Oslo University Hospital

Norwegian PSC Research Center

Annual report 2014

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

Annual report 2014

NoPSC ANNUAL REPORT 2014

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

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IN THE PICTURE (left to right): Xiaojun Jiang, Corey X. Tan and Evangelia Liaskou
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Leader´s comment

Photo: Øystein H. Horgmo, UiO

For all of the hard working NoPSC employees, the main event of 2014 was the granting of the future of the center by Stein Erik Hagen and Canica A/S. The first agreement with the University of Oslo was scheduled to end during 2016, and the renewed funding horizon from 2017–2026 allows for sustained activity and an unaltered focus of the research activity of all involved – PSC. Of course we are all extremely grateful for being able to see that what we've built over the last 7–8 years will continue operating, and hopefully grow further.

The support by Canica A/S over the first – and soon second – decade of substantial PSC funding in history ever provides opportunities for reflection. Not only on the structure of funding schemes, but also what it takes to deliver a translational research program spanning from understanding disease development to ultimately providing efficient patient management. Most common funding schemes have a horizon of 3 years, typically affiliated with post doc and PhD fellowships. Exceptions exist, most notably in the Norwegian Centers of Excellence ("SFF") program and a few EU level grants.

Starting out with a small group of 3-4 people, NoPSC has grown to encompass now 15–20 affiliated researchers, three formal research groups, a robust infrastructure (counting labs, animal facilities and one of the most robust biobanking systems in Norway). In addition, the International PSC study group, counting steadily 60–70 researchers worldwide is closely coordinated with the Oslo efforts (and vice versa). The scientific output of this large group – and the quality level of the scientific output – has increased tremendously, leading to recognition far beyond the reaches of the field of hepatologists as seen by citations of our PSC papers in prestigious articles in Nature and the likes.

Realistically, it would have been impossible to sustain the current level of funding for a rare disease like PSC

without the support provided by Canica A/S. However, there is a need to emphasize this increasing recognition of PSC as a key model disease for general disease mechanisms. Understanding the gut-liver axis aspects of the concurrent liver and bowel affection, the autoimmunity which somehow does not respond to immunosuppression and the peculiar – and unfortunate – high risk of cancer would represent major leaps in medical knowledge. In addition to the group being recognized as capable of delivering high-quality science, these challenges likely are the basis for the success in so many competitive funding applications last year (e.g. the major grants from the Research Council of Norway and Helse Sør-Øst in 2014, see page 5).

An important accomplishment during 2014 was the completion of several projects related to the HLA association in PSC and inflammatory bowel disease. This included technological advances in terms of new genotyping methods (a side initiative funded by an EU FP7 program), as well as major papers – including the 7th Nature Genetics publication affiliated with NoPSC (see separate theme on page 9). This publication is of interest for our reflections on time, since it was initiated exactly 10 years prior to the publication date. The philosophy of the project was to publish "when done" which is a rare opportunity in modern publication driven science, showing how the time-scale that is sometimes needed to make big discoveries is not necessarily that of the normal funding format.

When will we know what causes PSC and be able to cure it? Is 10 years enough? Will we be "done" when the full 20 years of NoPSC are over? Clearly it is beyond our thinking to forecast on these questions, but what is increasingly clear is that the funding situation generously provided us allows us to do the right type of research to bring us rapidly closer to such ambitious aims.

Oslo 20.04 2015
Professor Tom Hemming Karlsen
Leader of NoPSC

NOPSC
Norwegian PSC Research Center

What is PSC?

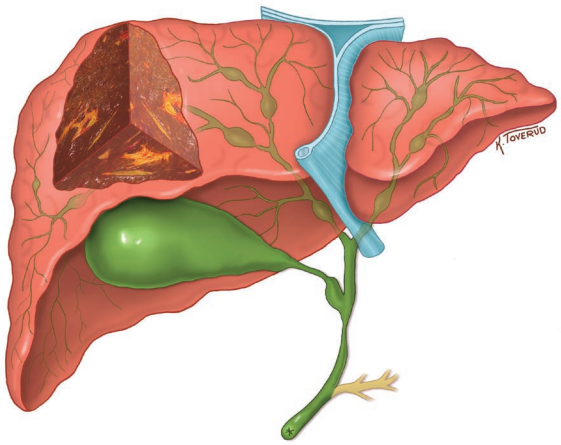
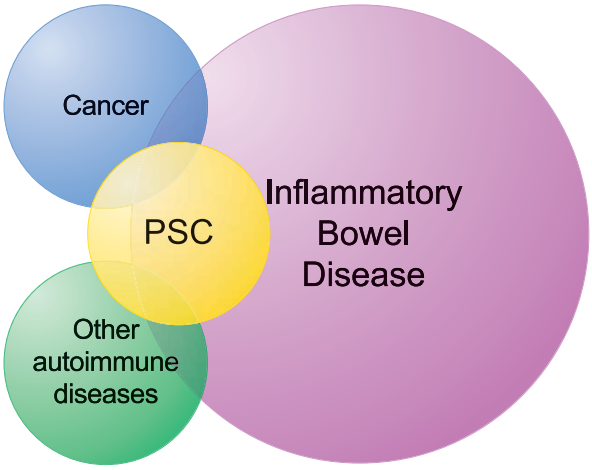


Illustration: © Kari C. Toverud, CMI (Certified Medical Illustrator)

PSC, *primary sclerosing cholangitis*, is a chronic inflammatory disorder of the bile ducts. PSC leads to progressive strictures of the bile ducts and ultimately to liver cirrhosis.

There is an increased risk of cancer of both the bile ducts *(160-1500x)* and the large bowel *(5x)*. PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. There is no effective medical treatment available, and PSC is one of the most common indication for liver transplantation in Scandinavia.

Affected individuals are typically young *(30-40 years old)* and have concurrent inflammatory bowel-disease *(IBD)* in 60-80% of the cases. Disease course is highly variable from patient to patient, but the median time from diagnosis to liver transplantation is 10-15 years.



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

Key NoPSC events in 2014

Photo: NoPSC

Member of the European Association for the study of the Liver (EASL) Governing Board

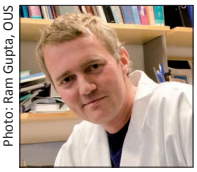


Photo: Ram Gupta, OUS

Tom Hemming Karlsen has since April 2014 served on the Scientific Committee of the European Association for the study of the Liver (EASL) Governing Board. EASL was founded in 1965 and has grown to become a major player in international hepatology, serving a broad educational and scientific portfolio, including an annual International Liver Congress (ILC) with more than 10 000 attendants. The contributions to the work of EASL ramify beyond PSC and relates to the importance of research and education on liver diseases on the international arena in general (for more information on EASL, see *www.easl.eu*).

Dissertation of Trine Folseraas

Photo: Ø. H. Horgmo, UiO

October 31st, Trine Folseraas defended her thesis "The immunegenetic susceptibility to primary sclerosing cholangitis" in an outstanding manner. The trial lecture was entitled "Autoimmunity of the liver". The opponents, Prof. Frank Lammert, Medizinzche Fakultät der Universität des Saarlandes, Homburg, Germany and Prof. Niklas Björkström, Karolinska Institutet, Sweden contributed to a great scientific discussion with the candidate. Tom H. Karlsen, Espen Melum and Bente Halvorsen were Folseraas' supervisors. Folseraas continues her work as clinician and researcher at the Department of Gastroenterology/NoPSC.

1st National Microbiota Conference

Photo: NoPSC

NoPSC post doc Johannes R. Hov and Jebsen (JIRC) post doc Marius Trøseid hosted the first national conference on "Gut Microbiota in Health and Disease" at Gardermoen November 19th. More than 90 people attended the meeting, which was a success. The speaker list included internationally renowned scientists, among these NoPSC Guest Professor Fredrik Bäckhed (Wallenberg Laboratory, University of Gothenburg) and Tore Midtvedt (Karolinska Institutet, Stockholm), but also several talks by Norwegian research groups.

International PSC study group (IPSCSG)

With the assistance of NoPSC two meetings were held in conjunction with the International Liver Congress (ILC/EASL) and the American Association of the Study of Liver Diseases (AASLD) meetings. In addition, the 3rd Biennial International PSC Study Group (IPSCSG) Workshop was held in Amsterdam, hosted by Prof. Ulrich Beuers and Prof. Cyriel Ponsioen. Please see separate presentation at page 18.

Visits from collaborating scientists

Photo: NoPSC

During 2014 we had two scientific visitors from collaborating research groups in Europe. In February, post doc Evaggelia Liaskou, who is working in Dr. Gideon Hirschfield's research group in Birmingham, UK, came for a three month long visit. See separate presentation of Liaskou at page 13. In May, Dr. Elisabeth Krones (right in the picture) from Prof. Peter Fickert's research group at the Medical University of Graz, Austria, came for a three week long visit, where she spent time in both the NoPSC lab and at the Dept. of Gastroenterology. At NoPSC, she participated in the daily activities in the lab and in the animal facility.

Bi-annual guest professor meetings

The bi-annual guest professor meetings were held in May and November. All scientific projects were critically reviewed in relevant sub-groups and the guest professors were, as always, highly appreciated discussion partners. The NoPSC guest professors, David Adams from University of Birmingham and Fredrik Bäckhed from University of Gothenburg, are experts in their field and their feed-back is essential to bring our projects to the highest international standard.

Prospective PSC biobanking in Norway

From November 2013 and throughout the first quarter of 2014, the first 20 patients of the Oslo based PSC prospective cohort were included with blood sampling, questionnaires and medical examination. NoPSC research nurse Mona Bjørnstad coordinated the patient visits. In Bergen, the second visit of the Bergen based PSC cohort was performed in parallel. These efforts are part of the initiative of the International PSC Study Group to include at least 1,000 patients for annual detailed evaluation and biobanking. The initiative has been warmly welcomed by the patients.

Nor-ursodeoxycholic acid (norUDCA) clinical trial

This phase II study, where three different dosages of norUDCA along with placebo, are tested in PSC patients, continued

in 2014. The last patient visit was performed in June. norUDCA has shown promising results in mice studies, and the project is an international multi center study. The local efforts were managed by Erik Schrumpf and research nurse Mona Bjørnstad, together with the clinical research department at OUS Rikshospitalet.

Students from Oslo and Akershus University College of Applied Science

From January to April we had two bachelor students from the Biotechnology and chemical engineering program at Oslo and Akershus University College of Applied Science (Høgskolen i Oslo og Akershus) working in our lab, Mette Nyberg og Eva Kristin Schjeldrup. Their project was entitled; Characterization of bowel microbiota in patients with primary sclerosing cholangitis by extraction and classification of bacterial DNA. Post doc Johannes Hov and PhD student Martin Kummen supervised the students, which led to a good bachelor thesis.

Second NoPSC scientific retreat

In September, the second annual NoPSC scientific retreat was held at Losby Gods. All members of NoPSC contributed with presentations during the two-day long scientific program. The retreat was funded by award money for one of top six outstanding original papers second half of 2012, awarded from Oslo University Hospital to Trine Folseraas, Espen Melum and co-workers for the paper: "Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci" published in Journal of Hepatology (PMID: 22521342).

K.G. Jebsen Inflammation Research Centre (JIRC)

A total of eight research groups working on inflammatory diseases in Oslo led by Guttorm Haraldsen, Kjetil Tasken, Johanna Olweus, Pål Aukrust, Dag Kvale, Benedicte Lie, Arne Yndestad, Tom Eirik Mollnes and Einar Martin Aandahl, together with NoPSC, have made an interactive research collaboration centered around 7 post docs. The post docs participate in projects in at least two of the groups, and the working format increases the interactions between these research groups. The collaboration has also fuelled the forming of a Norwegian Inflammation Research Network (NORIN) led by Guttorm Haraldsen. NoPSC is involved in several out of the 7 post doc projects. Please see separate presentation at page 12 of JIRC post doc Xiaojun Jiang, who has her daily work at NoPSC.

www.med.uio.no/klinmed/english/research/centres/kgj-inflammation/

A national guidance report for personalized medicine

Based on the experience from large-scale genetics in PSC and Inflammatory Bowel Disease, Tom Hemming Karlsen represented OUS in a working group to form a national guidance report for personalized medicine.

RESEARCH GRANTS TO NOPSC POST DOCS


Photo: Øystein H. Horgmo, UiO

NoPSC post doc Johannes R. Hov received a "Young talented researcher" grant from The Research Council of Norway for his project "NORGUT: Exploring the metabolic signatures of disease and drug associated genomic features of the gut microbiota in Norway". The funding will cover his 50 % position as researcher and group leader (see separate presentation at page 8) at Institute of Clinical Medicine at the University of Oslo, located at NoPSC. The project funding also covers a three year PhD position, and the recruitment will take place in the second half of 2015. Hov will in parallel continue his clinical work at the Department of Gastroenterology at OUS Rikshospitalet.


Photo: Øystein H. Horgmo, UiO

NoPSC post doc Espen Melum received a career grant from the South-Eastern Norway Regional Health Authority (HSØ) for his project "Regulation of bile duct inflammation". This will finance Melum as a researcher for 8 years in a 50 % position where he will continue as group leader of the Experimental hepatology research group (see separate presentation at page 7), in addition to clinical work. The grant also includes funding for a PhD position and we will try to recruit a talented new PhD student during spring 2015.

These funds are extremely competitive, and this is an acknowledgement of the high research and co-worker standards of NoPSC.

AWARDS

During the Annual Meeting of the Norwegian Gastroenterology Association at Lillehammer in February, PhD student Elisabeth Schrumpf and co-workers were awarded the prize for best experimental work for their project "Bile duct epithelial cells presents antigens to Natural Killer T Cells".

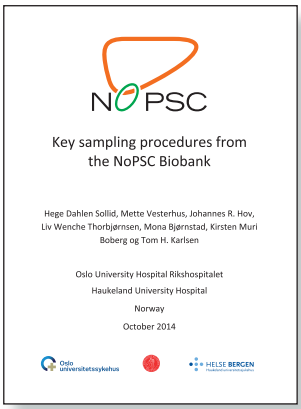
Espen Melum received the "Stabsmøtepris" Spring 2014 for his talk at "Stabsmøte" in January, entitled "Alvorlig leversykdom – hvilken nytte har vi av museforsøk?"

NoPSC project update

Clinical research group in Oslo and Bergen

PRINSIPAL INVESTIGATORS: **Mette Vesterhus**, **Kirsten Muri Boberg**
RESEARCHERS: **Trine Folseraas**, **Erik Schrumpf**, **Tom Hemming Karlsen**, **Kristin Kaasen Jørgensen** (affiliated), **Kristian Bjøro** (affiliated)
CORE STAFF: **Mona Bjørnstad** (study nurse), **Liv Wenche Thorbjørnsen** (medical lab. scientist, biobank), **Jorunn Bratlie** (affiliated engineer), **Aud Sissel Hjartholm** (affiliated engineer)

A major and very fortunate trend in PSC research over the last 2-3 years is the initiating of a large number of clinical trials in PSC. The trials target various aspects of PSC pathophysiology (Figure 1). The research team at NoPSC participates in trials that are eligible for recruitment in Norway, and patient inclusion and follow up in these trials are managed by Erik Schrumpf and research nurse Mona Bjørnstad.



The NoPSC biobank has continued to expand during 2014. A major undertaking is the prospective follow-up of patients, with annual sample collection in addition to the application of various novel imaging modalities. The prospective follow-up is also being performed at collaborating institutions in the International PSC study group throughout Europe and the US. This new resource will form the platform for biomarker and imaging surveys of PSC patients for years to come. As part of the initiative, the NoPSC biobank standard operating procedures were translated to English in 2014.

The first studies of new biomarkers in PSC were completed during 2014 and presented at the European Association for the study of the Liver (EASL) International Liver Congress in London. The results from the studies provide the first effective means of measuring disease stage and severity in PSC without the need of a liver biopsy. The results are not only important for providing patients with information about their prognosis, but also serve as a means of measuring the impact of medical therapy in PSC. The results were accepted for publication in Hepatology, the leading journal for liver disease research, and will throughout 2015 be considerably expanded. This means inclusion of more samples, of more biomarkers, and also comparison with a number of novel imaging techniques, including a novel magnetic resonance (MR) measure of fibrosis in PSC. Studies will be coupled with studies to follow PSC patients after liver transplantation, aiming for characterization and early detection of recurrent PSC.

The projects aimed at early diagnosis of cholangiocarcinoma in PSC continued throughout 2014. A major accomplishment was the validation of a previously published panel of epigenetic markers for cholangiocarcinoma in brush cytology specimens. In combination with novel serum- and urine-based methods for early cholangiocarcinoma detection, the findings warrant great hope for future compound risk scores that will help identify patients in need of an early liver transplantation. These results were also accepted for publication in Hepatology, and will now be prospectively evaluated.

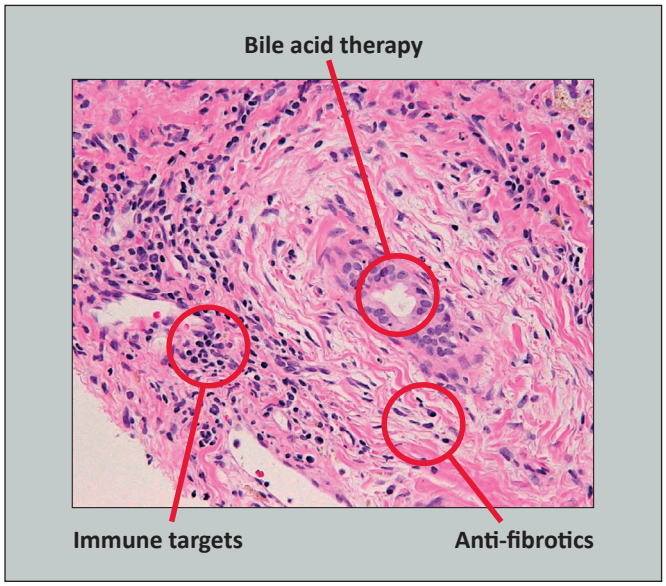


Figure 1: The ongoing clinical trials in PSC target various aspects of PSC pathophysiology: the inflammatory lesion, the fibrotic lesion and the bile acid toxicity aspects. Which aspect will serve as the most fruitful treatment target will soon become evident.

Clinical cancer genomics, i.e. the detection of genetic variants within cancer tissues to determine biological features of potential prognostic or therapeutic relevance, has been poorly explored in the context of cholangiocarcinoma in general, in PSC not at all. This is important, since for subtypes of cancers there may be effective treatment available. To meet this research gap, an Oslo-led initiative has been established, in which cholangiocarcinoma tissue from PSC patients will be characterized for the presence of known druggable and prognostic variants. Material from multiple European centers will be included and the first results are expected throughout 2015.

Upon the increasing activity on clinical trials in PSC, there has arisen a need to expand the patient base from the present Oslo- and Bergen-centered study populations and prospective cohorts, to a nation-wide initiative. The reason for this is that for each drug trial, only a small subset of patients are eligible, due to strict inclusion criteria. This work will be initiated throughout 2015, and will aim to provide a database of all PSC patients in Norway, centralized with the Oslo and Bergen activities. As a national supplement to the work in the International PSC study group, the work also aims to enhance awareness and standardization of follow-up of PSC patients in Norway.

NoPSC project update

Experimental hepatology

GROUP LEADER: **Espen Melum** LAB MANAGER: **Kristian Alfsnes** (Jan-July), **Tonje Bjørnetrø** (Aug-Jan 2015), **Anne Pharo** (from Jan 2015) POST DOC: **Xiaojun Jiang**
PHD STUDENTS: **Elisabeth Schrumpf**, **Natalie Lie Berntsen**, **Eva Kristine Klemsdal Henriksen** SCIENTIFIC ASSISTANT: **Corey Tan** (Jan-July)
WEB PAGE: *www.ous-research.no/melum/*

In 2014 the research activities in the Research Group for Experimental Hepatology increased considerably after a major recruitment phase in 2013. The main focus of the Group for Experimental Hepatology is to understand the regulatory mechanisms involved in bile duct inflammation. These mechanisms are believed to be among the key effector mechanisms in PSC. We specifically aim to understand the role of certain subsets of lymphocytes with regulatory properties within the immune system.

Photo: NoPSC

PhD student Elisabeth Schrumpf is inspecting the germ free mice in the animal facility at Karolinska Institutet, Stockholm, Sweden.

Xiaojun Jiang started as a post. doc. in January 2014 (see separate presentation at page 12). Xiaojun has her PhD from Heifei in China and has excellent expertise in animal models and liver immunology. She is working on a familiar form of PSC that is defined by a private mutation. Examinations of lymphocytes from the affected individuals compared to controls have revealed a specific immune phenotype. These studies have been done in collaboration with Niklas Björkström at Karolinska Institutet. Through studies done in the Taskén lab at the Biotechnology Centre of Oslo, it seems like the mutation leads to altered binding of proteins. Given these findings we have startet the generation of a point-mutated mouse using CRISPR/Cas9.

The ongoing studies on basic functions of Natural Killer T (NKT) were largely completed with a range of *in vivo* and *in vitro* experiments. These studies have shown that specific lipids have inhibitory effects on CD1d mediated antigen presentation.

The studies on the role of cholangiocytes in presentation of lipid antigens to NKT-cells were completed in 2014 and were supplemented with extensive characterization of CD1d in the bile ducts in samples from PSC and other liver diseases. Further, the role of NKT-cells in a mouse model of spontaneous inflammation of the bile ducts was extensively studied. Together with the genomics group we have demonstrated that the microbiota is altered in this model of spontaneous bile duct inflammation.

The development of a surgical model of bile duct inflammation was completed in 2014 and this model now constitutes a unique asset for the group. Using this model we have been able to demonstrate that Oxazolone induce bile duct inflammation and current studies are aimed at understanding the role of different lymphocyte subsets and the characteristics of the inflammatory process.

Together with the lab of Arthur Kaser at Addenbrooke's Hospital, Cambridge, UK, we have taken part in the projects related to GPR35 function and assays that can interrogate the effect in patient material have been established in the lab. Using paired patient material we have examined the TCR repertoire in samples from liver, intestine and blood to describe overlapping features.

A key resource for our activities is still access to animal facilities. Our presence at the Centre of Comparative Medicine has increased during 2014 and we now have a running capacity of 172 mouse cages making us one of the major users. We are also taking part in establishing a germ-free facility at the centre.

NoPSC project update

Genomics and metagenomics

GROUP LEADER: **Johannes R. Hov** RESEARCHER: **Marius Trøseid** (associated) POST DOC: **Trine Folseraas** (associated) PHD STUDENTS: **Sigrid Næss**, **Bjarte Fosby**, **Martin Kummen**, **Silje Jørgensen** (associated), **Cristiane Mayerhofer** (associated, from Jan 2015) CORE STAFF: **Kristian Holm** (Bioinformatician), **Liv Wenche Thorbjørnsen** (medical lab. scientist, biobank) and **Tonje Bjørnetrø** (Engineer, from Feb 2015) WEB PAGE: *www.ous-research.no/hov/*

Photo: NoPSC

The Norwegian Research Fair.

The PhD dissertation of Trine Folseraas on October 31th was a major event in the genomics and metagenomics group in 2014. Her thesis "The immunogenetic susceptibility to primary sclerosing cholangitis" was based on several of the major publications in this field the recent years with major contributions from the International PSC study group (IPSCSG) network. She is now half time post doc in the group (half time training as a gastroenterologist) dedicated to projects on the genetics of cholangiocarcinoma as well as contributing to the still ongoing large international genome-wide association study meta-analysis in PSC, which is based on NoPSC supported efforts in the UK and US.

The major achievements from the group in 2014 in terms of publications were also related to the immunogenetics of PSC. An almost 10-year running story on the mapping of a "third" PSC risk locus in the HLA complex was brought to conclusion, and clinically relevant genetic differences in small-duct PSC compared with large-duct PSC were identified, both with Sigrid Næss as the first author.

The current strongest research focus is the role of the gut microbiota in PSC other inflammatory conditions. An important milestone in 2014 was the finalization, benchmarking and application of a protocol for sequencing-based microbiota profiling, meaning that an entire pipeline from sampling to bioinformatic analysis is available in the context of the group. A modern sequencer for this purpose, an Illumina MiSeq, funded by the Fougner-Hartmann's family foundation, was purchased and is now housed and maintained at the Norwegian Sequencing Centre in Oslo.

Multiple studies are ongoing in PSC patients as well as other relevant phenotypes (diseases with bowel manifestations) and healthy controls to identify disease-related gut microbiota markers, how these influence PSC-relevant physiological parameters (metabolites) – and how these relationships can be altered by treatment targeting the gut. In addition, gut microbiota characterization has been performed in animal models used in the experimental group. Internally, this research strategy has lead to new collaborative efforts within the context of the Research Institute of International Medicine and K.G.Jebsen Inflammatory Research Centre, related to e.g. cardiovascular disease and HIV. Important external collaborators within the field of metabolomics include Hanns-Ulrich Marschall and Fredrik Bäckhed in Gothenburg and Rolf K. Berge in Bergen, while Andre Franke and John Baines in Kiel remain key collaborators in genomics and metagenomics.

On a more general level, the group was actively engaged in dissemination of our research both to the scientific community and the public, exemplified by the organization of the first national conference on gut microbiota and health in November and contribution to the Research Institute of Internal Medicine booth at the Norwegian Research Fair.

Group leader Johannes R. Hov with "Mike", an Illumina MiSeq sequencer, used for microbiota profiling at NoPSC.

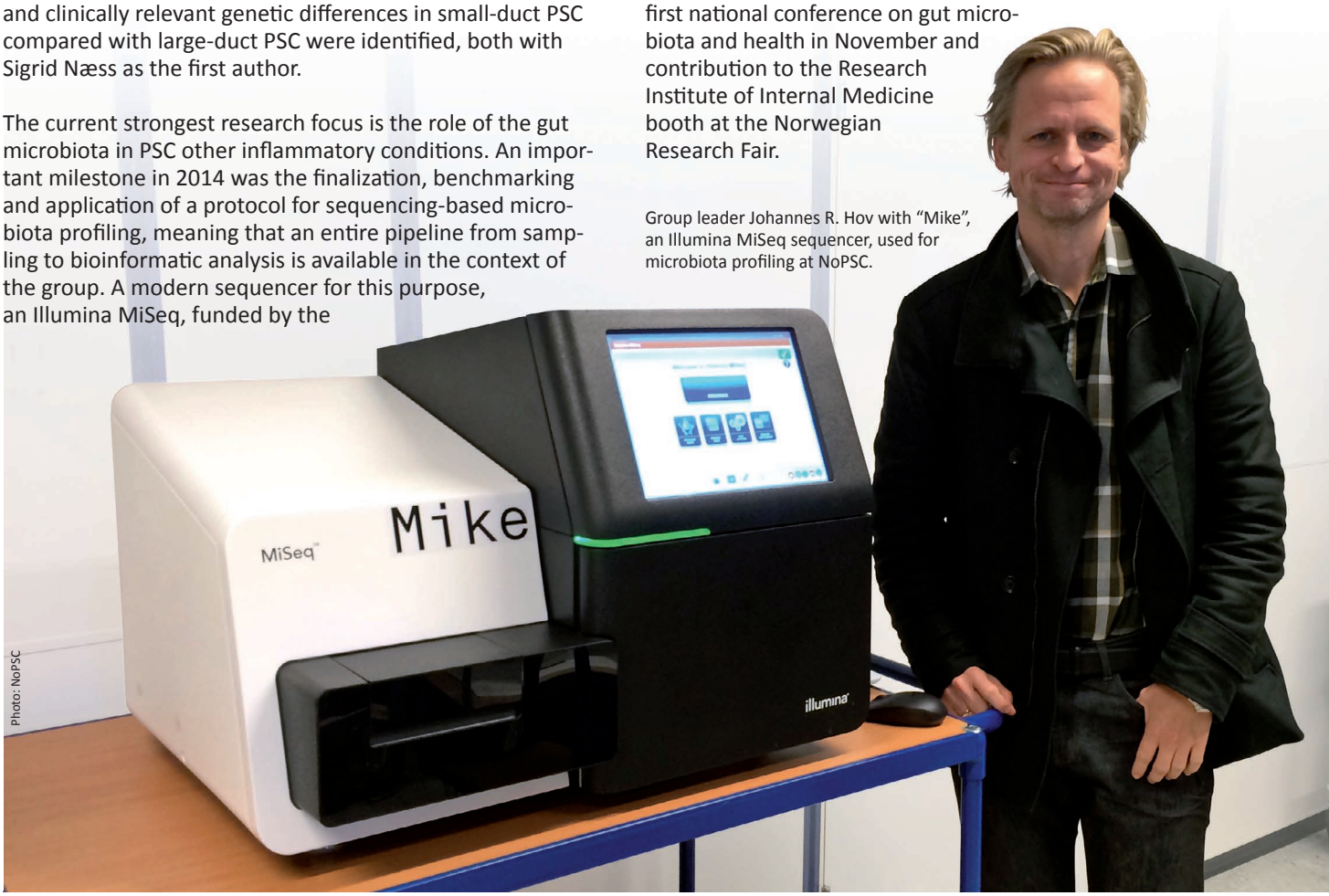


Photo: NoPSC

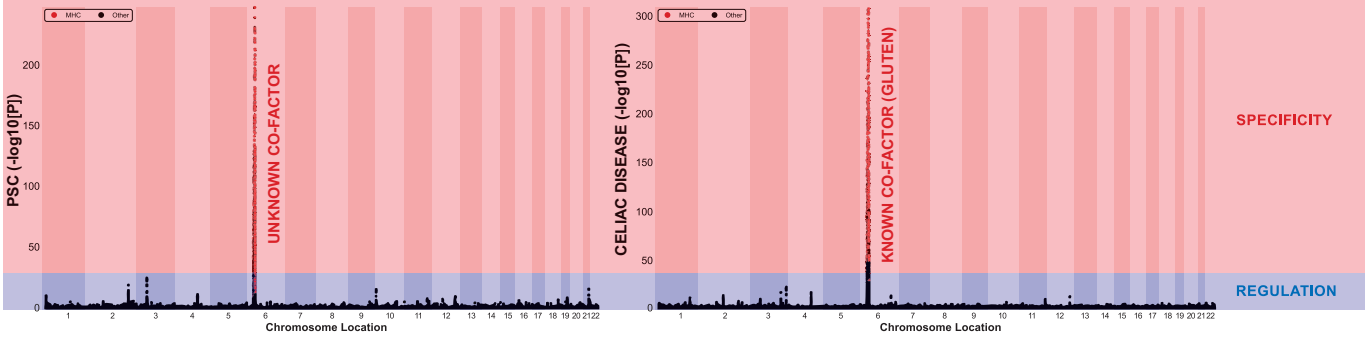
NoPSC project focus report:

What are the triggers of the immune response in PSC?

A small genetic region on chromosome 6 called the major histocompatibility complex (MHC) had since long before the invention of genome-wide association studies (GWAS) been known to confer risk for practically all immune-mediated diseases in humans. On the mapping of genome-wide susceptibility loci in these diseases by the application of GWAS, the profound relative role of MHC-associated susceptibility has become clear. In some diseases, including PSC, these susceptibility loci accounts for more than half of the genetic impact on disease development.

In most conditions that shows genetic associations with the MHC, the antigen-presenting HLA class I and II genes likely represent the key susceptibility factors at the MHC. In celiac disease as a model condition, the HLA class II variants interact with specific environmental factors (in this case gluten). In PSC, the antigens binding to the HLA variants are not yet known, and an important hypothesis to explore is whether antigens derived from the gut (dietary or microbial) bind to these variants and thereby cause the immune response observed in PSC.

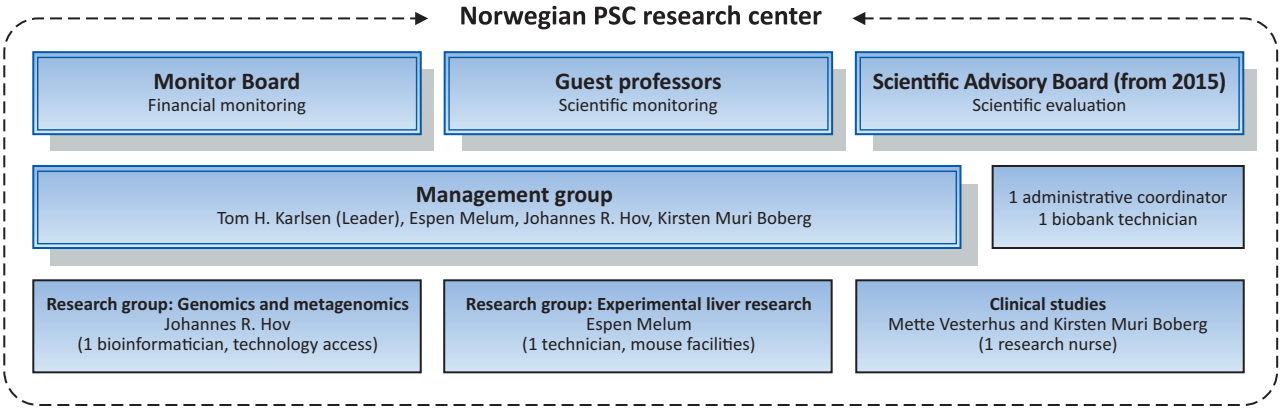
A series of ongoing studies at NoPSC are targeting this critical question (e.g. the visit from Lia Liaskou, see page 13), which is critical for the reason that the potential removal of such antigenic triggers (analogous with gluten in celiac disease) could have profound implications for disease understanding and patient management. A number of publications on the topic were completed throughout 2014 and published around Christmas (see facsimiles) and more papers will appear throughout 2015. An important deliverable was also the completion of the EU FP7 funded development of a new technology for determining the genetics of the MHC (sequencing based).



The genetics of PSC is very similar to celiac disease, actually the two conditions are among the most closely related immune-mediated diseases genetically speaking. Manhattan plot showing GWAS results (Y-axis shows P-values, X-axis represents chromosomal positions) in a case-control analysis across all chromosomes for primary sclerosing cholangitis (left) and celiac disease (right). Only upon an integrated appreciation of specificity (highlighted in red) as well as regulatory (highlighted in blue) aspects can a precise delineation of the impact of GWAS outcomes in PSC, and their environmental interaction partners, be accomplished.

Overview of Norwegian PSC Research Center (NoPSC)

NoPSC was established 19th of May 2008 at the Medical Department, Rikshospitalet, upon signing of a contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of this agreement was a donation from Stein Erik Hagen of NOK 100.000.000 made 22nd of September 2007. The funds are exclusively dedicated to research related to basic and clinical aspects of the chronic liver disease PSC.



NoPSC is a separate unit within the Division of Cancer Medicine, Surgery and Transplantation at Oslo University Hospital (OUS), Rikshospitalet and is also affiliated with the Research Institute for Internal Medicine, OUS, Rikshospitalet and the Institute of Clinical Medicine at the University of Oslo.

Organizational aims for the NoPSC unit

- **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**

Research topics at NoPSC in 2014

- **Clinical studies** (page 6)
- **Experimental studies** (page 7)
- **Genomic and metagenomic studies** (page 8)

NoPSC is organized with a monitor board, guest professors, a management group, the project units and support functions

The monitor board is monitoring the financial and formal aspects of the research center, and meet twice each year. In the fall, next year's budget is presented and before summer the annual report and the accounting is reviewed.

The guest professorships at NoPSC run in 3 year contracts. They visit the center at least twice each year, and are involved in both evaluation and critical discussion of the research projects, in addition to mentoring the PhD students and the post docs.

The management group is continuously staking out the future plans of the center and is of great support for the leader, Tom Hemming Karlsen.

The project units of NoPSC are defined by priorities of the management group. See project descriptions on pages 6-8.

In the new organization the overall **support functions**, administration and the NoPSC biobank, operates on behalf of the management group. The other key NoPSC support functions, bioinformatics, laboratory engineer and research nurse, are integrated within the three research groups, respectively. All support personnel are employed at the NoPSC organizational unit within the Department of Transplantation Medicine.

The monitor board

Leader	
Ivar Prydz Gladhaug	Institute of Clinical Medicine, University of Oslo
Hans Mossin	Institute of Clinical Medicine, University of Oslo
Nina Paulsen	Canica A/S
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People at NoPSC in 2014

Photo: Øystein H. Horgmo, UiO

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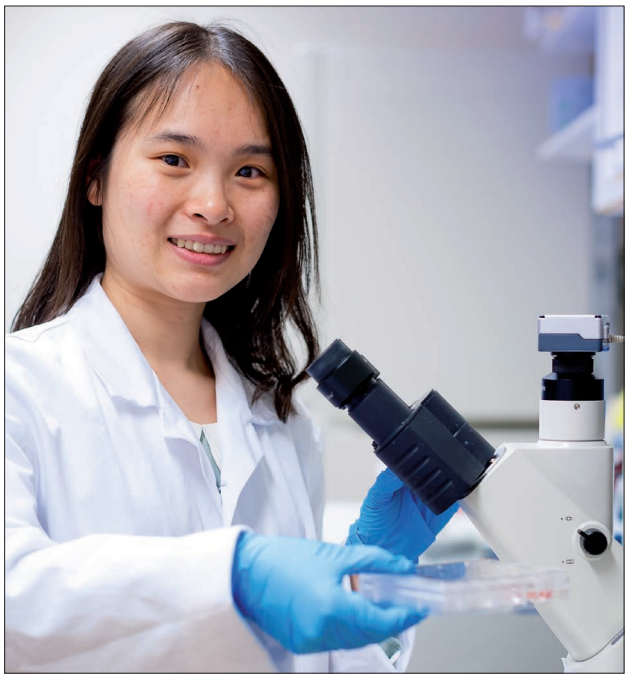
Post doctor profile: Xiaojun Jiang

Text by Xiaojun Jiang and Hege Dahlen Sollid.

Elucidating the disease cause in a Swedish PSC family

Xiaojun Jiang got her PhD degree in cell biology in 2013 in China. Her background is from liver immunology, mainly focusing on liver specific immune cell phenotypes, development and functions in mouse models. In 2013, she found the post doc position in Melums' group and the Jebsen Inflammation Research Center advertised on naturejobs.com, and she immediately found it to be very interesting.

Photo: Øystein H. Horgmo, UiO



Xiaojun Jiang in the NoPSC lab.

Jiang started as a post doc in January 2014, and her research focus is on DNA and cells from a Swedish family where several of the family members have PSC. The project aims at elucidating the disease cause in this family at a genetic level, and also to identify the molecular mechanisms leading to PSC disease phenotype.

Jiang, please tell us what your research priorities are?

"Firstly, we need to figure out the exact gene mutation apparently responsible for the disease. Then, we would like to know the biological characteristics of the molecule encoded by this gene, and how its function is altered after mutation at a cellular level."

Why is this project so important for the PSC patients?

"Until now, there is no efficient treatment for PSC, which is largely due to the unclear pathogenesis. If we could find a molecule that is responsible to PSC disease, we may provide new treatments to our patients by blocking its signal pathway or therapeutically influencing the pathogenic cell type."

So far, Jiang and the NoPSC team have found a mutation in an immune regulatory molecule specific to this PSC affected family. Based on the expression profile and immune phenotyping data, it seems like this mutation effects T-cell functions. It binds to more proteins compared to wildtype, and they are currently studying the functional implications of this. The plan is also to find out the downstream signal pathway of the mutation. Jiang plans to investigate the mutation in several new mouse models made specifically for the study.

How is it to be a researcher in Norway compared to China?

"Comparing to China, Norway is more peaceful and stressless. I was, for 7 years, in a big and mature immunology lab in China. There are very strict and detailed rules for everything there, and everyone has to pass the quality controls and might be checked at any time. We do experiments from Monday to Friday, have Journal club, group discussion each Saturday, and hand in our work summary on Sundays. All of these could lead a student to become a scientific researcher in an efficient way, but somehow, also means that we from time to time were a little tired. I feel a strong spirit of humanism here in Norway, and everyone respects each other very much. You could slow down a bit to have enough time to think about what is really meaningful. So it is more likely to enjoy science in Norway."

Jiang has so far enjoyed her time at NoPSC very much. She likes the support she receives and that everyone encourages her after presentations. When asked what her most memorable moment so far is, she answers: "It was a great experience to eat ice-cream and see all the beautiful bunad's on the national day. I also cannot forget Trine's PhD defense and the delicious fish soup!"

Lia Liaskou and Xiaojun Jiang enjoying a boat trip in the Oslo fjord with fellow NoPSC colleagues. From left: Eva Kristine Klemsdal Henriksen, Lia Liaskou, Natalie Lie Berntsen and Xiaojun Jiang.

Photo: NoPSC

Post doctor profile: Evaggelia Liaskou

Text by Evaggelia Liaskou and Hege Dahlen Sollid.

Understanding the triggers of the immune system – why are the bile ducts attacked?

Evaggelia (Lia) Liaskou has for several years been involved in collaborative projects with Tom Hemming Karlsen and NoPSC. In 2014 she spent three months at NoPSC as a visiting researcher with focus on the project "Multimodal immunogenetic approaches to autoantigen identification in primary sclerosing cholangitis". The visit was supported by an EASL Sheila Sherlock short-term training fellowship and a Wellcome Trust ISSF mobility award.

Photo: Øystein H. Horgmo, UiO

Lia Liaskou in the NoPSC lab.

Liaskou graduated from the department of Molecular Biology and Genetics, University of Thrace (Greece) in 2006. As an undergraduate student she moved to UK to carry out her diploma thesis at the Lung Cancer Centre at the University of Liverpool. She was then awarded a prestigious Marie Curie Early Stage Training Fellowship for her Ph.D. at the University of Birmingham, with Professor David Adams. Her Ph.D. also included conducting research for half a year at the laboratory of Professor Sirpa Jalkanen at the University of Turku in Finland. She received her Ph.D. in liver immunology in 2010. She is now a senior postdoctoral research fellow at the Centre for Liver Research and NIHR Birmingham Liver Biomedical Research Unit in Birmingham, UK, working with Dr Gideon Hirschfield on autoimmune liver diseases with particular interest on primary sclerosing cholangitis.

Liaskou, please tell us why this project is so important for the PSC patients?

"PSC has no treatment at present, other than liver transplantation, thus for patients it remains a devastating diagnosis. During the course of their illness patients may suffer from cholangitis, bile duct cancer, as well as ultimately liver failure. Understanding what triggers the immune system to attack the bile ducts will ultimately lead to rational therapy for patients. If the identified triggering antigen is exogenous, its removal can lead to treatment of disease, similar to celiac disease, in which gluten found in grains can induce immune cell activation, thus a strict gluten free diet is the only medical treatment for celiac disease patients. Our findings will further permit the creation of platforms for antibody screening and pathogenic T cell screening, which will ultimately allow for earlier diagnosis of disease, better options for treatment and reduction in mortality, morbidity and societal costs."

What was the scientific outcome of your stay?

"My stay at the NoPSC center promoted the scientific exchange between two well-established research units in PSC research, stimulated the gain of new skills, i.e. HLA typing, T cell receptor bioinformatics analysis and triggered the establishment of new and fruitful collaborative projects."

The results from this visit were presented as an oral presentation at the 6th European Club for Liver Cell Biology (ECLCB) (Italy, September 2014) and at a special workshop on HLA genetics, TCRs and BCRs (China, October 2014).

Liaskou's further plan is to establish herself as an independent investigator in the field of PSC immunopathogenesis. Currently, she has submitted a fellowship application for an ERC Starting Grant (February 2015) and these days she is preparing two more fellowship applications at MRC and Wellcome Trust.

Liaskou enjoyed living in Oslo, and she found working in Oslo an interesting experience, with people in the working environment being always friendly and outgoing, warm and generous. When asked what her most memorable moment was, she answered; "The boat trip at Oslo fjords with Tom, Eva Kristine, Natalie, Martin and Xiaojun, peeling shrimps and eating them on white bread with butter and lemon, just delicious!"

EVAGGELIA LIASKOU'S RESEARCH PRIORITIES:

- Identifying the triggering antigen(s) in PSC using liver-infiltrating plasma cell-produced antibodies and screening with protein arrays and bead-based arrays (in collaboration with Professor Tom Hemming Karlsen and Dr. Fridtjof Lund-Johansen).
- Linking gene susceptibility and environmental factors to biliary damage in PSC: the CD28/vitamin D axis. Here, we are evaluating a) how CD28 genotype (CD28 risk variant A, rs7426056, identified as a risk locus in PSC) effects the expression and function of CD28 in peripheral T cell populations, b) whether and how vitamin D can effect CD28 expression and function of T cells in genotyped healthy controls and patients with PSC.
- Understanding disease mechanisms and targeting therapies: stratified medicine in primary biliary cirrhosis (PBC). Here, we are studying: a) the phenotype of immune cells in PBC UDCA-responders and non-responders, b) the transcriptomic profile of T cells from PBC UDCA-responders and non-responders, and c) the ability of primary biliary epithelial cells under stress to polarize CD4+ T cells to Th1, Th17 and/or Tregs.

Collaborators

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)

Two separate research groups led by Espen Melum (*www.ous-research.no/melum/*) and Johannes Hov (*www.ous-research.no/hov/*) are operational at RIIM. Several collaborative projects are established with the other research groups at the institute and all employees of NoPSC participate in the every-day activities.

Section for Organ Transplantation

Clinic Deputy Head Dr. Pål-Dag Line, Prof. Aksel Foss and PhD student Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Pathology

Prof. Ole Petter Clausen, Prof. Helge Scott, Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models. Through the K.G. Jebsen Inflammation Research Centre (JIRC) we have several ongoing projects with Prof. Guttorm Haraldsen.

Department of Medical Genetics

The Immunogenetics group, led by Prof. Benedicte A. Lie (*www.med.uio.no/klinmed/english/research/groups/autoimmunity-cancer/index.html*) is involved in several projects related to the further characterization of the HLA association in PSC.

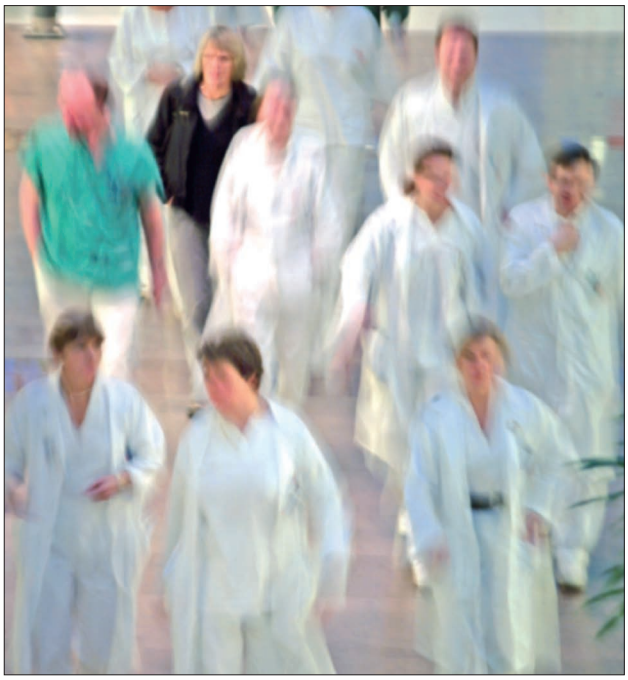


Photo: Oslo University Hospital

Institute of Immunology

NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular, the good collaborations with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, and the research group of Fridtjof Lund-Johansen, are important in the activities of NoPSC.

Department of Medical Biochemistry

In conjunction with the establishment of the NoPSC biobank quality control project for the NoPSC biobank, collaboration with Dr. Yngve Thomas Bliksrud is highly appreciated.

Center for Cancer Biomedicine

A collaboration with Prof. Ragnhild Lothe and Prof. Guro Lind at the Department of Cancer Prevention, OUS Radiumhospitalet (*www.ous-research.no/cancerprevention/*) is the basis for epigenetics-centered projects on early diagnosis of cholangiocarcinoma in PSC.

Department of Radiology

The involvement of the Department of Radiology at OUS Rikshospitalet in the prospective follow-up of PSC patients has been crucial for the success of the initiative. We are particularly grateful to Dr. Audun Berstad, Dr. Trygve Syversveen, Dr. Andreas Abildgaard, Dr. Günter Kemmerich and Dr. Knut Brabrand for their active contributions.

KEY NATIONAL COLLABORATORS

The IBSEN study group

The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is important for several of the basic genetic and meta-genomic studies at NoPSC. Blood samples of patients under-going magnetic resonance cholangiography (MRC) at the 20 years follow-up consultation are deposited in the NoPSC biobank. Dr. Anne Nergård and Dr. Aida Kapic Lunder are performing the MRCs at Akershus University Hospital.

Haukeland University Hospital and University of Bergen

For the prospective PSC cohort and advanced imaging modalities there is a close collaboration with several 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. In addition, Dr. Geir Folvik is involved in a project on cholestatic pruritus and pathophysiology of benign recurrent intrahepatic cholestasis.

KEY INTERNATIONAL COLLABORATORS

Institute for Clinical and Molecular Biology Christian-Albrechts University, Kiel, Germany

www.ikmb.uni-kiel.de
www.ikmb.uni-kiel.de/people/scientists/andre-franke

Several co-workers of Prof. Stefan Schreiber and Prof. Andre Franke's group in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and metagenomic projects. Prof. Andre Franke has served as a loyal and dedicated guest professor at NoPSC for 5 years. The group of Prof. Sebastian Zeissig is collaborating on the NKT-cell related project lead by Espen Melum. In addition, Prof. John Baines (joint position at Christian-Albrechts University and the Max Planck Institute of Evolutionary Biology in Plön) is an important collaborator in the metagenomic projects.

Cambridge Institute for Medical Research Cambridge, UK

www.cimr.cam.ac.uk

The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale and senior researcher James Traherne and Vasilis Kosmoliaptsis in Cambridge is invaluable for the progress of several of our functional genetic projects.

Dept of Medicine, University of Cambridge Addenbrooke's Hospital, Cambridge, UK

www.immunology.cam.ac.uk/directory/ak729@cam.ac.uk

Prof. Arthur Kaser is Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK. He served for 3 years as a NoPSC guest professor and is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes. The UKPSC initiative, that has recruited now more than 2,000 PSC patients, is managed by several co-workers at Addenbrooke's Hospital and the Wellcome Trust Sanger Institute in Cambridge.

University of Birmingham, Birmingham, UK

www.birmingham.ac.uk/research/activity/mds/centres/liver/index.aspx

Dr. Gideon Hirschfield, Dr. Evaggelia Liaskou and Prof. David Adams, from August 2013 a guest professor at NoPSC, at the Centre for Liver Research at the Institute of Biomedical Research, University of Birmingham collaborate on several projects related to the further characterization of the HLA related immune response in PSC.

The Mayo Clinic, Rochester, USA

www.mayo.edu/research/labs/genomic-hepatobiology/overview

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

Brigham and Women's Hospital Harvard Medical School, Boston, USA

http://researchfaculty.brighamandwomens.org/BRIProfile.aspx?id=2266

Prof. Richard Blumberg is an important collaborator in post.doc. Espen Melum's projects related to NKT cells. He is also the co-supervisor of PhD student Elisabeth Schrumpf.

Medical University of Vienna and Medical University of Graz, Austria

www.meduni-graz.at/en/
www.meduniwien.ac.at/index.php?id=372&language=2

In collaboration with Prof. Michael Trauner and Prof. Peter Fickert, ongoing projects aim at cross-validating findings in mouse models of PSC with human data. Prof. Michael Trauner has extensive experience in animal models of PSC and serves as an important collaborator related to the development of a bile duct specific Cre mouse.

The Nordic Liver Transplant Group

www.scandiatransplant.org

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

Karolinska University Hospital, Stockholm, Sweden

http://ki.se/en/medh/annika-bergquist-group
http://ki.se/en/medh/niklas-bjorkstrom-group

Prof. Annika Bergquist and assistant professor Niklas Björkström are involved in several projects at NoPSC. The clinical data and blood samples that were collected by Dr. Ulrika Broomé over more than a decade, still serve as a valuable resource for these collaborative projects.

IRCCS Instituto Clinico Humanitas, Milan, Italy

www.humanitas.it/pazienti/info/i-nostri-medici/141-invernizzi-pietro

Dr. Pietro Invernizzi and Dr. Ana Lleo in Milan are involved in several collaborative projects at NoPSC. The main projects are related to characterization of the HLA association in PSC in Italy, as well as evaluating serum biomarkers for cholangiocarcinoma in PSC.

University Hospital of Heidelberg, Germany

www.medizinische-fakultaet-hd.uni-heidelberg.de/Research.110019.0.html?&L=en

Prof. Daniel Gotthardt in Heidelberg is an important contributor to IPSCSG and he is running multiple projects with NoPSC as collaborator. Prof. Peter Schirmacher and Dr. Benjamin Göppert at the Department of Pathology in Heidelberg serve as key collaborators in projects related to the genetic characterisation of cholangiocarcinoma in PSC.

Liver Center, Yale University, New Haven, USA and University of Padova, Italy

www.celiver.org/index.php?lang=english

The collaboration with Prof. Mario Strazzabosco and Dr. Luca Fabris is important for several of the genetic projects. In particular, the experience in cholangiocyte biology of this group has proven essential in the establishing of the cholangiocyte isolation protocols.

Publications 2014

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Low use of surveillance and early diagnosis of hepatocellular carcinoma in Norway-A population-based cohort study
Cancer Epidemiol, 38 (6), 741-747 (in press)

2 *Fickert P, Pollheimer MJ, Beuers U, Lackner C, Hirschfield G, Housset C, Keitel V, Schramm C, Marschall HU,* ***Karlsen TH***, ***Melum E****, Kaser A, Eksteen B, Strazzabosco M, Manns M, Trauner M, International PSC Study Group (IPSCSG) (2014)*
Characterization of animal models for primary sclerosing cholangitis (PSC)
J Hepatol, 60 (6), 1290-303

3 *Flachsbart F, Caliebe A, Heinsen FA,* ***Hemming-Karlsen T****, Schreiber S, Franke A, Nebel A (2014)*
Investigation of complement component C4 copy number variation in human longevity
PLoS One, 9 (1), e86188

4 ***Folseraas T****, Liaskou E, Anderson CA,* ***Karlsen TH*** *(2014)*
Genetics in PSC: What Do the "Risk Genes" Teach Us?
Clin Rev Allergy Immunol (in press)

5 ***Fosby B***, ***Næss S***, ***Hov JR****, Traherne J,* ***Boberg KM****, Trowsdale J, Foss A, Line PD, Franke A,* ***Melum E****, Scott H,* ***Karlsen TH*** *(2014)*
HLA variants related to primary sclerosing cholangitis influence rejection after liver transplantation
World J Gastroenterol, 20 (14), 3986-4000

6 *Friedrich K, Wannhoff A, Kattner S, Brune M,* ***Hov JR****, Weiss KH, Antoni C, Dollinger M, Neumann-Haefelin C, Seufferlein T, Schemmer P, Schirmacher P, Stremmel W, Gotthardt DN (2014)*
PNPLA3 in end-stage liver disease: alcohol consumption, hepatocellular carcinoma development, and transplantation-free survival
J Gastroenterol Hepatol, 29 (7), 1477-84

7 ***Henriksen EK***, ***Melum E***, ***Karlsen TH*** *(2014)*
Update on primary sclerosing cholangitis genetics
Curr Opin Gastroenterol, 30 (3), 310-9

8 *Hirschfield GM,* ***Karlsen TH*** *(2014)*
Genetic risks link autoimmune hepatitis to other autoimmune liver disease
Gastroenterology, 147 (2), 270-3

9 *Huang YH, Zhu C, Kondo Y, Anderson AC, Gandhi A, Russell A, Dougan SK, Petersen BS,* ***Melum E****, Pertel T, Clayton KL, Raab M, Chen Q, Beauchemin N, Yazaki PJ, Pyzik M, Ostrowski MA, Glickman JN, Rudd CE, Ploegh HL, Franke A, Petsko GA, Kuchroo VK, Blumberg RS (2014)*
CEACAM1 regulates TIM-3-mediated tolerance and exhaustion
Nature (in press)

10 *Marie Vedeld H, Andresen K, Andrassy Eilertsen I, Nesbakken A, Seruca R, Gladhaug IP, Thiis-Evensen E, Rognum TO,* ***Muri Boberg K****, Lind GE (2014)*
The novel colorectal cancer biomarkers CDO1, ZSCAN18 and ZNF331 are frequently methylated across gastrointestinal cancers
Int J Cancer, 136 (4), 844-53

11 ***Naess S****, Björnsson E,* ***Anmarkrud JA****, Al Mamari S, Juran BD, Lazaridis KN, Chapman R, Bergquist A,* ***Melum E****, Marsh SG,* ***Schrumpf E****, Lie BA,* ***Boberg KM***, ***Karlsen TH***, ***Hov JR*** *(2014)*
Small duct primary sclerosing cholangitis without inflammatory bowel disease is genetically different from large duct disease
Liver Int, 34 (10), 1488-95

12 ***Næss S****, Lie BA,* ***Melum E****, Olsson M,* ***Hov JR****, Croucher PJ, Hampe J, Thorsby E, Bergquist A, Traherne JA,* ***Schrumpf E****,* ***Boberg KM****, Schreiber S, Franke A,* ***Karlsen TH*** *(2014)*
Refinement of the MHC risk map in a scandinavian primary sclerosing cholangitis population
PLoS One, 9 (12), e114486

13 *Rupp C, Friedrich K,* ***Folseraas T****, Wannhoff A, Bode KA, Weiss KH, Schirmacher P, Sauer P, Stremmel W, Gotthardt DN (2014)*
Fut2 genotype is a risk factor for dominant stenosis and biliary candida infections in primary sclerosing cholangitis
Aliment Pharmacol Ther, 39 (8), 873-82

14 *Trøseid M, Ueland T,* ***Hov JR****, Svardal A, Gregersen I, Dahl CP, Aakhus S, Gude E, Bjørndal B, Halvorsen B,* ***Karlsen TH****, Aukrust P, Gullestad L, Berge RK, Yndestad A (2014)*
Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure
J Intern Med (in press)

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Early-onset Crohn's disease and autoimmunity associated with a variant in CTLA-4
Gut (in press)

16 *Åberg F, Gissler M, Karlsen TH, Ericzon B, Foss A, Rasmussen A, Bennet W, Olausson M, Line P, Nordin A, Bergquist A,* ***Boberg KM****, Castedal M, Pedersen CR, Isoniemi H (2014)*
Differences in long-term survival among liver transplant recipients and the general population: A population-based nordic study
Hepatology (in press)

17 *Andreassen OA, McEvoy LK, Thompson WK, Wang Y, Reppe S, Schork AJ, Zuber V, Barrett-Connor E, Gautvik K, Aukrust P,* ***Karlsen TH****, Djurovic S, Desikan RS, Dale AM, International Consortium for Blood Pressure Genome-Wide Association Studies, Genetic Factors for Osteoporosis Consortium (2014)*
Identifying common genetic variants in blood pressure due to polygenic pleiotropy with associated phenotypes
Hypertension, 63 (4), 819-26

18 ***Karlsen TH***, ***Vesterhus M***, ***Boberg KM*** *(2014)*
Review article: controversies in the management of primary biliary cirrhosis and primary sclerosing cholangitis
Aliment Pharmacol Ther, 39 (3), 282-301

19 ***Andersen IM***, ***Tengesdal G****, Lie BA,* ***Boberg KM***, ***Karlsen TH***, ***Hov JR*** *(2013)*
Effects of coffee consumption, smoking, and hormones on risk for primary sclerosing cholangitis
Clin Gastroenterol Hepatol, 12 (6), 1019-28

Photo: Øystein H. Horgmo, UiO

Communications

Photo: Shutterstock

NoPSC international lectures 2014

Karlsen TH.

The genetics of primary sclerosing cholangitis

Falk Workshop Pathophysiology and Treatment of Cholangiocarcinoma
Tübingen, Germany January 23rd-24th

Melum E.

Immune regulation in PSC – where are the potential treatment targets?

Primary Sclerosing Cholangitis (PSC) Update Forum, ECCO 2014
Copenhagen, Denmark, February 19th

Karlsen TH.

Cholestatic liver diseases: What can we learn from genome-wide association studies?

1. Symposium Hepatology 2014, University Hospital of Bern
Bern, Switzerland, February 27th

Karlsen TH.

Primary Sclerosing Cholangitis and IgG4 cholangiopathy

Autoimmune & Congenital Liver Disorders, "Better Understanding & Better Management"
The Academy of Medical Sciences, London, UK March 12th

Karlsen TH.

Thirty years of PSC research – where do we stand and where do we go next?

Nordic Lights on Hepatology
Royal Free Hospital, UK April 8th

Hov JR.

Gut microbiota and bile acid homeostasis in PSC – will we ever treat PSC using antibiotics?

EASL-I-PSC-SG (International PSC Study Group) joint workshop, International Liver Congress (EASL)
London, UK, April 9th

Vesterhus M.

Novel protein markers identified in bile and serum are associated with a diagnosis of primary sclerosing cholangitis, disease severity and transplant-free survival

International Liver Congress (EASL), oral presentation.
London, UK, April 12th

Vesterhus M.

Enhanced Liver Fibrosis (ELF) score predicts transplant-free survival in PSC independently of the Mayo risk score

International Liver Congress (EASL), oral ePoster presentation.
London, UK, April 12th

Karlsen TH.

Norwegian Studies Measuring Disease Activity in PSC and **What Have We Learned from Genome Wide Association Studies in PSC**

PSC Partners Seeking A Cure Patient Conference
Denver, CO, USA, April 26th

Karlsen TH.

GWAS in liver and bowel diseases – what did we learn?

UEG Week,
Vienna, Austria October 21th

Karlsen TH.

PSC: New future treatment options?

UEG Week
Vienna, Austria Oct 21th

Melum E.

Acid sphingomyelinase regulates NKT cell development

CD1 club, Harvard University
Boston, USA, November 7th

Boberg KM.

Controversies in management of recurrent disease and colitis

Special Interest Group: Controversies in the management of primary sclerosing cholangitis in children and adults. American Association for the Study of Liver Disease (AASLD).
Boston, USA, November 9th

Karlsen TH.

Primary Sclerosing Cholangitis

Sheila Sherlock's "Update in Hepatology and Digestive Diseases"
Royal Free Hospital, UK Dec 5th

Karlsen TH.

Resolving HLA associations in PSC and IBD – genotyping resolution, mapping strategy or both?

ESGI user meeting
Berlin, Germany, Dec 16th

Publicity

PhD student **Elisabeth Schrumpf's project** was presented as ***"Project of the week"*** at HSØ official webpage in November.

www.helse-sorost.no/fagfolk_/forskning_/ukens-erapport_/Sider/Ukens-forskningsprosjekt---uke-48-2014.aspx

Post doc and group leader **Johannes Hov** commented on the paper ***"Human Genetics Shape the Gut Microbiome"*** by Goodrich JK et al published in Cell, in an article at viten.no.

www.nrk.no/viten/_slankande_-bakteriar-gar-i-arv_-viser-ny-studie-1.12038003

International PSC Study Group (IPSCSG) Annual report

In June 2010, a total of 45 active PSC researchers from Norway, Sweden, Finland, Germany, Switzerland, Austria, Italy, Spain, France, Belgium, the Netherlands, UK, Ireland, US and Canada met in Oslo and established the International PSC Study Group (IPSCGS). Entering 2015, the group includes researchers from 21 countries and more than 55 different institutions.

MEMBERS OF THE STEERING COMMITTEE

Prof. **Ulrich H. Beuers**, Amsterdam, the Netherlands
Dr. **Luca Fabris**, Padua, Italy
Prof. **Martti Färkkilä**, Helsinki, Finland
Dr. **Chris Bowlus**, Sacramento, USA
Prof. **Olivier Chazouilleres**, Paris, France
Dr. **Gideon Hirschfield**, Birmingham, UK
Prof. **Tom Hemming Karlsen**, Oslo, Norway
(coordinator/secretary)

Representation in IPSCSG is based on active participation in at least one ongoing study and meetings are held bi-annually during the International Liver Congress™ (ILC) organized by the European Association for the Study of the Liver (EASL) and the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

During 2014, the group met for their bi-annual meetings, first in London during the ILC April 12th and then in Boston during AASLD November 9th. During the ILC, an official EASL-IPSCSG joint workshop was also held and attracted a full auditorium on cholangiocyte biology and biliary disease, genetics of PSC and IBD, gut microbiota and bile acid homestasid and finally, discussions on implications for patients from basic research.

In June, the third biennial IPSCSG meeting was held in Amsterdam, hosted by Prof. Ulrich Beuers and Prof. Cyriel Ponsioen. The program contained a number of invited lectures to stimulate discussion. The working group breakout sessions on 6 different subjects were essential for the success of the workshop. These sessions was introduced by a 10 min. overview of one of the chair persons on the actual state of discussion and the actual needs.

In addition to this, a workshop was held during the ECCO meeting in Copenhagen in March, to increase awareness of PSC among gastroenterologists.

DURING 2014 THE GROUP MADE PROGRESS ON SEVERAL TOPICS:

- Collection of clinical data from 7,500 PSC patients for a clinical descriptive review completed (first results were presented at opening plenary session at the ILC in London 2014)
- Multicenter study initiated to evaluate the utility of Fibroscan in determining disease progression in PSC led by Olivier Chazoillieres
- Establishing of the prospective biobanking of PSC patients led by Gideon Hirschfield and Mette Vesterhus
- Contributions to the pruritus GWAS led by George Mells
- Contributions to the US/UK GWAS meta-analysis led by Kostas Lazaridis, Carl Anderson and Tom H. Karlsen
- Contributions to Immunochip supbphenotype project led by Cyriel Ponsioen
- Contributions to Immunochip cross-phenotype project led by Andre Franke and David Ellinghaus
- Participation in clinical trials (e.g. Dilstent2, nor-ursodeoxycholic acid)
- Establishing of a consensus document for phenotyping in mouse models of PSC (published in Journal of Hepatology)

PLANNED MEETINGS IN 2015:

During the ILC in Vienna in April IPSCSG has again been offered by EASL to hold the biannual meeting within the venue of the ILC, and the meeting will take place April 25th. The group will then celebrate their first 5 years with a cake. Again, a workshop has been set up within the official ILC meeting, covering topics from prognostic models and clinical trial end-points, regulatory aspects of clinical trials and the presence of specific PSC biomarker profile. The group will also meet in San Francisco in November during AASLD for the autumn biannual meeting.

INTERNATIONAL PSC STUDY GROUP NETWORK

Australia
Austria
Belgium
Canada
Denmark
Finland
France
Germany
Ireland
Iceland
Israel
Italy
Japan
Norway
Poland
Spain
Switzerland
Sweden
The Netherlands
UK
US

More information on: ***www.ipscsg.org***

Photo: Hanns-Ulrich Marschall

IPSCSG members at the third biennial IPSCSG meeting taking place in Amsterdam June 2014.

Accounting 2014

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2013	3 435 006		45 266 527	
Interest			564 088	
Other income	1 109 997			
Transfer from UiO	9 694 702			9 694 702
Wages		6 597 993		1 389 547
Overhead		141 579		207 985
Infrastructure		920 304		
Other operating expenses		4 787 502		28 239
Transfer to 2015 budget		**1 792 327**		**34 566 620**

UiO accounting revised by Riksrevisjonen. OUS accounting revised by PricewaterhouseCoopers.

All sums are in Norwegian kr.

Photo: Øystein H. Horgmo, UiO

NOPSC
Norwegian PSC Research Center

NoPSC PEOPLE IN THE PICTURE:
From left: Kristine Wiencke, Erik Schrumpf, Mona Bjørnstad, Liv Wenche Thorbjørnsen, Trine Folseraas, Kirsten Muri Boberg, Hege Dahlen Sollid, Anne Pharo, Xiaojun Jiang, Eva Kristine Klemsdal Henriksen, Elisabeth Schrumpf, Tonje Bjørnetrø, Natalie Lie Berntsen, Martin Kummen, Johannes R. Hov, Espen Melum, Tom Hemming Karlsen.
Not present: Kristian Holm, Mette Vesterhus, Bjarte Fosby, Sigrid Næss.

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www.ous-research.no/nopsc

www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/

UiO : University of Oslo

Oslo University Hospital

www.oslo-universitetssykehus.no

Oslo University Hospital is Norway's largest hospital, and conducts a major portion of medical research and education of medical personnel in Norway. Post: Oslo University Hospital, P O Box 4950 Nydalen, NO-0420 Oslo, Norway.

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