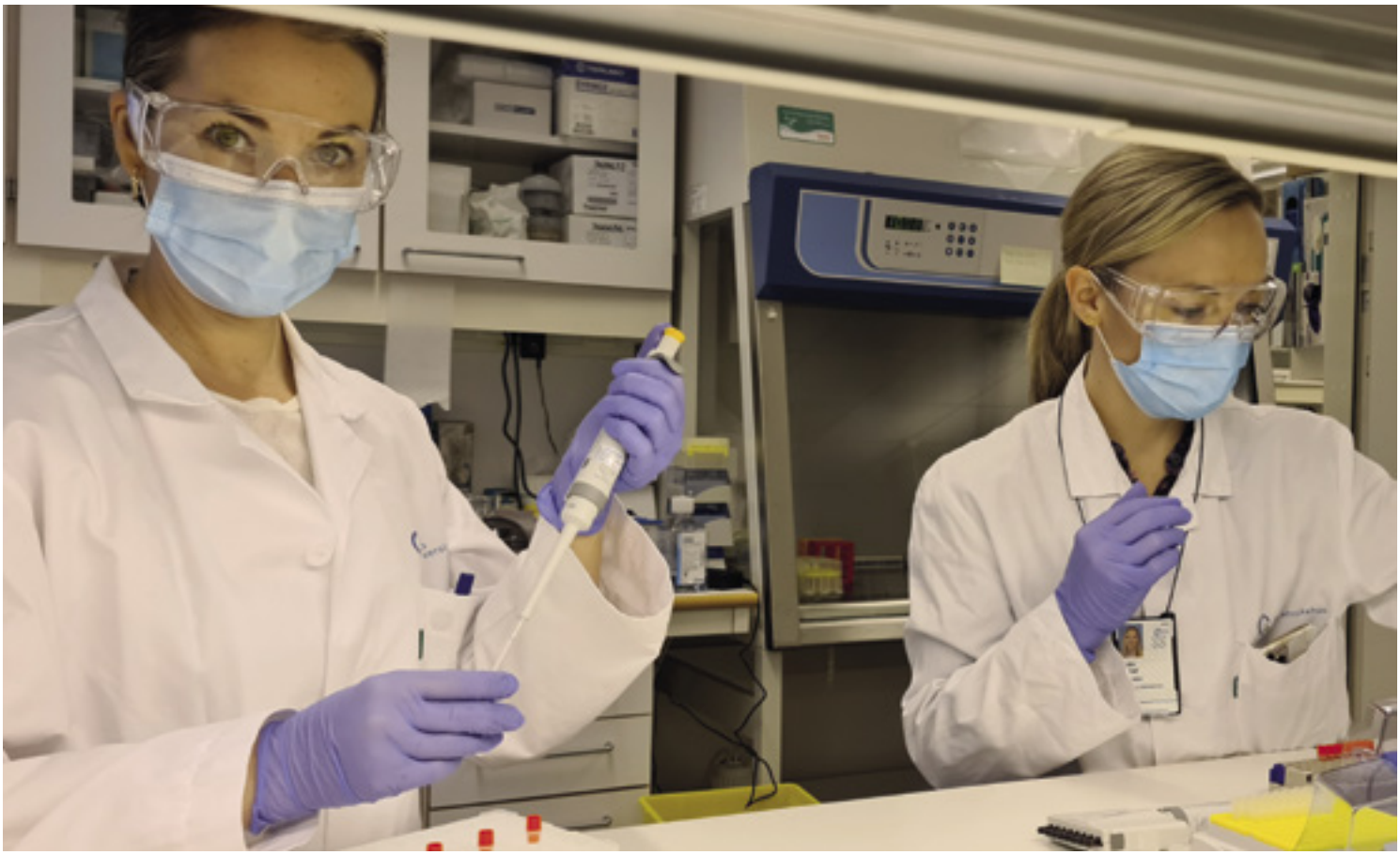
Oslo universitetssykehus



Norwegian PSC Research Center

ANNUAL REPORT 2020

NOPSC

Visit the NoPSC web pages: *www.ous-research.no/nopsc and www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/*

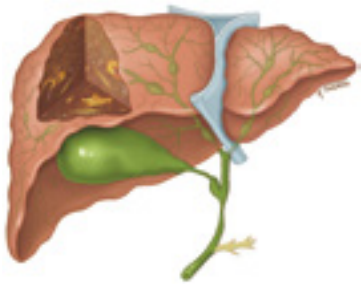
UiO : University of Oslo

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2020

What is PSC?

Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.



PSC is a chronic inflammatory disorder that leads to progressive strictures of the bile ducts and ultimately to liver cirrhosis.

There is an increased risk of cancer of both the bile ducts (160-1500x) and the large bowel (5x). PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. There is no effective medical treatment available, and PSC is one of the most common indications for liver transplantation in Scandinavia.

Affected individuals are typically young (30-40 years old) and have concurrent inflammatory bowel disease (IBD) in 60-80% of the cases. Disease course is highly variable from patient to patient, but the median time from diagnosis to liver transplantation is 10-15 years.

Primary Sclerosing Cholangitis (PSC) is a patchwork of different phenotypes in addition to the bile duct affection. Most important are inflammatory bowel disease (IBD), malignancy and other autoimmune diseases.

NOPSC Norwegian PSC Research Center

Content:

NOPSC ANNUAL REPORT 2020

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
FRONT PAGE: *Hanne Guldsten and Beate Vestad working in the lab.*
ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*
EDITOR: Merete Tysdahl
PUBLISHER: Oslo University Hospital
PRINT: Byråservice AS, 2021
SAMPLES: 220

On behalf of the Leadership,
Professor
Tom Hemming Karlsen
Head of NoPSC

Leader´s Corner

The main event of the year of 2020 was Covid-19, and its massive impact on most aspects of life for all of us requires no elaboration here. For those of us working with research and attending to PSC patients, several points however should be mentioned. In the early days of the pandemic, laboratories were closed, and researchers were re-oriented to clinical duties, e.g. Covid-19 testing. We saw a shifting towards telemedicine, meaning our patients were often seen at home, unable to contribute to clinical trials or biobanking. Inevitably, as a result of these many disruptions to "normal", some slowing down of our normally hectic groups happened. Restrictions to physical meetings, in the hospital, and abroad, also meant that inspiring academic discussions, which do from time to time require us to meet face-to-face, became impossible. In this digital world of restrictions, however, slowly over the course of the fall, thanks to the low burden of Covid-19 in Norway, activity has been restored at full speed.

During the most heavily closed down period in the spring of 2020, NoPSC also made a seminal contribution to Covid-19 research, over and above contributing to the running of Covid-19 related activities in the hospital, through the publishing of the first report in the world on the host genetic contribution to Covid-19 in New England Journal of Medicine (see further description on page 8-9). We did nothing more than what we do every day in PSC, but suddenly attention was massive, with headlines and shows in virtually any media across the globe, including CNN, New York Times and many others. To me as a leader, it shows the qualities of our team and our international network, enabling us to deliver a complete peer-reviewed report in the leading medical journal in less than three months (for genome-wide association studies it must be a world-record). Importantly, the funding was generously provided by Stein Erik Hagen and Canica, without hesitation, and thanks to their resolute decision to support the project, results were brought to the world almost half a year before other studies started appearing.

Rapidly, as labs re-opened, and we were allowed to resume our true mission, standards were restored for PSC research, and it is with reassurance I take notice that academic output in terms of research publications is stable and at high quality. A strong ambition for the ongoing 10-year period of "NoPSC 2" is the implementation of clinical tools and therapies. Key papers in that regard were published from all groups. From the clinical group in Oslo, a key step towards personalized therapy in cholangiocarcinoma was published. From the experimental group, long-standing pioneering work led to the establishing of the world's first pipeline towards a "bile duct on a chip" for drug testing and other research purposes. From the genomics group, the first paper ever on the full bacterial genome of the intestine of PSC patients means that we are one step closer to getting rid of toxic molecules from the gut. From the clinical group in Bergen, new and better biomarkers to measure drug efficacy in PSC were found.

Philanthropy made even another key contribution to PSC over 2020. Thanks to fresh funds from the Halloran Family foundation in the US, we are now in the process of establishing the world's largest natural history cohort, covering virtually all hospitals in Norway and Sweden, enabling patients to join for participation in various clinical studies, particularly those intending to find better biomarkers for PSC severity and treatment response. The network will also significantly enhance our capacity to engage in clinical trials, and from the patient perspective, will provide an opportunity to have access to such trials. Linking with other, similar initiatives over the coming future, we feel confident the natural history cohorts will provide an important component in the future path towards effective and licensed drugs for PSC.

We do have some concerns for the future. Institutional support, as evident from our funding sources (see page 6) is still lacking. Furthermore, until now, the annual "baseline" support from Canica has been strengthened by the governmental "gift reinforcement". The additional governmental funding has now stopped, for political reasons, meaning our total funding platform will shrink from 2021 onwards. Despite the success in achieving external, competitive grants, there is likely a roof as to how much competitive funds we are able to attract for a rare liver disease, and over the course of 2021 we will need to make decisions for future priorities. I remain optimistic, and the latest steps towards clinical and significant innovations warrant appreciation. The performance of the team during the challenges of Covid-19 does too, and I want to thank each and every one of the NoPSC staff for keeping up – energy, motivation, efforts – and our friendly working environment – through all of this difficult year.

Overview of the Norwegian PSC Research Center

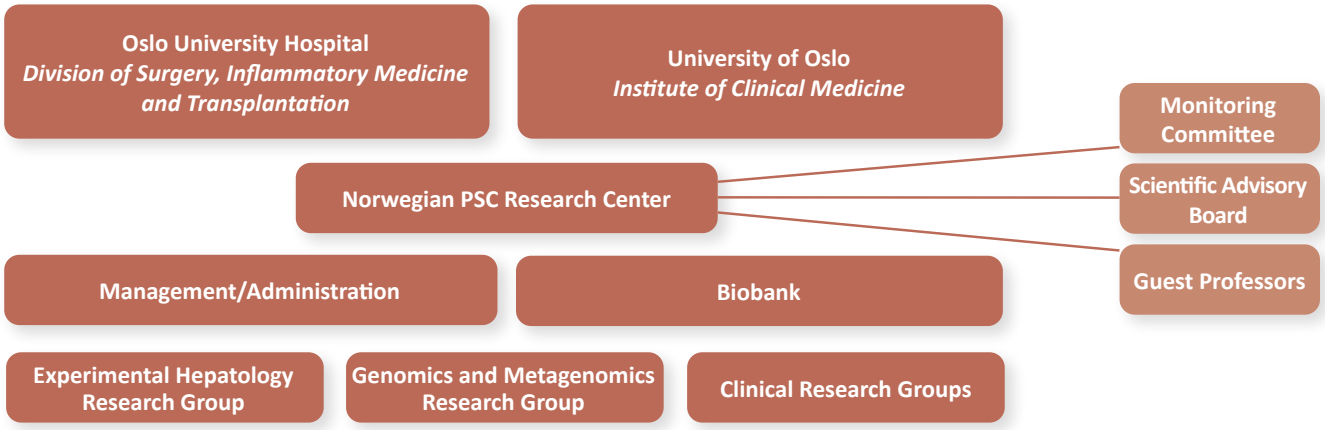
NoPSC was established May 2008 at the Medical Department, Rikshospitalet, upon signing the contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of this agreement was a donation from Stein Erik Hagen of NOK 100 millions made in September 2007 to substantially strengthen research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis. From 2017 Canica A/S has provided another NOK 50 millions for a another ten-year period based on a new contractual agreement between Canica A/S, Oslo University Hospital and the University of Oslo as of December 2014.

Aims of the PSC Research Center

- Ensure targeted and prudent management of the private donation
- Motivate high-quality PSC research in Norway
- Coordinate and distribute resources for PSC research in Norway
- Establish international collaborations when needed
- Establish and run Biobank and PSC Registry

ORGANIZATION

NoPSC has status as a center at the Medical Faculty, Institute of Clinical Medicine, University of Oslo and is organized within Oslo University Hospital as a section (level 4 unit) within the Department of Transplantation Medicine at the Division of Surgery, Inflammatory Medicine and Transplantation. The Experimental Hepatology Group and the Genomics and Metagenomics group are organized at the Research Institute of Internal Medicine, Oslo University Hospital, while the clinical groups are organized within the Section for Gastroenterology and Hepatology at the Department of Transplantation Medicine, Oslo University Hospital and Haraldsplass Deaconess Hospital, Bergen, respectively.



MONITORING BOARD

The Board monitors that the Center is managed according to the Aims. Next year's budget is discussed in the autumn while the Annual report and the accounting are reviewed at the spring/summer meeting. The center´s scientific activities are also presented at the Monitoring Board meetings.

LEADER
Prof. Dag Kvale,
Head of the Institute of Clinical Medicine, University of Oslo

Nina Paulsen
Canica A/S

Dr. Morten Tandberg Eriksen, *Head of Div. of Surgery, Inflammatory Medicine and Transplantation, OUH Rikshospitalet*

Hans Mossin
Adm. Head of the *Institute of Clinical Medicine, University of Oslo*

Daniel Sørli
Canica A/S

Prof. Bente Halvorsen, *Head of the Research Institute of Internal Medicine, OUH Rikshospitalet*

Prof. Tom Hemming Karlsen, *Center leader, is also part of the monitoring board.*

GUEST PROFESSORS

Ass. Prof. Niklas Björkström
Unit of Gastroentero-logy and Rheumatology, Karolinska University Hospital, Huddinge, Sweden

Prof. Massimo Pinzani, *Institute of Immunity & Transplantation Royal Free Hospital, London, UK*

SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) was formally established in 2015 and reviews the center biannually.

Prof. Herbert Tilg
University of Innsbruck, Austria

Prof. Terje Espevik
University of Science and Technology (NTNU), Trondheim, Norway

Prof. Tore Kvien
University of Oslo, Norway

MANAGEMENT

The management has the overall responsibility for the day-to-day work performed at the Center.

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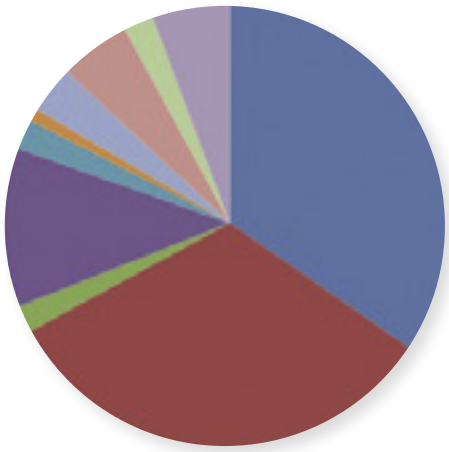
ACCOUNTING

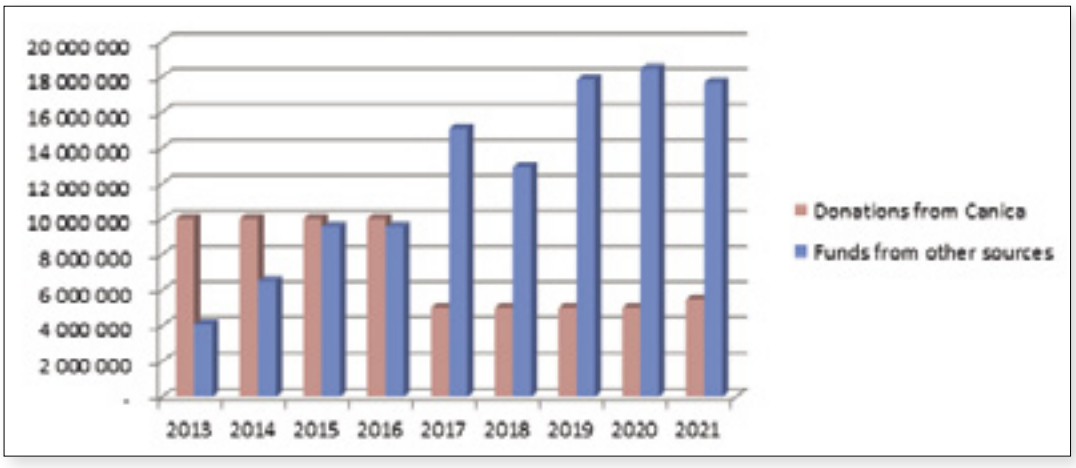
In 2020 the total amount of expenditures within the Center was 23.079.000,- NOK. Of these 8.442.000,- NOK (total expenditure minus other income) were from Canica funding, including 439.000,- NOK gift reinforcement funds from the Research Council of Norway. The remaining 14.637.000,- NOK expenses in 2020 were covered by independent grants, including additional funds from the Research Council of Norway.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	**EXPENSES**	**INCOME**	**EXPENSES**
TRANSFER FROM 2019	-825 123		9 667 530	
INTEREST			65 538	
FROM CANICA			5 500 000	
OTHER INCOME	1 320 090			
TRANSFER FROM UiO	7 566 114			7 566 114
WAGES		2 415 932		873 969
OVERHEAD		284 861		130 611
INFRASTRUCTURE		1 424		179 801
OTHER OPERATING EXPENCES		5 756 985		118 564
TRANFER TO 2021		**- 398 122**		**6 364 009**

	2020
Canica	8 003
S-E Norway Regional Health Authorithy	7 479
Gift reinforcement NRC	439
Norwegian Research Council	2 629
University of Oslo	500
EU funds (Dynaflow)	211
ERC grant	795
Strategic support funds OUH	1 200
ScandPSC	503
Other	1 320
Thousand NOK	**23 079**

This pie chart shows the expenditure distribution between the different funds:





Awards

At the Norwegian Gastroenterology Associations annual meeting at Lillehammer 6th to 8th of February 2020 our PhD student Mikal J. Hole (to the left) received an award of NOK 25.000 for his project “Gut mucosal Klebsiella pneumoniae is a disease modifier in PSC”.

Oslo University Hospital awards outstanding research articles twice a year. In spring 2020 the article “Genomewide Association Study of Severe Covid-19 with Respiratory Failure” in the New England Journal of Medicine received the prestigious award of NOK 50.000. Marit Mæhle Grimsrud received the prize on behalf of the authors from NoPSC; Marit Mæhle Grimsrud, Johannes R. Hov, Trine Folseraas and Tom Hemming Karlsen.

NoPSC and Covid-19 research

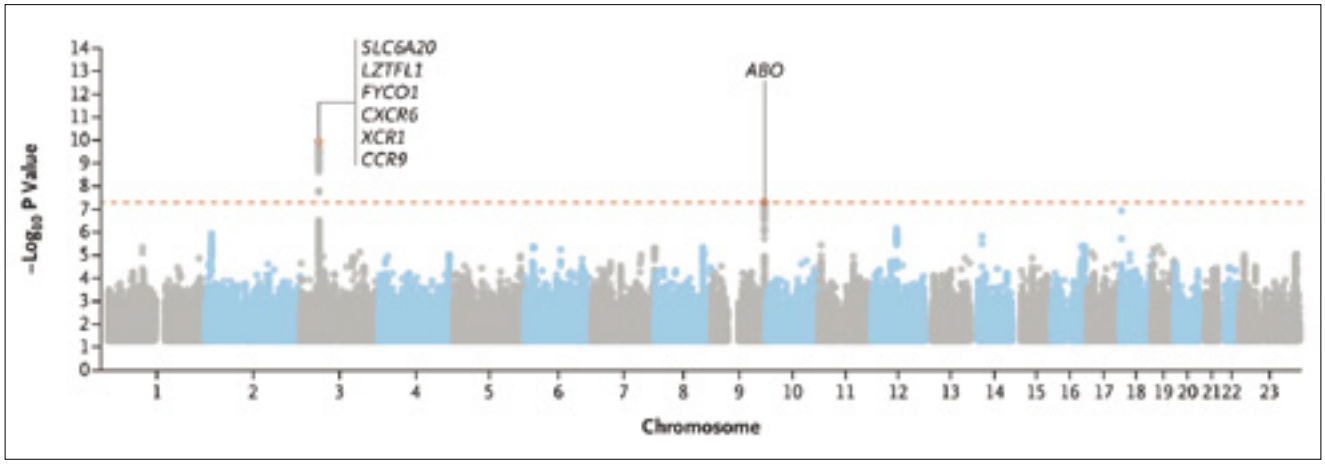
Johannes R. Hov and Trine Folseraas

Laboratory personnel in Italy preparing samples to send to Kiel

Covid-19 has made a major impact on all aspects of society and 2020 became a most unusual year. It has also been an extraordinary year for medical research. Extensive efforts from many groups have proven the fantastic potential in molecular medicine, from the early publication of the SARS-CoV-2 DNA sequence in 3-D models to finalization and approval of highly effective vaccines in less than a year. Other areas of research have not been that successful, with some important exceptions, few drug therapies have been really effective. In part, we could speculate that major efforts by smaller, very strong individual groups are what is necessary for breakthroughs in biochemistry and molecular biology, while large-scale clinical trials needed for therapeutic interventions require multicenter, cross-border collaborations that are more challenging to develop and maintain during a pandemic.

International collaborations on genetic studies have been one of the major successes in PSC research spearheaded by the Norwegian PSC Research Center and forming the basis for the International PSC study group. As Covid-19 hit Norway early March 2020, the SARS-CoV-2 virus itself had limited relevance for the ongoing PSC projects at the center. However, the leader of the center soon realized that we, based on our expertise, could give a meaningful contribution to better understand the severe disease outcomes of the virus. From his previous position as Secretary General of the European Association for the Study of the Liver (EASL) he had multiple hepatology contacts in Italy and Spain, where Covid-19 was at its epidemic maximum, and who had the possibility to provide samples from large numbers of severely affected Covid-19 patients. Our close friends and collaborators in Kiel, Germany were less affected at the time and were be able to receive and analyze these samples for genetic studies. The key question was; Why do some patients with Covid-19 develop severe pulmonary disease while some do not? Could this be due to predisposing genetic risk factors? Karlsen initiated the study and wrote the project proposal. The study was soon approved by ethical committees at all centers. Necessary funding was given as additional support from Canica A/S. More than 50 clinicians at seven hospitals in Northern Italy and Spain included in total around 2000 patients with severe pulmonary Covid-19, as defined by respiratory failure, i.e. the need for oxygen supply or respiratory support like a ventilator. Blood samples were sent to Kiel and millions of genetic variants across the entire genome were investigated and compared with a control group in a standard genome-wide association study. An analysis and writing group was in parallel established with participants from Kiel and Oslo.

The final results uncovered two regions (loci) of the genome where some genetic variants were more common in patients with severe pulmonary disease compared to the control population. The strongest risk factor was seen at chromosome 3, where several genes may be involved either as mediators of inflammation or they may change how the virus enters host cells. The other risk factor was in fact blood group status, where blood group O seems to be protective. The study was published in the highest ranking medical journal in the world, New England Journal of Medicine, in June, less than 3 months after the project was initiated. Later in 2020 additional studies started to emerge, confirming both these findings, suggesting that the chromosome 3 variant is a key risk factor for severe Covid-19 with pulmonary affection, while the ABO blood group system seems to influence the risk of actually being infected by the virus.



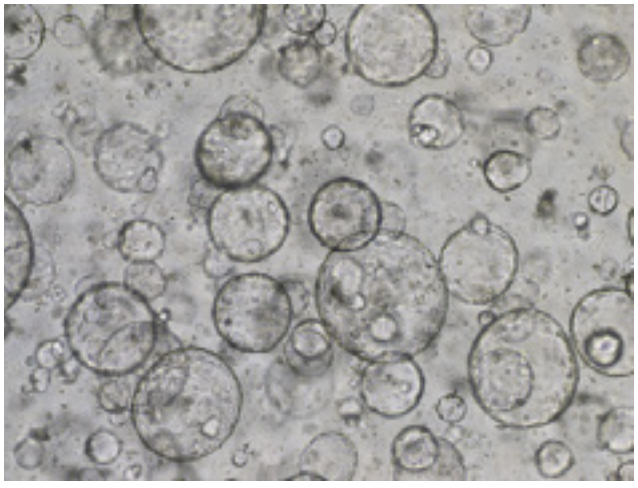
Manhattan plot showing the two susceptibility loci for Covid-19 from the NoPSC-led international project. The gene cluster on chromosome 3 associates with severe Covid-19, and the ABO blood type locus associates with risk of SARS-CoV-2 infection.

DUCT chip – PSC studies using a bile duct on a chip

Espen Melum

PROJECT BACKGROUND

Studies of the immunology in the bile ducts are a prerequisite for developing immune based therapies aiming to treat immune driven conditions such as primary sclerosing cholangitis (PSC). As in many related fields, animal models are still the gold standard for investigating immunological events ongoing during biliary disease progression. Many existing mouse models which are currently used to study these diseases fail to recapitulate all aspects of complicated diseases like PSC and can only allow small insights into the full pathology of these diseases. Significant differences in the disease progression and immunology between different species (mouse vs human), as well as technical challenges in reaching narrow structures as the bile ducts *in vivo*, further complicate our research.



Culture of cholangiocyte organoids

In vitro "Organ-on-a-chip"-technology, in which several cell populations can be assembled 3-dimensionally according to their actual *in vivo* microarchitecture, offers exciting new opportunities to remodel and understand disease progression in a highly manipulative and simplified way. Major advantages of these technologies are highly variable experimental conditions, the possibility to perform high-throughput pharmaceutical screenings, and the possibility to perform live-time imaging of ongoing events on a cellular level without technical challenges.

BILE DUCT ON A CHIP

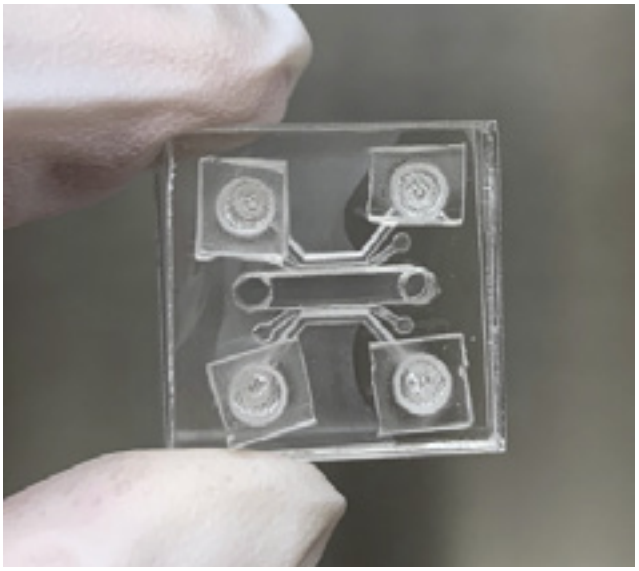
We aim to establish an *in vitro* microfluidic "bile duct on a chip" model that we have named the "DUCT chip". This model will contain all main cell types of the bile ducts and the liver sinusoids and closely resemble the *in vivo* microanatomy of the hepatic and biliary tissue. Primary cholangiocytes will be brought together with other primary liver cells into a double perfusable 3-channel system mimicking the bile duct, liver sinusoid and hepatic tissue. The chip will be perfused with bile and immune cells to establish an *in vitro* system closely modelling the *in vivo* situation in the bile ducts. Additional flow via the sinusoidal channel will offer fresh oxygen and nutrient supply to the cells and resemble the *in vivo* blood flow.

The DUCT chip will then be used to model immunological events ongoing during disease progression in the bile ducts and aid our understanding of fundamental cell specific mechanisms of disease progression. The system could further be used for high-throughput screening of new potential pharmacological approaches for diseases like PSC and PBC and thus fill the current gaps between drug testing in animal models and human clinical trials.

PROJECT STATUS 2020

A new line of collaboration with Prof. Stefan Krauss at the Hybrid-technology-hub at the University of Oslo was started in 2019. Mathias Busek joined our collaborators at the Hybrid-technology-hub as a postdoctoral fellow in March 2020 and started the microfabrication of various microfluidic and chip-based designs. Post-Doc Anna Frank re-joined NoPSC at the same time and started first trials for developing these human and murine biliary *in vitro* models. Using our previously established methods of culturing primary human or murine cholangiocytes under 3-dimensional conditions in form of organoids, we are now able to expand primary cholangiocytes at large scales

in vitro. Cells can be isolated from patients during routinely performed procedures (ERCP brushings), brought into cell culture and expanded according to specific needs, thereby offering possibilities to perform personalized *in vitro* studies. Using both human and murine cells will aid in the cross-validation of possible findings from the DUCT-chip in our established animal models.

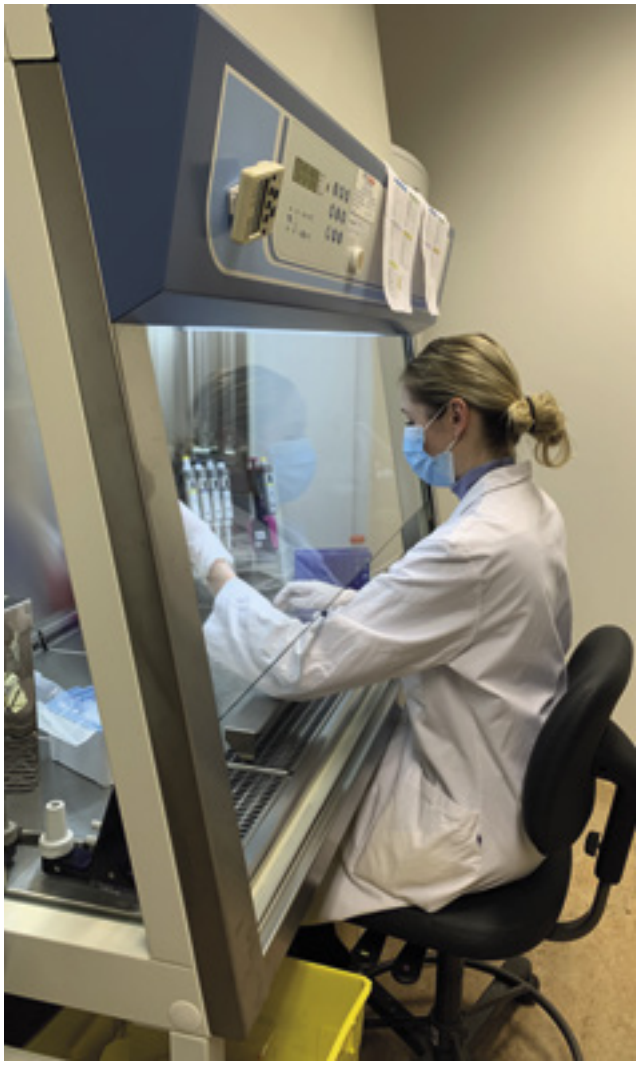


3-channel perfusable microchip

Primary liver cells needed to establish a liver-sinusoid-on-a-chip can be obtained and cultured using pre-established protocols. Our current project focus lies in the construction of stable and perfusable artificial bile ducts on a chip, which then in a next step will be extended to a model that includes the liver sinusoids and immune cells. Using different combinations of extracellular matrix components (laminin, collagen I and IV and Matrigel) and various chip designs, we achieved confluent attachment of primary human or murine cholangiocytes which tolerate culture under fluidic conditions. Small adjustments of the current chip design will be necessary to obtain stable channel barrier function. Parallel ongoing experiments with co-cultures of primary hepatocytes and liver sinusoidal endothelial cells in the chips have been performed.

FUNDING

Anna Frank is currently financed by a Scientia Fellowship, jointly financed by Canica through NoPSC and UiO. In December 2020, Espen Melum received funding from the Norwegian Research council for the project “DUCT chip – Immune studies using a bile duct on a chip”, which will provide funding for 2 new post-doctoral fellows and 1 PhD student for the project within the next years. The project also received additional innovation funding from the University of Oslo in November 2020, which will allow us to employ a temporary technician for cell culture-based laboratory work. Possible candidates for one post-doctoral position and the technician position will be evaluated in 2021. These awarded grants will allow a tremendous future expansion of the project, including cross-validation of possible findings from the DUCT-chip in our established animal models and pharmaceutical testing using the established DUCT-chip.



Post doc Anna Frank working with organoids

EXPERIMENTAL LIVER RESEARCH GROUP

From top left: Anna Frank, Xiaojun Jiang, Laura Valestrand, Anne Pharo, Espen Melum, Kari Otterdal, Kathrine Sivertsen Åsrud, Oda Helgesen Ramberg (new lab. manager), Tine Simensen Oldereid and Jonas Øgaard

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The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2020, the group consisted of the group leader, two senior researchers, two postdocs, four PhD students, the lab manager and one part-time technician. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome. Recently, we have also started to incorporate aspects of regenerative medicine. Our tools to

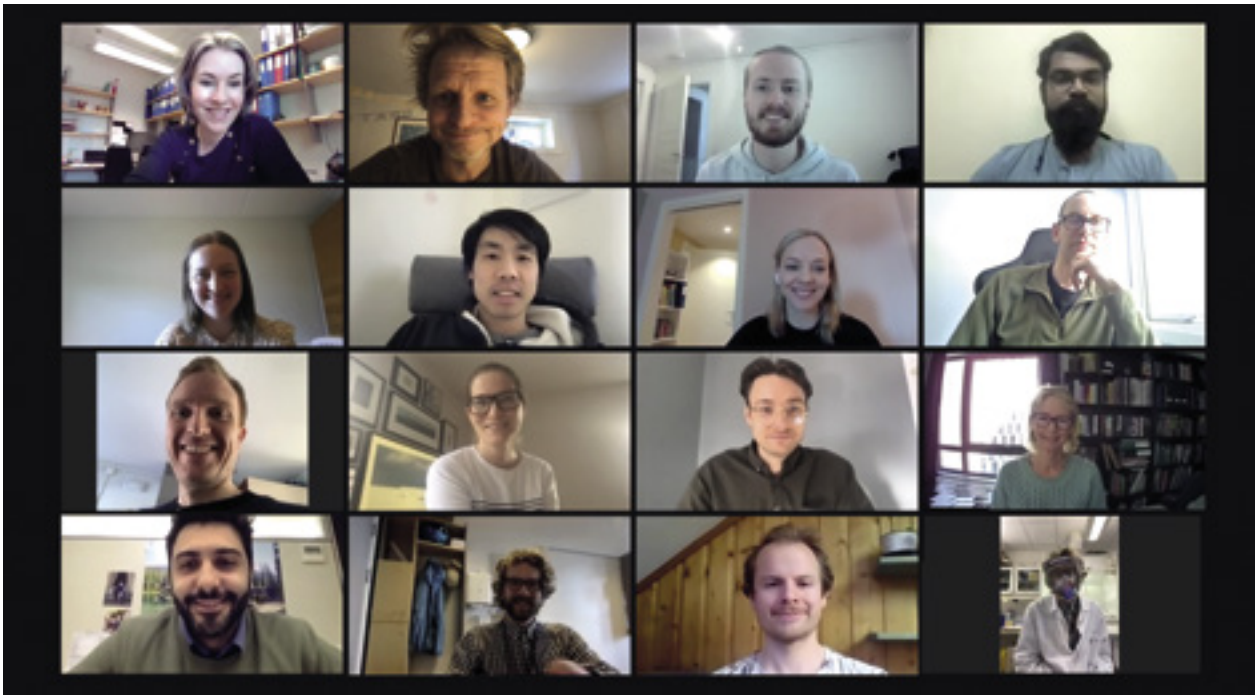
achieve this aim is to use patient material, animal models, advanced cell-culture in terms of organoid technology and recently organ-on-a chip systems.

During the last years one of our major lines of research has been to clarify the regulatory role of unconventional T-cells in bile duct inflammation and in 2020 we published a report demonstrating the presence of antigens activating natural killer T (NKT)-cells in bile. Similarly, we also demonstrated in another project that antigens for mucosal associated invariant T (MAIT)-cells are also present in bile and are defined by the microbiome. Extensive animal experiments clarifying the role of NKT-cells during cholestasis were also performed in 2020 focusing on CD1d on the bile duct epithelium and the contribution of type 1 vs type 2 NKT cells. Another major topic of our immunology studies has been the role of CD100, which we have found to regulate cholangitis in a familiar form of PSC, and in 2020 we have expanded our molecular understanding on how CD100 affect immunological function. In our studies using germ-free animals we have continued the work on clarification on how the timing of introduction of the microbiome affects the development of bile duct inflammation in the NOD.c3c4 model, that we have previously shown to be partly dependent upon the presence of bacteria. We have also performed ground-work using *in vitro* studies on metabolites in fecal material that will form the basis for *in vivo* mechanistic studies in 2021.

In 2020 we also generated the first prototypes for a bile duct on a chip together with the rest of the team at the Hybrid-technology-hub, Faculty of Medicine, University of Oslo. 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. As part of the expansion on the activities related to organoids, senior researcher Kari Otterdal has been engaged in this project.
Our RNA-based sequencing technology approaches were also expanded in 2020, with the establishment of spatial sequencing, which will be used by several projects in the experimental hepatology group and also by other projects at NoPSC. Jonas Øgaard, who has been in the group for several years as a technician, started his master project where he will investigate the spatial and temporal transcriptomic landscape of cholestasis using this technology.

Besides a little downtime in March-April 2020, the ongoing COVID-19 pandemic has not led to any major delays or reduction in scientific productivity for the group. Towards the end of the year, we received innovation funding 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.

GENOMICS AND METAGENOMICS RESEARCH GROUP



From top left: Hanne Guldsten, Johannes R. Hov, Peder Braadland, Sajan Raju, Marit Mæhle Grimsrud, Brian Chung, Beate Vestad, Kristian Holm, Martin Kummen, Lise Katrine Engesæther, Mikal J. Hole, Liv Wenche Thorbjørnsen, Marco Sanduzzi Zamparelli, Georg Schneditz, Simen Hyll Hansen and "the ideal lab worker"

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how alterations in the human genome and the gut microbial flora influence disease. We do this by applying modern

genotyping and sequencing technologies, as well as metabolomics. Increasingly, experimental approaches in vitro and in vivo are also relevant.

The main current interest of the group is the role of the gut microbiota in multiple inflammatory disease phenotypes, with a particular focus on primary sclerosing cholangitis (PSC). The main research agendas relevant for PSC are:

1) *Functional microbiomics*.
   Do differences in microbial functions and activity have clinical implications in PSC patients? We aim to delineate functional alterations of the gut microbiome by applying gut microbial profiling or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity. A major project on this was concluded with a Gastroenterology paper published online late 2020, showing that microbial metabolism of essential nutrients were altered, with vitamin B6 highlighted as particularly interesting.
2) *Recurrent PSC.*
   Recurrence of PSC after liver transplantation is a significant clinical problem, the extent of which is still not fully elucidated. This is a growing priority in the group, being the focus of an ERC Starting Grant and two independent PhD student projects. The expected outcome of this research axis is both updated epidemiological data, as well as extensive insights into pathogenetic and clinical/therapeutic aspects of this condition.
3) *Bioinformatics and biostatistics.*
   How can we apply advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome studies? This is a focus of a new PhD project involving a large cohort of patients with the PSC associated inflammatory bowel disease. In 2020, the major focus has been primary handling of the thousands of samples planned for.
4) *Post-genetic studies.*
   Could autoimmunity in PSC originate in the gut? "Identifying exogenous drivers of autoimmunity in the gut microbiome" is one of the active projects, while further studies of GPR35 in inflammatory disease are also ongoing.
5) *Clinical microbiota medicine.*
   Interventions targeting the gut microbiome to treat disease may provide substantial evidence of causal relationships between the gut microbiome and disease. This is a key topic of the Strategic research area at Oslo University Hospital that was awarded to the group in 2019, *"Personalized microbiota therapy in clinical medicine"*. The work has gained momentum and with the hiring of a national expert on fecal microbiota transplantation in 2020 (PHJ) we believe the formal establishing and start-up of a donor bank will take place in 2021.

FUNDING

The people in the group were in 2020 funded by one ERC Starting Grant, one grant from the Research Council of Norway (closing 2020), seven PhD or postdoc grants and one network grant from Regional Health Authorities of South Eastern Norway, one Strategic research area grant in Oslo University Hospital, in addition to Canica, funding one bioinformatician, and Nordforsk, funding one engineer. In a collaboration with the Experimental group and partners from the Baltic area (driven from Lithuania) we also received in 2020 funding from the EEA Baltic research funds, which will fund one post doc from 2021.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group is closely integrated with the clinical microbiology and microbiota medicine group, it has extensive collaborations ongoing within the Research Institute of Internal Medicine, multiple clinical research groups as well as pathology and radiology. A strong link to the experimental groups is also important, providing opportunities to understand disease mechanisms in more detail.

Regionally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator. Unfortunately, an annual ReMicS retreat was cancelled due to Covid-19, while we were able to host the seventh national conference on gut microbiota as an online event in November 2020.

Internationally, we continue multiple strong collaborations both within and outside the International PSC Study Group.

CLINICAL RESEARCH GROUP IN OSLO

From top left: Guri Fossdal, Merete Tysdahl, Marit Mæhle Grimsrud, Liv Wenche Thorbjørnsen, Siv Furholm, Kirsten Muri Boberg, Vemund Paulsen, Lars Aabakken, Erik Schrumpf, Trine Folseraas and Kristine Wiencke

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RESEARCH PROFILE

The projects of the Clinical PSC Research Group in Oslo aim at improving clinical outcomes for PSC patients. Over the last years we have had a particular focus on identification of early detection markers and treatment targets for PSC-associated biliary tract cancer.

Identification of early detection markers for PSC-associated biliary tract cancer.
We have several efforts ongoing exploring novel markers for early and more accurate detection of biliary tract cancer in PSC. In collaboration with the Epigenetics Group at the Department of Cancer Prevention, Institute for Cancer Research at the Norwegian Radium Hospital, we have analyzed a panel of DNA methylation markers in bile samples collected from more than 300 Norwegian, Swedish and Finnish

PSC patients. Findings strongly suggest that analyzing aberrant DNA methylation utilizing bile as liquid biopsy material may improve and complement current detection methods for cholangiocarcinoma (CCA) (manuscript under revision). New projects aiming at identifying additional markers for sensitive CCA detection are ongoing.

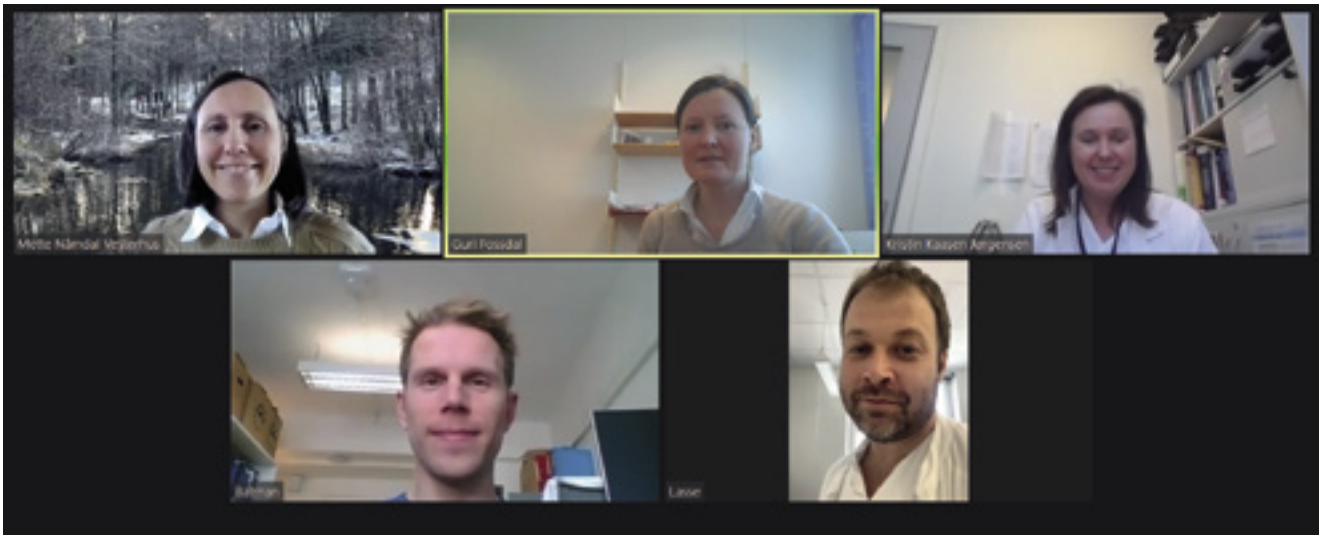
Molecular characterization and identification of drugable targets in PSC-associated biliary tract cancer.
In collaboration with IPSCSG and the Department of Pathology at the University Hospital of Heidelberg, we have established a large international collective of more than 180 tissue samples derived from PSC-patients with CCA from Europe and the US. In addition to histomorphological characterization, we performed tumor DNA sequencing at 42 known cancer-related genetic loci to detect mutations. The emphasis made in this project, for known cancer-related genes, allowed us to detect many putative therapeutic targets. This opens up for early phase clinical trials of molecular target drugs and personalized cancer treatment in PSC-associated biliary tract cancer. Furthermore, we demonstrated that CCA in PSC shows a distinct and homogeneous molecular and morphological phenotype, reminiscent of extrahepatic CCA. This work was published in Hepatology in 2020 (see section on highlighted publications in 2020). Future projects utilizing this valuable tissue collective is underway, including a more extensive genomic profiling effort in PSC-CCA.

Continued systematic biobanking and registration of clinical data on PSC patients and related collaborational projects.
The cross-sectional biobank and database of the Norwegian PSC Research Center is steadily growing (currently including clinical data and biological samples on close to 800 Norwegian PSC patients), and represent a valuable source for PSC research both nationally and internationally. We actively facilitate research on characterization, management and treatment of PSC and biliary tract cancers among others in collaboration with the National network for autoimmune liver diseases (see separate section from the clinical group in Bergen), the International PSC Study Group, the European Network for the Study of Cholangiocarcinoma and the COST-action on cholangiocarcinoma (see key collaborators below).

KEY COLLABORATORS

- The Department of Pathology, Oslo University Hospital, Rikshospitalet
- The Epigenetics Group at the Department of Cancer Prevention, Institute for Cancer Research, the Norwegian Radium Hospital
- Karolinska University Hospital, Stockholm, Sweden
- Helsinki University Hospital, Helsinki, Finland
- The Department of Pathology at the University Hospital of Heidelberg, Germany
- The Mayo Clinic, Rochester, USA
- The International PSC Study Group (IPSCSG)
- European Network for the Study of Cholangiocarcinoma (ENSCCA)
- The COST Action CA18122 EURO-CHOLANGIO-NET

CLINICAL RESEARCH GROUP IN BERGEN



From top left; Mette Vesterhus, Guri Fossdal, Kristin Kaasen Jørgensen, Anders B. Mjelle and Lasse M. Giil

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RESEARCH PROFILE

The main focus of the Clinical Research group in Bergen is the identification, evaluation and establishment of prognostic biomarkers and surrogate markers of disease activity and severity in PSC. We collaborate closely with the Metagenomics and Clinical groups in Oslo. The establishment of a large, prospective biobank and patient cohort is an important strategic aim in order to achieve the goals of establishing biomarkers to predict clinical outcome and improve our efforts to select and include PSC patients into clinical trials.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS IN PSC

We were the first to identify and validate the ELF®Test as an independent prognostic marker in PSC. The ELF test has status as an approved method in Norway based on a Health Technology Assessment report referring our research, and we are promoting the establishment of the ELF test for use in clinical practice in Norway. We have also contributed raw data to an application to the FDA aiming for obtaining biomarker qualification for the ELF test. We are now analyzing the year-to-year variation of ELF test compared to ALP and liver stiffness in PSC patients in a prospective study.

In collaboration with corporate partner Nordic Biosciences in Denmark and the Royal Free Hospital (London, UK), we have explored

novel, more specific and dynamic biomarkers of fibrosis in PSC, revealing interesting differences compared to other autoimmune liver diseases. Currently, we are exploring a broad biomarker panel reflecting suggested disease pathways in PSC. Preliminary results indicate that a combination of markers of inflammation and fibrosis increases our ability to capture disease risks and outcomes in patients.

IMAGING AND ARTIFICIAL INTELLIGENCE

Through a strategic collaboration with the Mayo Clinic, NoPSC is participating in studies involving artificial intelligence techniques investigating MRI in PSC. Two papers have emerged from this collaboration and a large study is ongoing. We are contributing to ongoing MRI-related studies initiated through the International PSC Study Group (IPSCSG). Due to the covid-19 pandemic, the 2020 annual meeting of the IPSCSG MRI Working Group was converted to a virtual meeting, but the next meeting is planned for Oslo in 2021.

Liver stiffness measurements using ultrasound elastography is one of the top candidate prognostic biomarkers in PSC. We have previously shown that the feasibility and reliability of liver stiffness measurements are reduced in the left compared to the right liver lobe in PSC. In a recent paper (2020), we have demonstrated good feasibility for three principally different ultrasound elastography techniques in PSC; however, indicating slightly poorer performance for one of the techniques (2D-SWE) which warrants further investigations. PhD student Anders B. Mjelle delivered his thesis on this project in 2020.

CLINICAL TRIALS

It is an important aim for NoPSC to contribute to drug development for PSC through the participation in clinical trials. The prospective cohorts also serve as a recruitment basis for clinical studies. NoPSC is currently involved in a phase III clinical trial for nor-ursodeoxycholic acid, with patients participating from Bergen, Ahus and Rikshospitalet. Funded by a recent Helse Vest grant and building on existing collaborations within the National network for autoimmune liver diseases, we are now planning a multicenter, proof-of-concept investigator-initiated clinical trial. In this project, we aim to investigate the effect and explore the mechanisms of a novel drug targeting pathways that are also involved in the promising effects of fibrates in other clinical trials in PSC.

NATIONAL NETWORK FOR AUTOIMMUNE LIVER DISEASES AND SCANDPSC

The National network for autoimmune liver diseases is a multicenter study including a research registry and a prospective research biobank for non-transplant patients with PSC, PBC or autoimmune hepatitis. The project comprises annual collection of data, imaging and biobanking as well as fecal samples for microbiota studies and patient-reported outcomes. It is approved for 10 years until 2029.
Formal establishment in March 2019 followed development and piloting of a web-based eCRF for data collection. The eCRF provided by VieDoc uses a platform with approval in all Norwegian health regions. In 2019, we were happy to attract funding from the Halloran Family Foundation, allowing us to establish the Prospective Scandinavian PSC biobank (described separately) as a further expansion of this prospective biobanking initiative.

Patient inclusions were initiated at Lovisenberg Deaconess Hospital in the fall of 2020, whereas the Covid-19 pandemic precluded most of the other planned expansions in 2020. Thus, there are now 4 actively recruiting centers and 225 PSC patients and 10 AIH patients are included. Expansion is expected to accelerate in 2021 as the burden on local laboratories and staff posed by the pandemic is reduced. In order to facilitate start-up at novel centers, Kristin K. Jørgensen will take the position as Project coordinator.

KEY COLLABORATORS

- UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, UK
- Nordic Biosciences, Denmark
- The Mayo Clinic, Rochester, USA
- Karolinska Institutet, Sweden
- International PSC Study Group (IPSCSG)
- Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, Haukeland University Hospital, Bergen

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

PROJECT BACKGROUND

Strategic Prospective Scandinavian PSC Biobank (ScandPSC) , funded by the Halloran family foundation, merges two strong scientific environments in Norway and Sweden with well-established PSC biobanks and more than 30 years of legacy in a collaborate effort to collect a large prospective biological and clinical sample collection. Scandinavia is a geographical “hot-spot” for PSC, with a high willingness in patients to participate in research studies and very good healthcare infrastructures coupled to unique national registries, altogether providing ideal conditions for high-quality, well-powered prospective studies.

PROJECT STATUS 2020

The prospective cohort includes biobank serum samples from 355 PSC patients, of which 225 in Norway and 130 in Sweden. One novel center started active patient inclusion in Norway in 2020, and a patient information folder in Norwegian and Swedish versions was published in 2020. Following the complete ban on clinical research activity in the spring of 2020 in Norway, the Covid-19 pandemic continued to severely affect the capacity of laboratories, study personnel and lead physicians at collaborating centers in both Norway and Sweden throughout 2020, leading to delays in the planned expansion to novel centers. By the end of 2020, agreements were made for novel project coordinators in Norway and Sweden in preparation for expansion to catch speed in 2021.

ECONOMY

Exspenses 2020		
Karolinska	kr 379 377	Salary and running costs
Bergen	kr 103 186	Salary
AHUS	kr 15 180	Test tubes
NoPSC	kr 2 450	Information folder
NoPSC	kr 2 423	Travelling
Sum expenses	**kr 502 616**	
Donation	kr -2 062 207	
Tranfer to 2021	**kr -1 559 591**	

In view of the challenges in successfully filling the project coordinator positions in both countries, a restructuring of the budget has been decided for 2021.

EXPANSION PLAN

In Norway, start-up is imminent at Bærum Hospital and several new centers, primarily in the South-East Health Region, which are actively preparing to start patient inclusion in 2021. Furthermore, additional patients will be recruited in the 4 existing active centers. In Sweden, recruitment of new patients is planned at Karolinska Institutet & Karolinska University Hospital throughout 2021 and all 7 university hospitals in Sweden are expected to start data collection and biobanking during 2021.

MANAGEMENT GROUP (LEADERSHIP TEAM)

Mette Vesterhus, Associate Professor, MD, PhD
Haraldsplass Deaconess Hospital, Bergen, Norway

Annika Bergquist, Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

Tom Hemming Karlsen, Professor, MD, PhD
Oslo University Hospital, Norway

Niklas Björkström, Associate Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

STEERING COMMITTEE

National PI Annika Bergquist (Sweden) and Mette Vesterhus (Norway), and lead physicians from collaborating centers (CI) in Norway and Sweden.

FUNDING

The project is funded by a generous donation from the Halloran family foundation.

MONITORING BOARD

The Monitoring Board of the Norwegian PSC Research Center (NoPSC) will oversee the management of the funds.

BIOBANK

The biobank comprises:

- Serum
- EDTA blood
- Feces
- Comprehensive biobaking at selected centers

The biobank material is prospectively collected at annual intervals.

The biobank is physically centralized to the fully automated Biobank Haukeland in Bergen for Norway and to a study specific ultra-freezer at Karolinska University Hospital for Sweden. Biobank material is transferred from participating centers at regular intervals.


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Highlights 2020

NOPSC RETREAT

NoPSCs annual retreat for 2020 was held at Holmenkollen Park Hotel in January. This year each research group invited a guest lecturer; Trine B. Rounge, Annika Bergquist, Andreas Abildgaard and Stefan Kraus. The guest lectures were followed by an update from the research groups. The retreat also included workshops and social activities. (1)

NORWEGIAN GASTROENTEROLOGY ASSOCIATION

Mette Vesterhus was leader of the Norwegian Gastroenterology Association (Norsk Gastroenterologisk Forening, NGF) in 2020. NoPSC had a large presence at the annual meeting at Lillehammer 6-8th of February 2020, and presentations where held by Kirsten Muri Boberg, Mette Vesterhus, Kristin Kaasen Jørgensen and Katrine Engesæter (2). Our PhD student Mikal J. Hole received a grant of NOK 25.000 for his project “Gut mucosal Klebsiella pneumoniae is a disease modifier in PSC”.


2

BIOMED ALLIANCE

In 2020 Tom Hemming Karlsen became a bord member of the Biomed Alliance: https://www.biomedeurope.org/

The Biomedical Alliance in Europe (BioMed Alliance) is a non-profit organisation representing 36 European research and medical societies uniting more than 400,000 researchers and healthcare professionals. Aiming to promote excellence and innovation in the European healthcare field with the goal of improving the health and well-being of all European citizens.

MONITORING BOARD MEETINGS

In 2020 the spring Monitoring Board meeting for NoPSC was held 17th of June. The accounting for 2019 and the annual report were presented. The second Monitoring Board meeting took place on the 11th of December 2020, where the budget for 2021 was presented and approved.

GUEST PROFESSOR MEETINGS

A guest professor meeting was planned for March 2020, but had to be cancelled because of the pandemic.

GUEST RESEARCHER

Marco Sanduzzi-Zamparelli (3) from BCLC in Barcelona visited the Hov group for 3 months during the autumn of 2020 (despite the challenges with Covid-19) forming the basis of a collaboration with the center. The visit was both a scientific and a social success.


3

PATIENT BOARD

With the focus on involving patients as active participants in the planning of research projects, we are grateful for the ongoing collaboration with the patient organization (Foreningen for Autoimmune Leversykdommer, FAL). In 2020 the annual meeting to discuss planned research initiatives was unfortunately cancelled due to the Covid-19 situation.

SEVENTH NATIONAL MICROBIOTA CONFERENCE

The 7th National Microbiota Conference was held 16th of November 2020 as a fully digital event, supported by Regional Health South-East Authority and Oslo University Hospital. The event drew close to 160 participants and covered a wide array of topics including microbiome-led mucosal barrier dysfunction, inflammasome activation in Covid-19 patients and gut leakage in heart failure patients. Our postdoc Brian Chung presented the topic: Altered Immune Recognition of Gut Bacteria by Immunoglobulins in Early Systemic Sclerosis. And NoPSC Group Leader Johannes R. Hov co-hosted as before. (4) The event was recorded av can be viewed here; https://microbiota.no/previous-conferences/


4

NEW EMPLOYEES

PhD student Simen Hyll Hansen and Postdoc Peder Braadland joined Johannes Hov's group at NoPSC in 2020. And Anna Frank, formerly a PhD student in Espen Melum's group, joined us again as a Scientia Fellow postdoc from February 2020.

RESEARCH COUNCIL OF NORWAY

In December 2020 Espen Melum received 12 mill NOK from the Research Council of Norway for the project "DUCT chip – Immune studies using a bile duct on a chip". The funding is for 4 years and includes financing of three positions, two postdocs and one PhD student. The project will start in 2021.

DISSERTATIONS

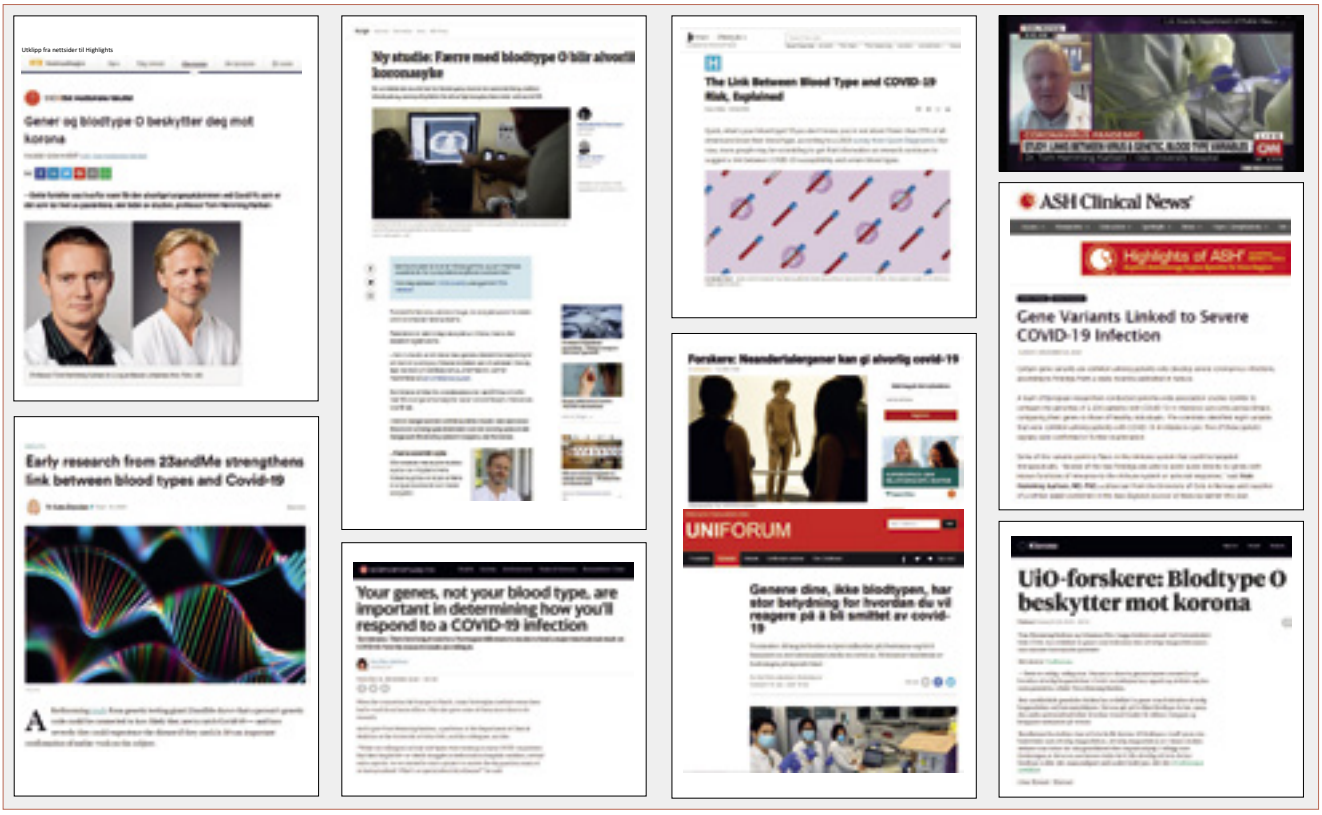
Two PhD students associated with the Hov group defended their thesis in 2020. Magnhild Eide Macpherson defended her thesis «Gut microbiota, lipid metabolism and systemic inflammation in common variable immunodeficiency - A translational research approach» on 16th of September, while Beate Vestad followed up with «Gut microbiota, extracellular vesicles and comorbidities in HIV infection; Exploring the drivers of metabolic disease risk and microbe-host crosstalk» on 30th of October , both with topics and methodology highly relevant for similar work in PSC.

Beate Vestad

Magnhild Eide Macpherson

IN THE MEDIA

Johannes Hov was the main focus on the 9o'clock news on NRK 3rd of June 2020 regarding the GWAS study on severe Covid-19 with respiratory failure, published in New England Journal of Medicine. This initiated a cascade of articles on the web from "Færre med blodtype 0 blir alvorlig coronasyke" on direct news at VG (direkte.VG.no) on the same day, to " UiO-forskere Blodtype0 beskytter mot korona" featuring Johnneas Hov and Tom Hemming Karlsen at the Khrono website 5th of June, "Two genetic regions links with severe COVID-19" with Tom Hemming Karlsen at www.the-scientist.com 8th of June to "Neandertalergener kan gi alvorlig covid-19» at NRK.no 7th of July. These articles where then spread to many other news websites among others; Dagbladet, Nettavisen, Telen, Fjordabladet and ABCnyheter. The intranet pages at OUS also featured this NEJM article under the title "Virkelig dugnadsånd" on the 22nd of June. Also CNN presented the findings from this article, with a short interview with Tom Hemming Karlsen on the 21st of July (archives.cnn.com). The fierce focus on the boodtypes lead to a clearifying article at Sciencenorway.no "Your genes, not your blood type are important in determining how you'll respond to a COVID-19 infection" with Trine Folseraas on the 19th of December 2020.



Networks

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)
The Institute is headed by Prof. Bente Halvorsen and the research groups led by Espen Melum and Johannes E.R. Hov respectively are located at RIIM. Several collaborative projects are established with, among others, Prof. Pål Aukrust, Dr. Børre Fevang, Dr. Thor Ueland and Prof. Bente Halvorsen groups.

Department of Transplantation Medicine
Department Head, Prof. Pål-Dag Line, Dr. Einar Martin Aandahl and Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Rheumatology, Dermatology and Infectious diseases
Ass. Prof. Marius Trøseid is a key collaborator for NoPSC on microbiome studies. Rheumatologists Prof. Øyvind Molberg and Dr. Anna-Maria Hoffmann-Vold also collaborate on immunology and microbiome studies.

Department of Pathology
Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models. Prof. Frode Jahnsen is a collaborator on microbiome studies.

Department of Gastroenterology at Ullevål
Prof. Bjørn Moum, department Head Dr. Asle Medhus and Dr. Marte Lie Høivik are important collaborators on multiple projects including the original IBSEN and the new IBSEN III study.

Department for Comparative Medicine
For many years NoPSC has had a close and productive collaboration with the Department Head, Dr. Henrik Rasmussen and the staff at the animal facility.

Department of Cardiology
Prof. Lars Gullestad is an important collaborator on microbiome of statins and cardiovascular disease.

Center for Clinical Heart Research
Prof. Ingebjørg Seljeflot is a collaborator on circulating biomarkers of the gut barrier.

Department of Infectious Diseases
Dr. Dag-Henrik Reikvam is another key collaborator on gut microbiome studies.

Department of Medical Genetics
The Immunogenetics group, led by Prof. Benedicte A. Lie is involved in several projects related to the further characterization of the HLA association in PSC. The Norwegian Sequencing Center hosts the NoPSC MiSeq next generation sequencing machine.

Institute of Immunology
NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular the good collaborations with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, and the research group of Dr. Fridtjof Lund-Johansen, are important for the activities of NoPSC.

Department of Medical Biochemistry
In conjunction with the establishment of the NoPSC Biobank quality control project the collaboration with Dr. Yngve Thomas Bliksrud is highly appreciated.

Institute for Cancer Research
A collaboration with Prof. Ragnhild Lothe and Prof. Guro Lind, Department of Molecular Oncology at Radium-hospitalet, is the basis for epigenetics-centered projects on early diagnosis of cholangiocarcinoma in PSC.

Department of Radiology
The involvement of the Department of Radiology at Rikshospitalet in the prospective follow-up of PSC patients has been crucial for the success of the initiative. We are particularly grateful to Dr. Andreas Abildgaard, Dr. Knut Brabrand, Vanja Cengija and Gunter Kemmerich for their active contributions.

Department of Paediatric Research
Department head Dr. Runar Almaas is an important collaborator on our livertransplant research and Dr. Gareth Sullivan on regenerative medicine.

Hybrid Technology Hub at University of Oslo
Resent work on organ on a chip includes a close collaboration with the Center of Excellence Hybrid Technology Hub and Center director, Prof. Stefan Krauss.

KEY NATIONAL COLLABORATORS

The IBSEN study group
The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is still important for several of the basic genetic and metagenomic studies at NoPSC.

Akershus University Hospital
The collaboration with Dr. Kristin Kaasen Jørgensen regarding the regional network for Autoimmune Liver Diseases is ongoing and will continue for many years to come. Prof Jørgen Jahnsen's group at Department of Gastroenterology and Dr. Anne Nergård and Dr. Aida Kapic Lunder at the Department of Radiology are important contributors and collaborators in MRI studies in both the IBSEN study and the new IBSEN III study.

Haukeland University Hospital and University of Bergen
For the prospective PSC cohort and advanced imaging modalities there is a close collaboration with Prof. Odd Helge Gilja and several other researchers at the Section for Gastroenterology and the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at the Medical Department at Haukeland University Hospital in Bergen. For the bile acid and microbiota projects Prof. Rolf Berge at the University of Bergen provides the serum lipid measurements.

BEVITAL AS
Prof. Per Magne Ueland and co-workers at BEVITAL are important collaborators in projects related to metabolomic biomarkers, including biomarkers of microbial function.

Haraldsplass Deaconess Hospital
Our leader for the clinical group in Bergen, Mette Vesterhus, has a permanent position at Haraldsplass Deaconess Hospital, hence we have a strong collaboration there too.

KEY INTERNATIONAL COLLABORATORS

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and has also participated in the genetics studies. Associate Prof. Niklas Björkström (Guest Professor at NoPSC) is involved in projects relating to human immunology in PSC. They are both a part of the management group of the Strategic Perospektive Scandinavian PSC Biobank (ScandPSC)

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Prof. Fredrik Bäckhed and Prof. Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed is an expert on gut microbiota, metabolism and gnotobiotic animals and has been an advisor and collaborator on gut microbiota studies in mice, while hepatologist Hanns-Ulrich Marschall contributes with bile acids expertise.

Nordic BioScience, Denmark
Morten Karsdal, CEO of Nordic Biosciences in Denmark, has focused his research on the discovery and development of novel biochemical markers of fibrosis, and collaborates with NoPSC on several projects related to the characterization of fibrosis and the development of new, targeted, PSC-specific fibrosis markers as prognostic tools in PSC.

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arne Nordin), Stockholm (Prof. Bo-Göran Ericzon and Dr. Carl Jorns), Gothenburg (Prof. William Bennet) and Copenhagen (Dr. Allan Rasmussen) are involved in several projects where data from the Nordic Liver Transplant Registry are required.

Institute for Clinical and Molecular Biology, Christian-Albrechts University, Kiel, Germany
Prof. Stefan Schreiber and Prof. Andre Franke's groups in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and metagenomic projects. In addition, Prof. John Baines is an important collaborator in the metagenomic projects.

Universitätsklinikum Dresden, Germany
There is a growing collaborative activity with Prof. Jochen Hampe and Prof. Sebastian Zeissig.

University Hospital Heidelberg, Germany
Prof. Peter Schirmacher, Head of Pathology at the University Hospital Heidelberg in Germany, represent a world-leading center expert in hepatobiliary pathology. Together with postdoc Benjamin Goeppert he provides pathology expertise to collaborational projects related to genomic profiling of PSC-associated biliary tract cancers. In Heidelberg, we also have a strong collaboration with the hepatologists, (PI Christian Rupp) in projects related to circulating biomarkers in PSC.

Department of Internal Medicine I, University of Bonn, Germany
Dr. Tobias J. Weismüller is leading the International PSC Study Group (IPSCSG) database project comprising more than 8000 PSC patients and is an important collaborator within the IPSCSG.

Netherlands, IPSCSG
The secretariat of the IPSCSG has been located in Amsterdam, The Netherlands, since 2018, in the capable hands of Prof. Cyriel Ponsioen and Prof. Ullrich Beuers at the University of Amsterdam's Faculty of Medicine.

Cambridge Institute for Medical Research, UK
The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale, senior researcher James Traherne and Vasilis Kosmoliaptsis in Cambridge is invaluable for the progress of several of our functional genetic projects. Also ongoing collaboration with Dr. Fotis Sampaziotis at Cambridge Biorepository for Translational Medicine and Prof. Ludovic Vallier at the Wellcome - MRC Cambridge Stem Cell Institute has proved extremely valuable regarding organoids and regenerative medicine.

University of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser (former Guest Professor at NoPSC), Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK, is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes; GPR35. This project was funded within the Scientia Fellows' program of the University of Oslo through 2018 and further by the Regional Health South-East Health Authority in Norway and involves postdoc Georg Schneditz and Dr. Nicole Kaneider-Kaser.

University of Birmingham, UK
Prof. David Adams (former Guest Professor at NoPSC) at the Center for Liver Research at the Institute of Biomedical Research, University of Birmingham, collaborate on several projects related to the further characterization of the HLA related immune response in PSC.

Royal Free Hospital London, UK
Prof. Massimo Pinzani (Guest Professor at NoPSC), director of the Institute for Liver and Digestive Health at UCL and the Royal Free Hospital in London, and Dr. Douglas Thorburn at the same institutions, collaborate with NoPSC on projects related to the characterization of fibrosis and the development of novel, targeted, PSC-specific fibrosis markers as prognostic tools in PSC in a tri-party collaboration with Nordic BioScience.

Medical University of Vienna and Medical University of Graz, Austria
In collaboration with Prof. Michael Trauner and Prof. Peter Fickert, ongoing projects aim at crossvalidating findings in mouse models of PSC with human data. Prof. Michael Trauner (former Guest Professor at NoPSC) has extensive experience in animal models of PSC and serves as an important collaborator related to the development of a bile duct specific Cre mouse.

Sapienza, Università di Roma, Italy
Prof. Eugenio Gaudio, Domenico Alvaro and coworkers are experts on biliary tree stemcells, and material from the NoPSC Biobank is used to explore these cells in PSC patients. In addition we have a close collaboration with the COST-Action European Cholangiocarcinoma Network where Prof. Vincenzo Cardinale serves as COST-Action chair.

Biodonostia Research Institute, Donostia University Hospital, San Sebastian, Spain
Dr. Jesus M. Banales is the Head of the Liver Diseases Group at the Biodonostia Research Institute and is also the coordinator of the European Network for the study of Cholangiocarcinoma. Dr. Banales serves as an important collaborator on projects related to PSC-associated biliary tract cancers.

Hospital Clinic of Barcelona, Spain
In 2020 we established collaboration with the Barcelona Clinic Liver Cancer (BCLC) group. This center, now lead by Maria Reig, is world leading on hepatocellular carcinoma research. Key collaborating researcher is Marco Sanduzzi-Zamparelli, who visited NoPSC for 3 months during the autumn 2020.

Toronto Centre for Liver Disease, Toronto General Hospital, Canada
Dr. Gideon Hirschfield (former Birmingham, UK) continues the collaboration with NoPSC regarding characterization of the HLA related immune response in PSC from Toronto. Biostatistician Bettina E. Hansen is leading the statistical analyses of clinical data collected in the International PSC Study Group (IPSCSG) database project, assisted by Dr. Aliya Gulamhusein at the same institution.

The Mayo Clinic, Rochester, USA
Collaboration with Dr. Konstantinos Lazaridis and Dr. Lewis Roberts at the Mayo Clinic in Rochester has been ongoing regarding our projects on the genetics of PSC. Via infrastructure at the Mayo Clinic, DNA from PSC patients in USA and Canada are collected and utilized in local projects as well as for verification of findings in genetic studies at NoPSC.

Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Prof. Richard Blumberg and Dr. Joshua Korzenik are important collaborators in Dr. Espen Melum's projects.

Lithuanian University of Health Sciences, Vilnius, Lithuania
In 2020 we were awarded a grant from the EEA Baltic research funds to the project "Gut-blood-liver axis: Circulating microbiome as non-invasive biomarker for Inflammatory Bowel Disease (IBD) and Primary Sclerosing Cholangitis". Ths project is chaired from Lithuania, where Gediminas Kiudelis is PI, and the project partners include both Latvian (Latvian Biomedical Research and Study Centre) and Estonian (University of Tarty) institutions. The project will run 2021-2023 and involve both the Hov and Melum groups.

Publications 2020

HIGHLIGHTED PUBLICATIONS

Goeppert B[#], **Folseraas T[#]**, Roessler S[#], Kloor M, Volckmar AL, Endris V, Buchhalter I, Stenzinger A, Grzyb K, **Grimsrud MM**, Gornicka B, von Seth E, Reynolds GM, Franke A, Gotthardt DN, Mehrabi A, Cheung A, Verheij J, Arola J, Mäkisalo H, Eide TJ, Weidemann S, Cheville JC, Mazza G, Hirschfield GM, Ponsioen CY, Bergquist A, Milkiewicz P, Lazaridis KN, Schramm C, Manns MP, Färkkilä M, Vogel A, International PSC Study Group; **Boberg KM**, Schirmacher P[##], **Karlsen TH[##]** (2020) [#]/[##] Contributed equally
***Genomic Characterization of Cholangiocarcinoma in Primary Sclerosing Cholangitis Reveals Therapeutic Opportunities**
Hepatology, 72 (4), 1253-1266

Patients with primary sclerosing cholangitis (PSC) have a 20% lifetime risk of biliary tract cancer (BTC) (cholangiocarcinoma and gallbladder cancer), posing an important psychological burden to the patients. Due to difficulties in distinguishing benign from malignant strictures, the cancer diagnosis is often established at a late, non-resectable stage. Whilst increasing insights to cancer biology and opportunities for targeted cancer therapy have been made through efforts like the Cancer Genome Atlas program, BTC from PSC patients are missing from these programs. We collected a large panel of tissue samples from 186 PSC patients with BTC from 11 centers in Europe and the US. In addition to extensive histomorphological and immunohistochemical characterization, we performed tumor DNA sequencing at 42 known cancer-related genetic loci to detect mutations, translocations and copy number variations. The emphasis made in this project, for known cancer-related genes, allowed us to detect many putative therapeutic targets (e.g. ERBB2) also found in other cancers. Furthermore, we demonstrated that BTC in PSC shows a distinct and homogeneous molecular and morphological phenotype, reminiscent of extrahepatic BTC. The tumors exhibited this phenotype independent of the anatomical location of the tumor, i.e. even the 60 tumors with an intrahepatic localization showed histological and mutational characteristics of extrahepatic BTC.

The size of the study alone makes it an important reference point in the field, and the findings advance our understanding of PSC-associated cholangiocarcinogenesis and may provide incentives for clinical trials to test genome-based treatment strategies in PSC-BTC.

Kummen M, Thingholm LB, Rühlemann MC, **Holm K**, **Hansen SH**, Moitinho-Silva L, Liwinski T, Zenouzi R, **Storm-Larsen C**, Midttun Ø, McCann A, Ueland PM, Høivik ML, **Vesterhus M**, Trøseid M, Laudes M, Lieb W, **Karlsen TH**, Bang C, Schramm C, Franke A, **Hov JR** (2020)
***Altered gut microbial metabolism of essential nutrients in primary sclerosing cholangitis**
Gastroenterology, 5085 (20), 35622-5

Everything we eat meets the gut microbes first and is modified by this biochemical factory. A key paper this year was therefore a long-awaited first microbiome study in PSC using full metagenomic «shotgun» sequencing, where sequencing of all bacterial DNA of the stool samples makes it possible to measure the potential microbial metabolism. Importantly, the by-products or «fingerprint» of microbial activity are likely of high importance for human health. In the study we detected major alterations in the bacterial metabolism of essential nutrients like B vitamins and some amino acids. One key example was that genes enabling synthesis of vitamin B6 were reduced in PSC. Vitamin B6 was also reduced in blood, and low levels of this vitamin associated with severe disease. One possibility is therefore that a true deficiency of this vitamin in patients with PSC influences disease. The project was driven by the Hov group with postdoc Martin Kummen as frontrunner, in a close collaboration with our friends in Kiel.

Valestrand L, **Berntsen NL**, **Zheng F**, **Schrumpf E**, **Hansen SH**, **Karlsen TH**, Blumberg RS, **Hov JR**, **Jiang X**, **Melum E** (2020)
***Lipid antigens in bile from patients with chronic liver diseases activate natural killer T cells**
Clin Exp Immunol, 203 (2),304-314

Natural killer T (NKT) cells are an abundant subset of immune cells in the liver. NKT cells are activated by lipids presented on CD1d molecules that are expressed by biliary epithelial cells. In this article we aimed to determine if bile from patients with chronic liver diseases contains lipids that can activate NKT cells. We investigated the presence of lipid antigens in bile collected from the gallbladder of patients undergoing liver transplantation due to end stage liver disease. We found that the patient bile samples contain lipids that activate eight different NKT cell lines and that some of these lipids are highly potent. In a second panel of bile samples, we demonstrated that 12/21 bile samples resulted in activation, of which three gave a strong activation. Four out of twelve activating bile samples contained microbial DNA, suggesting that the activating antigens are of both endogenous and exogenous nature. Our results reveal an immunological pathway that could be of critical importance in biliary immunology.

ADDITIONAL RESEARCH ARTICLES

Primary articles marked with an asterix

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Clin Infect Dis, 71 (8), e359-e367

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Sci Rep, 10 (1), 5397

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Hepatology (in press)

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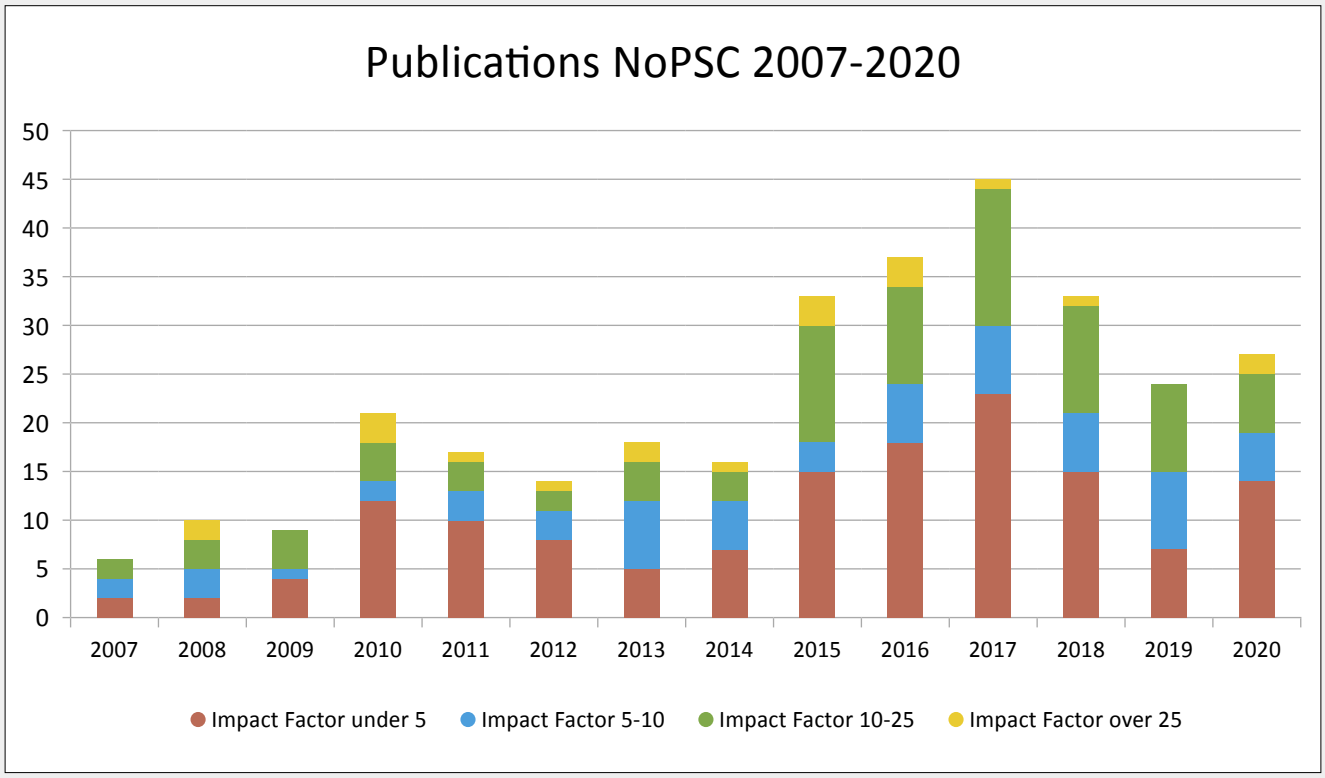

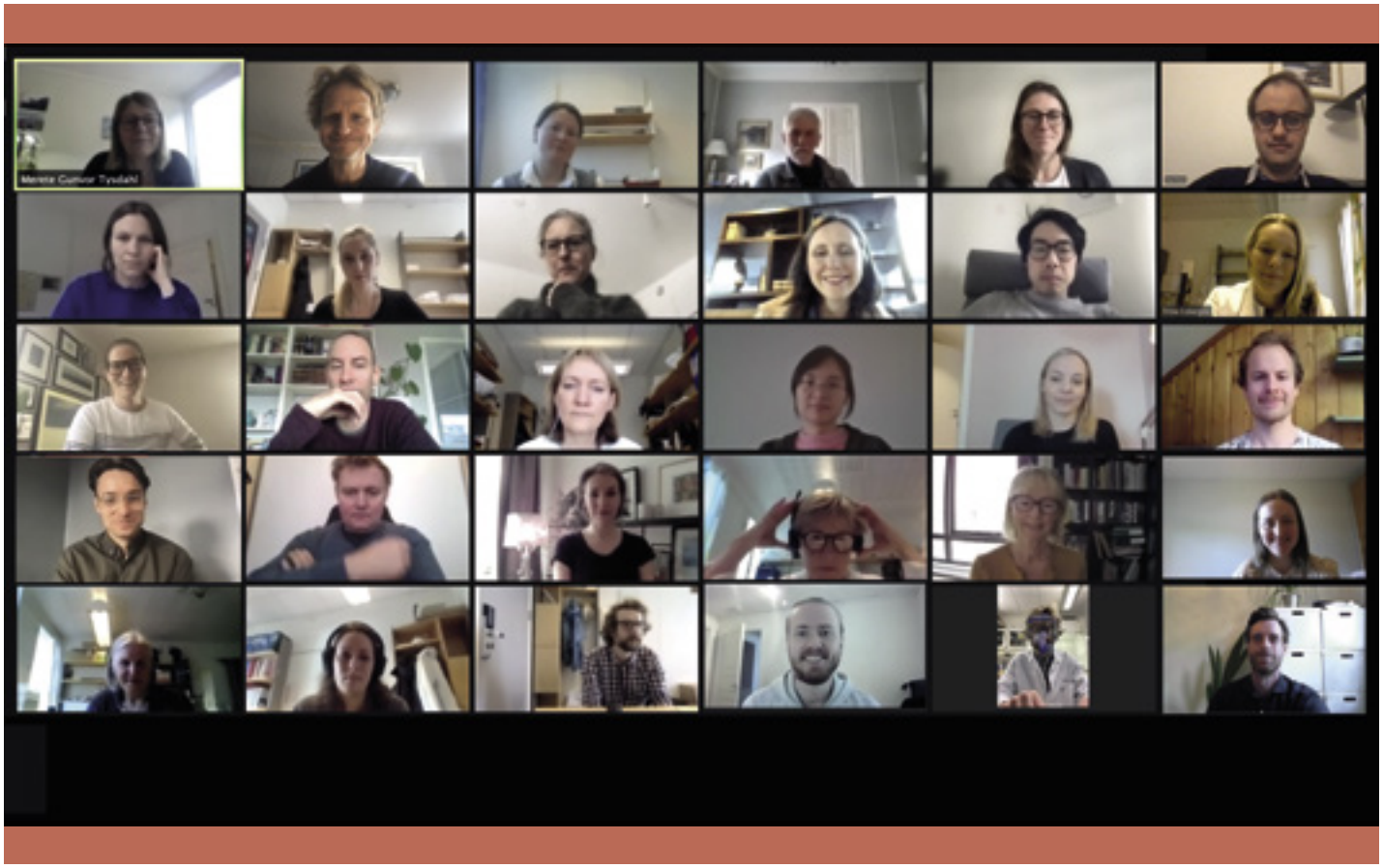

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