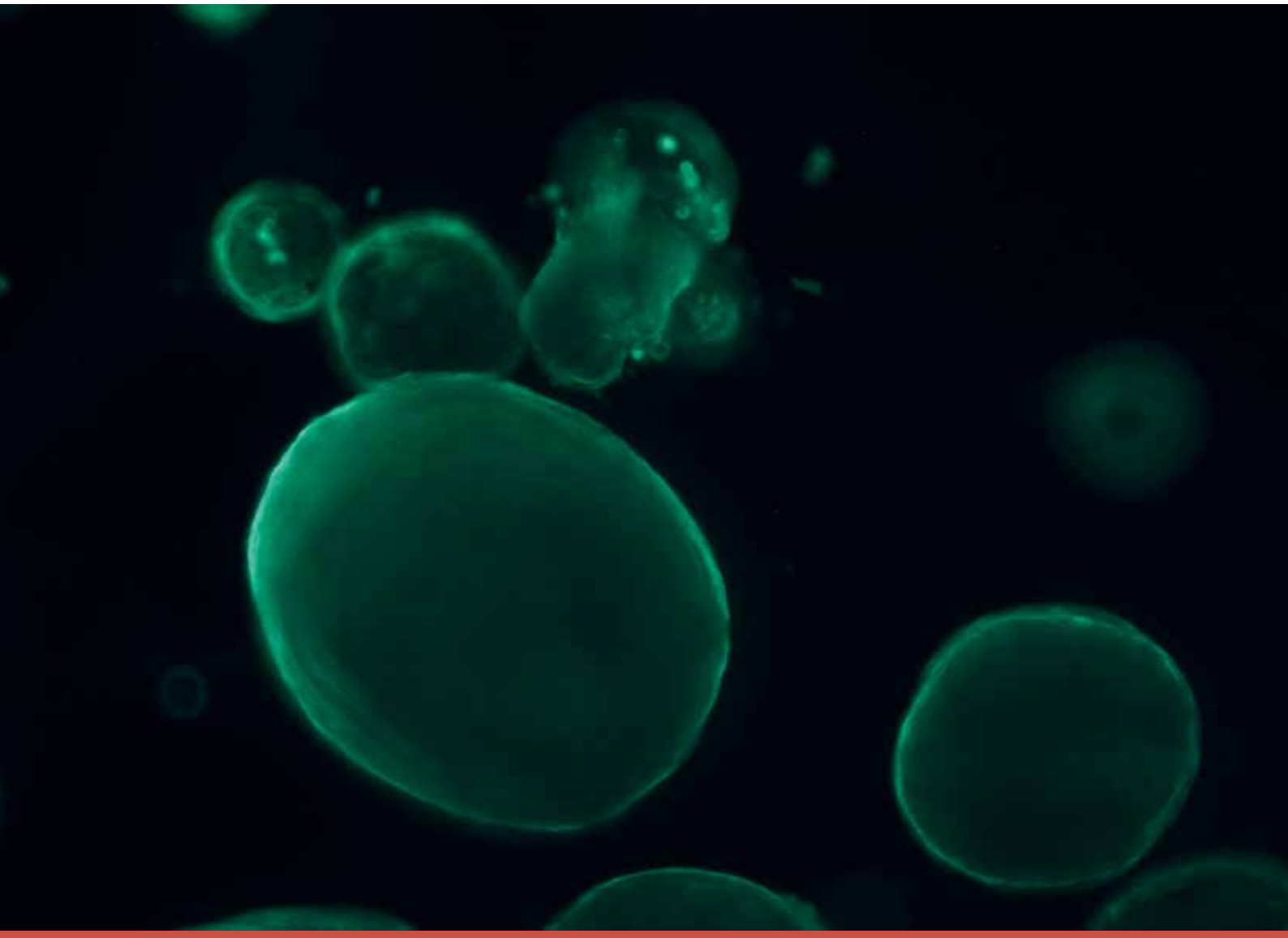
Oslo University Hospital

UiO : University of Oslo



Norwegian PSC Research Center

ANNUAL REPORT 2018

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 2018

What is PSC?

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

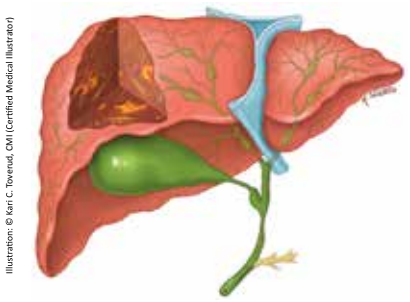
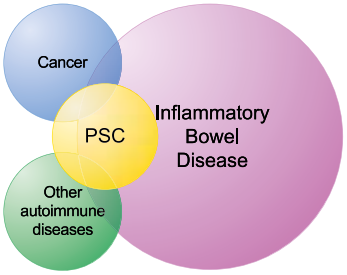


Illustration: © Kari C. Tovenad, CMI (Certified Medical Illustrator)

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 2018

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
FRONT PAGE: *Organoids from cholangiocytes*
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

From the leadership perspective, the year of 2018 has more than anything been a year of stability for NoPSC. The organization is now mature, with the four groups steadily working towards their objectives, steadily publishing papers, and steadily applying for external grants with high success rates. The support functions of NoPSC, under the steady steer of Merete Tysdahl, are also operating at steady state, ensuring the smooth everyday functioning of all practical aspects at NoPSC.

The two most prestigious moments of the year were the awarding of the Anders Jahre prize for young medical researchers to Espen Melum and the acquisition of a European Research Council (ERC) Starting Grant by Johannes Hov. The former is mostly a recognition of the excellence and international standing of Espen Melum as a researcher, but also a tribute to his present and past group members as well as the overall quality of research at NoPSC. The latter event, over and above the funds involved, serves as a token of the independence and international quality of Johannes Hov and his group. However, equally important, the ERC grant serves as proof-of-concept that PSC as a research topic is able to compete at the highest international standards, and that the research questions we are working with at NoPSC are found worthwhile high-level international funding.

Within the clinical research groups in Oslo and Bergen, under the leadership of Trine Folseraas and Mette Vesterhus, significant progress has been made in the establishing of a Norwegian network of centers to build a prospective cohort of PSC patients for annual data collection and biobanking. Such a cohort is an important initiative to test biomarkers for PSC severity and treatment response as well as early cholangiocarcinoma detection, some of which have been developed by NoPSC (examples in the publication list). Importantly, such a prospective cohort also would serve as a platform for performing clinical trials of new drugs, an important part of the clinical research agenda for NoPSC in the coming 10-year period. In December, Helse Vest granted a 3-year PhD student position to support this important work.

A key philosophy of NoPSC has been to collaborate wherever needed, whilst still establishing front-end technology and methodology skills on a few selected areas. Throughout 2018 we have succeeded in establishing two new platforms for research within our center, related to biliary organoids and gut bacterial whole-genome sequencing. The biliary organoids (see front cover) are grown from biliary brush samples collected at endoscopy or from surplus liver tissue samples. After years of pioneering work (based in Cambridge), the method is now stable and successfully implemented. The organoids allow for more realistic testing of drugs and other experimental conditions than single cells, and the human origin means that results are more relevant than if done in mice. The whole-genome sequencing technology for bacteria ("metagenomes") will allow us to look into gut factors for PSC development (the so-called "gut-liver axis") at a much greater detail than before. Ongoing, and hopefully in place throughout 2019, is to expand our clinical biomarker analysis repertoire to incorporate methods related to artificial intelligence (deep learning).

NoPSC has always had a strong international orientation. The transfer of the responsibility for the management of the International PSC Study Group (IPSCSG) to Amsterdam in 2017 has been successful, and the group is now operated from outside of Oslo for the first time since its formation. The biennial meeting of the IPSCSG was hosted in Paris in June and gathered almost 80 PSC researchers from all over the world. The clinical groups are closely engaged with the European Network for the Study of Cholangiocarcinoma (ENSCCA), providing a platform to extend the research portfolio of NoPSC which is related to this dreaded complication. My own engagement with the European Association for the Study of the Liver (as Secretary General) involved a broad range of activities, and possibly for 2018 most importantly led to the forming of a Lancet Commission on Liver Disease in Europe which I will be co-chairing even after my term with EASL has ended in 2019. The commission will deal with many aspects of relevance to PSC patients, including inequities and variation in healthcare offers, as well as stigmatization and the need for adequate education.

In brief, I think we have had a good start to our second 10-year period of collaboration with Canica. We are financially sustainable, yet still in almost total lack of institutional funding, we are moving our translational research closer to the clinic, and I hold strong hopes that within the next 10-year period we will see - and contribute to - several medical management options entering clinical practice, alongside appropriate tools to inform the patients and ourselves on the problems we are dealing with.

Overview of the Norwegian PSC Research Center

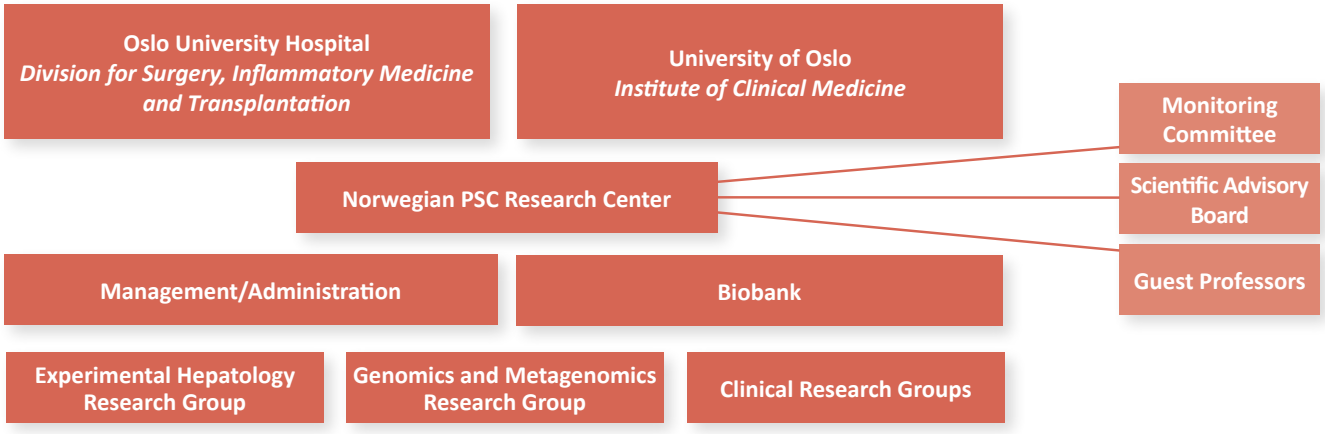
NoPSC was established May 2008 at the Medical Department, Rikshospitalet, upon signing the contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of this agreement was a donation from Stein Erik Hagen of NOK 100 millions made in September 2007 to 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 Haraldsplass Deaconess Hospital.



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 during the meeting in the summer. The center´s scientific activities are also presented at the monitoring board meetings.

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

Niklas Björkström
Unit of Gastroenterology and Rheumatology, Karolinska University Hospital, Huddinge, Sweden

Michael Trauner
Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria

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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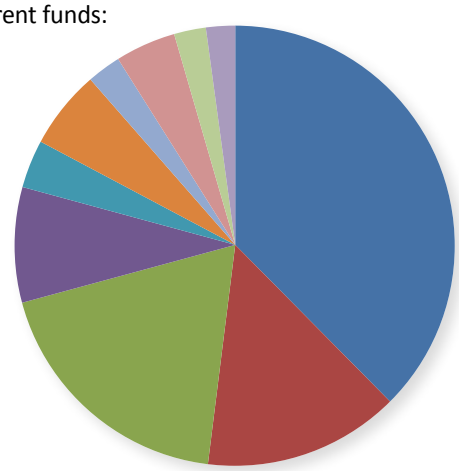
ACCOUNTING

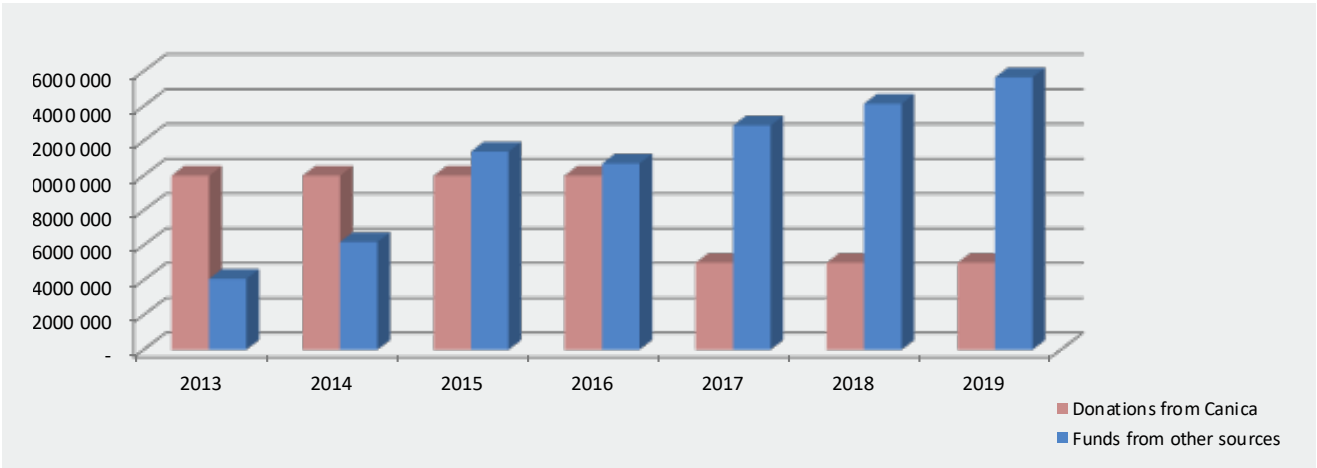
The expenditures of the Center amounted to 20.836 mill NOK in 2018. Out of these 7.833 mill NOK were from the Canica donation and 1.958 mill NOK were gift reinforcement provided by the Norwegian Research Council, adding to a total of 9.791 mill NOK of Canica-related expenditures in 2018. The remaining expenses in 2018 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 2017	-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 2019		**-743 856**		**12 335 315**

	2018
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:





Focus area 2018

PERSONALIZED APPROACH TO DETECT AND TREAT CHOLANGIOCARCINOMA IN PRIMARY SCLEROSING CHOLANGITIS

Johannes R. Hov and Trine Folseraas

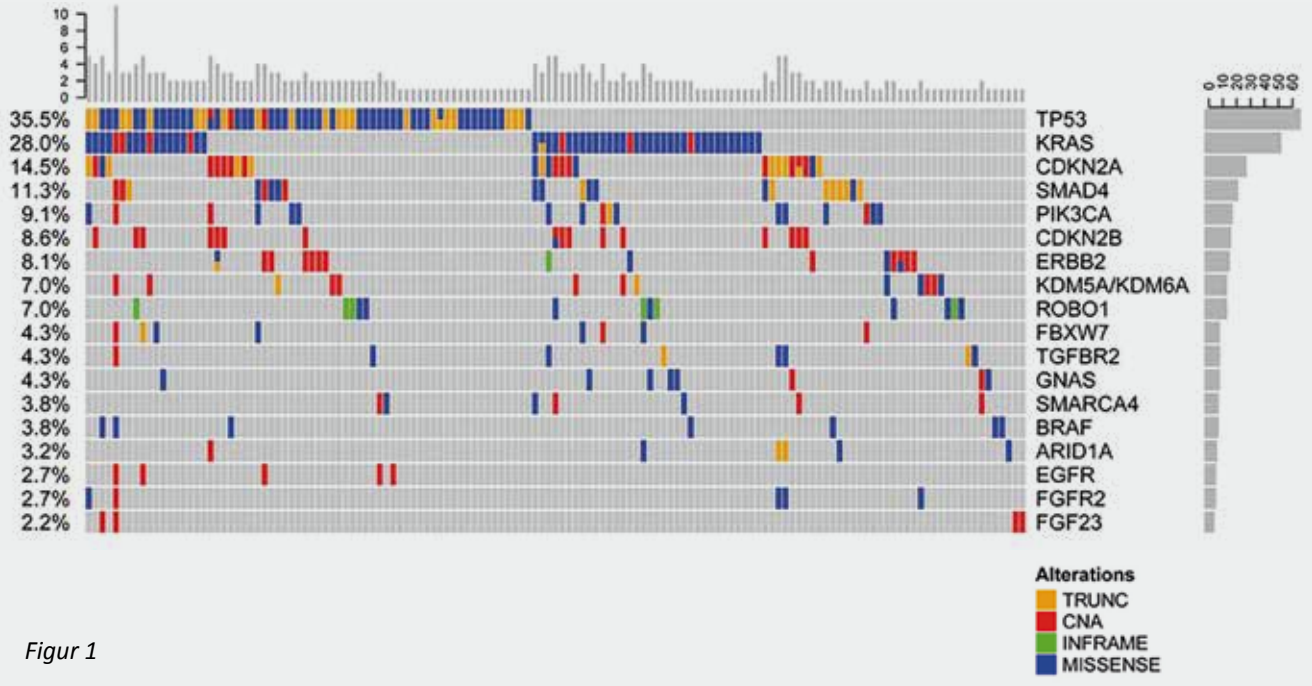
In personalized cancer medicine understanding of the molecular alterations involved in the disease process is used to tailor monitoring and treatment of the individual patient. A major clinical problem in PSC is cancer of the bile ducts, cholangiocarcinoma (CCA), which occurs in up to 20% of the patients. Due to difficulties in distinguishing benign from malignant biliary changes in PSC CCA diagnosis is often made late with limited treatment options available. The CCA-related care is clinically the most critical challenge in this patient group, and may profit from a personalized approach. The critical steps to better CCA care in PSC are 1) to identify PSC patients at increased risk for CCA 2) to establish tools for surveillance and early detection of CCA and 3) to provide novel molecular based treatment options of CCA.

IDENTIFICATION OF PSC PATIENTS AT INCREASED RISK FOR CCA

How to identify PSC patients at increased risk of CCA for further detailed work-up during decades of follow-up? In stable periods, a PSC patient is typically seen by a specialist twice a year with blood samples and ultrasound and/or MRI annually. Currently PSC is mainly referred to CCA diagnostics based on indication, clinical, biochemical or radiological deterioration, but these are not sensitive or specific tools. Are there molecular markers separating PSC patients at high risk of developing CCA from low risk individuals? Ideally, we would have a simple and sensitive tool to stratify patients according to high or low risk of CCA, and then perform personalized surveillance according to risk. One example is anti-GP2 IgA antibodies, which we recently found in about half of the patients with PSC. Anti-GP2 negative patients only had 3-4% CCA occurrence compared with 13-20% in the anti GP2 positive (1), suggesting that there is potential to identify predictive biomarkers providing a molecular map to guide personalized care in the future.

TOOLS FOR SURVEILLANCE AND EARLY DETECTION OF CCA

Tools for surveillance and diagnosis should be accurate, i.e. sensitive and specific. In addition, simplicity, availability



Figur 1

and costs are essential for effective surveillance. Personalization may be less relevant for these tools. Still, the currently most common marker, circulating carbohydrate antigen 19-9 (CA19-9) is in part genetically determined (2), but the specificity of CA19-9 is too low to warrant genetic testing to personalize CA19-9 based follow-up. Other important work at NoPSC focuses on diagnostic tests based on epigenetic changes in DNA obtained from biliary brush material and bile (3).

NOVEL MOLECULAR BASED TREATMENT OPTIONS

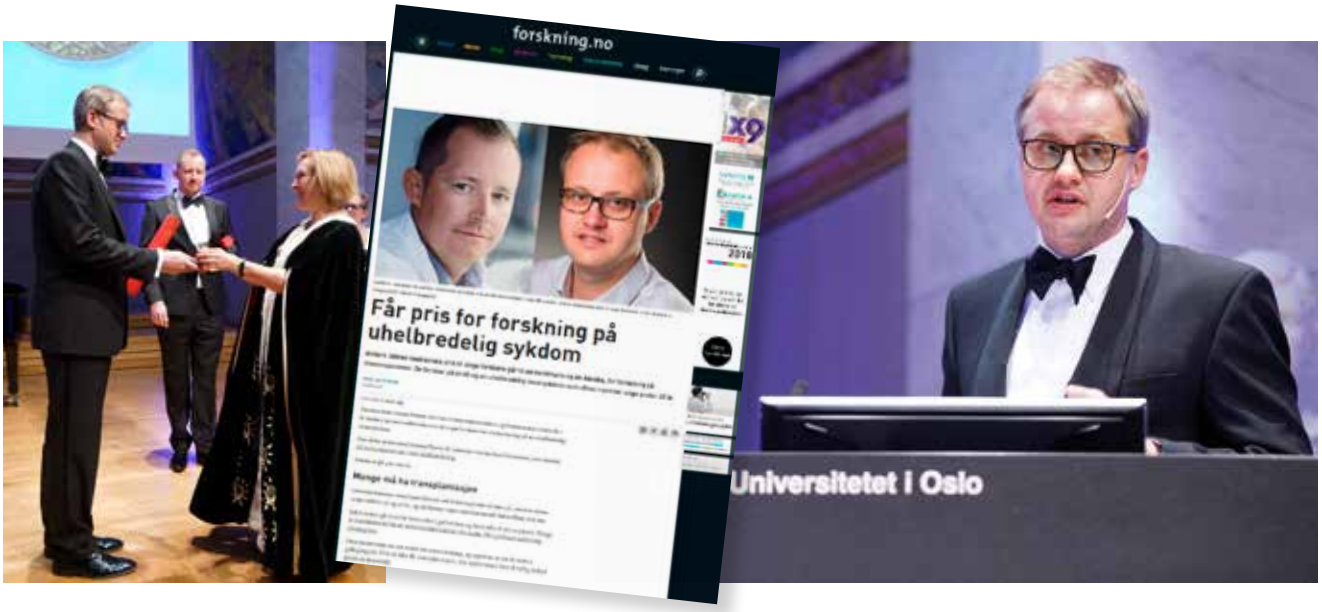
CCA is the most frequent cause of PSC-associated death. Only one-third of the patients are candidates for radical surgery at time of CCA diagnosis and even after surgery with curative intent there is a high recurrence rate. Benefit of current palliative chemotherapy regimens is limited. Traditionally, choice of cancer treatment is based on tumor origin and distribution. However, it has become evident that a wide range of molecular alterations may be important drivers of neoplasia in different cancers, and some of these may be inhibited by specific drugs, i.e. tyrosin kinase inhibitors in chronic myeloid leukemia and human epidermal growth factor 2 (HER2) antibodies in breast cancer. While programs like Cancer Genome Atlas have increase insight into cancer biology and opportunities for targeted therapy in many other cancers, CCA from PSC patients are missing from these programs. Could personalized cancer therapy be an option also in PSC-CCA? In an international project driven in a collaboration between NoPSC and the University Hospital in Heidelberg, molecular characterization has been performed by sequencing candidate genes in tumor DNA extracted from formalin-fixed PSC-CCA tissue obtained from clinical biobanks. At least one candidate gene mutation was identified in about 78% of the tumors (Figure 1). When reviewing these according to the TARGET (tumor alterations relevant for genomics-driven therapy) database (http://archive.broadinstitute.org/cancer/cga./target), 62 % could potentially be relevant for specific therapy. Keeping in mind that this was only a retrospective study utilizing archived material, it does suggests that there may be a potential for clinical testing of specific drugs in CCA in PSC.

1. Jendrek ST, Gotthardt D, Nitzsche T, Widmann L, Korf T, Michaels MA, Weiss KH, Liaskou E, Vesterhus M, Karlsen TH, Mindorf S, Schemmer P, Bar F, Teegen B, Schroder T, Ehlers M, Hammers CM, Komorowski L, Lehnert H, Fellermann K, Derer S, Hov JR, Sina C. Anti-GP2 IgA autoantibodies are associated with poor survival and cholangiocarcinoma in primary sclerosing cholangitis. Gut. 2017;66(1):137-44.

2. Wannhoff A, Hov JR, Folseraas T, Rupp C, Friedrich K, Anmarkrud JA, Weiss KH, Sauer P, Schirmacher P, Boberg KM, Stremmel W, Karlsen TH, Gotthardt DN. FUT2 and FUT3 genotype determines CA19-9 cut-off values for detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol. 2013;59(6):1278-84.

3. Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen O, Aabakken L, Schrumpf E, Lothe RA, Lind GE. Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma. Hepatology. 2015;61(5):1651-9.

Prizes and awards



Dr. Espen Melum received in 2018 prestigious Anders Jahres prize for young researchers.

- Dr. Melum was awarded the prize for his research on PSC.
  The prize ceremony was at held the University Aula in Oslo 11th of October 2018, followed by a gala dinner.
- November 19th 2018, during the Fifth National Microbiota Conference, post doc Martin Kummen received the Tore Midtvedt's Award for the best abstract.

NEW GUEST PROFESSOR AT OUR CENTER IN 2018

Fotograf: Markus Marcetic

Niklas Björkström is a resident physician in clinical microbiology at Karolinska University hospital, Huddinge, Sweden, and an Associate Professor in Immunology. He leads a research team within Center for Infectious Medicine at ANA Futura - a newly built research facility at Karolinska Institutet. The main focus of the research group is to understand more about the biology behind tissue-resident natural killer (NK) cells. The previous hypothesis that NK cells mainly recirculate from tissue to blood has been re-evaluated in recent years, and it is now known that NK cells are much more tissue-specific than what was earlier believed. One part of the groups research is to gain better insight into the function and course of development of uterine resident NK cells, by detailed characteriztion of their cell surface expression of killer immunoglobulin-like receptors (KIR). Another interest of the group is resident NK cells in the liver. The goal is to understand how these cells might be involved in the pathogenesis of different liver diseases, such as primary sclerosing cholangitis (PSC), steatohepatitis (NASH), and hepatitis virus infections (HBV, HCV, HDV), all inflammatory conditions associated with an increased risk of tumor development. The group is specialized in advanced 30-parameter flow cytometry and microscopy, and use these techniques for phenotypic and functional studies of NK cells in health and disease. Recently they have also developed a sensitive method for isolating and analyzing immune cells from the bile duct tree, which so far is a relatively unexplored organ from an immunological point of view.

Project portfolio // Research groups

GENOMICS AND METAGENOMICS IN INFLAMMATORY DISEASES

Photo: Øystein Horgmo, University of Oslo

From left to right: Simen Hyll Hansen, Marit Mæhle Grimsrud, Martin Kummen, Alexandra Götz, Georg Schneditz, Lise Katrine Engesæter, Liv Wenche Thorbjørnsen, Brian Chung, Johannes R. Hov, Magnhild Eide Macpherson, Silje Jørgensen and Murat Gainullin

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characte-

rize 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:

1. 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. We will in 2019 finalize our first full metagenome sequencing data project, aiming to identify altered microbial functions in disease and guiding metabolomics efforts
2. Recurrent PSC is a significant clinical problem, the extent of which is still not fully elucidated. This is a growing priority in the group, fueled by funding of two PhD students as well as the new ERC Starting Grant, which was one of the major achievements in 2018. The project StopAutoimmunity (Recurrent disease in the liver transplant: window to identify and stop gut signals driving autoimmunity) was awarded in total 1.5 million euros over 5 years. The expected outcome of this research axis is both updated epidemiological data, as well as extensive insights into pathogenetic and therapeutic aspects of this condition.
3. Could autoimmunity in PSC originate in the gut? This is the topic of the post doc project entitled “Identifying exogenous drivers of autoimmunity in the gut microbiome”.
4. 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, six grants from Regional Health Authorities of South Eastern Norway (one new PhD granted in 2018), one grant from National association for public health, Canica funding one bioinformatician and the ERC Starting Grant from Spring 2019.

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 continued its work with a collaborative research network centered on the meetings in the regional interest group Oslo microbiota forum. This network was formally funded from late 2018 with the name ReMicS (Regional research network for clinical Microbiota Science).
In addition, the group hosted the fifth national conference on gut microbiota in November 2018 with about 110 participants and more than 20 abstracts submitted.
Internationally, we continue multiple strong collaborations both within and outside the International PSC Study Group.

CLINICAL RESEARCH GROUP, OSLO

Photo: Øystein H. Horgmo, University of Oslo

From left: Marit Mæhle Grimsrud, Kirsten Muri Boberg, Lars Aabakken, Liv Wenche Thorbjørnsen, Trine Folseraas, Krsitine Wiencke, Merete Tysdahl, Siv Furholm and Vemund Paulsen

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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. National and local regulations hampered the establishment of a web-based platform for this prospective database; therefore, in 2017, we initiated the expansion using a paper based solution, congruent with our existing database. Throughout 2018, we have been working on the development of an eCRF for data collection using a web-based platform provided by VieDoc, with the goal of launching the eCRF for use in the first

quarter of 2019. Associate professor Mette Vesterhus, University of Bergen and Haraldsplass Deaconess Hospital has coordinated the work together with 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 2019.

THE INTERNATIONAL PSC STUDY GROUP (IPSCSG) DATABASE

The collaboration within the IPSCSG has made it possible to define disease characteristics and factors influencing the disease course across a large number of PSC patients. We recently demonstrated the significant impact of sex, age, inflammatory bowel disease (IBD) and PSC subtype on prognosis in a study including 7121 patients from 37 centers in 17 countries (Weismüller T et al., Gastroenterology 2017). We have now recruited additional patient cohorts to the IPSCSG database, including patients from centers in India, China, Japan, Australia, and Argentina. We have thus collected data on clinical presentation, survival, liver transplantation, IBD phenotype, and hepatobiliary malignancy from 8467 individual patients from 43 institutions across 22 countries and 5 continents. This multi-center study shows that the geographical region has a significant impact on transplant free survival as well as risk of malignancy in PSC (Weismüller T et al., abstract, The AASLD Liver Meeting 2018). Details on center-specific strategies for malignancy surveillance, transplant allocation, and ursodeoxycholic (UDCA) use during defined time periods have been recorded, and the impact of these variables on outcome will be assessed in ongoing analyses.

PSC DEFINITIONS

Several aspects of PSC lack clear and unified definitions, and a need to specify various diseaseassociated terms has been recognized. We are participating in a working group appointed by the IPSCSG that aims to arrive at disease definitions by applying a hybrid between a Delphi consensus and Nominal group process. The results of this process will be summarized and published.

DEVELOPMENT OF METHODS FOR EARLY DETECTION- AND PERSONALIZED TREATMENT OF PSC-ASSOCIATED BILIARY TRACT CANCER

Patients with PSC have an up to 20% lifetime risk of biliary tract cancer (BTC), including cholangiocarcinoma (CCA). 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 novel methods for early detection- and personalized 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 diagnostic modality for CCA consisting of a panel of four DNA methylation biomarkers utilized on biliary brush material (Andresen K et al, Hepatology 2015). In continued collaboration with the Lind's group, these promising methylation biomarkers have been analyzed in serial bile samples collected from more than 200 patients, including PSC patients with and without CCA. By performing DNA promotor methylation analyses these four biomarkers accurately predicted CCA in small volumes of bile, even before standard detection modalities. The findings suggest that analyzing aberrant DNA methylation utilizing bile may complement current detection methods for CCA (manuscript in submission). Validation of these findings in utilizing an independent panel of bile samples from PSC patients with and without CCA is ongoing.

The mutational profile of different subtypes of BTC have been established, but to what extent genetic changes found in non-PSC BTC and other cancers are found in PSC-BTC is unknown. In collaboration with IPSCSG and the Department of Pathology at the University Hospital of Heidelberg, we established a large international collection of 186 tissue samples from PSC-patients with CCA. By performing histomorphological characterization and tumor DNA sequencing of 42 known cancer-related genetic loci to detect mutations utilizing this tissue collective, we have detected a large number of genomic alterations, many of which represent putative actionable therapeutic targets (manuscript in submission). The large number of potentially druggable mutations provides strong incentives for early phase clinical trials of molecular target drugs and personalized cancer treatment in PSC-associated BTC. Future projects further utilizing this valuable tissue collection is underway.

CLINICAL RESEARCH GROUP, BERGEN

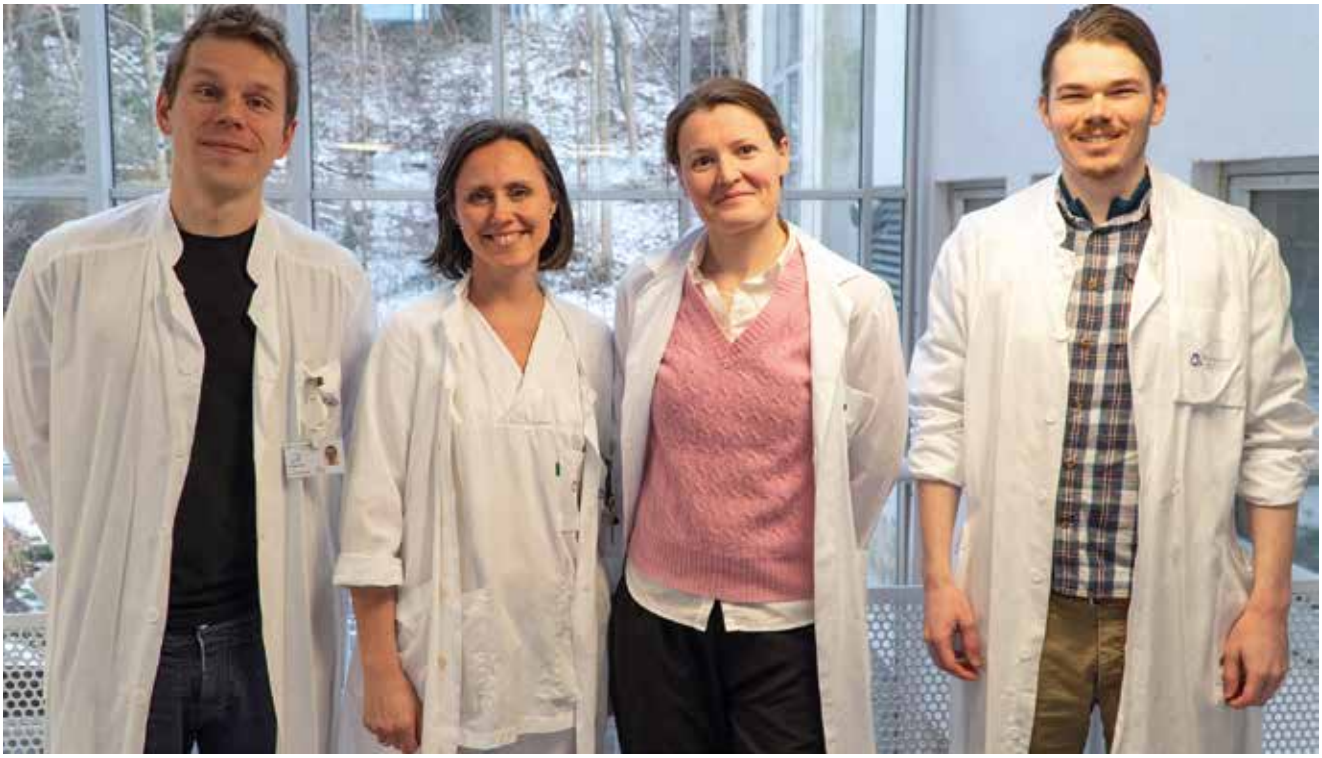

Photo: Private

From left: Anders B. Mjelle, Mette Vesterhus, Guri Fossdal and Aleksander Dahlman

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RESEARCH PROFILE

The main focus of the clinical research group in Bergen is on the identification, evaluation and establishment of prognostic biomarkers and surrogate markers of disease activity and severity in PSC. The establishment of biomarkers to predict clinical outcome would alleviate patients' concerns, allow for personalized follow-up based on risk stratification and facilitate the development of effective treatment.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS IN PSC

Following our identification and subsequent international multicenter validation of the ELF®Test as an independent prognostic marker in PSC in 2015 and 2017, respectively, we have pursued our interest in markers of fibrosis in an international collaboration including corporate partner Nordic Biosciences in Denmark and the Royal Free Hospital (London, UK), exploring novel, more specific and dynamic biomarkers in PSC. However, our results have also highlighted the role of inflammation and neutrophilic pathways in PSC. Based on findings during recent years, an interesting question which we want to explore is whether we can identify a biomarker panel which better captures all aspects of the disease than single markers.
In collaboration with international partners, we have contributed to the development of two novel clinical scoring systems for outcome prediction in PSC, both of which

were published in 2018; one of which was derived using machine-learning techniques. Furthermore, we have participated in the formation of an International PSC Meta-analysis group in 2018, which will focus on the evaluation of clinical predictors of outcome in existing databases from collaborating centers from several countries.

IMAGING

We are involved in studies investigating MRI in PSC, but our main focus regarding imaging is on liver stiffness measurements using ultrasound elastography. This 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. We are also studying the variability in liver stiffness meassurement between different centers, different elastography platforms and over time in PSC. These issues are highly relevant for patients with PSC who are typically followed both over time and seen at different centers (local – tertiary).

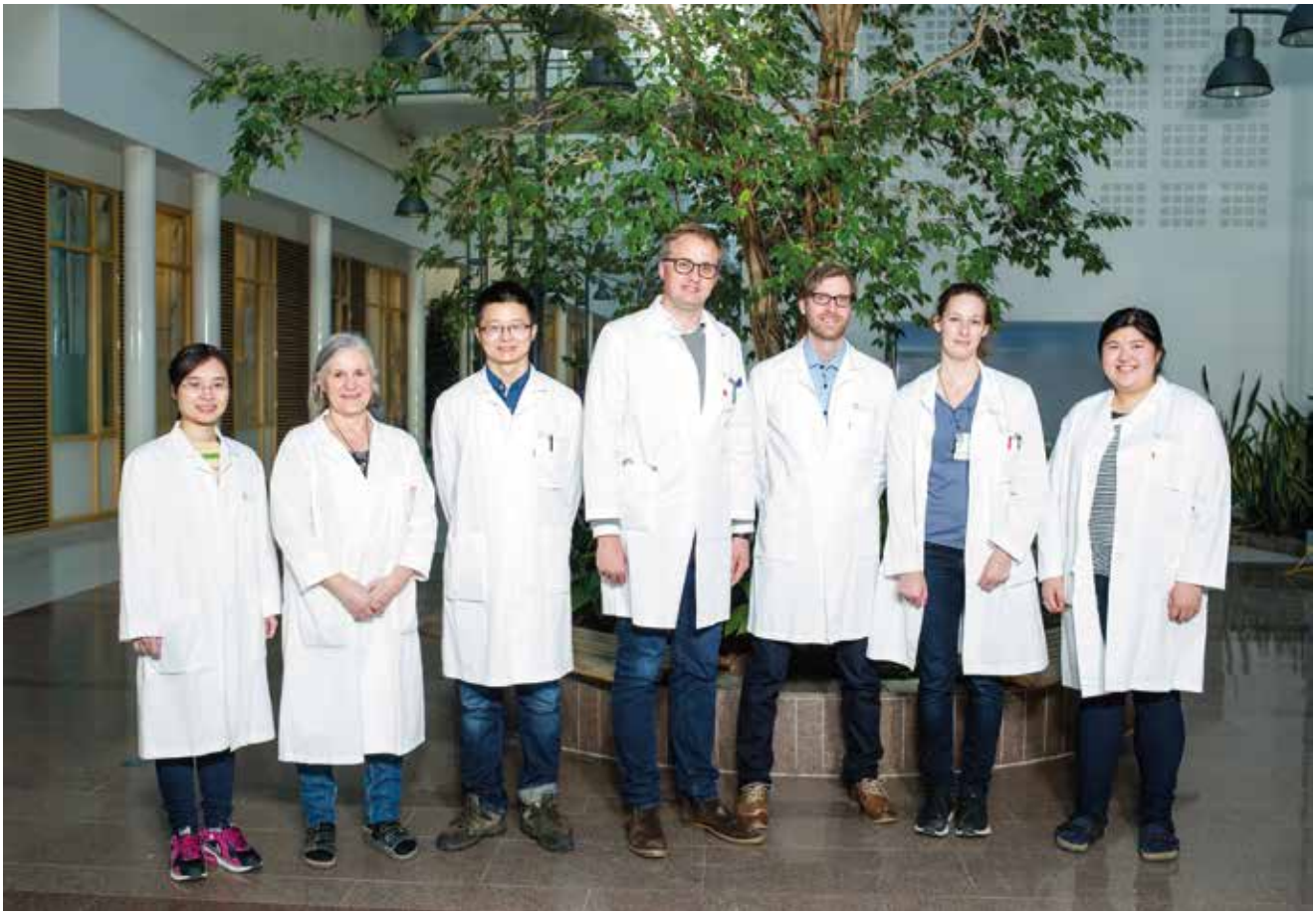
PROSPECTIVE COHORTS, EXPANSION AND CLINICAL TRIALS

We spearheaded the establishment of a large local prospective cohort of patients with PSC in 2013, now counting 85 patients, with annual collection of data, imaging, biobanking (including fecal samples for microbiota studies), and patient-reported outcomes. Taken together, the prospective cohorts in Bergen and Oslo now host approximately 150 patients. These cohorts also serve as recruitment bases for clinical studies. We previously participated in a phase II study and all three centers are currently involved in a phase III clinical trial. An important part of our work is related to the coordination of the expansion of the NoPSC prospective data and biobank collection initiative in close collaboration with the clinical group in Oslo. PhD student Guri Fossdal joined the group in December 2018 and will take care of the practical support and data monitoring as we expect to expand into new centers in the Western and South-Eastern Norwegian health regions in 2019.

KEY COLLABORATORS

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

THE EXPERIMENTAL LIVER RESEARCH GROUP



From left: Xiaojun Jiang, Anne Pharo, Fei (Freeman) Zheng, Espen Melum, Jonas Øgård, Katrine Sivertsen Aasrud and Lisa Yuen Løvold

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RESEARCH PROFILE

The experimental liver research 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. The group represents one of the three research group at the Norwegian PSC research center. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2018, the group consisted of the group leader, one post.doc., four PhD students, and a lab manager. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology but also now incorporating aspects of regenerative medicine. In addition to the cholangitis focused studies, we are also doing basic research related

to the funktion of natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the Pathology of PSC and and uncover potential novel treatment target for PSC.
The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2018, we demonstrated for the first time that NKT cells can drive experimental cholangitis that can be treated by monoclonal antibodies. These results corroborate our earlier results on the role of cholangiocytes as antigen-presenting cells. As part of a collaboration with our former guest professor guest professor Frank Tacke from Aachen Anna Frank worked in the group as a visiting PhD student during 2018. As part of her project she established protocols for generating biliary organoids from both murine livers, human livers and brush samples acquired during ERCP.
These techniques are now being used in studies aiming to understand PSC cholangiocyte biology as well as the role of the cholangiocyte in immunology.

Highlights 2018

NOPSC RETREAT

NoPSCs annual retreat for 2018 was held at Holmen Fjordhotel in January. In 2018 the main focus of the retreat was NoPSC; the past, the present and the future. The program also included several sessions about PhD student and postdoc supervision, updates on news from the research groups and social activities. Overall the retreat was a great event gathering more than 30 NoPSC affiliates. (1)

RESEARCHER OF THE MONTH MARCH 2018

Health South-East presents a researcher each month, and in March 2018 the researcher of the month was our Espen Melum, group leader for the Experimental Hepatology group at NoPSC (https://www.helse-sorost.no/nyheter/forsker-med-sjelden-nysgjerrighet-pa-leversykdom). The article emphasis is on the necessity of understanding how the inflammation in the bile ducts occurs, before we can focus on new possible treatments. The goal of the research group is to understand how the immune system is involved in the different processes, and through that possibly find new knowledge and treatment targets. (2)

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

Tom H. Karlsen has had the role as General Secretary for the Governing Board of the European Association for the Study of the Liver (EASL) since April 2017, and continued through 2018, ending his term in April 2019. His engagement in international liver research and health care politics through EASL continues to be of great importance. (3)

RIIM SPRING SEMINAR

The Research Institute for Internal Medicine where NoPSC is physically located at Oslo University Hospital arranges each year a spring conference. In 2018 the Conference was at Lysebu. This one day event consisted of a scientific program with many well know guest speakers and gathered more than 50 people.

MONITORING BOARD MEETING

In 2018 the first Monitoring Board meeting for NoPSC was on the 31st of May. Here the accounting for 2017 and the annual report was presented and approved. The second Monitoring board meeting took place on the 13th of December and the budget for 2019 was presented and approved.

IPSCSG MEETING IN PARIS

The International PSC Study Group has a biannual meeting, and in 2018 this meeting was held in Paris 18th to 19th of June. A delegation consisting of all the group leaders, Tom Hemming Karlsen, Kristen Muri Boberg, Marit Mæhle Grimsrud and Merete Tysdahl participated. (4)

ENSCCA IN ROME

The European Network for the Study of Cholangiocarcinoma (ENS-CCA) held its second Biennal


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Congress 21st to 23rd June 2018 in the Sapienza University of Rome. Group leader Trine Folseraas from the Clinical research group participated from us. (5)

ERC FUNDING

Johannes Hov at NoPSC was awarded an European Research Council (ERC) Starting Grant of EUR 1,5 million over 5 years to further develop his research on the importance of intestinal bacteria as a cause of disease. The project is called “Stop Autoimmunity - Recurrent disease in the liver transplant: window to identify and stop gut signals driving autoimmunity”. The project will have its startup in April 2019. (6)

LANCET-EASL COMMISSION ON LIVER DISEASES IN EUROPE

As General Secretary of EASL Tom Hemming Karlsen has been an important part in initiating the Lancet-EASL Commission on liver diseases in Europe. EASL partnered with The Lancet, through 2018, to bring together stakeholders and develop new solutions in order to identify key challenges and opportunities for tackling the challenging and diverse landscape of liver diseases in Europe. (7)

GUEST PROFESSOR MEETINGS

NoPSC typically hosts two guest professor meetings each year, where our your PhD student and Post docs recieves valuable advice and feedback on their projects and careers. In 2018 the first meeting was held September 11th to 12th. Dr. Michael Trauner Medical University of Vienna, Austria, also served at guest professor at NoPSC in 2018.

PATIENT BOARD

The last years it has become an increasing focus on involving patients as active participants in the planning of research projects. As part of this initiative we have the last years invited representatives from the patient organization to meet with us and discuss our planned research initiatives. The 2018 meeting was hosted in September.

PATIENT ORGANIZATION CONFERENCE

FAL (Foreningen for Autoimmune Leversykdommer/ The association for Autoimmune Liver diseases, https://www.fal.link/) arranges a biannial conference for patients. As usual this was located to Rikshospitalet and and was hosted on September 14th 2018. Many of NoPSC staff contributed with lecturers and practical support. (8)

NOPSC ON TV

Group leader Johannes Hov was invited to participate in the popular TV program; Praktisk info med Jon Almås,

aired in September 2018. The program intends to educate people about different practical issues in a fun and entertaining way, and the theme of this program was the gut. Johannes Hov introduced the public to the microbiota in an excellent way.

UEGW

Our Tom Hemming Karlsen was key note speaker at the United European Gastroenterology Week (UEGW) in Vienna, Austria, 20-24 October. (9)

THE LIVER MEETING

NoPSC also sent a delegation at The Liver Meeting, the American Association for the Study of Liver Diseases annual conference in San Francisco 9th to 13th of November. During the congress, NoPSC leader Tom Hemming Karlsen gave the state-of-the-art lecture ”President’s choice” on the topic of ”Genomics, microbiomics and personalized hepatology”.

FIFTH NATIONAL MICROBIOTA CONFERENCE

For the fifth time NoPSC Group Leader Johannes R. Hov co-hosted the national conference on “Gut Microbiota in Health and Disease” in Oslo, November 19th 2018. More than 110 participants joined this year. At the conference our postdoc Martin Kummen received Tore Midtvedts prize. (10)

NORDIC MASTERCLASS IN HEPATOLOGY

Headed by Kirsten Muri Boberg and Trine Folseraas Oslo University Hospital hosted the Nordic Masterclass in Hepatology 29th to 30th of November 2018. In this two day event the participating MDs got insight into the latest development in research and clinical practice in Hepatology. (11)

NOPSC IN THE MEDIA

14th of December the University of Oslo published on their internet an article about NoPSC, summarizing the growth of the research environment of PSC, (https://www.med.uio.no/klinmed/om/aktuelt/aktuelle-saker/2018/langsiktig-satsing-gir-verdensledende-forskning.html). (12)

NEW EMPLOYEES

In 2018 we had several new employees joining our ranks: Study nurse Siv Furholm, PhD student Lise Katrine Engesæter, PhD exchange student Anna Frank, Engineer Jonas Øgård, Engineer Alexandra Götz, PhD student Marti Mæhle Grimsrud and Bioinformataician Simen Hyll Hansen.

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SOCIAL MEET UPS

The social activities gather the NoPSC emplyees outside work. In 2018 we have had plent of opportunities for that, among others; Pay check meetup at Villa Paradiso and TukTuk Thai, Summer party at Liv Wenche, several ice-cream lunches over the summer, minigolf tournament in September, Jingle and Mingle - the NoPSC Christmas party and the RIIM Christmas party.

FUNDING FROM HORIZON 2020

The EU funded project "DYNAFLOW: Dynamic bile flow modeling and cellular sensing in primary sclerosing cholangitis" is still running and has been prolongen for another year till May 2020. Our engineer Lisa Løvold is still financed through this project which strengthens key aspects of our research and the biobank collaborations with the Department of Pathology at Oslo University Hospital.

FUNDS FROM BERGESEN STIFTELSEN

The clinical research group applied in 2018 for funds from Bergesen stiftelsen to finance exome sequencing of tissue from cholangiocarcinoma. A generous donation of 690.000,- NOK will greatly help this important work move forward.

SOUTH -EASTERN HEALTH AUTHORITIES

In December 2018 we got the good news that our applications for funds from the South-Eastern Health Authorities had resulted in funding for one postdoc (Georg Schneditz's continuing his projects), one PhD student on a project involving germfree mice, supervised by Henrik Rasmussen and Espen Melum and one PhD student supervised by Johannes Hov in a project expending upon the ERC grant. In addition Johannes Hov and Marius Trøseid received funds for a Microbiota network.

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, Børre Fevang, Thor Ueland and Bente Halvorsen groups.

Department of Transplantation Medicine
Department Head, Prof. Pål-Dag Line, Dr. Einar Martin Aandahl and Head of the section 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 Rheumatology, Dermatology and Infectious diseases
Assoc. Prof. Marius Trøseid is a key collaborator for NoPSC on microbiome studies. Rheumatologists Prof. Øyvind Molberg and post doc 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 (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 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
Post doc 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 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 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 in 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 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 HelgeGilja 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.

Haraldsplass Deaconess Hospital
Our leader for the clinical group in Bergen, Dr. Mette Vesterhus, has moved to a permanent position at Haraldsplass Deaconess Hospital, hence we now 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 (now our guest professor) is involved in projects relating to human immunology in PSC.

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 (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.

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. Prof. 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.

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 novel, targeted, PSC-specific fibrosis markers as prognostic tools in PSC.

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arne Nordin and 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.

Universitätsklinikum Dresden, Germany
There is a growing collaborative activity with Prof. Jochen Hampe and Prof. Sebastian Zeissig. With Prof. Hampe We collaborate within the framework of the Horizon2020 program; Dynaflow. Prof. 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 Pathology at the University Hospital Heidelberg in 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.

Department of Internal Medicine I, University of Bonn, 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 was moved from Oslo to Amsterdam, The Netherlands in 2018. Into the capable

hands of the new leaders; 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 and senior researcher James Traherne and Vasilis Kosmoliaptsis in Cambridge is invaluable for the progress of several of our functional genetic projects.

Dept of Medicine, Univerity of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser (former Guest Professor at NoPSC) is 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 involves post.doc. Georg Schneditz and his daily supervisor 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.
Post.doc. and Scientia Fellow Brian Chung participates actively in these projects from Oslo through 2018.

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 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 Biosciences. 26

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 (Guest Professor at NoPSC through 2018) 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 stemcells in biliary tree, and material from the NoPSC Biobank is used to explore these cells in PSC pateints.

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.

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 his new place of employment at Toronto Centre for Liver Disease, Toronto General Hospital, Canada. 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 is an important collaborator in Dr. Espen Melum's projects related to NKT cells.

Publications 2018

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Factors Associated With Outcomes of Patients With Primary Sclerosing Cholangitis and Development and Validation of a Risk Scoring System
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2. Colombo M, **Karlsen TH** (2018)
The EASL International Liver Foundation: A growing pup with missions that are distinct yet integrated with those of its mother
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3. Maroni L, Pinto C, Giordano DM, Saccomanno S, Banales JM, Spallacci D, Albertini MC, Orlando F, Provinciali M, Milkiewicz M, **Melum E**, Ciriza IL, Milkiewicz P, Rychlicki C, Trozzi L, Scarpelli M, Benedetti A, Svegliati Baroni G, Marzioni M (2018)
Ageing-related expression of Twinfilin-1 regulates cholangiocyte biological response to injury
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4. Lunder AK, Bakstad LT, Jahnsen J, Borthne A, **Roksund Hov J**, Vatn M, Negård A, IBSEN Study (2018)
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5. **Storm-Larsen C**, Stiksrud B, Eriksen C, Nowak P, **Holm K**, Thalme A, Dyrhol-Riise AM, Brix S, **Hov JR**, Trøseid M (2018)
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6. Pihlstrøm HK, Mjøen G, Mucha S, Franke A, Jardine A, Fellström B, Dahle DO, Holdaas H, **Melum E** (2018)
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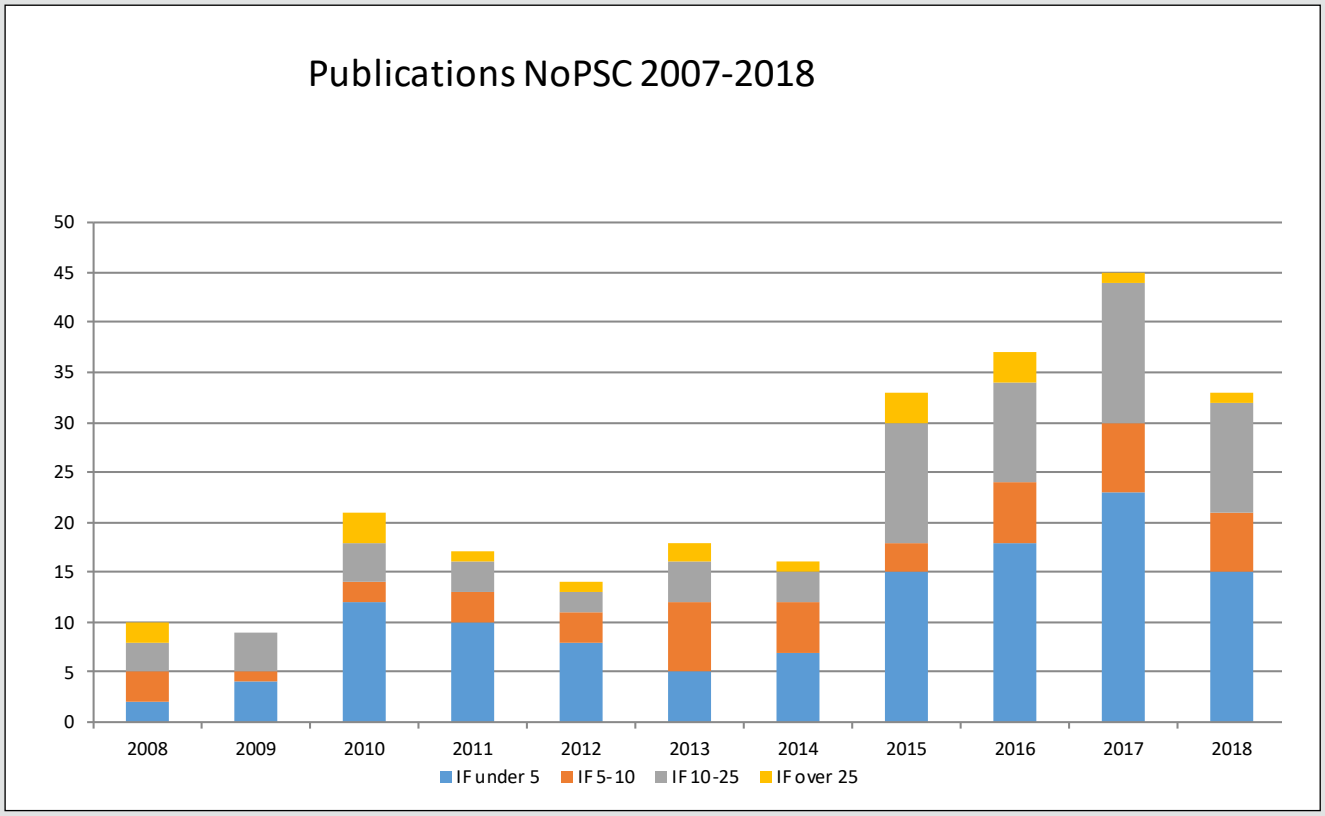

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