Leader’s comments

The 2nd full year of “Norsk Senter for primær skleroserende cholangitt” has come to an end. The structure of our group has largely been unchanged during 2009. The core facility still consists of 5 persons with Tom Hemming Karlsen in a full time leadership position. During 2010 most of the routine administration will be transferred from Tom to other persons in the core facility – in particular Hege Dahlen Sollid – so that Tom will be able to spend more time with the patients. Our main focus has also been unchanged: to construct a solid base for future research. In pursuing this goal we have

1. Continued our sampling of material in our biobank. By the end of 2009 the bank contains close to 23000 different samples from more than 300 individuals – most from PSC patients – but also from normal controls and other patients going to serve as controls. But equally important is the collection of DNA internationally which is now approaching samples from almost 4000 PSC patients.

2. Continued our building of relations with relevant groups nationally and internationally. The EASL Monothematic Conference on PSC which took place in Oslo June 21–23rd, 2009 was particularly important in this context. The list of top level invited speakers and the participation from all continents both secured the great success of the meeting and also contributed significantly to the building of important research relations.

3. Appointed Arthur Kaser from Innsbruck as guest professor at the University of Oslo with similar obligations as professor Andre Franke from Kiel: to visit our group twice annually and to participate actively in joint research projects.
The project groups “Cholangiocarcinoma in PSC” and “Inflammatory Bowel Disease in PSC” are unchanged and are headed by Kirsten Muri Boberg. The “Functional genetics in PSC” and “Hepatic transplantation in PSC”, both headed by Tom Hemming Karlsen, have from 2009 onwards been merged into one group. This group had by the end of 2009 four research fellows, the other two groups had one research fellow each. All have had significant progress, Espen Melum (Functional genetics) is defending his thesis May 2010. Johannes Hov (Functional genetics) and Kristin Kaasen Jørgensen (IBD in PSC) are both planning to submit their thesis before the end of 2010.

The paper “Catalytically impaired hMYH and NEIL 1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma” by M Forsbring, ES Vik, B Dalhus, TH Karlsen, A Bergquist, E Schrumpf, M Bjarås, KM Boberg and I Alseth, Carcinogenesis 2009; 30: 1147-54 received the price for the best Norwegian paper within hepatology 2009.

We are definitely optimistic for the future. We foresee an increasing output of scientific reports from our group in the years to come – as a result of the building up of the biobank, the tailormade database and the international collaboration combined with hard work within the group. In June 2010 we will host a meeting in Oslo with 43 participants from “all” major PSC research centres abroad. The main goal of the meeting is to establish The International PSC Study Group.

Erik Schrumpf
Leader of the management group

What is PSC?

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 Norway. 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. However, given an average time from diagnosis to liver transplantation of 10–15 years, PSC should be considered a serious and important condition.

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.
NoPSC 2009 in brief

Following the establishment of the formal infrastructure of the NoPSC in 2008, the main focus for 2009 was the creation of sustainable and autonomous activity at the core facility. This included the building of the new biobank-facility and the accompanying laboratory near the endoscopy ward at the 1st floor of Rikshospitalet.

The building activities were completed during the first half of 2009, and greatly accelerated the biobanking which by the end of the year had collected more than 20,000 specimens from several hundred patients and healthy controls. The employment of a dedicated research nurse for clinical data collection and patient management was also important.

KEY EVENTS IN 2009

The key event during 2009 was the hosting of the European Association for the Study of the Liver “Monothematic conference” on PSC in June with almost 150 participants from 36 countries from all over the world. In addition several other contributions were made, most importantly to the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases practice guidelines on PSC. In addition, the writing of the chapter on PSC in the upcoming Zakim and Boyer Textbook of Hepatology was an important summary of the expertise at NoPSC.

NoPSC personnel paid from the donation:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Date</th>
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<tbody>
<tr>
<td>Tom Hemming Karlsen</td>
<td>Exec. Manager</td>
<td>01.09.07 - today</td>
</tr>
<tr>
<td>Bente Woldseth</td>
<td>Laboratory</td>
<td>01.02.08 - today</td>
</tr>
<tr>
<td>Hege Dahlen Sollid</td>
<td>Biobank</td>
<td>01.03.08 - today</td>
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<tr>
<td>Liv Wenche Thorbjørnsen</td>
<td>Biobank</td>
<td>01.08.09 - today</td>
</tr>
<tr>
<td>Mona Skeivig</td>
<td>Research nurse</td>
<td>01.03.09 - today</td>
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<tr>
<td>Kristian Holm (50%)</td>
<td>Informatics</td>
<td>01.09.08 - today</td>
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<tr>
<td>Johannes Roksund Hov</td>
<td>PhD student</td>
<td>01.12.07 - today</td>
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<tr>
<td>Espen Melum</td>
<td>PhD student</td>
<td>15.08.08 - today</td>
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<tr>
<td>Kim Andresen</td>
<td>PhD student</td>
<td>21.11.08 - today</td>
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<tr>
<td>Trine Folseraas</td>
<td>PhD student</td>
<td>01.11.09 - today</td>
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<tr>
<td>Andre Franke (20%)</td>
<td>Guest professor</td>
<td>01.04.08 - today</td>
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<tr>
<td>Arthur Kaser (20%)</td>
<td>Guest professor</td>
<td>01.11.09 - today</td>
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KEY PLANS FOR 2010

- Strengthen collaboration in the international PSC research community by establishing an International PSC study group (startup meeting hosted in Oslo June 14th-15th 2010).
- Translational efforts in the genetics group with an emphasis on transforming genetic findings in 2008 and 2009 into knowledge on pathogenetic mechanisms.
- Characterize the overlap between PSC and other immune-mediated diseases by coordinating and genotyping a total of 4,000 PSC DNA samples in the “immunochip” project.
- Test novel cholangiocarcinoma markers in brush cytology and histological specimens.
- Characterize the clinical course of IBD in PSC following colectomy and liver transplantation.

KEY SCIENTIFIC ACHIEVEMENTS IN 2009

Work package 1: Establishing new methodologies. New PSC genes found and characterized.
Work package 2: Detection of new cholangiocarcinoma markers in a cell line system.
Work package 3: Clinical and histological characterization of IBD in 110 patients with PSC.
Work package 4: Now incorporated in work package 1.
The Norwegian PSC research center

The Norwegian PSC research center (NoPSC) was established 19th of May 2008 at the Medical Department, Rikshospitalet, Oslo, Norway upon signing of a contract between the University of Oslo and Oslo University Hospital, 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 primary sclerosing cholangitis (PSC). NoPSC is a separate unit within the Clinic for Specialized Medicine and Surgery at Oslo University Hospital, Rikshospitalet, and is also affiliated with the Research Institute for Internal Medicine at 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

- Functional genetics (work package 1).
- Cancer in PSC (work package 2).
- IBD in PSC (work package 3).
- Liver transplantation in PSC (incorporated in work package 1 from 2009 onwards).
- Medical treatment of PSC (work package not yet defined).
- Endoscopy in PSC (work package not yet defined).

Organisation

THE ADVISORY BOARD

Present members of the advisory board:

Frode Vartdal (leader) Institute of Clinical Medicine University of Oslo
Solveig Hatling Institute of Clinical Medicine University of Oslo
Kristian Bjørn Clinic for Specialized Medicine and Surgery Oslo University Hospital, Rikshospitalet
Pål Aukrust Clinic for Specialized Medicine and Surgery Oslo University Hospital, Rikshospitalet
Nina Paulsen Canica A/S
Peter Ruzicka Canica A/S

THE MANAGEMENT GROUP

The NoPSC is led by the Management group:

Prof. Erik Schrumpf (leader)
Dr. Kirsten Muri Boberg
Dr. Tom Hemming Karlsen (executive manager)

THE CORE FACILITY

The Core facility of NoPSC runs support functions of general importance for the project units (biobank, data registry, laboratory assistance, computer support etc.). In addition to the Management, a total of 5 persons are presently employed in this unit:

Hege Dahlen Solild (biobank, on maternity leave 01.08.09 - today)
Liv Wenche Thorbjørnsen (biobank, 01.08.09 - today)
Kristian Holm (informatics)
Mona Skjøvel (research nurse)
Bente Woldseth (general laboratory support)

THE PROJECT UNITS

The Project units of NoPSC are built around work packages defined by priorities of the Management group. At present, four work packages have been established within the context of NoPSC. Each of the corresponding project units are presented separately on pages 6-9.
Work package 1

Functional genetics

NoPSC project leader: Tom Hemming Karlsen • Research group website: http://www.rr-research.no/karlsen/
NoPSC affiliated PhD students: Espen Melum, Johannes R. Hov, Trine Folseraas, Bjarte Fosby

BACKGROUND

The etiology of PSC is not known. Genetic risk factors are likely to be important, as shown by an increased risk of disease in first degree relatives of patients with PSC (9-39%). By studying disease genes and their function, the mechanisms by which PSC develops and eventually may be treated can be defined. Since PSC is a rare disease where probably many different types of genetic variants contribute to disease development, there are no expectations for genetics to be useful for diagnostic testing. In PSC, an association with genes in the so-called HLA complex has been known since the first genetic study in PSC by Prof. Erik Schrumpf in 1982. PSC genes are likely to exist outside this genetic region, and the aim of the functional genetics group is to identify these genes and alongside the HLA determine their function in the disease process of PSC. Since 80% of the patients with PSC also have ulcerative colitis (UC), both diseases are studied in parallel.

CHALLENGES

• The low impact from each of the disease variants in multifactorial diseases like PSC means that large groups of patients are required to detect as many of the disease genes as possible. Much effort in 2009 has therefore been invested in supporting the collection of DNA samples in other countries for collaborative projects (in particular in Germany, the US and the UK).

• The recently completed genome-wide association study firmly established the importance of the HLA in PSC. Since the more than 250 genes in this genetic region are strongly linked, it has proven extremely difficult to define the exact disease gene(-s) in this region. Several ongoing projects in the group are aimed at defining the biological basis of the HLA association in PSC.

• There has been a systematic focus at establishing methodologies for gene discovery and functional studies in the group during 2009. Of particular importance are the tools for microarray genotype analysis and novel sequencing technologies (SOLiD and Roche 454). For several of the functional studies that have been initiated, international collaborations have been essential to gain access to relevant methods, antibodies and/or mouse models.
The etiology of PSC is not known. Genetic risk factors are likely to be important, as shown by an increased risk of disease in first-degree relatives of patients with PSC. Studies in the TGR5 gene in PSC. The first manuscript from the project has been submitted and will be published in 2010. Studies in Italian PSC patients were completed and supported findings in Northern Europe that the HLA-C gene may be of importance. The manuscript from the project has been submitted and will be published in Journal of Hepatology in 2010. Several methodological studies were performed to assess the quality of basic techniques used by the group. The most important study was the comparison of different types of new machines for detecting genetic variation ("next-generation" sequencing). The manuscript from this project has been submitted and will be published in Human Mutation in 2010.

MAIN PROJECTS COMPLETED IN 2009

- Scandinavian and German genome-wide association studies in PSC and UC. Several new disease genes were identified. Three manuscripts from the projects have been submitted so far and will be published in 2010 (one in Gastroenterology on PSC, one in Nature Genetics on UC and one PSC manuscript is still under review).

- Detection and functional characterization of novel mutations in the TGR5 gene in PSC. The first manuscript from the project has been submitted and will be published in 2010.

- Studies in Italian PSC patients were completed and supported findings in Northern Europe that the HLA-C gene may be of importance. The manuscript from the project has been submitted and will be published in Journal of Hepatology in 2010.

- Several methodological studies were performed to assess the quality of basic techniques used by the group. The most important study was the comparison of different types of new machines for detecting genetic variation ("next-generation" sequencing). The manuscript from this project has been submitted and will be published in Human Mutation in 2010.

MAIN ONGOING PROJECTS IN 2010

- Immunochip-project. The project is aimed at describing the genetic overlap between various immune mediated diseases using a custom genotyping-chip designed by the Sanger Centre in the UK and Illumina. For a rare disease like PSC, participation will be particularly important, since data may help in determining whether drugs developed in one disease could be expected to influence PSC.

- Further search for new disease genes. Existing data will be analyzed using new strategies and combined with data from studies in the US and the UK to detect more PSC specific genes. In addition, PSC families with more than 3 affected members from throughout the world will be studied carefully to detect particularly strong risk factors.

- Genetic risk factors for rejection following liver transplantation in PSC. The laboratory work in this project (previously called work package 4) was completed in 2009 and several statistical strategies are presently under evaluation.

- Translational efforts. Several activities are aimed at translating the genetic findings into pathogenetic knowledge. One aspect of this is the many efforts to acquire novel methods, for instance by PhD student and post doc exchange programs. Johannes Hov will work in the laboratory of prof. Dieter Häussinger in Düsseldorf during spring 2010, and from September 2010, Espen Melum will work on projects in the laboratory of Prof. Richard Blumberg in Boston. New projects have been initiated to characterize the influence of genetic variation on gene expression and function in the tissues of PSC patients and also in various mouse models. By integrating the data with results from the genetic projects (in particular the Immunochip-project), it is anticipated that a picture of initiating and propagating factors in PSC development will emerge. One priority will be to establish tests for early diagnosis of PSC based on this information, and during autumn 2010 a post doc will be dedicated to this work.

The University of Oslo Titan computercluster consists of >650 computers and has been heavily involved in several projects in work package 1.
### BACKGROUND

Primary sclerosing cholangitis (PSC) is strongly associated with the development of cholangiocarcinoma (CCA). CCA presents a poor survival rate and is a major cause of death among PSC patients. PSC can be cured by liver transplantation, but concurrent CCA significantly reduces survival post transplantation. So far, clinically useful parameters that can identify the patients at highest risk of CCA are lacking. It is therefore important to:

1) Identify CCA that has already developed and that in the majority of cases will represent a contraindication to liver transplantation due to a high recurrence rate.

2) Detect premalignant or early malignant stages (CCA in situ) that can be radically resected by liver transplantation.

Advances in molecular pathogenesis have highlighted the importance of epigenetic changes in carcinogenesis. Epigenetic changes are heritable through cell division and result in changes in gene expression without causing changes in the DNA sequence. DNA methylation is one of the best studied epigenetic mechanisms and is associated with loss of gene expression.

### CHALLENGES

DNA methylation has been shown to play an important role in early tumorigenesis. However, few DNA methylation target genes have so far been identified in CCAs. We have previously identified epigenetic markers that are well suited for early detection of colorectal cancer. The same experimental strategy is now used to identify epigenetically regulated target genes in CCAs that can subsequently be tested as early markers of bile duct cancer.

### PROJECTS

- **Epigenetic analyses of CCA cell lines.** Microarray experiments were performed using CCA cell lines before and after treatment with epigenetic drugs. Genes that responded to epigenetic treatment in the cell lines and simultaneously were downregulated in primary tumors compared with normal tissue (previously published expression profiles) were considered potential epigenetically regulated targets. These candidate genes were subject to methylation-specific polymerase chain reaction (MSP). In addition to CCA, cell lines from gall bladder, liver and pancreas were investigated in order to determine the epigenetic profile in hepatopancreatobiliary cancers. From the cancer cell line analyses we have identified hypermethylation in several genes not previously described as epigenetically regulated. Further work in patient material is however necessary in order to establish the suitability of the novel methylation targets for detecting CCA at an early stage.

- **Epigenetic analyses of biliary brush samples.** In a pilot-study we have analyzed brush cytology specimens from PSC patients with and without CCA using the previously identified colorectal cancer biomarker panel and quantitative methylation-specific polymerase chain reaction (qMSP). Hypermethylation was detected in patients with CCA while patients without tumor were unmethylated across all markers. By investigating brush cytology specimens and paired tumor samples in a validation series we will further investigate the diagnostic potential of these markers in CCA.
Work package 3
Inflammatory bowel disease in PSC

NoPSC project leader: Kirsten Muri Boberg • NoPSC affiliated PhD students: Kristin Kaasen Jørgensen

BACKGROUND
Primary sclerosing cholangitis (PSC) is strongly associated with inflammatory bowel disease (IBD). The prevalence of IBD in PSC patients in Northern Europe and North America is in the range 60-80%. The IBD in PSC is classified as ulcerative colitis (UC) in the majority (80%) of cases. The remaining patients are diagnosed with Crohn’s disease or IBD unclassified.

IBD in PSC appears to differ from IBD unrelated to hepatobiliary disease in several regards. The patients most often have a total colitis, typically with a quiescent clinical course. Rectal sparing and “backwash” ileitis have been reported to be more frequent in UC associated with PSC than in ordinary UC. Interestingly, the colitis in PSC appears to carry an increased risk of malignancy as compared with colitis without concomitant PSC. The etiopathogenetic relationship between PSC and IBD is largely unknown. Previous studies from our group have suggested that the genetic basis for PSC-IBD differs from that of IBD in general.

CHALLENGES
A detailed characterization of the IBD associated with PSC is required as a basis for better understanding of the pathogenetic mechanisms as well as for improved treatment and follow-up. The course of IBD in liver transplanted PSC patients may be complicated and represents a particular challenge.

PROJECTS
- Clinical characterisation of IBD in liver transplanted and non-transplanted PSC patients. We have carried out colonoscopy with biopsies and a clinical interview in a prospective study of PSC patients admitted to our department during a 3-year period. We have described in detail the distribution and activity of macroscopic and microscopic inflammation, both according to segmental findings in the colon and to findings in the individual patients. Of note, inflammatory findings were considerably more frequent by histology than by endoscopy. Histopathological signs of inflammation involved the right colon in the majority of patients. About ¼ of the patients had pure right-sided colitis, not previously documented in PSC. The overall disease activity was low, but interestingly, the liver transplanted patients as a group had lower clinical as well as histological IBD activity than the non-transplanted group.

- Clinical course and outcome in colectomised PSC-IBD patients. We have carried out endoscopic investigation and a clinical interview of colectomised PSC-IBD patients and in addition retrieved data from the records of deceased patients to describe the clinical course and outcome in this subgroup of PSC-IBD. Findings will be compared with those in a matched control group of Swedish IBD patients without PSC.

- IBD and colorectal malignancies in liver transplanted PSC patients. Data have been collected for approx. 400 liver transplanted PSC patients in the Nordic countries and will be the basis for this project comparing the course of IBD before and after liver transplantation along with an assessment of risk of colorectal malignancy.
The people

Leader of the management group, Professor Erik Schrumpf, during the opening ceremony of the EASL Mono thematic meeting on PSC.

Kirsten Muri Boberg during the presentation “Surveillance and early diagnosis of cholangiocarcinoma” at the EASL Mono thematic meeting on PSC.

Research nurse Mona Skevig manages the clinical database of NoPSC and keeps track of the patient consents.

PhD student Johannes R. Hov in the laboratory.

Bioengineer Bente Woldseth and PhD student Trine Folsaraas during RNA preparation prior to gene expression analysis.
Kristian Holm manages the billions of datapoints going into the projects of NoPSC.

Liv Wenche Thorbjørnsen has in an excellent manner taken over the daily routines of the NoPSC biobank while Hege Dahlen Sollid is on maternity leave.

PhD student Espen Melum during the finalization of his PhD thesis.

Tom H. Karlsen during the visit to the Mayo Clinic in Rochester. Key collaborator Konstantinos Lazaridis (to the right) has initiated a NoPSC-like program in the US named PROGRESS.

PhD student Johannes R. Hov and executive manager Tom H. Karlsen during the informal summer celebration of NoPSC which took place at one of the Oslofjord islands.

PhD student Kim Andresen while performing analyses within work package 2 together with supervisor Professor Ragnhild Lothe.
Apart from the research activities, the most important initiative from NoPSC in 2009 was the hosting of an European Association of the Study of the Liver conference on PSC in Oslo June 21st to 23rd. The conference was part of the EASL “Monothematic” series, and covered all main topics of PSC research world-wide: the epidemiology, pathogenesis and natural history of PSC, malignancies in PSC, as well as challenges associated with treatment of PSC and liver transplantation. The 27 lectures at the conference were given by leading experts within each field, each of whom delivered state-of-the art presentations of extraordinarily high quality (see program). An important aspect of the meeting was the social activities, not only in between the scientific sessions, but also in the evenings. The almost 150 participants from more than 36 countries from all over the world had a unique opportunity to discuss topics related to PSC and also plan for future collaborations. The weather of Oslo was at its best, and the feedback from the participants was uniformly that of an unforgettable event.
Professor Roger Chapman and Tom H. Karlsen discuss the UK PSC DNA collection during the lunch.

Top left picture: Professor Erik Schrumpf during the closing session of the meeting concluding that the meeting had been a great success while NoPSC manager Tom H. Karlsen (lower right hand corner) was listening carefully.

Picture to the right: Professor Keith Lindor from the Mayo Clinic in Rochester during his presentation of results from the latest treatment trial in PSC.

Picture to the far right: PhD student Kim Andresen during the poster presentation.

### Tuesday, June 23, 2009

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>08:30-10:45</td>
<td>Malignancies in PSC</td>
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<td>Chairs: Gregory Gores, USA</td>
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<td>Raymond Løthe, Norway</td>
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<tr>
<td>08:30</td>
<td>Cholangiocarcinogenesis</td>
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<td>Gregory Gores, USA</td>
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<td>09:00</td>
<td>Relevance of NK22D in inflammatory carcinogenesis</td>
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<td>Yinan Bryceason, Sweden</td>
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<td>09:25</td>
<td>Surveillance and early diagnosis of cholangiocarcinoma</td>
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<td>Kirsten Huri Boberg, Norway</td>
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<td>09:55</td>
<td>Colorectal malignancies in PSC</td>
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<td>Annika Bergquist, Sweden</td>
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<td>10:15</td>
<td>Liver transplantation in cholangiocarcinoma</td>
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<td>Julie Hembach, USA</td>
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<td>10:45-11:15</td>
<td>Coffee Break and Poster Viewing</td>
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<td>11:15-13:30</td>
<td>Clinical Practice</td>
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<td>Chairs: Peter Jansen, The Netherlands</td>
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<td>Martti Färkkilä, Finland</td>
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<td>11:15</td>
<td>Unadjuvantized chemotherapy therapy in PSC - who benefits?</td>
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<td></td>
<td>Keith Lindor, USA</td>
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<td>11:35</td>
<td>Endpoints and design of future PSC trials</td>
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<td>Roger Chapman, UK</td>
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<td>12:00</td>
<td>Discussion: Endoscopic treatment in PSC - a critical appraisal</td>
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<td>Adolf Kristin, Germany</td>
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<td>Lars Aastakkken, Norway</td>
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<td>12:30</td>
<td>Timing and results of liver transplantation in PSC</td>
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<td>Kristian Ørnes, Norway</td>
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<td>12:50</td>
<td>Pathogenesis, diagnosis and prognosis of recurrent PSC</td>
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<td>Andrew K. Burroughs, UK</td>
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<td>13:15</td>
<td>Concluding remarks</td>
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<td>Erik Schrumpf, Norway</td>
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<tr>
<td>13:30-14:30</td>
<td>Lunch</td>
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### Pathogenec of PSC 1

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<tr>
<td>11:15-13:00</td>
<td>Pathogenesis of PSC</td>
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<td>Pietro Envenutoz, Italy</td>
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<td>Pathogenesis of PSC</td>
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<td>Chairs: Michael F. Mann, Germany</td>
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<td>11:45</td>
<td>Genetic epidemiology of PSC</td>
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<td>Tom H. Karlsen, Norway</td>
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<td>12:10</td>
<td>Aberrant lymphocyte homing in PSC - only a hypothesis</td>
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<td>David Adams, UK</td>
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<td>Pathogenesis of IBD in PSC</td>
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<td>Arthur Kaiser, Austria</td>
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<td>13:00-14:00</td>
<td>Lunch and Poster Viewing</td>
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<td>14:00-15:30</td>
<td>Pathogenesis of PSC II</td>
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<td>Chairs: David Adams, UK</td>
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<td>Steve Peroski, UK</td>
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<tr>
<td>14:00</td>
<td>Relevance of mouse models in PSC</td>
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<td>Peter Pickert, Austria</td>
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<td>14:20</td>
<td>Role of bile acids in inflammation and carcinogenesis</td>
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<td>Michael Trauner, Austria</td>
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<td>14:50</td>
<td>Role of cholangiocytes in PSC</td>
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<td>Marco Marzolli, Italy</td>
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<td>15:10</td>
<td>Pathogenesis of bile duct fibrosis and liver cirrhosis in PSC</td>
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<td>David Brenner, USA</td>
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<tr>
<td>15:30-16:00</td>
<td>Coffee Break and Poster Viewing</td>
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<tr>
<td>16:00-17:25</td>
<td>Overlap Syndrome and Autoimmunity in PSC</td>
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<td>Chairs: Kirsten Huri Boberg, Norway</td>
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<td>George Webster, UK</td>
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<td>16:00</td>
<td>Innter immune responses in PSC</td>
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<td>Christopher Bonvilus, USA</td>
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<td>16:20</td>
<td>Pathogenec importance of autoantibodies in PSC</td>
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<td>Ulrich Spengler, Germany</td>
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<td>16:45</td>
<td>PSC overlap syndrome</td>
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<td>Giorgina Matic-Vergani, UK</td>
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<td>17:05</td>
<td>Lessons learnt from IgG-associated cholangitis</td>
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<td>Ulrich Beavers, The Netherlands</td>
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<td>18:00-19:30</td>
<td>Reception and Tour at Oslo City Hall</td>
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Network

KEY LOCAL COLLABORATORS

RESEARCH INSTITUTE FOR INTERNAL MEDICINE
The integration of NoPSC within the Research Institute for Internal Medicine (IIF) (http://www.rr-research.no/riim/) was practically accomplished by the building of the new NoPSC biobank and the accompanying laboratories. Formally, work package 1 is now established at IIF as a separate group (http://www.rr-research.no/karlsen/) and in two newly initiated projects the members of this group collaborate closely with the groups of Prof. Pål Aukrust and Prof. Bente Halvorsen.

SECTION FOR ORGAN TRANSPLANTATION
Head of Department Pål-Dag Line, Dr. Aksel Foss and PhD student Dr. Bjarte Fosby at the Institute for Surgical Research (http://www.surgicalresearch.net/) collaborate with NoPSC on projects related to liver transplantation in PSC.

DEPARTMENT OF PATHOLOGY
Prof. Ole Petter Clausen, Prof. Helge Scott, Dr. Peter Jebsen and Dr. Grzyb Krzysztof are involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients.

INSTITUTE OF IMMUNOLOGY
The Immunogenetics group, led by senior researcher Benedicte A. Lie (http://www.med.uio.no/rh/immri/research/immunogenetics/benedicte_lie.html), is involved in several projects related to the further characterization of the HLA association in PSC.

CENTER FOR CANCER BIOMEDICINE
A collaboration with Prof. Ragnhild Lothe’s group, Post. doc. Guro Lind in particular, at the Center for Cancer Biomedicine (http://www.cancerbiomed.net/groups/rl/) is the basis for work package 2 on diagnosis of cholangiocarcinoma in PSC.

THE IBSEN STUDY GROUP
The infrastructure utilized in work package 3 on IBD in PSC (biobank, protocols etc.) are 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 studies in work package 1.

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE
Recently, the collaboration with Jon Lærdal within the Bioinformatics group (http://www.cmbn.no/group-rognes.php) at the CMBN on structural modeling has been a great resource and inspiration for the genetic projects within work package 1.
KEY INTERNATIONAL COLLABORATORS

JOHN RADCLIFFE HOSPITAL
OXFORD, UK

Prof. Roger Chapman (http://www.oxfordradcliffe.nhs.uk/forpatients/departments/gi/gastroenterology/consultants.aspx) has set up a consortium of key hepatologists in the UK with financial support of NoPSC. The aim of the consortium is to collect DNA for genetic studies, and the initiative is managed by several co-workers at Addenbrooke’s Hospital in Cambridge (Dr. Simon Rushbrook, Dr. Graeme Alexander and Dr. Richard Sandford in particular).

INSTITUTE FOR CLINICAL AND MOLECULAR BIOLOGY
KIEL, GERMANY

Several co-workers of Prof. Stefan Schreiber in the German excellence cluster “Inflammation at interfaces” (http://www.inflammation-at-interfaces.de/en_startseite.phtml) are involved in technically advanced projects within work package 1. Prof. Andre Franke has been assigned a 3 year guest professorship to participate in this work package. Recently, Dr. Robert Häsler has taken on a leading role for technological aspects of gene expression profiling projects in PSC.

THE MAYO CLINIC
ROCHESTER, USA

A collaboration with Dr. Konstantinos Lazaridis at the Mayo Clinic in Rochester (http://mayoresearch.mayo.edu/mayo/research/lazaridis_lab/) has been established within work package 1 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.

DEP. OF GASTROENTEROLOGY AND HEPATOLOGY
INNSBRUCK MEDICAL UNIVERSITY
INNSBRUCK, AUSTRIA

In conjunction with the transformation of activity within work-package 1 from gene identification to translational efforts, Dr. Arthur Kaser (http://www.i-med.ac.at/mypoint/news/2009103001.xml) was recently appointed as a guest professor for 3 years and will help guide the establishment of novel methodologies within the work package.

HEINRICH-HEINE-UNIVERSITY
DÜSSELDORF, GERMANY

Functional characterization of genetic variation of the bile acid receptor TGR5 within work package 1 is performed together with Prof. Dieter Häussinger and senior researcher Verena Keitel in Düsseldorf (http://www.uniklinik-duesseldorf.de/englisch/departments/departementofgastroenterologyhepatology-andinfectiology/page.html).

MEDICAL UNIVERSITY GRAZ
GRAZ, AUSTRIA

Together with Prof. Michael Trauner and senior researcher Peter Fickert in Graz (http://lipotox.uni-graz.at/F08.html) findings from mouse models of PSC are being evaluated in human tissue sampled during liver transplantation by the Oslo biobank.

THE NORDIC LIVER TRANSPLANT GROUP

Collaborators in Helsinki (Prof. Krister Höckerstedt, Dr. Helena Isoniemi), Stockholm (Prof. Bo-Göran Ericzon), Gothenburg (Prof. Styrbjörn Friman), Uppsala (Dr. Frans Durai), Copenhagen (Prof. Preben Kierkegaard) are involved in projects in several work packages where data from the Nordic Liver Transplant Registry are required (www.scandiatransplant.org).

KAROLINSKA UNIVERSITY HOSPITAL
STOCKHOLM, SWEDEN

Associate professor Annika Bergquist is involved in several projects in work packages 1 and 3 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.

CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH
CAMBRIDGE, UK

The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale and senior researcher James Traherne in Cambridge (http://www.cimr.cam.ac.uk/investigators/trowsdale/profile.html) are invaluable for the progress of several projects on this topic in work package 1.

IRCCS ISTITUTO CLINICO HUMANITAS
MILAN, ITALY

Dr. Pietro Invernizzi and co-workers Carlo Selmi and Ana Lleo in Milan (http://www.humanitas.it/cms/en/index.html) are involved in several collaborative projects at NoPSC. The main projects are related to characterization of the HLA association in PSC in Italy (work package 1), as well as evaluating serum biomarkers for cholangiocarcinoma in PSC (work package 2).
General contributions in 2009

CONTRIBUTIONS TO CLINICAL PRACTICE GUIDELINES
Management of cholestatic liver disease (EASL) and Diagnosis and management of primary sclerosing cholangitis (AASLD)

EASL Clinical Practice Guidelines. Management of cholestatic liver diseases.

This panel of experts from various European centers was invited by the European Association for the Study of the Liver (EASL) Governing Board to write practice guidelines on the management of cholestatic liver diseases. Prof. Ulrich Beuers, University of Amsterdam, was chairman of the group. Each participant was invited to contribute a specific chapter, including suggestions for the corresponding recommendations. After exchange of all manuscripts, the group met in Amsterdam for a one-day intensive work-shop. We also agreed on the grading of each recommendation. Subsequently, Prof. Beuers assessed all contributions into one document. After a review process, the EASL Governing Board endorsed the guidelines. According to the EASL policy, the organization itself undertook the responsible authorship.


Prof. Gregory Gores, Mayo Clinic, Rochester, MN, chaired this group that was invited by the American Association for the Study of the Liver (AASLD) to develop practice guidelines on primary sclerosing cholangitis. The panel included members from the US as well as from Europe. We first agreed on an outline that was approved by the AASLD Practice Guidelines Committee. Then each member wrote specific parts of the document, including suggestions for the point-by-point recommendations. Prof. Gores compiled the contributions. After exchange of comments by e-mail, we had a conference call to discuss and agree on some items. The Chair of the Practice Guidelines Committee forwarded the approved document to the AASLD Governing Board for endorsement and recommendation for publication. The AASLD assumed the responsibility for the recommendations. The invited Chair and writing group remained the principle authors.
CONTRIBUTIONS TO BASIC SCIENCE PRACTICE IN HEPATOLOGY

Karlsen TH, Melum E, Franke A.
The utility of genome-wide association studies in hepatology.
Hepatology 2010 May; 51(5): 1833-42.
Following an invitation from the Editor, Prof. Keith Lindor, Mayo Clinic, Rochester, MN, Tom H. Karlsen and Espen Melum of NoPSC along with NoPSC guest professor Andre Franke from Kiel put much effort during 2009 into generating guidelines for the rational application of the genome-wide association study design in hepatology. The application of these types of studies in PSC requires large efforts in terms of the collection of a sufficient number of DNA samples from multiple centers throughout the world. However, based on the experience from other conditions, valuable insight into the biological basis of PSC may be gained, even if the studies are only capable of detecting rather common genetic variants (frequencies >5% in the general population).

Karlsen TH, Hov JR.
Genetics of cholestatic liver disease in 2010.
Following an invitation from the Editor, Prof. Gregory Gores, Mayo Clinic, Rochester, MN, Tom H. Karlsen and Johannes R. Hov of NoPSC reviewed the recent paradigm of genetics in cholestatic liver diseases and proposed guidelines for the translation of genetic findings into biological knowledge. Genome-wide association studies and other ways to search for disease genes only provide a starting point for further studies, and it can be postulated that the biological reality is far more complex than a dichotomy of “disease gene or not”. Systematic collection of genetic variation at PSC genes is likely to yield a wide spectrum from rare, deleterious mutations causing disease in individual patients, to more subtle variants which require additional effects from other genes or environmental factors to cause disease.

CONTRIBUTION TO ZAKIM AND BOYER: A textbook of Hepatology, 6th edition

Karlsen TH, Boberg KM, Schrumpf E.
Primary Sclerosing Cholangitis.
In press.
Following an invitation from one of the Editors, Prof. Michael Manns, Hanover Medical School, Germany, the management group of NoPSC put much effort during 2009 into providing a chapter on primary sclerosing cholangitis for the 6th edition of the well-renowned Zakim and Boyer: A textbook of Hepatology. Almost 500 articles were carefully reviewed and constituted the basis of the 80 A4 pages of text that constituted the final chapter. All aspects of PSC were represented: Epidemiology, pathogenesis, clinical presentation and treatment. The chapter represents an important summary of the expertise and experience of the management group of NoPSC.
Publications 2009

Karlsen TH
Genome-wide association studies reach hepatology.

Forsbring M, Vik ES, Dalhus B, Karlsen TH, Bergquist A, Schrumpf E, Bjørds M, Boberg KM, Alseth I.
Catalytically impaired MYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma. Carcinogenesis. 2009 Jul; 30(7): 1147-54.

Melum E, Franke A, Karlsen TH.


European Association for the Study of the Liver.

Publications 2008


Karlsen TH, Schrumpf E, Boberg KM.

Hov JR, Boberg KM, Karlsen TH.


Melum E, Karlsen TH, Bergquist A, Schrumpf E, Boberg KM.
An interleukin-6 (IL-6) receptor polymorphism affecting serum levels of IL-6 does not increase the risk of cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol 2008; 103(4): 1045; author reply -6.

* Shared first authorship

AWARDS 2009

Helge Bells price for good clinical research in hepatology for 2009 was awarded to the research group of Ingrun Alseth at the Centre for Molecular Biology and Neuroscience. 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. The price was awarded for the article “Catalytically impaired MYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma” which was published in Carcinogenesis. The work was done in close collaboration with several researchers at NoPSC.
## Communications

**NoPSC international lectures by invitation 2009**

*Boberg KM.*  
**Diagnosis of cholangiocarcinoma in primary sclerosing cholangitis.**  

*Boberg KM.*  
**Surveillance and early diagnosis of cholangiocarcinoma.**  

*Boberg KM.*  
**Cholangiocarcinoma: surveillance for early detection and diagnosis.**  
International Liver Cancer Association (ILCA) Third Annual Conference, Milan, Italy, September 4 - 6, 2009.

*Karlsen TH.*  
**Genetic epidemiology of PSC.**  

*Karlsen TH.*  
**Genetic epidemiology of PSC.**  

*Karlsen TH.*  
**Differences and Similarities Between PSC-IBD and UC – Lessons Learned from Genome-Wide Association Studies.**  

*Karlsen TH.*  
**Genetics in PSC.**  
European Association for the Study of the Liver (EASL) Clinical School of Hepatology: Autoimmune Hepatitis, PBC and PSC. Hannover, Germany, December 3 – 5, 2009.

*Schrumpf E.*  
**Recurrent cholestatic diseases.**  
44th Annual Meeting of the European Association for the Study of the Liver (EASL), Copenhagen, Denmark, April 22 – 26, 2009.

*Schrumpf E.*  
**Therapeutic challenges in PSC.**  

## Accounting 2009

**The Norwegian PSC Research Center**

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<tr>
<th>RIKHSOPITALET</th>
<th>UNIVERSITY OF OSLO</th>
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<tr>
<td></td>
<td>INCOME</td>
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<td>Transfer from 2008</td>
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<td>Canica funds 2009</td>
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<td>Transfer from UiO 2009</td>
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<td>Infrastructure/equipment 2009</td>
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<td>Other operating expenses 2009</td>
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<td>Transfer to 2010 budget</td>
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All sums are in Norwegian kr.
Oslo University Hospital HF is owned by the Norwegian Health Region South-east and consists of the previous Aker University Hospital, Rikshospitalet University Hospital and Ullevål University Hospital.

The Norwegian PSC research center

www.rikshospitalet.no/nopsc