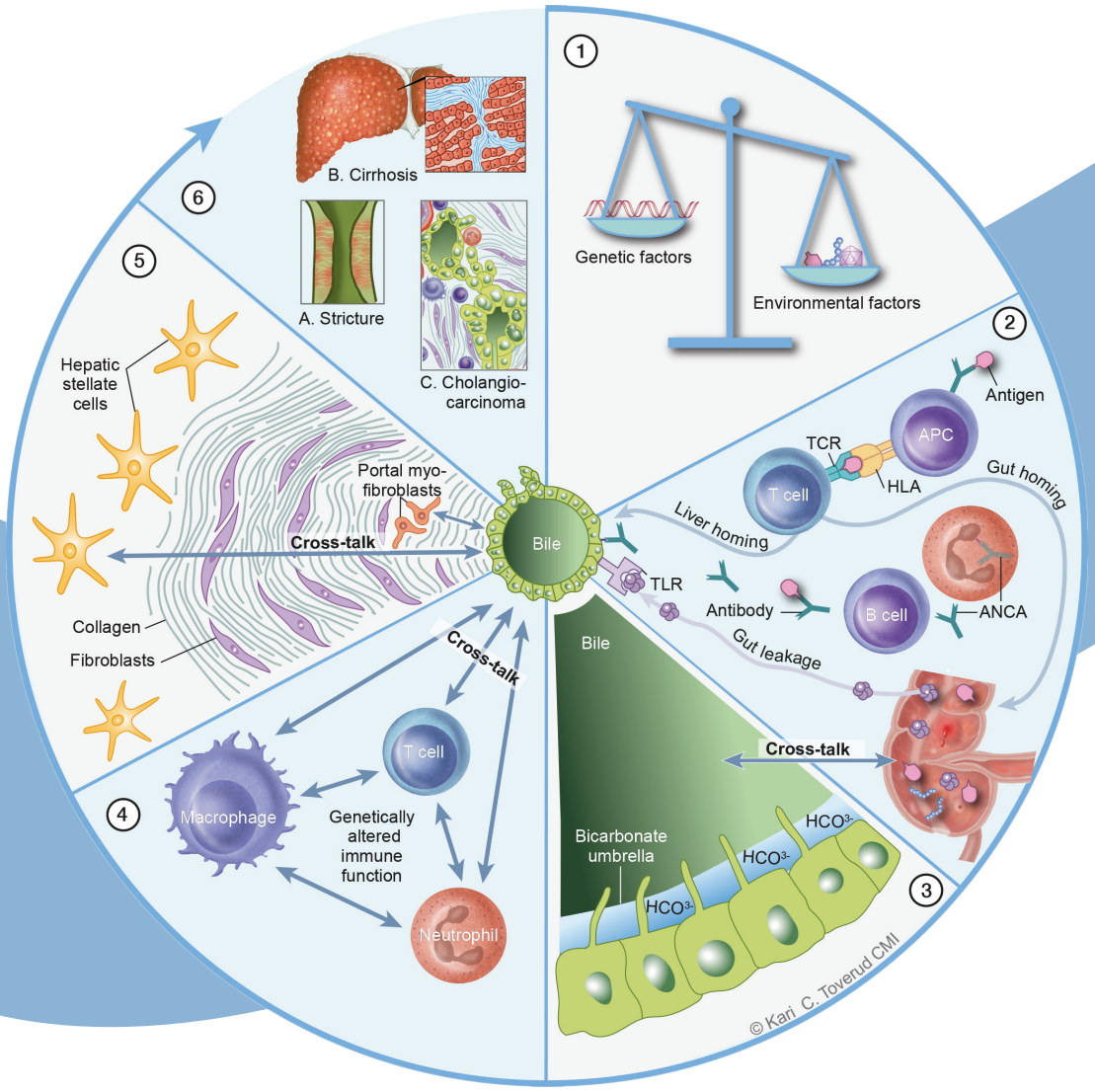
Oslo University Hospital

UiO : University of Oslo



Norwegian PSC Research Center

ANNUAL REPORT 2017

NOPSC

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

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2017

What is PSC?

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

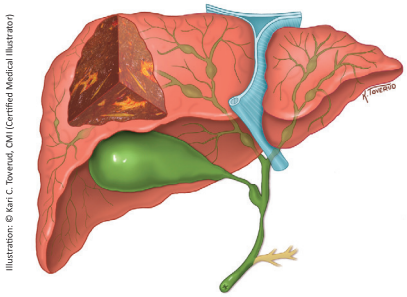
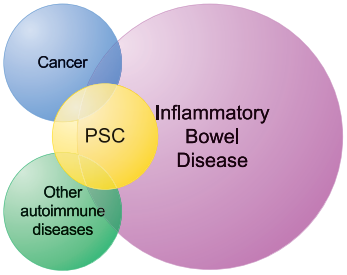


Illustration: © Karl C. Tovenud, CMI (Certified Medical Illustrator)

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 2017

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
FRONT PAGE: *From "Primary sclerosing cholangitis – a comprehensive review", Karlsen et al. J. Hepatol 2017.*
ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*
EDITORS: Tom Hemming Karlsen and Merete Tysdahl
PUBLISHER: Oslo University Hospital
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SAMPLES: 220

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

Leader´s Corner

The year 2017 marked the formal entry to the new 10-year contract period for the Norwegian PSC research center. Thanks to the generous support from Canica AS, now extended for an additional 10 years with the total amount of NOK 50 million, the center will continue its activities at the same level of operations. From the pie chart on page 6 showing the distribution of funds for NoPSC, it goes without saying that without the support from Canica AS, NoPSC would not be able to maintain current standards. Financially, times are challenging for both the university and the hospital systems, and it has not been possible for the host institutions to follow up on the repeated criticism from the Scientific Advisory Board on the lack of internal funding. Other sources of funding continue to be scrutinized, lately including EU funds exemplified by the Dynaflow participation as well as the two ERC starting grant application filed in 2017 by group leaders Johannes R. Hov and Espen Melum.

NoPSC is now a mature research center, hosting four groups (three in Oslo and one in Bergen) led by senior group leaders. Intentionally built, the research portfolio covers the entire translational spectrum - from basic biliary and immunological research to clinical studies. The comprehensive setup is world-wide unique, and the team will strive to continue to push forward the research front in the coming 10-year period. Of particular importance in the next period is to aim for clinical implementation and innovation related to the research discoveries as the highest priority. The discoveries should be developed further for routine use in the clinic, ranging from tools for early PSC or cholangiocarcinoma detection to biomarkers for measuring disease activity or drug efficacy. Whilst unprecedented impact has already been made in the research space, we want the next 10 years to set a footprint in the everyday practice of clinicians managing patients with PSC.

A major accomplishment of NoPSC has been the establishing of the International PSC study group (IPSCSG), which was initiated in Oslo in 2010. The majority of PSC researchers world-wide are currently affiliated with the group, now counting representatives from more than 25 countries. To ensure the further growth and dynamics of the group, it became important to establish a governance system not only relying on the Oslo base. As such, a milestone in the life of the IPSCSG was the election of the next coordinating center in April 2017, leading to the transition to the Amsterdam base over the remainder of 2017. Similar rotations will be done every fourth year onward, and will allow new ideas to be brought into the management of this highly respected group. The representation of NoPSC in the international arena is still considerable, myself serving from 2017-2019 as the secretary general of the European Association for the Study of the Liver.

The publication list of 2017 is impressive and speaks for itself as to the academic standing of the center. Not only does the center push for its own dedicated research, but has now acquired many unique methodological and practical skills, which are attractive among both national and international collaborators. Given the time involved in related sharing of NoPSC resources and the limited amount of institutional funding, there is an increasing need to focus on the core objectives of NoPSC. The NoPSC monitoring board has encouraged this strategic priority. To maintain a world-leading position also means to abandon other opportunities, and it could be considered part of the challenge of the next 10 years to keep the growing research portfolio aligned. Besides the growth and the success, what makes me happy from the leadership perspective is the way we have been able to maintain the positive working spirit at NoPSC. This makes me confident that we will be able to cope with current and future developments and challenges.

Stor takk til Hagen

Det ble avisdebatt i oktober da Stein Erik Hagen donerte 100 millioner kroner til forskning på en sjelden leversykdom. – Gi oss ti år og vi skal vise at midlene kommer mange pasientgrupper til gode, sier forskerne som allerede nå ligger i verdenstoppen med PSC-forskning.

Erik Schrumpf, Tom Hemming Karlsen og Kirsten Muri Boberg, som er de sentrale i PSC-forskergruppen, opplever nå det enhver forsker bare drømmer om. Takket være Hagens interesse for medisinsk grunnforskning generelt og for primær skleroserende cholangitt (PSC) spesielt, har de nå forskningsmidler nok i ti år fremover til å kunne konsentrere seg om det viktigste, nemlig å forske.

Facsimile from the OUS news when NoPSC was formed in 2007.

Overview of the Norwegian PSC Research Center

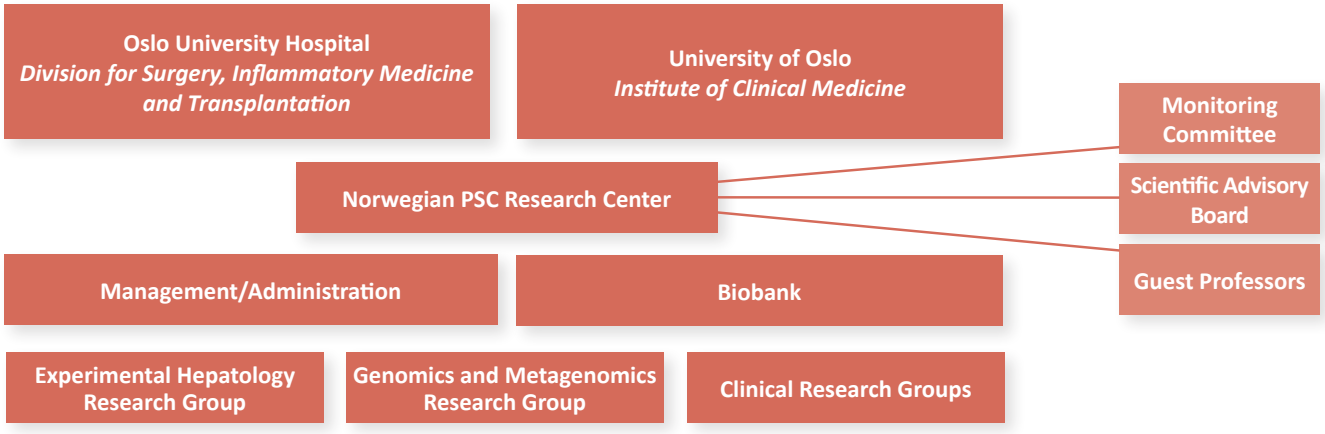
NoPSC was established May 2008 at the Medical Department, Rikshospitalet, upon signing the contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of this agreement was a donation from Stein Erik Hagen of NOK 100 millions made in September 2007 to 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 new ten-year period based on a contractual agreement between Canica A/S 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 "center status" at the Medical Faculty, 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 for Surgery, Inflammatory Medicine and Transplantation. The Experimental Hepatology Group and the Genomic and metagenomics group are organized at the Research Institute of Internal Medicine, Oslo University Hospital (OUH), whilst the clinical groups are organized within the Section for Gastroenterology and Hepatology at the Department of Transplantation Medicine, Oslo University Hospital (OUH) and Haukeland University Hospital in Bergen.

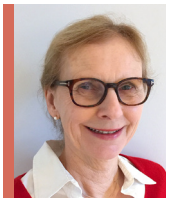


MONITORING BOARD

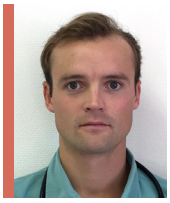
The Board monitors and approve all official agreements and financial documents of the Center. Next year's budget is discussed in the autumn while the Annual report and the accounting are reviewed during the meeting in the summer. The center´s scientific activities are also presented to the monitoring board.

LEADER
Prof. Ivar Prydz Gladhaug
Head of the Institute of Clinical Medicine, University of Oslo

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

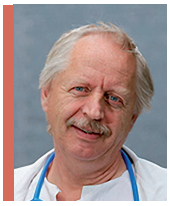


Nina Paulsen
Canica A/S



Daniel Sørli
Canica A/S

Prof. Kristian Bjøro
Div. of Surgery, Inflammatory Medicine and Transplantation, OUS Rikshospitalet



Prof. Pål Aukrust
Div. of Surgery, Inflammatory Medicine and Transplantation, OUS Rikshospitalet

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

GUEST PROFESSORS

Frank Tacke
Dept. of Medicine III; Gastroenterology, Metabolic Diseases and Intensive Care Medicine, University Hospital Aachen, Germany

Michael Trauner
Division of Gastro-enterology and Hepatology, Medical University of Vienna, Austria

SCIENTIFIC ADVISORY BOARD

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

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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Prof. Kirsten Muri Boberg
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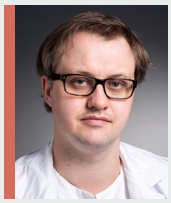

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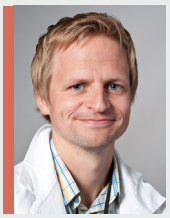

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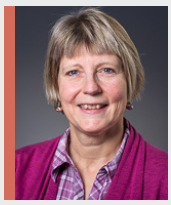

Merete Gunvor Tysdahl
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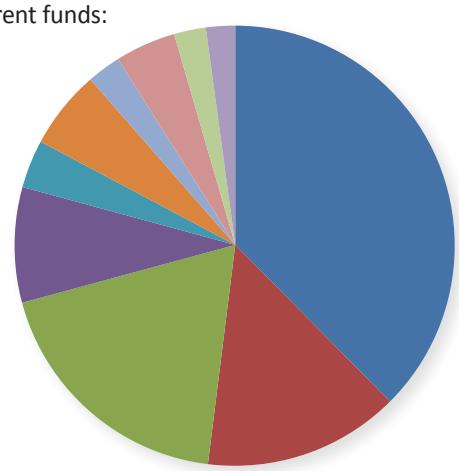
ACCOUNTING

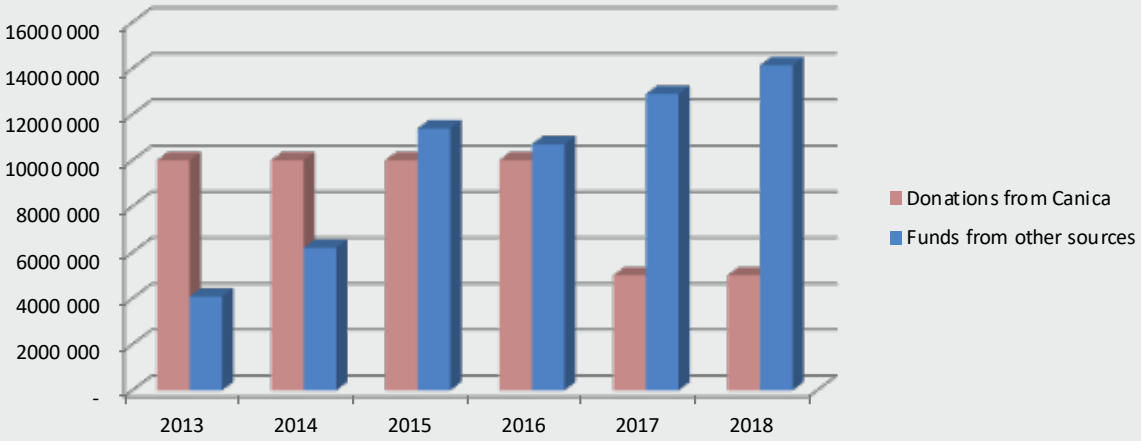
The expenditures of the Center amounted to 20.836 mill NOK in 2017. Out of these 7.833 mill NOK were from the Canica donation and 1.958 mill NOK were gift reinforcement provided by the Norwegian Research Council, adding to a total of 9.791 mill NOK of Canica-related expenditures in 2017. The remaining expenses in 2017 were covered by independent grants (also including additional funds from the Norwegian Research Council), in accordance with our goal to keep increasing the external fraction of the overall Center funding.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENSES	INCOME	EXPENSES
TRANSFER FROM 2016	-592 942		16 481 408	
INTEREST			73 801	
OTHER INCOME	1 179 574		5 571 512	
TRANSFER FROM UiO	7 202 888			7 202 888
WAGES		4 090 751		2 142 603
OVERHEAD		639 087		248 969
INFRASTRUCTURE		63 844		12 350
OTHER OPERATING EXPENCES		3 739 697		184 597
TRANFER TO 2018		**-743 856**		**12 335 315**

	2017
Canica	7 833
S-E Norway Regional Health Authorithy	2 997
Norwegian Research Council	3 918
Jebsen Inflammation Research Centre	1 760
University of Oslo	736
EU funds (Dynaflow)	1 207
Oslo University Hospital	520
Scientia Fellow (EU)	929
PSC partner (USA)	489
Other contributions	447
Thousand NOK	**20 836**

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





PhD theses 2017

DISSERTATION OF ELISABETH SCHRUMPF

June 6th Elisabeth Schrumpf defended her thesis "The role of natural killer T cells and gut microbiota in biliary inflammation".

Biliary inflammation is one of the key features of the diseases primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). The etiologies of these diseases are unclear and the treatment options are limited. The aim of this research has been to better understand which underlying factors contribute to biliary inflammation, as seen in these diseases.

In the thesis Schrumpf and colleagues explored the role of the innate-like lymphocytes natural killer T (NKT) cells and the antigen presenting molecule CD1d in biliary inflammation. Further they investigated whether the gut microbiota contributes to inflammation in the bile ducts.

With flow cytometry, western blotting and immuno-fluorescence it was demonstrated that the biliary epithelial cells expressed CD1d, a molecule presenting lipid antigens to NKT cells. They demonstrated that the CD1d expression on the biliary epithelium is down-regulated in diseased livers. Further they found in in vitro and ex vivo assays that the biliary epithelium can present lipid antigens to and activate NKT cells. They explored the role of NKT cells in a mouse model with biliary disease (NOD.c3c4) and saw that the proportion of NKT cells was higher and the NKT cells were more activated in NOD.c3c4 mice compared to control mice, but activation or pharmacological and genetically removal of NKT cells did not affect the disease of these mice.

Bilde privat

Elisabeth Schrumpf in front of her main supervisor, the evaluating committee and the acting dean, after defending her thesis.

Finally they explored the role of the gut microbiota in NOD.c3c4 mice and saw that NOD.c3c4 mice harbored a different gut microbiota compared to control mice. It was also demonstrated that NOD.c3c4 mice born and raised in a germ free facility or antibiotic treated NOD.c3c4 mice develop a milder biliary disease phenotype compared to conventionally raised mice.

In summary their findings implicate NKT cells and the gut microbiota as possible modulators of biliary inflammation, and can be considered as possible therapeutic targets in human biliary disease if their role is clarified.

DISSERTATION OF EVA KRISTINE KLEMSDAL HENRIKSEN

October 4th Eva Kristine Klemsdal Henriksen defended her thesis "T-cell receptors and human leukocyte antigens in primary sclerosing cholangitis".

The focus of her thesis was to characterize the T-cell repertoire of patients with PSC using high-throughput sequencing of their T-cell receptors (TCRs), and further investigate whether studying admixed or multi-ethnic populations might aid in fine mapping the human leukocyte antigen (HLA) association in PSC.

Henriksen and colleagues observed a diverse, polyclonal T-cell repertoire in PSC-affected livers, and detected eight PSC-associated amino acid clonotypes with signs of antigen-driven clonal selection. Henriksen and colleagues further confirmed the presence of gut and liver T cells of common clonal origin in patients with concurrent PSC and IBD. Finally, their data support efforts to systematically collect samples from PSC patients of admixed or non-European ancestry for the purpose of pinpointing the causative HLA alleles in PSC in genetic association analyses.

Project portfolio // Research groups

CLINICAL RESEARCH GROUP, OSLO

Photo: Kristin Ellefsen, University of Oslo

From left to right: Kirsten Muri Boberg, Kjetil K. Garborg, Kristian Bjøro, Kristine Wiencke, Siv Furholm, Trine Folseraas, Liv Wenche Thorbjørnsen and Merete Tysdahl.

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RESEARCH PROFILE

In 2015 we invited colleagues at other hospitals in our region (Helse Sør-Øst) to participate in a regional network for autoimmune liver diseases (AILD) with the aim to follow patients prospectively at regular intervals and in a standardized protocol including clinical data, biochemical parameters and radiological imaging in addition to serum

biobanking. We had already established a clinical database where we entered our local patients. In 2016 and 2017 efforts have been made to establish a web-based platform for this database, but so far it has been difficult due to national and local regulations. In 2017 we therefore decided to start with a paperform solution and have established this in congruence with our database. MD, PhD Mette Vesterhus, Haukeland University Hospital in Bergen, who has experience from prospective patient data collection, has coordinated the work together with MD, PhD Kristine Wiencke, professor Kirsten Muri Boberg, professor Erik Schrumpf and other members of the NoPSC Clinical Group. So far Akershus University Hospital is recruited to the network and has started to enroll their AILD patients and there are plans for recruiting new hospitals in 2018.

THE INTERNATIONAL PSC STUDY GROUP (IPSCSG) DATABASE

We have previously contributed to the establishment of a database for the IPSCSG, containing basic clinical features of PSC patients. Based on a total of 7121 patients from 37 centres in 17 countries, we have described how age, sex, and inflammatory bowel disease phenotype affect the PSC clinical course (Weismüller T et al., Gastroenterology 2017). Including additional, interesting patient cohorts from Japan, China, Argentina, and India, we are now investigating if there are significant geographical variations in disease characteristics. The database will also serve as a platform for other international collaborations.

CANCER RISK IN LIVER TRANSPLANTED PATIENTS

PSC is the most frequent indication for liver transplantation in the Nordic countries. Liver transplanted patients in general carry a higher risk of developing malignancies compared with the background population. We have participated in a large study combining data from the Nordic Liver Transplant Registry (1982-2013) with the respective cancer registries in the Nordic countries. The overall standardized incidence ratio (SIR) was 2.22 (95% CI, 2.02-2.43), however, declining over time. SIRs were especially increased for colorectal cancer in recipients with PSC (4.04) and for lung cancer in recipients with alcoholic liver disease (4.96) (Nordin A et al., Am J Transplant 2017).

DEVELOPMENT OF METHODS FOR EARLY DETECTION AND TAILORED TREATMENT OF PSC-ASSOCIATED CHOLANGIOCARCINOMA

Cholangiocarcinoma (CCA) is a major complication of PSC. The lack of accurate methods for early detecting and firmly diagnosing CCA and the limited therapeutic options once CCA is diagnosed by available techniques, represents major unmet clinical needs in the current handling of PSC patients. Long term objectives for the group is therefore to develop methods for early detection and individually tailored treatment of PSC-associated CCA.
In collaboration with the Epigenetics group at the Department of Cancer Prevention, Institute for Cancer Research at the Norwegian Radium Hospital, led by professor Guro E. Lind, we have previously identified a promising novel diagnostic modality for CCA consisting of a panel of DNA methylation biomarkers utilizied on biliary brush material (Andresen K et al, Hepatology 2015). In continued collaboration with the Epigenetics group at the Norwegian Radium Hospital, promising methylation biomarkers identified in the analysis of biliary brushes are currently being analyzed in serial bile samples collected from more than 300 PSC patients. In addition, we are collecting tissue from PSC patients with and without CCA to enable a more detailed methylation characterization in tissue. The overall aim with these efforts is to identify biomarkers for early detection and diagnosis of CCA in PSC.

The mutational profile of different subtypes of biliary tract cancers have been established, but largescale studies in PSC-associated CCA have so far been lacking. In collaboration with the Department of Pathology at the University Hospital of Heidelberg, we have established a large international collective of close to 200 tissue samples from PSC-patients with CCA. By performing targeted sequencing, covering hotspot mutations, in established cancer related genes utilizing this tissue collective, we have identified a significant number of potential novel therapeutic targets, which could provide basis for early phase clinical trials of molecular target drugs and personalized cancer treatment of PSC-CCA. This longterm project is now approaching publication, while future projects further utilizing this valuable tissue collection is underway.

KEY COLLABORATORS

- Department of Pathology, Oslo University Hospital, Rikshospitalet
- Department of Radiology, Oslo University Hospital, Rikshospitalet
- Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Rikshospitalet
- Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet
- International PSC Study Group (IPSCSG)
- Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany .
- The European Network for the Study of Cholangiocarcinoma (ENS-CCA).

CLINICAL RESEARCH GROUP, BERGEN

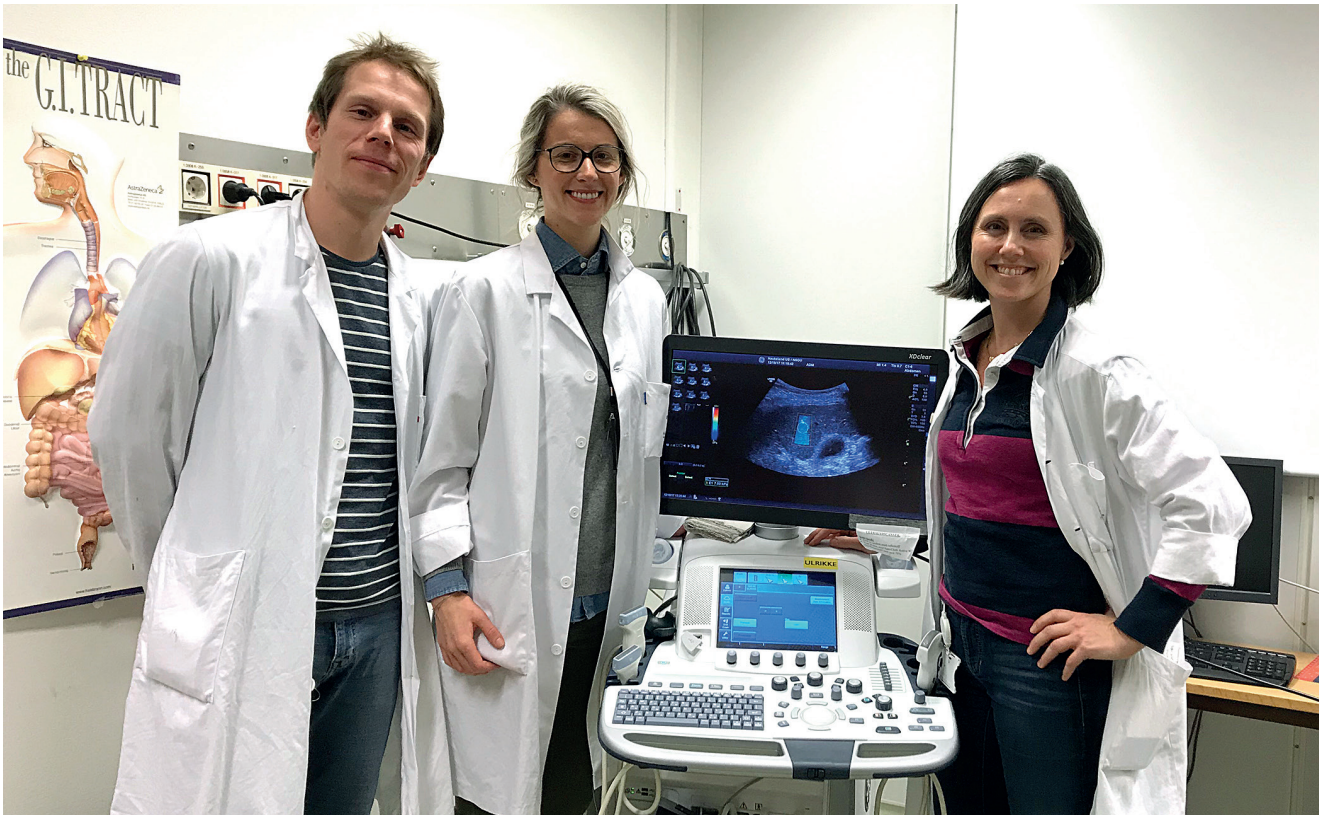

Photo privat

From left: Anders B. Mjelle, Anesa Mulabecirovic and Mette Vesterhus.

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RESEARCH PROFILE

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS IN PSC

Patients with PSC experience a wide variation in disease activity and prognosis. The lack of established biomarkers to predict clinical outcome is a major burden to patients, prevents personalized follow-up based on risk stratification and hampers the development of effective treatment. The group has had a strong contribution to the emergence of putative prognostic biomarkers in PSC over recent years. The final establishment and clinical implementation of such tools is a major goal for NoPSC. Following the exciting identification of the ELF®Test as an independent prognostic marker in PSC, we were able to validate our findings in an international, multicenter study. Our findings underscore the importance of fibrosis assessment for stratification and prognostication in PSC and leave this patented fibrosis marker panel a highly promising candidate for clinical application. In an effort to explore the characteristics and dynamics of fibrosis in PSC and tailor an improved, PSC-specific biomarker panel for prognostic purposes, the group has established a long-term strategic collaboration with corporate partner Nordic Biosciences (Denmark) and the Royal Free

Hospital (London, UK). Preliminary findings of this project with high innovative potential were presented at international liver congresses (EASL-ILC 2016, AASLD 2017). However, in an exploratory study in bile, our results highlighted the role of inflammation and neutrophilic pathways in PSC, and IL-8 and calprotectin (a clinically established tool to gauge inflammatory activity in IBD) emerged as associated with prognosis.

IMAGING TECHNIQUES AS TOOLS TO ASSESS DISEASE ACTIVITY AND PROGNOSIS

Aiming to improve and harmonize the use of imaging in PSC, we have contributed to a recent position paper from the International PSC Study Group on the use of MRI in PSC. Liver stiffness measurements using ultrasound elastography is increasingly being implemented in the management of chronic liver diseases, and liver stiffness has showed promising potential as a prognostic biomarker in PSC. We are conducting a prospective study to evaluate the predictive ability of liver stiffness in PSC. In collaboration with the National Center for Ultrasound in Gastroenterology, we have engaged in methodological studies necessary for the clinical implementation of liver stiffness evaluation using various equipment. In collaboration with the Dept. of Radiology at OUH Rikshospitalet, we have initiated a multicenter study to evaluate the agreement of liver stiffness measurements between centers, which will be important for patients with PSC who are typically followed both at a tertiary center and their local hospital.

PROSPECTIVE PSC COHORT: PROSPECTIVE DATA COLLECTION AND BIOBANKING

Per 2017 the group is running a prospective PSC cohort and a local biobank now counting 80 PSC patients, with annual collection of data, imaging and liver stiffness assessment, biobanking (serum and fecal samples for microbiota studies), and patient-reported outcomes. Taken together, the prospective cohorts in Bergen and Oslo now host 110 patients, 60 of which has reached five year follow-up.

KEY COLLABORATORS

- UCL Institute for Liver and Digestive Health, Royal Free Hospital London, UK
- Nordic BioScience, Denmark
- Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, Medical Department, Haukeland University Hospital, Bergen

GENOMICS AND METAGENOMICS RESEARCH GROUP

Photo: Øystein H. Horgmo, University of Oslo

From left: Johannes R. Hov, Martin Kummen, Lise Katrine Engesæter, Liv Wenche Thorbjørnsen, Christopher Storm-Larsen, Magnhild Eide Macpherson, Brain Chung, Silje Jørgensen, Beate Vestad, Hanne Guldsten and Amandeep Kaur Dhillon.

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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.

PROJECTS

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:

Clinical implications of the functional microbial alterations in PSC, aiming to delineate functional alterations of the gut microbiome and applying gut microbial profile or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity. Our first full metagenome sequencing data were generated in 2017, serving as a tool to identify altered microbial functions in disease and guiding metabolomics efforts.

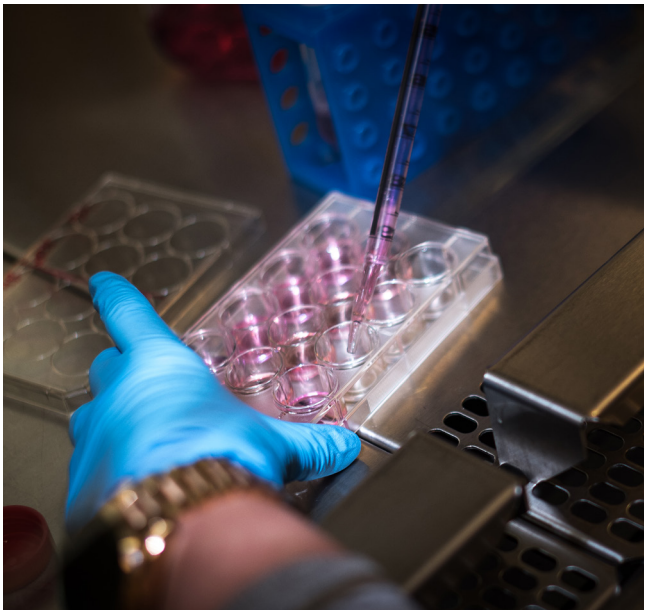
Recurrent PSC is a significant clinical problem, the extent of which is still not fully elucidated. A PhD project is now ongoing to provide updated epidemiological data based on structured follow-up in the gastro department over many years, providing a basis for translational research opportunities.

Could autoimmunity in PSC originate in the gut? This is a topic of a new post doc project entitled “Identifying exogenous drivers of autoimmunity in the gut microbiome”.

Interventions targeting the gut microbiome to treat disease may provide substantial evidence of causal relationships between the gut microbiome and disease. In addition, the new field of pharmacomicrobiomics suggest that multiple drugs used in human medicine actual target or is modulated by the gut.

FUNDING

The people in the group are currently funded by one grant from the Research Council of Norway, five grants from Regional Health Authorities of South Eastern Norway (one new in 2017, a postdoc grant to Brian Chung), one grant from National association for public health in addition to Canica, funding our bioinformatician. We have also a project focused grant from PSC Partners Seeking a Cure and multiple smaller amounts from other sources.



KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group has extensive collaborations ongoing within the Research Institute of Internal Medicine, with clinical research group as well as pathology. A strong link to the experimental group is also important, providing opportunities to understand disease mechanisms in more detail.
Of particular importance for the gut microbiome field was the opening of a germ-free research animal unit at the hospital in 2017, which has been developed by the experimental group together with the animal facility.

Regionally, the group has continued its work with a collaborative research network centered on the meetings in the regional interest group Oslo microbiota forum. In addition, the group hosted the fourth National conference on gut microbiota in November 2017 with an all-time high of about 110 participants and more than 20 abstracts submitted.
Internationally, we continue multiple strong collaborations both within and outside the International PSC Study Group.

EXPERIMENTAL HEPATOLOGY RESEARCH GROUP

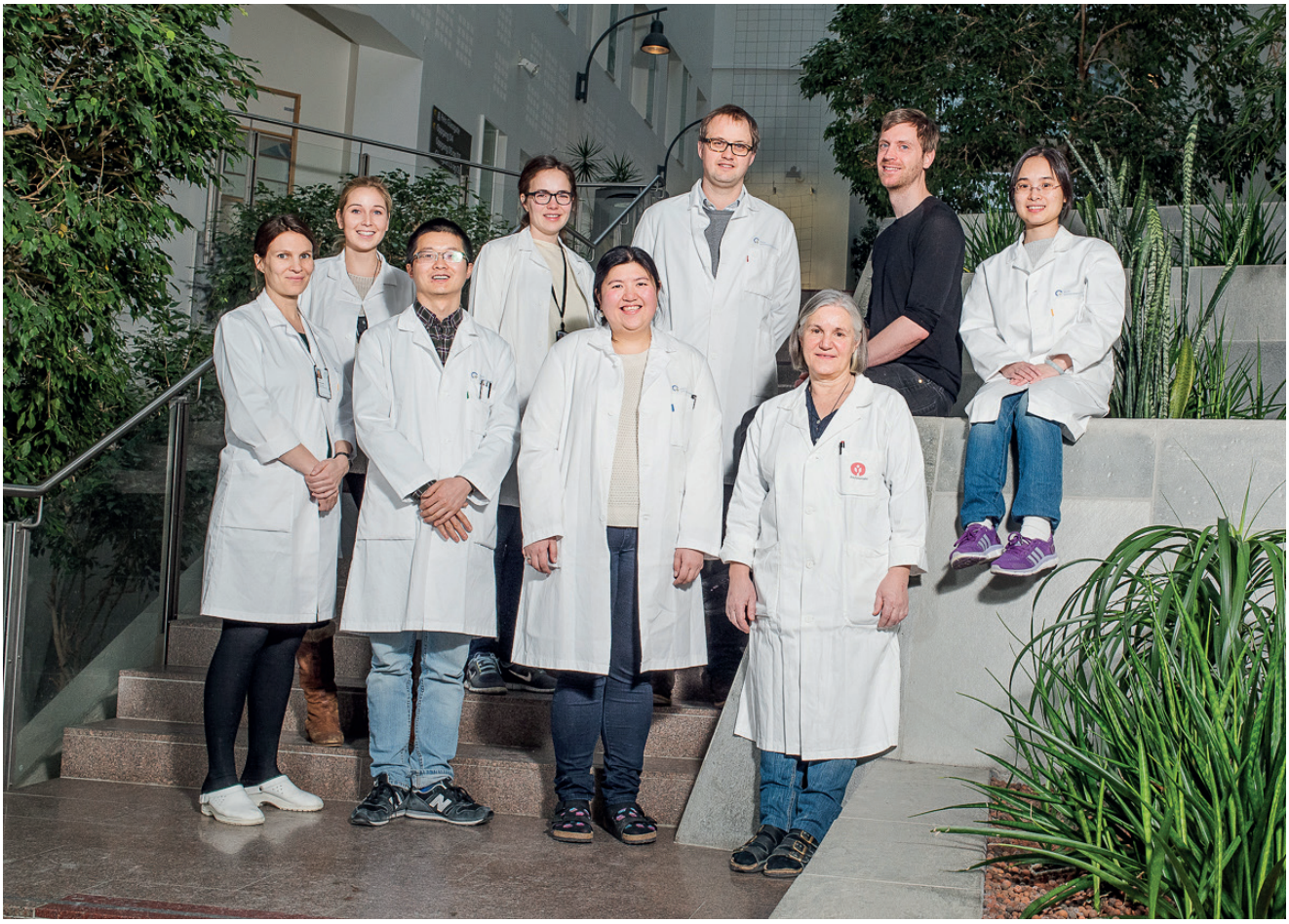


Photo: Kristin Ellefsen, University of Oslo

From left: Laura Valestrand, Anna Frank, Freeman (Fei) Zheng, Natalie Lie Berntsen, Lisa Yuen Løvold, Espen Melum, Anne Pharo, Jonas Øgaard and Xiaojun Jiang

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RESEARCH PROFILE

The experimental hepatology group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The most important tools in our research are mouse models that model aspects of cholangitis development. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2017, the group consisted of the group leader, one post.doc., five PhD students, and a lab manager. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology. In addition to the cholangitis focused studies, we are also doing basic research related to the function of natural killer T-cells,

mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represent unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment targets for PSC.

The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2017, we published results clarifying the role of NKT cells in a mouse model with spontaneous cholangitis. We have also done extensive method development to be able to challenge the bile ducts with antigens and this methodological work was finished and published in 2017. As part of the PhD of Eva Kristine Klemsdal Henriksens, work on the HLA in PSC and clonal similarities of T-cells in the gut and liver were finished. The work on unconventional T-cells is planned to be expanded and the group leader received a young research talent grant from the Norwegian Research Council in 2017 involving integrated murine and human studies.

In 2017 the two first PhD students from the group defended their theses, which both represented major events. Elisabeth Schrumpf defended her thesis in June with Agnes Lehuen from Paris as the first opponent and Eva Kristine Klemsdal Henriksen defended her thesis in October with Steven Lee as the first opponent.

KEY COLLABORATORS

- Brigham and Women's Hospit Harvard Medical School, Boston, USA
- Karolinska University Hospital, Stockholm, Sweden
- Universitätsklinikum Dresden, Germany
- University of Cambridge, UK

Awards

- The annual meeting of the Norwegian Gastroenterological Society in February 2017 awarded Laura Valestrand with a scientific award and a research grant.

- In May 2017 Johannes Hov received Oslo University Hospital's high ranking Early Career Award. The evaluation commitee stated: Johannes Espolin Roksund Hov defended his PhD thesis in 2011 and has been most productive in the immediate post-doc period, with high profile publications. His field of research is gut microbiota in human disease. He has established a research group within the field that has produced several scientific papers and the first PhD student defended his thesis in 2016. Dr. Hov is driving and developing the field of the gut microbiome and has excellent communication skills that he uses to spread knowledge of the area.

- Johannes R. Hov received the prestigious Rising Star award at the United European Gastroenterology Week (UEGW) in Barcelona, October 2017. The National Societies Committee and the UEG Scientific Committee jointly select 6-8 emerging clinical scientists as Rising Stars every year, based on a track record of international quality research and developing scientific independence prestigious award.

GUEST PROFESSOR AT OUR CENTER IN 2016 AND 2017

Our thanks goes to Frank Tacke who completed his two year engagement as guest professor at NoPSC in 2017. Frank Tacke has been and still is simultaneously Associate Professor of Hepato-Gastroenterology at RWTH University Aachen and Executive Senior Physician at the Department of Medicine III, University Hospital Aachen, Germany. He began his career at the Medical School Hannover (MHH) and carried out a student research fellowship at MD Anderson Cancer Center, Houston, USA before achieving his MD in 2002 and PhD in gastroenterology and hepatology in 2004 at MHH. After a postdoctoral fellowship at Mount Sinai School of Medicine, New York, USA, Professor Tacke became a Research Group Leader and Clinical Fellow at University Hospital Aachen in 2006. He later became a Senior Physician in Internal Medicine, Gastroenterology and Hepatology and took on his current clinical position in 2012. Board certified in internal medicine, gastroenterology, intensive care medicine and infectious diseases, Professor Tacke's research interests include clinical and experimental hepatology, liver immunology, viral hepatitis, critical care medicine, and monocyte/macrophage biology. He is currently the Vice-Secretary General of EASL, and has contributed to over 310 original and review papers.

A particular clinical and scientific interest is the role of monocytes and macrophages in non-alcoholic fatty liver disease (NAFLD), the most common chronic liver disease worldwide. Macrophages are key players in the progression of NAFLD to hepatic fibrosis and hepatocellular carcinoma. Combining innovative technical approaches (e.g., intravital multiphoton-microscopy, single cell RNA sequencing, liver-on-a-microchip) in experimental mouse models and human samples help to decipher pathogenic roles of macrophage subsets in disease progression and resolution, leading to new promising therapeutic approaches.

Highlights 2017

FUNDING FROM HORIZON 2020

The project "DYNAFLOW: Dynamic bile flow modeling and cellular sensing in primary sclerosing cholangitis" was continued through 2017. The consortium is headed by Professor Jochen Hampe, University Clinic Dresden, Germany. Beside NoPSC leader, Professor Tom H. Karlsen the principal investigators are Professor Michael Trauner, University of Vienna, Austria, Professor Marino Zerial, Max Planck Institute of Cell Biology and Genetics, Dresden, Germany, Professor Josue Sznitman, Israel Institute of Technology, Dr. Patrick Delmas, CNRS AMU, Marseilles, France. In 2017 Dynaflow funds financed PhD student Freeman Fei Cheng and engineer Lisa Yuen Løvold. This project strengthens key aspects of our research and biobank collaborations with the Department of Pathology at Oslo University Hospital, Rikshospitalet.

SCIENTIA FELLOWS

NoPSC is a part of this international postdoctoral fellowship program in health sciences funded jointly by EU's Marie Curie program, the Faculty of Medicine, University of Oslo and NoPSC. Candidates spend time at two collaborating institutions. NoPSC had two Scientia Fellows in 2017. Dr. Brian Chung worked at the University of Birmingham till July 2017 and continued his work in Oslo from August. Dr. Georg Schneditz, also a Scientia fellow, worked at the University of Cambridge in 2017 and will join the NoPSC staff in Oslo early 2018.

GUEST PROFESSOR MEETINGS

These biannual events are important scientific highlights in NoPSC. During these visits all scientific projects are critically reviewed one on one or in relevant sub-groups to enlarge the effect of knowledge transfer between the Guest professors and the young researchers of the Center. Michael Trauner from Medical University of Vienna, Austria and Frank Tacke, University Hospital Aachen, Germany, both served as Guest professors at NoPSC in 2017.

FOURTH NATIONAL MICROBIOTA CONFERENCE

NoPSC Group Leader Johannes R. Hov co-hosted the fourth national conference on "Gut Microbiota in Health and Disease" in Oslo on November 9th 2017. The conference gathered about 110 participants and more than 20 abstracts.

EXPERIMENTAL LIVER IMMUNOLOGY WORKSHOP

The third Experimental Liver Immunology Workshop was held in Stockholm in September 2017. There were more than 25 participants in total, and the contingent from Oslo counted 7 (photo below). Collaborative projects and future plans were intensively discussed and scientific relationships where created and renewed.

K.G. JEBSEN INFLAMMATION RESEARCH CENTRE

The K.G.Jebsen Inflammation Research Centre (JIRC) officially had its last year in 2017, with Tom H. Karlsen still as one of the Principal Investigators. In 2017 JIRC continued to fund our Post Doc Xiaojun Jiang, and also Scientia Fellow Post Doc Eva Ellinghaus. Eva Ellinghaus also have funding through 2018, even if JIRC has completed.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

From April 2017 Tom H. Karlsen took over the role as Secretary General for the Governing Board of the European Association for the Study of the Liver (EASL), as the first Norwegian ever possessing this position. The engagement into international liver research and health care politics is important given the generally weaker standing of hepatology compared with other medical disciplines. EASL provides a key platform for engagement in European Union priorities as to both research funding programs and regulations.

SOUTH-EASTERN HEALTH AUTHORITIES

NoPSC received one grant from the South-Eastern Health Authorities in 2017. The grant will fund the project "Identifying exogenous drivers of autoimmunity in the gut microbiome". This will allow Post Doc Brian Chung to continue his work with us for another three years after his Scientia Fellow engagement finishes in November 2018.

PSC PARTNERS

PSC Partners seeking a cure is a PSC patient organization in USA that offers grants financing research. The organization graciously granted two of our projects funds in 2016 and in 2017.

GERM FREE FACILITY AT OSLO UNIVERSITY HOSPITAL

Thursday 16th of February 2017 marked the official opening of the Tore Midtvedt Research Unit for Experimental Gnotobiology at Oslo University Hospital (photo from opening seminar). This was the result of several years of preparation and building, and the joined efforts and financing of NoPSC and Comparative Medicine department at OUH. The primary "ex vivo" phase of validating autoclaving and import routines was completed during Nov-Dec 2016. The first 6 germfree C57Bl/6J mice from University of Bern were introduced on 30th of March. The unit has 4 breeding and 4 experimental isolators, each isolator type holding up to 14 and 4 cages, respectively. Daily routines have settled, the staff is now well trained and the unit has not had any breaches of sterility and the secondary or "in vivo" validation phase is completed. The first pilot experiment with exposure to sterile fecal filtrate was performed in Aug-Oct 2017. While the study was inconclusive, valuable experience on working in the experimental isolators was gained.

NORWEGIAN RESEARCH COUNCIL

Espen Melum received a highly competitive young researcher talent grant from the Norwegian research council to fund the project "Unconventional T-cells in bile duct inflammation". The grant will fund a PhD student and a post doc along with running costs.

NOPSC RETREAT

NoPSCs annual retreat for 2017 was held at Holmen Fjordhotel in January. The main theme of the Retreat was communication of science, both written and oral. More than 30 people attended.

SCIENTIFIC ADVISORY BOARD

The NoPSC Scientific Advisory Board had their meeting 23rd of May 2017. From their report : "SAB is impressed by the excellent progress of the Centre. The research groups have a good and optimal structure and they are completing each other's research in a way that promotes synergy. The NoPSC continues to be a productive Centre with an impressive amount of publications. SAB is particularly impressed by the papers published in high impact journals such as Nature Genetics, Gastroenterology, Gut and J Hepatology."

KIEL-OSLO WORKSHOP

As a result of receiving funds from Deutsch-Norwegisches Studienzentrum the inaugural 'Human leukocyte antigen (HLA) genetics of primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD)' workshop was held on 20th of March 2017 in Oslo. The workshop was a great success with 20 participants, 11 from Oslo, 7 from Kiel and 2 from Birmingham.

Networks

KEY LOCAL COLLABORATORS

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

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

Department of Pathology
Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are involved in the histological and immuno-histochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models. Through the K.G. Jebsen Inflammation Research Centre (JIRC) we have had several projects with Prof. Guttorm Haraldsen. Prof. Frode Jahnsen is collaborator on microbiome studies.

Department of Gastroenterology (Ullevål)
Prof. Bjørn Moum, department head Asle Medhus and post doc Marte Lie Høivik are important collaborators on multiple projects including the original IBSEN and the new IBSEN III study.

Department of Rheumatology, Dermatology and Infectious diseases
Assoc. Prof. Marius Trøseid is key collaborator on microbiome studies. Rheumatologists Prof. Øyvind Molberg and post doc Anna-Maria Hoffmann-Vold collaborate on immunology and microbiome studies.

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

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

Department of Infectious Diseases
Post doc Dag-Henrik Reikvam is key collaborator on gut microbiome studies, originating from the previous K.G.Jebsen Inflammation Research Centre.

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 Fridtjof Lund-Johansen, are important in 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.

Center for Cancer Biomedicine
A collaboration with Prof. Ragnhild Lothe and Prof. Guro Lind at the Department of Cancer Prevention, OUS Radiumhospitalet 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 OUS 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.

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 important for several of the basic genetic and metagenomic studies at NoPSC.

Akershus University Hospital
The close collaboration with Dr. Kristin Kaasen Jørgensen has lead to the first inclusion of patients for the Regional Registry for Autoimmune Liver Diseases initiated by NoPSC in 2017. This work will continue for many years to come. Prof. Jørgen Jahnsen group at Department of Gastroenterology, Dr. Anne Nergård and Dr. Aida Kapic Lunder at the Department of Radiology are important contributors and collaborators in MRI studies in 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. Prof. Torunn Fiskerstrand at Center for medical genetics collaborates on intestinal diseases.

KEY INTERNATIONAL COLLABORATORS

Institute for Clinical and Molecular Biology Christian-Albrechts University, Kiel, Germany
Several co-workers of Prof. Stefan Schreiber and Prof. Andre Franke's group in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and metagenomic projects. Prof. Andre Franke has served as a loyal and dedicated guest professor at NoPSC for 5 years. In addition, Prof. John Baines (joint position at Christian-Albrechts University and the Max Planck Institute of Evolutionary Biology in Plön) is an important collaborator in the metagenomic projects.

Universitätsklinikum Dresden, Germany
There is a growing collaborative activity with Professors Jochen Hampe and Sebastian Zeissig. With Professor Hampe there is a system biology project under initiation, for which EU funding within the Horizon2020 program has been obtained. Professor Zeissig is participating in the NKT-related projects that are being performed in the Experimental Group.

Institute of Pathology, University Hospital Heidelberg, Germany
Prof. Peter Schirmacher, Head of the Pathology Department at the University Hospital in Heidelberg, Germany, represent a world-leading center expert in hepato-biliary pathology. Together with post.doc Benjamin Goeppert he provides pathology expertise to collaborational projects related to genomic profiling of PSC-associated biliary tract cancers.

University of Cambridge, UK
A new collaboration on regenerative medicine with Dr. Fotio Sampaziotis is in its early stages. We have great expectations for the future of this project.

Dept of Medicine, University of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser is Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK. He served for 3 years as a NoPSC guest professor and is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes. This project is funded within the Scientia Fellows' program of the University of Oslo and involves post.doc. Georg Schneditz and his daily supervisor Dr. Nicole Kaneider-Kaser.

University of Birmingham, UK
Prof. David Adams, a former Guest Professor at NoPSC, and Dr. Gideon Hirschfield at the Centre 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. Post.doc. and Scientia Fellow Brian Chung participates actively in these projects supervised by Dr. Evaggelia Liaskou until he continued his work at NoPSC in Oslo from July 2017.

Royal Free Hospital London, UK
Prof. Massimo Pinzani, director of the UCL 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 several 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.

The Mayo Clinic, Rochester, USA
Collaboration with Dr. Konstantinos Lazaridis and Dr. Lewis Roberts at the Mayo Clinic in Rochester has been established within 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 is an important collaborator in Dr. Espen Melum's projects related to NKT cells. He has also been the co-supervisor of Dr. Elisabeth Schrumpf who defended her thesis in 2017.

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 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.

Nordic Bioscience, Denmark
Morten Karsdal, CEO of Nordic Bioscience 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 novel, targeted, PSC-specific fibrosis markers as prognostic tools in PSC.

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

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and has also participated in the genetics projects. Associate Prof. Niklas Björkström is involved in projects relating to human immunology in PSC and has accepted a position as guest professor at NoPSC from 2018.

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Fredrik Bäckhed and Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed, being a guest professor at NoPSC from 2012 till 2015 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.

Sapienza, Università di Roma, Italy
Professors Eugenio Gaudio, Domenico Alvaro and co-workers are experts on stemcells in the biliary tree, and the NoPSC Biobank material is used to explore these in PSC.

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 the coordinator of European Network for the study of Cholangiocarcinoma. and serves as an important collaborator on projects related to PSC-associated biliary tract cancers.

IPSCSG
International PSC Study Group

INTERNATIONAL PSC STUDY GROUP (IPSCSG)

From October 2017 the secretary of the International PSC Study Group changed from Prof. Tom Hemming Karlsen, Oslo, Norway, to Dr. Cyriel Pensioen and Prof. Ulrich Beuers, Amsterdam, Netherlands. The new secretary takes over a large and thriving group interested in PSC, consisting of over 180 people from more than 20 countries in Europe, America and Asia.

STEERING COMMITTEE FROM 2017

SECRETARY
Dr. Cyriel Ponsioen, Amsterdam, Netherlands
Prof. Ulrich Beuers, Amsterdam, Netherlands

MEMBERS
Prof. Tom Hemming Karlsen Oslo, Norway
Prof. Christoph Schramm, Hamburg-Eppendorf, Germany
Prof. Cynthia Levy, Miami, USA
Prof. Chris Bowlus, Sacramento, USA
Prof. Olivier Chazouilleres, Paris, France
Prof. Gideon Hirschfield, Birmingham, UK

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Deepak Joshi
David Jones
Alastair Burt
Simon Rushbrook
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Emma L. Culver
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Saul J. Karpen
Jesse Kirkpatrick
Yury V. Popov
Detlef Schuppan
Mark Deneau

This hat was the farewell gift to former secretary Prof. Tom Hemming Karlsen from the IPSCSG members.

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1. Bende F, Mulabecirovic A, Sporea I, Popescu A, Sirli R, Gilja OH, **Vesterhus M**, Havre RF (2017)
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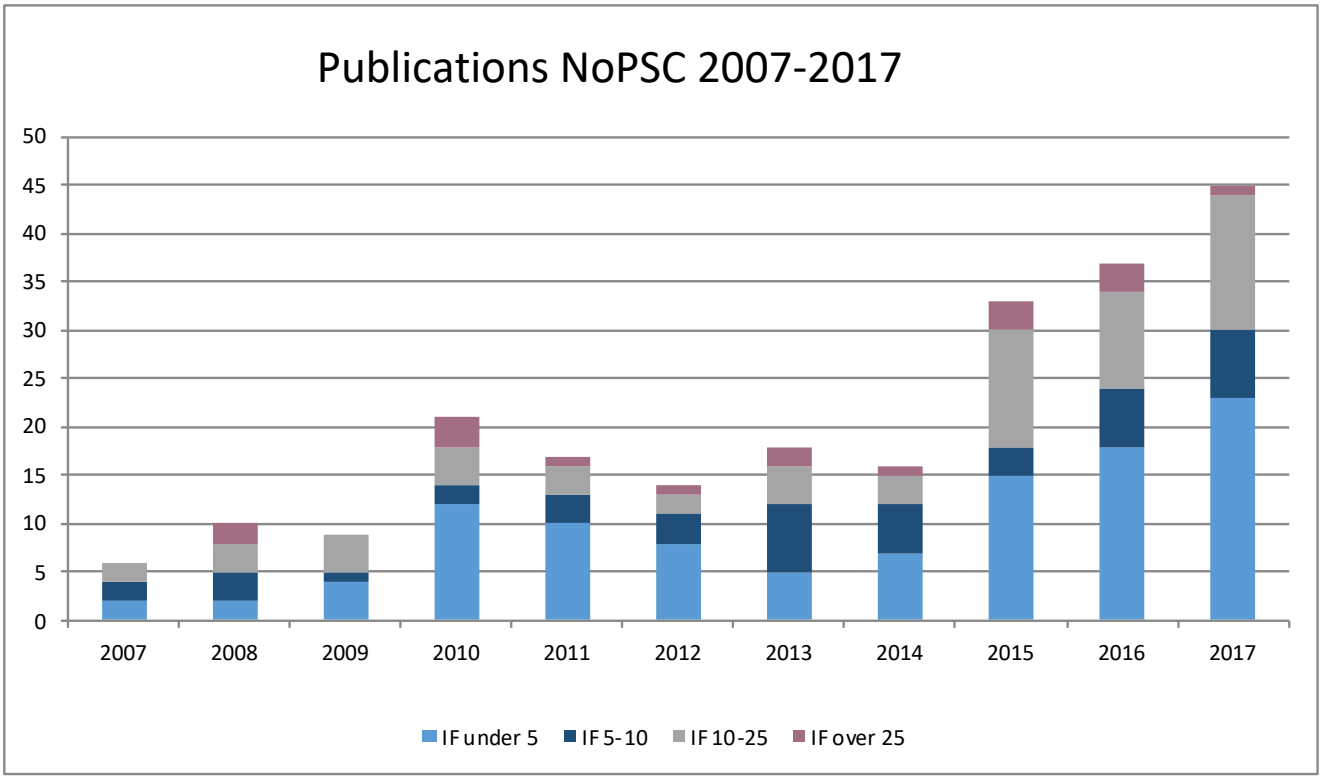
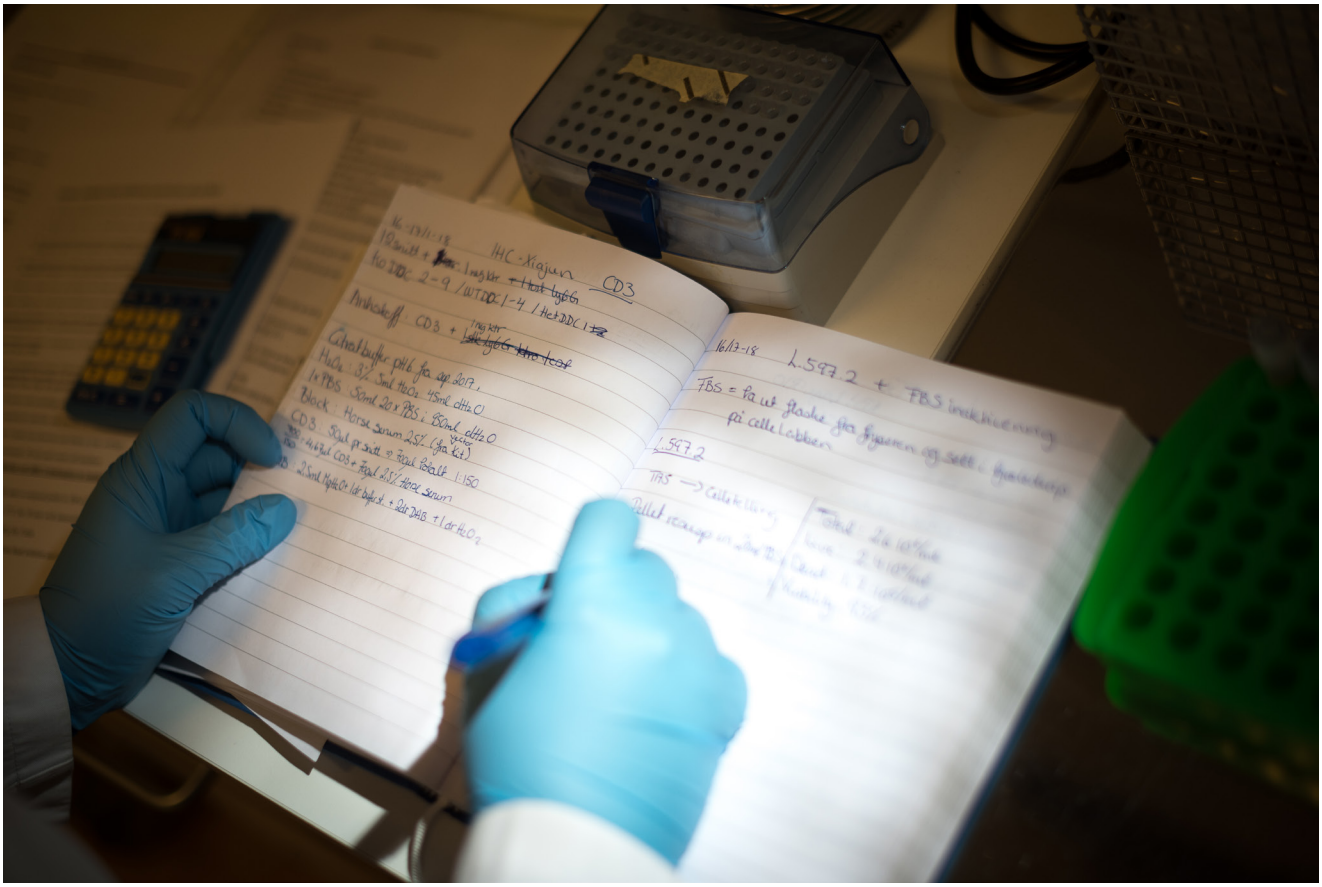


The diagram shows the Center's publication development including Impact factor (IF). Publications are registered in the year they were first published



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