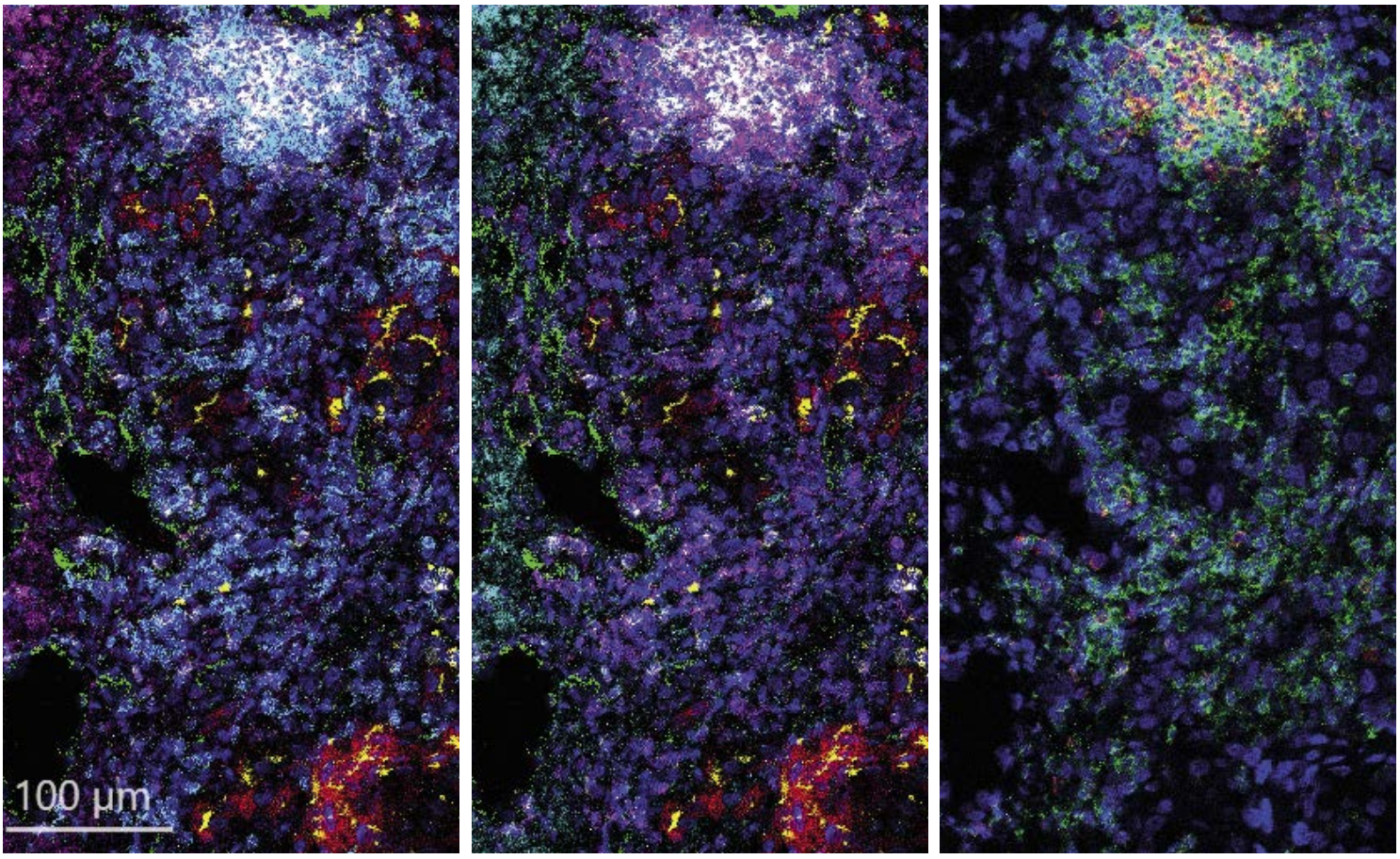
OSLO UNIVERSITETSSYKEHUS



Norwegian PSC Research Center

ANNUAL REPORT 2022

NOPSC

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

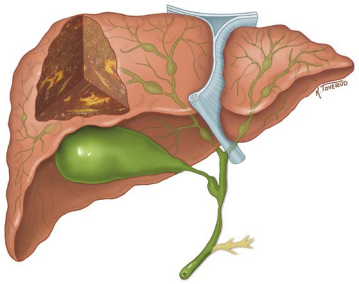
UiO : University of Oslo

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2022

What is PSC?

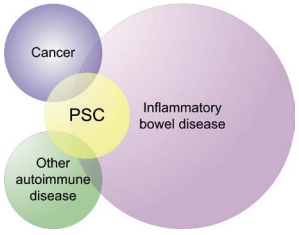
Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.



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

There is an increased risk of cancer of both the bile ducts (160-1500x) and the large bowel (5x). PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. There is currently 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 often have concurrent inflammatory bowel disease (IBD). Disease course is highly variable, and the time from diagnosis to liver transplantation may thus vary from 10-25 years. Individuals with PSC often suffer from fatigue, itching and repeated bacterial infections.



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

NOPSC
Norwegian PSC Research Center

Content:

NOPSC ANNUAL REPORT 2022

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
FRONT PAGE: *Using an advanced imaging technology (Imaging Mass Cytometry with a 39-color panel), cells in PSC livers are illuminated and distinguished by colorful surface markers.*
ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*
EDITOR: Merete Tysdahl
PUBLISHER: Oslo University Hospital
PRINT: Byråservice AS, 2023
SAMPLES: 220

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

Leader´s Corner

The year of 2022 exhibited two key developments: the start of the upscaling of activities to account for the expanded support granted by Canica A/S and the normalization of activities after Covid-19.

After the fading of omicron throughout the spring of 2022, activities in research and the clinic slowly returned to normal. Without doubt, the energy associated with face-to-face interactions in "real" meetings brings added value related to inspiration and generation of new ideas. For the team to finally be able to meet without restrictions whenever needed, also revitalized the NoPSC identity and belonging for our researchers, after two years on mostly Zoom and Teams for center-scale meetings. For the clinical research projects, the ScandPSC cohort in particular, the ending of Covid-restrictions also meant that recruitment of participants could continue, a point of major importance in the ongoing strengthening of the clinical research portfolio of NoPSC.

The upscaling of NoPSC to account for the expansion in the philanthropic donation from Canica A/S was a key point of emphasis of the NoPSC leadership throughout 2022. The overarching objective is to bring innovations to clinical management of people with PSC, and the dedicated advisory meeting hosted immediately after Covid-19, including external professors Fredrik Bäckhed, Massimo Pinzani and Arthur Kaser, provided important advise for strengthening the NoPSC governance, e.g. with innovation-oriented guest professor and a visiting scientist program to connect NoPSC research with international research groups with related initiatives. Our Scientific Advisory Board has also been renewed, accounting for the new perspective. A connection between NoPSC and the UiO:Growth House has provided invaluable assistance in a the new orientation, and our experimental research group is increasingly involved in the UiO:Lifescience scene, strengthening ties between NoPSC and the overall strategic orientation of our hosting institutions.

Several flagship activities were initiated throughout 2022. The two investigator-initiated clinical trials, related to vitamin B6 supplementation and PPAR-related drug targets, are moving towards their first recruitments, with support from two newly employed research nurses – a category of employees for which we never before had the privilege. Secondly, the generation of a "3D" molecular and cellular map of PSC affected livers and bile ducts has started, using a combination of various new technologies, spatial and single cell transcriptomics included. Furthermore, aligning with the orientation of PSC towards innovation and drug development, the basis of a collaboration with Novartis Institutes for Biomedical Research was laid throughout 2022, opening for the utilization of the organoid technology of the experimental group in the context of the Novartis drug screening platform. The Novartis collaboration also found a consolidation with a PSC oriented post doc to work in the group of Jan Tchorz in Basel, supported by material from the NoPSC biobank. In all we feel that important steps were taken towards the "new" NoPSC.

The generous philanthropic support for NoPSC remains the cornerstone for the activities and as evident from the accounts comprises a current 1/3 of the annual budget. In times where research grants are becoming more challenging to obtain, NoPSC still has ongoing success in several funding schemes, even from the Research Council of Norway, where the funds available have become very scarce. In many ways the successful grant applications from NoPSC researchers, can be considered a result of the baseline philanthropic support, and confirms the high quality of the ongoing research. Institutional support is still limited, but we are very happy to now receive a post doctoral position from the University of Oslo, as well as temporary technical support for the experimental research group provided by the Research Institute of Internal Medicine.

I would like to use the opportunity to thank all NoPSC employees and affiliated researchers for their dedication and hard work throughout 2022, and feel increasingly confident that we are heading towards major improvements in our understanding and capacity to deal with PSC.

Overview of the Norwegian PSC Research Center

NoPSC was established in 2007 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 NoPSC is the philanthropic donations from Stein Erik Hagen, having been made regularly since 2007 to substantially strengthen long-term research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis.

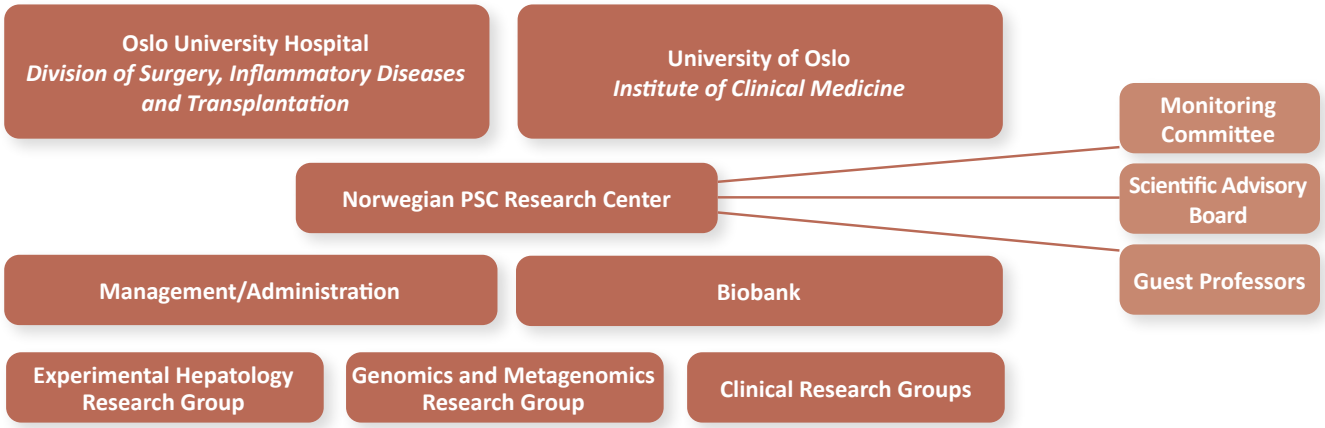
The philantropic funding is made with a grand vision to make a difference for people with PSC, and has given the research environment stability to prosperously grow its activity with 10 year horizons for each funding period.

Aims of the NoPSC organization

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

ORGANIZATION

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



MONITORING BOARD

The Monitoring Board oversees that the Center is managed according to the aims. Scientific plans and next years budget is dicussed in the autumn, while the Annual report and the accouting is rewieved at the spring/summer meeting.

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

Astrid Aksnessæther
Assistant director, Institute of Clinical Medicine, University of Oslo

Nina Paulsen
Canica A/S

MD Daniel Sørli
Canica A/S

Ass. Prof. Morten Tandberg Eriksen,
Head of Div. of Surgery, Inflammatory Diseases and Transplantation, OUH Rikshospitalet

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

Jan Ole Stangeland
CEO, Canica A/S

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

GUEST PROFESSORS 2018-2022

Ass. Prof. Niklas Björkström
Center for Infectious Medicine, Karolinska University Hospital, Huddinge, Sweden

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

SCIENTIFIC ADVISORY BOARD 2015-2022

The Scientific Advisory Board (SAB) reviews the center biannually. 2022 was the last meeting for this SAB.

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 GROUP

The Management Group has the overall responsibility for the research activities performed at the Center and the day-to-day management.

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Administrative coordinator.
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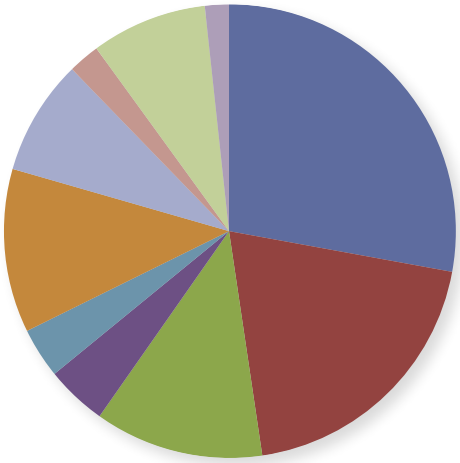
Accounting

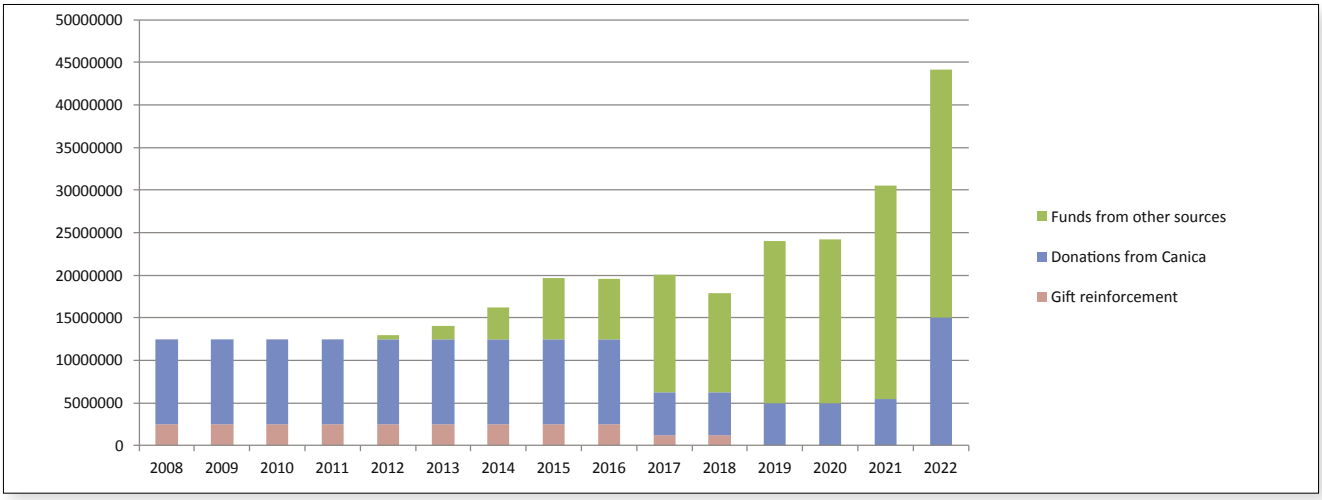
Expenditures from Canica funding in 2022 was NOK 9.042.769,-. The overall expenditure of all projects within the center amounted to NOK 32.443.000,- of these NOK 4.408.000,- was provided by UiO and OUS and NOK 19.292.000,- were from independent competitive grants, largely from Regional Health Authorities, the Norwegian Research Council, the Halloran Family Foundation and EU.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	**EXPENSES**	**INCOME**	**EXPENSES**
TRANSFER FROM 2021	-2 821 563		6 186 401	
INTEREST			103 143	
FROM CANICA			15 000 000	
OTHER INCOME	582 300		75 200	
TRANSFER FROM UiO	8 119 306			8 119 306
WAGES		2 796 532		1 778 798
OVERHEAD		161 829		270 674
INFRASTRUCTURE		13 729		14 550
OTHER OPERATING EXPENCES		3 829 891		176 766
TRANFER TO 2023		**-921 938**		**11 004 650**

	2022
Canica	9 043
Regional Health Authorithies in Norway	6 417
Norwegian Research Council	3 914
University of Oslo	1 418
EEA Baltic research funds	1 171
EU funding (ERC/Scientia Fellow)	3 815
OUH (Strategic, RIIM and ATX)	2 690
PSC Partners	733
The Halloran Family Foundation	2 688
Other	554
Thousand NOK	**32 443**

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





Using inflammatory bowel disease (IBD) to understand PSC

Johannes R. Hov

Most people with PSC are at some point diagnosed with IBD. The majority are diagnosed with IBD before a diagnosis of PSC can be made, but IBD presentation may also happen years after a PSC diagnosis or even after liver transplantation for PSC. The strong link nevertheless suggests that the disease mechanisms are related. Are there shared causes or is one disease causing the other? At NoPSC we have used the occurrence of IBD to guide our understanding of PSC for a long time. There are several features of PSC-IBD related to distribution and activity, which lead us to think that IBD in PSC is different from "normal" IBD without PSC.[1,2] Large international studies of genetic factors in PSC, in part driven from Oslo, provided the clear message that PSC (and PSC with IBD) is genetically something more than just IBD[3], supporting these clinical observations.
Furthermore, in detailed studies of the immune cells in PSC with IBD, we see similarities between the gut and liver, compatible with a similar immune involvement of both organs.[4,5]

We have limited knowledge on how the activity and treatment of IBD affects PSC and vice versa. The current recommendation is therefore to treat IBD according to guidelines irrespective of PSC. This means to aim for inducing and keeping remission and a normal gut mucosa. In people with IBD, there should be a low threshold for suspecting and evaluating the liver for the presence of PSC. This is also important since we believe detecting PSC early could be relevant to ensure that therapy for slowing disease progression allows to work before liver injury is too extensive. One important difference between PSC-IBD and IBD without PSC is that colonoscopy surveillance for development of malignancy should be initiated earlier in PSC with IBD (from diagnosis) and preferably be done on an annual basis, due to the enhanced risk of colorectal cancer in IBD with PSC.

Ongoing research priorities in IBD at NoPSC are to define who will develop PSC, to diagnose PSC as early as possible, and mechanistic studies, particularly addressing the question on how IBD activity and microbial features in the gut may influence the liver. We have shown that the gut microbiota composition is different in PSC compared with healthy individuals and individuals with IBD but no PSC, while only subtle differences are seen in PSC with and without IBD.[6,7] In order to understand more about how the gut microbiota influences IBD and IBD phenotypes, we are currently investigating thousands of stool samples from people included in the Inflammatory Bowel Disease in South-Eastern Norway (IBSEN) III study. We are in parallel investigating the frequency of PSC in this population after 5 years of IBD, by performing MRC screening in people without a clear suspicion of liver disease.[8] Taken together, we may define the utility of the microbiota as a clinical tool for prediction of prognosis in IBD or the occurrence of PSC, and, moreover, potentially also understand the microbial contribution to PSC development in IBD.

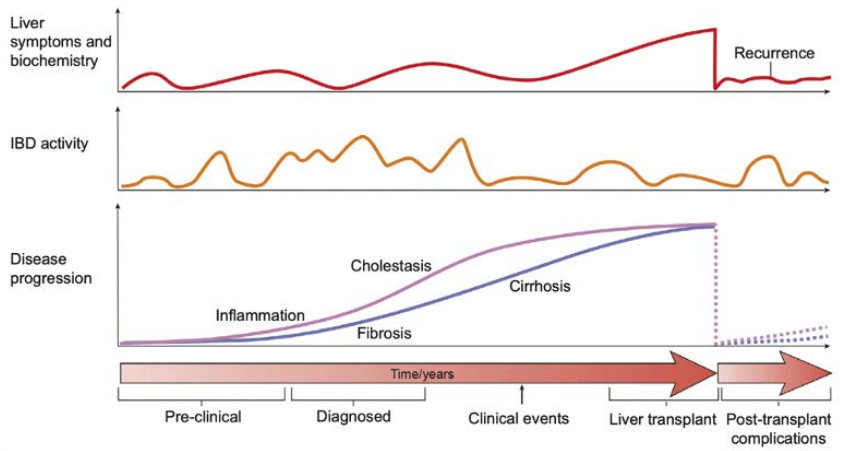


Figure: *The graphic illustrates the variable natural course of PSC and IBD in PSC, where it is clinically often difficult to find a pattern. A more detalied understanding of the underlying process in the gut and its relation to biliary disease will be important to improve the clinical care in PSC and PSC with IBD.*

1. *Fausa, O., Schrumpf, E. & Elgjo, K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. Semin. Liver Dis. 11, 31-39 (1991).*
2. *Jorgensen, K. K. et al. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflamm. Bowel Dis. 18, 536-545 (2012).*
3. *Ji, S. G. et al. Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. Nat. Genet. 49, 269-273 (2017).*
4. *Chung, B. K. et al. Gut and Liver B Cells of Common Clonal Origin in Primary Sclerosing Cholangitis-Inflammatory Bowel Disease. Hepatol Commun 2, 956-967 (2018).*
5. *Henriksen, E. K. et al. Gut and liver T-cells of common clonal origin in primary sclerosing cholangitis-inflammatory bowel disease. J. Hepatol. 66, 116-122 (2017).*
6. *Kummen, M. et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. Gut 66, 611-619 (2017).*
7. *Hole, M. J. et al. A shared mucosal gut microbiota signature in primary sclerosing cholangitis before and after liver transplantation. Hepatology 77, 715-728 (2023).*
8. *Lunder, A. K. et al. Prevalence of Sclerosing Cholangitis, Detected by Magnetic Resonance Cholangiography, in Patients with Long-term Inflammatory Bowel Disease. Gastroenterology (2016).*

Recurrent PSC – clinical challenge and window to the disease process

Johannes R. Hov, Lise Katrine Engesæter and Tom H. Karlsen

Liver transplantation is an important treatment option in PSC. In the Scandinavian countries, PSC has been the most common indication for transplantation over time. In Norway, the reasons for transplantation in PSC are typically either advanced stage liver disease with severely reduced liver function and other complications, severe symptoms related to bile duct obstruction that is not amenable to endoscopic dilatation, and in selected cases, suspicion of early-stage malignancy in the bile ducts. Outcomes after liver transplantation in PSC are in general good, making this a beneficial option when the disease has reached an advanced stage and complications become a significant problem.

A key clinical challenge is that PSC may recur in the new liver. The proportion with recurrent PSC (rPSC) is often reported to be 20-25% at some time point after liver transplantation. It is hard to predict whether rPSC will become a significant clinical problem or not. For some people with rPSC, there is slow progression with little impact on the liver and quality of life, but some individuals may over time develop severe rPSC with need of another another liver transplantation. It has been hard to know the true frequency of recurrent disease. Post-transplant care varies between centers, and if routine MRI or liver biopsies are performed, rPSC is likely to be diagnosed in more people.

It has also been difficult to define what predisposes to PSC recurrence. Acute rejection in the post-transplant phase has been associated with rPSC, while colectomy before transplant may be slightly protective. Based on these important questions, an ongoing project at NoPSC aims to characterize the clinical history of all individuals transplanted for PSC in Norway, including details on how and when PSC recurs. This is a large collaboration with the departments of radiology and pathology, since all available MRI investigations and liver biopsies are re-evaluated in the process. The project will also use data from the Nordic Liver Transplantation registry, which is administrated from Oslo (by Espen Melum). In addition to establishing exactly how common rPSC is in Norway, we will learn more about the risk factors of rPSC and the outcomes.

Recurrence of PSC after transplantation is scientifically intriguing because it occurs despite treatment with potent immunosuppression. The recurrence of disease in a new and healthy liver suggests that the disease involves factors from outside the liver, and points to the involvement of mechanisms which are not easily controlled by immunosuppressive drugs. Taken together, the recurrence after liver transplantation represents a research opportunity.

In the project *StopAutoimmunity*, funded by an EU grant (so called "ERC Starting Grant") to Johannes Hov, the idea is to use the follow-up of transplanted individuals with PSC as a window to study PSC pathogenesis (**Figure**). Parallel features of PSC before and after liver transplantation will be investigated to define non-immune factors driving both PSC and rPSC, such as the microbial composition of the gut. In the first study applying this design[1], the microbiota composition was investigated in biopsies from the gut mucosa in transplanted and non-transplanted individuals. We have so far made two key observations: 1) The gut microbiota after transplantation does not normalize and 2) There are shared features in the gut microbiota composition of those with PSC and those with rPSC. In addition, we have found that biochemical features potentially related to the microbiota (vitamin B6 deficiency) also persist after liver transplantation[2]. Overall, this strengthens the rationale for studying how the gut microbiota may be driving PSC and rPSC. Notably, in combination with detailed clinical data on recurrence, we may identify new opportunities related to (early) treatment or even prevention of recurrence – which could even hold relevance for PSC before liver transplantation.

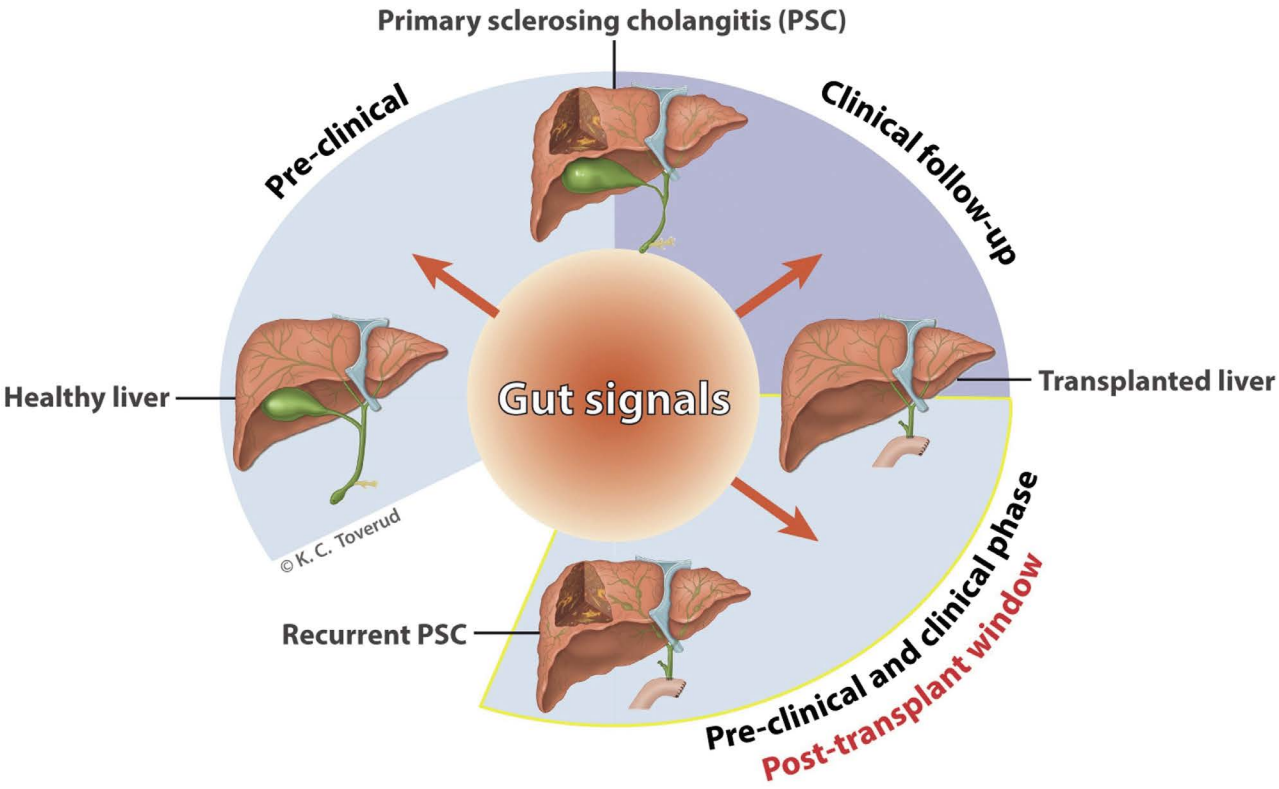


Figure: *Outline of the natural history of PSC (clockwise circle) and how recurrent disease may occur and help elucidate disease mechanisms in PSC through post-transplant research. There is probably a long pre-clinical phase about which we know very little, followed by PSC diagnosis (12 o´clock). Some individuals will over time need a liver transplantation (3 o´clock), and in a subset of these PSC will recur. The figure illustrates how research on recurrent disease (a "human model") in the post-transplant "window" could potentially shed light on disease mechanisms, which are active also before transplantation, e.g., microbial factors from the gut. Figure printed with permission from Kari Toverud, CMI.*

1. *Hole, M. J. et al. A shared mucosal gut microbiota signature in primary sclerosing cholangitis before and after liver transplantation. Hepatology 77, 715-728 (2023).*
2. *Braadland, P.B. et al. Clinical and biochemical impact of vitamin B6 deficiency in primary sclerosing cholangitis before and after liver transplantation. J Hepatol In press (2023).*

GENOMICS AND METAGENOMICS RESEARCH GROUP

From top left: Jørgen D. Rønneberg, Simen Hyll-Hansen, Mikal J. Hole, Kristian Holm, Indre Karaliute (exchange PhD student from Lituania), Petra Hradicka, Hanne Lyche Alme, Brian Chung, Johannes R. Hov, Georg Schneditz, Lise Katrine Engesæter and Beate Vestad. Not present: Maria Maseng, Peder Braadland and Antonio Molinaro.

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RESEARCH PROFILE

The Genomics and Metagenomics Research Group aims to characterize and understand how the human genome and the gut microbiome influence inflammatory disease, and how this knowledge can be applied clinically. Our general approach is to use nontargeted high-throughput omics like sequencing and metabolomics, followed by targeted or hypothesisdriven methods, supported by bioinformatics and biostatistics including machine-learning. Increasingly, experimental approaches in vitro and in vivo (mouse models) are important to define cause-or-effect and disease mechanisms.

Our main interest is primary sclerosing cholangitis, which we study both before and after liver transplantation (with or without recurrence) together with healthy individuals and patients with inflammatory bowel disease (IBD). Our main human materials are blood and fecal samples, but we are also

establishing methodology for microbiota profiling in low-biomass material (blood, tissue, bile), while our experimental agenda involves germ-free and conventional mice with induced biliary or intestinal disease, in collaboration with the Experimental Hepatology Group.

Our current main working hypothesis is that biochemical footprints of microbial activity is driving disease. We aim to define altered functional microbial changes using metagenome sequencing (i.e. the study of all microbial genes) and metabolomics. Our first interesting finding was that altered microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 as a potential disease-modifying factor caused by microbiome changes. A clinical trial focusing on translational aspects of vitamin B6 supplementation is on its way. This represents an example on how we work to identify and potentially treat altered microbial functions, defining their clinical impact as biomarkers or in therapy.

Recurrence of PSC after liver transplantation is a significant clinical problem, and our work to describe it in detail (clinically) in the Norwegian population is in its final phase. An important question is whether PSC and recurrent PSC represent the same disease, which would make recurrence useful as a "human model" of disease. This is the underlying idea of the ERC Starting Grant project *Stop-Autoimmunity*, which directs many of the priorities in the group. The first data on gut microbiota in this setting was published in 2022 (see presentation elsewhere), identifying overlapping features in PSC before and after liver transplantation.

With growing data size and complexity, we increasingly depend on bioinformatics and statistics. In our IBD focused projects, now comprising thousands of samples, in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we now apply more advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The group also works more disease independent with *Clinical microbiota medicine*, as part of a Strategic research area at Oslo University Hospital awarded to the group in 2019. Interventions targeting the gut microbiome to treat disease may provide evidence of causal relationships between the gut microbiome and disease. In 2022, MD Christopher Storm-Ligaard defended his thesis "Clinical interventions of the human gut microbiota" on this topic. The annual National Microbiota conference in November was also a success – the ninth consecutive event since 2014.

Finally, we continue our agenda on the targets of autoimmunity in PSC - does it originate in the gut? And further studies of GPR35 in inflammatory disease are also ongoing, supported by funding to the center leader Karlsen and post doc Georg Schneditz.

FUNDING

The people in the group were in 2022 funded by one ERC Starting Grant, five grants from Regional Health Authorities of South Eastern Norway, Nordforsk, one PhD student following an industrial PhD scheme (funded by Research Council of Norway), one Strategic research area grant in Oslo University Hospital and one postdoc funded by a grant from UEG and Canica. Canica is also funding one bioinformatician. In a collaboration with the Experimental Hepatology Group and partners from the Baltic area (driven from Lithuania) we also have funding from the EEA Baltic research funds, which is funding one post doc.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group has extensive collaborations ongoing within NoPSC and the Research Institute of Internal Medicine, multiple clinical research groups (including in particular the IBD group at the Ullevål campus) as well as pathology and radiology.

Regionally and nationally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator.

Internationally, we continue strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish groups in Stockholm, Gothenburg and Uppsala.

CLINICAL RESEARCH GROUP IN OSLO

From left; Kirsten Muri Boberg, Merete Tysdahl, Sigurd Breder, Kristine Wiencke, Trine Folseraas and Liv Wenche Thorbjørnsen.

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RESEARCH PROFILE

The projects of the Clinical Research Group in Oslo aim at improving clinical outcomes for PSC patients. Over the last years, we have had a particular focus on molecular characterization and identification of early detection markers and treatment targets for PSC-associated cholangiocarcinoma (PSC-CCA).

IDENTIFICATION OF EARLY MARKERS FOR PSC-ASSOCIATED BILIARY TRACT CANCER

We have several ongoing projects exploring novel markers for early and more accurate detection of biliary tract cancer in PSC. The main aim of these efforts is to provide PSC patients with meaningful surveillance for CCA and to enable an early and more precise diagnosis of CCA in PSC.

In collaboration with the Epigenetics group at the Department of Cancer Prevention, Institute for Cancer Research at the Norwegian Radium Hospital, we have previously identified four DNA methylation markers that may improve early detection of CCA in patients with PSC. We are now utilizing whole-genome methylome sequencing on PSC-CCA tissue samples to detect

additional, potentially more accurate markers for early CCA in PSC. In the near future, our aim is to test novel, promising epigenetic markers in a large discovery and validation panel of bile and serum samples derived from our biobank.

In another collaboration with the Biodonostia Institute, Donostia University Hospital, San Sebastian, Spain, we aim to analyse the protein content of extracellular vesicles derived from multiple bile samples from patients with PSC and/or CCA to look for prognostic, predictive and diagnostic protein signatures for CCA in PSC.

MOLECULAR CHARACTERIZATION AND IDENTIFICATION OF DRUGABLE TARGETS IN PSC-ASSOCIATED BILIARY TRACT CANCER (BTC)

We have over the last years had a close collaboration with the Department of Pathology at the University Hospital of Heidelberg and the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, aiming to characterize the genomic landscape of PSC-BTC by exome sequencing using a large panel of samples from PSC-BTC tumors. By this, we have identified multiple novel genetic drivers, prognostic markers and actionable targets in PSC-BTC. Absence of signature mutations for small duct type CCA in intrahepatic tumours from patients with PSC provides further evidence that PSC-associated BTC represents a homogenous large duct histological subtype. We plan to submit and hopefully publish this work within 2023. In continuation of this project, we plan additional sequencing efforts using cell-free DNA derived from liquid biopsy specimens from patients with PSC and PSC-BTC to see if we can improve early detection and selection of targeted therapies in PSC-BTC.

STATUS AND PROJECTS RELATED TO THE NORWEGIAN PSC BIOBANK

The cross-sectional biobank and database of the Norwegian PSC Research Center are steadily growing, and represent a valuable source for PSC research both nationally and internationally. Currently we have included clinical data and biological samples on approximately 1000 Norwegian PSC patients and more than 1000 disease controls. In 2022 we started a larger update of the NoPSC database aiming to include a broader set of prospective and cumulative data categories.

By contributing patient data to other clinical registries administered by the National network for autoimmune liver diseases, the International PSC Study Group and the European Network for the Study of Cholangiocarcinoma, we actively facilitate research on characterization, management and treatment of PSC and CCA. In 2022 we have contributed to several research articles outgoing from these collaborations (see publication list for details).

CLINICAL TRIALS

It is of importance for NoPSC to contribute to drug development in PSC and CCA through the participation in clinical trials. NoPSC is currently involved in a phase III clinical trial for nor-ursodeoxycholic acid, and we aim to actively recruit patients for additional clinical trials that are planned in the near future.

KEY COLLABORATORS

- The Department of Pathology, Rikshospitalet, Norway
- The Epigenetics Group at the Department of Cancer Prevention, Institute for Cancer Research, the Norwegian Radium Hospital, Norway
- Karolinska University Hospital, Stockholm, Sweden
- Helsinki University Hospital, Helsinki, Finland
- Biotech Research and Innovation Centre, Department of Health and Medical Sciences, University of Copenhagen, Denmark
- Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, Germany
- The Department of Pathology at the University Hospital of Heidelberg, Germany
- Biodonostia Institute, Donostia University Hospital, San Sebastian, Spain
- The Mayo Clinic, Rochester, USA
- The International PSC Study Group (IPSCSG)
- European Network for the Study of Cholangiocarcinoma (ENSCCA)
- The COST Action CA18122 EURO-CHOLANGIO-NET

CLINICAL RESEARCH GROUP IN BERGEN

From left: Lasse M Giil, Holmfridur Helgadottir, Mette Vesterhus, Karen Rønneberg and Ingeborg Brønstad.
From top right: Kristin Kaasen Jørgensen and Guri Fossdal.

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RESEARCH PROFILE

The projects of the Clinical Research Group in Bergen aim to identify, evaluate and establish prognostic biomarkers and surrogate markers of disease activity and severity in PSC. Our ultimate goal is to contribute to the development of tools that will be implemented for prognostication and tailored, personalized clinical follow-up, and for improved patient selection and effect assessment in clinical trials. The establishment of a large, prospective, Scandinavian biobank and a national patient cohort are important strategic aims in order to achieve these goals and to facilitate patient inclusion into clinical trials.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS

We were the first to identify and validate the ELF®Test as an independent prognostic marker in PSC, and our studies have contributed knowledge about the variation of ELF test and liver stiffness in PSC patients. Current EASL guidelines now recommend using the ELF test and liver stiffness measurements in PSC to assess prognosis and fibrosis progression.

NoPSC has contributed substantially to the identification of a range of other biomarkers associated with clinical outcome in PSC. Moreover, we are exploring novel, tailored, and dynamic biomarkers of fibrosis in PSC in collaboration with corporate partner Nordic Biosciences in Denmark. Preliminary results in a Norwegian patient panel indicated that a combination of markers of inflammation, gut microbiota metabolism, and fibrosis increased our ability to capture disease risks and outcomes in patients. Pursuing this, we are now exploring a broad range of biomarkers reflecting various disease pathways in PSC in two large patient panels from Scandinavia and the Mayo Clinic.

IMAGING AND ARTIFICIAL INTELLIGENCE

Through a strategic collaboration with the Mayo Clinic, NoPSC is involved in several studies investigating artificial intelligence in MRI in PSC for which results were published in 2022. We have contributed to several MRI-related papers initiated through the International PSC Study Group (IPSCSG). The 2022 annual meeting of the IPSCSG MRI Working Group was successfully held in Oslo.

CLINICAL TRIALS

Contribution to drug development for PSC through increasing involvement in clinical trials is an important aim, and we are involved in an ongoing phase III clinical trial for nor-ursodeoxycholic acid. Approval is pending for a multicenter, proof-of-concept investigator-initiated clinical trial funded by grants from Helse Vest and the Halloran Family Foundation. In this project, we aim to investigate the effect on parameters reflecting disease severity or pruritus and explore the mechanisms of action of a novel pan-PPAR agonist in PSC.

KEY COLLABORATORS

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

NATIONAL NETWORK FOR AUTOIMMUNE LIVER DISEASES

National network for autoimmune liver diseases is a multicenter study established 2019. The prospective research registry and biobank for non-transplant patients with PSC, PBC or autoimmune hepatitis includes annual collection of data, imaging, biological samples, and patient-reported outcomes. The ultimate goal is to include all eligible patients nationally.

PROJECT AIMS

The project aims to study prognostic factors, biomarkers of disease activity and prognosis, and patient-reported outcome measures in PSC, PBC and AIH, to provide a platform facilitating patient recruitment to clinical trials and to promote access to optimal and equal clinical management for patients with autoimmune liver diseases across Norway.

STATUS

In 2022, patient recruitment increased substantially, and the number of active centers was doubled. All university hospitals and all four health regions are now involved. Further expansion is planned for 2023. There are now 413 PSC patients included from 17 active centers. Descriptive data were presented at the Annual Meeting of the Norwegian Gastroenterology Society.

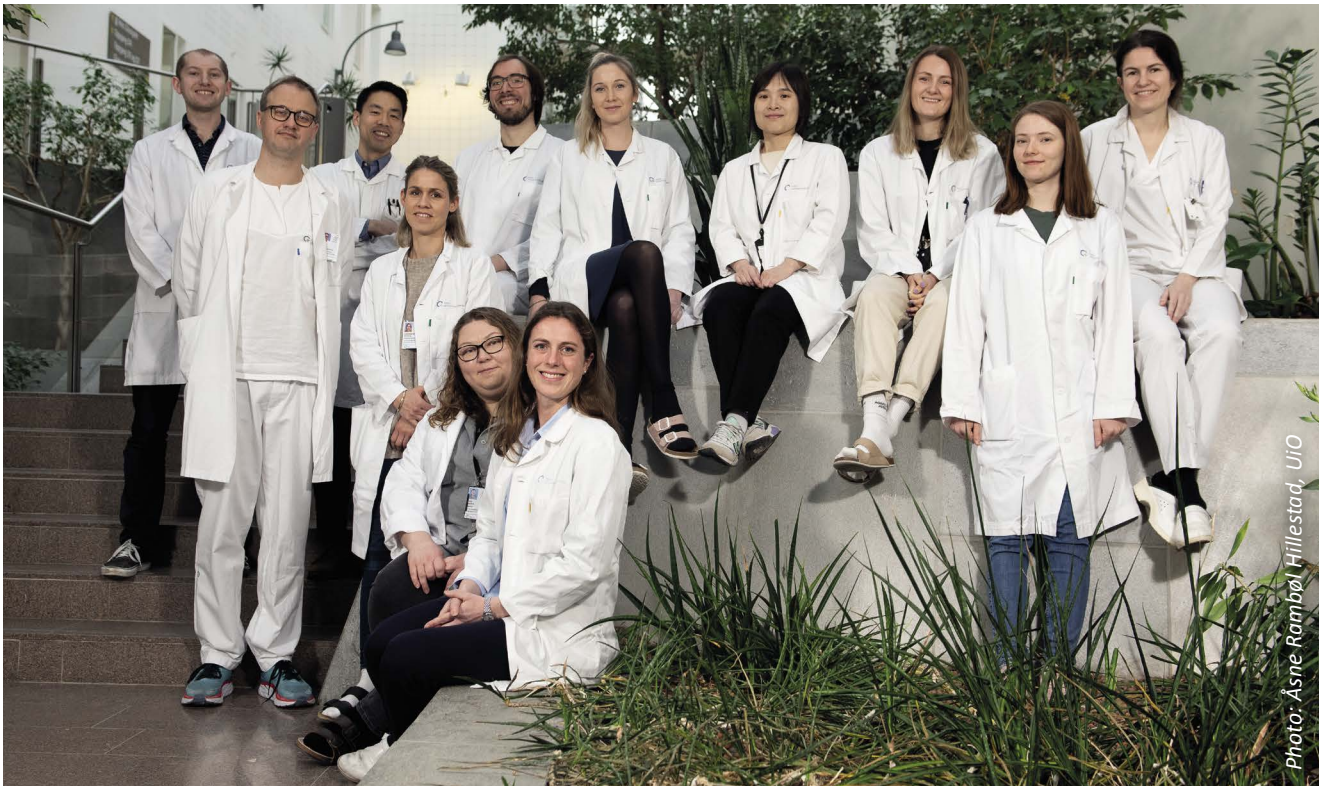
PROJECT LEADER
Mette Vesterhus, NoPSC

PROJECT COORDINATOR
Kristin K. Jørgensen

BOARD LEADER GROUP
Mette Vesterhus (NoPSC)
Trine Folseraas (NoPSC)

BOARD MEMBERS
Kristin K. Jørgensen (HSØ)
Svein Oskar Frigstad (HSØ)
Lars N. Karlsen (HV)
Åse Kjellmo (FAL, patient representative)

EXPERIMENTAL HEPATOLOGY RESEARCH GROUP



From top left: Henry W. Hoyle, Brian Chung, Markus Jördens, Anna Frank, Xiaojun Jiang, Enya Amundsen-Isaksen, Elisabeth Schrumpf, Espen Melum, Oda Helgesen Ramberg, Yuliia Boichuk, Tine Simensen Oldereid and Lisa Brynjulfsen.

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The Experimental Hepatology Research Group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research Institute of Internal Medicine. In 2022 the group consisted of the group leader, two senior researchers, four postdocs, five PhD students, the lab manager, one researcher and two technicians. The overall main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and what role the cholangiocytes play in propagation of the inflammatory process.

Our strong collaboration with the Hybrid-technology-hub on establishing a bile-duct-on-a-chip was in 2022 strengthened by the recruitment of Henry W. Hoyle who joined the group in June. Henry has an ideal background for the project with a combination of molecular biology and physics. He defended his PhD thesis at the University of Durham before joining NoPSC. His main responsibility will be to improve the chip design and its integration with cholangiocyte organoids and immune cells. The organoid and bile-duct-on-a-chip projects were also strengthened in 2022 by Yuliia Boichuk who contacted us through the Science of Ukraine initiative where NoPSC offered to help Ukrainian scientists. Yuliia was one of the two Ukrainian colleagues that joined NoPSC. She has a solid background in molecular biology and long experience with advanced cell culture and was therefore an ideal fit for the ongoing work on organoids and chip-based technologies. At the end of the year her position was prolonged by a grant from “Fondsstiftelsen” at Oslo University Hospital.

In an extensive follow-up study to our 2021 paper on CD100 in Science Translational Medicine we have in 2022 investigated the direct interaction of cells from CD100 mutated mice with cholangiocytes and discovered a clear Th17 profile. These data were presented at the International Liver Congress in London as an oral presentation and was well received. The large project addressing the timing of introduction of the microbiome in the NOD.c3c4 mouse model was concluded in 2022, with detailed characterization of the immune phenotype using high-dimensional flowcytometry with 25-colors using the BD Symphony located at the flow-cytometry core facility.

In 2022 we published a report demonstrating the presence of antigens for mucosal associated invariant T (MAIT)-cells in the bile of patients with PSC and that these antigens were largely defined by the microbiome. Using organoids as a platform for detailed studies on the role of interaction of NKT cells with cholangiocytes, we were able to further dissect the antigen presentation potential of cholangiocytes themselves. These observations will be followed up in relevant mouse models with genetically altered antigen presentation specifically in the bile ducts.

We have expanded our work using 10x technology to examine the single cells and spatial transcriptomics in two different mouse models that we have used for many years in the group; NOD.c3c4 mice with spontaneous bile duct inflammation and induced bile duct inflammation following direct injection of oxazolone in the bile ducts. These two projects will be part of the PhD work of Markus Jördens and will accompany studies using the same methodologies in a large panel of PSC patients. In new a PhD project, which was awarded funding by The South-Eastern health authorities, we will also use sequencing-based technologies to potentially define antigens for PSC. In this project we have recruited Lisa Bynjulfsen as a PhD student and she will be supervised by senior scientist Brian Chung as the main supervisor.

Lisa Brynjulfsen working in the lab.

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

PROJECT BACKGROUND

ScandPSC merges two strong research environments in Norway and Sweden in a collaborate effort to collect a large prospective biological and clinical sample collection. In Scandinavia, a PSC "hot-spot", high willingness among people with PSC to participate in research studies and limited loss to follow-up coupled with good national registries, provide ideal conditions for high-quality, well-powered prospective studies.

MANAGEMENT GROUP

Mette Vesterhus, Prof. MD, PhD
Haraldsplass Deaconess Hospital, Bergen, Norway

Annika Bergquist, Prof. MD, PhD
Karolinska University Hospital, Huddinge, Sweden

Trine Folseraas, MD, PhD
Oslo University Hospital, Norway

Niklas Björkström, Ass. Prof. MD, PhD
Karolinska University Hospital, Huddinge, Sweden

STEERING COMMITTEE

National PIs Annika Bergquist (Sweden) and Mette Vesterhus (Norway)
Lead physicians from collaborating centers (CI) in Norway and Sweden

MONITORING BOARD

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

EMPLOYED PROJECT COLLABORATIVE

Kristin K. Jørgensen, MD PhD, Norway

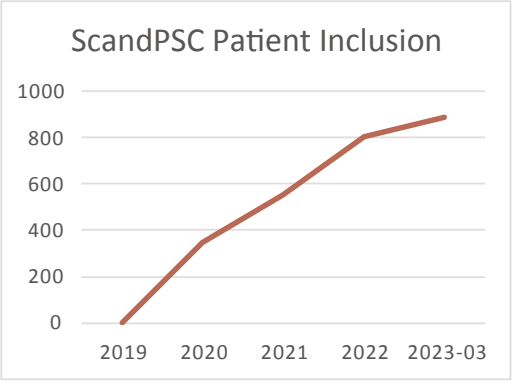
There were 3 ScandPSC Board Meetings in 2022. Annual Meetings for collaborating centers were held in Norway and Sweden, respectively.

FUNDING

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

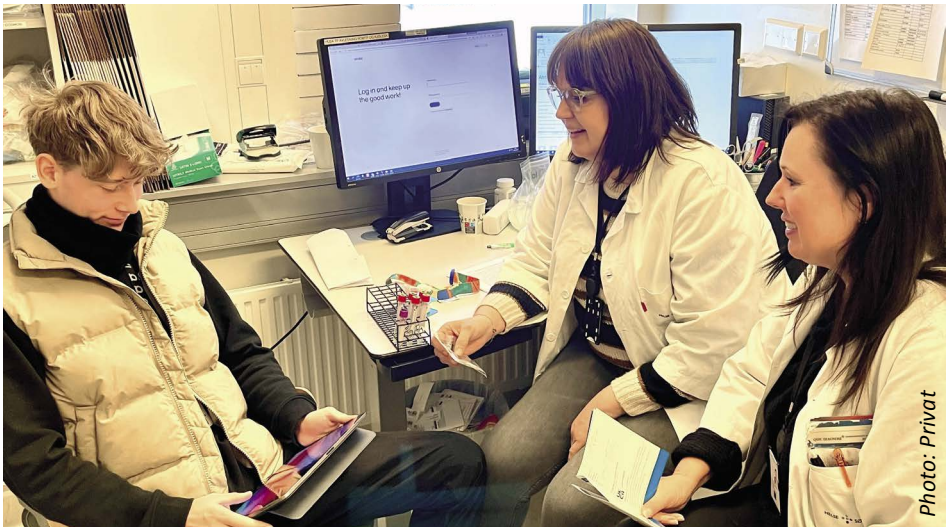
PROJECT STATUS 2022

By 31.12.2022, the prospective cohort included biobank serum samples from 803 individuals with PSC (512 in 2021), of which 413 in Norway and 390 in Sweden. This represents a 57% increase over the last year. By 01.03.2023, a total of 886 patients were included. The participants demonstrate typical demographic characteristics: a median age of about 37 years at inclusion; the majority are male (65%) and have IBD (ca 80%); about 10% have PSC-AIH and 30% have another autoimmune disease. Several novel centers started inclusion in 2022, increasing the number of active centers to 24 (Norway 17, Sweden 7). During 2022, nation-wide recruitment was accomplished in both Norway and Sweden.



AIMS

ScandPSC aims to establish the world's largest prospective PSC biobank and register and use this as a platform for clinical trials and biomarker discovery.



From left: AIL patient, study nurse Synnøve Aure and local PI Kristin K. Jørgensen during an annual follow up.

ECONOMY

Exspenses 2021		
Norway	Salaries	269 290
	Biobank- and visit-related expenses	480 189
	Fibroscan	748 932
	VAT, will be compensated	222 036
Sweden	Biobank- and visit-related expenses	961 884
SUM Expenses		**2 682 330**
Income	From 2021 and new donation	-3 327 784
Transfered to 2023		**-645 454**

PRIORITIES FOR 2023

The main goal is to secure recruitment of additional participants in all active centers in Norway and Sweden, particularly in more recent start-up centers. In Sweden, all university hospitals recruit prospectively and expansion is completed. In Norway, patients are now recruited from all university hospitals and all four health regions; moreover, start-up is planned at 3 new centers in 2023. Important priorities in 2023 will be monitoring of data quality and streamlining the workflow for extraction of data and biological samples in order to prepare for active utilization of the resources. A ScandPSC meeting of all investigators is planned for 2023.

BIOBANK

The biobank is constituted of annually collected samples of

- Serum
- EDTA blood
- Comprehensive biobanking at selected centers

ACTIVELY RECRUITING CENTERS AND PIs

NORWAY	**National PI: Mette Vesterhus Coordinator: Kristin Kaasen Jørgensen**
Haraldsplass Deaconess Center	Mette Vesterhus
Stavanger University Hospital	Lars Normann Karlsen
Akershus University Hospital	Kristin Kaasen Jørgensen
Oslo University Hospital Rikshospitalet	Trine Folseraas
Oslo University Hospital Ullevål	Håvard Midgard
Vestre Viken HF Bærum Hospital	Svein Oskar Frigstad
Lovisenberg Deaconess Hospital	Hans Lannerstedt
Diakonhjemmet Hospital	Raziye Boyar Cetinkaya
Vestfold Hospital	Øystein Rose
Hospital Innlandet HF Lillehammer	Tone Søberg
Hospital Innlandet HF Hamar	Jan-Arne Skjold
Hospital Innlandet HF Gjøvik	Simen Vatn
Hospital Innlandet HF Elverum	Carl Magnus Ystrøm
Hospital Østfold Kalnes	Rogelio Oswaldo Barreto Rios
Ålesund Hospital	Gabriel AR Bergmaier
St. Olav's Hospital	Kristin Aasarød
University Hospital of North Norway	Hege Kileng
SWEDEN	**National PI: Annika Bergquist Coordinator: Lina Lindström**
Karolinska University Hospital	Annika Bergquist
Academic Hospital Uppsala	Fredrik Rorsman
Skåne University Hospital	Emma Nilsson
Linköping University Hospital	Stergios Kechagias
Sahlgrenska University Hospital	Hanns-Ulrich Marschall
Örebro University Hospital	Nils Nyhlin
Norrland University Hospital	Mårten Werner

Highlights 2022

IN THE MEDIA

The newspaper "Dagens Medisin" interviewed Mette Vesterhus 27th of January 2022 under the headline "Forventer dobling av sykdomsbyrden for alvorlig leversykdom». The key message is that liver diseases are given little attention both from doctors and the public, and the article proposes a new strategy for liver disease. This was also suggested in an article in "Tidsskrift for Legeforeningen" the same month, authored by Mette Vesterhus, Tom Hemming Karlsen and 3 others. Trine Folseraas had a popular science article in the newspaper "Verdens gang/VG" 22nd of February with the title: "Blodtype kan avsløre sykdomsrisiko".

NORWEGIAN GASTROENTEROLOGY ASSOCIATION

Mette Vesterhus was leader of the Norwegian Gastroenterology Association (Norsk Gastroenterologisk Forening, NGF) in 2022 and Espen Melum was in charge of NGF's research funds. At NGF's annual meeting 10-12th of February at Lillehammer, PhD students Sigurd Breder received a grant and Tine S. Oldereid a prize for best work. NoPSC also contributed with two articles in the NGF news magazine (NGF-nytt) in 2022; Guri Fossdal "Spontan ALF-reduksjon ved PSC i en skandinavisk prospektiv kohort (ScandPSC)" and Kirsten Muri Boberg, Tom Hemming Karlsen and Erik Schrumpf wrote "Historien om PSC" on the basis of the Oslo research activities.

GUEST SCIENTISTS FROM UKRAINE

After the major escalation of the war in Ukraine in February 2022, thousands of Ukrainians wanted to leave the country. Espen Melum was inspired by an initiative called #ScienceForUkraine aimed at helping Ukrainian scientists, and with NoPSC he posted an offer for scientists with a background relevant to our research, which we would support to come to Norway. Through this initiative, we invited MSc Yuliia Boichuk and MD Taiisia Sazonova to NoPSC in Oslo for 3 months engagements. Taiisia was later accepted into a Master program at Oxford and left us after 6 months, while Yuliia received additional funding and is still here. Our invitation of Ukrainian guest scientists was featured on The University of Oslo website in April and their newsletter "Uniforum" in June.

SCIENTIFIC ADVISORY BOARD

Long overdue because of the pandemic, we finally gathered the members of our Scientific Advisory Board (SAB) for a last meeting 10th of May in Oslo (from 2023 the SAB will have new members). The SAB continues to be impressed by the high quality of the research and the very good achievements of the Centre. They specifically mention the importance of the Scand-PSC biobank and registry as a valuable resource for future translational research.

THE HALLORAN FAMILY FOUNDATION

On 12th of May NoPSC had visitors from the Halloran Familiy Foundation, which funds our ScandPSC biobank and a proof-of-concept trial. We had a full-day program to present the ongoing research projects at NoPSC, ending with a view of Oslo from the Ekeberg Restaurant.

EXTRA ADVISORY BOARD FOR NOPSC REORIENTATION

On the 3rd of June we hosted three past visiting professors at NoPSC for an "extra" advisory board meeting to discuss the orientation and re-orientation of NoPSC following the expansion of the support from Canica A/S. Prof. Massimo Pinzani (London, UK), Prof. Fredrik Bäckhed (Gothenburg, Sweden) and Prof. Arthur Kaser (Cambridge, UK) joined for a comprehensive review of the existing research portfolio and future opportunities, with a key emphasis on innovation and how to bring existing research closer to clinical applications.

MONITORING BOARD MEETINGS

The Spring Monitoring Board meeting for NoPSC happened first on the 16th of September. As usual, Tom Hemming Karlsen presented the accounting and the annual report from last year. In addition, Anna Frank presented an exciting new collaboration project with Novartis. The second Monitoring Board meeting in 2022 was digital only and took place on 15th of December. There the budget for 2023 was presented and approved.

IPSCSG

The biennial International PSC Study Group's (IPSCSG) meeting was cancelled in 2020, so it was great to meet up for a face-to-face event at University College London 20-21st of June 2022. Tom Hemming Karlsen, Mette Vesterhus, Espen Melum, Trine Folseraas, Kristine Wiencke, Holmfridur Helgadottir, Katrine Engesæter, Brian Chung and Merete Tysdahl represented NoPSC. Mette Vesterhus was elected as a new Board Member. IPSCSG also had a meeting during "The Liver Meeting" in Boston in November where Kirsten Muri Boberg and Espen Melum participated. 26th of September 2022 NoPSC hosted the annual meeting of the IPSCSG MRI working Group in Oslo.

THE INTERNATIONAL LIVER CONFERENCE

In 2022, the annual International Liver Conference organized by the European Association for Study of the Liver (EASL) was held in London 22nd to 26th of June. A large delegation consisting of Johannes R. Hov, Espen Melum, Kathrine Nordhus, Anna Frank, Brian Chung, Katrine Engesæter, Peder Braadland, Markus Jördens and Mikal J. Hole represented NoPSC at the conference (photo below). NoPSC contributed with oral presentations by Espen Melum and Brian Chung and poster presentations by Mikal J. Hole, Brian Chung, Katrine Nordhus and Anna Frank. In addition, Johannes R. Hov chaired one session.

Photo: Privat

THE EUROPEAN NETWORK FOR THE STUDY OF CHOLANGIOCARCINOMA

NoPSC is a member of the European Network for the Study of Cholangiocarcinoma (ENS-CCA) which consists of research groups located in 13 European countries and represents CCA interests from basic, translational and clinical research. At their biannual meeting 8th of July 2022 Trine Folseraas held a webinar with the title "The role of primary sclerosing cholangitis in cholangiocarcinoma pathogenesis".

VISITING SCIENTIST

The concept "Visiting scientist" at NoPSC was initiated in 2022, where we invite researchers for one-day visits. The visit includes discussion of our projects, identifying collaboration opportunities in the future and a guest lecture by the scientist. Dr. Anna Saborowski visited in September and Dr. Jan Tchorz in November 2022.

FORENINGEN FOR AUTOIMMUNE LEVERSYKDOMMER (FAL)

We are grateful for the ongoing collaboration with the patient organization FAL, and glad to be able to involve patients as active participants in the planning of new research projects. For practical reasons we met digitally 24th of August 2022 to discuss upcoming research initiatives. FAL held their annual conference 14-15th of October 2022 in Oslo, and Johannes R. Hov was the keynote speaker and Kristine Wiencke, Kirsten Muri Boberg and Lise Katrine Engesæter contributed with disease specific sessions. For the first time FAL also had a conference for young participants with Trine Folseraas as the main contributor from NoPSC.

SOCIAL ACTIVITIES

As NoPSC grows and the pandemic is over, there has been more social activities going on like Escape room or shuffleboard, or just meeting up outside work. One of these events was an after work garden party with pizza and drinks in Marit Grimsrud's garden. It is nice to see such activities contributing to the good working environment.

INTERNATIONAL CHOLANGIOCARCINOMA NETWORK

International Cholangiocarcinoma Network is a pan-European-wide interdisciplinary co-operative network of stakeholders, including scientists, clinicians, regulatory authorities, small/medium enterprises (SMEs) and industry partners, to address challenges with CCA. The network is organized into 7 Working Groups dealing with interrelated aspects of CCA, where Trine Folseraas is vice leader for the Molecular profiling Working Group.
The network also hosts a seminar series where Trine Folseraas presented the following: "The role and impact of primary sclerosing cholangitis in bile duct disease and cholangiocarcinoma" in October 2022.

NINTH NATIONAL MICROBIOTA CONFERENCE

The 9th National Microbiota Conference was held as an in person event 10th of November 2022. NoPSC group leader Johannes R. Hov co-hosted the event with Marius Trøseid. From NoPSC postdoc Petra Hradicka had a presentation with the title “Human faecal microbiota transplant in mice (hFMT): how to increase the efficacy to resemble human microbiota composition?”. In addition Dr. Peter Holger Johnsen (University of Tromsø), who is associated with NoPSC, was key note speaker with the presentation ”Update on fecal microbiota transplantation: Where are we - where are we moving”.

THE BIOMEDICAL ALLIANCE IN EUROPE

Prof. Tom H. Karlsen was in November elected treasurer for the Biomed Alliance. The Biomedical Alliance in Europe is the result of a unique initiative of 36 leading European medical societies that together include more than 400,000 researchers and health professionals.
The focus of the organization is lobbying for increased research funding in Brussels and coordination of policy related work of medical organizations in Europe.

THE LIVER MEETING

The American Association for Study of the Liver Diseases (AASLD) annual meeting, “The Liver Meeting”, was held in Washington 4-8th of November 2022. Espen Melum, Mikal J. Hole, Kristine Wiencke and Kirsten Muri Boberg represented NoPSC. PhD student Mikal J. Hole had a poster presentation titled “In PSC, ever-smoking associated with a 71% reduced chance of death or liver transplantation after adjusting for Mayo PSC risk score” (photo below).

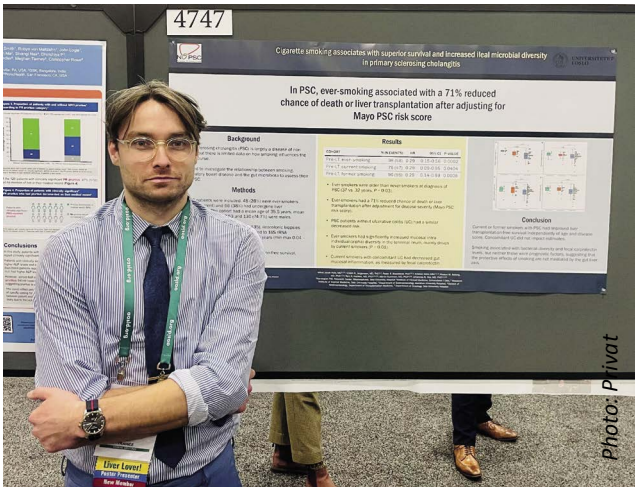


Photo: Privat

Networks and collaborations

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)
The Institute was headed by Prof. Bente Halvorsen and Espen Melum from the summer 2022. The research groups led by Espen Melum and Johannes R. Hov respectively are located at RIIM and several collaborative projects are established with the groups of, among others, Prof. Marius Trøseid, Dr. Thor Ueland and Prof. Bente Halvorsen.

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

Department of Rheumatology, Dermatology and Infectious diseases
Rheumatologists Prof. Øyvind Molberg and Dr. Anna-Maria Hoffmann-Vold collaborate with NoPSC on immunology and microbiome studies.

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

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

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

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

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

Department of Medical Genetics
The Immunogenetics group, led by Prof. Benedicte A. Lie is involved in several projects related to the further characterization of the HLA association in PSC.

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

Institute for Cancer Research
A collaboration with Prof. Guro Lind, Department of Molecular Oncology at 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 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, Gunter Kemmerich and Ida Björk for their active contributions.

Department of Paediatric Research
Department head Ass. Prof. Runar Almaas is an important collaborator on liver transplantion research and pediatric PSC, and Dr. Gareth Sullivan on regenerative medicine.

KEY NATIONAL COLLABORATORS

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

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

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

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

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

Haraldsplass Deaconess Hospital, Bergen
The NoPSC Clinical Research Group in Bergen, led by Prof. Mette Vesterhus, is located here. This encompasses other strong collaborations at Haraldsplass Deaconess Hospital.

KEY INTERNATIONAL COLLABORATORS

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

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. Ass. Prof. Niklas Björkström (Guest Professor at NoPSC) is involved in projects relating to human immunology in PSC. They are both a part of the management group of the Strategic Prospective Scandinavian PSC Biobank (ScandPSC).

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Prof. Fredrik Bäckhed and Prof. Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed is an expert on gut microbiota, metabolism and gnotobiotic animals and has been an advisor and collaborator on gut microbiota studies in mice, while hepatologist Hanns-Ulrich Marschall contributes with bile acids expertise. In the context of this collaboration, Antonio Molinaro from Gothenburg is a post doctor at NoPSC from December 2022. Funded by a UEG grant and Canica.

Uppsala University, Sweden
Associate Prof. Daniel Globisch is an increasingly important collaborator, providing unique expertise on the biochemistry of microbial metabolites.

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

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.

University Hospital Heidelberg, Germany
Prof. Peter Schirmacher, Head of Pathology at the University Hospital Heidelberg in Germany, represent a world-leading center expert in hepatobiliary pathology. Together with Prof. Stephanie Roessler he provides pathology expertise to collaborational projects related to genomic profiling of PSC-associated biliary tract cancers.

Department of Internal Medicine, Vivantes Humboldt Hospital, Germany
Dr. Tobias J. Weismüller is an important collaborator within the International PSC Study Group (IPSCSG), particularly regarding the database project comprising more than 8000 PSC patients.

Netherlands, IPSCSG
The secretariat of the IPSCSG was located in Amsterdam, The Netherlands, for the last year in 2022, in the capable hands of Prof. Cyriel Ponsioen and Prof. Ulrich Beuers at the University of Amsterdam's Faculty of Medicine.

University of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser (former Guest Professor at NoPSC), Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes; GPR35. This project was funded within the Scientia Fellows' program of the University of Oslo through 2018 and further by the Regional Health South-East Health Authority in Norway and involves postdoc Georg Schneditz and Dr. Nicole Kaneider-Kaser. Also ongoing collaboration with Dr. Fotis Sampaziotis at Cambridge Biorepository for Translational Medicine at the Wellcome - MRC Cambridge Stem Cell Institute has proved extremely valuable regarding organoids and regenerative medicine.

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

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

Toronto Centre for Liver Disease, Toronto General Hospital, Canada
Dr. Gideon Hirschfield (former Birmingham, UK) continues the collaboration with NoPSC regarding characterization of the HLA related immune response in PSC from Toronto, 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
Close collaborations between NoPSC and the Mayo clinic has been ongoing for many years as a result of the strong PSC orientation at both centers. Whilst initial work was much related to the genetic studies with Prof. Konstantinos Lazaridis, the more recent collaboration focuses on artificial intelligence and multi-omic applications, including using metabolomics for the mapping of potential environmental drivers for PSC. NoPSC participates in the RC2 NIH (NIDDK) grant on PSC which is hosted at the Mayo Clinic.

Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Prof. Richard Blumberg is an important collaborator in Prof. Espen Melum's projects related to NKT cells.
In addition, a collaboration with Dr. Joshua Korzenik on PSC pathogenesis is ongoing.

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

Dissertation

August 26th 2022 Cand.med. Christopher Storm-Ligaard defended his thesis *"Clinical interventions of the human gut microbiota"* for the degree of PhD (Philosophiae Doctor). Principal Supervisor: Professor Johannes R. Hov, Institute of Clinical Medicine, University of Oslo

Photo: Øystein Horgmo, UiO

Growing evidence suggests that bacteria residing in the intestines have a significant impact on factors related to human health and disease. An increasing number of reports have demonstrated associations between gut microbiota and human diseases; however, most studies have yet to demonstrate causality. Knowledge on how we could induce alterations of gut microbiota through targeted interventions would increase our understanding of the complex interplay within this intricate ecosystem. This thesis includes three clinical trials aiming to induce perturbations in the gut microbial composition of individuals with an altered gut microbiota compared to healthy individuals.

First, the gut microbiota of people infected with HIV was targeted using a probiotic milk supplement. Second, the effects on the gut microbiota of a common disease-modifying drug used for multiple sclerosis were evaluated with emphasis on the relationship with drug-associated gastrointestinal symptoms. Last, the effect of omega-3 fatty acids on the gut microbiota and blood lipids was tested in a population with familial hypercholesterolemia.

The treatments modulated the gut microbiota to a varying degree, and in this thesis, the author discusses factors related to the observed effects and the clinical relevance of these perturbations. A critical review of the methodology used is provided, with emphasis on the limitations that may have caused clinically relevant effects to be overlooked. Lastly, the author presents the experiences the research team has had after targeting the gut microbiota in three different clinical trials and concerns that should be considered when designing a clinical trial to target the gut microbiota.

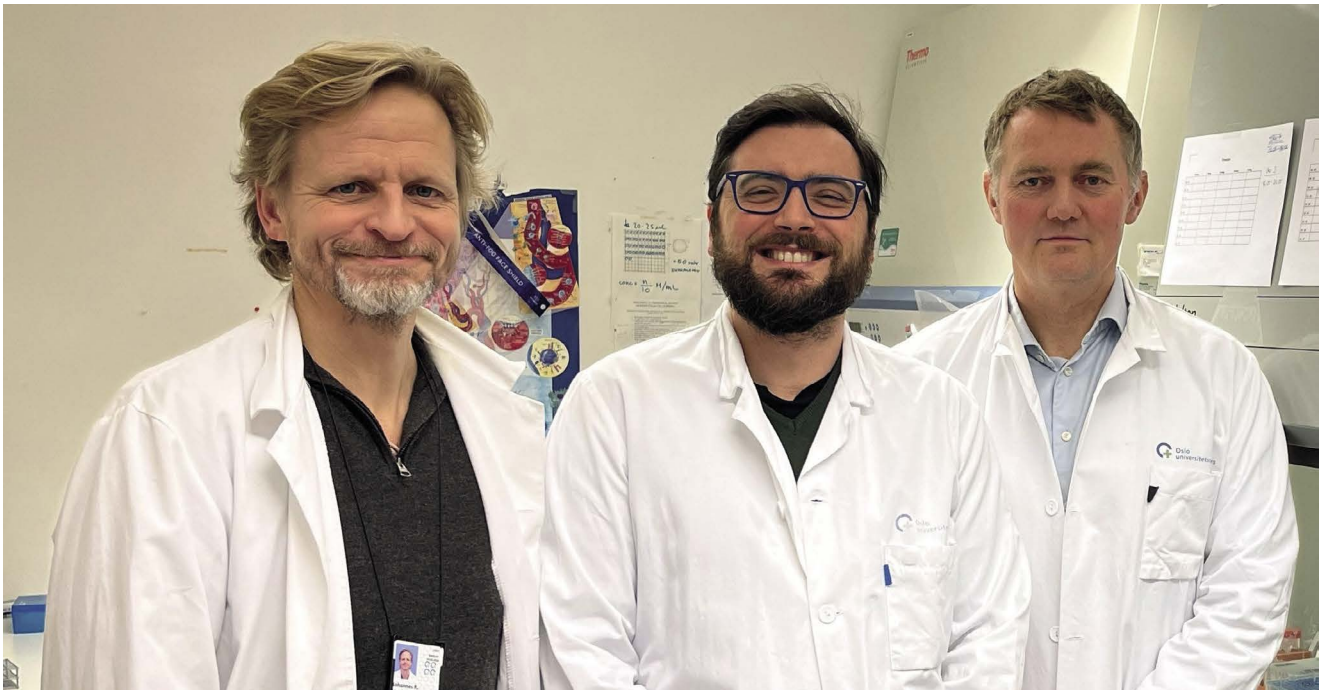
New grants

- MD Dr. Antonio Molinaro from Götenborg University was selected as the awardee for the United European Gastroenterology (UEG) Research Fellowship in 2022. The grant of 50,000 Euro goes to the host institution (Oslo University Hospital) and supports him spending two years at NoPSC on a half-time basis carrying out research within projects on PSC and other relevant conditions. Molinaro will be working in the group of Johannes Hov.

- PhD student Sigurd Breder received a grant of NOK 60 000 for his study "Early diagnosis of cholangiocarcinoma in primary sclerosing cholangitis" at the Norwegian Gastroenterology Association's annual meeting 10-12th of February 2022 at Lillehammer.

- A three-year post doctor grant of NOK 3 675 000 from South-Estern Norway Regional Health Authorities was awarded for the project "Clinical impact of microbial metabolism on diseases of the gut-liver axis: new targets uncovered by transplantation". The PI for this project is Johannes R. Hov.

- Funds from Fondsstiftelsen at Oslo University Hospital was awarded NoPSC which supports a project involving one of the Ukrainian guest researchers for 7 months, a total of NOK 400 000. PI for this project is Espen Melum.

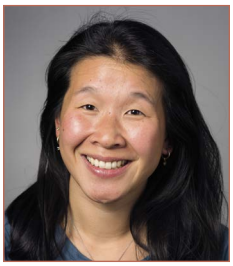


Johannes R. Hov, UEG Research Fellowship Awardee Antonio Molinaro and Tom Hemming Karlsen in the NoPSC laboratory.

Awards

- At the Norwegian Gastroenterology Association's annual meeting 10-12th of February 2022 at Lillehammer PhD student Tine S. Oldereid received a prize for best work in the category "Liver, bile and pancreatic research" for her abstract "Microbial exposure during early life regulates development of bile duct inflammation".

New employees



Hanne Lyche Alme, BSc
Study nurse
"Full time nurse and the patients biggest supporter. Together, let's cure this disease!"
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Yuliia Boichuk, MSc
Guest researcher
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Karen Rønneberg, BSc
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Post doctor
"Contributing to PSC research gives me energy, hoping for future results that will help both PSC patients and physicians."
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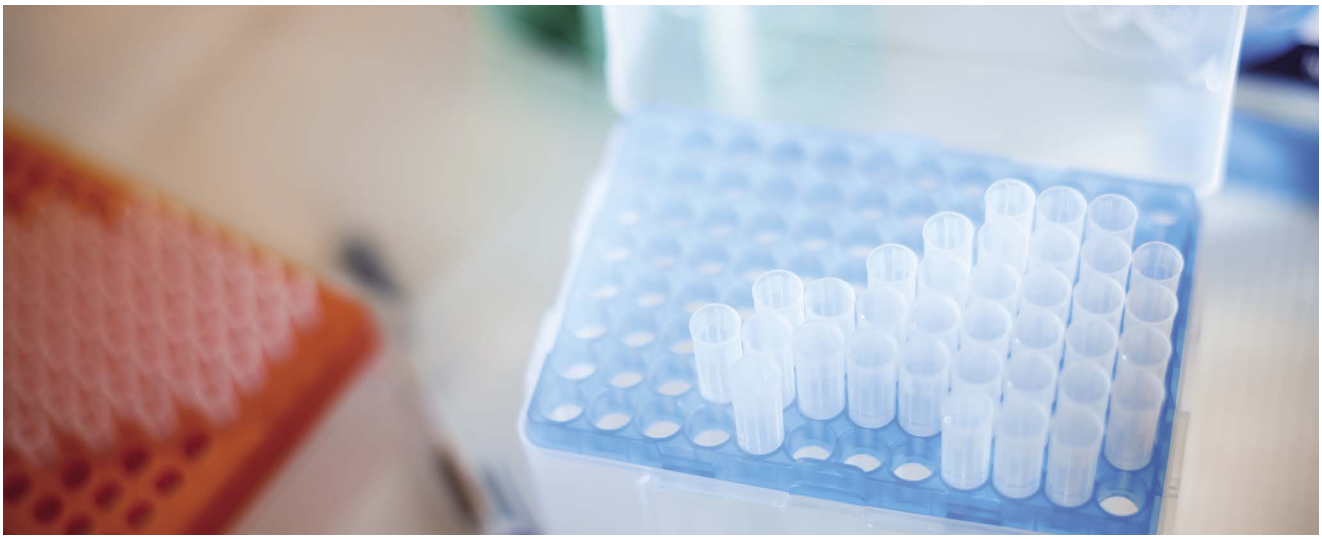
Antonio Molinaro, MD PhD
Post doctor
"Part time clinician in Sweden and part time researcher in Norway, with focus on metabolites and PSC."
Antonio.Molinaro@wlab.gu.se



Publications 2022

HIGHLIGHTED PUBLICATIONS

Braadland PR, Schneider KM, Bergquist A, Molinaro A, Lövgren-Sandblom A, Henricsson M, **Karlsen TH**, **Vesterhus M**, Trautwein C, **Hov JR**, Marschall HU (2022)
Suppression of bile acid synthesis as a tipping point in the disease course of primary sclerosing cholangitis
JHEP Rep, 4 (11), 100561

Inhibiting the bile acid synthesis pathway is an interesting treatment strategy in cholestatic diseases such as primary sclerosing cholangitis (PSC). In this study, we wanted to investigate whether reduced bile acid synthesis could predict outcomes in people with PSC not receiving such therapies. The liver synthesizes bile acids in several steps, and the product of one of these steps, C4 (biochemical name 7α-hydroxy-4-cholesten-3-one), can be used as a measure of the synthesis activity. C4 was measured in blood from healthy controls and two groups of people with PSC from Norway and Sweden. The results showed (as expected) that people with PSC accumulated bile acids, which associated with lowered bile acid synthesis (low C4). Furthermore, individuals with low C4 in blood more rapidly either needed a liver transplantation or died. In the most severe cases, bile acid synthesis appeared fully suppressed, suggesting that the affected individuals had likely passed a tipping point where treatment targeting bile acid synthesis would probably have no effect.

Valestrand L, **Zheng F**, **Hansen SH**, **Øgaard J**, **Hov JR**, Björkström NK, **Karlsen TH**, **Jiang X**, **Melum E** (2022)
Bile from Patients with Primary Sclerosing Cholangitis Contains Mucosal-Associated Invariant T-Cell Antigens
Am J Pathol, 192 (4), 629-641

In this paper we investigated the presence of potential MAIT cell antigens in the bile of PSC patients. We used bile from 28 patients collected at the time of liver transplantation due to PSC and incubated the bile samples with peripheral blood mononuclear cells from healthy donors followed by analysis of the immune cells with flow cytometry. These analyses revealed that MAIT cells were activated by antigens in eight of the 28 samples, suggesting a role in regulating the immune response against bile-derived pathogens. The activation was partly MR1-dependent in five of the eight bile samples, implying the involvement of the MR1-T-cell receptor pathway. Microbial DNA was detected in 15 of 28 bile samples, including the five bile samples leading to MR1-dependent activation.

ADDITIONAL RESEARCH ARTICLES

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Titers of antibodies against ancestral SARS-CoV-2 correlate with levels of neutralizing antibodies to multiple variants
NPJ Vaccines, 7 (1), 174

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Fecal level of butyric acid, a microbiome-derived metabolite, is increased in patients with severe carotid atherosclerosis
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Phenylacetylglutamine From the Gut Microbiota: A Future Therapeutic Target in Heart Failure? (Editorial)
Circ Heart Fail, 16 (1), e010222

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Eur Radiol Exp, 6 (1), 58

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Scand J Gastroenterol, 58 (5), 512-520

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Tidsskr Nor Laegeforen, 142 (14)

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Duodenal inflammation in common variable immunodeficiency has altered transcriptional response to viruses
J Allergy Clin Immunol, 151 (3), 767-777

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Survey uncovering variations in the management of primary sclerosing cholangitis across Europe
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Scand J Clin Lab Invest, 82 (5), 363-370

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BMC Public Health, 22 (1), 1385

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Spatial transcriptomics identifies enriched gene expression and cell types in human liver fibrosis
Hepatol Commun, 6 (9), 2538-2550

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Gut, 72 (4), 671-685

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J Infect Dis, 225 (11), 1948-1954

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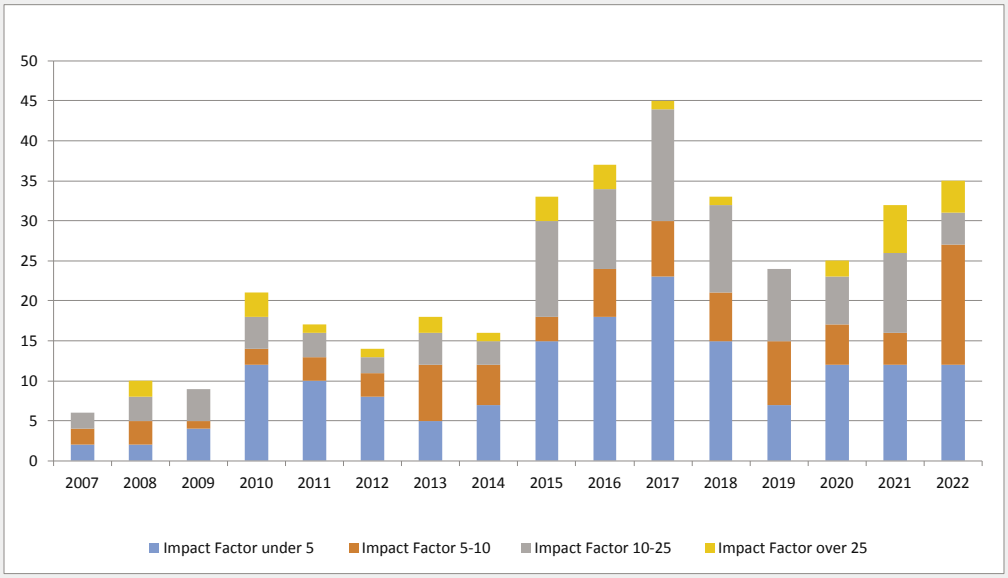

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