Oslo University Hospital

UiO : University of Oslo

Norwegian PSC Research Center

ANNUAL REPORT 2016

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 2016

Content:

NOPSC ANNUAL REPORT 2016

Front page:
International PSC Study group meeting in New Haven, USA, June 2016

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/index.html

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What is PSC?

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

PSC is a chronic inflammatory disorder of the bile ducts. PSC 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 trans-plantation is 10-15 years.

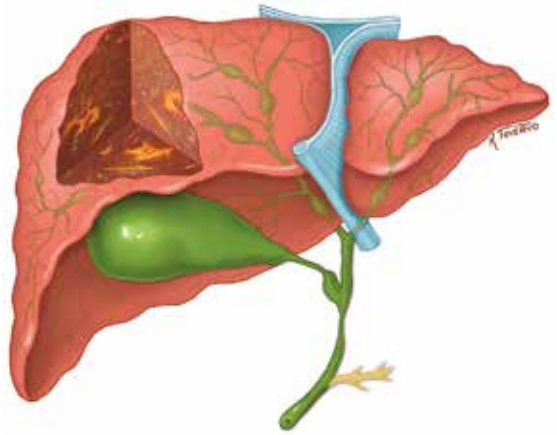
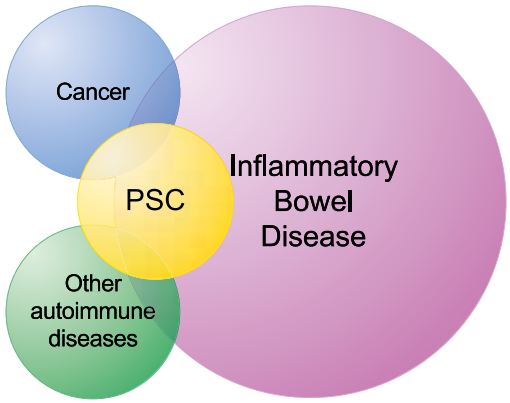


Illustration: © Kari C. Toverud, CMI (Certified Medical Illustrator)



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.

NO PSC
Norwegian PSC Research Center

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

The Leader´s Corner

Professor Tom Hemming Karlsen

With three major publications in Nature Genetics, the year of 2016 saw the conclusion of one research avenue and a firm celebration of the opening of another. More than 10 years of genetics studies, counting a large number of coworkers at NoPSC and within the International PSC Study Group, were concluded with the publishing of two large meta-analyses in Nature Genetics, in which NoPSC held leading roles. The genetic skills that have been acquired at the center over the years have gradually been shifted to assessments of the bacterial genome. The first landmark paper from these efforts, also published in Nature Genetics, demonstrated how human genetics influence the gut microbiota, and how these two research avenues are related to each other.

The three research groups of NoPSC are now well established and growing. We are very proud that one of the group leaders, Espen Melum, received the 2016 "Early Career" award from the Oslo University Hospital. The award is a demonstration of the quality of the research in his group, and that the NoPSC deliberate strategy on providing emerging research talents opportunities for growth as independent group leaders has been successful. Toward the end of the year, there has been a transition from Kirsten Muri Boberg to Trine Folseraas as to leadership for the clinical group. With the genomics group led by Johannes Hov, young researchers now lead all our three groups. NoPSC continues to engage in the broader research environment in Oslo. A major investment of funds and activity during 2016 was the establishing of the germ-free research facility, which was led by Henrik Rasmussen, chair of the Oslo University Hospital animal facilities. Several new collaborations have been initiated within the University of Oslo campus, and Espen Melum has been appointed associated researcher at the Biotechnology center. The local collaborations also attract funding, and we successfully obtained three Helse Sør-Øst research fellowships in 2016.

Despite the success in obtaining external funding, it is timely to point out that we still receive no institutional financial support for NoPSC. This situation was pointed out by the scientific advisory board (SAB), who met in May to evaluate the research at the center. The SAB comprises Prof. Herbert Tilg (Austria), Prof. Terje Espevik (Trondheim) and Prof. Tore Kvien (Oslo), and provided very useful input for further improvement of the research at the center.

The year of 2016 has been another successful year for the International PSC Study Group. In addition to the regular meetings that are held during the big international liver congresses in Europe and the USA two times yearly, we had the fourth two-day meeting of the group, hosted by the Yale University in New Haven. The three previous meetings (Oslo, Hamburg, Amsterdam) were all popular, but this year one had to cap the attendance at 100 researchers from all over the world. This popularity is impressive, particularly since there is no sponsorships from pharmaceutical industry, and a token of the high quality activities in the group.

One particularly successful element of the meeting in New Haven was the co-hosting of a symposium together with the American patient organization, PSC partners. Several hundred patients attended the symposium, which covered many questions of common relevance to both researchers and patients. The perspectives of the patients into the research priorities have also been incorporated locally, and a system has been set in place where we meet with representatives from the Norwegian patient association for autoimmune liver diseases once a year. We are also happy for all the useful discussions we have with the patients during their annual meeting at Rikshospitalet.

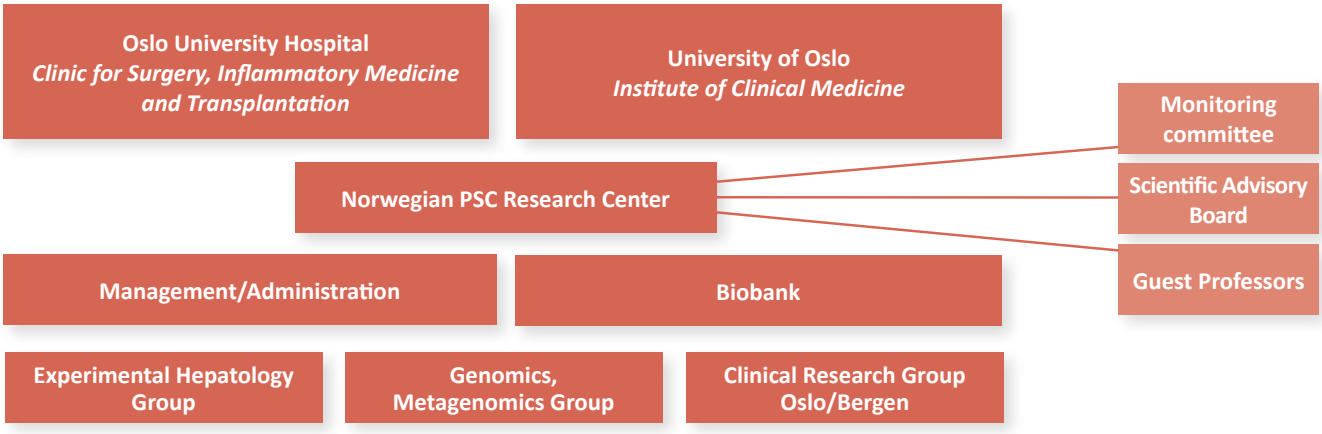
The year of 2016 concludes the first formal 10 year period of funding from Canica A/S. During these 10 years the research environment has grown into a comprehensive machinery for translational research in a disease with great unmet needs. Critical developments have been made, and we are now uniquely positioned for major breakthroughs in the next 10 years to come. We are proud of what we have accomplished, and will have to work hard to continue the success.

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. Approaching the end of this donation period the Center is proud to announce that Canica A/S has provided another NOK 50 millions for a new ten-year period starting in 2017 on the basis of a contractual agreement between Canica A/S and the University of Oslo as of December 2014.

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 Clinic for Surgery, Inflammatory Medicine and Transplantation. To maximize the translational opportunities of NoPSC, two of the three research groups comprising NoPSC is organized at the Research Institute of Internal Medicine, Oslo University Hospital (OUS) and one within the Section for Gastroenterology and Hepatology at the Department of Transplantation Medicine.



Guestprofessor meeting spring 2016, from left: Julia Ferkis, Kirsten Muri Boberg, André Franke, David Adams, Frank Tacke, Espen Melum and Tom Hemming Karlsen.

Photo Øystein H. Horgmo, University of Oslo

MONITORING COMMITTEE

The Committee is supervising all official agreements and financial documents of the Center, and meets twice a year. Apart from presenting all activities, next year's budget is discussed on the autumn meeting while the Annual report and the accounting are reviewed during the meeting in the summer.

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

SCIENTIFIC ADVISORY BOARD

In 2015 the Scientific Advisory Board (SAB) was formally established. The Center has great expectations regarding this highly competent board to evaluate the research being performed and the advice our scientists will receive on their professional development and career perspectives.

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

GUEST PROFESSORS

David Adams
College of Medical and Dental Sciences, University of Birmingham, UK
Until Sept 2016

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

Michael Traüner
Division of Gastro-enterology and Hepatology, Medical University of Vienna, Austria
From August 2016

MANAGEMENT

The management consists of the three research group leaders and the head of the Center. Together with the Center's administration, the management has the overall responsibility for the day-to-day work performed at the Center. Apart from all scientific and academic obligations, the Management, in close contact with the Monitoring Committee, the SAB and the guest professors, continuously plans all future activities and makes sure that all administrative routines are in place for the optimal functioning of the Center.

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ACCOUNTING

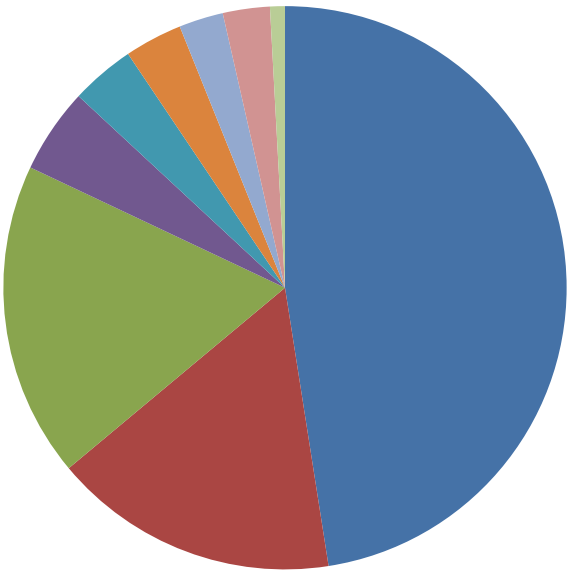
The core expenditures of the Center amounted to 18.981 mill NOK in 2016. Out of these 9.021 mill NOK were from the Canica donation and 2.255 mill NOK were gift reinforcement provided by the Norwegian Research Council, adding to a total of 11.276 mill NOK of Canica-related expenditures in 2016.

The remaining expenses in 2016 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 2015	3 333 685		23 385 107	
INTEREST			115 962	
OTHER INCOME	1 146 386		547 679	
TRANSFER FROM UiO	4 682 633			4 682 633
WAGES		5 328 205		2 228 847
OVERHEAD		286 281		255 081
INFRASTRUCTURE		479 044		326 690
OTHER OPERATING EXPENCES		3 662 116		74 089
TRANFER TO 2016		-592 942		**16 481 408**

Canica	9 021
S-E Norway Regional Health Authorithy	3 114
Norwegian Research Council	3 434
Jebsen Inflammation Research Centre	927
University of Oslo	699
Oslo University Hospital	629
Scientia Fellows (EU)	483
PSC Partners (USA)	512
Small contributions	162
Thousand NOK	**18 728**

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



Dissertations 2016

DISSERTATION OF BJARTE FOSBY

On June 21st Bjarte Fosby defended his thesis "Liver transplantation in the Nordic countries with emphasis on patients with Primary Sclerosing Cholangitis".
Fosby's first paper provides a comprehensive overview of the evolution and results of liver transplantation in the five Nordic countries since the start in 1982 to the end of 2013.
The second paper descriptively reports the main features of our liver transplantation program for PSC patients and the observed outcome. The five-year patient survival was 83% for PSC patients with suspected neoplasia compared to 92 % for PSC patients undergoing liver transplantation due to impaired quality of life/end stage liver disease.
In the last paper Fosby and collaborators report a significant impact from PSC-associated HLA variants on the risk of acute rejection after liver transplantation. The findings were similar in PSC and non-PSC recipients, suggesting that this immunological genotype is of general importance for the pathophysiology in acute rejection.
The trial lecture was «Er levertransplantasjon et behandlingsalternativ for levermetastaser og primære maligne leversvulster andre enn HCC?». The opponents, Associate Professor Jens Hillingsø, Institute for Clinical Medicine, University of Copenhagen, Associate Professor II Georg Gjorgji Dimcevski, Clinical Institute, University of Bergen and Professor Else Marit Løberg, Department of Pathology, Institute for Clinical Medicine, University of Oslo, made the dissertation an interesting event with good discussions. Pål-Dag Line, Tom Hemming Karlsen and Helge Scott were Bjarte Fosby's supervisors.

DISSERTATION OF MARTIN KUMMEN

On October 4th Martin Kummen defended his thesis "Primary sclerosing cholangitis and the gut microbiota – a study on mice, man and microbes".

The aim of the thesis was to explore the role of the gut microbiota in PSC, through characterization of the gut microbiota in human PSC. One sought to complement this by investigating the gut microbiota-dependant metabolite trimethylamine-N-oxide (TMAO) in PSC, and explore the role of the gut microbiota in a mouse model with spontaneous bile duct inflammation (NOD.c3c4).

Overall, the results implicate the gut microbiota in the pathogenesis of PSC and bile duct inflammation, providing a strong basis and rationale for further studies of the microbiota both related to pathophysiology and clinical utility in PSC.

Kummen was given the following title for his trial lecture "The impact of gut microbiota on immune regulation and primary sclerosing cholangitis". Opponents were Associate Professor Bernd Schnabl, Division of Gastroenterology, School of Medicine, University of California, San Diego, USA, Senior researcher Merete Eggesbø, Environmental Exposure and Epidemiology, Norwegian Institute of Public Health, Oslo, and Professor John-Anker Zwart, Clinic for Neurology, Institute of Clinical Medicine, University of Oslo. Johannes R.Hov, Tom Hemming Karlsen and Pål Aukrust were his supervisors.

Martin Kummen being questioned by his first opponent Professor Bernard Schnabl during his dissertation.

Highlights 2016

SCIENTIA FELLOWS

NoPSC participates in this international postdoctoral fellowship program in health sciences funded jointly by EU's Marie Curie program and the Faculty of Medicine, University of Oslo. Candidates are to spend time at the collaborating institutions, where NoPSC is one of the hosts. Dr. Brian Chung spent 2016 at the University of Birmingham and will continue his work at NoPSC in Oslo form mid-2017. Dr. Schneditz likewise is working as a Scientia fellow at the University of Cambridge and will join the NoPSC staff in Oslo some time in 2017. Both candidates have achieved a prolongation of their time in Oslo for 6 months.

GUEST PROFESSOR MEETINGS

These annual events are one of the most important scientific highlights in the life of 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 these experienced scientists and the young researchers of the Center. David Adams from the University of Birmingham, UK, completed his Guest professorship in 2016 and the position was taken over by Michael Trauner from Medical University of Vienna, Austria. Also Frank Tacke, University Hospital Aachen, Germany, joined with NoPSC in 2016 as a Guest professor.

VISITS FROM COLLABORATING SCIENTISTS

With increasing international profile, we experience a great interest in visiting the Norwegian PSC Research Center, both for strategic and collaborative discussions. Visitors from 2016 include:
June 2nd : Professor Andre Franke, Christian Albrecht University, Kiel
June 7th: Professor and Secretary General of EASL, Laurent Castera, University of Paris, France
October 18th: Professor Gregory Gores, Mayo Clinic, Rochester, USA
October 18th: Post Doc Benjamin Goeppert, Institute of Pathology, University Hospital Heidelberg, Germany
November 29th: Post Doc Magdalena Flak, William Harvey Research Institute, London, UK

FUNDING FROM HORIZON 2020

The project "DYNAFLOW: Dynamic bile flow modeling and cellular sensing in primary sclerosing cholangitis" had its start up in 2016. 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.
The project serves to strengthen key aspects of our research and the biobank collaborations with the Department of Pathology at Oslo University Hospital, Rikshospitalet.

THIRD NATIONAL MICROBIOTA CONFERENCE

NoPSC Group Leader Johannes R. Hov co-hosted the third national conference on "Gut Microbiota in Health and Disease" in Oslo on November 1st 2016. The conference gathered close to 100 participants and more than 21 abstracts where accepted of which 8 speakers was presented oral and 13 as posters. Key note speaker were Tore Midtvedt, Karsten Kristiansen and Susanne Brix.

EXPERIMENTAL LIVER IMMUNOLOGY WORKSHOP

There has for many years been a close collaboration between Karolinska Huddinge and Rikshospitalet resulting in the second Experimental Liver Immunology Workshop in Oslo 2016. There were approximately 20 articipants that took active part in the informal discussions. We have a range of collaborative projects, and the ongoing projects as well as future plans were intensively discussed.

K.G. JEBSEN INFLAMMATION RESEARCH CENTRE (JIRC)

NoPSC leader Tom H. Karlsen serves as one of the Principal Investigators in JIRC which has been a great success for NoPSC. Our Post Doc Xiaojun Jiang, which is funded by JIRC, got an extension for a year and JIRC also funded a Sciantia Fellow, Eva Ellinghaus, for a year, who started in November 2016. NoPSC greatly appreciates the collaboration and scientific work going on within JIRC.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Tom H. Karlsen has served as vice general secretary for the steering committee of the European Association for the Study of the Liver in 2016. The engagement into international liver research and health care politics is still 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 3 grants from the South-Eastern Health Authorities in 2016, all running for three years. The Grants will fund one post doc on the project "The role of a mutation in a familial syndrome of sclerosing cholangitis", and two PhD projects "Personalized medicine applications in diagnosis and treatment of cholangiocarcinoma in patients with primary sclerosing cholangitis" and "Clinical impact of the gut microbiome after liver transplantation". These new positions will be filled in 2017.

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, with the option for the same grant in 2017. The projects where "Mutational profiling for therapeutic targets in primary sclerosing cholangitis-associated biliary tract cancer" and "Functional microbial biomarkers in primary sclerosing cholangitis"

Photo Øystein H. Horgmo, University of Oslo

Research groups

EXPERIMENTAL HEPATOLOGY GROUP

Photo Øystein H. Horgmo, University of Oslo

From front and to the left: Espen Melum, Anne Pharo, Xiaojun Jiang, Laura Valestrand, Natalie Lie Berntsen and Zheng Fei (Freeman).

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Photo Øystein H. Horgmo, University of Oslo

The experimental liver research group is managing the experimental studies at the Norwegian PSC research center. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2016, 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 and mucosal associated invariant T (MAIT)-cells. NKT and MAIT cells 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 target for PSC.

The most important tools in our research are mouse models that model aspects of cholangitis development. The mouse models we use are immune driven and inspired by the fact that most genes associated with PSC are involved in the immune response. In 2016, we published results showing how the microbiome affects the disease process in mice with bile duct inflammation by using germ-free animals and antibiotics treatment. We also published an extensive report that clarified the role of NKT-cells in murine cholangitis by using genetic crosses and bone-marrow chimeras. This study complement our previous results where we had demonstrated that cholangiocytes activate NKT-cells. In 2016 we continued the studies on NKT cells and bile duct pathologies and started to investigate the mechanisms whereby they affect cholestasis, which is a common condition in PSC patients.

In September 2016 Zheng Fei (Freeman) started as a scientific assistant in the group and was rapidly recruited as a PhD student. He will work on the role of MAIT-cells in bile duct inflammation. To do this we will use mice that overexpress MAIT cells and challenge them with antigens that activate MAIT-cells directly in the bile ducts. In addition, we will in a collaborative project with the section of transplantation surgery investigate the role of MAIT cells in PSC patients undergoing liver transplantation.

The group has in 2016 been heavily involved in the establishment of a germ-free facility at Rikshospitalet together with Henrik Rasmussen. This unit will enable us to extend our studies on the role of the microbiota during bile duct inflammation by enable us to do interventional studies.

At the end 2016 Elisabeth Schrumpf and Eva Kristine Klemsdal Henriksen finished their PhD's and their theses will be defended in 2017.

Photo Øystein H. Horgmo, University of Oslo

Anne Pharo, Laura Valestrand and Zheng Fei discussing results.

GENOMICS AND METAGENOMICS GROUP

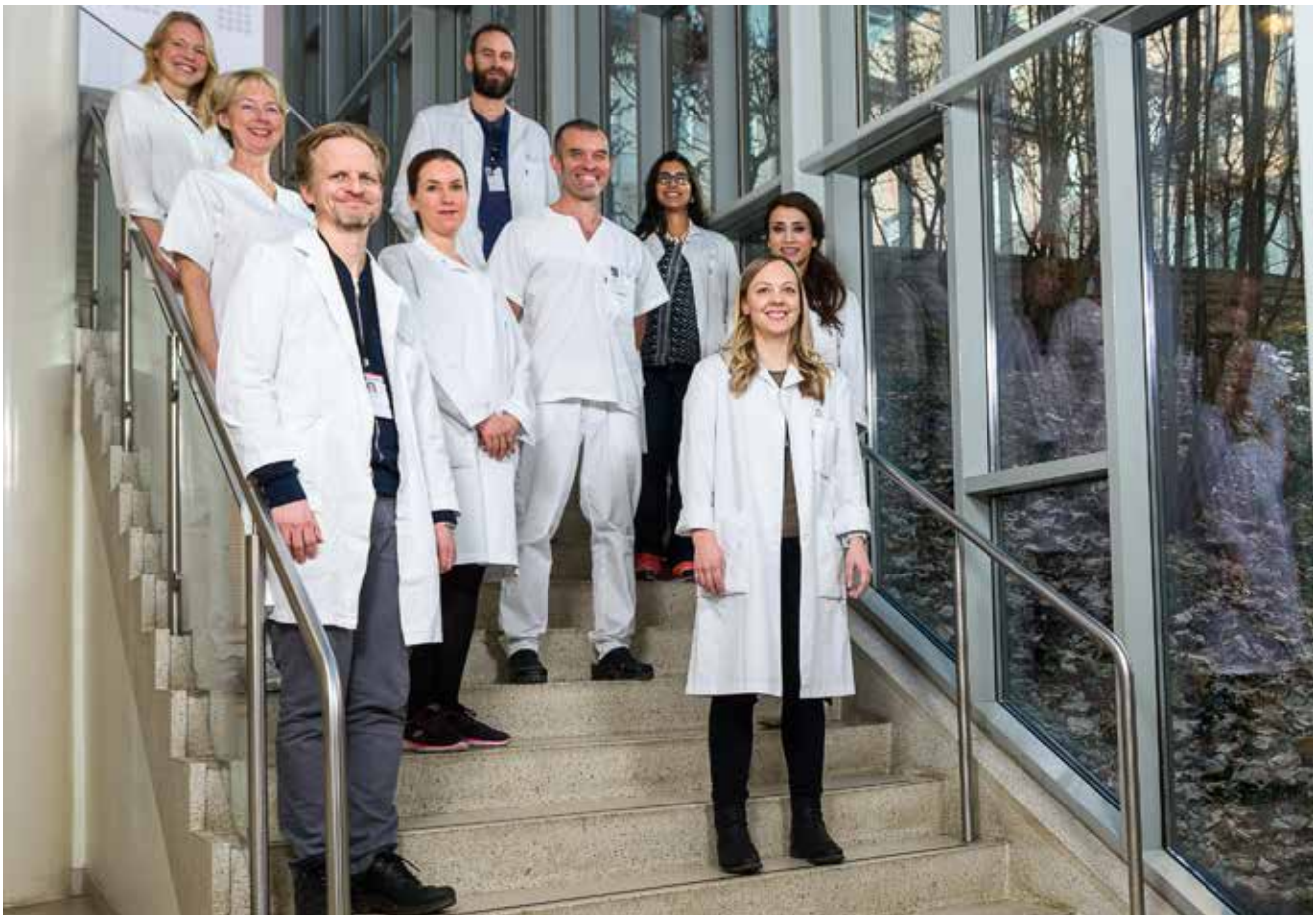

Photo Øystein H. Horgmo, University of Oslo

From front and to the left: Johannes R. Hov, Beate Vestad, Liv Wenche Thorbjørnsen, Hanne Guldsten (started in 2017), Marius Trøseid, Amandeep Kaur Dhillon, Trine Folseraas, Kristian Holm and Cristiane Mayerhofer.

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The PhD dissertation of Martin Kummen on October 4 was a major event in the genomics and metagenomics group in 2016. His thesis "Primary sclerosing cholangitis and the gut microbiota – a study on mice, man and microbes" represents a milestone not only for Martin – and PSC – but also for the group and for the gut microbiota research at the hospital and in Norway.

The first paper of the thesis was one of the most important publications of the group in 2016 – the first large-scale characterization of the luminal gut microbiota in PSC (accepted in Gut, one of the top-ranking journals in the field). The study was also the first in print entirely based on in-house skills and methods, from sampling via sequencing to bioinformatics and statistics. The same pipeline has been applied with success in several other disease phenotypes under study at the research institute of internal medicine and provides the basis for the over-arching theme of the group, which is currently "Clinical microbiota medicine".

Clinical impact of basic research can be achieved early if we keep clinical translation in mind at all times. In PSC, we observed that circulating markers of microbial metabolism could act as biomarker for disease severity, suggesting that further research should evaluate gut microbial profile as a clinically relevant test in PSC. Considering the available data, there is also a rationale for gut-targeted treatment trials in PSC. The group also contributed to Norwegian-German collaboration on the autoantibody anti-GP2 IgA, which was identified as a biomarker of severe disease and cholangiocarcinoma in PSC, which may become clinically relevant. Interestingly, GP2 is an intestinal protein binding gut microbes.

A step away from clinical relevance was the finalization of a long-term collaborative project between Oslo and Kiel on the genetic influence on the gut microbiota in the population, which was published in Nature Genetics late 2016. While PSC was not the aim of the study, this landmark story provided important evidence on the bi-directional interactions between host and microbes which may also influence PSC relevant physiology, in particular the regulation of bile acid homeostasis. We are also very proud of the successful collaboration with the experimental group led by Espen Melum, which resulted in a very interesting story on how the gut microbiota has a direct impact on the severity of a spontaneous mouse model of biliary disease. We now eagerly await the new facility for germ-free animal research at Rikshospitalet.

The group continues to receive funding. Martin Kummen continues as post doc after his thesis, funded by Helse Sør-Øst. We received a new Helse Sør-Øst grant late 2016, which will cover studies on recurrent PSC and the gut microbiota. The group also received a grant from the US patient organization PSC Partners to cover more extensive and expensive metagenomic projects in PSC. The Jebsen Inflammation Research Centre will be discontinued in 2017 but has been important for the development of microbiota research in diseases of chronic inflammation. The centre will also contribute some of its funds to cover a one-year project position as engineer in our group.

Overall, the group is about to finish the first stage of the gut microbiome era in human disease and is eager to translate this into clinical practice. Together with Marius Trøseid we aim to develop a regional research network in the field, which we are confident will become a success. Importantly, the third national conference on gut microbiota was organized in November 2016 once again a great meeting with about 100 participants and more than twenty abstracts presented.

Photo Øystein H. Horgmo, University of Oslo

Amandeep Kaur Dhillon in the lab.

CLINICAL RESEARCH GROUP IN OSLO

Photo Øystein H. Horgmo, University of Oslo

Front and from the left: Kirsten Muri Boberg, Liv Wenche Thorbjørnsen, Trine Folseraas, Erik Schrumpf, Siv Furholm and Lars Aabakken.

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REGIONAL RESEARCH AND REFERENCE NETWORK IN AUTOIMMUNE LIVER DISEASES (AILD)

The term autoimmune liver diseases (AILD) comprise primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH). Approximately 10% of both PSC and PBC patients present with biochemical and histological features that overlap with characteristic findings of AIH ("overlap syndromes") and may require treatment along the same guidelines as AIH. In a previous Norwegian epidemiological study, the prevalence of PSC, PBC and AIH was 8.5, 14.6 and 16.9 per 100 000 inhabitants, respectively. Although being relatively rare, these disorders are important since they may significantly impact on patient health and prognosis. They may all progress to liver cirrhosis and become indications for liver transplantation. In this regard, AILD are conditions with important areas of unmet needs.

As previously reported, we have invited colleagues at all major hospitals in Helse Sør-Øst to participate in a regional network for AILD. The aim is to follow patients prospectively at regular intervals and according to standardized protocols regarding clinical data, biochemical parameters and radiological imaging. We have now developed a Medinsight database for this purpose. The database is linked with the NoPSC biobank. Unfortunately, it has proven to be impossible for Medinsight to provide a web-based platform for the time being. We hope for a solution, but have decided to meanwhile collect data on paper forms that will be sent to NoPSC and entered into the database here. Post doc Mette Vesterhus, Haukeland University Hospital, has experience from following PSC patients systematically for several years (see separate section on The Bergen PSC Clinical Group). She will coordinate the further organization of the regional network, supported by professor Kirsten Muri Boberg, professor Erik Schrumpf, PhD Kristine Wiencke and other members of the NoPSC Clinical Group.

INTERNATIONAL STUDY OF THE CLINICAL COURSE OF PSC PATIENTS

As part of the collaboration within the International PSC Study Group (IPSCSG) we have participated in a study of the clinical course of the largest cohort of PSC patients ever assembled, including a total of 7121 patients from 37 centers in 17 countries and demonstrating how various clinical phenotypes influence on the outcome. We are very pleased that the manuscript "Risk Stratification through Clinical Phenotypes in Primary Sclerosing Cholangitis" has been accepted for publication in Gastroenterology. Further studies to characterize clinical features in this international cohort of PSC patients are planned.

EARLY DETECTION OF PSC-ASSOCIATED BILIARY TRACT CANCERS

Biliary tract cancers, including cholangiocarcinoma (CCA) and gallbladder carcinoma, complicate PSC in 15-20% of cases. Implementation of surveillance with ultrasound or magnetic resonance imaging (MRI) for early detection of gallbladder mass lesions followed by cholecystectomy in case of findings has improved overall survival for this subgroup of PSC patients. However, treatment outcomes and survival for patients with PSC-associated CCA remain exceptionally poor. Lack of early diagnostic markers account for late diagnosis of CCA, and the majority of patients are diagnosed at an advanced, incurable stage of disease. At present, surgery with complete resection represents the only curative intent treatment for CCA, but only one-third of the patients are candidates for radical resection at time of CCA diagnosis. Benefit of current palliative systemic chemotherapy regimens is limited with median overall survival approaching 12 months using current first-line treatment.

The lack of accurate methods for early detecting and firmly diagnosing PSC-CCA and the limited therapeutic options once CCA is diagnosed by available techniques, represent major unmet clinical needs in the current handling of PSC patients. Our main research focus in PSC-associated CCA is therefore to establish biomarkers for premalignant or early stage CCA that might be curable by radical surgery and to provide a detailed genetic- and molecular characterization of PSC-associated CCAs that could serve as basis for improved treatment strategies.

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 recently identified a panel of promising DNA methylation biomarkers for CCA, including CDO1, CNRIP1, SEPT9 and VIM. By analyzing biliary brushes from PSC ➜

patients with and without cancer, this biomarker panel detected CCA with high precision (85% sensitivity and 98% specificity), outperforming conventional biliary brush cytology (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 150 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 diagnosis of CCA in PSC.

ESTABLISHMENT OF NEW TREATMENT STRATEGIES OF PSC-ASSOCIATED BILIARY TRACT CANCERS

Mutations in different tumor suppressor genes and oncogenes have been detected in different subtypes of biliary tract cancers, but dedicated genetic studies in PSC-associated biliary tract cancers are missing. NoPSC, in collaboration with the Department of Pathology, University Hospital of Heidelberg, Germany, is leading a study in which genomic DNA extracted from archived formalin fixed, paraffin embedded PSC-associated biliary tract cancer specimens are analyzed by targeted, massive parallel sequencing covering hotspot mutations in cancer related genes. Throughout 2016 a large collective of more than 200 tissue samples from PSC-patients with biliary tract cancers have been established by national- and international collaboration. Preliminary analyses show 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-associated biliary tract cancers. Preliminary data from this project was presented in abstract form at the International Liver Congress in Barcelona in April 2016 and orally at the International Monothematic Conference on Cholangiocarcinoma in San Sebastian in May 2016.

Photo Tom H. Karlsen

Trine Folseraas, Kirsten Muri Boberg, Kristine Wiencke and Erik Schrumpf having an informal corridor meeting.

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In PSC, reliable tools to gauge disease activity and predict prognosis are lacking. This is a major concern for patients, their doctors and researchers alike. The search for biomarkers of disease activity and prognosis is currently a main focus for NoPSC and for the international PSC research community. Prospective studies based on annual patient follow-up are needed to identify and validate prognostic biomarkers. For this purpose, in 2013, NoPSC established the Bergen PSC Clinical Research Group (NoPSC-Bergen) as a node within the NoPSC organization.

NoPSC-Bergen is situated at Haukeland University Hospital in Bergen, the second largest hospital in Norway, responsible for a local population of near 400,000 patients and a regional referral population of 1.1 million patients, and thus well suited for prospective studies embracing patients in all stages of PSC. Mette Vesterhus, MD PhD, is the leader of the node. In 2016, the group expanded to include PhD student Anders B. Mjelle and medical student Aleksander Dahlman, while Tom H. Karlsen and Johannes R. Hov are associated members from NoPSC in Oslo. Core personnel includes bioengineer Ingeborg Brønstad, who manages the biobank in close collaboration with bioengineer Liv Wenche Thorbjørnsen at the main NoPSC biobank in Oslo.

The main emphasis of the NoPSC-Bergen node has been the establishment and running of a prospective PSC cohort and biobank, and studies of biomarkers of prognosis and disease severity in PSC including ultrasound-based assessment of fibrosis. Vesterhus led the building of infrastructure for a local biobank, the development of protocols and a database for the collection of prospective data, and initiated the Bergen PSC Prospective Cohort in January 2013. The PSC patients are followed with annual visits including clinical evaluation, laboratory testing, extensive biobanking and advanced ultrasound evaluation including liver stiffness assessment by ultrasound elastography. In addition, medical student Dahlman is devoted to the database development for symptom assessment tools for the PSC patients.

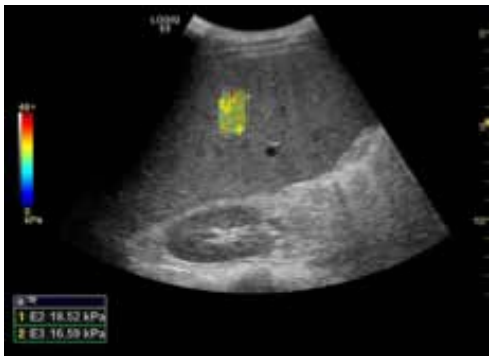
The cohort now includes about 80 non-transplant PSC patients, about half of which have four years of follow-up. More than 20,500 matrix tubes of biological samples from about 300 individual visits are currently stored in the Bergen NoPSC biobank, not including DNA samples and fecal samples for microbiota studies, which are stored separately. The biobank and database have already come to use in NoPSC-led papers describing the microbiota and liver stiffness (as evaluated by ultrasound elastography) in PSC patients, as well as providing data for international collaborators exploring novel prognostic markers in PSC or the impact of TNF-alpha treatment in PSC (analyses ongoing).

Haukeland University Hospital is the home of the Norwegian National Centre of excellence for Ultrasound in Gastroenterology. Headed by Prof. Odd Helge Gilja, President of the →

European ultrasound federation EFSUMB, this well-respected environment is renowned for its long-standing and broad expertise in the field of advanced ultrasonography. In recent years, a spectrum of ultrasound based methods has been launched for the assessment of liver fibrosis through liver stiffness measurements (elastography), showing promising potential as prognostic biomarkers in PSC. Baseline results for ultrasound elastography of the Bergen PSC prospective cohort were published in 2016, and analyses of the predictive ability of this method are planned to be performed in 2018-2019 when a majority of the cohort will have five years follow-up. However, both methodological studies and validation in prospective clinical studies are needed before implementation in patient follow-up, and this is one focus of NoPSC-Bergen. PhD student Anders B. Mjelle is working on these issues.

NoPSC has had a strong contribution to the emergence of putative prognostic biomarkers in PSC based on retrospective studies over recent years. Vesterhus & Hov published a study in Hepatology 2015 showing that the Enhanced Liver Fibrosis (ELF®) Test reliably predicted prognosis in PSC in two independent patient panels, and this result was recently validated in an international, multi-center study with Vesterhus as senior author. This exciting finding underscores the importance of fibrosis assessment for stratification and prognostication in PSC. NoPSC-Bergen has established a long-term collaboration with Nordic Biosciences (Denmark) and the Royal Free Hospital (London, UK) aiming to explore a "fibrosis fingerprint" in PSC and tailor a PSC-specific biomarker panel for prognostic purposes. Biomarkers of other pathological processes may also be of importance, however, exemplified with NoPSC-coauthored publications suggesting ANCA and anti-GP2 as stratifiers in PSC. In a paper accepted for publication in Journal of Hepatology in 2017, Vesterhus and colleagues explored putative biomarkers in bile, highlighting the importance of inflammation and neutrophilic pathways in PSC, particularly IL-8. Interestingly, analyses in bile indicated that the biomarker best fit to discriminate mild from severe PSC was calprotectin, well-known as a fecal test used for IBD activity assessment, and findings in plasma supported an association of calprotectin with prognosis. Further evaluation in a prospective setting of the ELF® Test and calprotectin (both commercially available), and other suggested prognostic biomarkers is eagerly awaited. The main goal of the prospective biobank and imaging is to form a unique and highly valuable resource for the establishment of validated tools for patient stratification enabling personalized clinical follow-up of patients with PSC as well as paving the way for improved patient recruitment and effect assessment for therapeutic clinical trials. Within the next few years, the prospective cohort will become ripe and ready for harvesting of sorely needed results regarding biomarkers for risk stratification and prognostication in PSC, hopefully translating to clinical application.

From left: Haukeland University Hospital and the Laboratory building where the biobank is located.



Above: Ultrasound elastography image of the liver. Right: Mette Vesterhus using the Philips iU22 machine for Ultrasound Elastography.

Awards

- Oslo University Hospital's Award for outstanding article 2nd half of 2015 was recieved by Johannes Hov and Mette Vesterhus for the article "Enhanced liver Fibrosis Score Predicts Transplant-Free Survival in Primary Sclerosing Cholangitis"

- The annual meeting of the Norwegian Gastroentero-logical Society in February 2016 awarded Laura Valestrand with a price for the best experimental work.

- In May 2016 Espen Melum recieved Oslo University Hospital's high ranking Early Career Award for his research on processes that regulate inflammation in the bile ducts.

- Johannes Hov and Marius Trøseid received "Stabsmøte-prisen på Rikshospitalet" a price for best lecture during hospital Grand rounds for spring 2016, for a lecture on the gut microbiome and personalized medicine.

From right: Espen Melum recieving his Early Career Award together with Pål Aukrust (Excellent Researcher Award) and Therese Seierstad (also Early Career Award).

Awards ceremony for outstanding research articles in the 2nd half of 2015 was recieved by (from left) Ellen Ruud, Jarle Jortveit, Johannes Roksund Hov (NoPSC), Klaus Murbræch, Jarle Brunn and Markus Krohn.

Photos: Oslo University Hospital

Liver transplantation

Kirsten Muri Boberg and Espen Melum

PSC is in most patients a progressive disorder that develops into liver cirrhosis with complications associated with end-stage liver disease. As there is no effective medical therapy that slows down disease progression liver transplantation (LTX) is the only potential curative treatment option for PSC. PSC patients also experience a highly increased risk of cholangiocarcinoma (CCA) (1) that complicates the evaluation for a potential LTX. The survival from PSC diagnosis until death or LTX is up to 21 years in population based studies and 13.2 years for patients referred to liver transplant centers (2), this discrepancy is most likely explained by referral bias. PSC has been the main indication (15%) for LTX in the Nordic countries for many years (3) and accounts for approximately 5% of all indications in Europe and the US. Impaired quality of life, mainly due to refractory pruritus or recurrent bacterial cholangitis, is considered a transplant indication in selected patients in some LTX centers (4). CCA is considered a contraindication to LTX. Some centers transplant PSC patients due to findings of cholangiocellular dysplasia in biliary brush specimens without evident tumor on radiology imaging, aiming to remove premalignant lesions or early stage CCA and prevent progression to invasive cancer (5). Patients with limited stage hilar CCA are in a few centers considered for liver transplantation, following an extensive preoperative protocol to reduce the tumor burden (6). Results after liver transplantation for PSC are favorable (3) and among PSC patients transplanted in Oslo during the last 10 years the 1, 3 and 5 year survival were 99%, 94% and 92%, respectively (Figure 1). To remove as much as possible of the affected extrahepatic bile ducts, a hepatico-jejunostomy has been the preferred surgical technique. In these patients, ERC has to be performed by using the balloon-enteroscopy technique. A duct-to-duct biliary anastomosis is sometimes selected. More recently, the alternative of a constructing a hepatico-duodenostomy has been used to re-establish bile drainage.

Recurrent PSC in the transplanted liver is diagnosed when cholangiographical (MRC or ERC) findings (>90 days post transplant) and/or histological features of PSC in a liver biopsy are compatible with PSC and potential causes of secondary sclerosing cholangitis have been excluded with reasonable certainty (7). The reported prevalence of recurrent PSC varies widely, from around 6 to 60%, with median time to recurrence ranging from 8.5 to 68 months (8–10). An intact colon after liver transplantation (11) and the presence of inflammatory bowel disease (9, 10) , appear to increase the risk of PSC recurrence. A number of other potential risk factors for recurrent disease have been also reported, but most of these have not been reproduced (8). Recurrent PSC is an important clinical entity as it is associated with reduced graft survival and increased risk of patient death (9).

The immunosuppression given after LTX would be expected to improve the disease activity in patients with IBD, given that some of the immunosuppressive drugs used after transplant are also effective treatments for IBD. The course of IBD after LTX has, however, proven to be variable. Among 14 studies, including 609 PSC-IBD patients with an intact colon at time of transplantation (16 – 218 patients in each study; median follow-up 4.8 years), 31% experienced improvement in IBD activity after transplantation, 39% remained unchanged, whereas 30% deteriorated (12). It is recommended to continue 5-aminosalicylate therapy post transplant (13, 14). The risk of colorectal cancer after LTX appears to be significantly higher in PSC-IBD patients than in patients transplanted for non-PSC indications (15). The risk of colorectal neoplasia may even be increased in PSC-IBD patients after as compared with before transplantation (16). Guidelines recommend yearly colonoscopy screening post transplant in PSC patients with IBD (17, 18).

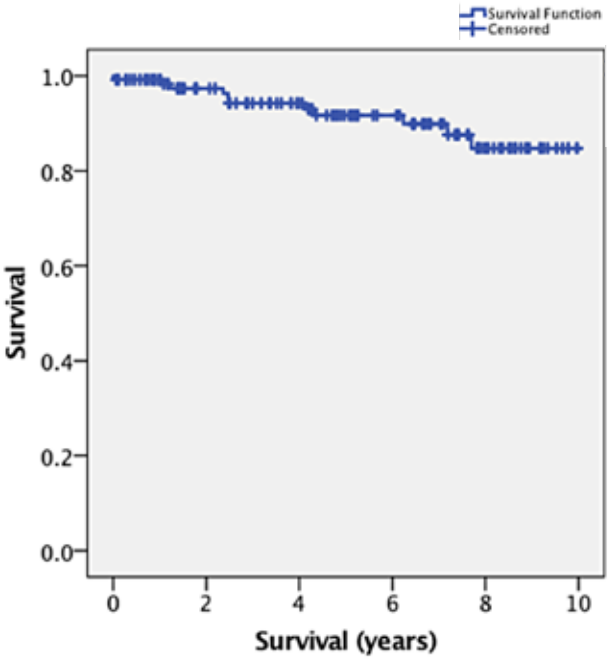


Figure 1. Survival of PSC patients transplanted in Oslo during 2006-2015.

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forening for autoimmune leversykdommer

FAL

Forening for autoimmune leversykdommer/Association for autoimmune liver diseases

FAL is a nonprofit association and exists for patients, relatives, friends and others who are interested in sharing experiences, knowledge and thoughts relating to the diagnosis of PSC, PBC and AIH. The aim of the Association is to be a channel of information and a meeting place for people diagnosed with one of these diseases.

FAL was founded in 2013, since then we have had three conferences, where we gather scientists and experts on the three diagnoses to update us on the latest news and answer questions from patients. Last year we had focus on research at PSC, new medi-
cines and fatigue. We also had a session where all the patients were gathered in groups to share knowledge and experience with each other. We have an upcoming conference in 2018 where we among other topics will focus on the social and psychological aspects of living with an autoimmune disease.

We are expanding our international network, and hopefully we will be able to have international guest's coming to our conference and meetings from time to time. So far, PSC Patients Europe (PSCPE) with seat in the Netherlands is our closest international collaborator.

Last year FAL was invited to join NoPSC in yearly meetings concerning research, and participating in this work. It means a lot for our association to be involved in this, and be able to actually influence the future research on PSC. We also invite researchers from NoPSC to give lectures on our conferences.

In addition to our next conference, our goal the next two years is to educate some of our members in peer-to-peer work, and continue the cooperation with Oslo Universitetssykehus on making guidelines for general practitioners and health professionals to follow up patients.

Espen Bunæs

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 stablished with the other research groups.

DEPARTMENT OF TRANSPLANTATION MEDICINE

Department Head, Prof. Pål-Dag Line, Prof. Aksel Foss, 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 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. Through the K.G. Jebsen Inflammation Research Centre (JIRC) we have several ongoing projects with Prof. Guttorm Haraldsen.

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 and Dr. Knut Brabrand 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 meta-genomic studies at NoPSC. Blood samples of patients undergoing magnetic resonance cholangiography (MRC) at the 20 years follow-up consultation are deposited in the NoPSC Biobank. Dr. Anne Nergård and Dr. Aida Kapic Lunder are performing the MRCs at Akershus University Hospital. Dr. Kristin Kaasen Jørgensen has entered a combined consultant–researcher position at Akershus University Hospital and continues her collaboration on PSC with the Center.

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.

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

Professor 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.

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, UNIVERSITY OF CAMBRIDGE ADDENBROOKE '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 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 under the daily supervision of Dr. Evaggelia Liaskou.

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 is has also been the co-supervisor of PhD student Elisabeth Schrumpf.

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 24 the development of a bile duct specific Cre mouse.

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 Professor Niklas Björkström 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, 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 coworkers are experts on stemcells in biliary tree, and the NoPSC Biobank material is used to explore these in PSC.

Photo Øystein H. Horgmo, University of Oslo

International PSC Study Group

Photo: Tom H. Karlsen

IPSCSG meeting at AASLD in Boston.

2016 was a particularly productive year for the International PSC Study Group (IPSCSG). The main event was the biennial meeting, which this time was hosted by the liver group at the Yale University in New Haven. This was the 4th IPSCSG biennial meeting (previous meetings in Oslo 2010, Hamburg 2012 and Amsterdam 2016). With more than 100 registered participants, notably without a single industry sponsor, the meeting was also the largest IPSCSG meeting ever held. Due to the size, break-out parallel sessions were crucial for the productivity of the meeting, and important progress were made along several key project avenues.

The work during the conference led to the formation of a new working group format: Animal & cellular models and pathophysiology, led by Mario Strazzabosco and Michael Trauner, Natural history and biomarkers, led by Cyriel Ponsioen and Chris Bowlus, Clinical Trial Design, led by David Assis and Gideon Hirschfield, Malignancies, led by Luca Fabris and Jesus Banales, Imaging studies, led by Christoph Schramm and John Eaton. The concept of the working groups is to coordinate collaborative projects within each thematic area, with one US and one European leader each.

Another key event during the Yale meeting was the joint symposium with the PSC Partners seeking a cure annual meeting. The patients held their annual meeting just before the IPSCSG conference, and it was decided to host a joint symposium to foster the relationship between patient representatives and scientists. The symposium was a great success, and should form the basis for future collaborations.

One important initiative initiated is the work to establish a validated method for cataloguing patient reported outcome measures (PROMs) in studies of PSC. This work is spearheaded by Doug Thorburn in the UK and David Assis in the US.

In addition to the two-day meeting at Yale, the regular update meetings were held during the International Liver Congress by the European Association for the Study of the Liver (EASL) in Barcelona in the spring, as well as during the Liver Meeting by AASLD in Boston in the fall. Many studies are reporting exciting progress, to mention a few the FICUS elastography/biomarker studies led by Olivier Chazouillieres has reached its recruitment goals (n>500) and the DILSTENT trial led by Cyriel Ponsioen was concluded with extremely important outcomes for the future endoscopic management of PSC patients.

During the Barcelona meeting, the transition of the secretariat functions from Oslo to a new base was initiated. Oslo has coordinated the group since it was established in 2010, and it is becoming timely to allow for a rotation, both for the sake of over time allowing for new types of ideas and input to the organizing, as well as to share the burden of coordinator efforts (which has been Tom Hemming Karlsen for all these years, who is now becoming increasingly busy, both at the local institutional level and as the upcoming secretary general of the governing board of EASL). The first step of this process was to establish status as to the functioning of the group. The second step of the process was to find a mechanism for the replacement, which will be that of an institutional anchoring. An application process as to which center will take over is currently open.

A critical effort of the group in 2016 was the conclusion of the big database project led by Tobias Weismüller, Kirsten Muri Boberg, Bettina Hansen and Palak Trivedi. The paper, reporting on clinical data from more than 7,000 PSC patients, was accepted for publication in Gastroenterology, and initiated discussions as to what would be the next steps of the clinical databases. Still there are opportunities for retrospective studies, and many such studies are already being initiated. Still, the major trend is that of a transition into prospective data collection with associated biobanking. Since data collection is mostly done in a decentralized manner, it is crucial for the group to register data in a standardized format. Much thanks to the driving force of Chris Bowlus, an initiative was therefore conducted to establish data definitions for a core set of common data. The progress in the imaging working group requires particular mentioning. Over two meetings, of which the last one was held in 2016, Christoph Schramm in Hamburg has been hosting a multidisciplinary meeting with gastroenterologists and radiologists to try drive standardizing of the use of magnetic resonance imaging (MRI) in PSC. The process has been very fruitful and has led to the writing of a position paper from the IPSCSG that will be published in 2017. Finally, but not least, 2016 was the year of the first IPSCSG accomplishment award. The award, which is being financially supported by NoPSC, comprises 5,000 Euro and is to be provided every second year from 2016 onward in conjunction with biennial meetings. The award is provided on the basis of nominations of young, emerging PSC researchers that have made a particular emphasis on PSC in their research. The first award recipient was Kirsten Boonstra from Amsterdam, and the justification was all her work done to set up a population-based cohort of PSC patients in the Netherlands in which many studies have already been performed.

Photo: Tom H. Karlsen

Kirsten Boonstra receiving the first IPSCSG award, celebrating with Erik Schrumpf.

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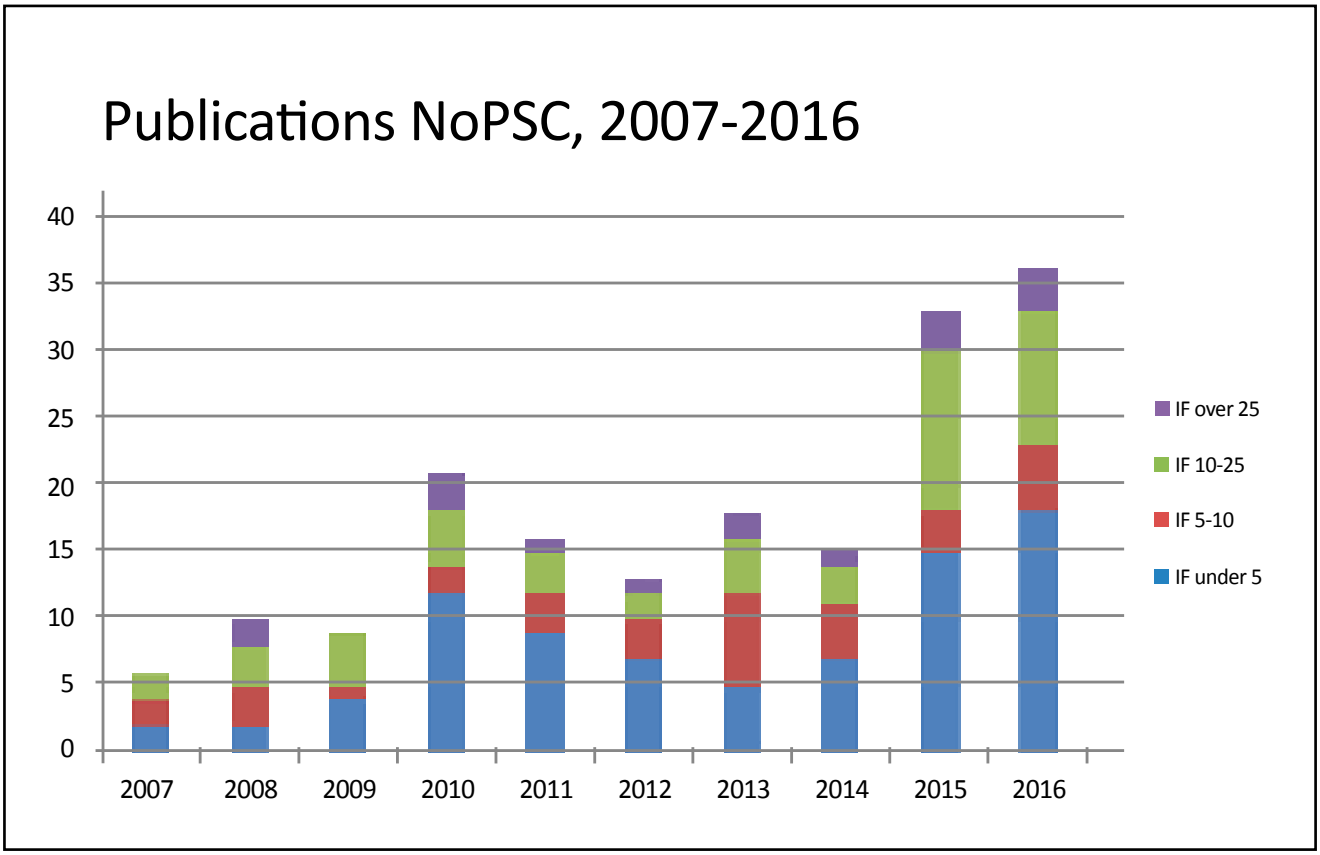

The diagram shows the Center's publication development including Impact factor (IF). Publications are registered in the year they were first published.

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