UiO : University of Oslo

CoE HYBRID TECHNOLOGY HUB – FOR ORGAN ON A CHIP TECHNOLOGY

ANNUAL REPORT 2019

Oslo University Hospital

University of Glasgow

Imperial College London

Norwegian Centre of Excellence

The Research Council of Norway

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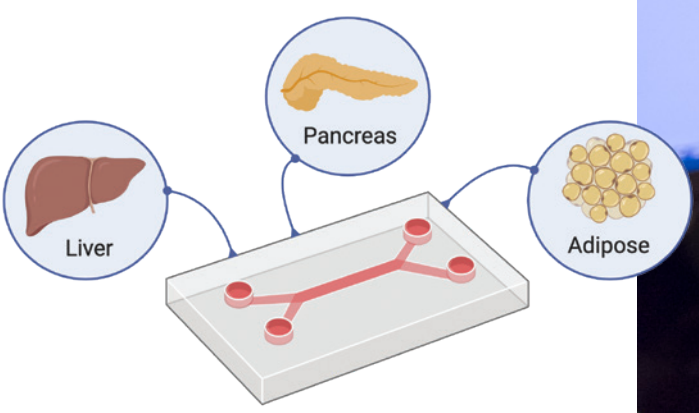
Photos by Gunnar Fredrik Lothe unless otherwise noted

Cover photo: iPSC-derived liver spheroid. Hepatocytes
express albumin (red color), HNF4a (cyan/turkey color)
and E-cadherin (green color). Photo by Aleksandra Aizenshtadt

CONTENTS

DEVELOPING ORGAN ON A CHIP TECHNOLOGY

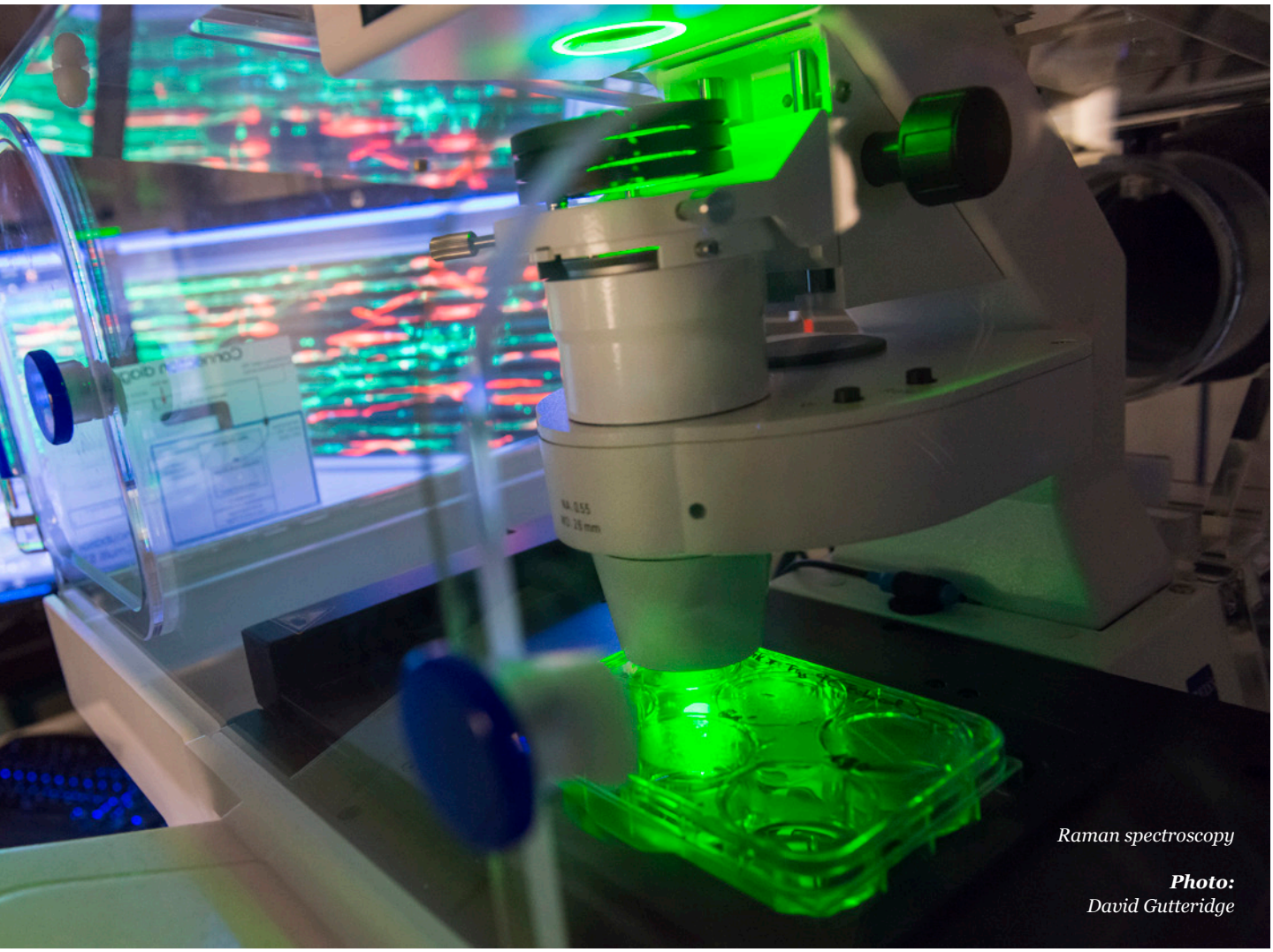


Stefan Krauss
Centre Director

Advances in biomedical research are increasingly revealing new and unexpected levels of complexity underlying human body functions. To understand this complexity, biomedical science and technology are challenged to develop methodology that could measure and understand these processes, and to supply technology that allows delivering better, more precise and more patient-tailored intervention regimes in medical practice.

"Organ-on-a-chip" (OoC) is such an enabling technology that is seen as a key tool for future preclinical drug development and personalized clinical patient care as it fills the gaps between cell culture, animal models and the human body. The goal of this technology is to recreate testable core functions of organs by combining a microfluidic platform with integrated miniaturized organ or "organoid" functionalities. To develop to 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 emerging technologies, including biomaterials for the microfluidic platform, bio-printing, microfluidic functionalities such as flow regulating entities, imaging technology, sensor technology, biological material, and data interpretation and integration.

In recent years, rapidly increasing evidence suggests that OoC technology could lead to a widespread use in academia and acceptance in the pharmaceutical and cosmetics industry, as much needed alternatives to animal testing. Not only could OoC technology mitigate ethical issues associated with animal use, but could also recapitulate complex human-specific physiology in complex organs such as the brain, the heart and the liver with accompanying vasculature and a representation of the immune system while being read out in real time. Human models may even be personalized with biopsy and cell material from donors, or by using induced pluripotent stem cells (hiPSC) derived cells. Improving disease models and personalized screens will enable the development of new drugs, repurposing of existing drugs, and optimization



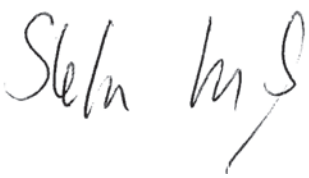
Raman spectroscopy

Photo:
David Gutteridge

of individual therapy regimes through patient stratification and individualized pre-treatment testing.

Within the broad area of OoC development, the Centre of Excellence "Hybrid Technology Hub" focuses on OoC technology in energy metabolism regulating organs. In the past year, the Centre went through a considerable built up phase. The Centre core facility containing a barrier facility, cell culture facilities, printing units, specialized equipment as well as general lab space and office space has been inaugurated and is now fully functional. Specialized staff on the PhD and post-doctoral level was hired and the Oslo core of the Centre was integrated with the partners at the University of Glasgow and at Imperial College London. Projects within platform design, organoid development, imaging, sensor technology and data analysis were initiated, advanced and combined in a way that we start to see the amalgamation of a solid technological basis with pioneering technologies that is so crucial for moving the boundaries in the field.

I want to thank all the researchers and staff in the Centre for a remarkable input to get over the hurdles of a starting a new research Centre, while moving their research projects. 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 Oslo:Life Science for very significant contributions to the center.



RESEARCH GROUPS AT THE HYBRID TECHNOLOGY HUB

iPS cell culture

Photo:
David Gutteridge

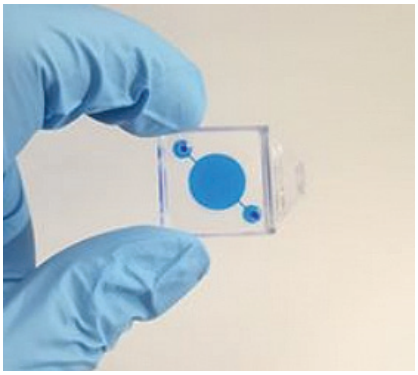
GADEGAARD GROUP – CHIP DESIGN

THE GADEGAARD GROUP SPECIALISES IN BIOMEDICAL ENGINEERING. THEIR EXPERTISE LIES IN INTERFACING NOVEL MATERIALS WITH BIOLOGICAL MATERIAL

Nikolaj Gadegaard
Principal Investigator

Over the past year, work in Glasgow has focused on 3 main areas: development of a platform to produce injection molded thermoplastic microfluidic devices, validation of the chips using liver organoids, and the design of devices to facilitate further experimentation with the organ-on-a-chip technology. With regards to developing a platform for manufacture of chips, we have shown that 3D printed polymer tooling can be used to manufacture many identical devices in a pseudo-industrial process. The use of a 3D printed inlay permits masters to be produced without the expertise and time required for CNC milled tooling or those produced through traditional semiconductor methods. A critical part of the manufacturing process is creating sealed devices. Here two methods have been explored: ultrasonic welding and lamination – both used industrially. The combination of using a 3D printed inlay and the described sealing methods has shortened the time required to produce a device to one working day, a feat that had not been realized previously. Examples of chip designs are shown in figure 1 with 1A showing the chips used for organoid experiments and 1B showing a typical fat-on-a-chip design.

The functionality of these first generation chips has also been achieved. For this work, Neil Convery (PhD student at University of Glasgow) spent 3 months at the Hybrid Technology Hub in Oslo to integrate the chips with organoids. During this visit, methods were developed to both load the organoids into the devices and maintain them for up to seven days in the chips. Viability test indicated that the organoids were successfully maintained in the chips. An image of this set up and results can be seen in figure 2A and 2B respectively. This work was then reproduced at the labs in Glasgow, highlighting the robustness of the methodology. During Neil's visit at the Centre, a 3D printing facility was established to allow the Hub to design and prototype their own devices in polydimethylsiloxane (PDMS). Training on the equipment was also provided. The digital nature of 3D printing means that chips designed and prototyped in Norway can easily be shared electronically with the lab in Glasgow and, once a final design is decided upon, chips can be manufactured in bulk to facilitate further, impactful research.



Prototype of microfludic chip
***Photo:** Neil Convery*

STEVENS GROUP – SENSOR TECHNOLOGY

THE STEVENS GROUP IS A HIGHLY CROSS-DISCIPLINARY RESEARCH GROUP WORKING ON DIFFERENT ASPECTS OF THE DEVELOPMENT OF ORGAN-ON-A-CHIP

Molly Stevens
Principal Investigator

The Stevens group is focusing on the development of techniques and technologies to monitor the functionality of the organoids on the chip and measure their changes upon drug treatment.

The group has extensive expertise in Raman spectroscopy based techniques. Raman spectroscopy is a non-destructive analysis technique that provides chemical and structural information. It can be applied to live cells and tissues. Stevens and co-workers previously developed a computational framework for 3D Raman imaging and analysis. They are now using it to assess healthy and steatotic (fatty liver disease) liver organoids. The accumulation of retinol, glycogen and lipids within liver organoids can be detected and quantified. In addition, the distribution of cytochrome C is visualized. The technology is being progressed for incorporation within the organ-on-a-chip platform. Upon exposure to therapeutic compounds, 3D Raman analysis will be used to measure drug metabolism and assess the condition of liver organoids, thereby advancing the technology towards a drug-screening platform.

Furthermore, Stevens has recently published in Advanced Materials a technique for nanoscale volumetric biomolecular mapping. This technique, called immuno-gold FIB-SEM, combines labelling of antigens with gold-conjugated antibodies with a slice-and-view electron microscopy technique. It provides simultaneous structural and biomolecular information with high spatial resolution. This technique, correlated with 3D Raman imaging, has the potential to broaden the insight into cellular processes when organoids are interrogated with therapeutic tools.

Raman spectroscopy can also be used to develop label-free sensing systems. The Stevens group has recently published in Nature Communications an “artificial nose” that can distinguish the fingerprints of different cell lysates using label-free surface-enhanced Raman spectroscopy. It is based on plasmonic surfaces functionalized with mildly selective self-assembled monolayers. The interaction of biomolecules with each sensor generates a signature that allows the analysis and identification of complex biological matrices. The experience of the group with plasmonic sensors is currently being leveraged to design advanced biosensors for

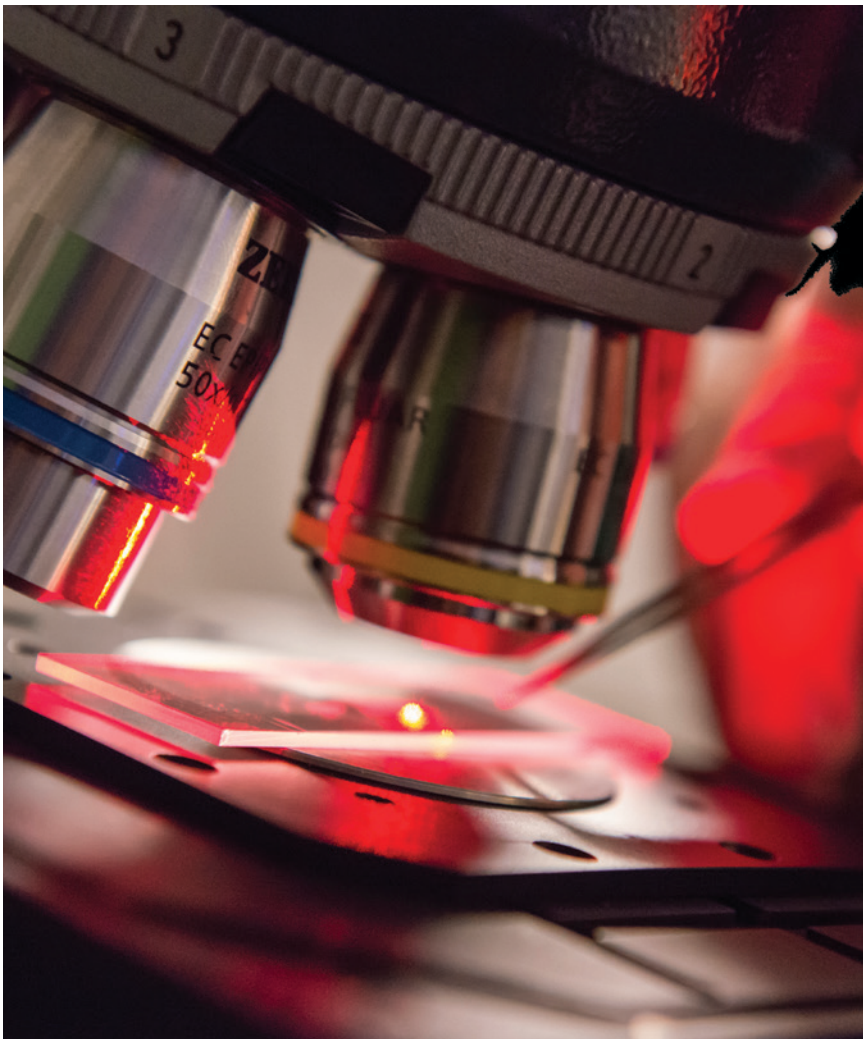
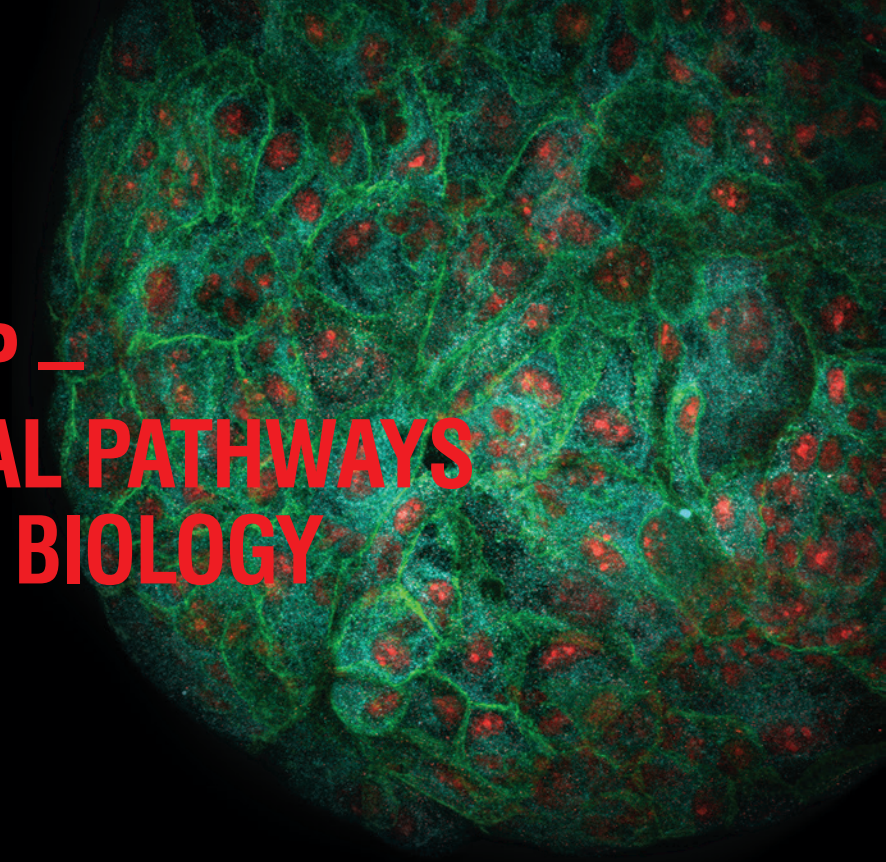


Photo:
David Gutteridge

real-time monitoring on organ-on-a-chip platforms. Sensors that can detect and quantify in real-time specific biomarkers as they are produced by the cells are being developed.

In addition, the Stevens group is exploiting its expertise in printing techniques to pattern surfaces with a number of different activators/inhibitors of the WNT pathway via inkjet printing. Stevens is studying how these patterned substrates stimulate the cells and could guide the differentiation of induced pluripotent cells into functional organoids. Through the UK Regenerative Medicine Platform "Smart Acellular Materials Hub", a 10 institutions research consortium directed by Stevens, the group has access to materials for further exploring 3D culture of organoids.

Finally, Stevens has been working with the Rayner group on setting up a Minio - node at Imperial College London. The Minio Platform will serve as a data warehouse with improved data access and management. In order to distribute the workload of the warehouse, a working node had to be set up at each university involved in the project. A new research data store of 20 TB has been allocated and a virtual machine has been set up by Imperial College ICT. This will facilitate collaborative efforts across the Centre.



KRAUSS GROUP – DEVELOPMENTAL PATHWAYS AND CHEMICAL BIOLOGY

Stefan Krauss
Centre Director

iPSC-derived liver spheroids expressing A1AT and HFN4a

Photo:
Aleksandra Aizenshtadt

The Krauss group focuses on applying developmental biology and chemical biology to organ-on-a-chip technology.

The Krauss group has established a program for phenocopying spatial and temporal processes in the development of the embryonic liver, and in collaboration with Hanne Scholz for the embryonic pancreas *in vitro*. Using such processes, we aim to develop more structured organoids than hitherto possible and at the same time achieve better subsequent maturation and functionality. This is fundamental for a viable personalized drug testing platform. In parallel, we work towards standardizing adult human tissue for organ-on-a-chip integration and benchmarking. For testing the biological structures by various analytical and imaging platforms, we have established collaborations with the research groups of Hanne Scholz, Molly Stevens, Steven Wilson, Espen Mellum, Ørjan Martinsen and Philipp Häflinger. For components of the immune system, a collaboration with Aleksandre Corthay has been initiated.

The Krauss group together with Petter A Olsen is also working on lineage reporters in iPS cells. The reporters provide tools for determining the activity of developmental signaling pathways *in vitro*, the differentiation status of organoids and the environmental signals such as sheer stress and oxygen levels. A focus is on WNT and hippo signaling reporters.

In the chemical biology program, the group has further advanced its Tankyrase inhibitor program with the lead compound OM-153 that has reached preclinical candidate status and is currently undergoing extensive toxicology tests. This program has led to a published patent (WO2019/243822), two articles that are currently in press in Communications Biology and one article that is under revision in the Journal of Medicinal Chemistry. The chemical biology program, which has received several supporting innovation grants, is closely coordinated with project leader Jo Waaler.

SCHOLZ GROUP – ISLETS

THE SCHOLZ GROUP SPECIALISES IN UNDERSTANDING HUMAN ISLET BIOLOGY AND THE DEVELOPMENT OF REPLACEMENT THERAPIES FOR BETA CELLS, THE BODY'S INSULIN PRODUCING CELLS

Hanne Scholz
Vice Director

3D bioprinting of cell-laden scaffolds

Photo: *Essi Niemi*

The group consist of 10 members with research background in medicine, biology, stem cell biology, tissue engineering, transplantation and laboratory engineer. Our research focused on the development of beta cell replacement therapy for type 1 diabetes and on understanding human islet cell biology. Human islet consists mainly of insulin producing beta cells, and glucagon producing alpha cells responsible for the fine-tune regulation of our glucose level in our body. The laboratory aims to improve the care for diabetic patients and has a clear and strong focus of clinical translation based on experimental research.

Along the experimental research line, the group has contributed to several studies showing that human islets can be protected from a diabetic micro-environmental stress such inflammation and hyperglycaemia. We actively participate in European networks of leading islet laboratories that investigate and improve the methodology for the isolation process of islets from donor pancreas as documented by a series of publications. We are continuing to develop innovative approaches using 3D bioprinting technology for delivery of pancreatic islets with supporting cells that will allow us to define alternative graft sites. These studies form a basis for optimizing the design of an OoC platform for ex vivo islet survival and long-term functionality.

In the past year, the laboratory has started in collaboration with prof. Helge Ræder and Assoc. prof. Simona Chera at University of Bergen to deploy iPS technology for in vitro differentiation of human stem cells towards mature beta cells. The Scholz lab. is advancing this research further in the newly UiO:Life Science funded project «Artificial Biomimetic systems – the Niche of Islet Organoids (ABINO)» that joins researchers from three Centres of Excellence (CoE) (RITMO, HTH, CCSE).

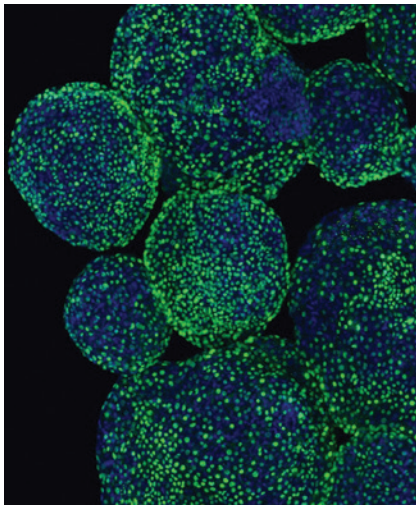
SULLIVAN GROUP – ORGANOIDS

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 are exploring within the Centre include understanding differentiation – this will provide important insight into the derivation of mature functional cell types from human pluripotent stem cells (hPSCs), in addition to providing tools for interrogation of disease/toxicology models. To enable this we have been developing both 3D hepatic and adipose organoid models.

Over the year we have further refined our small molecule approach originally designed to generated hepatocytes in 2D, (doi.org/10.1016/j.stemcr.2015.04.001) to produce 3D scalable liver organoids. We have performed a battery of functional assays to demonstrate functional equivalence to primary tissue for example the production of vitamin K dependent coagulation factors and Phase I and II drug metabolism. We have conducted single cell RNAseq analysis demonstrating the presence of both parenchymal (hepatocytes and cholangiocytes) and non-parenchymal cells types (Stellate, Kupffer and liver sinusoidal endothelium). Another feature of the organoids is that they display enhanced function and longevity as compared to their 2D counterparts being maintained in culture for over 100 days. Interestingly, the liver organoids are vascularised, this being the first example of de novo vascularization described. A drawback of current hepatic organoid approaches is the reliance of extracellular matrix, which is a major bottleneck with respect to scaling i.e. generated in the 10´s to 100´s, here we can mass produce hepatic organoids at the 100,000´s to millions (manuscript in preparation).

In parallel, we have developed methodologies to produce adipose tissue. We have assessed different sources of hPSC derived mesenchymal stem cells (MSCs) for their ability to produce adipocytes. We have now developed robust methods to produce expandable neural crest cells, which have been directed to peripheral neurons. This neural crest population can be differentiated towards a MSC population. We have now established a rapid protocol to generate neural crest derived MSCs that are capable of tri-lineage differentiation. This MSC population is expandable and can be cryopreserved. Using the neural crest derived MSCs, we have developed an optimised procedure to produce white adipocytes. This white fat population express key markers such as PPARγ2, FABP4 and Perilipin etc. Importantly, the white adipocytes can accumulate fat droplets over time. We have recently initiated benchmarking of the hiPSC derived white fat against human primary material.



HNF4a positive hepatic organoids

Photo:
Sean Harrison

RAYNER GROUP BIOINFORMATICS

Simon Rayner
Principal Investigator

The primary goal of the Computational Biology group is to develop a secure, user friendly data solution to integrate and share the data being generated by the Centre. However, the broad range of expertise within the Centre makes this particularly challenging as each group generates diverse data types. Moreover, rather than working as independent units, the HTH and partner research centers commonly work together in cross-functional teams to achieve particular goals. This means that the data handling solutions need to be dynamic to accommodate the changing needs of the Centre.

We need (i) cloud storage, (ii) a version control system (iii) a system to ensure metadata quality & (iv) the ability to implement privacy and security requirements as necessary. Standard tools such as Dropbox or Google Drive provide a shared solution, but fail to provide the required privacy and cannot be shaped to our specific needs. Hence, to meet the four targets described above, we have been developing our own cloud based solution.

Our solution implements a distributed mult-layer architecture, deployed through Docker containers and orchestrated by Docker Swarm. All partner institutions of the Centre support this architecture, which makes it feasible to build a cross site solution that can incorporate additional partners if needed.

The cloud storage is implemented using MinIO, providing data encryption, identity management and access control. Version control is handled using a S3 implemented version of Git. Data quality is handled by requiring users to supply data descriptors in the form of metadata, and then using a Hyperledger solution to ensure users adopt these descriptors. By bringing the described technologies together, we can fully integrate data in a way that reflects the research that is being performed in the Centre. For example, an OoC experiment might bring together a cell population; a 3D printed organoid; a chip design with associated microfluidics; and a sensor set to capture the data generated by the integrated system. Each of these components must be characterized individually and then collectively as part of the final system. The version control system allows us to track the evolution of the individual component design and link them to the experimental data as it is collected for the integrated design. As users are required to include metadata in order to submit their data, this will ultimately provide us with a rich data set that can be used to help interpret experimental results and aid the design of future experiments.

A further advantage of this data solution is that is achieves a level of compliance with FAIR (Findability, Accessibility, Interoperability, Reusability) goals. This is something that is supported by the Research Council of Norway (RCN) and the European Research Council (ERC). Our architecture is flexible enough to be adopted by other larger scale projects and can help them meet the FAIR data goals of the RCN and ERC.

To date, we have been working with test data but our next goal is to demonstrate the value of our work by performing a standardization test across the three nodes of the Centre (Oslo, Glasgow & London) using a shared chip design and cell populations. To our knowledge, this will be the first study of its kind in the organ-on-a-chip research field.

SOLBAKK GROUP – ETHICS

THE SOLBAKK GROUP FOCUSES ON THE DEVELOPMENT OF THE CENTERS ETHICS PLATFORM

Jan Helge Solbakk
Principal Investigator

In 2019, the main focus of our work has been on objective 1 of the Ethics platform: to develop a methodological framework to study qualitative uncertainty pertaining to 'organ-on-a-chip' drug responses. Towards this goal we have been reviewing the literature on qualitative uncertainty and addressing the epistemological question how we might generate scientifically valid knowledge when the sample size approaches one.

To this end the precision paradox concept has been coined. The concept was introduced and discussed in a paper entitled 'The precision paradox of personalised medicine - how can we know what works when statistics do not apply?', by Vogt, H., Hofmann, B, and Solbakk, JH. This paper was presented at the 33rd European Conference on Philosophy of Medicine & Health Care in Oslo in august last year.

In the paper, 'The precision paradox - How personalized medicine increases uncertainty', which is to be included in a book on the philosophy and ethics of precision medicine forthcoming at Oxford University Press, Vogt addresses three aspects of what we have dubbed the precision paradox: that precision medicine - despite its promise - may increase uncertainty, at least in an interim phase; that the increasing complexity of data and models and inclusion of more dimensions about each person in precision measurements might increase imprecision; and third, that precision medicine risks a general medicalization.

Last year Henrik Vogt's and co-authors' paper, 'How precision medicine and screening with big data could increase overdiagnosis', BMJ, was hailed by Bob Steele at the Scottish Cancer Preventive network (SCPN) as 'the paper of the year' (*https://scpnblog.wordpress.com/2019/12/02/paper-of-the-year-2019-professor-bob-steele/*).

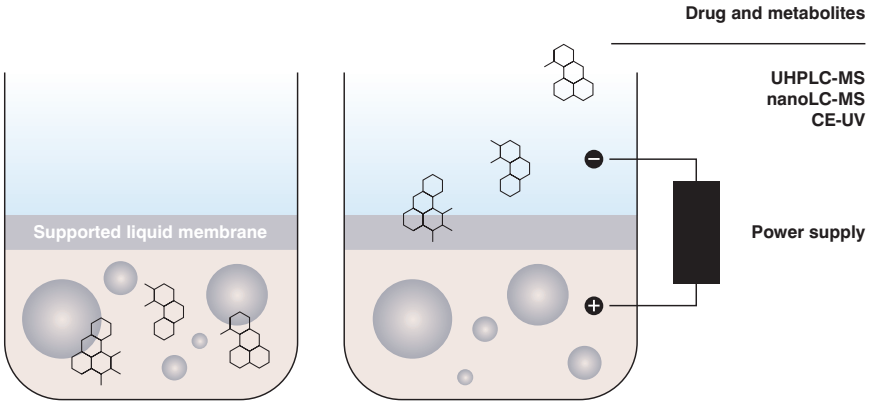
The paper also resulted in interviews both in New York Times ('In This Doctor's Office, a Physical Exam Like No Other', 5.09, 2019, and in the Danish Weekendavisen ('De sidste raske', 20.09, 2019).

PRESENTATION OF ASSOCIATED GROUPS

WILSON GROUP – MASS SPECTROMETRY

THE WILSON GROUP HAS EXTENSIVE EXPERTISE IN THE FIELD OF BIOANALYTICAL CHEMISTRY, BOTH DEVELOPING NOVEL METHODS AND HARDWARE FOR THE SEPARATION AND DETECTION OF COMPOUNDS AT MINIMAL ABUNDANCE

Steven Ray Haakon Wilson
Assosciated partner



By applying an electrical current, analytes can be transported across a supported liquid membrane for high degree of sample clean-up

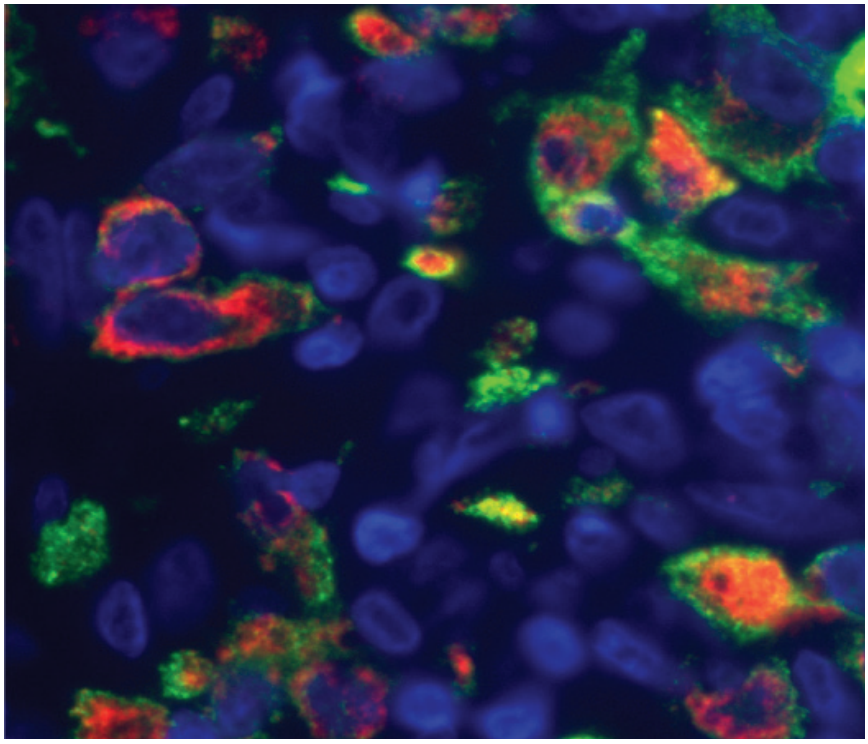
Illustration: *Frøydis Sved Skottvoll*

Within the Wilson group, we have been developing technology to study the metabolic activity of organoids with the aim of describing the similarity and dissimilarity of organoids compared to full-scale adult human organs. If organoids can mimic their full-scale counterparts, they can be used to predict their behavior, aiding efficient drug development and testing. We have focused on liver-like organoids, testing how they break down drugs (a key function of the human liver). In this work, we have collaborated strongly with OUS researchers in forensic toxicology, studying the degradation of drugs of abuse e.g. heroin. Encouragingly, we have found that organoids indeed share properties with human livers regarding drug degradation in the tested pathway. Hitherto, studying drug metabolism in organoids has been challenging, due to sizes limitations. To meet these challenges, custom technology had to be developed. We have built our monitoring methods around mass spectrometry allowing to monitor whether heroin has been transformed to morphine, as expected to happen in a liver.

Mass spectrometry is a highly relevant technique in chemical analysis. Our group hosts a significant number of students enrolled at the Department of Chemistry, and they are deeply involved in research collaborations with seasoned national and international researchers. Our students are major contributors to researcher manuscripts and papers from our work in the Centre. They are also participating in scientific meetings, contributing with scientific posters and talks. Two of our students, Stian Kogler and Frøydis Sved Skottvoll, were both finalists in oral presentation competitions at one of the largest international conferences in analytical chemistry (HPLC2019, Milano, Italy). Both of these students are currently preparing manuscript which they co-author, detailing their work with “online” mass spectrometric analysis of organoids. In addition, our group has also hosted several international researchers. For example, Ann Lin, who was recently highlighted in Forbes Magazine in an article on “30 scientists under 30”.

CORTHAY GROUP – IMMUNOLOGY

THE CORTHAY GROUP IS WORKING ON RECREATING COMPLEX TUMOR MICROENVIRONMENT ON-A-CHIP FOR THE STUDY OF THE IMMUNE SYSTEMS ROLE IN CANCER



Immunofluorescence image of a human lung tumor reveals the presence of many immune cells such as macrophages (in red and green; cell nuclei are blue) in the tumor

Photo: *Astri Frafjord*

Alexandre Corthay
Associated partner

The Corthay lab investigates the interplay between the immune system and tissue with a main focus on two types of immune cells, namely tumor-specific T cells and macrophages. Our research vision is to increase the understanding of how the immune system naturally fights cancer in order to develop novel strategies for cancer immunotherapy, and at the same time pave the ground for testing immune interactions with other tissues. We perform both in vivo and in vitro experiments with experimental mouse models, cell lines and tumor tissue from patients with non-small cell lung cancer (NSCLC). The Corthay group joined the Hybrid Technology Hub in 2019 with the task of developing a chip with components of the immune system in which cell interactions and key processes (such as cell division and death) will be visualized over several days by high-content video-microscopy. Using an in-built perfusion system, the effect of drugs on the interactions will be monitored live minute-by-minute.

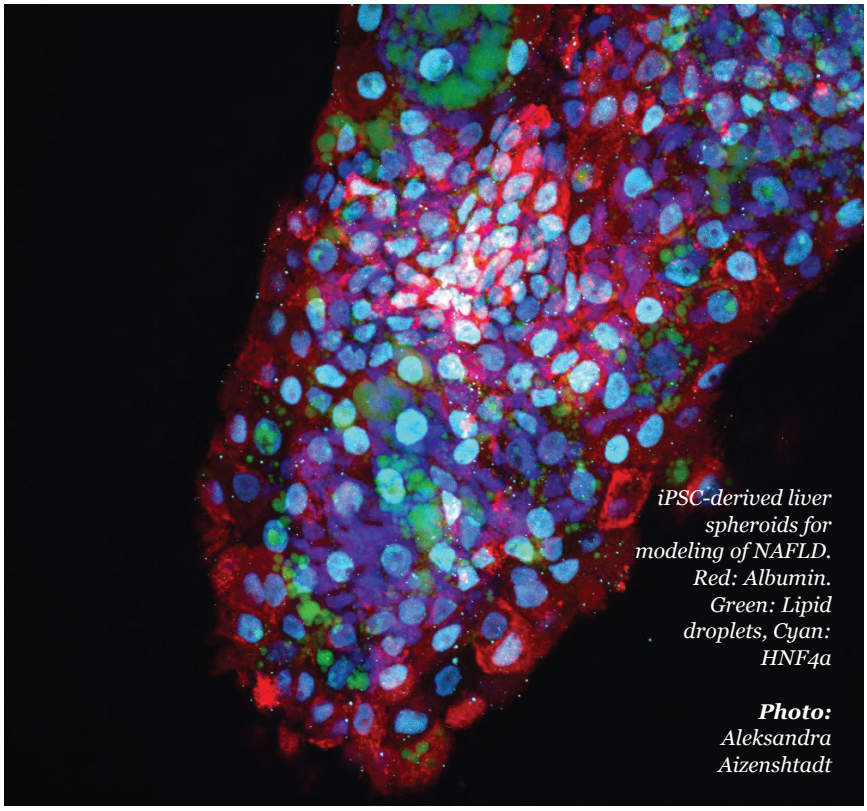
MELUM GROUP – LIVER

Espen Melum
Associated partner

The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The group represents one of the three research groups at the Norwegian PSC research Centre. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology but also now incorporating aspects of regenerative medicine. In addition to the cholangitis focused studies, we are also doing basic research related to the function natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The most important tools in our research are mouse models that reproduce aspects of cholangitis development. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment target for PSC.

In 2019, new lines of collaborations with Stefan Krauss and Hanne Scholz at the Centre of excellence Hybrid Technology Hub were started. We have in 2019 used our organoid technology from the bile ducts in pilot single sequencing projects which we will extend functionally in 2020. Currently, we are establishing methods related to single cell sequencing in our laboratory that can benefit the rest of the researchers at HTH.

The group has also recruited a new Scientia Fellow postdoctoral researcher who will be mainly working on projects in collaboration with HTH that will model the bile ducts using an OoC system.



iPSC-derived liver spheroids for modeling of NAFLD. Red: Albumin. Green: Lipid droplets, Cyan: HNF4a

Photo: *Aleksandra Aizenshtadt*

INNOVATION AT THE HYBRID TECHNOLOGY HUB

INNOVATION DRIVES MANY OF THE CENTERS KEY AREAS. NOVEL APPLICATIONS FOR EXITING TECHNOLOGIES ARE BEING IMPLEMENTED ACROSS ALL GROUPS AND TECHNOLOGIES ARE DEVELOPED AND OPTIMIZED FOR THE USE WITH ORGAN-ON-A-CHIP

The Centre is still at an early stage of the innovation cycle. In this phase, core technologies are established and solidified while first explorative tests towards new technologies are made. Yet, already a few developments can be seen.

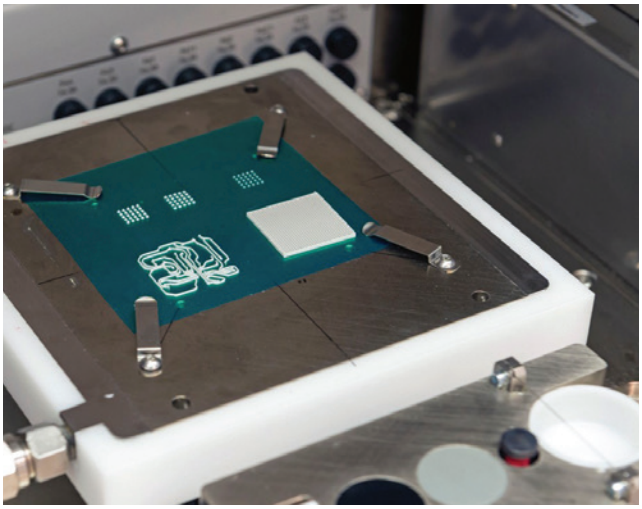
Electro Membrane extraction (EME) is a technique developed at the University of Oslo, comprising of metabolite electrophoresis across an oil membrane. EME is highly suited for extracting drugs and metabolites from bio-samples for subsequent analysis, by e.g. mass spectrometry. Since EME separates small drugs and metabolites from other biomolecules such as proteins, analyses are highly robust as there are few sources to contamination. The Wilson group is using EME actively for studying drug metabolism of organoids, in combination with proteomics analysis. Currently, we are performing method development for EME-on-a-chip, which will allow for automated analysis of organoid drug metabolism.

Organ in a column (OiC) is an entirely novel concept developed by Stian Kogler in the Wilson group that merges technology from separation science with organoids. In this technology, column housings for liquid chromatography are charged with organoids allowing them to be directly connected to downstream separation units allowing to perform on-line monitoring of a wide range of molecules by mass spectrometry. The Wilson group is now collaborating with the other PIs in the Centre in studying interactions between various organoids and islets.

The Scholz laboratory is doing pioneering work on bio-printing of matrix embedded islets, enabling enhanced functionality and superior transplantation.

The Sullivan group has developed robust methods to produce expandable neural crest cells, which can be differentiated towards a Mesenchymal Stem Cell (MSC) population. Using these neural crest derived MSCs, the group has developed an optimised procedure to produce white adipocytes.

The drug discovery program that was initiated by Krauss and Waaler



Left: *Kayoko Hirayama Shoji creating alginate filaments, packed with living cells.* **Right:** *The bioplotter enables the production of living 3D-scaffolds*

Photos:
Gunnar Fredrik Lothe

before the Centre was established, but forming an integral part of the Centre, has seen substantial progress. The core aim of this program is to develop a chemical inhibitor that addresses the central WNT signaling pathway through blocking the catalytic domain of Tankyrase. So far, no Tankyrase inhibitor has reached clinical trials, and given the broad role of WNT signaling in development and diseases, the program is of broad interest in the field. The WNT inhibitor has also implications for in vitro differentiation protocols and hence for OoC development. In 2019, the chemical structure patent (WO2019/243822) was published and a preclinical lead was identified. So far, the lead structure has not shown significant liabilities and, after extensive process research, is currently undergoing toxicological tests as a precondition for clinical testing. This project is carried out with the industry partner and award-winning Dutch chemistry company Mercachem, acting as a close scientific and business partner, while IPR/patents are handled by Inven2, the Technical Transfer Office of the University. Two publications are in press in Communications Biology (Nature journal family).

NORDIC ORGAN ON A CHIP CONFERENCE

The Hybrid Technology Hub hosted the Nordic OoC conference on the 12th of February 2019. The conference had a packed program with 22 speakers, primarily from the Nordic countries, but also a few contributions from leading researchers in the field from other European countries. The symposium also included a poster session and social event for PhDs and postdocs working on OoC-related themes. The conference was very well received and 150 participants attended the full 10 hour program. The conference was followed up by a more practical and workshop oriented event in August 2019 hosted by the Body-on-chip – Centre of Excellence in Tampere, FI.

CENTRE RETREAT TO LOFOTEN

In the first week of September 2019, 29 Hybrid Technology Hub employees travelled together and spent 3 days in Henningsvær / Lofoten. In between the tight schedule of project presentations, group discussions and Skype-talks from world leading OoC researchers there was room for extended lunch breaks and joint activities. Activities consisted of a mountain hike to Festvågtinden (541m a.s.l.) and a fishing trip on a traditional Lofoten fishing boat. The retreat was an excellent experience and it allowed researchers employed at the different nodes to interact in both academic and social contexts.

PhD student Neil Convery at the University of Glasgow ascending Festvågtinden above Henningsvær

Photo: *Stefan Krauss*

HYBRID TECHNOLOGY CENTRE OF EXCELLENCE TEAM MEMBERS IN 2019

Group photo from centre retreat in Lofoten, September 2019. ***From left to right:*** *Frøydis Sved Skottvoll, Molly Stevens, Stefan Krauss, Elisabeth Dybing, Steffen Nøvik, Jelle Penders, Cecil Echalier, Alexandre Corthay, Daniel Boland, Shadab Abadpour, Aleksandra Aizenshtadt, Neil Convery, Hanne Scholz, Christine Schuelke, Essi Niemi, Haakon Berg Johnsen, Mikel Amirola Martinez, Petter Angell Olsen, Øystein Stakkestad, Nikolai Gadegaard, Vernon Lalone, Steven Ray Wilson, Inger Øynebråten, Jo Waaler, Ola Nilsen*

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Hanne Scholz
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Haakon Berg Johnsen
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Petter Angell Olsen
Facility manager

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Associated Partners

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Pavel Vazquez

Alexandra Aizenshtadt

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Henrik Vogt

Siqing Liu

Shadab Abadpour

Øystein Stakkestad

PhD candidates

Saphira Felicitas Baumgarten

Frøydis Sved Skottvoll

Steffen Nøvik

Essi Niemi

Neil Convery

Mikel Amirola Martinez

Technicians

Endalkachew Ashenafi Alemu

Elisabeth Dybing

Stian Kogler

Ida Johnsen

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Photo:
David Gutteridge

PUBLICATIONS 2019

Book chapters

Korsgren, Olle; Scholz, Hanne; *Cellular therapies in preclinical and clinical islet transplantation: Mesenchymal stem cells*; Transplantation, Bioengineering, and Regeneration of the Endocrine Pancreas

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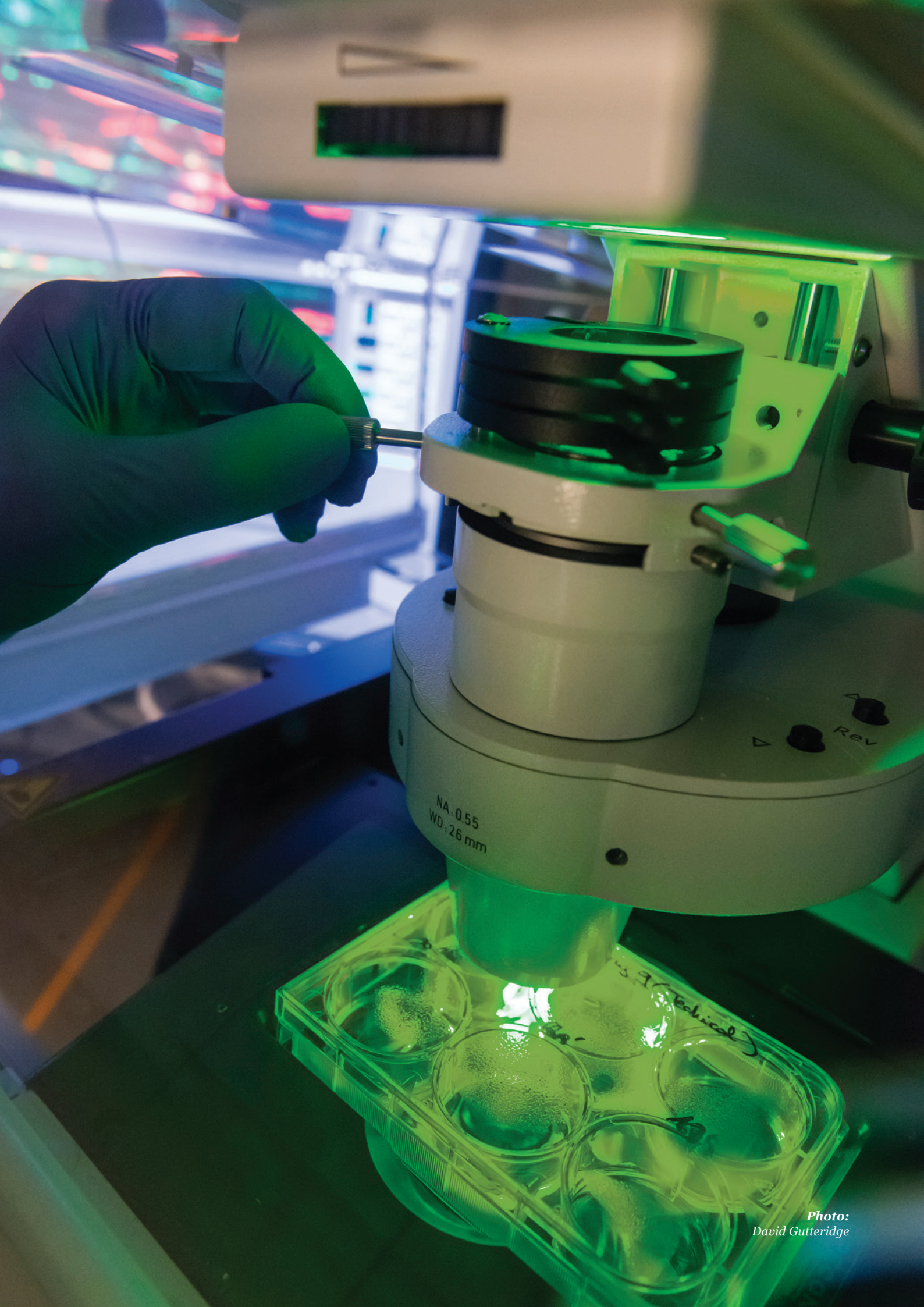

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Annual Report 2019

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