Oslo University Hospital

Annual report 2012

Norwegian PSC Research Center

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 2012

NoPSC ANNUAL REPORT 2012

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

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Leader´s comments

The year 2012 was inevitably marked by the retirement of Erik Schrumpf from his position at the Section for Gastroenterology and University of Oslo in August. Main responsibilities for the clinical department and the NoPSC research unit were now to be maintained by the two other members of the NoPSC management group, Kirsten Muri Boberg and myself, respectively. We are happy that Erik Schrumpf continues to serve in the management group, and also to welcome post doc Espen Melum to be part of this group. The principle of having a management group rather than single-person leadership involved in all NoPSC decision-making has been successful in ensuring broad thinking for critical research priorities and will continue.

At the organizational level, NoPSC was formally established as a separate section within the Department of Transplantation Medicine during 2012. In a time where the clinical organizational structures of gastroenterology and hepatology at Oslo University Hospital as a whole has not finally settled, this serves to secure the unit within the structures where it has arisen and where the patients are mainly served. It is also an acknowledgement of the NoPSC research infrastructure by the leadership of the department and the clinic which we greatly appreciate.

NoPSC has been successful and care must be taken when developing the organization further not to interfere with "success elements". However, accomplishments made so far were intended as basis for more work only and some important directions had to be taken throughout 2012. Most important, the basic knowledge obtained from the genetic and clinical characterization must now be systematically transformed into projects aiming for diagnostic and therapeutic applications. This has led to the forming of two new project units at NoPSC; the "experimental group" – led by post doc Espen Melum – focusing on the manipulation of immune reactions in the liver; and the "gut microbiota group" – led by post doc Johannes R. Hov – focusing on the role of intestinal bacteria in PSC and bile-acid physiology.

The size of the NoPSC unit is now at an "effective maximum" and an increase in number of positions is not sought. However, actively searching highly motivated and skilled replacements for scientific personnel at the end of their 3 year terms has been part of the strategic work in 2012, accounting both for PhD students, post docs and the guest professors. The benchmarking of our research by the guest professors will from 2013-2015 be performed by professor David Adams from Birmingham and professor Fredrik Bäckhed from Gothenburg, world experts on topics of relevance to the two new project units.

The NoPSC biobank has received much attention due to the integrated database and state-of-the-art tracking system. Throughout 2012, a process was initiated to shift from recruiting "as

many patients as possible", to start prospectively following a smaller number of patients more closely over time. The effort is driven by NoPSC post doc Mette Vesterhus, who has included the first 50 patients for annual controls including blood samples, clinical review and advanced imaging at the collaborating Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at the Haukeland University Hospital in Bergen, led by Prof. Odd Helge Gilja. These prospective blood biobank and imaging studies will serve as a basis to determine new biomarkers for diagnosis and prognosis of PSC and cholangiocarcinoma. Both for the individual patient and for the testing of new medications such biomarkers are sorely needed.

The activities of NoPSC continue to have local and international ramifications. Within the Research Institute of Internal Medicine and at collaborating hospitals in Norway, several projects now rely on NoPSC infrastructure and technical skills. These collaborations mutually enrich the NoPSC research agenda with complementary expertise and also serve as a means of securing broader implications from the PSC research. The International PSC Study Group (IPSCSG) has become a great success, and now serves as the coordinating forum for all PSC research world-wide. While the initiative originates from NoPSC, the momentum of the group is now formed by multiple strongly committed research institutions from more than 19 countries. In 2012, a two-day meeting of the IPSCSG was hosted and sponsored by the Hamburg PSC research group, attracting more than 50 participants.

An important responsibility for the leader of the management group is to consider critically the financial basis of NoPSC for the future. The project period supported by the generous donation from Canica A/S officially ends in 2017, and soon efforts must be made to ensure that the research activities can continue in the future. Maintaining the same scale of financing for a rare disease like PSC will be difficult regardless of the quality of our research, meaning we may also need to seek alliances for broader research themes. In addition to supporting now several positions at NoPSC from other funding sources (including Helse Sør-Øst), we were in 2012 part of the successful application to form a K.G. Jebsen Inflammation Research Centre, led by Prof. Guttorm Haraldsen. The center will finance one dedicated NoPSC post doc and three partially NoPSC affiliated post doc positions from 2013.

I wish to thank the staff of the NoPSC and all collaborators and contributors for their continued support and enthusiasm in 2012. We have all the good reasons to be proud, but many challenges remain and we must not rest on previous achievements.

Oslo 2013-05-12
Professor Tom Hemming Karlsen
Leader of NoPSC Management Group

NOPSC
Norwegian PSC Research Center

What is PSC?

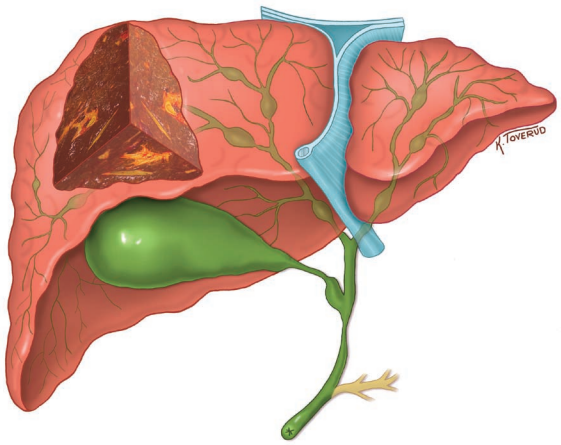
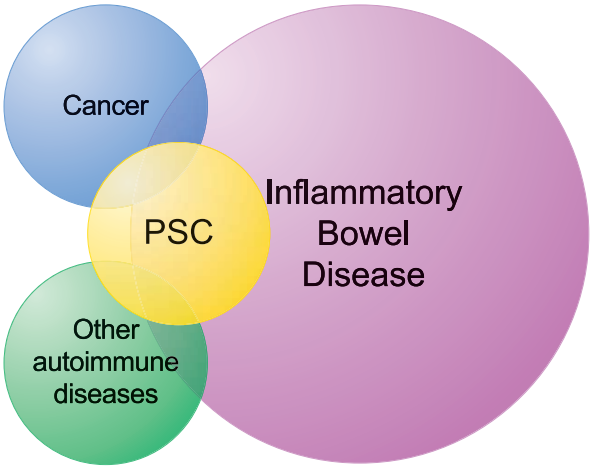


Illustration: © Kari C. Toverud, CMI (Certified Medical Illustrator)

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 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 average 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 2012

January 1st Tom Hemming Karlsen took over as leader of the management group at NoPSC, consisting of Tom Hemming Karlsen, Erik Schrumpf, Kirsten Muri Boberg and Espen Melum. September 1st, Erik Schrumpf retired from his position as Head of Section for Gastroenterology at the Department of Transplantation Medicine at Rikshospitalet and as university professor. Erik Schrumpf worked at Rikshospitalet for more than 30 years and we are pleased to know that he will continue to participate in the scientific projects at NoPSC and as member of the management group over the coming years.

The Immunochip project

In 2012, the finalizing steps of processing the PSC Immunochip data were performed. The PSC Immunochip study is the largest ever genetic study in PSC, and includes a total of 3,789 PSC cases (recruited from more than 200 hospitals) and 25,079 healthy controls. The study identified 9 new PSC genes, meaning that altogether 16 PSC genes have been discovered at NoPSC since the set out in 2008. The genes provide information about PSC pathogenesis and guides further research into diagnosis and treatment. Of particular importance is the identification of an additional 33 genes that are shared with other diseases, showing at what points PSC research is likely to be relevant across traditional disease boundaries. The results from the study will be published in Nature Genetics in the first half of 2013.

Establishment of the *in vivo* experimental working group

In June 2012 post doc Espen Melum returned to the NoPSC laboratory after having spent the last two years in Prof. Richard Blumberg's laboratory at Harvard (Brigham and Women's Hospital), Boston, US. The skills acquired during this post doc exchange was throughout fall of 2012 translated into an extensive expansion at the local animal facility to allow for *in vivo* studies on immune regulation in mice. The activities build on the genetic findings, and is planned to expand rapidly to enable the forming of an independent experimentally focused research group under the NoPSC umbrella in 2013. See further presentation at page 8.

Establishment of the gut microbiota working group

The gut microbiota interacts with the immune system and bile acid metabolism. As also guided by the genetic findings, the study of gut microbiota in PSC patients has become a prioritized assignment at NoPSC, and the project is firmly led by post doc Johannes R. Hov. In 2012 NoPSC established routines for efficient sampling and processing of intestinal biopsies and feces. Several patient groups and large, well-characterized healthy control populations are currently being enrolled for these studies. See further presentation at pages 6 and 13.

Annual guest professor meeting

In September, all NoPSC research projects underwent critical evaluation by our guest professors Andre Franke and Arthur Kaser. Since the group is now too big for plenary discussions to be productive, all projects were discussed in relevant sub-groups, and project plans were adjusted according to the highest possible standards. In November, Prof. Kaser ended his 3 year long employment as guest professor, but the collaboration will continue by the establishment of a joint project aimed at determining the immunological and clinical implications of the PSC risk gene GPR35. This project will have extensive activities both in Prof. Kaser's laboratory in Cambridge and at NoPSC. Prof. Kaser will from January 1st 2013 be replaced by Prof. Fredrik Bäckhed. See separate presentation at page 11.

Erik Schrumpf honorary symposium

September 6th a symposium was held at Oslo University Hospital, Rikshospitalet to honor Erik Schrumpf's long career, both as clinician within the field of gastroenterology and hepatology, and as active researcher with a main focus on PSC. The symposium covered the beginning, the present

Photo: Vemund Paulsen, OUS

Prof. Roger Chapman and Prof. Erik Schrumpf during the symposium. Prof. Chapman is a long time collaborator and friend of Prof. Schrumpf, and together with researchers from the Mayo Clinic in Rochester, US, they were involved in the first series of systematic PSC research in the early 1980's.

and the future of research in hepatology with presentations from both local and international collaborators. Invited speakers were Prof. Roger Chapman (Oxford, UK), Prof. Krister Höckerstedt (Helsinki, Finland), Prof. Andre Franke (Kiel, Germany) and Prof. Arthur Kaser (Cambridge, UK). A formal honorary dinner was held in the evening.

International PSC study group

NoPSC organized two meetings of the International PSC Study Group throughout 2012. Multiple projects are performed within this group (see separate presentation at page 16), not only those driven and financed by NoPSC. The group has attracted some of the leading scientists in the field of liver diseases in general and is now considered the main international arena for development and discussion of PSC projects in need of collaborative efforts.

Establishment of satellite biobank at Haukeland University Hospital

During the fall of 2012, post doc Mette Vesterhus established a new biobank at Haukeland University Hospital, based upon the same infrastructure and SOPs as the NoPSC biobank at Rikshospitalet. Bioengineer Aud Sissel Hjartholm assists in the sample processing. The biobank will include patients for prospective follow-up, i.e. patients will be seen annually, both for blood sample collection and for imaging, something which is not feasible at Rikshospitalet as a tertiary referral center for liver transplantation. 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 University Hospital in Bergen.

Procurement of a web-based biobank system for the South-Eastern Regional Health Authority

During 2012, Hege Dahlen Sollid participated in the eBiobank project, a co-operative project within the South-Eastern Norway Regional Health Authority. The main scope for the project was the acquirement of the same web-based biobank sample information management and tracking system for all hospitals in the region. The project started in 2008, and Sollid was recruited in 2012 as an experienced user of the NoPSC biobank system. Sollid made case scenarios for the venders to demonstrate their system by. In addition, Sollid participated in the evaluation of the vendors. In 2013 pilot groups will start to use the selected biobank system (Labware), and during 2014 a modified version of the Labware biobank system will be ready for all research groups.

AWARDS

First author Trine Folseraas (in the middle of the picture) is accepting the award on behalf of NoPSC for best original paper (six awards) at Oslo University Hospital for second half of 2012.

Photo: Ram Eivind Gupta, OUS

Erik Schrumpf was assigned Honorary President of EASL for the year 2012 – 2013 during the International Liver Meeting™ in Barcelona 2012.

Tom Hemming Karlsen was awarded the United European Gastroenterology recognition award to young scientists for his work performed in determining disease genes in ulcerative colitis and PSC.

Trine Folseraas and **Espen Melum** were given the price for one of top six outstanding original papers July – December 2012 from Oslo University Hospital (see picture above).

Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci
J Hepatol, 57 (2), 366-75

Folseraas T, **Melum E**, Rausch P, Juran BD, Ellinghaus E, **Shiryaev A**, Laerdahl JK, Ellinghaus D, Schramm C, Weismüller TJ, Gotthardt DN, **Hov JR**, Clausen OP, Weersma RK, Janse M, **Boberg KM**, Björnsson E, Marschall HU, Cleynen I, Rosenstiel P, **Holm K**, Teufel A, Rust C, Gieger C, Wichmann HE, Bergquist A, Ryu E,Ponsioen CY, Runz H, Sterneck M, Vermeire S, Beuers U, Wijmenga C, **Schrumpf E**, Manns MP, Lazaridis KN, Schreiber S, Baines JF, Franke A, **Karlsen TH**

Kristin Kaasen Jørgensen was awarded Helge Bell´s price for good clinical research in hepatology for 2012. The price is given on an annual basis for the best Norwegian article published in the area of clinical or translational basic research in hepatology.

Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients
Inflamm Bowel Dis, 18 (3), 536-45

Jørgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, **Schrumpf E**, Vatn MH, **Boberg KM**

NoPSC project update

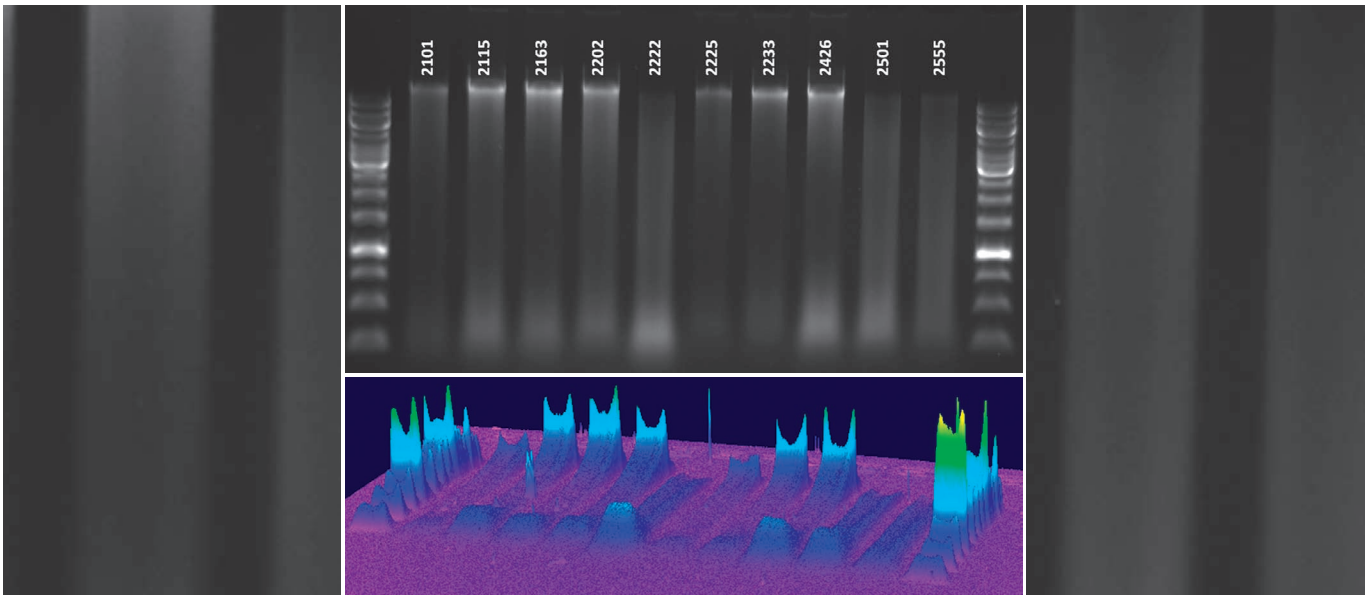
Genomic studies

PRINCIPAL INVESTIGATOR: **Tom Hemming Karlsen** AFFILIATED POST DOCS: **Johannes R. Hov**, **Espen Melum**, one new post doc to be assigned during 2013
AFFILIATED PHD STUDENTS: **Trine Folseraas**, **Sigrid Næss**, **Bjarte Fosby**, **Martin Kummen** (from 2013)

During 2012 several genetic studies in PSC and ulcerative colitis (UC) at NoPSC were completed with publications in high ranking journals (two important PSC articles appeared in Hepatology and Journal of Hepatology, respectively, and we contributed to one UC article published in Nature). Importantly, the group also completed the Immunochip project, which included approximately 4,000 PSC patients recruited from more than 200 hospitals in 14 different countries. The recruitment and DNA collection alone had taken more than 5 years to accomplish and the genetic data from the patients were analyzed together with data from 25,000 healthy controls to define 9 new PSC genes. In total, the PSC genetics group at NoPSC has thus in total identified 16 PSC genes. In addition, the group identified 33 genes that were shared with other immune mediated diseases, potentially allowing for transfer of pathogenetic knowledge, and even therapeutics, between PSC and these diseases (UC, Crohn's disease, sarcoidosis, psoriasis, celiac disease, type 1 diabetes and rheumatoid arthritis). The article reporting on the project will be published in Nature Genetics in 2013. Two other large-scale genetic analyses (genome-wide association studies from the UK and the US, altogether more than 2,500 patients) have also been supported by the NoPSC genomics group in 2012 and will be completed throughout 2013 together with several smaller projects.

The most important genetic risk locus in PSC remains the HLA complex on chromosome 6. Following several rounds of technology improvement, the 200,000 Euros obtained from the EU ESGI program (www.esgi-infrastructure.eu/) has successfully resulted in the ability to exactly determine the genetic sequence at the genes within this region. Several projects reporting on the details of the HLA association in PSC and UC, as well as in PSC with small-duct affection only and IgG4-associated PSC, were completed and will be published in 2013. In collaboration with several other groups, the sequencing data from the new technology will be incorporated with data on T- and B-cell reactivity, as well as autoantibody profiles, with the overall aim to identify the factor (antigen) responsible for the HLA-related immune response. As exemplified in celiac disease (where removal of gluten from the diet cures the disease), the identification of HLA related antigens may be extremely important for disease prevention and understanding pathogenesis.

Bile acids are metabolized by intestinal bacteria and some of these metabolites are ligands for nuclear receptors involved in metabolic and immunological regulation, e.g. farnesoid X receptor which is a regulator of cholesterol, triglyceride and bile acid synthesis. Given the influence of PSC risk genes (e.g. FUT2) on intestinal bacterial composition (the gut "microbiota") defined by the genetic studies, this opens research avenues of broad relevance for not only a bile duct disease like PSC, but also other inflammatory diseases and even cardiovascular disorders. Throughout 2012, sample collection and preparation protocols (stool and intestinal biopsies) for genomic based analysis of bacteria (the "microbiome") were established at NoPSC, and analysis in PSC and a wide range of control conditions (healthy as well as diseased) was initiated. Data from the analyses show that the gut microbiota in PSC differs from that of other diseases and the healthy state. This opens up for the possibility to treat PSC



not only by interfering with immune function, but also via influencing the gut bacteria (e.g. by diet, antibiotics or pro/pre-biotics). One intervention study has already been initiated.

The track record for advanced genomic analysis at NoPSC has also made the new skills in microbiomics an attractive resource for those studying the role of gut bacteria in other diseases (e.g. atherosclerosis). To supervise during the expansion of this important aspect of research at NoPSC, Prof. Fredrik Bäckhed from Gothenburg was appointed as the new guest professor for the period 2013 – 2015 (after Prof. Andre Franke, Kiel). The aim of the further expansion of the gut microbiota project portfolio throughout 2013 – 2014 is to make the activity autonomous under the leadership of post doc Johannes R. Hov. The remaining HLA-related immunogenetics of the genomics group will in parallel be incorporated in the activities of the newly established K.G. Jebsen Inflammation Research Centre. Read more on the web pages:
www.med.uio.no/klinmed/english/research/centres/kgj-inflammation/

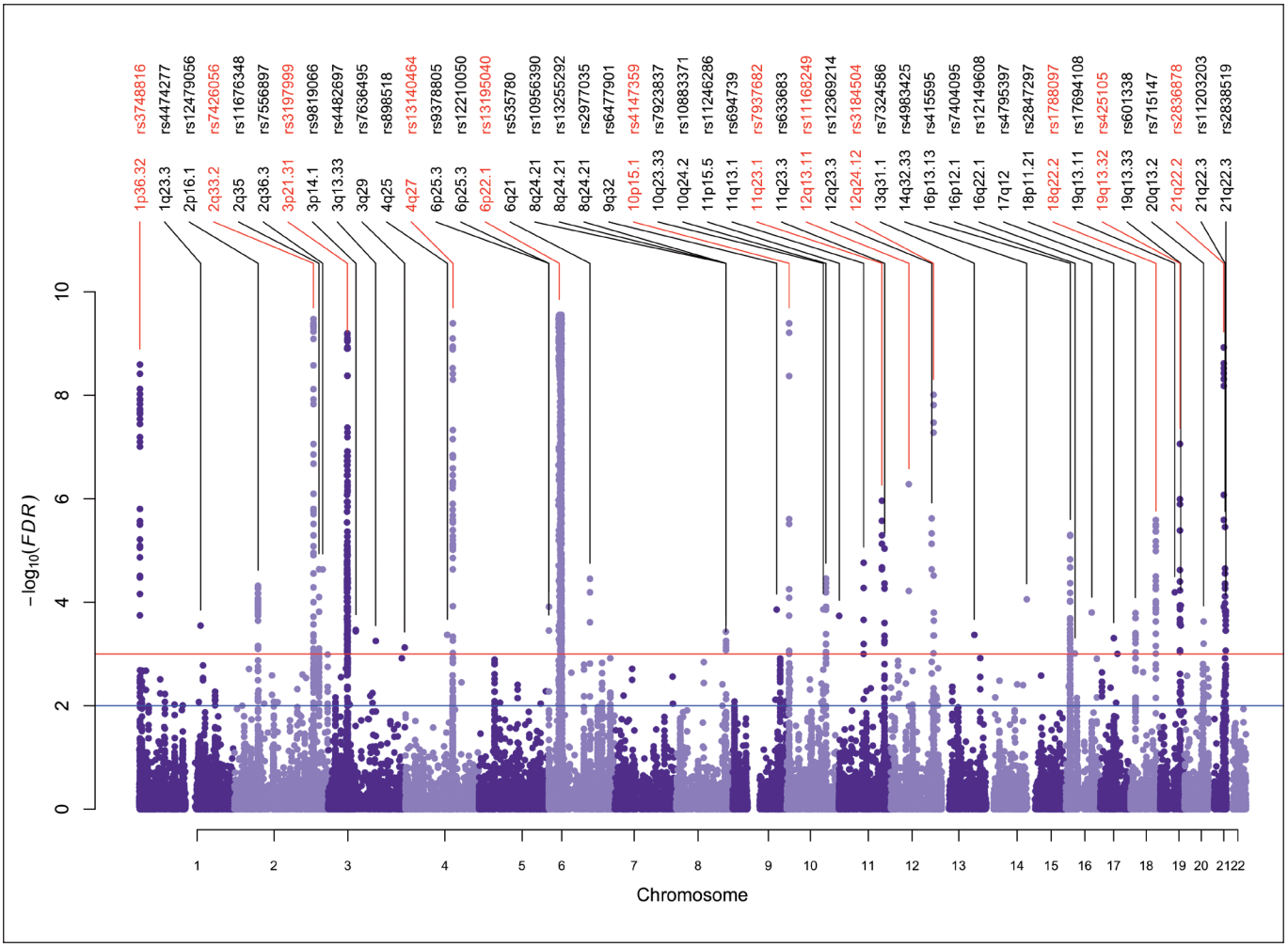
The genetic studies at NoPSC has overall detected 16 PSC risk genes which demonstrates that PSC is a separate disease, not only a complication to inflammatory bowel disease. In addition, which is shown in the figure, we have detected 33 genes that are shared between PSC and other immune-mediated diseases like type 1 diabetes, celiac disease, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis. Jointly, all these genes have opened up the avenues for research into PSC pathogenesis and therapy that are presently being explored.

REFERENCE

Liu JZ, Hov JR, Folseraas T, Ellinghaus E, et. al

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

Nat Genet (2013) 45 (6), 670-5



NoPSC project update

Experimental studies

PRINCIPAL INVESTIGATOR: **Espen Melum**, **Tom Hemming Karlsen** AFFILIATED POST DOCS: **Alexey Shiryaev** (until spring 2013), one new post doc to be assigned during 2013
AFFILIATED PHD STUDENTS: **Elisabeth Schrumpf**, two new PhD students to be assigned during 2013

Photo: Øystein H. Horgmo, UiO

The work performed by post doc Espen Melum during his two year stay at Harvard forms the basis for several of the experimental research activities taking place at NoPSC. In 2013 these activities are intended to segregate as a separate research group within NoPSC under the leadership of Melum.

The work initiated at Harvard will be completed in 2013 and report on several novel aspects of the regulation of natural killer T cells (NKT cells) of relevance to PSC. NKT cells form an important regulatory lymphocyte population in the liver and hold prospects as targets for therapeutic interventions aimed to reduce liver and bile duct injury during inflammation.

As a part of transferring the tools required for his own experiments to NoPSC from Harvard, Melum has gradually throughout 2012 transformed and expanded the previous laboratory capacities of NoPSC with state-of-the-art animal research models that also incorporates several PSC models. This work involved integration with other groups working in mice model systems at the Research Institute of Internal Medicine, that has generously provided space for the rapidly expanding activity.

Two models for sclerosing cholangitis will incorporate with the studies on NKT cell function, one spontaneous (PhD student Elisabeth Schrumpf), one induced (new PhD student). Various means of manipulating NKT cell function will be explored *in vivo* and *in vitro* with the ultimate aim of determining novel strategies for the treatment of immune mediated sclerosing cholangitis. The work has involved extensive *in vitro* characterization of the antigen-presenting capabilities of cholangiocytes and will be published in 2013.

In addition to the NKT-related projects, one of the risk genes detected by the genomics group will be explored in a collaborative project with previous guest professor Arthur Kaser in Cambridge. The project was set up during the final year of the post doc period of Alexey Shiryaev and the first *in vivo* and *in vitro* data suggests a critical role in immune regulation and epithelial cell function resulting from loss of gene function. The further work-load of the extensive work package will be split between Oslo and Cambridge in a manner where the Oslo group (new PhD student, Oslo funded) will focus on the *in vitro* experiments and further genetic work in humans, whereas the Cambridge group will focus on work in the mouse models (several mouse models of relevance already available) and aspects related to therapeutic manipulation (Cambridge PhD student Zaeem Cader, Cambridge funded).

The experimental research is time- and resource demanding, particularly when involving animal models. The translational aspect represented by the studies is nevertheless required to move from the basic genomic and clinical characterization into an understanding of disease mechanisms in PSC that may ultimately be relevant to patient management. The projects will integrate with the activities of the newly established K.G. Jebsen Inflammation Research Centre (which will provide funding for one full post doc position for an exploration of a novel gene found by the genomics group to cause PSC in a Swedish family), and also involve multiple aspects related to the gut microbiota (germ free as well as colonization/manipulation) project portfolio. To supervise during the expansion of the experimental aspects of research at NoPSC, Prof. David Adams from Birmingham has been appointed as guest professor for the next three year period.

NoPSC project update

Clinical studies

PRINCIPAL INVESTIGATOR: **Kirsten Muri Boberg**, **Tom Hemming Karlsen**, **Erik Schrumpf** AFFILIATED POST DOCS: **Anders Holm** (until spring 2013), **Mette Vesterhus**, **Johannes R. Hov**, one new post doc to be assigned during 2013 AFFILIATED PHD AND MD STUDENTS: **Kristin Kaasen Jørgensen**, **Kim Andresen**, **Ina Marie Andersen**

Two of the PhD students within the clinical studies work-package completed their work throughout 2012 and will defend their PhD thesis during 2013. Kristin Kaasen Jørgensen's thesis involves three articles related to inflammatory bowel disease in PSC, focusing on disease characteristics before and after liver transplantation and risk factors for the development of colonic cancer in patients with PSC. Kim Andresen's thesis involves several works related to biomarkers for early cholangiocarcinoma detection in patients with PSC at the epigenetic level performed together with the groups of Guro Lind and Prof. Ragnhild Lothe, OUS, Radiumhospitalet. The development of cholangiocarcinoma remains one of the main clinical challenges in managing patients with PSC and since diagnosis is typically late, cholangiocarcinoma is still a leading cause of death among the patients. The clinical studies group has also been involved in studies of biomarkers for cholangiocarcinoma in urine, from which one article was published in 2012. The cholangiocarcinoma projects will continue with high priority in 2013, aiming to benefit from the extensive genomic experience of Trine Folseraas after she has completed her PhD thesis (i.e. as post doc).

Another clinical challenge in PSC is to determine disease severity. This is not only of interest to the individual patient who wants to know his risk of developing liver failure over time, but also for performing clinical trials of new drugs. When testing new drugs in PSC, it is difficult to know whether the drug is effective or not, for the simple reason that simple markers for measuring disease activity (e.g. a blood test) hasn't been available. Over a period of two years, post doc Anders Holm has set up a system to measure the level of more than 1,700 proteins in bile. The system has been applied to bile from patients with PSC that has undergone cholangiography as part of the clinical investigation and has resulted in the determination of a biomarker panel that seems to measure quite reliably disease activity in patients with PSC. The findings were also tested in blood samples and analyzed with the help from post doc Mette Vesterhus and post doc Johannes R. Hov, and the complete results from this major effort will be published in 2013. As part of her post doc period, Vesterhus plans to measure the same markers in blood samples from PSC patients followed over time (5 years). The prospective collection of samples over time will not only be done in Norway, but also involve more than 1,000 PSC patients world-wide, allowing for refinement of the markers already available. The international cohort will also collect urine for biomarkers for cholangiocarcinoma to be tested before as well as at early and established stages of malignancy, and may thus also improve these biomarker test panels.

The diagnosis of PSC also remains a challenge. Early diagnosis is probably required for medical treatment to be effective. As part of the combined position of post doc Mette Vesterhus at both NoPSC and the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at the Haukeland University Hospital in Bergen, patients in the Norwegian PSC cohort will undergo annual ultrasound and magnetic resonance imaging (MRI) with improved techniques for better detection of strictures and fibrosis. MRI of the bile ducts has also throughout 2012 been performed for all patients in the 20 years follow-up of the Inflammatory Bowel Disease in South Eastern Norway (IBSEN) study. This has led to new figures for the frequency of PSC among patients with inflammatory bowel disease. Comparison of the imaging findings in the IBD patients with the new biomarker panels will be performed throughout 2013.

Ultimately, the studies of PSC pathogenesis in the genomic and experimental studies aim to provide targets for effective medical treatment in PSC. So far, endoscopic treatment and liver transplantation remains the only effective management. Erik Schrumpf and research nurse Mona Bjørnstad have throughout 2012 established the practical and formal requirements for clinical trials participation at NoPSC. The first study, enrolling patients early 2013, is the nor-ursodeoxycholic study from the pharmaceutical company FALK. NoPSC plans to participate actively in clinical trials also from other pharmaceutical companies. Ultimately, the logistics and the local infrastructure experience set up in this work will prepare the organization for performing NoPSC-initiated clinical trials when availability of potentially effective targets and pre-clinical assessments allows for it over the coming few years.

Point Shear Wave Elastography of the right liver lobe, where a region of interest (ROI) is marked by a ROI cursor (rectangular box) between 2 cm below the liver capsule and 8 cm from the skin surface, and shear wave velocity (SWV) is measured and reported in m/s. SWV > 1.8 m/s is reported to correspond to cirrhosis. Elastography forms only a small part of the extensive prospective follow-up of patients now undertaken internationally to determine end-points for clinical trials and prognostic markers in PSC.

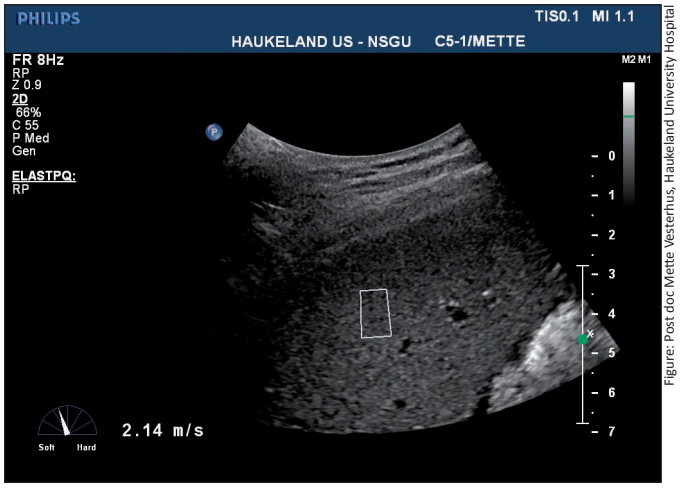


Figure: Post doc Mette Vesterhus, Haukeland University Hospital

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 now 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 2012

- **Genomic studies** (page 6)
- **Experimental studies** (page 8)
- **Clinical studies** (page 9)

Photo: Tone Thorbjørnsen

NoPSC IS ORGANIZED WITH A MANAGEMENT GROUP, A CORE UNIT, THE PROJECT UNITS AND AN ADVISORY BOARD

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 core unit runs support functions of general importance for the project units and the research center in general. This includes a state-of-the-art biobank and data registry in the MEDinsight database (clinical, technical and biological information). In addition, all projects are given laboratory assistance, and the technical level in e.g. HLA typing is world class. We also have a dedicated bioinformatician, who is providing computer support on all levels. Administrative support is also given by personnel in the core unit.

The project units of NoPSC are defined by priorities of the management group *(see project description on pages 6-9)*.

The advisory 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 ADVISORY BOARD:

Ivar Prydz Gladhaug *Leader*	Institute of Clinical Medicine University of Oslo
Hans Mossin	Institute of Clinical Medicine University of Oslo
Kristian Bjøro	Division of Cancer Medicine, Surgery and Transplantation Oslo University Hospital, Rikshospitalet
Pål Aukrust	Division of Cancer Medicine, Surgery and Transplantation Oslo University Hospital, Rikshospitalet
Nina Paulsen	Canica A/S
Peter Ruzicka	Canica A/S

People at NoPSC in 2012

Management group

Tom Hemming Karlsen
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New guest professor

Fredrik Bäckhed
Guest professor at our research center from January 1st 2013.

Fredrik Bäckhed is professor at the Institute of Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden. Bäckhed is an expert in cellular microbiology and mouse physiology, and combines clinical oriented research with gnotobiotic mouse models to address the role of the gut microbiota various disease states.

Fredrik Bäckhed has a PhD from the Microbiology and Tumor Biology Center, Karolinska Institute in Stockholm. He has received several prestigious awards, among these the Chorafas Prize (2003), Ingvar Carlsson Award (2006), Dr Eric K Fernström Foundation's Prize to Young Swedish Scientists (2010) and The DPLU/LUDC Nordic Prize for an Outstanding Young Diabetes Investigator (2010). He has been elected to the Young Academy of Sweden hosted by the Royal Academy of Sciences (2011). He is a regularly invited speaker at international scientific meetings, sits in several trusts, has written book chapters and holds three patents. His publication list now holds more than 56 papers in prestigious journals like Nature and Science.

Three most important publications:

1. Reinhardt C., Bergentall M., Greiner T.U., Schaffner F., Österlund-Lundén G., Petersen L.C., Ruf W., Bäckhed F. (2012) **Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling.** Nature. 483: 627-631

2. Sayin, S. I., Wahlström A., Felin J., Jäntti S., Marschall H.U., Bamberg K., Angelin B., Hyötylöinen T., Orešič M., Bäckhed F. (2013) **Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-betamuricholic acid, a naturally occurring FXR antagonist.** Cell Metabolism. 17(2):225-35.

3. Karlsson F., Tremaroli V., Nookaew I., Bergström G., Behre C. J., Fagerberg B., Nielsen J., Bäckhed F. (2013) **Gut metagenome in European women with normal, impaired and diabetic glucose control.** Nature. In Press.

More information, please see:
www.wlab.gu.se/backhed

Kristian Holm
– at the computational vertex of PSC research

NoPSC currently has one bioinformatician in the group, Kristian Holm, who joined the team in 2008. Holm has a cand.scient. degree in informatics from the University of Oslo. He has a large number of projects in progress, and collaborates with statisticians and bioinformaticians from Christian-Albrechts University in Kiel.


Photo: Øystein H. Horgmo, UiO

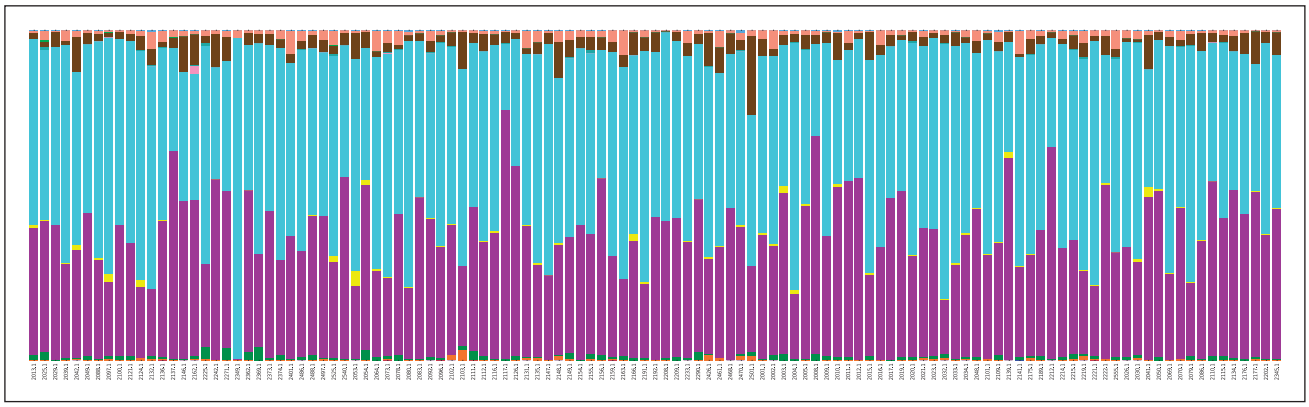
In biology, bioinformatics is an interdisciplinary field that develops and improves upon methods for storing, retrieving, organizing and analyzing biological data. The primary goal of bioinformatics is to increase the understanding of biological processes with focus on developing and applying computationally intensive techniques to achieve this goal. For the purpose of processing and interpreting the biological data, bioinformatics uses many areas of computer science, mathematics and engineering.

During the years NoPSC has been involved in several projects where different levels of bioinformatic involvement have been crucial. The genome-wide single nucleotide polymorphism (SNP) association studies around 2008 were our first major task at this and created a foundation for later work. Knowledge was established for handling relatively large data sets of more than 1,000,000 DNA variants in thousands of individuals, and computationally intensive statistical methods were applied.

As part of many projects, gene expression studies using microarrays and later full transcriptome sequencing (RNAseq) have been conducted. These arrays reveal the expression of many thousands of genes simultaneously. For the RNAseq applications, a whole new set of software tools were needed for the processing of the massive amounts of data created by this technology. Hundreds of millions of short sequences (a few hundred base pairs each) needed to be positioned at its best match in a reference genome.

As part of the efforts in determining the role of gut microbiota in PSC pathogenesis, high throughput sequencing of the 16s rRNA gene in bacteria found in the human gut has been performed. Also here the data handling and analysis has required new software tools. The large natural variations of the microbiota in all humans are one of the many challenges in these studies, and as rapidly as this field is currently developing, the bioinformatic challenges are increasing.

For a selection of these projects, neither data handling nor analysis would be possible without access to the computer cluster facility at the University of Oslo. It allows us to run many computational tasks in parallel, where each require both memory capabilities and computing power far beyond those of a desktop computer.



Distribution of bacterial phyla in a normal population. Each vertical bar-plot represents one individual. Each color represents the relative abundance of one bacterial species.

NoPSC infrastructure
– an important resource beyond PSC

Due to skills and our particular interest in inflammatory diseases of the intestine and the impact of the gut microbes (microbiota) on disease development, NoPSC is now an interaction partner in multiple collaborative efforts.

Together with Dr. Knut Lundin and the IBSEN study group we have developed a structured protocol for biobanking of biological material from patients with various intestinal diseases at the Section for Gastroenterology, Oslo University Hospital (OUS), Rikshospitalet. The biobank is built into the existing infrastructure developed for NoPSC. These samples will be of value for many types of studies, both within NoPSC and in research groups with a slightly different focus.

Common variable immunodeficiency (CVID) is an immunodeficiency state characterized by chronic inflammation and autoimmunity, including liver and intestinal disease. The CVID samples collected within the NoPSC infrastructure are intended for several projects at the Department of Infectious Diseases, OUS Rikshospitalet. In collaboration with the core unit of NoPSC, the CVID group has also performed a large-scale cross sectional stool sampling with a pipeline established in 2012 (see picture). This pipeline was developed within NoPSC to collect samples from patients with PSC, inflammatory bowel disease (IBD), CVID, and other patient groups as well as healthy controls. The same infrastructure and routines are also used by researchers at the University of Bergen (Torunn Fiskerstrand and Rune Tronstad) in the study of a familial chronic diarrheal condition caused by mutations in the GUCY2C gene that they recently characterized (Fiskerstrand et al., N Eng J Med, 2012).

During 2012, we have established collaborations with the Department of Cardiovascular Disease at OUS, Rikshospitalet. The collaboration was initiated together with the research groups at Research Institute of Internal Medicine that have their focus on inflammation and atherosclerosis (led by prof. Pål Aukrust and Arne Yndestad). The basis of the collaboration is the close interaction between bile acid metabolism and lipid metabolism on one side and inflammation and gut microbiota on the other. With

Photo: NoPSC

Equipment used for stool sampling.

the help of our fecal sampling pipeline, a project is now initiated to explore the effects of cardio protective drugs on the gut microbiota. The project pipeline will serve as a model when similar treatment efforts can potentially be undertaken in PSC.

Besides the biobank for intestinal diseases, we have also initiated another collaborative project to further study the particular relationship between PSC and IBD. A large cohort of patients with IBD has been followed since the early 1990s in the Inflammatory Bowel diseases in South Eastern Norway (IBSEN) study, led by prof. Morten Vatn and prof. Bjørn Moum. As part of the ongoing 20 year follow-up, all individuals will also be offered to perform magnetic resonance imaging (MRI) of the bile ducts to determine whether PSC is present. The proposal has increased collaboration with the IBSEN study group even further, and the NoPSC biobank framework is used for long-term storage for some of the collected blood samples in the IBSEN 20 study.

Overall, several collaborative efforts have been initiated at the interface of research fields related to PSC and the multiple other conditions where intestinal phenotypes and gut microbes may be of relevance. As illustrated above, these are not pure scientific collaborations, but also do involve our infrastructure for biobanking and bioinformatics.

Collaborators

KEY LOCAL COLLABORATORS

RESEARCH INSTITUTE FOR INTERNAL MEDICINE

NoPSC is both affiliated with Research Institute for Internal Medicine (RIIM) (*www.ous-research.no/riim*) as a research center, but also as a separate research group led by Tom Hemming Karlsen (*www.ous-research.no/karlsen/*). Several collaborative projects are now established with the other research groups at RIIM and all employees of NoPSC participate in the every-day activities at the institute.

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 (*www.surgicalresearch.net/*) 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 and Dr. Grzyb Krzysztof 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.

INSTITUTE OF IMMUNOLOGY

NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular, the good collaboration with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, is important in the activities of NoPSC.

DEPARTMENT OF MEDICAL BIOCHEMISTRY

In conjunction with post doc Hov's IgG4 project and the establishment of a quality control cohort for the NoPSC biobank, collaboration with respectively Dr. Olav Klingenberg and Dr. Yngve Thomas Bliksrud is highly appreciated.

CENTER FOR CANCER BIOMEDICINE

A collaboration with Prof. Ragnhild Lothe's group, and senior researcher and project group leader Guro Lind in particular, at the Department of Cancer Prevention, OUS, Radiumhospitalet (*www.ous-research.no/cancerprevention/*), is the basis for our projects on diagnosis of cholangiocarcinoma in PSC.

KEY NATIONAL COLLABORATORS

THE IBSEN STUDY GROUP

The infrastructure utilized in our projects on IBD in PSC (biobank, protocols etc.) is derived from the IBSEN II project. The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is also important for basic genetic studies. Blood samples of patients undergoing magnetic resonance cholangiography (MRC) in the follow up project, IBSEN20, are deposited in the NoPSC biobank. Dr. Anne Nergård is 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

(*http://inflammation-at-interfaces.de/?set_language=en* and *www.ikmb.uni-kiel.de/cms/en/about-us/staff/staffpage/andre-franke/*)
Several co-workers of Prof. Stefan Schreiber in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and translational projects. Prof. Andre Franke is assigned as guest professor to participate in this work package.

JOHN RADCLIFFE HOSPITAL OXFORD, UK

(*www.ouh.nhs.uk/services/departments/gastrointestinal/gastroenterology/default.aspx*)
Prof. Roger Chapman has set up a consortium of key hepatologists in the UK with financial and infrastructural (database and protocols) support from NoPSC. The initiative 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, Dr. Richard Sandford, Dr. Brijesh Srivastava and Dr. Carl Anderson).

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 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.

UNIVERSITY OF BIRMINGHAM, BIRMINGHAM, UK

(*www.birmingham.ac.uk/staff/profiles/iandi/hirschfield-gideon.aspx* and *www.birmingham.ac.uk/staff/profiles/iandi/adams-david.aspx*)
Dr. Gideon Hirschfield and Prof. David Adams 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

(*http://mayoresearch.mayo.edu/lazaridis_lab/*)
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.


Photo: Shutterstock

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 project 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/* and *www.meduniwien.ac.at/index.php?id=372&language=2*)
In collaboration with Prof. Michael Trauner and Dr. 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, Dr. 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

(*http://ki.se/ki/jsp/polopoly.jsp?d=41833&l=en*)
Associate professor Annika Bergquist is 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 co-workers Carlo Selmi and 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 bio-markers for cholangiocarcinoma in PSC.

LIVER CENTER, YALE UNIVERSITY, NEW HAVEN, USA AND UNIVERSITY OF PADOVA, ITALY

(*www.celiver.org/index.php*)
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 2013, 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 ongoing studies and meetings are held biannually during the International Liver Congress™ (ILC™) by European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) conferences. During 2012 the group first met in Barcelona during the ILC™ April 20th and then in Boston during AASLD November 12th.

In addition, IPSCSG meets every second year for a two-day focus workshop, in 2012 hosted and sponsored by the Hamburg PSC research group of Prof. Christoph Schramm and Prof. Ansgar Lohse at the Hotel Hafen in Hamburg, June 11-12th. Four different working groups were held as parallel sessions, facilitating detailed discussions focusing particularly on development of the database for clinical studies and prospective biobanking, cholangiocarcinoma, the role of gut microbiota in PSC as well as further development of the basic research groups within the IPSCSG.

DURING 2012 THE GROUP HAS MADE PROGRESS ON SEVERAL TOPICS:

- Contributions to the Immunochip project completed (DNA from >4,000 PSC patients)
- Collection of clinical data from 7,500 PSC patients for a clinical descriptive review
- Multicenter study to evaluate the utility of Fibroscan in determining disease progression in PSC
- Multiple contributions to the pruritus GWAS study led by George Mells
- Multiple contributions to the US/UK GWAS meta-analysis
- Participation in clinical trials (Dilstent2, nor-ursodeoxycholic acid)

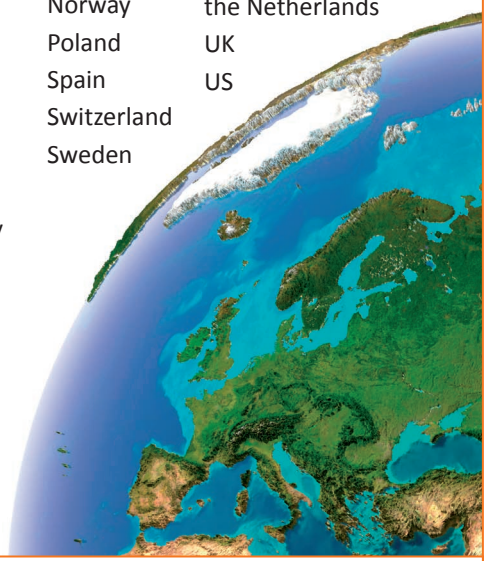
PLANNED MEETINGS IN 2013:

During the ILC™ in Amsterdam IPSCSG will have two meetings; Wednesday April 24th a joint workshop will be held within the official EASL ILC program and at Friday April 20th the biannual meeting will take place. The group will also meet in November during AASLD in Washington DC for the second biannual meeting. The next two-day meeting will be hosted and sponsored by the Amsterdam PSC research group (June 2014).

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***

Communications

NoPSC international lectures 2012

Karlsen TH.
Genetics of primary sclerosing cholangitis
John Squire Club, School of Immunity and Infection and the MRC Centre for Immune Regulation, University of Birmingham Medical School.
Birmingham, UK, February 17th

Boberg KM.
Current consensus on the management of primary sclerosing cholangitis
Fortis International Liver Summit 2012
Chandigarh, India, March 9th

Boberg KM.
Role of liver transplantation in PSC
Fortis International Liver Summit 2012
Chandigarh, India, March 10th

Jørgensen KK.
Colorectal neoplasia/PSC
Nordic Liver Transplant Group (NLTG) meeting
Stockholm, Sweden, March 19th

Boberg KM.
Grand Round Session on Cholestatic Liver Disease
Invited organizer and moderator of the Grand Round Session
International Liver Congress
Barcelona, Spain, April 20th

Boberg KM.
Timing of transplantation for sclerosing cholangitis
International Liver Congress.
Early morning workshop
Barcelona, Spain, April 21st

Boberg KM.
Cancer in primary sclerosing cholangitis
Digestive Disease Week (DDW)
San Diego, USA, May 19th

Jørgensen KK.
Colorectal neoplasia in PSC patients undergoing liver transplantation: a Nordic multicenter study
Digestive Disease Week (DDW)
San Diego, USA, May 21st

Jørgensen KK.
Clinical course of inflammatory bowel disease in liver transplanted PSC patients: a Nordic multicenter study
Digestive Disease Week (DDW)
San Diego, USA, May 19th

Photo: United European Gastroenterology

Jørgensen KK.
Clinical course of inflammatory bowel disease in liver transplanted PSC patients: a Nordic multicenter study
24th international congress of the Transplantation society (TTS)
Berlin, Germany, July 16th

Karlsen TH.
Update on the genetics of primary sclerosing cholangitis
XXII International Bile Acid Meeting
Vienna, Italy, September 14-15th

Karlsen TH.
Primary Sclerosing Cholangitis
Oxford Master Class 2012
Oxford, UK, September 4-6th

Boberg KM.
Management of PSC in 2012
Annual Meeting, Swiss Gastro-enterological Association
Interlaken, Switzerland, Sept 20th

Karlsen TH.
Primary sclerosing cholangitis – is it always primary?
United European Gastroenterology Week (UEGW).
Amsterdam, the Netherlands, October 20-24th

Karlsen TH.
Genome-wide association studies in ulcerative colitis and primary sclerosing cholangitis
United European Gastroenterology Week (UEGW).
Amsterdam, the Netherlands, October 20-24th

Hov JR.
Survey of nongenetic risk factors suggests that tobacco exposure, coffee consumption, the use of oral contraception and the number of pregnancies could affect disease risk or presentation of primary sclerosing cholangitis
AASLD, The Liver Meeting
Boston, USA, November 9-13th

Karlsen TH.
Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis
AASLD, The Liver Meeting
Boston, USA, November 9-13th

Karlsen TH.
Novel insights into autoimmune liver diseases provided by genome-wide association studies
AISF - SIICA Joint Meeting
Milan, Italy, December 5-7th

Publications 2012

Photo: Øystein H. Horgmo, UiO

1. ***Andresen K, Boberg KM**, Vedeld HM, Honne H, Hektoen M, Wadsworth CA, Clausen OP, **Karlsen TH**, Foss A, Mathisen O, **Schrumpf E**, Lothe RA, Lind GE*
Novel target genes and a valid biomarker panel identified for cholangiocarcinoma
Epigenetics, 7 (11), 1249-57

2. ***Eskesen AN**, **Melum E**, Moghaddam A, Bjøro K, Verbaan H, Ring-Larsen H, Dalgard O*
Genetic variants at the ITPA locus protect against ribavirin-induced hemolytic anemia and dose reduction in an HCV G2/G3 cohort
Eur J Gastroenterol Hepatol, 24 (8), 890-6

3. ***Folseraas T, Melum E**, Rausch P, Juran BD, Ellinghaus E, **Shiryaev A**, Laerdahl JK, Ellinghaus D, Schramm C, Weismüller TJ, Gotthardt DN, **Hov JR**, Clausen OP, Weersma RK, Janse M, **Boberg KM**, Björnsson E, Marschall HU, Cleynen I, Rosenstiel P, **Holm K**, Teufel A, Rust C, Gieger C, Wichmann HE, Bergquist A, Ryu E,Ponsioen CY, Runz H, Sterneck M, Vermeire S, Beuers U, Wijmenga C, **Schrumpf E**, Manns MP, Lazaridis KN, Schreiber S, Baines JF, Franke A, **Karlsen TH***
Extended analysis of a genome-wide association study in primary sclerosing cholangitis detects multiple novel risk loci
J Hepatol, 57 (2), 366-75

4. ***Fosby B, Karlsen TH, Melum E***
Recurrence and rejection in liver transplantation for primary sclerosing cholangitis
World J Gastroenterol, 18 (1), 1-15

5. ***Holm A**, Wu W, Lund-Johansen F*
Antibody array analysis of labelled proteomes: how should we control specificity?
N Biotechnol, 29 (5), 578-85

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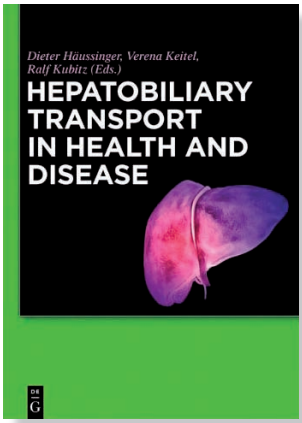
Scand J Gastroenterol, 47 (7), 820-6

General contributions in 2012



HEPATOBILIARY TRANSPORT IN HEALTH AND DISEASE

Editors: Häussinger D, Keitel V, Kubitz R
de Gruyter, Berlin, released in May 2012

Hov JR, Schrumpf E, Karlsen TH.
Molecular basis of primary sclerosing cholangitis

In this book chapter, the available data from genetics, experimental studies and animal models are discussed in order to define molecular mechanisms that can explain the clinical and pathologic characteristics of PSC. Please see annual report 2011 for more information.

Publicity in 2012

www.med.uio.no/om/aktuelt/aktuelle-saker/2012/internasjonalisering/norsk-senter-for-psc.html

Accounting 2012

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2011	3.481.023		69.209.085	
Interest			1.023.333	
Own share			256.475	
Reimbursement*	250.000			
Transfer from UiO	8.576.260			8.576.260
Wages		3.414.226		2.451.258
Wage related expenses		990.831		987.609
Overhead		580.650		674.381
Refund NAV			355.871	
Infrastructure/equipment		544.390		
Other operating expenses		3.984.922		2.813
Transfer to 2013 budget		**2.792.264**		**58.152.444**

*Reimbursement from Department of Cardiology due to laboratory establishment in 2008.
UiO accounting revised by Riksrevisjonen. OUS accounting revised by PricewaterhouseCoopers.

All sums are in Norwegian kr.

Photo: Øystein H. Horgmo, UiO

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UiO : University of Oslo

Oslo University Hospital

NoPSC PEOPLE IN THE PICTURE: ***Back:*** Johannes R. Hov, Kim Andresen, Ina M. Andersen, Anders Holm, Espen Melum, Kristian Holm, Jarl Andreas Anmarkrud, Alexey Shiryaev. ***Middle:*** Trine Folseraas, Erik Schrumpf, Mona Bjørnstad, Tom H. Karlsen, Kristin Kaasen Jørgensen, Liv Wenche Thorbjørnsen. ***Front:*** Kirsten Muri Boberg, Hege Dahlen Sollid, Sigrid Næss, Elisabeth Schrumpf. ***Not present:*** Bjarte Fosby, Mette Vesterhus

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