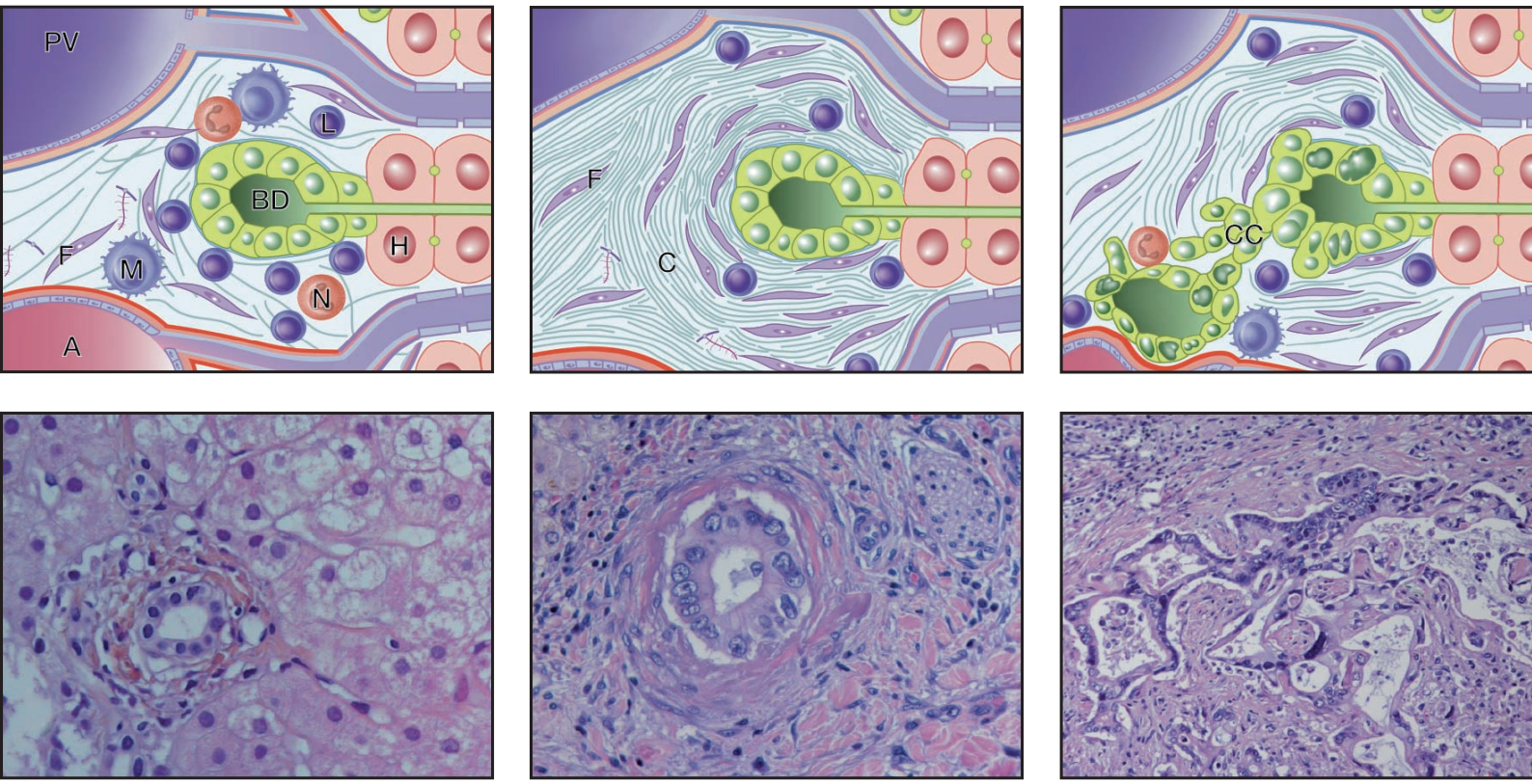
Oslo University Hospital



INFLAMMATION FIBROSIS MALIGNANCY

Norwegian PSC Research Center

Annual report 2013

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 2013

NoPSC ANNUAL REPORT 2013

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

EDITORS: Tom Hemming Karlsen and Hege Dahlen Sollid, NoPSC
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Leader´s comments

Photo: Øystein H. Horgmo, UiO

The year of 2013 has been a year of maturation for the new subgroups at NoPSC.
The groups of Espen Melum ("Experimental liver research") and Johannes Roksund Hov ("Genomics and metagenomics in inflammatory disorders") have received official status as research groups within the Division of Cancer Medicine, Surgery and Transplantation, and are jointly organized within a "Section of molecular hepatology" at the Research Institute of Internal Medicine. The activities of both these groups, which are described later in this document, are made feasible due to the generous availability of laboratory space at the institute. Both groups interact closely with other translational research activities at the institute, allowing for mutual enrichment of ideas and methodology.

Throughout 2013 several events marked the forming of a clinical research group within NoPSC. The strengthening of the clinical research portfolio forms a logical extension from the focus on disease mechanisms in the first years of NoPSC. Importantly, several clinical trials are now underway, and NoPSC is actively participating. The clinical trials are managed by prof. Erik Schrumpf, as a continuation of his lifelong engagement in PSC research. Planned trials target several aspects of PSC pathogenesis including the immune system, bile regulation and scar formation (fibrosis). The next 2-3 years will inform us on which of these targets that will give us the most effective treatment.

A major accomplishment in 2013 was the establishing of several biomarkers for PSC severity and two main papers will be published in 2014 reporting the findings. These biomarkers will become crucial for the clinical research, since they may measure the effect of medication. They are also of interest to the individual patient, since they may inform on prognosis. Annual blood samples and other detailed investigations are now being offered PSC patients in Oslo, Bergen and several other countries (an international prospective PSC cohort).

We are extremely privileged to be working in a friendly and highly skilled collaborative network. The International PSC Study Group keeps growing in popularity and impact, and the biannual meetings at the big liver meetings in Europe and USA now typically have between 50 and 70 attendants from the more than 20 countries now represented. A major next step for the group will be to position itself for EU funding within the Horizon 2020 program. The national networks of the K.G. Jebsen Inflammation Research Center in Oslo and the National Centre for Ultrasound in Gastroenterology in Bergen throughout 2013 became the platform for several NoPSC affiliated post docs and will be productive arenas for PSC related research in the years to come.

The publishing of the Immunochip paper in PSC in Nature Genetics in 2013 was another milestone for the genetics research at NoPSC. Only at the logistic level the project was a massive undertaking, including patients recruited at more than 200 hospitals in 14 countries. Importantly, the recruitment process and studies have not stopped in these countries, and the genetic collaborations have fuelled the basis of strong research hubs for PSC in Germany, the Netherlands, the UK and the US. The US group at the Mayo Clinic in Rochester and the UK group in Cambridge are in charge of the next big genetic study in PSC, partly supported by NoPSC, and have also obtained large independent grants that will secure the future of their activities.

The main challenge from the administrative side of NoPSC is the securing of funding for sustained activities after the official funding period from Stein Erik Hagen and Canica A/S ends December 2016. Several financing models are under assessment and likely 2014 will see the materializing of concrete plans for continuing the high research activity. We will have to work hard to maintain the present level of accomplishments, but we have a mature and vital organization that in all means is heading in the right direction.

Oslo 08.04 2014
Professor Tom Hemming Karlsen
Leader of NoPSC Management Group

NOPSC
Norwegian PSC Research Center

What is PSC?

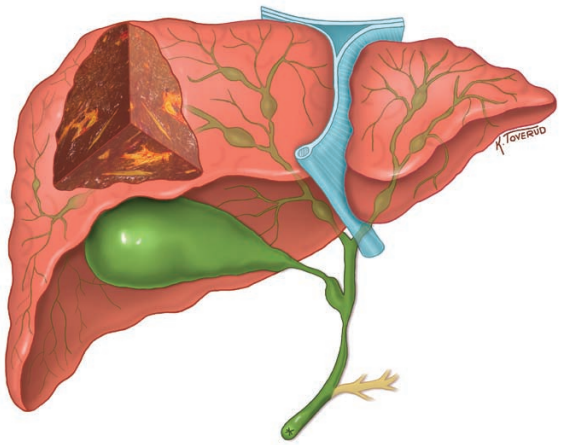
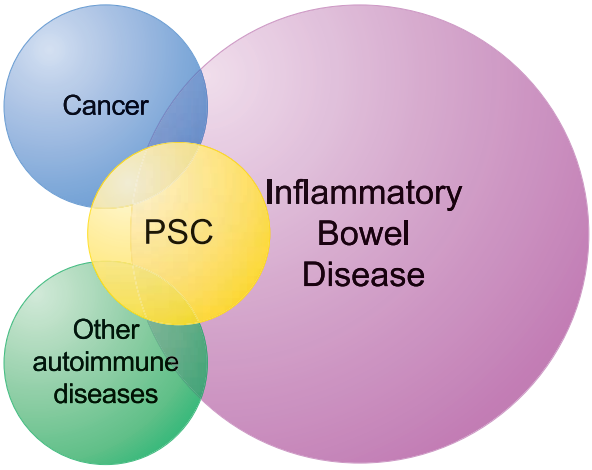


Illustration: © Kari C. Toverud, CMI (Certified Medical Illustrator)

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.

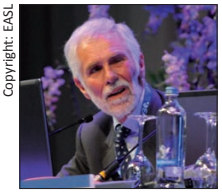


Primary sclerosing cholangitis (PSC) is a patchwork of different phenotypes in addition to the bile duct affection. Most important are inflammatory bowel disease (IBD), malignancy and other autoimmune diseases.

Key NoPSC events in 2013

The year of 2013 marked "conclusion of PSC genetics" and the full materialization of the post-genomics agenda at NoPSC. The forming of the three research groups – experimental, metagenomic and clinical – stakes out the course for the main targets of NoPSC research over the coming years.

Erik Schrumpf was appointed Honorary President of The International Liver Congress (ILC) 2013


Copyright: EASL

The career of PSC research for Erik Schrumpf started with the presentation of his study on HLA typing at the 16th annual EASL meeting in 1981. Erik Schrumpf has contributed to EASL over many years, and his achievements were awarded with the role of Honorary President at the International Liver Congress (ILC) of EASL in April 2013. In his talk at the presidential dinner, Erik Schrumpf emphasized that less prevalent liver diseases like PSC must not be forgotten in research priorities.

Dissertation of Kim Andresen


Photo: Private

May 22nd, MSc Kim Andresen defended his thesis "Novel epimarkers in cholangiocarcinoma and their clinical potential". The trial lecture was entitled "The role of microRNA in the development and progression of cancer". Opponents were Prof. Lars Andreas Akslen from Haukeland University Hospital, Tone Ikdahl, PhD from Oslo University Hospital and Prof. Ola Røkke, Division of Surgery, Institute of Clinical Medicine, University of Oslo. In his thesis, Kim Andresen and co-workers identified novel epigenetic biomarkers for early detection of cholangiocarcinoma. They identified a panel of four epigenetic biomarkers which could detect patients with malignant development with higher performance compared with existing clinical modalities. The team is now investigating the potential of these biomarkers to detect early stages of cholangiocarcinoma in samples taken at different stages of primary sclerosing cholangitis.

Dissertation of Kristin Kaasen Jørgensen


Photo: Private

November 21st, MD Kristin Kaasen Jørgensen defended her thesis "Inflammatory Bowel Disease in Primary Sclerosing Cholangitis: Clinical Characteristics in Liver Transplanted and Non-Transplanted Patients". The trial lecture was entitled "The role of new endoscopic techniques". The opponents were Prof Martti Färkkilä from Helsinki University Central Hospital, Prof Arne Kristian Sandvik from Norwegian University of Science and Technology and Associate professor Glenny Cecilie Alfsen, Division of Medicine

and Laboratory Science, Institute of Clinical Medicine, University of Oslo. In her thesis, Kaasen Jørgensen has described the clinical features of IBD in PSC with special emphasis on IBD disease activity and development of colorectal neoplasia in both liver transplanted and non-transplanted patients. The studies are the largest performed so far on the topic, and the results will guide in the development of better treatment for PSC patients with inflammatory bowel disease. The goal is to reduce the colonic inflammation and the risk of colorectal cancer development.

International PSC study group

With the practical assistance of NoPSC, two meetings of the International PSC Study Group were held throughout 2013 (at the EASL and AASLD meetings). Multiple projects are performed within this group (see separate presentation at page 16), most of which are neither driven nor financed by NoPSC. The group has grown to become the main collaborative arena for PSC research worldwide and the number of participants at the biannual meetings are now relatively stable around 60 people.

The Immunochip project

The publishing of the Immunochip paper in Nature Genetics was by far the main accomplishment of the International PSC study group (*www.ipscsg.org*). With contributions from more than 200 hospitals in 14 different countries, the study represents a logistical challenge beyond any previous study done in PSC. The study provided extremely valuable insight on the relationship between PSC and other immune-mediated diseases, an insight that may form the basis for shared utilization of therapeutic strategies between different conditions. For the first time, it was also demonstrated how the genetics of PSC differ from the genetics of IBD, suggesting more than ever that PSC is a distinct disease and something more than a complication occurring secondary to IBD.

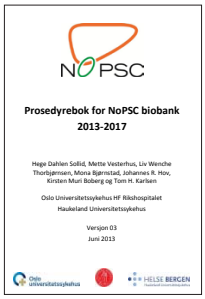
Nor-ursodeoxycholic acid clinical trial

This is a phase II study where three different dosages of norursodeoxycholic acid (norUDCA), along with placebo, are tested in PSC patients. norUDCA has shown promising results in mice studies, and the project is an international multi center study. This trial marks a shift in PSC research in many aspects. It is the first of a series of planned clinical trials with a variety of drugs, and the many initiatives offer new hope for an effective medical treatment. The local efforts are being managed by Erik Schrumpf and research nurse Mona Bjørnstad, together with the clinical research department at OUS Rikshospitalet.

Prospective PSC banking in Norway

During January and February 2013, NoPSC post doc Mette Vesterhus at Haukeland University Hospital established a cohort of PSC patients for prospective follow-up. The patients will be seen annually, both for blood sample collection, questionnaires and for advanced imaging. The cohort will serve as a basis for biomarker evaluation and evaluation of novel imaging technologies at the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at Haukeland. In November 2013, the first patients of the same initiative were included at Rikshospitalet. The efforts are part of an initiative of the International PSC Study Group which aims at a total cohort for prospective follow up of at least 1,000 patients. The initiative has been warmly welcomed by the patients.

3rd version of the NoPSC biobank standard operating procedures



In July, the 3rd version of the NoPSC biobank standard operating procedures was distributed. The first two versions came out in 2008 and 2009, and in conjunction with the establishment of prospective biobanking the document needed revision. The book covers everything from practical aspects related to patient inclusion procedures to how we (in detail) collect, prepare, store and retrieve our samples. In addition, the document covers all relevant consent forms, questionnaires used, sample requisitions and the standard MTA and DTA documents required by Oslo University Hospital when sharing samples in national and international collaborative projects.

www.ous-research.no/home/nopsc/NoPSC%20biobank/10846

Establishment of NoPSC biobank quality control project

During 2013, bioengineer Liv Wenche Thorbjørnsen started the storage quality control project for the NoPSC biobank. The biobank now holds more than 60,000 unique tubes of biomaterial, and to determine the effects of storage over time, a selected set of clinical chemistry analysis will now be performed at an

annual basis. The initiative is critical for the precision of future studies on this world-wide unique collection of PSC-related material.

Annual guest professor meeting

Twice each year our guest professors visit NoPSC, and in 2013 the meetings were held in January and November. All projects are discussed in relevant subgroups, and the guest professors evaluate them critically. Projects plans are then adjusted according to high international standards. Guest professorships at NoPSC run in 3 year contracts, and in April, Prof. Franke ended his rotation term as highly valued guest professor, but the collaboration between Oslo and Kiel will continue. Prof. David Adams from the University of Birmingham took over the position for the next 3 years in August, and will, with his vast experience in liver immunology, serve as a valuable source of guidance and input to the experimental research portfolio (see separate presentation at page 11). The other guest professorship is held by Prof Fredrik Bäckhed from the University of Gothenburg, Sweden, and he started as guest professor January 1st 2013. Please see separate presentation in the annual report 2012.

First NoPSC scientific retreat

In May, the first NoPSC scientific retreat was held at Losby Gods. The seminar was funded by award money (one of top six outstanding original papers Jan-July 2011) rewarded from Oslo University Hospital to Espen Melum and co-workers for the paper:
Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci, published in Nature Genetics (PMID: 21151127).
A two-day scientific program was held, and all aspects of our activity were presented and discussed.

Establishment of patient organization and first network meeting

Photo: Foreningen for PSC og PBC

During the patient network seminar, Kristian Bjøro held a presentation entitled "PSC and PBC, liver transplantations in the Nordic countries".

In February 2013, the patient organization for primary sclerosing cholangitis (PSC) and primary biliary sclerosis (PBC) in Norway was established. The organization aims at being a channel for information and a network for patients with PSC and PBC. In November, the first patient network meeting took place at Rikshospitalet. Patients and relatives who attended the meeting greatly appreciated the lectures and discussions with PSC and PBC experts, and a next meeting has already been planned for spring 2015. From NoPSC Erik Schrumpf, Kristian Bjøro, Elisabeth Schrumpf and Mona Bjørnstad contributed.

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 that will participate in projects in at least two groups at the same time. The style of working will increase interactions between the groups and has also fuelled the forming of a Norwegian Inflammation Research Network (NORIN) led by Prof. Guttorm Haraldsen. NoPSC is involved in 4 out of the 7 post doc projects.

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

AWARDS

Oslo University Hospital Early Career Awards

Photo: Ram Gupta, OUS

In 2013, **Tom Hemming Karlsen** and our collaborator **Guro Lind** were both independently awarded the Oslo University Hospital first ever Early Career Awards.
The awards are given to outstanding young researchers. Karlsen was selected due to having "demonstrated independence and (he has) already reached far as a recognized researcher in the gastrointestinal field. He has an excellent publication record and has recruited several external grants. He has created a strong and most active research group and has taken on several responsibilities within the broader research arena".

Researcher of the month in Southern and Eastern Norway Regional Health Authority (HRSE)

In November, **Tom Hemming Karlsen** was profiled as the researcher of the month with an interview at the official web pages of HRSE.

www.helse-sorost.no/aktuelt_/nyheter_/Sider/manedens-forsker-november-2013.aspx

NoPSC project update

Clinical research group

PRINCIPAL INVESTIGATORS: **Kirsten Muri Boberg, Mette Vesterhus, Erik Schrumpf, Tom Hemming Karlsen**
AFFILIATED GROUP MEMBERS: **Trine Folseraas** (PhD student/physician), **Kristin Kaasen Jørgensen** (physician), **Mona Bjørnstad** (study nurse) **Kristian Bjøro** (physician), **Jorunn Bratlie** (engineer), **Liv Wenche Thorbjørnsen** (medical laboratory technician), **Aud Sissel Hjartholm** (engineer)
WEB PAGE: *www.ous-research.no/nopsc/?k=nopsc%2FClicial+studies&aid=13954*

The PhD dissertations of Kim Andresen and Kristin Kaasen Jørgensen were major events in the clinical research portfolio at NoPSC and the Section of Gastroenterology in 2013. The PhD work of Kim Andresen included 3 articles related to the use of epigenetic markers in the early detection of cholangiocarcinoma. The work was performed in close collaboration with the Department of Cancer Prevention and the group of Prof. Ragnhild Lothe and Prof. Guro Lind. Ongoing work is aimed at validating findings in larger patient materials. There are also multiple ongoing efforts within the International PSC study group network to further clarify the role of other biomarkers in cholangiocarcinoma detection, both using proteomic and genomic technologies. After her PhD dissertation on PSC genetics in 2014, Trine Folseraas will join the cholangiocarcinoma research.

The PhD work of Kristin Kaasen Jørgensen included 3 articles on the clinical aspects of inflammatory bowel disease in PSC before and after liver transplantation. The project, which was led by prof. Kirsten Muri Boberg, has formed the basis for ongoing queries into the optimal use of immunosuppression after liver transplantation for PSC. The project was performed in close collaboration with the IBSENII study group, in which also other PSC-related projects are currently being performed (e.g. magnetic resonance imaging of the liver of all patients with IBD). Importantly, the large collection of biomaterial from almost 200 PSC patients with IBD that was done as part of the project is now being utilized in multiple translational projects in the experimental and genomic groups. These projects include diverse topics from T cell characterization to determination of gut microbiota characteristics. The sample collection system is also being used for other inflammatory bowel disease patients seen at the Section of gastroenterology, forming a distinct and valuable subset of the NoPSC biobank which is being coordinated by Knut Lundin, Jorunn Bratlie og Mona Bjørnstad.

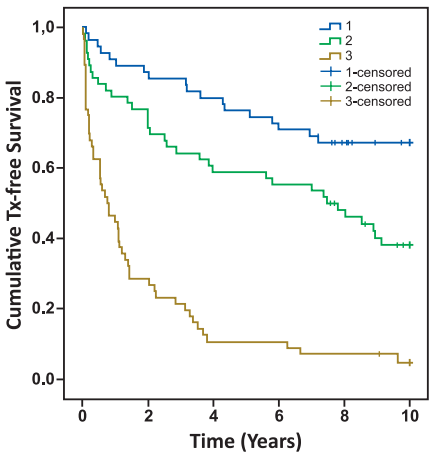


Figure:
The Kaplan-Meier curves illustrate transplant-free survival in 167 Norwegian PSC patients stratified by tertiles of a fibrosis score based on measurement of serum biomarkers.

The efforts initiated by post doc Mette Vesterhus at the National Centre for Ultrasound in Gastroenterology at Haukeland University Hospital in Bergen have pioneered the establishing of the prospective PSC cohort. This is an initiative to which centers within the International PSC study contribute at various levels. Some centers collect only basic clinical information and a minimum of biological samples (e.g. serum). Other centers involve in more extensive biobanking and also one or more of the ongoing imaging studies. In Bergen and Oslo, patients are offered comprehensive assessments, including evaluation by advanced ultrasound for the determination of liver stiffness and magnetic resonance cholangiography. In 2014, these assessments will also involve new contrast agents to determine the level of inflammation. Over time, the prospective biobank and imaging will form a unique and sorely needed resource for a molecular and imaging based rationale for the perfect clinical follow-up of patients with PSC.

Based on the NoPSC biobank, and also biobanking efforts performed prior to the establishing of NoPSC, biomarker studies performed by post docs Anders Holm and Mette Vesterhus have now led to the identification of new means to measure both the degree of scarring (fibrosis) in livers of PSC patients and also to what extent inflammation is involved. These new biomarkers will be useful at many levels. First of all they provide methods to measure the effect of novel drugs in clinical trials in PSC. A liver biopsy, which is often used to measure such effects in other liver diseases, is not useful in PSC (and potentially harmful to the patients) since the disease has a very patchy affection. Imaging is also so far not useful, and patients can obviously not be treated in a trial for years until they might – or hopefully might not – need a liver transplantation. As such, the establishing of “surrogate markers” for PSC severity is a major breakthrough.

The most exciting trend in PSC research throughout 2013 is the emergence of multiple clinical trials for drugs targeting aspects of PSC pathogenesis that have now been established. NoPSC participates in these trials to the extent that they are compatible with Norwegian regulatory aspects (ethical clearance) in close collaboration with the clinical research unit at Oslo University Hospital Rikshospitalet.

In principle, three targets for PSC therapy is now available:

1) Bile acid treatment – with ongoing clinical trials for norursodeoxycholic acid and trials expected for obeticholic acid.

2) Immunological treatment – particularly vedolizumab and VAP-1 inhibition.

3) Anti-fibrotic treatment – particularly anti-loxl2.

NoPSC project update

Experimental hepatology

GROUP LEADER: **Espen Melum** LAB MANAGER: **Jarl Andreas Anmarkrud** (Jan-Aug), **Kristian Alfsnes** (Aug-Dec) POST DOCS: **Xiaojun Jiang** (from 2014)
PHD STUDENTS: **Elisabeth Schrumpf**, **Natalie Lie Berntsen**, **Eva Kristine Klemsdal Henriksen** SCIENTIFIC ASSISTANT: **Corey Tan**
WEB PAGE: *www.ous-research.no/melum/*

Photos: NoPSC

Photo left: Elisabeth Schrumpf at the AASLD conference in Washington where she had an oral presentation.

Photo right: Natalie Lie Berntsen performing mouse surgery together with Prof. Fickert in Graz.

In June 2013 the Research Group for Experimental Hepatology was formed as an integral part of the Norwegian PSC Research Center (NoPSC) and is also an independent group at the Research Institute for Internal Medicine.

The group started out with three NoPSC members: Espen Melum, Jarl Andreas Anmarkrud and Elisabeth Schrumpf. The aim of this group is to gather and organize the experimental activities at NoPSC. The experimental studies are mainly related to mouse models, but we do not restrict ourselves to murine systems and will complement ongoing studies with experiments using human material. During 2013 the group has gone through a major recruitment phase and we have hired Natalie Lie Berntsen, Eva Kristine Klemsdal Henriksen and Corey Tan. Kristian Alfsnes has served as the lab manager during Jarl Andreas Anmarkrud's paternity leave. 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 with regulatory properties within the immune system.

The studies on basic functions of Natural Killer T (NKT) cells were expanded in 2014 and identified specific lipids inhibiting NKT antigen presentation. The results were presented at the biannual NKT meeting in Tours, France. To further expand on the *in vivo* relevance of the findings key additional experiments are currently being performed. Elisabeth Schrumpf is working on an animal model with spontaneous inflammation of the bile ducts. This animal model is developed on a general autoimmune background, which can be argued to parallel the situation in PSC patients as exemplified by the genetic studies previously performed by NoPSC. Dr. Jon Sponheim has, together with Corey Tan, worked to establish immunhistochemical techniques in the group for characterization of bile-duct specific expression and pathology in human samples.

Eva Kristine Klemsdal Henriksen started as a PhD student in August 2013 and took over the responsibility for the GPR35 project in collaboration with PhD student Zaeem Cader in the lab of Arthur Kaser in Cambridge. Initial progress on the role of LPS induced immune activation has been complemented by careful investigation of the phenotype of knock-out cells from mice. Natalie Lie Berntsen started as a PhD student in June and has during the rest of 2013 developed, together with Bjarte Fosby, a surgical model for bile duct inflammation by using microsurgical techniques and subsequent molecular biology methods to quantify the induced pathology. This model will further be applied for studying various external challenges in the bile duct.

Through the K.G. Jebsen Inflammation Research Centre and in collaboration with the Taskén lab (Sigrid Skånland in particular) we have started the molecular characterization of a familiar form of PSC. It has been confirmed that the genetic variant in question is a private variant only seen within this family, and that it is likely to be an overactive variant. To work on this project we have recruited Xiaojun Jiang from Heifei in China. Xiaojun has excellent expertise in animal models and liver immunology and we have great expectations for this project in 2014.

A key resource for our activities is access to animal facilities. Our presence at the Centre of Comparative Medicine has increased during 2013 and we now have a running capacity of approximately 130 mouse cages making us one of the major users. As the space of this facility is limited, we will establish additional project activities at the animal facility of the Institute of Basic Medical Sciences during 2014.

NoPSC project update

Genomics and metagenomics

GROUP LEADER: **Johannes R. Hov** POST DOCS: **Marius Trøseid** (post doc., K.G. Jebsen Inflammation Research Centre)
PHD STUDENTS: **Trine Folseraas**, **Sigrid Næss**, **Bjarte Fosby**, **Martin Kummen**, **Silje Jørgensen** (associated) BIOINFORMATICIAN: **Kristian Holm**
WEB PAGE: *www.ous-research.no/hov/*

Photo: NoPSC

The genomics and metagenomics group is involved in a large collaborative project exploring environment-host-microbiota interactions in a population-based sample from Northern Germany (the Popgen study). The collaboration includes multiple German groups (Andre Franke´s group in Kiel, John Baines´ group in Kiel/Plön, Wolfgang Lieb´s group in Kiel as well as Ute Nöthling´s group in Bonn). The picture is taken at the fourth Popgen workshop, which was held in Oslo in January 2014.

During 2013, the genomics and metagenomics activities were formally organized in a separate research group at the Research Institute of Internal Medicine with Johannes R. Hov as group leader. The main achievements in terms of publications in 2013 were related to genomic studies. The largest genetic study in PSC so far, the immunochip study, was published in Nature Genetics in June 2013. This concluded a several year-long effort undertaken by the International PSC study group led from Norway. Several substudies are still in progress, including specific analyses of PSC subphenotypes as well as studies assessing similarities and differences with related inflammatory diseases. A large international genome-wide association meta-analysis in PSC which is based on NoPSC supported efforts in the UK and US, has been completed and will be submitted in 2014.

Elucidation of the functional consequences of the HLA associations in PSC will most likely represent a major leap forward in our understanding of the disease mechanisms in PSC, and this region will remain an important priority. Over the last couple of years, collaborations with the Centre for Liver Research in Birmingham have developed which focus on the specific targets of the immune responses in PSC, using genetic and proteomic methods. Professor David Adams, the director of the Centre for Liver Research, was appointed a new guest professor at NoPSC in 2013. Several projects within the Jebsen Inflammation Research Centre are also relevant for the HLA complex and adaptive immunity in PSC, of which the groups of Johanna Olweus and Fridtjof Lund-Johansen are extremely valuable.

The gut microbiota represents a link between the environment and the body. Studies of the impact from gut microbiota – metagenomics – in PSC have been a priority in 2013 and the first studies have been completed and will be published in 2014.

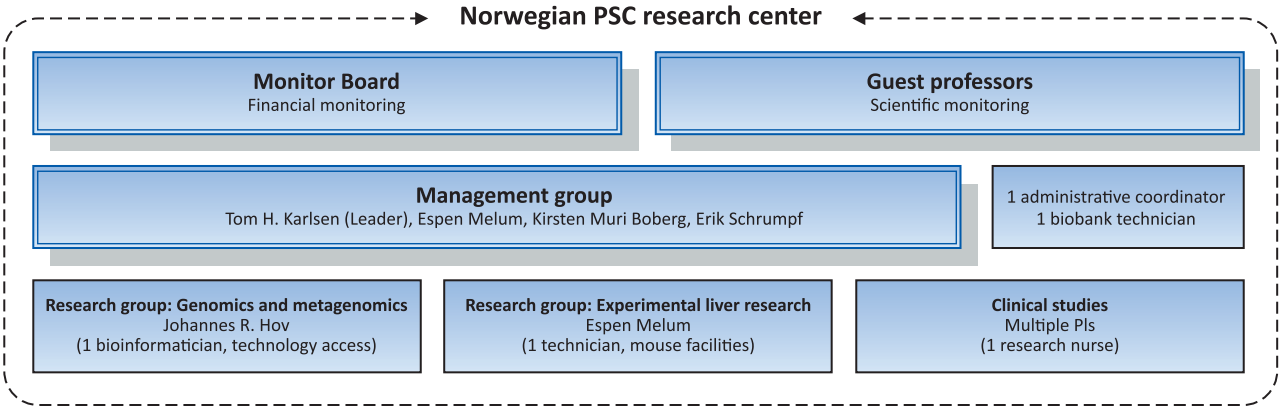
Important projects include cross-sectional studies in PSC and related phenotypes, as well as PSC-relevant physiology in a large population sample, the latter in close collaboration with several German research groups. The gut microbiota is the focus of PhD student Martin Kummen. Bioinformatician Kristian Holm has a key role in these projects, performing the primary analysis of sequencing-based microbiota data. At the end of 2013, NoPSC received an external grant from the Fougner-Hartmann's family fund to partially cover the costs of a next-generation sequencer (MiSeq). A major goal of 2014 is therefore to finally establish the full pipeline necessary for modern microbiota studies at NoPSC.

Besides defining how the PSC microbiota differs from controls, ongoing study designs include prospective and interventional studies, as well as the assessment of the role of the gut microbiota in the experimental models of PSC under study in the Research Group of Experimental Hepatology.

Overall, the major aims for 2014 are, besides publication of ongoing and near-completed genetics and metagenomic projects and the finalization of the practical sequencing pipline, the launching of a cancer genetics project portefolio (Trine Folseraas, who has now completed her PhD).

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 September 22nd 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 2013

- **Clinical studies** (page 7)
- **Experimental studies** (page 8)
- **Genomic and metagenomic studies** (page 9)

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 December, 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 7-9.

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
Kristian Bjøro	Div. of Cancer Medicine, Surgery and Transplantation Oslo University Hospital, Rikshospitalet
Pål Aukrust	Div. of Cancer Medicine, Surgery and Transplantation Oslo University Hospital, Rikshospitalet
Nina Paulsen	Canica A/S
Peter Ruzicka	Canica A/S

People at NoPSC in 2013

Management group

Tom Hemming Karlsen
MD, PhD, Professor/Leader
t.h.karlsen@medisin.uio.no

Erik Schrumpf
MD, PhD, Prof. emeritus
erik.schrumpf@medisin.uio.no

Kirsten Muri Boberg
MD, PhD, Professor
kboberg@ous-hf.no

Espen Melum
MD, PhD, Post doc
espen.melum@medisin.uio.no

Scientific personnel

Johannes Roksund Hov
MD, PhD, Post doc. Part of management group from Jan. 2014
j.e.r.hov@medisin.uio.no

Mette Vesterhus
MD, PhD, Post doc
Haukeland University Hospital
mette.vesterhus@helse-bergen.no

Alexey Shiryaev
MD, PhD, Post doc, until April 2013

Anders Holm
PhD, Post doc, until April 2013

Kristin Kaasen Jørgensen
MD, PhD student, until Nov. 2013
kristin.kaasen.jorgensen@ous-hf.no

Trine Folseraas
MD, PhD student
trine.folseraas@medisin.uio.no

Sigrid Næss
MD, PhD student
sigrid.nass@medisin.uio.no

Bjarte Fosby
MD, PhD student
bfosby@ous-hf.no

Elisabeth Schrumpf
MD, PhD student
elisabeth.schrumpf@medisin.uio.no

Martin Kummen
MD, PhD student
martin.kummen@medisin.uio.no

Natalie Lie Berntsen
MD, Scientific project assistant
from Jan. 2013 - June 2013
MD, PhD student, from June 2013
natalie.lie.berntsen@rr-research.no

Eva Kristine Klemsdal Henriksen
MSc, PhD student, from Aug. 2013
eva.kristine.klemsdal.henriksen@rr-research.no

Corey X. Tan
BSc, Scientific research assistant
from Aug. 2013 - Aug. 2014
ctan827@gmail.com

Ina Marie Andersen
MD, Scientific project assistant
from Aug. 2012 - Feb. 2013

Core unit personnel

Hege Dahlen Sollid
MSc, Administrative coordinator
hege.dahlen.sollid@rr-research.no

Kristian Holm
Cand.scient, Bioinformatician
kholm@ous-hf.no

Mona Bjørnstad
Research nurse
mona.bjornstad@ous-hf.no

Liv Wenche Thorbjørnsen
Biobank/Bioengineer
liv.wenche.thorbjornsen@ous-hf.no

Jarl Andreas Anmarkrud
PhD, Lab. manager
On leave from Sept. 2013 - Feb. 2014
jarl.andreas.anmarkrud@rr-research.no

Kristian Alfsnes
PhD, Lab. manager, Aug. 2013 - June 2014
kristian.alfsnes@rr-research.no

NoPSC guest professors

Fredrik Bäckhed
Institute of Medicine, Wallenberg Laboratory
University of Gothenburg, Sweden
www.wlab.gu.se/backhed

David Adams
College of Medical and Dental Sciences
University of Birmingham, UK
www.birmingham.ac.uk/staff/profiles/iandi/adams-david.aspx

Affiliated researchers

Benedicte A. Lie
PhD, Professor
Department of Medical Genetics
Oslo University Hospital, Ullevål

Ragnhild Lothe
PhD, Professor/Head of Department
Department of Cancer Prevention
Oslo University Hospital, Radiumhospitalet

Guro Elisabeth Lind
PhD, Professor
Department of Cancer Prevention
Oslo University Hospital, Radiumhospitalet

Lars Aabakken
MD, PhD, Professor
Section for Gastroenterology
Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Morten H. Vatn
MD, PhD, Professor emeritus
Section for Gastroenterology
Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Kristian Bjøro
MD, PhD, Professor
Section for Gastroenterology
Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Bård I. Røsok
MD, PhD
Consultant HPB surgeon
Dept. of Gastrointestinal Surgery
Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Günter Kemmerich
MD, Fellow
Dept. of Radiology
Division of Diagnostics and Intervention
Oslo University Hospital, Rikshospitalet

Jon Sponheim
MD, PhD
Section for Gastroenterology
Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Guest professor at our research center from August 2013

David Adams is Professor of Hepatology and Dean of Medicine for the College of Medical and Dental Sciences, University of Birmingham, UK. He is also director of the Centre for Liver Research and the National Institute for Health Research (NIHR) Birmingham Liver Biomedical Research Unit and lead for translational research in the MRC Centre for Immune Regulation.

Prof Adams clinical interests are transplant hepatology and autoimmune liver disease. Laboratory research interests are focused on mechanisms of immune-mediated liver disease. Prof Adams is currently an associate editor of Liver Transplantation and the American Journal of Physiology and special section editor for the Journal of hepatology. He served on the scientific committee and governing board of the European Association for Study of the Liver between 2004 and 2007 and currently sits on its Ethics committee. He was a councilor for the European Society for Organ Transplantation between 2004 and 2008. He was made a Fellow of the Academy of Medical Sciences in 2000. He has a long-standing interest in understanding how leukocyte-endothelial interactions regulate the recruitment of effector cells in chronic liver disease and his group has defined molecular mechanisms used by hepatic endothelium to control the entry of leukocytes from the blood. They have recently begun to use this information to develop cell therapy for liver disease by targeting pathways involved in the recruit-ment of damaging effector cells or by pro-moting the recruitment of therapeutic cells including dendritic cells, stem cells and regulatory T cells that may be used to manipulate immune responses in patients *in vivo*.

Three most important publications:

1. *Lalor PF, Sun PJ, Weston CJ, Martin-Santos A, Wakelam MJ, Adams DH*
   Activation of vascular adhesion protein-1 on liver endothelium results in an NF-kappaB-dependent increase in lymphocyte adhesion
   Hepatology. 2007 Feb;45(2):465-74.
2. *Eksteen B, Mora JR, Haughton EL, Henderson NC, Lee-Turner L, Villablanca EJ, Curbishley SM, Aspinall AI, von Andrian UH, Adams DH*
   Gut homing receptors on CD8 T cells are retinoic acid dependent and not maintained by liver dendritic or stellate cells
   Gastroenterology. 2009 Jul;137(1):320-9. doi: 10.1053/j.gastro.2009.02.046. Epub 2009 Feb. 21.
3. *Shetty S, Weston CJ, Oo YH, Westerlund N, Stamataki Z, Youster J, Hubscher SG, Salmi M, Jalkanen S, Lalor PF, Adams DH*
   Common lymphatic endothelial and vascular endothelial receptor-1 mediates the trans-migration of regulatory T cells across human hepatic sinusoidal endothelium
   J Immunol. 2011 Apr 1;186(7):4147-55. doi: 10.4049/jimmunol.1002961. Epub 2011 Mar. 2.

Adapted from:
www.birmingham.ac.uk/staff/profiles/iandi/adams-david.aspx

Post doctor profile: Mette Vesterhus

Creating a prospective PSC cohort

Mette Vesterhus graduated as an MD from the University of Bergen in 1999. She is a specialist in Internal Medicine and is currently pursuing the specialty of Gastroenterology in a 50% position as resident in the Section for Gastroenterology, Dept. of Medicine, Haukeland University Hospital, working 50% also with clinical PSC research.

Photo: Eva Elisabeth Fosse

Professor Odd Helge Gilja, head of the National Centre for Ultrasound in Gastroenterology, and postdoc Mette Vesterhus with the Philips iU22 ultrasound equipment used for liver fibrosis measurements in PSC patients at Haukeland University Hospital in Bergen

She received her Ph.D. in medicine in 2009, based on research spanning from the molecular level through cell lines and mouse studies to clinical research, also including a one year research stay at the laboratory of Professor C. Ronald Kahn at Harvard Medical School in Boston.

Mette Vesterhus joined NoPSC in September 2012 as a 50% post doc. fellow and represents the "Bergen branch" of NoPSC. She has built a biobank following the same physical infrastructure and protocols as the NoPSC biobank in Oslo, although focusing on the prospective follow-up of patients. She was instrumental in translating these experiences into the activities of the International PSC Study Group, and similar initiatives are now being set up at many centers throughout Europe. In Bergen, 53 PSC patients have been included with clinical data and biobank samples.

Part of Vesterhus' post doc. position is linked to the National Center for Ultrasound in Gastroenterology (NCUG) at Haukeland University Hospital, headed by professor Odd Helge Gilja, thus introducing liver research to a strong research environment within the field of gastroenterological ultrasound.

As a national center since 2001, the NCUG has been exploring a broad range of advanced ultrasound modalities. Point shear wave elastography is a recent development within advanced ultrasonography, used to measure liver stiffness as an indicator of liver fibrosis, exploiting the fact that acoustic push pulses from the ultrasound transducer induce shear waves spreading into the liver tissue with a speed correlating with liver stiffness. Liver stiffness measurement by a similar technique was recently suggested as a prognostic marker in PSC. Annual liver stiffness measurement by point shear wave elastography, as well as visualization of inflammation by means of contrast media, is part of the follow-up of the patients of Vesterhus.

Biomarkers and imaging of PSC disease activity and progression are the main focus of Vesterhus' research. Her studies this far have revealed that the commercially available Enhanced liver Fibrosis (ELF®) biomarker panel is a potent prognostic marker in PSC, providing incremental information to the Mayo risk score for the prediction of transplant-free survival. Furthermore, proteomic biomarker profiling studies in bile based on an antibody array platform previously has identified several novel biomarkers associated with the diagnosis of PSC, disease severity, and transplant-free survival. Both of these studies have gained attention and will be presented as oral ePoster and oral presentation, respectively, at the EASL International Liver Congress (ILC) in London in 2014.

More information regarding the NCUG can be found at: *www.helse-bergen.no/omoss/avdelinger/gastroenterologisk-ultrasonografi/Sider/enhet.aspx*

Post doctor profile: Espen Melum
Creating a PSC laboratory

Espen Melum is currently a group leader for the research group for Experimental hepatology that covers the experimental studies at NoPSC.

Espen defended his thesis on PSC genetics in 2010. To expand his research to experimental studies he was a post doc. in the lab of Richard S. Blumberg at Brigham and Women's Hospital / Harvard in Boston for two years.

During his post doctoral research Espen aimed to work with genetically modified animals and learn key experimental techniques. Richard Blumberg's lab has focused on mucosal immunology and inflammatory bowel disease in particular since the beginning of the 1990s. Inflammatory bowel disease is seen in up to 80% of the patients with PSC, making this lab especially suitable to learn such techniques.

The Blumberg lab consists of 8-9 post docs mainly from Europe and Asia that work there for 2-3 years before returning to their home country. In addition to the post docs, a lab manager and 1-2 technicians take part in the daily work. The post docs are responsible for their own project, but there is extensive collaboration between the projects. The fact that most of the post docs are from abroad makes the atmosphere in the lab very international and everyone is extremely hard working.

Espen says that it is an understatement to say that Harvard University is a fantastic place to receive postdoctoral training. But it is not the place itself that makes it superb, it is the all the dedicated people from all over the world that comes there to pursue various scientific problems. What he found particularly engaging were the dynamic and collaborative aspects of the scientific environment at Harvard Medical School.

In addition to the lab where he worked he was able to collaborate with other labs at the Harvard Medical School campus. Several of these labs are top-tier groups within the field and the network of Prof. Blumberg enables such collaboration. Given the high density of good labs it is possible to find someone with top expertise on almost all relevant topics.

Photo: Øystein H. Horgmo, UiO

To perform additional experiments in his studies Espen transferred several of the mouse models and in vitro systems to the lab in Oslo. This was also important to establish the models for future studies taking place in Oslo in close collaboration with Prof. Blumberg's lab in Boston. Establishment of these models and the associated in vitro systems formed the basis for the experimental research portfolio.

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 at the Institute for Surgical Research 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.

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: Øystein H. Horgmo, UiO

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, OUH 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 metagenomic studies at NoPSC. Blood samples of patients undergoing magnetic resonance cholangiography (MRC) at the 20 years follow-up consultation are deposited in the NoPSC biobank. Dr. Anne Nergård and Dr. Aida Kapic Lunder are performing the MRCs at Akershus University Hospital.

Haukeland University Hospital

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, resulting from the professor II appointment of Tom Hemming Karlsen with the University of Bergen and the 50% NoPSC affiliation for post doc Mette Vesterhus. For the bile acid and microbiota projects, Prof. Rolf Berge at the Section for Medical Biochemistry 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 metagenomics.

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 (including Dr. George Mells, Dr. Simon Rushbrook, Dr. Graeme Alexander and Dr. Richard Sandford).

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 projects in several projects where data from the Nordic Liver Transplant Registry are required.

Karolinska University Hospital, Stockholm, Sweden

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

Professor 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 Istituto 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

Dr. Daniel Gotthardt in Heidelberg is an important contributor to IPSCSG and he is running multiple projects with NoPSC as collaborator.

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.

International PSC Study Group (IPSCSG) Annual report

In Oslo 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 and established the International PSC Study Group (IPSCGS) (www.ipscsg.org, password required). Entering 2014, the group includes researchers from 19 countries and more than 50 different institutions.

MEMBERS OF THE STEERING COMMITTEE

Prof. **Michael E. Manns**, Hannover, Germany
Prof. **Konstantinos N. Lazaridis**, Rochester, MN, US
Prof. **Michael Trauner**, Vienna, Austria
Prof. **Ulrich H. Beuers**, Amsterdam, the Netherlands
Dr. **Luca Fabris**, Padua, Italy
Prof. **Martti Färkkilä**, Helsinki, Finland
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 biannually during the International Liver Congress™ (ILC) by 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 2013 the group first met in Amsterdam during the ILC April 26th and then in Washington DC during AASLD November 12th. During the ILC, an official EASL-IPSCSG joint workshop was also held and attracted a full auditorium on the topic of state of the art metagenomics, large cohort management, imaging and mouse model aspects of relevance to PSC.

During 2013 the group made progress on several topics:

- The Immunochip project completed (DNA from >4,000 PSC patients)
- Collection of clinical data from 7,500 PSC patients for a clinical descriptive review completed (results will be 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 study led by George Mells
- Contributions to the US/UK GWAS meta-analysis led by Kostas Lazaridis and Carl Anderson
- Contributions to Immunochip supbphenotype project led by Cyriel Ponsioen
- Contributions to Immunochip cross-phenotype project led by Andre Franke
- Participation in clinical trials (Dilstent2, nor-ursodeoxycholic acid)
- Establishing of a consensus document for phenotyping in mouse models of PSC (published in Journal of Hepatology)

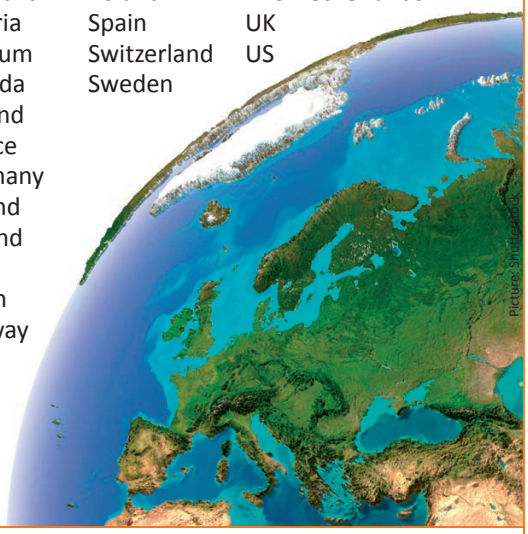
PLANNED MEETINGS IN 2014:

During the ILC in London IPSCSG has been accommodated by EASL to hold the biannual meeting within the venue of the ILC. This is an important recognition and also is likely to increase attendance even further for the reason of practical simplicity. Also, a workshop has been set up within the official ECCO meeting in February to increase awareness of PSC among gastroenterologists. In June, the next biennial two-day IPSCSG meeting will be held in Amsterdam, hosted by Ulrich Beuers and Cyriel Ponsioen. The group will also meet in November during AASLD in Boston for the second biannual meeting.

INTERNATIONAL PSC STUDY GROUP NETWORK

COUNTRIES

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



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

Publications 2013

Picture: Shutterstock

1 ***Boberg KM***, *Wisløff T, Kjøllesdal KS, Støvring H, Kristiansen IS (2013)*
Cost and health consequences of treatment of primary biliary cirrhosis with ursodeoxycholic acid
Aliment Pharmacol Ther, 38 (7), 794-803

2 *Ellinghaus D,* ***Folseraas T, Holm K****, Ellinghaus E,* ***Melum E****, Balschun T, Laerdahl JK,* ***Shiryaev A****, Gotthardt DN, Weismüller TJ, Schramm C, Wittig M, Bergquist A, Björnsson E, Marschall HU, Vatn M, Teufel A, Rust C, Gieger C, Wichmann HE, Runz H, Sterneck M, Rupp C, Braun F, Weersma RK, Wijmenga C, Ponsioen CY, Mathew CG, Rutgeerts P, Vermeire S,* ***Schrumpf E****,* ***Hov JR****, Manns MP,* ***Boberg KM****, Schreiber S, Franke A,* ***Karlsen TH*** *(2013)*
Genome-wide association analysis in primary sclerosing cholangitis and ulcerative colitis identifies risk loci at GPR35 and TCF4
Hepatology, 58 (3), 1074-83

3 *Ellinghaus D, Zhang H, Zeissig S, Lipinski S, Till A, Jiang T, Stade B, Bromberg Y, Ellinghaus E, Keller A, Rivas MA, Skieceviciene J, Doncheva NT, Liu X, Liu Q, Jiang F, Forster M, Mayr G, Albrecht M, Häsler R, Boehm BO, Goodall J, Berzuini CR, Lee J, Andersen V, Vogel U, Kupcinskas L, Kayser M, Krawczak M, Nikolaus S, Weersma RK, Ponsioen CY, Sans M, Wijmenga C, Strachan DP, McArdle WL, Vermeire S, Rutgeerts P, Sanderson JD, Mathew CG, Vatn MH, Wang J, Nöthen MM, Duerr RH, Büning C, Brand S, Glas J, Winkelmann J, Illig T, Latiano A, Annese V, Halfvarson J, D'Amato M, Daly MJ, Nothnagel M,* ***Karlsen TH****, Subramani S, Rosenstiel P, Schreiber S, Parkes M, Franke A (2013)*
Association between variants of PRDM1 and NDP52 and Crohn's disease, based on exome sequencing and functional studies
Gastroenterology, 145 (2), 339-47

4 *Forster M, Forster P, Elsharawy A, Hemmrich G, Kreck B, Wittig M, Thomsen I, Stade B, Barann M, Ellinghaus D, Petersen BS, May S,* ***Melum E****, Schilhabel MB, Keller A, Schreiber S, Rosenstiel P, Franke A (2013)*
From next-generation sequencing alignments to accurate comparison and validation of single-nucleotide variants: the pibase software
Nucleic Acids Res, 41 (1), e16

5 *Friedrich K, Rupp C,* ***Hov JR****, Steinebrunner N, Weiss KH, Stiehl A, Brune M, Schaefer PK, Schemmer P, Sauer P, Schirmacher P, Runz H,* ***Karlsen TH****, Stremmel W, Gotthardt DN (2013)*
A frequent PNPLA3 variant is a sex specific disease modifier in PSC patients with bile duct stenosis
PLoS One, 8 (3), e58734

6 *Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B,* ***Boberg KM****, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S (2013)*
Liver transplantation for nonresectable liver metastases from colorectal cancer
Ann Surg, 257 (5), 800-6

7 *Hirschfield GM,* ***Karlsen TH****, Lindor KD, Adams DH (2013)*
Primary sclerosing cholangitis
Lancet, 382 (9904), 1587-99

8 ***Jørgensen KK****, Lindström L, Cvancarova M,* ***Karlsen TH****, Castedal M, Friman S,* ***Schrumpf E****, Foss A, Isoniemi H, Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH,* ***Boberg KM*** *(2013)*
Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease
Clin Gastroenterol Hepatol, 11 (5), 517-23

9 ***Karlsen TH, Boberg KM*** *(2013)*
Update on primary sclerosing cholangitis
J Hepatol, 59 (3), 571-82

10 ***Kummen M, Schrumpf E, Boberg KM*** *(2013)*
Liver abnormalities in bowel diseases
Best Pract Res Clin Gastroenterol, 27 (4), 531-42

11 *Lindström L, Hultcrantz R,* ***Boberg KM****, Friis-Liby I, Bergquist A (2013)*
Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis
Clin Gastroenterol Hepatol, 11 (7), 841-6

12 *Liu JZ,* ***Hov JR, Folseraas T****, Ellinghaus E, Rushbrook SM, Doncheva NT, Andreassen OA, Weersma RK, Weismüller TJ, Eksteen B, Invernizzi P, Hirschfield GM, Gotthardt DN, Pares A, Ellinghaus D, Shah T, Juran BD, Milkiewicz P, Rust C, Schramm C, Müller T, Srivastava B, Dalekos G, Nöthen MM, Herms S, Winkelmann J, Mitrovic M,Braun F, Ponsioen CY, Croucher PJ, Sterneck M, Teufel A, Mason AL, Saarela J, Leppa V, Dorfman R, Alvaro D, Floreani A, Onengut-Gumuscu S, Rich SS, Thompson WK, Schork AJ,* ***Næss S****, Thomsen I, Mayr G, König IR, Hveem K, Cleynen I, Gutierrez-Achury J, Ricaño-Ponce I, van Heel D, Björnsson E, Sandford RN, Durie PR, Melum E, Vatn MH, Silverberg MS, Duerr RH, Padyukov L, Brand S, Sans M, Annese V, Achkar JP,* ***Boberg KM****, Marschall HU, Chazouillères O, Bowlus CL, Wijmenga C,* ***Schrumpf E****, Vermeire S, Albrecht M, UK-PSCSC Consortium, International IBD Genetics Consortium, Rioux JD, Alexander G, Bergquist A, Cho J, Schreiber S, Manns MP, Färkkilä M, Dale AM, Chapman RW, Lazaridis KN, International PSC Study Group, Franke A, Anderson CA,* ***Karlsen TH*** *(2013)*
Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis
Nat Genet, 45 (6), 670-5

13 *Mells GF, Kaser A,* ***Karlsen TH*** *(2013)*
Novel insights into autoimmune liver diseases provided by genome-wide association studies
J Autoimmun, 46, 41-54

14 *Metzger J, Negm AA, Plentz RR, Weismüller TJ, Wedemeyer J,* ***Karlsen TH****, Dakna M, Mullen W, Mischak H, Manns MP, Lankisch TO (2013)*
Urine proteomic analysis differentiates cholangiocarcinoma from primary sclerosing cholangitis and other benign biliary disorders
Gut, 62 (1), 122-30

15 *Shi JH, Liu SZ, Wierød L, Scholz H,* ***Anmarkrud JA****, Huitfeldt HS, Zhang SJ, Line PD (2013)*
RAF-targeted therapy for hepatocellular carcinoma in the regenerating liver
J Surg Oncol, 107 (4), 393-401

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

17 *Zeissig S, Olszak T,* ***Melum E****, Blumberg RS (2013)*
Analyzing antigen recognition by Natural Killer T cells
Methods Mol Biol, 960, 557-72

Publicity

Post doc Johannes R. Hov and co-authors received massive attention to the paper (early online Sept 25th):

Andersen IM, Tengesdal G, Lie BA, Boberg KM, Karlsen TH, Hov JR

Effects of Coffee Consumption, Smoking, and Hormones on Risk for Primary Sclerosing Cholangitis

Clin Gastroenterol Hepatol (DOI: 10.1016/j.cgh.2013.09.024)

The paper was put on the front page of VG Dec. 29th. Several hundred international news distributors referred to the study, in addition to more than 100 twitter messages.

The year-long effort regarding the Immunochip project led in 2013 to the paper:

Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis

Nat Genet, 45 (6), 670-5 (PubMed ID: 23603763)

with several NoPSC members on the author list. The paper received publicity in, among others, Dagens medisin and forskning.no.

www.dagensmedisin.no/nyheter/genfremskritt-ved-galleveisbetennelse/

Photo: NoPSC

Post doc Hov and the microbiota related research at NoPSC were also fronted in Apollon (no 3/2013), and in conjunction with that Hov was interview at NRK P1. "Kveldsåpent" Sept. 8th.

www.apollon.uio.no/artikler/2013/3_dna_feses.html

Communications

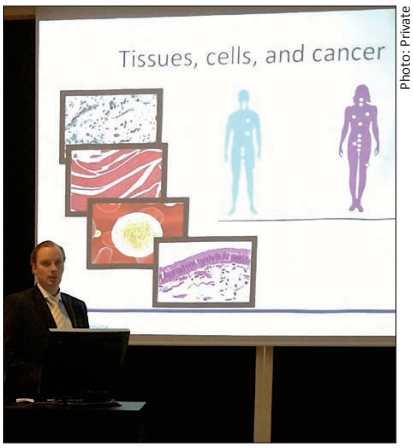


Photo: Private

NoPSC international lectures 2013

Karlsen TH.
Genome-wide association studies in human liver diseases
EASL monothematic conference
"Systems Biology of the Liver:
Systems biology and clinics face à face"
Luxembourg, February 23

Boberg KM.
Liver disease associated with IBD: what should the gastroenterologist know?
Belgian Week of Gastroenterology
Antwerpen, Belgium, February 28

Karlsen TH.
Primary sclerosing cholangitis – what have we learned from genetics?
DEGH and NVGE meeting
Veldhoven, The Netherlands, March 21-22

Karlsen TH.
Genetics in primary sclerosing cholangitis
International Liver Congress 2013 (EASL)
Amsterdam, the Netherland, April 26

Boberg KM.
PSC and malignancies
EASL Basic School of Hepatology,
Clinico-Pathological
Leuven, Belgium, June 6

Karlsen TH.
Pathogenesis of PSC – genes, inflammation or infection?
Juselius Symposium on "Diagnosis and Therapy of Severe Liver Diseases"
Helsinki, Finland, June 10

Melum E.
Acid sphingomyelinase regulates NKT cell development
7th International Symposium
on CD1 and NKT cells
Tours, France, September 14

Vesterhus M.
Point Shear Wave Elastography of the Liver in Patients with Primary Sclerosing Cholangitis
Euroson Congress 2013
Stuttgart, Germany, October 9-12

Karlsen TH.
Sclerosing cholangitis and PBC
UEG Week Postgraduate Teaching Programme, UEGW
Berlin, Germany, October 13

Berntsen NL.
Genetic and clinical differences in primary sclerosing cholangitis patients with high IgG4
UEG Week Oral Presentation
Berlin, Germany, October 14

Karlsen TH.
The role of genetics in the pathogenesis of primary sclerosing cholangitis
Yale Digestive Diseases Research Seminar Series/Liver Center Research Seminar
New Haven, CT, US October 30

Berntsen NL.
Genetic and clinical differences in primary sclerosing cholangitis patients with high IgG4
The Liver Meeting, AASLD, Oral Presentation
Washington DC, US, November 3

Schrumpf E.
Cholangiocytes present antigens to NKT cells
AASLD Cholangiocyte Biology Parallel Session
Washington DC, USA, November 4

Karlsen TH.
Genetics in liver diseases
EASL Master Class
Bordeaux, France, November 14-16

Accounting 2013

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2012	2 792 265		58 152 444	
Interest			815 670	
Own share			22 973	
Transfer from UiO	11 055 491			11 055 491
Wages		4 586 320		1 645 360
Wage related expences		1 414 337		622 032
Overhead		723 102		392 082
Infrastructure/equipment		311 537		
Other operating expenses		3 276 162		9 595
Transfer to 2014 budget		**3 536 298**		**48 802 825**

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

Division of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet
P.O. Box 4950 Nydalen, 0424 Oslo, Norway

Tel: +47 23 07 00 00
Email: nopsc@ous-hf.no

www.ous-research.no/nopsc

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

UiO : University of Oslo

Oslo University Hospital

NoPSC PEOPLE IN THE PICTURE: ***Front:*** Liv Wenche Thorbjørnsen, Kristin Kaasen Jørgensen, Hege Dahlen Sollid, Trine Folseraas, Elisabeth Schrumpf, Kirsten Muri Boberg, Corey Tan, Eva Kristine Klemsdal Henriksen, Erik Schrumpf, Natalie Lie Berntsen, Tom H. Karlsen. ***Back:*** Jarl Andreas Anmarkrud, Espen Melum, Johannes R. Hov, Mona Bjørnstad, Kristian Alfsnes, Martin Kummen, Kristian Holm. ***Not present:*** Mette Vesterhus, Sigrid Næss, Bjarte Fosby

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.

Switchboard: +47 91 50 27 70