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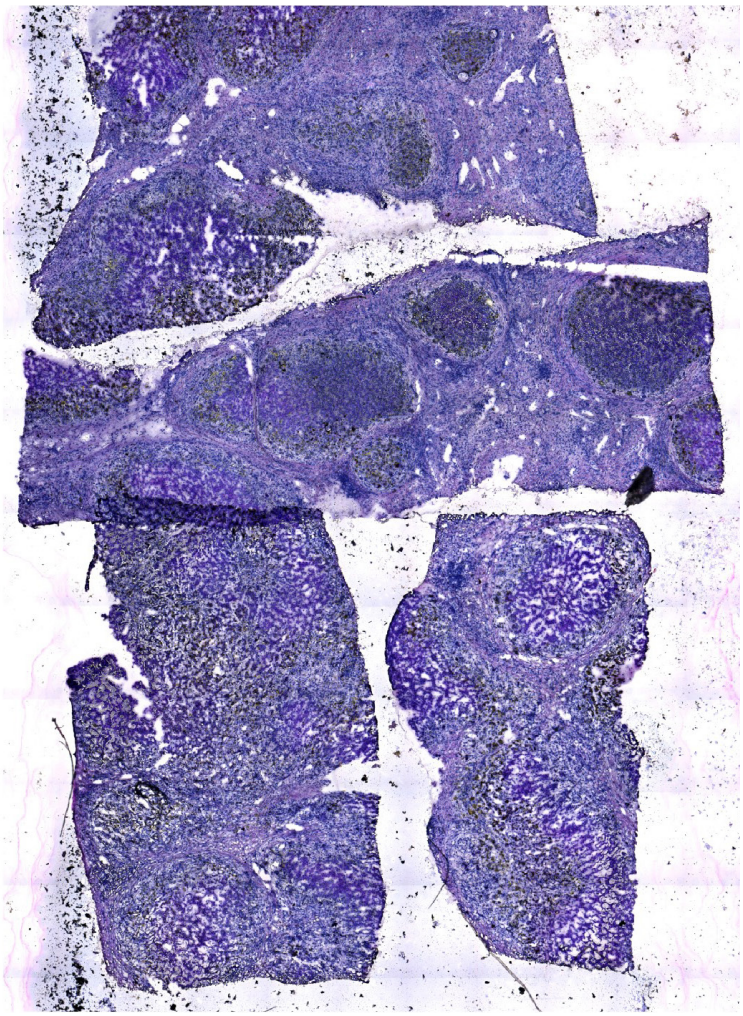
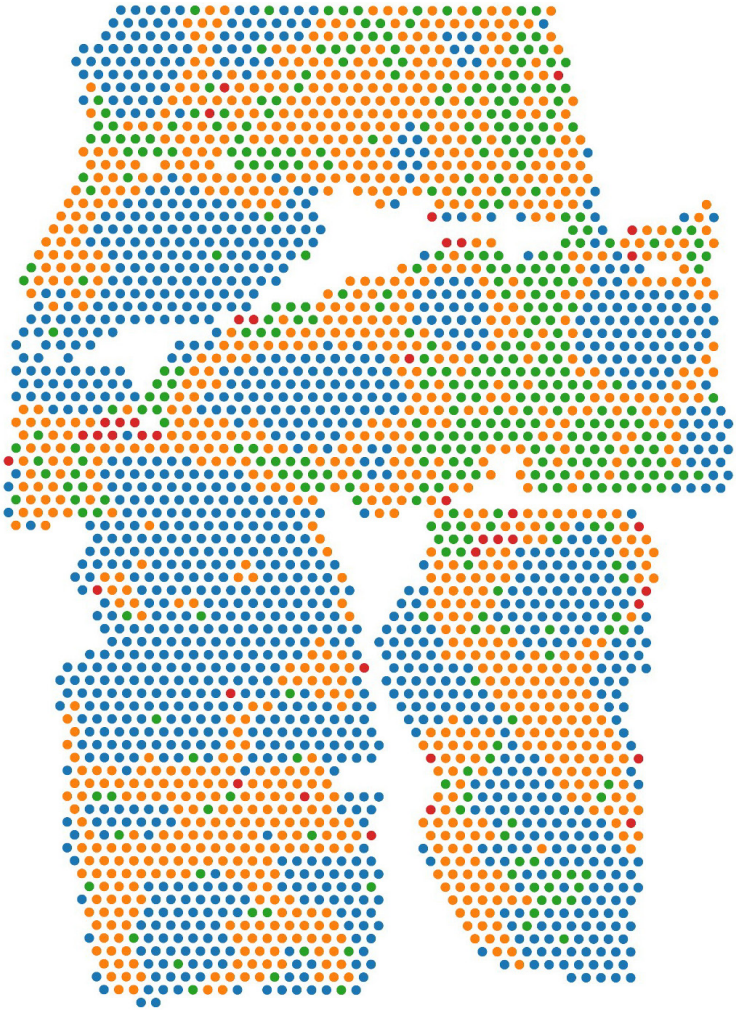




Norwegian PSC Research Center

ANNUAL REPORT 2023

NOPSC

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

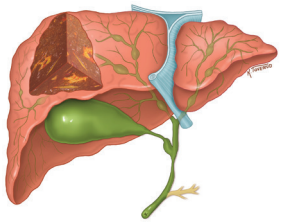
UiO : University of Oslo

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2023

What is PSC?

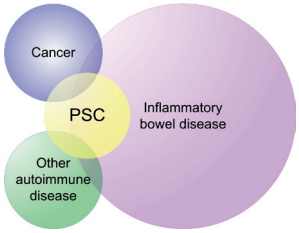
Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.



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 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.

Content:

NOPSC Norwegian PSC Research Center

NOPSC ANNUAL REPORT 2023

FRONT PAGE: *Spatial transcriptomics of PSC liver tissue.*
Left image: Hematoxylin and eosin staining of explant liver tissue from patient with PSC.
Right image: Spatial transcriptomics of same liver section showing different tissue states based on gene expression (red, blue, orange, green).

ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*

EDITOR: Merete Tysdahl

PUBLISHER: Oslo University Hospital

PRINT: Byråservice AS, 2024

SAMPLES: 220

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

Leader´s comments

The year of 2023 was a key year for the new orientation of NoPSC – aiming for innovation and clinical implementation, marked by three concrete actions.

First of all, during the year, establishing of the formal basis for clinical trials at NoPSC was initiated. This may seem trivial, but there are major deficits and challenges in designing clinical trials in PSC, also serving as a barrier for the pharmaceutical industry to work on PSC. For NoPSC now to perform investigator initiated clinical trials thus serves several purposes. First of all, to clarify the impact on PSC severity from vitamin B6 supplementation and so-called PPAR agonists, is important. But implicit to the activity is also to improve standards in clinical trial design and choice of endpoints in clinical trials in PSC, where our own work over the years on serum fibrosis tests now comes into practical application. Furthermore, beyond the first two compounds to be tested, for NoPSC to have the "machinery" to continue engaging in clinical trials of other drugs is an important part of our new orientation, and biobank material collected during the trials will "feed back" to the translational research portfolio, expanding via proof-of-concept interventions insights in disease pathophysiology as a basis for discovering further drug candidates.

Systematic drug discovery activities ("drug screening") in PSC have so far been difficult. Thanks to the systematic work done over the recent years within the Experimental research group, NoPSC now has the toolset – in the form of bile duct organoids from PSC patients – that can be utilized for such activities. To enter into such drug-screening activities at the highest possible standards, a collaboration has been set up with a laboratory facility of Novartis in Basel, to which external collaborators might be granted access under special circumstances (the "FastLab"-concept within Novartis Biomedical Research). Thanks to assistance from the UiO "Growth House" in setting up the contractual framework for such a public-private partnership, Scientia Fellows Anna Frank worked in the Novartis laboratories in Basel over large parts of the autumn of 2023 in initiating this portfolio, with the aim of performing the first large screening experiment during 2024.

The NoPSC biobank managed by the Clinical research group at Rikshospitalet has been growing since the initiation of NoPSC, and currently hosts materials of almost 1000 persons with PSC and supports dozens of PSC projects world-wide with relevant biomaterials. It is timely to mention that at end of 2023, our "biobank manager", Liv Wenche Thorbjørnsen, retired, after having worked at NoPSC for almost 15 years. The stability in key staff positions has become a hallmark of the working environment of NoPSC, in many ways reflecting the long-term and stability provided by the core support from Canica A/S.

The expansion of the biobanking at NoPSC in the ScandPSC natural history cohort supported by the Halloran Family Foundation successfully moved forward for arrival at its goal of following 1,300 PSC patients in Norway and Sweden in an observational study with biobanking and data collection associated with annual, routine clinical follow-up. The first projects are now being initiated on the basis of the ScandPSC cohort, including both biomarker studies and the above mentioned clinical trials. The gathering of 35 principle ScandPSC investigators and study nurses in Bergen end of August in 2023 was a landmark event, which paid credit to and hopefully served to onward motivate this large team driving forward this key initiative.

Lastly, it is worth mentioning the ongoing technological developments in research at NoPSC. We have always tried to maintain a stronghold at cutting edge technology to maximize insights in our PSC research, previously most notable for genetics/genomics technologies and microbiome-related analysis. A particular emphasis was throughout 2023 put on so-called "spatial" technologies, which allows the molecular characterization of disease process in 3D at a rapidly increasing resolution. Furthermore, the NoPSC metabolomics agenda is also rapidly evolving, following the successful experiences made during the ERC starting grant of Johannes Hov, who is now applying for the next level "consolidator grant". Following up on the ERC project, we have employed a post doc to work at a specialized metabolomics facility in Uppsala in furthering our own capacity in this methodological space.

All in all, the intended (re)orientation of NoPSC is successfully ongoing. Growing research activities has to be done carefully and stepwise, and whilst some effort is still required to reach the new cruising altitude intended for our next phase, the first steps are robust and will serve a firm basis for reaching our overarching goal – which is for our research to improve patient care.

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.

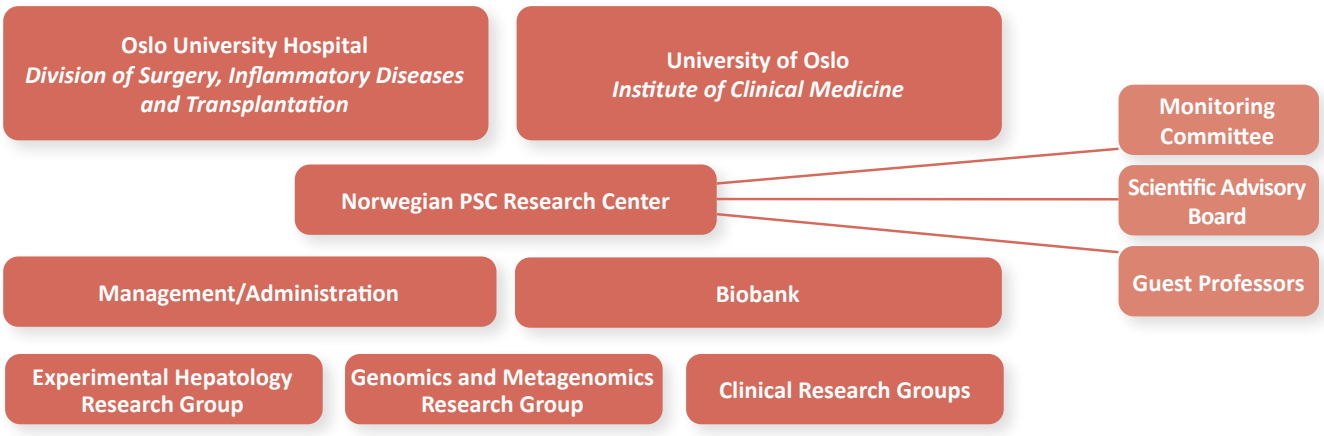
The philantropic funding is made with a grand vision to make a difference for people with PSC, and has given the research environment stability to prosperously grow its activity with 10 year horizons for each funding period.

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 and Specialized Medicine. 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, Haraldsplass Deaconess Hospital, Bergen and Akershus University Hospital, 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.

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

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Canica A/S

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Canica A/S

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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 2023-2025

Dr. Jan Tchorz
Institutes for BioMedical Research, Basel, Switzerland

Dr. Fotios Sampaziotis
Wellcome - MRC Cambridge Stem Cell Institute, UK

Prof. Tom Lüdde
University of Düsseldorf, Germany

SCIENTIFIC ADVISORY BOARD 2023-2026

The Scientific Advisory Board (SAB) reviews the center biannually.

Prof. Ole Andreassen
Universitetet i Oslo, Norway

Prof. Pål Rasmus Njølstad
University of Bergen, Norway

Prof. Frank Tacke
Charité - Universitäts-medizin Berlin, Germany

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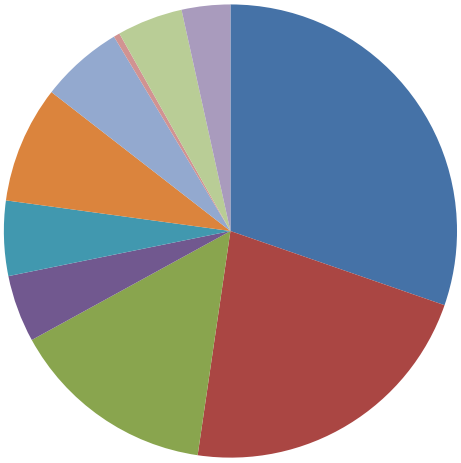
Accounting

Expenditures from Canica AS funding in 2023 was NOK 11.817.765,- . The overall expenditure of all projects within the center amounted to NOK 38.993.000,- of these NOK 4.171.000,- was provided by University of Oslo and Oslo University Hospital, and NOK 19.654.000,- was from independent competitive grants from Regional Health Authorities, the Norwegian Research Council and EU. The remaining NOK 3.350.000,- was from various public and private institutions, with the main contributions being generously provided by the Halloran Family Foundation in the US.

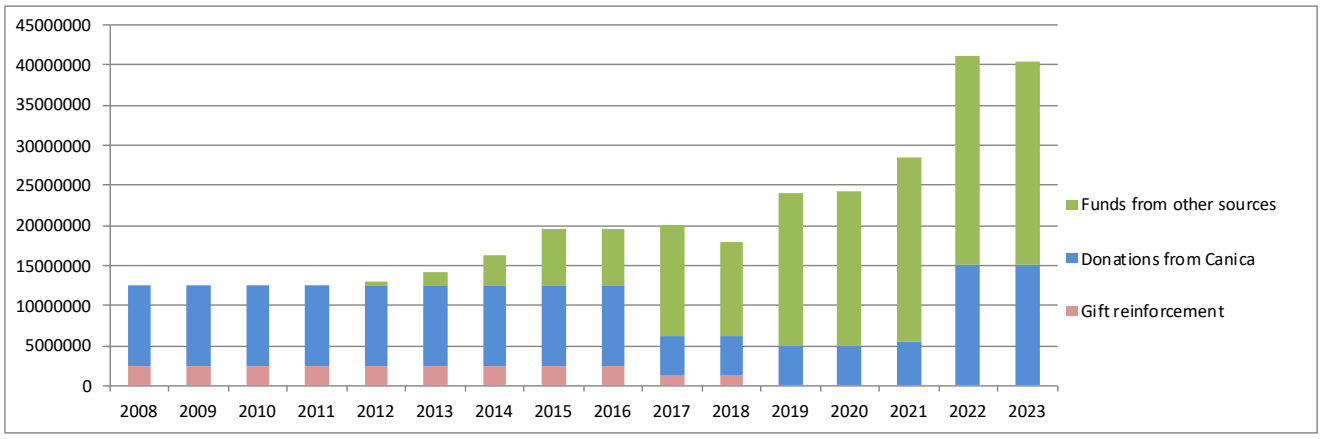
2023	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENSES	INCOME	EXPENSES
TRANSFER FROM 2022	-921 939		11 004 650	
INTEREST			547 004	
FROM CANICA			15 000 000	
OTHER INCOME	370 209		56 000	
TRANSFER FROM UiO	5 906 947			5 906 947
WAGES		3 717 534		2 174 274
OVERHEAD		219 075		196 681
OPERATING EXPENCES		5 025 510		484 692
TRANFER TO 2023		**- 3 606 901**		**17 854 059**

Expenditures	2023
Canica	11 818
Regional Health Authorities in Norway	8 580
Norwegian Research Council	5 734
University of Oslo	1 869
EEA Baltic research funds	2 086
EU funding (ERC/Scientia Fellow)	3 254
OUH (Strategic, RIIM and ATX)	2 302
PSC Partners	171
The Halloran Family Foundation	1 828
Other	1 351
Thousand NOK	**38 993**

The pie chart shows the expenditure distribution between different sources:



FUNDING



Spatial transcriptomics - dissecting local pathogenesis of PSC in search of new treatment targets

Brian K. Chung

PSC is characterized by inflammation, scarring and narrowing of the bile ducts that typically leads to cholestasis, fibrosis and liver damage.(1,2) The exact cause of PSC remains unclear but liver afflictions in patients often appear 'patchy' – some liver areas are severely affected whilst others appear relatively healthy.(3) The unevenness of liver damage in PSC is a major obstacle limiting the identification of new drug targets as key interactions may be restricted to specific areas and difficult to unpick with conventional methods only sensitive to general disease features.

To investigate if important interactions occur in defined hepatic regions, we are using spatial transcriptomics – a cutting-edge, high-throughput sequencing methodology – to analyze gene expression (transcriptome) in defined 'spaces' of the liver.(4) Spatial transcriptomics greatly improves upon traditional methods because it is unbiased by prior assumptions and can simultaneously map the expression of hundreds of genes to precise liver regions as small as the diameter of an average human hair (50 microns). Critically, spatial transcriptomics can be combined with other liver assessments to prioritize potential drug targets in PSC that could be shared with other diseases which may already have effective treatments.

Using spatial transcriptomics, we have shown that different liver regions indeed express distinct gene content dependent on disease stage that can be correlated to specific cell types, such as hepatocytes, cholangiocytes (bile duct cells) and immune cells(5). To further our understanding of local disease processes in PSC, we are now analyzing liver tissue from 23 PSC patients and 7 non-PSC controls by spatial transcriptomics and complementing this approach with high-resolution, single-cell methods. With our complementary datasets, we will create a spatial gene expression 'atlas' and map disease interactions at specific stages of liver disease in PSC. We are also applying spatial transcriptomics to assess if diseased liver regions in patients that develop recurrent PSC is distinct from those with 'first-time' PSC and whether spatial transcriptomics can identify novel disease interactions in animal models of PSC relevant to human disease.(6-8) Most current studies using spatial technology have focused on the liver, and as part of expanding this technological axis at NoPSC, we will perform dedicated studies of bile ducts - the primary site of disease affection in PSC. This development is helped by next generation, high resolution spatial transcriptomics platforms currently being implemented.

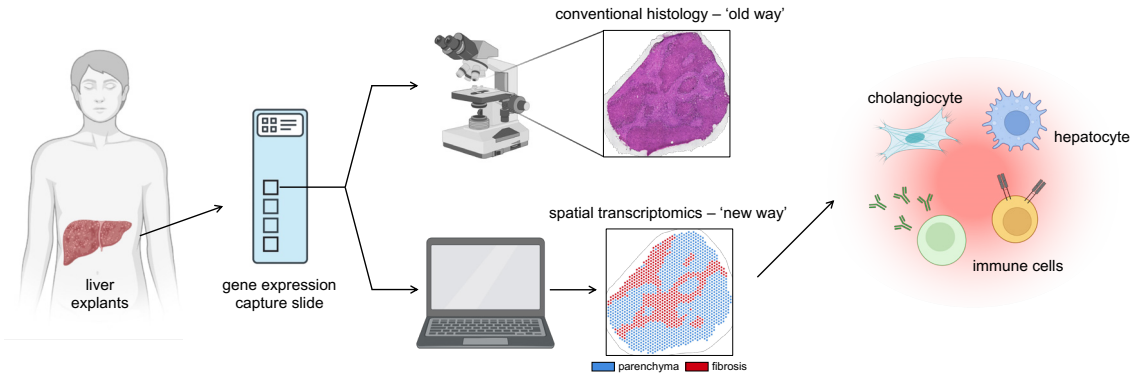


Figure. *Spatial transcriptomics identifies localized gene expression in liver explants. Liver tissue from PSC and non-PSC patients is collected at time of liver transplantation. Tissue is sectioned and mounted on gene expression capture slides. Staining and imaging for conventional histology is performed; tissue is then permeabilized and gene expression is captured, sequenced and analyzed by spatial transcriptomics. Local gene content (e.g. parenchyma or fibrosis) is assigned to distinct cell types, such as hepatocytes, cholangiocytes and immune cells using complementary single-cell methodologies.*

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Identification of pre-drugs for modulating the disease course of PSC

- A collaboration between NoPSC and the Novartis BioMedical Research (NBR)

Anna K. Frank

PROJECT BACKGROUND

Biliary epithelial cells (cholangiocytes) are the main target of destruction in primary sclerosing cholangitis (PSC), yet their exact role in driving the disease progression is not completely characterized.(1) It has been shown that cholangiocytes become activated in biliary disease and actively participate in modulating disease progression through secretion of specific molecules that can influence and worsen the disease outcome.(2) During biliary scarring for example, activated cholangiocytes actively contribute to the increase of scarring severity by releasing driving molecules such as connective tissue growth factor (CTGF).(3) Besides from becoming activated, diseased cholangiocytes can also undergo a transformation towards a more quiescent cell type that is characterized by the expression of specific molecules such as SA-β-Gal, p21, H2AX and p16. This cholangiocyte cell type is increased in PSC and might be of high relevance for the disease outcome through increasing the overall liver inflammation and disease phenotype.(2) Further study on how diseased cholangiocytes influence PSC severity is warranted.

Fig.1: The Novartis BioMedical Research campus in Basel, Switzerland.

PROJECT DESCRIPTION

We can model different disease-associated cholangiocyte changes, such as CTGF release, or the transformation towards a quiescent cell type, outside of the human liver by using patient-derived cholangiocytes that are cultured under 3D conditions in our laboratories. Our culture method allows us to expand patient-derived cells in form of "mini-organs" (organoids) efficiently and in large quantities, giving us highly functionable primary cells available for personalized studies(4). When treated with a well-defined cocktail of specific molecules, which have previously been shown to be present at increased levels in diseased livers, the cells undergo a transformation towards an activated diseased cell type (unpublished data). In this project, we are planning to use this cell culture model in a large-scale drug screen in collaboration with NBR. The aim of the project is to identify novel pre-drugs that can modulate/inhibit the secretion of disease-driving molecules from cholangiocytes during disease, thus influencing the overall disease severity and outcome.

As part of the project and the FAST Lab (see info below) collaboration between NoPSC and NBR, two NoPSC researchers, Anna Frank and Enya Amundsen Isaksen, visited the NBR campus in Basel, Switzerland (Fig.1) from August 2023 until April 2024 with the goal to design and to develop a half-automated large-scale cholangiocyte organoid screening assay (Fig.2) that can be used to screen a Novartis toolbox of public available pre-drugs in our model system.

THE NBR "FACILITATED ACCESS TO SCREENING TECHNOLOGIES (FAST) LAB" PROGRAM

Within the scope of the FAST Lab program, NBR provides external academic collaborators access to drug/compound screening technologies at its research sites in Cambridge, USA and in Basel, Switzerland. The purpose of the FAST Lab program is to collaborate with external scientists on the evaluation of innovative ideas and projects related to early biomedical research. NBR hereby provides screening facilities, non-proprietary compounds and technical/scientific project support from internal screening experts and drug discovery scientists. All data obtained during the project can be freely used by the academic collaborator, publications are encouraged, and the collaborator is free to further pursue all findings from the project.

References

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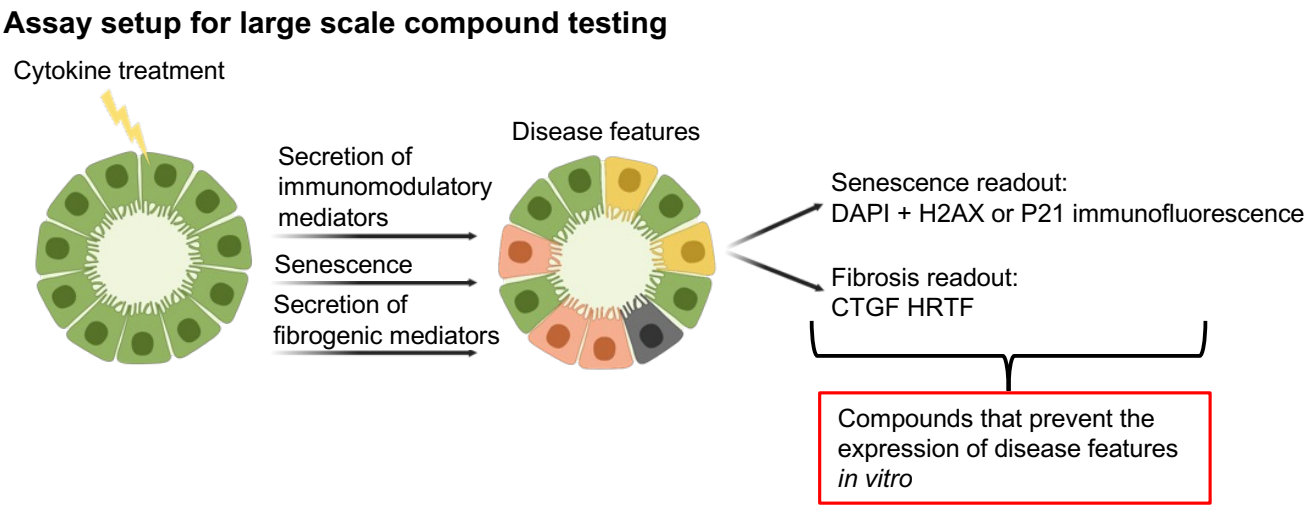
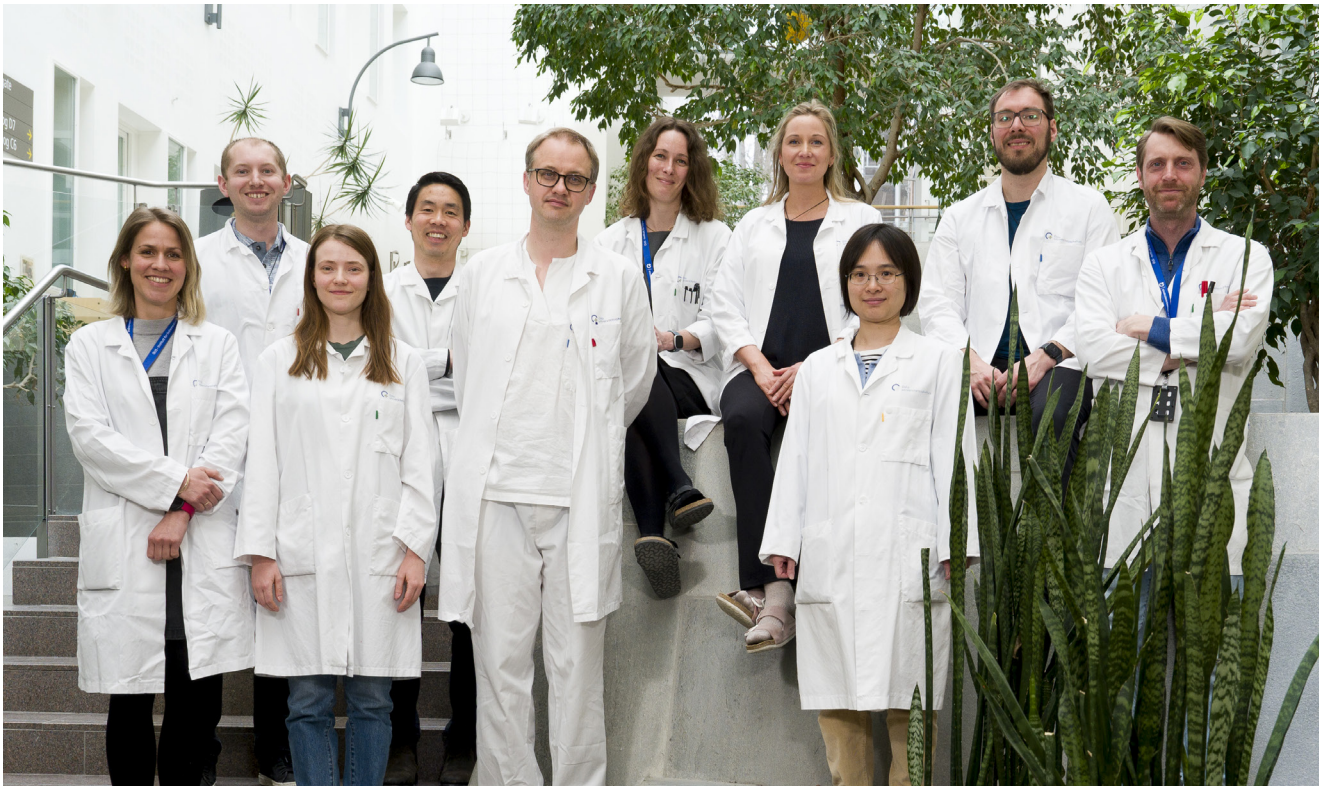


Fig.2: Assay design for large scale compound testing.

EXPERIMENTAL HEPATOLOGY RESEARCH GROUP



From top left: Henry W. Hoyle, Brian Chung, Kathrine Sivertsen Nordhus, Anna Frank, Markus Jördens and Jonas Øgaard. From front left; Oda Helgesen Ramberg, Lisa Brynjulfsen, Espen Melum and Xiaojun Jiang.

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The experimental hepatology research group is one of the three NoPSC research groups based in Oslo and focuses on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2023 the group consisted of the group leader, four senior researchers, two postdocs, four PhD students, the lab manager, one researcher and two technicians. The overarching topic in the group is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and the role of cholangiocytes in propagation of inflammatory processes.

Our strong collaboration with the Hybrid-technology-hub on establishing a bile-duct-on-a-chip continued and in 2023 the project moved from the prototype stage into a system that is useable in a range of experimental conditions. Seeding organoids in the chip now leads to a tight barrier allowing flow of relevant compounds through the duct. We have also tested how this barrier respond to pharmacological substances. The bile-duct-on-a-chip system was also in 2023 accepted into the University of Oslo's SPARK program for commercialization. This project will be led by Dr. Henry W. Hoyle and Dr. Anne Frank from the group. Being admitted to the SPARK program allows us to follow up on the commercial potential of the system and to get a dedicated mentor from the industry. In 2023 we used our experience with organoids coming out of the collaboration with HTH in a large project with Novartis in Basel where we use their automated systems to examine the impact of various pharmacological substances on an induced inflammatory phenotype in the organoids.

In a follow-up study of our previous work on CD100 we got a paper describing a direct interaction of T-cells with cholangiocytes that leads to a clear Th17 profile driving inflammation accepted for publication in Gastroenterology. We also established a joint collaboration with the Seoul National University, SINTEF and OsloMet that was funded through the National Research Foundation of Korea. This project is headed from our side by senior scientist Xiaojun Jiang. A new concept on integration of big data with genetics for patient stratification was funded by a HSØ grant towards the end of the year.

The group also has large projects related to single-cell sequencing and spatial transcriptomics using both human and murine material. The laboratory work and sequencing in several of these projects were finished in 2023 and bioinformatics analyses are currently ongoing. In our project examining liver infiltrating mononuclear cells we finished the sequencing and initial bioinformatics analysis of samples from a range of different liver diseases. Preliminary data from this project was presented at Norwegian Society of Immunology meeting. To comply with the current regulations when expanding our sequencing-based studies in humans we have developed secure bioinformatics pipelines for single cell and spatial transcriptomics data through TSD (="Tjenester for sensitive data") at the University of Oslo. All ongoing projects have been adapted to this infrastructure.

Our projects using germ-free animals to assess the importance of timing of microbiome introduction on development of bile duct inflammation using the NOD.c3c4 model and immune maturation in wild-type mice were accepted for publication in 2023. The project using the bile-duct injection model for assessing MAIT-driven inflammation in the bile duct was in 2023 supplemented by a range of immunohistochemical assessments and additional analyses. For investigating the specific role of CD1d on the bile duct epithelium we have established a conditional knock-out mouse model and have used this model together with our bile-duct injection technique using oxazolone to further dissect the role of NKT-cells in the bile ducts.

GENOMICS AND METAGENOMICS RESEARCH GROUP

From left: Georg Schneditz, Jørgen D. Rønneberg , Lise Katrine Engesæter, Petra Hradicka, Simen Hyll Hansen, Johannes R. Hov, Hanne Guldsten, Hanne Lyche Alme and Kristian Holm. Portraits from left: Maria Maseng, Sara Tjønnfjord, Mikal J. Hole, Peder Braadland, Beate Vestad and Antonio Molinaro.

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RESEARCH PROFILE

The genomics and metagenomics group aim 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 hypothesis-driven methods, supported by bioinformatics and biostatistics including machine-learning. Increasingly, experimental approaches in vitro and in vivo (mouse models) are important both as a discovery tool and to define cause-or-effect and disease mechanisms.
We study primary sclerosing cholan-

gitis both before and after liver transplantation (with or without recurrence) together with healthy individuals and patients with inflammatory bowel disease. 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, gnotobiotic 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. This has been further substantiated in a study published in 2023 (Journal of Hepatology) and a clinical trial focusing on translational aspects of vitamin B6 supplementation has been approved and opens in 2024. This represents an example on how we work to identify and potential 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 StopAutoimmunity, where we among other observations have identified overlapping features in PSC before and after liver transplantation (Hepatology 2023).

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 groups also work 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. The activity in the donorbank for fecal microbiota transplantion has been growing in 2023. The annual National Microbiota conference in November was also a success – the tenth consecutive event since 2014. For 2024 we plan to expand to a Nordic event.

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 2023 funded by one ERC Starting Grant, five grants from Regional Health Authorities of South Eastern Norway, one PhD student following an industrial PhD scheme (funded by Research Council of Norway), one Strategic research area grant in Oslo University Hospital, one postdoc is funded by a grant from UEG, in addition to Canica, funding one bioinformatician, and Nordforsk. In a collaboration with the Experimental Hepatology group and partners from the Baltic area (driven from Lithuania) we also had funding from the EEA Baltic research funds, covering 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 LIVER RESEARCH GROUP, OSLO UNIVERSITY HOSPITAL

From top left: August T. Juliebø. Erik Schrumpf, Kristian Bjøro, Kirsten Muri Boberg, Kristine Wiencke, Lars Aabakken, Liv Wenche Thornjørnsen, Sigrud Breder, Sissel Åkra, Trine Folseraas, Vemund Paulsen, Merete Tysdahl and Marit Mæhle Grimsrud

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RESEARCH PROFILE

The projects of the Clinical Liver Research Group aim at improving clinical outcomes for PSC patients. We have had a particular focus on discovery and establishment of markers for early detection and targeted treatment of PSC-associated cholangiocarcinoma (PSC-CCA). We are responsible for the daily recruitment of patients and collection of valuable material to the NoPSC database and biobank, which facilitates research across the different research groups within NoPSC and other external collaborations focusing on PSC research.

PROJECTS RELATED TO PSC-ASSOCIATED BILIARY TRACT CANCER

Identification of early detection markers for PSC-associated cholangiocarcinoma (CCA)

Several ongoing projects explore novel candidates for early detection of CCA in PSC. The main aim of these efforts is to provide PSC patients with meaningful surveillance and early diagnosis of CCA.

In collaboration with the Epigenetics group at the Institute for Cancer Research at the Norwegian Radium Hospital, we have applied whole-genome methylome sequencing on fresh frozen liver tissue from patients with PSC and PSC-CCA to detect candidate markers for early diagnosis of CCA. A panel of promising methylation markers with high sensitivity and specificity for CCA in PSC has been detected. We are now validating and testing these candidate markers for their utility using a large panel of bile samples derived from the PSC biobanks in Norway, Sweden and Finland. In parallel we are testing this methylation marker panel for their utility in blood. The results and manuscript from this study is expected to be finalized in 2024.

In collaboration with the Biodonostia Institute, Donostia University Hospital, San Sebastian, Spain, we have analysed the protein content of extracellular vesicles from bile samples derived from the NoPSC biobank from patients with PSC and/or CCA. By this we have identified promising protein biomarkers for prediction and accurate diagnosis of CCA in patients with PSC. This manuscript is also expected to be finalized by 2024.

Genetic characterization of PSC-associated biliary tract cancer (BTC)
We have in close collaboration with Department of Pathology at the University Hospital of Heidelberg and the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, performed whole exome sequencing of tumors from 52 well-characterized patients with PSC-associated biliary tract cancer (PSC-BTC). In this effort we found many well-stablished cancer genes to be implicated in PSC-BTC, among these some putative therapeutic targets in PSC-BTC, such as FGFR3, ERBB2, MDM2, BRAF. We have also identified a smaller number of novel candidate genes in BTC, where further translational studies will be needed to establish their functional role in PSC-BTC development. The genetic alterations identified confirm that CCA in PSC mainly arises from the large bile ducts (large-duct type CCA). The manuscript from this project was accepted for publication in Hepatology Communications and will be publicly available in 2024.

PROJECTS RELATED TO LIVER TRANSPLANTATION IN PSC WITH BILE DUCT NEOPLASIA

In collaboration with colleagues at Karolinska Institutet, Stockholm, Sweden, we are performing retrospective studies on a cohort of 512 patients with PSC that underwent liver transplantation between 2000 to 2021, primarily to evaluate diagnosis, selection and outcome for patients that were treated with liver transplantation based on an indication of suspected biliary dysplasia or CCA. Manuscripts form these efforts are expected to be finalized in 2024.

STATUS AND PROJECTS RELATED TO THE NORWEGIAN PSC BIOBANK AND PATIENT DATABASE

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 from 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 2023 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 the phase III clinical trial and extension phase for nor-ursodeoxycholic acid. The prospective PSC patient cohort followed by our group at Rikshospitalet since 2013 will provide an important recruitment base for further clinical trials that are in development.

KEY COLLABORATORS

- The Department of Pathology, Oslo University Hospital, 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 IPSCR, Amsterdam AMC, the Netherlands
- The International PSC Study Group (IPSCSG)
- European Network for the Study of Cholangiocarcinoma (ENSCCA)

CLINICAL LIVER RESEARCH GROUP, HARALDSPLASS DEACONESS HOSPITAL, BERGEN

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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 is an important strategic activity to achieve these goals.

SCANDPSC AND AIL

The Haraldsplass group initiated and is responsible for the ScandPSC prospective cohort, both at the national and overall level. The ScandPSC is an extension of the national network for autoimmune liver diseases (AIL-study), which also receives project support from the other clinical reseach groups at NoPSC. The networks form the critical infrastructure of our research agenda on non-invasive biomarkers in PSC. For details on ScandPSC and AIL, see separate description on pages 18-20.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS IN PSC

We were the first to identify and validate the ELF®Test as an independent prognostic marker in PSC, 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 other large patient panels from Scandinavia and the Mayo Clinic.

From left: Lasse M. Gill, Holmfridur Helgadottir, Mette Vesterhus, Karen Rønneberg, Ingeborg Brønstad og Guri Fossdal.

Postdoc Helgadottir serves a leading role in the analysis and writing of this project.

Guri Fossdal in our group defended in 2023 her PhD thesis on biomarkers in PSC (see page 20).

PRURITUS AND PROMS

Pruritus may significantly reduce the quality of life of patients with PSC; however, knowledge regarding the pathogenesis of cholestatic itch as well as therapeutic options are limited. In an ongoing study, led by postdoc Helgadottir, we aim to identify potential pruritogens and therapeutic targets. Acknowledging the importance of patient-reported outcomes (PROMs), we have translated and pilot tested a PSC-specific PROM instrument.

CLINICAL TRIALS

Contribution to drug development for PSC through increasing involvement in clinical trials is an important aim for NoPSC, and we are involved in an ongoing phase III clinical trial for nor-ursodeoxycholic acid and will contribute to the investigator initiated clinical trials assessing the efficacy of vitamin B6 supplementation and fibrates which are run by the entire NoPSC.

CLINICAL LIVER RESEARCH GROUP, AKERSHUS UNIVERSITY HOSPITAL (AHUS)

From left: Kristin Kaasen Jorgensen, Mari Vingdal, Stine Dommersnes and Usha Tharmathas

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RESEARCH PROFILE

We perform clinical liver research aiming to explore disease progression in PSC and management of the disease by drug development through clinical trials.

PROJECTS INVESTIGATOR-INITIATED CLINICAL STUDIES

AIL-study

Our research group contributes to and administers, in close collaboration with the clinical research group in Bergen, the National Network for Autoimmune Liver Diseases (AIL-study). This multicenter, observational cohort study has included 700 patients with PSC from more than 20 study centres across all health regions in Norway, out of which approximately 120 patients are followed at AHUS. The collaboration also includes work in a parallel Swedish initiative, jointly comprising the ScandPSC cohort (see separate presentation on page 18-19), now encompassing 1300 prospectively followed patients with PSC. During the annual follow-up visits, clinical data and biologic material is collected. We cooperate closely with the primary investigators at other centers to secure follow-up of patients according to the study outline. An important ongoing activity is the implementation of a robust data monitoring plan for the AIL as a whole, to secure robustness and "regulatory quality" of collected data. We are also currently working to streamline the workflow for data extraction and biological samples, to prepare for scientific utilization of the huge resource represented by the cohorts. Initial descriptive work (e.g. clinical, biochemical and radiological characteristics) is now feasible, and will be taken forward in the context of a PhD project with a particular emphasis on disease severity markers of PSC in the context of clinical trials.

Pyridoxine Treatment in Primary Sclerosing Cholangitis (PiPSC)

This multicentre, phase II double-blinded randomized controlled cross-over study investigates outcomes of pyridoxine supplementation compared with placebo. Our group contributes to screening inclusion and follow-up of patients in this study. The PhD candidate Tharmathas will contribute to the preparation and analyses of study data, with a particular emphasis on exploratory biomarkers for efficacy assessments.

Bezafibrate Treatment in Primary Sclerosing Cholangitis (BEZANOR)

The formal basis for a double-blinded, randomized controlled parallel-group phase II study to compare the safety and tolerability of treatment with oral bezafibrate compared with placebo in participants with PSC is being finalized , and patient recruitment will be initiated in Q1/2025. Our centre is part of the project group and have been actively involved in the planning of the study. Our group will be central in the coordination and implementation of the study and PhD candidate Tharmathas is planned to serve a leading role in this trial.

IBSEN III: Liver disease in inflammatory bowel disease (IBD)

We collaborate with the IBSEN III group that runs a large, population-based inception cohort, which includes all incident IBD patients in the South-Eastern Health Region over a three-year period (2017-2019). In particular, we contribute to the PSC-screening branch of the study by performing liver MRIs in conjunction with the five-year follow-up, with the aim of exploring the incidence and type of liver pathology in a large cohort of Norwegian IBD-patients.

INDUSTRY-INITIATED CLINICAL STUDIES

We participate in several industry-initiated phase II and III clinical trials regarding medical treatment of autoimmune liver diseases (PSC and primary biliary cholangitis) involving compounds as norucholic acid, obeticholic acid and bezafibrate and provide scientific advice to industry on drug development in these diseases.

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

PROJECT BACKGROUND

ScandPSC merges two strong scientific 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 in patients to participate in research studies and limited loss to follow-up coupled to unique national registries, provide ideal conditi-ons for high-quality, well-powered prospective studies.

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.

MANAGEMENT GROUP

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Trine Folseraas, MD, PhD
Oslo University Hospital, Norway

Niklas Björkström, Prof. MD, PhD
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STEERING COMMITTEE

National PI 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) will oversee the management of the funds.

EMPLOYED PROJECT COORDINATOR

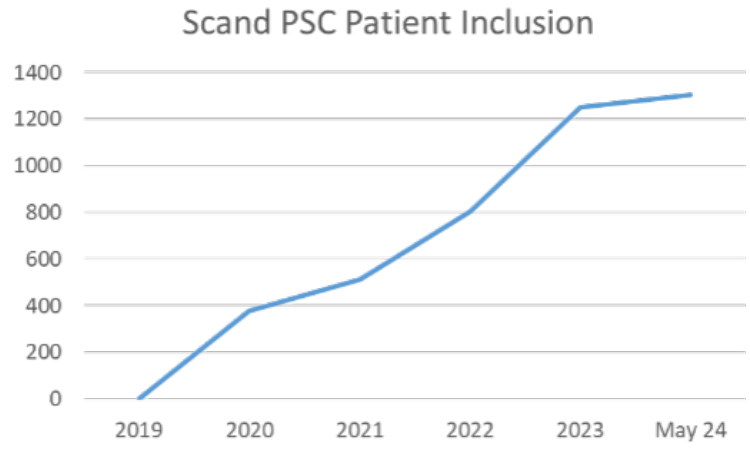
Kristin K. Jørgensen, MD PhD, Norway

FUNDING

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

PROJECT STATUS 2023

By 31.12.2023, the prospective cohort included biobank serum samples from 1230 PSC patients (803 in 2022 and 512 in 2021), of which 650 in Norway and 580 in Sweden. This represents a 35% increase of inclusion over the last year. By 01.05.2024, a total of 1305 patients were included (615 in Sweden and 690 in Norway). The patient panel demonstrates typical demographic characteristics with median age of about 37 years at inclusion, a majority og males (65%) and where 80% of patients have IBD. Several novel centers started active patient inclusion in 2023, increasing the number of active centers to 31 (Norway 21, Sweden 10).



ECONOMY

Expenses 2023		
Norway	Salaries	279 410
	Biobank- and visit-related expenses	865 172
	PI meeting	86 234
	VAT, will be compensated	120 793
Sweden	Biobank- and visit-related expenses	483 174
SUM Expenses		**1 834 783**
Income	From 2022 and new donation	-3 934 542
Transfered to 2023		**- 2 099 759**

PRIORITIES FOR 2024

The main goal is to continue the recruitment of additional patients at all active centers in Norway and Sweden. In Sweden, all university hospitals recruit patients and expansion is completed. In Norway, patients are recruited from all university hospitals in all four health regions, start-up is planned at three new centres in 2024. Important priorities in 2024 will be to cooperate closely with the primary investigators to secure follow-up of patients according to the study outline, monitoring of study data and streamlining the workflow for data extraction and biological samples, to prepare for active utilization of the resources.

SCANDPSC RETREAT IN BERGEN AUG 31-SEPT 1 2023

At the end of August 2023, 36 participants, both physicians and study nurses, from over 20 inclusion centers in Norway and Sweden met in Bergen for a two-days PSC retreat. The meeting included a mixture of lectures regarding how to manage patients with PSC based on the novel EASL guidelines, patient related outcome measures, treatment of cholestatic pruritus, cancer surveillance and prognostication of PSC. Additionally, workshops were held to discuss how to manage clinical studies. Clinical cases were also presented and discussed.

View from Ulriken taken during the retreat

Fully concentrated retreat participants during the lectures

Throughout the two days and also during the evening dinner, experiences with study inclusion, follow-up of patients and managing study visits were widely discussed between the participants.

There was interest for a new meeting among the participants, and we plan for a new meeting in the future.

Participants at the ScandPSC retreat in Bergen

ACTIVELY RECRUITING CENTERS AND LOCAL 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
Levanger Hospital	Even Ness-Jensen
Kristiansund Hospital	Ellen Melsom
Sørlandet Hospital, Kristiansand	Håvard Wiik
Sørlandet Hospital, Arendal	Geir Noraberg
SWEDEN	**National PI: Annika Bergquist Coordinator: Lina Lindström**
Karolinska University Hospital, Huddinge	Lina Lindstrøm
Karolinska University Hospital, Solna	Charlotte Hedin
Academic Hospital Uppsala	Fredrik Rorsman
Skåne University Hospital	Emma Nilsson
Linköping University Hospital	Stergios Kechagias
Sahlgrenska University Hospital	Antonio Molinaro
Örebro University Hospital	Nils Nyhlin
Norrland University Hospital	Mårten Werner
Danderyds Hospital	Anna Haeggstrøm
Karlstad Central Hospital	Imante Lasyte

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, primary biliary cholangitis 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

To study prognostic factors, biomarkers of disease activity and prognosis, and patient-reported outcome measures in PSC, primary biliary cholangitis and autoimmune hepatitis; and 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 2023, both recruitment of centers and patients increased substantially. All university hospitals and all four health regions are now involved. Further expansion is planned for 2024. There are pr Dec 31, 2023 650 patients with PSC included from 21 active centers. Descriptive data will be presented at the Annual Meeting of the Norwegian Gastroenterology Society. The AIL-project is a sub-project of ScandPSC

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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)

Dissertation

On December 1st, 2023, Guri Fossdal, MD, defended her thesis «Surrogate Markers of Natural History, Disease Severity, and Prognosis in Primary Sclerosing Cholangitis" for the degree of PhD (Philosophiae Doctor) at University of Bergen.
Principal Supervisor: Professor Mette Vesterhus, University of Bergen
Co-supervisor: Professor Tom Hemming Karlsen and Dr. Trine Folseraas, University of Oslo, and Dr. Eystein Husebye, University of Bergen.

The disease course in PSC demonstrates a considerable variation between individuals, and established liver biochemistries in PSC do not mirror the disease progression well. There is an explicit need to establish new, non-invasive biomarkers for risk stratification and prognostication in designing pharmaceutical trials and tailoring patient follow-up in clinical practice.

Development of fibrosis is characteristic of disease progression in PSC. The project sought to describe the association between biomarkers of fibrosis in blood samples and liver stiffness measurements (LSM) and the disease course in PSC. We demonstrated that the Enhanced Liver Fibrosis test (ELF) in blood samples and liver stiffness measurements increased over time and that ELF might be a stronger predictor for risk stratification. We also explored advanced statistical methods for combining biomarkers from different pathological pathways. In the multimarker study, we found a panel of biomarkers reflecting fibrosis (ELF), inflammation (kynurenin-tryptophan ratio; KT-ratio), and a microbial metabolite (pyridoxal 5'-phosphate; PLP) resulting in stronger prediction.

Furthermore, several studies have demonstrated an association between mitochondrial function and several liver diseases, prompting us to investigate the fatty acid profile in people with PSC. We found elevated mono-unsaturated fatty acids (MUFA) levels but reduced long-chained saturated fatty acids (SFA), omega-3, and -6 fatty acids. These alterations suggest that the mitochondria participate in the disease process in PSC and might point toward possible targets for future pharmaceutical trials.

Highlights 2023

NOPSC RETREAT

The annual NoPSC research retreat 2023 was hosted at Holmenkollen Park Hotel 12th to 13th of January. The program had a strong emphasis on innovation and career building, in line with ongoing priorities at NoPSC. A new element of the retreat program was “flash talks”, where all PhD students and post docs were challenged to present innovative components of their own project in only 3 minutes. Biobanking and cohort building at NoPSC were discussed in the perspective of experiences from the HUNT biobank which was presented by guest speaker Kristian Hveem.

SPARK

The UiO:Life Science board admitted six new teams to the innovation program SPARK Norway 27th of January, of which “DUCT chip – An artificial bile duct on a chip recapitulating immune functions” was awarded. Henry Hoyle from NoPSC is the project leader with a team consisting of Anna Katharina Frank, Espen Melum, Stefan Krauss (UiO/OUS), Mathias Busek (UiO), Aleksandra Aizenshtadt (UiO) and Kayoko Shoji (UiO). They will develop the bile-duct-on-a-chip concept further and explore innovation opportunities within health-related life sciences for the benefit of PSC patients.

NORWEGIAN GASTROENTEROLOGY ASSOCIATION

In 2023 Sigurd Breder contributed as board member in the Norwegian Gastroenterology Association (Norsk Gastroenterologisk Forening, NGF),Kristin Kaasen Jørgensen as leader and Trine Folseraas as board member in the NGF Interest group for NGF Liver Disease and Espen Melum in charge of NGF’s research funds. At NGF’s annual meeting 9-11th of February 2023 at Lillehammer Lise Katrine Engesæter received a prize for best work in the “Liver, bile and Pencreas” category with her presentation; “Organoider derivert fra børsteprøver samlet ved ERCP hos pasienter med PSC”. NoPSC also contributed with two articles in the NGF news magazine (NGF-nytt) in 2023; Thomas Bergsmark and Espen Melum with “Langtidsoverlevelse etter levertransplantasjon for alkoholrelatert leversykdom i Norden”, and Mette Vesterhus with «Nettverkssamling for AIL-Studien – ScandPSC Retreat».

IN THE MEDIA

The University of Oslo, Faculty of Medicine, featured Anna Frank from NoPSC on their website news feed in January 2023 under the headline «Organ-on-a-chip: Development through interdisciplinary work”. The article highlights the benefit and results of collaboration within the Scientia fellow program.
https://www.med.uio.no/english/research/scientia-fellows/news-and-events/news/2023/development-through-interdisciplinary-work

GUEST PROFESSOR MEETINGS

The guest professor program at NoPSC was renewed in 2023, and engaged three new guest professors: from academia Professor Tom Lüdde from University Clinic, Dusseldorf, Germany, and Dr. Fotios Sampaziotis from University of Cambridge, UK and from the pharmaceutical industry Dr. Jan Tchorz from Novartis, Basel, Switzerland. Prof. Lüdde and Dr. Sampaziotis had their first guest professor meeting with us 26th to 26th of September and Dr. Tchorz, accompanied by his postdoc Alexandro Landshammer, on 28th of November. Both meetings included sessions with groups and individuals for discussions and supervision.

ONLINE COLLABORATION SEMINARS PROGRAM

An online collaborations seminars program with key PSC research institutions was initiated in 2023. This comprises regular Zoom calls where the teams link up online for

a seminar of around 90 minutes durations, with project presentations from both sides and associated discussions. Such online collaboration seminars are currently being hosted with the Mayo Clinic (the team of Prof. Konstantinos Lazaridis), Brigham and Women´s hospital (the team of Prof. Joshua Korzenic) and Institute of Clinical and Molecular Biology in Kiel (the team of Prof. Andre Franke).

RESEARCH INSTITUTE OF INTERNAL MEDICINE

For the first part of 2023 Espen Melum served as the head of the Research Institute of Internal Medicine (RIIM) at Oslo University Hospital and University of Oslo. One part of his duties was to host the RIIM spring seminar 14th of April at Radisson Blue Scandinavia Hotel in Oslo, where the two NoPSC groups at RIIM was strongly represented.

MONITORING BOARD MEETINGS

The regular Monitoring Board meetings for NoPSC was hosted the 15th of June and the 14th of December. Key topics for discussion were the ongoing upscaling of activities following the new donation from Stein Erik Hagen and Canica A/S. An ongoing project to describe the importances of philanthropy in rare diseases like PSC has been initiated by Petter Skavlan, who participated in the spring monitoring board meeting.

IPSCSG

In 2023 the administration of IPSCSG (International PSC study Group) was transferred to the capable hands of Prof. Christoph Schramm and Prof. Ansgar Lohse at University Medical Center Hamburg, Germany. NoPSC maintains financial support to this secretariat as an integral part of the annual budget. In addition to the meetings for IPSCSG at the International Liver Conference (EASL) in Vienna in June and at “The Liver Meeting” in Boston in November, the new leadership also arranged a “Young Investigator Workshop on Basic Science and Translational immunology in PSC” 25th to 26th of May in Hamburg. Espen Melum was an invited speaker at this event, and Anna Frank and Markus Jördens participated from NoPSC. The aim of the workshop was to strengthen collaborations amongst the next generation of translational researchers in PSC.

VISITING SCIENTIST

The visiting scientist program was further developed during 2023, with the aim of providing stimulating discussions on specific topics represented by emerging leaders in the field. The 15th of June Professor Harry Sokol from Saint Antoine Hospital, Paris, an expert in microbiome research, visited.

THE NORWEGIAN LIVER MEETING

At the annual Norwegian/National Liver Meeting 12th of September 2023 in Oslo, conducted by the Interest group for liver disease in Norway, many NoPSC members were present, and Lise Katrine Engesæter, Johannes E. Hov and Trine Folseraas gave presentations on recurrent PSC, evaluation of liver disease of unknown etiology and genetics in liver disease.

THE INTERNATIONAL LIVER CONGRESS

The annual International Liver Congress organized by the European Association for Study of the Liver (EASL) was hosted in Vienna, Austria, 21st to 25th of June 2023 with ten registered participants from NoPSC. Anna Frank and Markus Jördens presented two PSC abstracts each, while Guri Fossdal, Mikal J. Hole and Petra Hradicka presented one PSC abstract each. Tom H. Karlsen gave the clinical state-of-the-art lecture of the congress, reporting from the EASL-Lancet Commission on Liver Disease in Europe.

PSC PARTNERS MEETING

From the 7th to 10th of September Espen Melum and Johannes R. Hov participated in the PSC Partners Patient & Caregiver Conference in Henderson, Nevada, which was preceded by a meeting in the associated “PSC Partners International Collaborative Research Network”. The activities were highly successful with strong scientific contributions and collaborative discussions focusing on the critical research questions in PSC in the context of a patient and caregiver conference.

SCANDPSC RETREAT

31st of August to 1st of September Mette Vesterhus hosted the first ScandPSC retreat at Haraldsplass Deaconess Hospital in Bergen. The meeting gathered 35 Principal investigators and study nurses involved in the

ScandPSC study, and was a great success. For more information on ScandPSC, see page 18-19.

RESEARCH EXCHANGE

From 22th to 28th of October, Professor Cyriel Ponsioen from the University of Amsterdam visited NoPSC as part of his sabbatical. During his stay, he was introduced to both clinical routines as well as relevant research projects. He also contributed valuable insights on his own extensive research program in PSC and the visit served further discussions on mutual research interests in PSC.

THE LIVER MEETING

The American Association for Study of the Liver Diseases (AASLD) annual meeting "The Liver Meeting" was held in Boston 10-14th of November 2023. Kirsten Muri Boberg and Lise Katrine Engesæter represented NoPSC.

TENTH NATIONAL MICROBIOTA CONFERENCE

The 10th National Microbiota Conference in Oslo 7th November 2023 was for the last time co-hosted by NoPSC group leader Johannes R. Hov. NoPSC was responsible for several presentations, including talks by postdocs Antonio Molinaro, Petra Hradicka, Peder Braadland and PhD student Simen Hyll Hansen. After ten consecutive years as a national event, this NoPSC initiated event now will be expanded into a Nordic event in Denmark in 2024, no longer co-hosted by NoPSC.

FORENINGEN FOR AUTOIMMUNE LEVERSYKDOMMER (FAL)

The ongoing collaboration with the patient organization FAL is both useful and enjoyable, and we are very pleased to involve patients as active participants in reviewing new and ongoing research projects. Our meeting with FAL on the 30th of November focused mainly on their agenda and programs in regards to how to provide the best support to PSC patients.

THE BIOMEDICAL ALLIANCE IN EUROPE

The Biomedical Alliance in Europe (BioMed Alliance) is a unique Brussels-based initiative comprising most leading European medical societies that aim to facilitate and improve biomedical research in Europe, with a particular emphasis on EU research funding and harmonization of EU regulations of relevance to research. In 2023, Tom Hemming Karlsen was voted the President-Elect of the Biomed Alliance Board of Directors.

EUROPEAN NETWORK FOR THE STUDY OF CHOLANGIOCARCINOMA

NoPSC is a member of the European Network for the Study of Cholangiocarcinoma (ENS-CCA) which constitutes of research groups located in 13 European countries and represents CCA interests from basic, translational and clinical research. Trine Folseraas serves as a management commitee member in ENS-CCA.

ERN RARE-LIVER

Trine Folseraas and collaboration partner of NoPSC, pediatrician Dr. Runar Almaas, serve as Norwegian representatives in the European Reference network (ERN) for rare liver disease (Rare-Liver) for adult and pediatric liver disease, respectively. They both participated at the biannual ERN Rare-Liver member meeting in Hamburg 11th to 12th of December 2023. The ERN serves a critical role in implementing clinical practice standards in rare diseases like PSC, and thus serves as link between research at NoPSC and clinical benefits for patients.

SOCIAL ACTIVITIES

We are proud of the friendly working environment at NoPSC. Troughout the year, several social gatherings like "after work meet-up", ecape-room, Christmas-trolly or ski-days, gives the NoPSC researchers some enjoyable variability from everyday work.

Networks and collaborations

KEY LOCAL COLLABORATORS, OSLO UNIVERSITY

Research Institute for Internal Medicine (RIIM)
The head of the Institute was Espen Melum until August 2023, when Prof. Bente Halvorsen returned. The research groups led by Espen Melum and Johannes E.R. Hov, respectively, are located at RIIM and several collaborative projects are established with the groups of, among others, Prof. Marius Trøseid, Prof. 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
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
Department Head Prof. Asle Medhus (from late 2023 leader of the Division of Medicine at OUH) and IBD research group leader Prof. Marte Lie Høivik are important collaborators on IBD related projects.

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.

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.

Institute for Cancer Research
A collaboration with Prof. Guro Lind and post.doc. Hege Marie Vedeld, 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 transplant 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 Prof. Hanne Scholz and Center director Prof. Stefan Krauss at the Center of Excellence Hybrid Technology Hub.

Akershus University Hospital
The NoPSC Clinical Liver Research Group, Ahus, Led by Dr. Kristin Kaasen Jørgensen is located here. 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. Prof. Em. Rolf Berge, at the University of Bergen, has over many years provided fatty acid-related analyses in collaborative projects.

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 also other strong collaborations at Haraldsplass Deaconess Hospital.

KEY INTERNATIONAL COLLABORATORS

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arno Nordin), Stockholm (Dr. Carl Jorns), Got-

henburg (Ass. 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. Prof. Niklas Björkström (former 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.

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Prof. Fredrik Bäckhed and Prof. Hanns-Ulrich Marschall (passed away on August 1, 2023) have been collaborators related to the gut-liver 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 was a world leading bile acids expert.

Uppsala University, Sweden
Associate prof. Daniel Globisch is an increasingly import collaborator, providing unique expertise on the biochemistry of microbial metabolites, now comprising a shared postdoc working in the Globisch lab.

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. NoPSC collaborates with Nordic BioScience 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.

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

University Hospital Heidelberg, Germany
Prof. Peter Schirmacher and dr. Stephanie Roessler, Institute of Pathology at the University Hospital Heidelberg, provides expertise to collaborational projects related to genomic profiling of PSC-associated biliary tract cancers.

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

University Medical Center Hamburg, IPSCSG
In 2023 the administration of IPSCSG was transferred to the capable hands of Prof. Christoph Schramm and Prof. Ansgar Lohse at University Medical Center Hamburg, Germany.

Amsterdam medical Center, Netherlands, IPSCR
We have a close collaboration with Prof. Cyriel Ponsioen and Prof. Ulrich Beuers at the University of Amsterdam's Faculty of Medicine, among other related to projects outgoing from the International PSC registry (IPSCR) initiative led by Prof. Cyriel Ponsioen.

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

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

Biodonostia Research Institute, Donostia University Hospital, San Sebastian, Spain
Prof. 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 and post.doc. Ainhoa Lapitz serve as an important collaborators on projects related to PSC-associated biliary tract cancers.

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

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 Centre for Liver Disease, Toronto General Hospital, Canada. Biostatistician Bettina E. Hansen is leading the statistical analyses of clinical data collected in the International PSC Study Group (IPSCSG) database project, assisted by Dr. Aliya Gulamhusein at the same institution.

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

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

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 Tartu) institutions. The project was completed end of 2023 and involved both the Hov and Melum groups.

New grants and awards in 2023

NEW GRANTS

- From the South-Eastern Norway Regional Health Authorities researcher Xiaojun Jiang and group leader Trine Folseraas received a three-year grant of NOK 3.882.000 from for a PhD student each. The PhD student supervised by Xiaojun Jiang will work on the project "Spatial multi-Omics building Functional hierarchy for disease genes in inflamed bile ducts" and the PhD student supervised by Trine Folseraas on the project "Bringing next generation diagnostics and risk prediction tools for cholangiocarcinoma to the clinic".

- The UiO:Life Science board admitted six new teams to the innovation program SPARK Norway in January 2023 of which "DUCT chip – An artificial bile duct on a chip recapitulating immune functions" with Henry Hoyle from NoPSC as the project leader. The innovation program includes a grant of NOK 1.000.000.

- NoPSC joined a collaboration project with Seoul National University in 2023 entitled: "Single-cell multi-omics-based diagnosis markers and treatments for rare and intractable diseases - AI platform development for target discovery". The project PI at NoPSC is Xioajun Jiang, and about 440.000 NOK is allocated to finance this project at OUS over the next years.

AWARDS

- At the Norwegian Gastroenterology Association's annual meeting 9-11th of February 2023 at Lillehammer Lise Katrine Engesæter received a prize for best work in the "Liver, bile and Pancreas" category with her presentation; "Organoider derivert fra børsteprøver samlet ved ERCP hos pasienter med PSC".

New employees

Sissel Åkra
MSc
Biobank Manager
"With a passion for bio-banking"
UXKRSI@ous-hf.no

Sara Kristina Viberg Tjønnfjord
MD
PHD student
"Energetically enthusiastic about hepatology - bridging gaps in PSC and microbiome knowledge"
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Retired

Liv Wenche Thorbjørnsen NoPSC employee 2009-2023

Warm greetings from the Biobank Manager at NOPSC, reflecting on 14 rewarding years: I am immensely grateful for my 14-year journey in this field, alongside so many wonderful and inspiring colleagues. My background is in Biomedical Laboratory Science, and prior to August 2009, I worked in hospital settings. Seeking a change in my career path, I was fortunate to transition into the fascinating world of biobanking. Despite my extensive experience in laboratory domains like clinical chemistry and hematology, entering the realm of molecular biology was a refreshing challenge that piqued my interest.

In addition to collecting samples from patients with Autoimmune Liver Diseases (AIL), such as PSC, I also conducted DNA and RNA extractions for further research. My role provided many opportunities for professional development through various courses akin to continuous education. I have also collaborated closely with Biobank research infrastructures such as Biobank Norway (National) and BBMRI-ERIC (International) on matters of quality assurance and standardization in biobanking.

The NoPSC center has truly been a special place to work, characterized by its friendly atmosphere and supportive team dynamics. The trust and confidence shown by management are crucial in this line of work, fostering deep loyalty and a sense of responsibility to excel. Through this role, I have gained profound insights into AIL diseases, particularly PSC, understanding patient experiences, symptoms, and treatments like ERCP and liver transplantations.

In sum, my tenure as a Biobank Manager was both intellectually stimulating and rewarding. I extend my best wishes to the team and ongoing research efforts. As I embark on retirement, I eagerly anticipate advancements in understanding and treating AIL diseases in the coming years.

Publications 2023

HIGHLIGHTED PUBLICATIONS

Jiang X, Otterdal K, **Chung BK**, Maucourant C, **Rønneberg JD**, Zimmer CL, **Øgaard J**, **Boichuk Y**, Holm S, Geanon D, **Schneditz G**, Bergquist A, Björkström NK, **Melum E** (2023)
Cholangiocytes modulate CD100 expression in the liver and facilitate pathogenic Th17 differentiation
Gastroenterology 166(4), 667-679

Any disease can be explained by the combined effect of genetic and environmental factors, and primary sclerosing cholangitis (PSC) is no exception. In our previous studies, we identified a causal mutation from a family with PSC and observed a loss-of-protection mechanism in disease pathogenesis. However, significant concerns have been raised in terms of to what extent the knowledge generated from an extreme genetic condition can be generalized to the common PSC population, and how it reflects the fundamental principle in immunology. In a recent study, we found that the causal mutation is involved in a previously undescribed pathogenic process mediated by cholangiocytes, the epithelial cells lining bile ducts. We demonstrated that the physical interaction between cholangiocytes and T cells can facilitate the differentiation of Th17 cells, which is the predominant pathogenic cell type extensively documented in common PSC livers. The fact that the causal mutation can enhance this specific disease event strongly supports the generalization potential of the family study and opens the possibility of using mutation-specific tools to understand universal PSC pathogenesis. Additionally, the finding that the Th17 cell fate can be shaped by biliary epithelial cells during disease also provides new insights into T cell biology and liver local immunity.

Hole MJ, Jørgensen KK, Holm K, Braadland PR, Meyer-Myklestad MH, Medhus AW, Reikvam DH, **Götz A**, Grzyb K, **Boberg KM, Karlsen TH, Kummen M, Hov JR** (2023)
A shared mucosal gut microbiota signature in primary sclerosing cholangitis before and after liver transplantation
Hepatology, 77 (3), 715-728

We have previously performed several studies on the fecal microbiota in PSC. In this paper, we used biopsy material collected and stored as part of Kristin K Jørgensen's PhD work aiming to characterize the IBD in PSC, aiming to assess the mucosal microbiota in PSC before and after liver transplantation. The most important observation was that the gut microbiota does not normalize after transplantation, rather it becomes more dysbiotic. Recurrent PSC is a significant clinical problem, and this observation suggests that gut microbial factors could contribute to disease recurrence, providing a rationale for further studies of the disease mechanisms. We also observed a limited number of bacteria overlapping between PSC and rPSC, which could represent key PSC bacteria associated with more severe disease.

Braadland PR, Bergquist A, **Kummen M**, Bossen L, **Engesæter LK**, Reims HM, Björk I, Grzyb K, Abildgaard A, Småstuen MC, **Folseraas T**, **Trøseid M**, Ulvik A, Ueland PM, **Melum E**, Line PD, Høivik ML, Grønbæk H, **Karlsen TH, Vesterhus M, Hov JR** (2023)
Clinical and biochemical impact of vitamin B6 deficiency in primary sclerosing cholangitis before and after liver transplantation
J Hepatol, 79 (4), 955-966

In a previous study we showed that people with primary sclerosing cholangitis (PSC) had a reduced gut microbial potential to produce vitamin B6 (PLP), a cofactor critical for human health. In the current study we investigated the extent and clinical impact of B6 deficiency in both untransplanted and liver transplanted people with PSC and relevant disease controls from several centers. Whereas B6 deficiency is rare in the general population, B6 deficiency was prevalent (17-38%) in PSC and more prevalent than in people with inflammatory bowel disease without PSC. Reduced levels of blood PLP associated with clear signs of functional B6 deficiency and shorter liver transplantation-free survival, but the B6 status was only modestly improved after liver transplantation. In individuals with recurrent PSC after liver transplantation, reduced blood PLP associated with shorter survival without re-transplantation. Our findings suggest that B6 deficiency may drive the progression of PSC and form a rationale for assessing the B6 status in people with PSC. The findings also provide the basis for a recently initiated randomized clinical trial to test the efficacy of B6 supplements in PSC.

ADDITIONAL RESEARCH ARTICLES

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Whole blood RNA sequencing identifies transcriptional differences between primary sclerosing cholangitis and ulcerative colitis.
JHEP Rep 6(2), 100988

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Scand J Gastroenterol 59 (3), 369-377

Oldereid TS, Jiang X, Nordhus KS, Ponzetta A, Bjørnholt JV, Björkström MK, **Melum M, Rasmussen H** (2023)
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FASEB J, 37 (11), e23220

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Gastroenterology, 2023 Oct;165(4):946-962.e13.

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JAMA Dermatol, 159 (9), 923-929

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CONGRESS ABSTRACT

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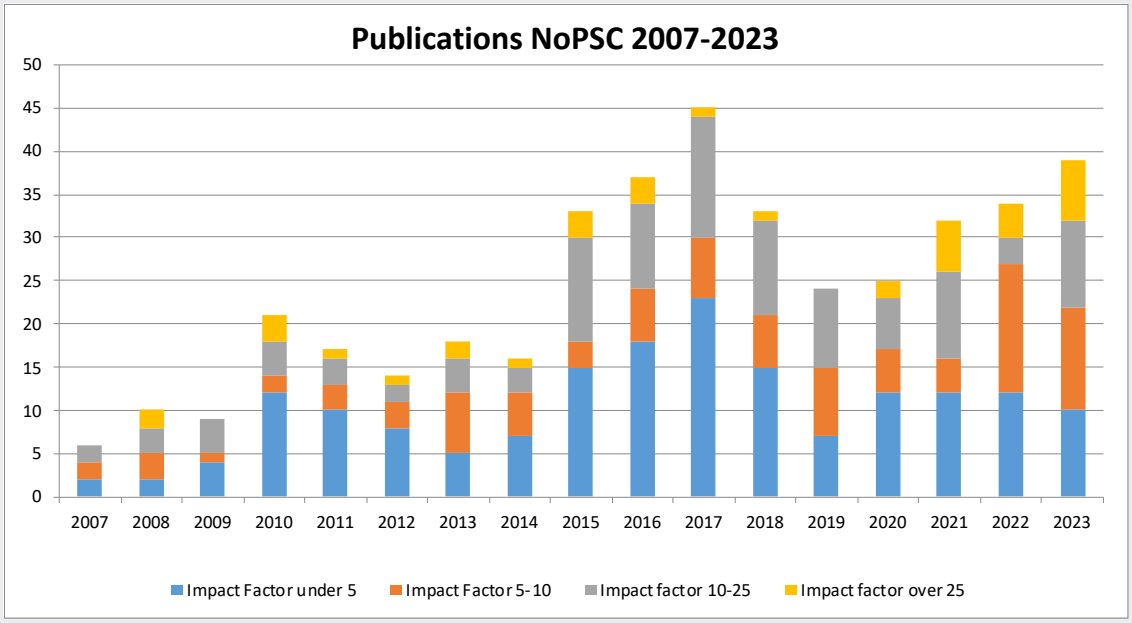

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