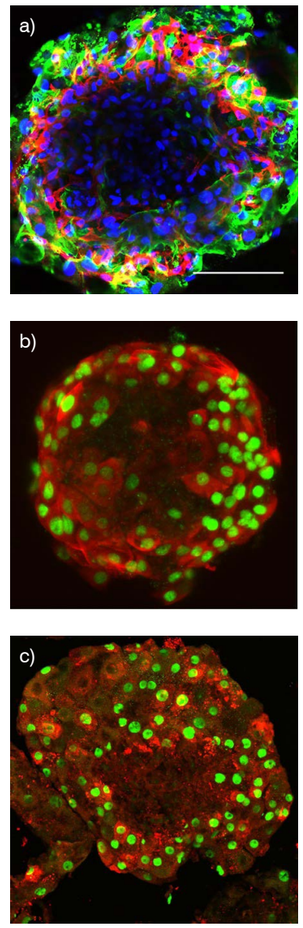
Our small molecule driven liver organoid protocol has been the focus of further refinement during 2020 leveraging off key collaborations with members of the Centre. This work has now culminated in the submission to a high tier journal, as well as preprint to BioXriv. This innovative work has also been filed for a patent through Inven2. We have initiated a number of collaborations to exploit our liver organoid model. This includes exploring the utilisation of the organoids in toxicology combined with mass spectroscopy to investigate opioid metabolism with Prof S. Wilson (HTH PI) and this work has been recently accepted for publication. We are also exploring the utility of the organoids to model vitamin K dependent coagulation disease in the dish with Prof. Per Morten Sandset (UiO). We have also initiated a collaboration with an international partner, Prof Niels Bent Larsen at DTU (Copenhagen) where we are exploiting the fact we can mass produce hepatic organoids at scale (100,000´s to millions). We are combining hepatic organoids, which act as building blocks for tissue assembly, with 3D printed chip formats to produce functionally long lived liver tissue chunks. We are also exploring the utility of our organoids with a commercial partner, combining our “mini livers” with organ-on-a-chip technology.

In parallel, we have developing methodologies to produce white adipose tissue. After assessing sources of hPSC derived mesenchymal stem cells (MSCs) for adipocyte potential, we have focused on the neural crest lineage. To that end we have developed a robust method to produce an expandable neural crest population, which are then guided towards a MSC fate. The resulting MSC population is also expandable and can be cryopreserved. We have now developed a protocol that directs neural crest derived MSCs to white fat. The resulting white fat population express key markers such as PPARgamma2, FABP4 and Perilipin etc. Importantly, the adipocytes accumulate fat droplets over time. In a collaboration with Prof. Volker Lauschke (Karolinska Institutet, Sweden) and Prof. Philippe Collas (UiO), we are benchmarking hiPSC derived white fat against human primary material and a manuscript is now in preparation.

Research groups

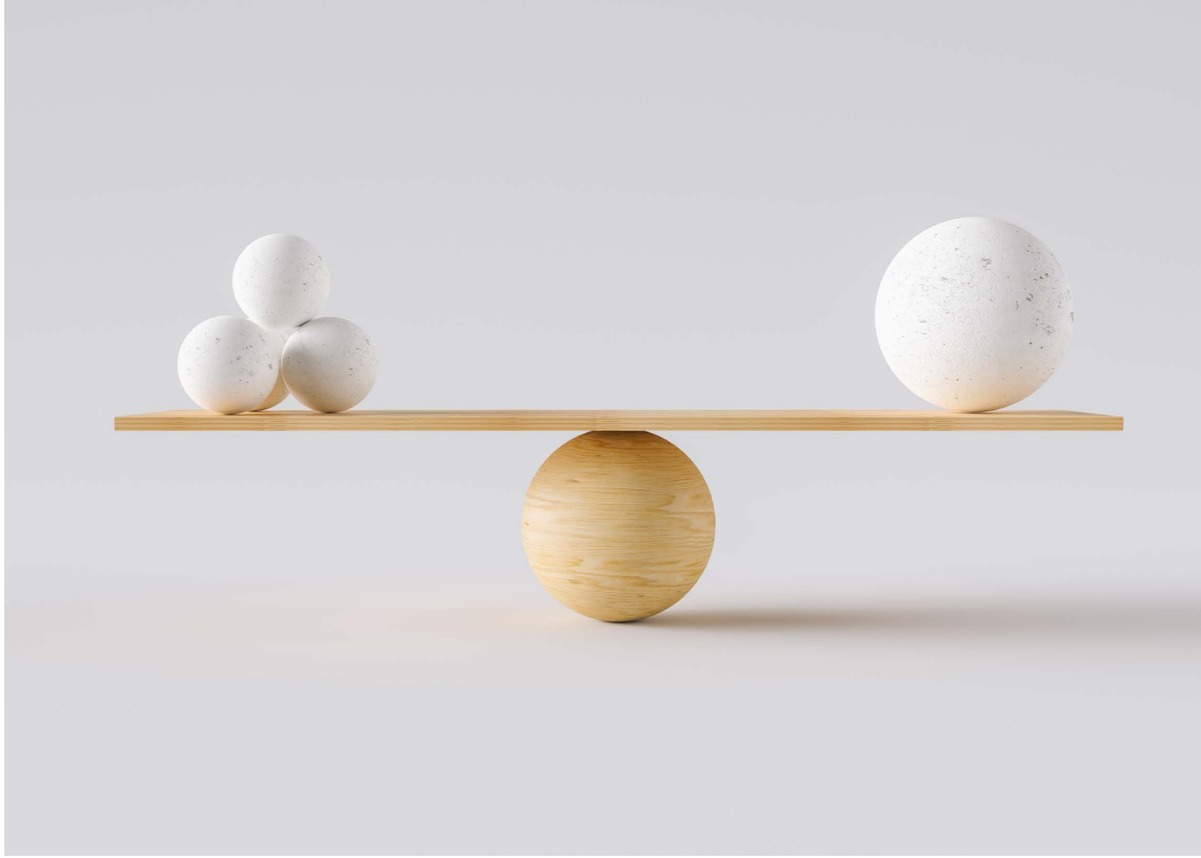
Our small molecule driven liver organoid protocol has been the focus of further refinement during 2020 leveraging off key collaborations with members of the Centre.

Whole-mount immunostaining of organoids showing: a) Expression of mesenchymal and stellate cell associated proteins (green: aSMA and red: laminin) beneath the hepatocyte layer of organoids. (scale bars are 100 μm). b) Expression of the hepatocyte markers HNF4A (green) and glutamine synthase (red) in the outer most layer of the liver organoid. c) Expression of the hepatocyte markers HNF4A (green) and albumin (red) in the outer most layer of the liver organoid.



Solbakk group
Ethics

Jan Helge Solbakk
Principal Investigator



In the frame of the Centre, the Solbakk group focuses on qualitative uncertainty in the context of organoids/ organ-on-a-chip technology.

All the dedicated medical-philosophical journals were searched for publications that can illuminate the key question in WP6: How to handle qualitative uncertainty, that is, how do we know what works in precision medicine when statistical analyses are impossible due to too few research subjects (n --> 1 situations). Although organoids are a special case in the development of personalized medicine, WP6 has judged that the underlying epistemological questions are very much the same, and that insight into how these questions of personalization have been answered before. This material will be sought developed into a paper at a later stage.

The PD Henrik Voigt has then developed a paper based on a case of personalization in cancer medicine that has received a lot of attention in Norway where the Board of Health Supervision (Helsetilsynet) reversed a hospital decision to give a sick person a cancer drug. This paper illustrates how the epistemology in changing the decision-making and the idea of what is ”obviously shown to work” changes. This is highly relevant also to decision-making based on findings in organs-on-chip used for personalization. The paper will be submitted shortly.

The PD also published a chapter (”Personalized medicine - Problems of translation into the human domain”) in the newly published book ”De-Sequencing”, edited by Dana Mahr (published by Palgrave-MacMillian). The publication highlights different stages and associated challenges in translation from basic science to useful interventions, especially disease prevention, in personalized medicine. The chapter was written with Prof. Sara Green of the University of Copenhagen.

The year has also seen the PD finishing a book chapter on uncertainty, and how it in some ways may be seen to increase, in precision medicine. The chapter, called ”The Precision paradox”, will be published in a book edited by Prof. Michael Barilan from Israel (publisher Oxford University Press). It looks directly at some of the challenges underlying personalization and knowing what works in precision medicine and points out the return of the ”Art of medicine” in the midst of high technology. Additionally, the PD has published a book chapter on “over-diagnosis” in big data based personalized medicine, a challenge that will also be critical for the utility of organs-on-chip used for disease prevention at a later stage. The book

> Our work highlights different stages and associated challenges in translation from basic science to useful interventions, especially disease prevention, in personalized medicine.
>
> ***Jan Helge Solbakk***

title is: De raske patienter i personlige medicin: Sygdomsforebyggelse og overdiagnosticering. Chapter 7. In: Personlig medicin: Filosofiske og tværvidenskabelige perspektiver, Eds: Harnow Klausen & Christiansen (Munksgaard, 2020) and was written along with professors Sara Green and John Brodersen.

In 2020, the EU Horizon SwafS28 proposal, “HYBRIDA: Embedding a comprehensive ethical dimension to organoïd-based research and resulting technologies”, coordinated by Prof. J.H. Solbakk, received maximum scores by the reviewers and 3 million EURO for the period of 01.02.21-31.01.24. The aim of HYBRIDA is to study three different kinds of uncertainty. First, conceptual uncertainty (ontological uncertainty): how should one conceive of entities that cannot be categorized as either persons or things? What are they? Second, epistemological and methodological uncertainty: How do we know the characteristics of these entities called organoids? How do we address forms of uncertainty that cannot be evaluated through the use of statistical methods, i.e. risk? Third, regulatory uncertainty: this uncertainty emerges because parts of regulatory frameworks concerning the rights and duties of persons have been merged with elements of regulation dealing with the stewardship of objects or things. HYBRIDA aims to address how these uncertainties arise in organoid research and develop a conceptual and regulatory framework able to handle these uncertainties.

Wilson group
Mass Spectrometry

Steven Wilson
Principal Investigator

The Wilson group is focusing on hyphenating organoids/organ-on-a-chip systems with mass spectrometry.

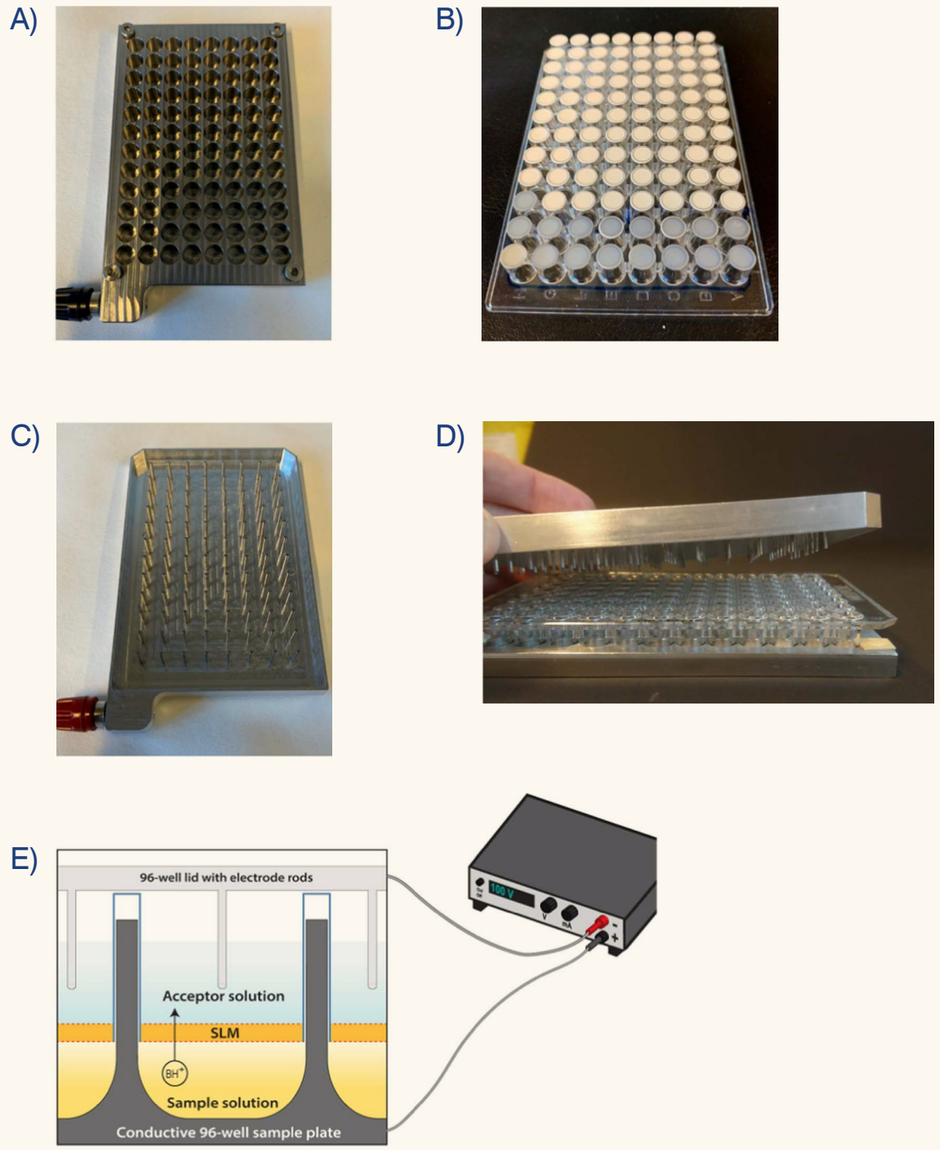
Mass spectrometry is a key technique in bioanalytical chemistry, used for e.g. drug analysis, metabolomics and proteomics. However, the novel coupling of mass spectrometry and organoids/organ-on-a-chip can be challenging. Wilson and co-workers have begun to establish several prototypes for organ-on-a-chip/mass spectrometry. In one version, the chips feature electromembrane extraction (EME), which allows for drugs and metabolites to be selectively extracted from the chip and into the mass spectrometer for pharmacokinetic profiling. Wilson and co-workers in 2020 released a preprint that introduced the concept of EME for the purpose of organ model analysis, which is now published in Analytical Chemistry (American Chemistry Society). In the end of 2020, Wilson´s PhD student Frøydis Sved Skottvoll utilized EME to perform single system organ-on-a-chip/mass spectrometry (a first of its kind) for automated studies of drug metabolism. These results are to be submitted for publication in 2021.

> EME allows for drugs and metabolites to be selectively extracted from an organoid into the mass spectrometer.
>
> ***Steven Wilson***

In a second variant, PhD student Stian Kogler has developed an “organoid-in-a-column”, which allows for organoids to be directly studied by mass spectrometry without extraction steps. A preprint of the initial results has been published, and will be subject to peer-review in 2021.

Wilson´s team has engaged in providing global proteomics analysis of organoids; In the area of proteomics, Wilson is a PI in a newly NRC-funded Infrastructure (National network of Advanced Proteomics Infrastructure, see napi.uio.no). Wilson´s team has also made initial steps in developing fully automated targeted proteomics (including online reaction chemistry/sample preparation) of insulin and related compounds for the analysis of islets, as a first step in single system organ-on-a-chip/proteomics.

Experimental setup of 96-well parallel-electromembrane extraction (EME)



↑ (A) Ninty-six well sample reservoir plate constituting the donor solution. (B) Ninty-six well filter plate, constituting the acceptor solution. (C) Aluminum lid with 96 electrode rods. (D) All plates clamped together. (E) Illustration of the extraction setup of parallel-EME coupled to the external power supply.

Associated groups

Melum group
Liver

Espen Melum
Associated partner

The Melum group is focusing on experimental and translational studies related to the chronic liver disease primary sclerosing cholangitis (PSC).

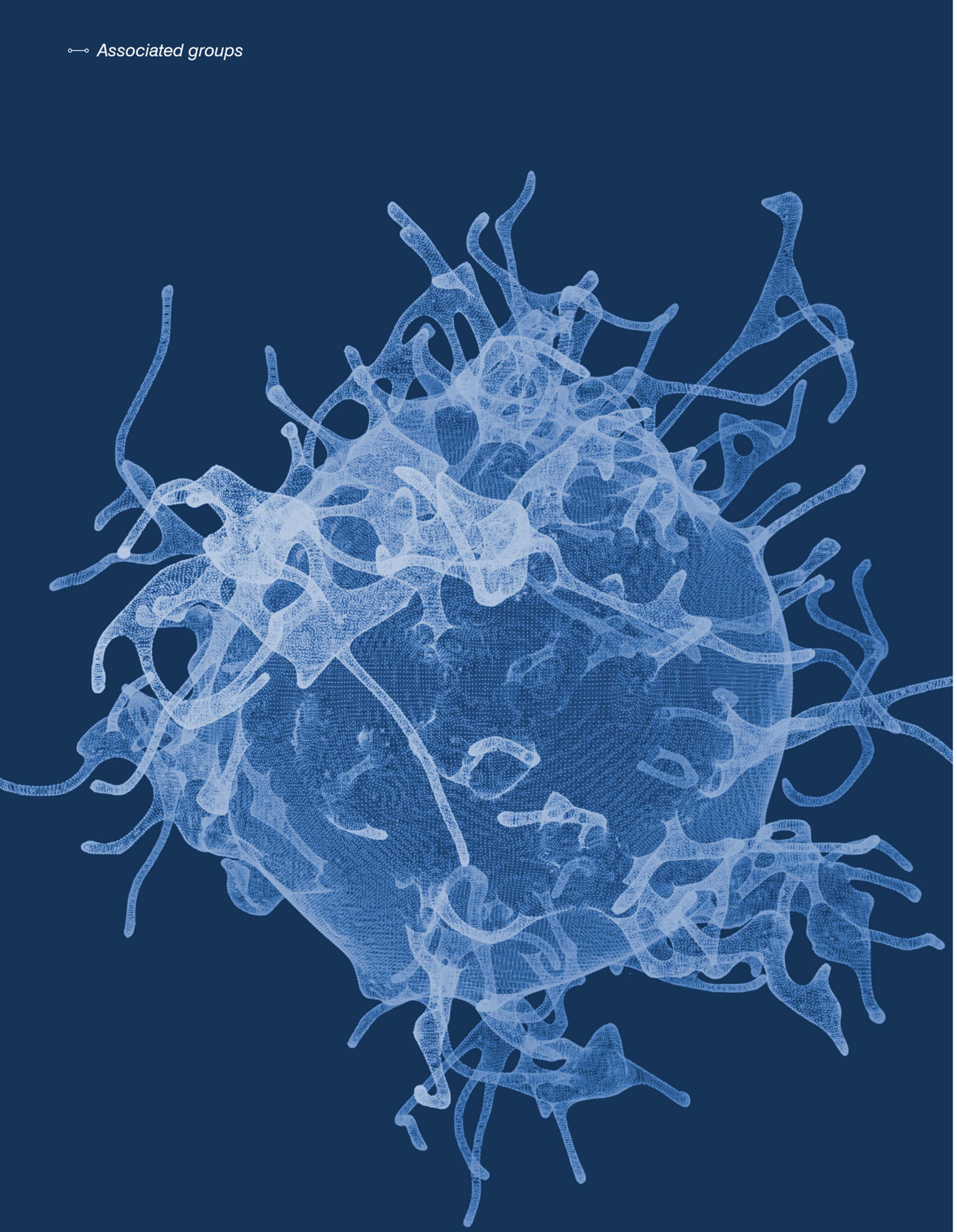
The main aim of the research is to understand mechanisms regulating cholangitis with a clear focus on immunology but it also incorporates aspects of regenerative medicine. The tools that the group uses is patient material, animal models, advanced cell-culture in terms of organoid technology and recently organ-on-a chip systems.

In 2020 we generated the first prototypes for a bile duct-on-a-chip together with the rest of the team at the Centre of Excellence Hybrid Technology Hub. This work was facilitated by the recruitment of Anna Frank as a Scientia Fellows postdoc that will work on the collaborative projects between the Norwegian PSC research center and the Hybrid Technology Hub. We also continued research on the basic properties of organoids by doing single-cell sequencing of cholangiocyte organoids generated from brushings of the bile ducts from patients with PSC. The RNA-based sequencing technology approaches were also expanded with the establishment of spatial sequencing, which will be used by several projects in the experimental hepatology group and also at the center. As part of these increased efforts in the group, Jonas Øgaard and Kari Otterdal have also been engaged in the projects related to organoids and spatial sequencing.

> In 2020 we generated the first prototypes for a bile duct-on-a-chip.
>
> ***Espen Melum***

Towards the end of the year, we received an innovation grant from the University of Oslo that will fund part of the position for a cell-culture technician and a Research Council of Norway grant of 12 mill NOK that will fund two additional postdocs and one PhD student to work on the bile-duct-on-a-chip system.

↑ Cholangiocyte organoids in culture in the Melum lab

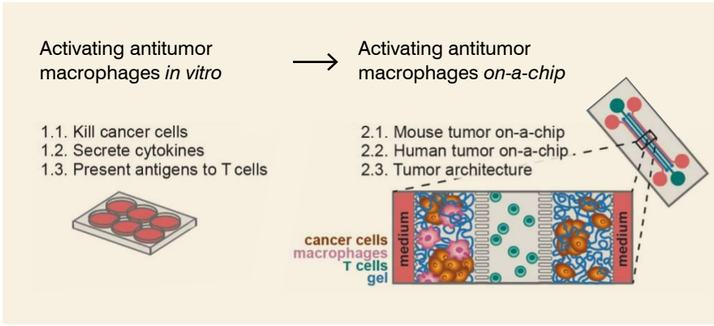


Corthay group
Immunology

Alexandre Corthay
Associated partner

The Corthay group works on a platform that allows to reconstruct an Immunocompetent Microenvironment on a chip.

In this project, we are establishing and developing is a first iteration a tumor-on-a-chip platform. A tumor microenvironment (including cancer cells, fibroblasts, endothelial cells, and various types of immune cells) are being recreated in microfluidic devices (chips) as 3D co-cultures in biomimetic hydrogel. Cell interactions and key processes such as cell division and death are visualized over several days by high-content video-microscopy. Using an in-built perfusion system, the effect of drugs on the tumor microenvironment is being monitored live minute-by-minute. In 2020, we have established functional in vitro assays to investigate three key functions of macrophages. We have also established a tight collaboration with Luca Businaro (Rome, Italy), a pioneer in tumor-on-a-chip technology, who is providing chips of his design for the experiments and helping to establish the technology in Oslo.



↑ The figure shows the immune competent chip. Using innovative molecular tools, protocols for macrophage activation are being established in vitro and in a complex microenvironment on-a-chip.

Team members
2020

Management

Stefan Krauss
Centre Director

Hanne Scholz
Vice Director

Haakon Berg Johnsen
Administrative coordinator

Petter Angell Olsen
Facility manager

Principle Investigators

Nikolaj Gadegaard

Molly Stevens

Gareth Sullivan

Simon Rayner

Steven Wilson

Jan Helge Solbakk

Stefan Krauss

Hanne Scholz

Associated Partners

Alexandre Corthay

Espen Melum

Project leader

Jo Waaler

Postdoctoral fellows and researchers


Pavel Vazquez


Alexandra Aizenshtadt


Kayoko Shoji


Sean Harrison


Henrik Vogt


Anna Frank


Shadab Abadpour


Mathias Busek


Cecil Echalier


Thomas Combriat


Vernon LaLone


Olga Bibikova


Jelle Penders


Hyemin Kim

PhD candidates


Saphira Felicitas Baumgarten


Frøydis Sved Skottvoll


Steffen Nøvik


Essi Niemi


Neil Convery


Mikel Amirola Martinez


Chencheng Wang


Dongho Daniel Kwak

Technicians


Elisabeth Dybing


Stian Kogler

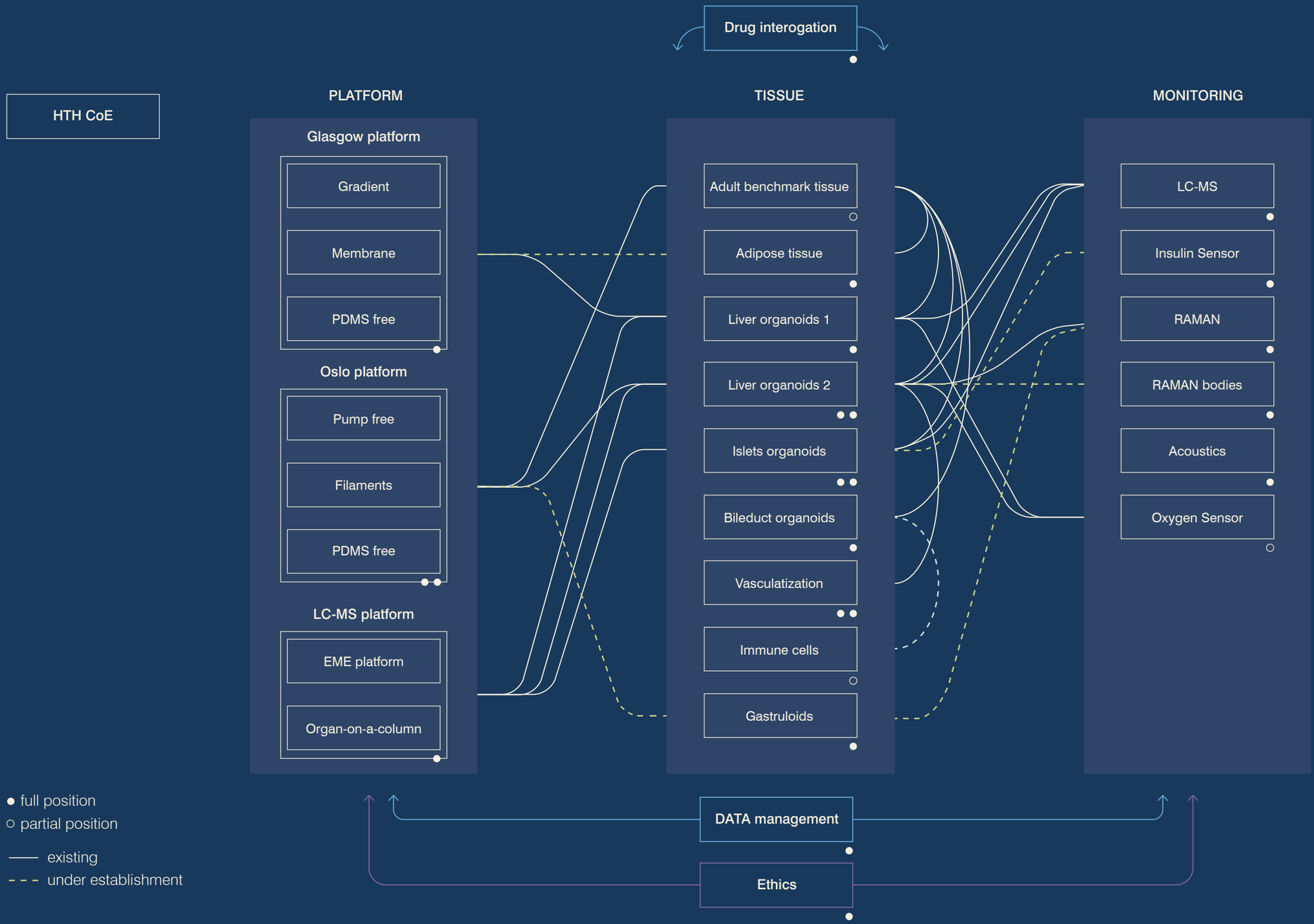

Ida Johnsen


Kristine Dolva


Shoshy Mahmuda


Justyna Stokowiec

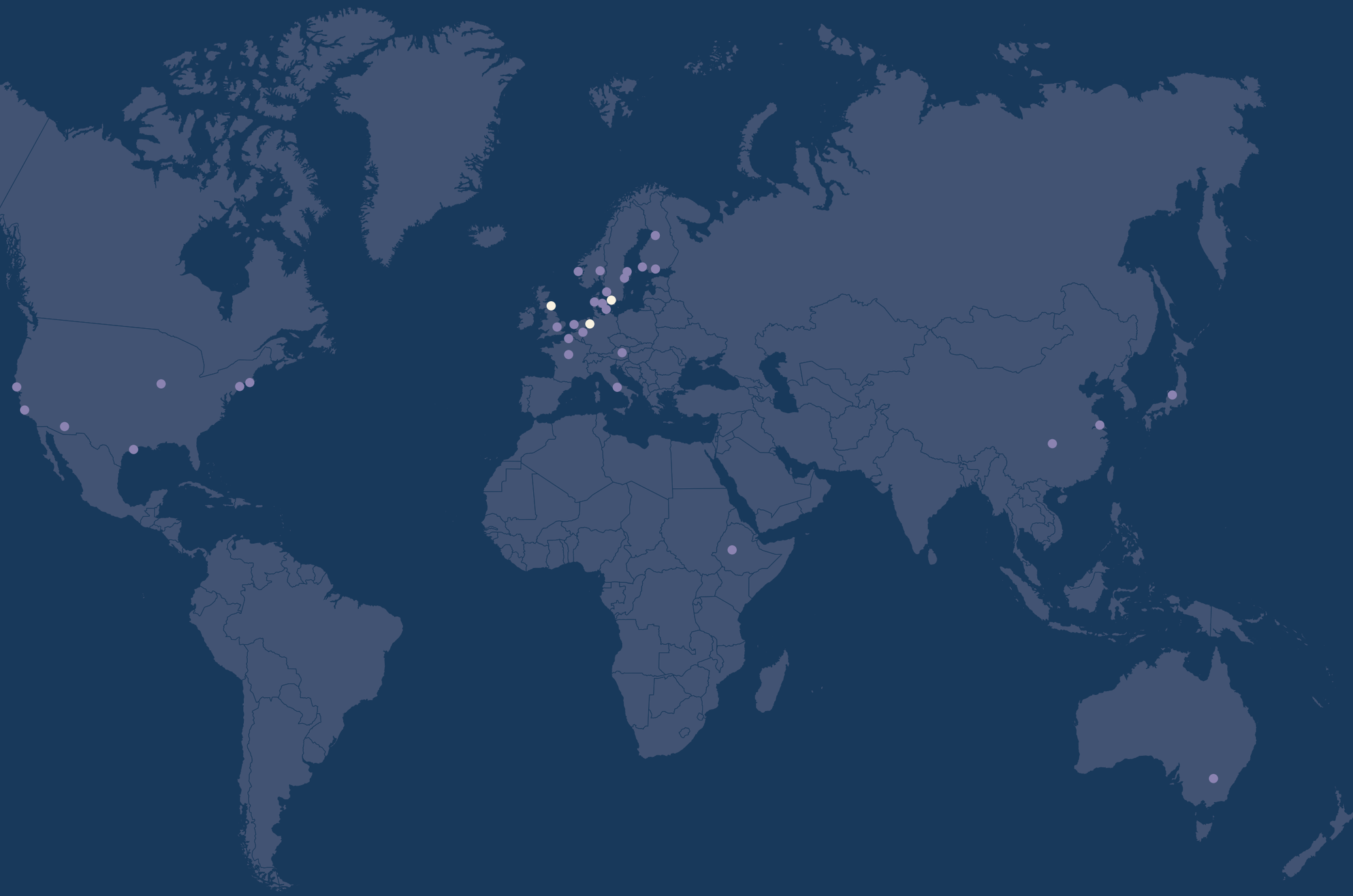
Organization chart



● full position
○ partial position

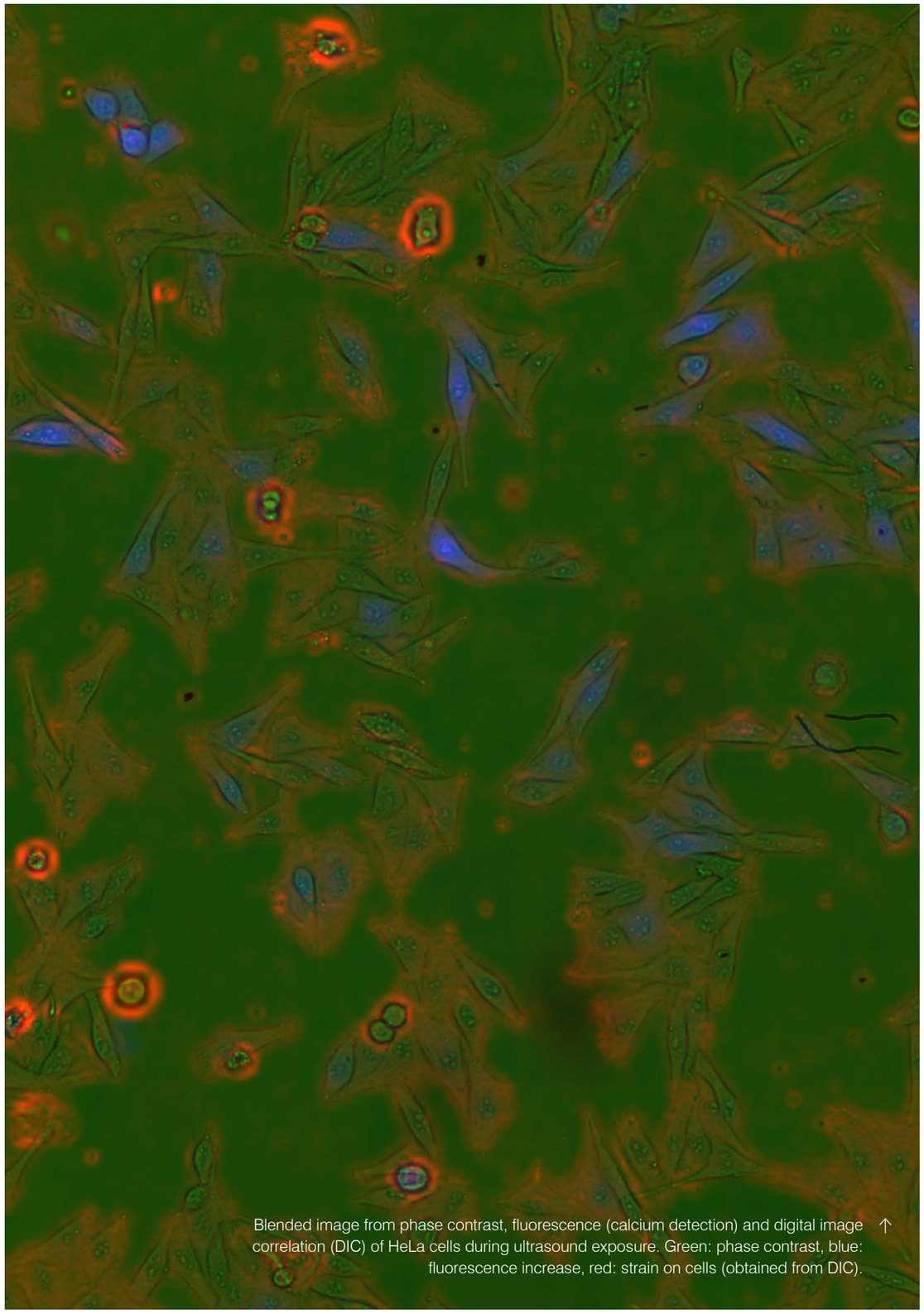
—— existing
- - - under establishment

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
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
RMIT University
Technical University of Denmark
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
FibroFind Inc
Mercachem Inc



Blended image from phase contrast, fluorescence (calcium detection) and digital image correlation (DIC) of HeLa cells during ultrasound exposure. Green: phase contrast, blue: fluorescence increase, red: strain on cells (obtained from DIC). ↑

Presentation of the ABINO UiO

Life science convergence environment

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Department of Physics and CoE-CCSE

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Chencheng Wang
Doctoral research fellow, CoE-HTH

Dongho Daniel Kwak
Doctoral research fellow, CoE-RITMO

UiO: Life Science has a bi-yearly competitive call to fund interdisciplinary consortia that work on ambitious projects.

The HTH - Center of Excellence (CoE) has attracted two such “convergence environments”, one coordinated by Stefan Krauss, called CHIP that focuses on liver organoids was funded in 2017, and a second is coordinated by Hanne Scholz, called ABINO, received funding in 2019.

ABINO focuses on innovative methods for stem cell differentiation with the aim of advancing insulin producing beta-cell development. The project integrates knowledge of islet biology and stem cell differentiation pathways, together with expertise in matrices and acoustic-mechanical stimuli, deep learning and modeling approaches to develop novel stem cell differentiation protocols that improve differentiation efficiency and functionality. The ABINO project is led by HTH-CoE co-director Hanne Scholz and is a collaboration between the three UiO hosted CoE’s: Centre for Interdisciplinary Studies in Rhythm, Time and Motion (RITMO); Centre for Computing in Science Education (CCSE) and the Hybrid Technology Hub (HTH-CoE). In addition, the Department of Physics at UiO is involved.

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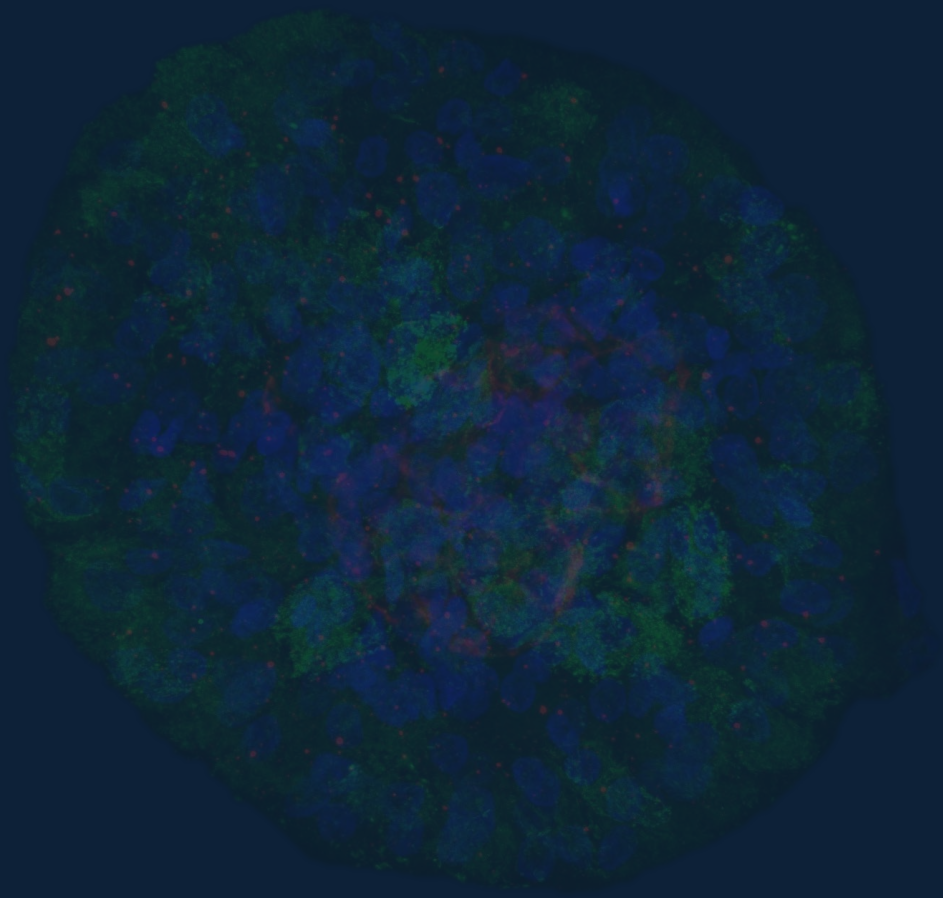

Cover: Immunofluorescence confocal microscopy of a iPSC derived hepatic organoid and Raman spectroscopic imaging (embedded box) of a human hepatocyte spheroid.

Hybrid Technology Hub
– Center for Organ-on-a-chip Technology

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