Annual report 2008

The Norwegian PSC research center

Rikshospitalet University Hospital

NO PSC

2008 - comments from the leader

The first full year of *"Norsk Senter for primær skleroserende cholangitt"* has been completed.
Our main focus for this year has been – in parallel with ongoing research – to construct a solid base for future activities by

1. Building a core facility to serve the different research projects
2. Improve relations to other groups – internationally in particular

The building of a the core facility has been completed. It consists of 5 persons with Tom Hemming Karlsen as leader, two bio-engineers, one research nurse and one person responsible for data-bases, economy and other administrative matters. A major task during 2008 has been the planning and building of our biobank in an area at Rikshospitalet kindly provided by the University of Oslo and Rikshospitalet in a joint effort. Important mile stones in this process have been the construction of a tailor made data-base in collaboration with Medinsight, the selection of appropriate tools, and collection of all necessary approvals for the biobank activities. The official opening of the biobank took place April 21st 2009.

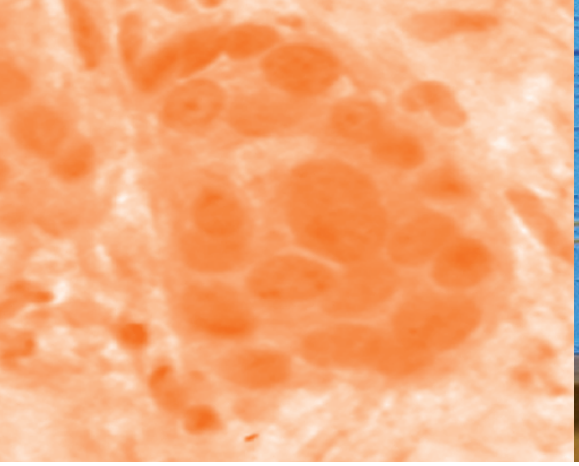
Our link to the Cancer research group of professor Ragnhild Lothe at Radiumhospitalet was strengthened by the appointment of a joint research fellow by the end of the year. Our link to the University in Kiel has been strengthened by appointing Andre Franke as guest professor at the University of Oslo.

By inviting researchers from Kiel, Oxford and Amsterdam to a meeting at Holmenkollen Park early in 2008 our link to different European centers was further improved. For the time being these and other relations have lead to the collection of DNA samples from up to 2000-2500 PSC patients from Sweden, UK, Germany, Netherlands, Italy and USA. Relations have also been established with Austria for joint studies.

At the moment we have 4 different project groups: *"Cholangiocarcinoma in PSC"* and *"Inflammatory Bowel Disease"* in PSC both headed by Kirsten Muri Boberg, and *"Functional genetics in PSC"* and *"Hepatic transplantation in PSC"* both headed by Tom Hemming Karlsen. *"Functional genetics in PSC"* has since August 2008 had two research fellows assigned, whereas the remaining research groups have one each for the time being. Espen Melum has received the price for best Norwegian paper in hepatology during 2008 *(E. Melum, TH Karlsen, E Schrumpf, A Bergquist, E Thorsby, KM Boberg, B Lie. Cholangicarcinoma in PSC is associated with natural killer cell receptor G2D polymorphisms. Hepatology 2008; 47: 90-96.)*

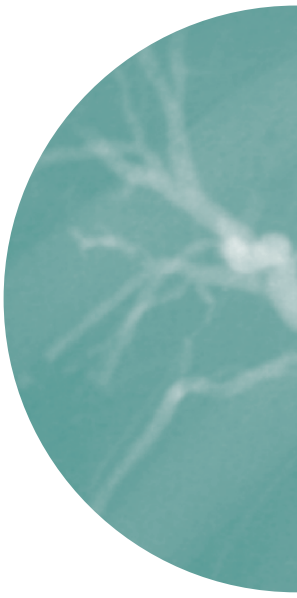
We are optimistic for the future. In June 2009 we will host EASL Monothematic Conference on PSC in Oslo. "All" important researchers world wide with interest in PSC research will participate. This will provide us with a possibility for further building of important relations in forthcoming research activities.

Erik Schrumpf
Leader of the management group



Annual report 2008

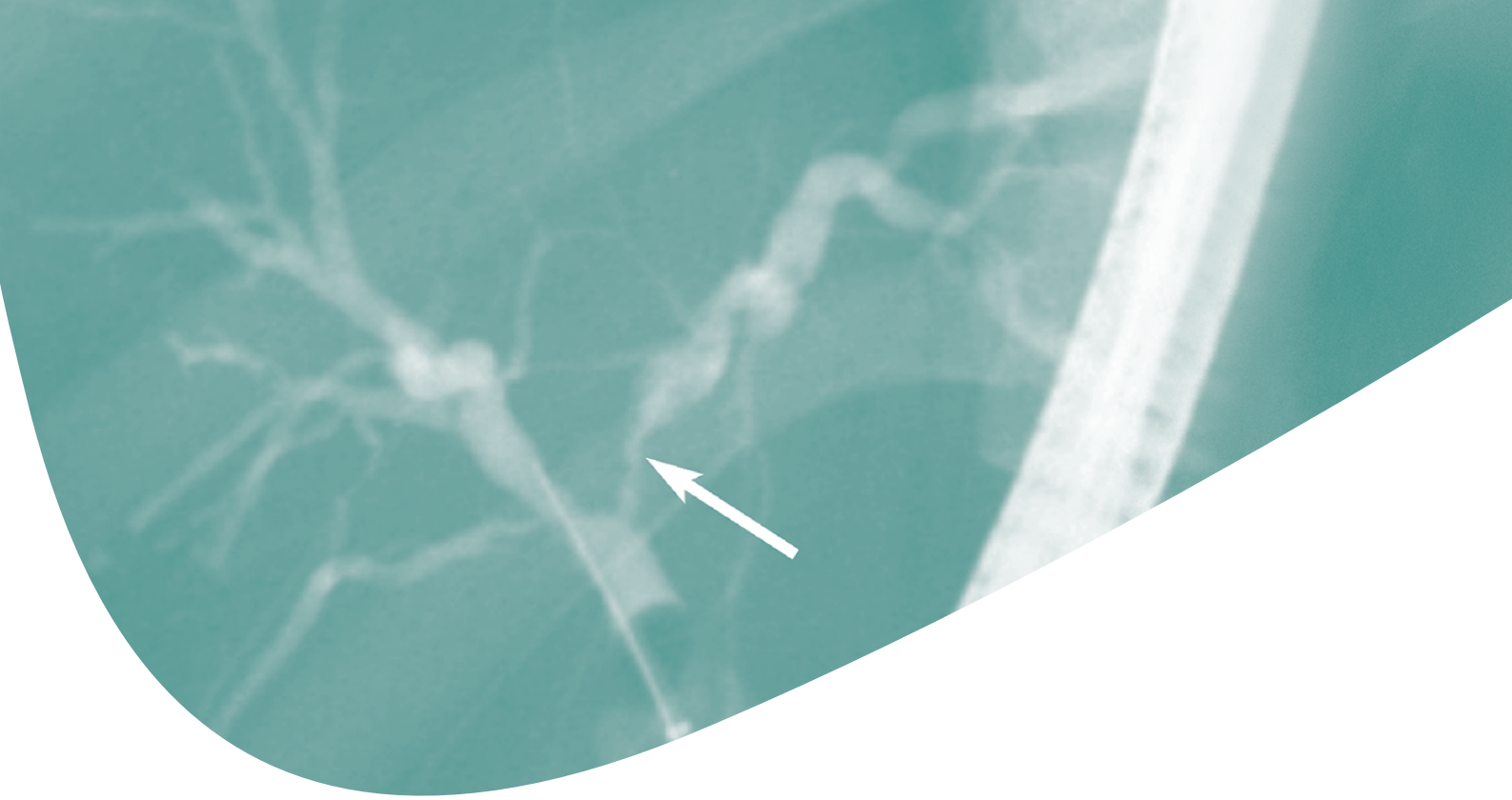
The Norwegian PSC research center



ANNUAL REPORT 2008

More information at the web pages
www.rikshospitalet.no/nopsc

TEXT: Tom Hemming Karlsen, NoPSC
PUBLISHER: Rikshospitalet University Hospital
LAYOUT: Tor Halland, TorDesign
PRINT: Møklegaard Print Shop AS, 2009
SAMPLES: 100

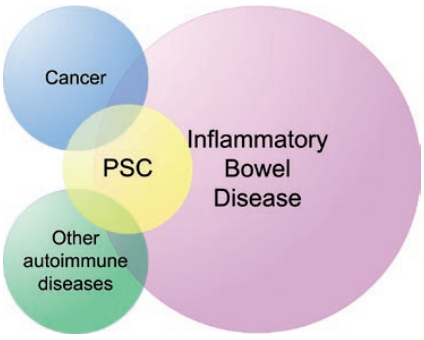


PSC

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 patch-work of different phenotypes in addition to the bile duct affection. Most important are inflammatory bowel disease (IBD), malignancy and other autoimmune diseases. Many of the research topics are thus of general importance and it is anticipated that findings in NoPSC projects will yield insight into several of these related conditions.

NoPSC 2008 in brief

Formally, 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 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)*.

KEY ORGANIZATIONAL ACHIEVEMENTS IN 2008

- Establishment of the formal infrastructure of the NoPSC *(legal, ethical clearances, financial system)*.
- Modern biobank-facility in conjunction with a new research database *(Medinsight)*.
- Laboratory facilities at the Institute of Immunology and Research Institute for Internal Medicine.
- Extensive strengthening of the international collaboration.
- In 2008 the following NoPSC personnel was paid directly from the donation:

Tom Hemming Karlsen	*Manager*	01.01.08 - today
Bente Woldseth	*Laboratory*	01.02.08 - today
Hege Dahlen Sollid	*Biobank*	01.03.08 - today
Kristian Holm *(50%)*	*Informatics*	01.09.08 - today
Johannes Roksund Hov	*PhD student*	01.01.08 - today
Espen Melum	*PhD student*	15.08.08 - today
Kim Andresen	*PhD student*	21.11.08 - today
Andre Franke *(20%)*	*Guest professor*	01.04.08 - today
Morten Eike	*Post doc*	01.09.08 - 31.12.08

KEY SCIENTIFIC ACHIEVEMENTS IN 2008

- Work package 1: The identification of several new disease genes in PSC and ulcerative colitis.
- Work package 2: Establishment of cholangiocarcinoma cell line system for methylation studies.
- Work package 3: Completion of the PSC-IBD biobank with intestinal biopsies from 220 PSC patients.
- Work package 4: Establishment of a project biobank from diagnostic DNA samples and biopsies.

KEY PLANS FOR 2009

- Support further biobanking for genetic studies *(Finland, Sweden, Germany, Belgium, Netherlands, UK, USA)*.
- Characterization of 2 of the 3 new disease genes discovered by the functional genetics group in 2008 and continue the search for further genes.
- Clarify diagnostic importance of DNA methylation status in cholangiocarcinoma.
- Characterize inflammatory bowel disease in PSC.
- Identify causes of rejection and graft loss following liver transplantation for PSC.
- Organize international PSC congress *(www.easl.ch/oslo2009)*.
- Author a chapter on PSC in a reputable textbook on liver diseases *(Zakim & Boyer Textbook of Hepatology)*.

The Norwegian PSC research center

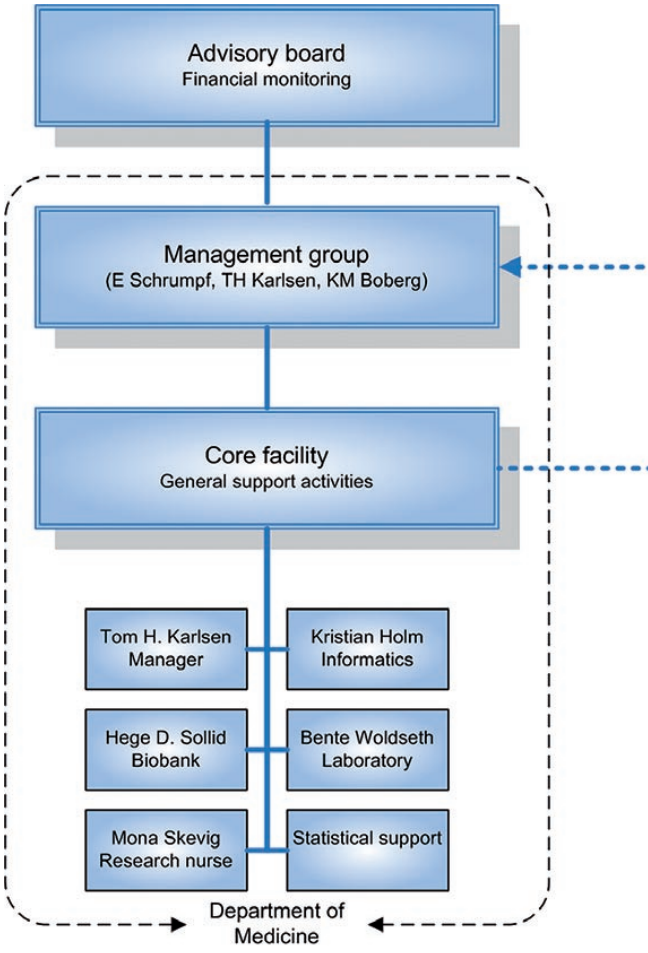
The Norwegian PSC research center *(NoPSC)* was formally established May 19th 2008. The basis of the establishment is a donation of 100.000.000 NOK by Stein Erik Hagen on October 22nd 2007. NoPSC is a separate unit within the Medical Department at Oslo University Hospital, Rikshospitalet.

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 *(work package 4)*.
- Medical treatment of PSC *(work package not yet defined)*.
- Endoscopy in PSC *(work package not yet defined)*.



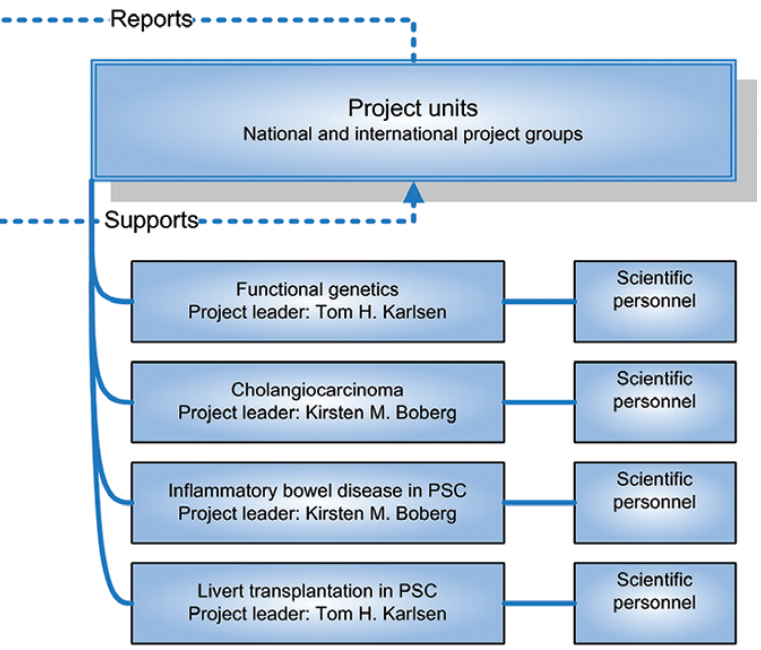
Organisation

THE ADVISORY BOARD

The Advisory board functions to monitor that the management of the donation from Stein Erik Hagen is in line with the purpose implicit in a) the contract between Canica A/S and the University of Oslo, and b) the official guidelines of "gift reinforcement" by The Research Council of Norway. *http://www.regjeringen.no/nb/dep/kd/dok/lover_regler/retningslinjer/2008/reviderte-retningslinjer-for-ordningen-m.html?id=520368*
Twice annually, the management group of NoPSC reports to the Advisory board on progress and plans.

Present members of the advisory board:

Frode Vartdal *(leader)*	Faculty Division Rikshospitalet University of Oslo
Solveig Hatling	Faculty Division Rikshospitalet University of Oslo
Kristian Bjøro	Medical Department Oslo University Hospital, Rikshospitalet
Pål Aukrust	Medical Department Oslo University Hospital, Rikshospitalet
Nina Paulsen	Canica A/S
Peter Ruzicka	Canica A/S



The principal organisational structure of NoPSC.

THE MANAGEMENT GROUP

The NoPSC is led by a management group consisting of:

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

All members of the management group serve clinical duties at the Section of Gastroenterology and Hepatology, Medical Department, Rikshospitalet University Hospital, in addition to their work for NoPSC.

THE CORE FACILITY

The Core facility of NoPSC runs support functions of general importance for the project units *(biobank, data registry, computer support etc.)*. In addition to the management group, a total of 4 persons are presently employed in this unit:

Hege Dahlen Sollid *(biobank)*
Kristian Holm *(informatics)*
Mona Skevig *(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 14-17.

Establishing the NoPSC

Much time and effort during 2008 went into generating a sustainable infrastructure of the NoPSC. On one side, this distracted personnel of NoPSC from the production of science. On the other side, the formal and physical infrastructure now established is likely to efficiently facilitate the scientific activities over years to come.

FORMAL INFRASTRUCTURE

The contract between Canica A/S and the University of Oslo was signed 22.10.07. From the side of Canica A/S, a total of NOK 100.000.000 for long-perspective research on PSC is guaranteed. From the side of the University of Oslo, prudent management of the donation is guaranteed. The University of Oslo is responsible for handling the gift reinforcement system via The Research Council of Norway. The donation will be made available from Canica A/S over a 10-years period *(2007-2016)* in annual rates of NOK 10.000.000.

The contract between the University of Oslo and Rikshospitalet University Hospital was signed 19.05.08. The contract defines the mutual responsibilities of these parts in the management of NoPSC with regard to:

a) role of the Advisory board

b) budgets and accounting

c) employments

d) publishing and ownership of data based on research activities at NoPSC

Scientific personnel to be paid via NoPSC are employed by the University of Oslo, whereas technical personnel of the core facility of NoPSC are employed by the Rikshospitalet University Hospital. All running expenses are accounted for by the financial department of Rikshospitalet University Hospital via quarterly transfers from the financial department of the University of Oslo *(according to budgets)*.

The NoPSC is formally a section at the Medical Department, Rikshospitalet University Hospital. Laboratory space at the Research Institute for Internal Medicine was allocated by the hospital administration 19.02.2008. The internal management of the NoPSC unit at Rikshospitalet is described in the documents ***"Etablering av Norsk senter for PSC"*** *(20.05.2008; Tom H. Karlsen)* and ***"Intern tildeling vedrørende gave fra: Canica AS (via UIO)"*** *(08.10.2008; Pål Bakke)*. Each annual budget for NoPSC is approved by Head of the Medical Department *(presently prof. Kristian Bjøro)* based on directions from the NoPSC Advisory board. Presently, the responsibility for accounting is allocated to Elisabeth Hallsjø *(Rikshospitalet University Hospital)* and Monica Carlosama *(University of Oslo)*.

License from the Norwegian Data Inspectorate for the handling of clinical patient data at NoPSC was obtained 14.08.08 *(reference 08/01052-2/CAO)*.

License from the Norwegian Directorate of Health for the NoPSC biobank was obtained 16.08.08 *(biobank no. 2295)*.

Clearance of novel projects at NoPSC by The National Committees for Research Ethics in Norway was throughout 2008 obtained by project leaders Kirsten Muri Boberg *(reference S-08512b)* and Tom Hemming Karlsen *(references S-08872b, S-08751b and S-08873b)*.

PHYSICAL INFRASTRUCTURE

In contrast to more common diseases *(e.g. coronary heart disease)*, PSC patients are scarce. It takes time to gather clinical data and various types of biological material in sufficient numbers for basic science research projects to generate meaningful results. It was therefore essential to the early stage of the NoPSC establishing process to upgrade the system for collection and storage of clinical data and biological material. The NoPSC biobank was established.

Laboratory facilities outside the context of the PSC biobank will be established as required by the project units. It will never be the aim of NoPSC to establish large laboratory facilities covering all methods required by the projects. Instead, a three-level system has been adopted where

a) general and simple methods required by several project units will be established at the NoPSC laboratory *(e.g. the purchase in 2008 of an ABI7900 real-time instrument)*.

b) methods established at collaborating laboratories at Rikshospitalet University Hospital or at other collaborating institutions in Norway and abroad will be performed there.

c) technology not available elsewhere may be purchased from service providers in Norway or abroad *(e.g. http://www.cigene.no/snp-services.html)*.

The rationale behind this strategy is to avoid investment in expensive, redundant and rapidly obsolete technical equipment.

The NoPSC biobank

AIMS

The NoPSC biobank will prepare and store biological material and operate as a shared resource for all projects supported by NoPSC. An important aspect of this intention is to avoid single-person "ownership" of any material in the PSC biobank. The long-term perspective of the NoPSC investment means that a storage and retrieval system needs to be extremely reliable and independent from "personal arrangements" by individual technical or scientific personnel. The biobank resource generated is likely to be of great value not only during the 10-year period of financial support by Canica A/S, but also the years to follow.

STORAGE SYSTEM

A two-dimensional barcode-based system by Thermo Fisher *(Matrix®; http://www.matrixtechcorp.com/storage-systems/overview.aspx)* was chosen based on price and quality assessments. The system is also used at other Norwegian biobanks like The Norwegian Institute of Public Health and the HUNT biobank.

INVENTORY SYSTEM

With the programming skills of Odd Røyne at the MEDinsight department of Rikshospitalet University Hospital, a unique system of sample deposition, positioning and retrieval has been built. The system is completely integrated with the NoPSC clinical database, and the system is thus able to directly generate lists of various types of material based on particular clinical parameters.

MATERIALS

From blood, serum, plasma *(with and without protease inhibitors)*, RNA and DNA are stored. In addition, bile and surplus tissue samples are stored in conjunction with various procedures *(ERC, liver transplantation)*. Tissue sampling from the diseased liver during liver transplantation is performed on a 24 hour voluntary basis by medically educated scientific personnel.

STANDARD OPERATING PROCEDURES

In close collaboration with experts from a variety of research fields, detailed protocols for material collection and preparation have been established. The operating procedure for each type of material is standardized and labeled with a specific version code which is stored in the inventory along with other data regarding the sample collection *(e.g. fasting status)*. This system ensures a 1:1 relationship between a stored sample and a written protocol document, and thus the possibility to extract homogeneously prepared samples from the biobank.

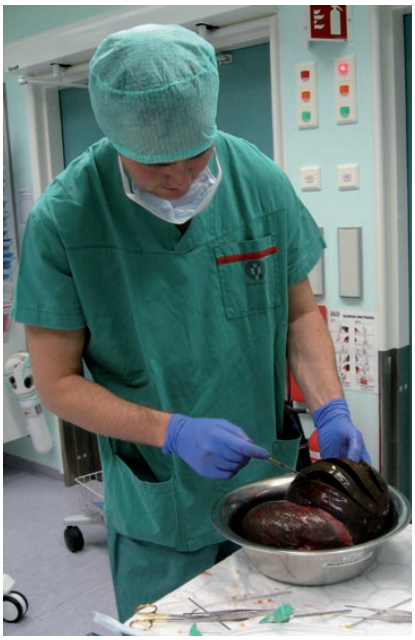
QUALITY CONTROL

The quality of all samples is thoroughly tested at deposition, and for particular analyses also at regular time intervals to monitor for sample degradation over time.

PHYSICAL STORAGE FACILITY

Parts of the NoPSC laboratory space at Rikshospitalet University Hospital has been changed into a modern storage facility. All blood and bile samples are stored in several large -80°C freezers and tissue samples in liquid nitrogen. Prior to storage, position is automatically assigned and electronically stored based on barcode labeling of tubes as well as each individual box. Sample preparation is performed in a new laboratory in immediate vicinity.

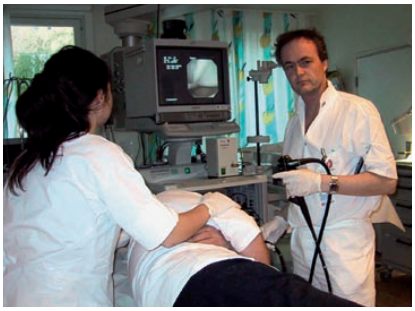
The people



Tom H. Karlsen has one of the most diverse positions at NoPSC. In addition to administrative and financial responsibilities, he runs several of the research projects on top of clinical duties. Here he is collecting biomaterial for the NoPSC biobank at liver transplantation.

Bjarte Fosby *(PhD student)* performs research on top of clinical duties as a liver transplant surgeon. Here he is together with a small fraction of the patient records he has reviewed as part of his project.

The Management group; Erik Schrumpf, Kirsten Muri Boberg and Tom Hemming Karlsen shortly after the donation from Canica A/S was made. Albeit grateful and excited, the large sum meant equally large responsibilities and hard work.



Lars Aabakken is chief of the endoscopy department, which serves the NoPSC biobank with valuable samples taken in conjunction with diagnostic and therapeutic procedures *(e.g. bile duct brushings)*.

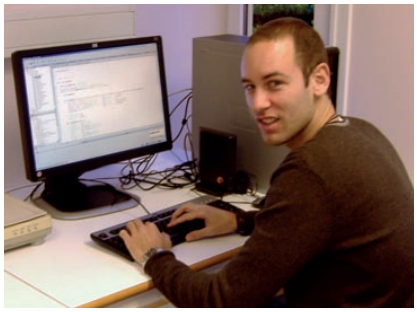
Johannes Hov *(PhD student)* works on several projects related to the immunogenetics of PSC. Here he is at the animal facility with a rat strain particularly susceptible to hydrophobic adjuvants.

Kim Andresen *(PhD student)* aims to identify biomarkers for cholangiocarcinoma in PSC. Here he is at the laboratory facilities at Radiumhospitalet.

Bente Woldseth manages the local laboratory facilities at NoPSC. Here she is setting up genotyping at the newly purchased ABI 7900.

Espen Melum *(PhD student)* works on several computer-intensive genetic studies. Here he is in Kiel together with guest professor at NoPSC, Andre Franke, at one of the second generation sequencers from Applied Biosystems *(SOLiD®)*.

Mona Skevig manages the relationship between the clinical units at the Section of Gastroenterology and Hepatology at Rikshospitalet and NoPSC research projects. Here she checks with the database systems whether a patient has given a written consent for blood sample collection.



Kristian Holm manages the IT systems at NoPSC. Here he is setting up the genetic database of work package 1.

Hege Dahlen Sollid manages the NoPSC biobank. Here she is collecting blood samples from the first patient ever to be included in the new NoPSC biobank *(picture with permission from the patient)*.

Kristin Kaasen Jørgensen *(PhD student)* has collected a unique material of biopsies and clinical data from PSC patients with inflammatory bowel disease. Here she is working at the endoscopy database.

Network

LOCAL NETWORK

DEPARTMENT OF SURGERY

Head of department Pål-Dag Line, Dr. Aksel Foss and PhD student Bjarte Fosby at the Institute for Surgical Research *(http://www.surgicalresearch.net/)* collaborate closely with NoPSC within work package 4 on projects related to risk of rejections following liver transplantation in PSC. Dr. Øystein Mathisen and Dr. Ivar Gladhaug are closely involved in projects within work package 2 on cholangiocarcinoma.

DEPARTMENT OF PATHOLOGY

Several co-workers at the Department of Pathology are heavily involved in all work packages at NoPSC. Prof. Ole Petter Clausen, Prof. Helge Scott, Dr. Peter Jebsen and Dr. Krzysztof Grzyb need to be mentioned in particular, and are involved in the histological and immunohisto-chemical evaluation of tissue samples from PSC patients.

INSTITUTE OF IMMUNOLOGY

The collaboration with the Institute of Immunology on the HLA association in PSC dates all the way back to the first report ever on an HLA association in PSC in 1982. This study, mainly performed by Prof. Erik Schrumpf and Prof. Erik Thorsby, set the stage for a collaboration that is still active. Today, the Immunogenetics group, led by senior researcher Benedicte A. Lie *(http://www.med.uio.no/rh/immi/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

Within work package 2 on cholangiocarcinoma in PSC, a collaboration with prof. Ragnhild Lothe's group at the Center for Cancer Biomedicine *(http://www.cancerbiomed.net/groups/rl/)* has recently been established. Post doc Guro Lind is responsible for evaluating the diagnostic potential of determining promoter methylation of genes in cholangiocarcinoma.

DEPARTMENT OF ANATOMY

Prof. Sigbjørn Fossum and associate professor Michael Daws at the Department of Anatomy *(http://www.med.uio.no/imb/anatomi/immunobiolab/index.html)* within the Institute of Basic Medical Sciences *(http://www.med.uio.no/imb/english/)* have been involved in an evaluation of immunological effects of bile acids.

THE IBSEN STUDY GROUP

The infrastructure utilized in work package 3 on IBD in PSC *(biobank, protocols etc.)* is derived from the IBSEN II project. Prof. Morten Vatn and several other co-workers of the IBSEN study group are thus involved in projects within this work package.

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE

Two groups at the CMBN are involved in projects at NoPSC. Prof. Magnar Bjørås and senior researcher Ingrun Alseth at the Laboratory for molecular biology *(http://www.cmbn.no/group-bjoras.html)* are involved in the characterization of oxidative DNA repair mechanisms in cholangiocarcinoma. Jon Lærdal within the Bioinformatics group *(http://www.cmbn.no/group-rognes.php)* performs in silico analyses of mutations detected by sequencing projects within work package 1.

INTERNATIONAL NETWORK

JOHN RADCLIFFE HOSPITAL OXFORD, UK

The collaboration with Prof. Roger Chapman *(http://www.oxfordradcliffe.nhs.uk/forpatients/departments/gi/gastroenterology/consultants.aspx)* has been active for more than 10 years. Recently, a consortium of key hepatologists in the UK has been set up with the financial support of NoPSC. The aim of the consortium is to collect DNA for genetic studies, and the initiative is led by Prof. Roger Chapman together with post doc Simon Rushbrook at Addenbrooke's Hospital in Cambridge.

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 heavily involved in technically advanced projects within work package 4. For running projects, microchip-genotyping *(Affymetrix®)* and second generation sequencing technology *(SOLiD® from Applied Biosystems)* are likely to speed up the pace of disease gene discovery and disease gene characterization in PSC. As part of the establishment of work package 1, Prof. Andre Franke at IKMB was assigned a 3 year guest professorship at NoPSC.

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. Parts of this initiative is funded by the NoPSC.

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 Duraj)*, Copenhagen *(Prof. Preben Kierkegaard)* are involved in projects in work packages 3 and 4 that are derived from the Nordic Liver Transplant Registry *(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 collaborative projects.

SAHLGRENSKA UNIVERSITY HOSPITAL GOTHENBURG, SWEDEN

Prof. Einar Björnsson is involved in several projects in work package 1. In particular, a multi-center consortium for the study of genetic risk factors of small-duct PSC has been established, with contributions from Norway, Sweden, UK and USA.

CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH CAMBRIDGE, UK

Two collaborative projects have been initiated together with Prof. John Trowsdale and senior researcher James Traherne in Cambridge *(http://www.cimr.cam.ac.uk/investigators/trowsdale/profile.html)* related to the HLA projects in work package 1.

HEINRICH-HEINE-UNIVERSITY DÜSSELDORF, GERMANY

A collaboration with Prof. Dieter Häussinger and senior researcher Verena Keitel in Düsseldorf *(http://www.uniklinik-duesseldorf.de/englisch/departments/departmentofgastroenterologyhepatologyandinfectiology/page.html)* was recently initiated related to the functional characterization of one of the disease genes recently discovered in work package 1.

INTERNATIONAL AUTOIMMUNE HEPATITIS GROUP

Within the IAIHG, a collaboration with prof. Ansgar Lohse *(Hamburg, Germany)*, prof. Michael Manns *(Hannover, Germany)*, prof. Roger Chapman *(Oxford, UK)* and prof. Jenny Heathcote *(Toronto, Canada)* aims to define the characteristics of overlap syndromes *(PSC vs. autoimmune hepatitis and PBC vs. autoimmune hepatitis)*.

RF&UCL MEDICAL SCHOOL LONDON, UK

Within work package 2, a collaboration with Dr. Steven Pereira *(http://www.ucl.ac.uk/stemcells/researchers/SP)* has been initiated with the aim of identifying protein or RNA biomarkers for cholangiocarcinoma in PSC.

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 biomarkers for cholangiocarcinoma in PSC *(work package 2)*.

MEDICAL UNIVERSITY GRAZ GRAZ, AUSTRIA

Closely related to the NoPSC biobanking efforts, a collaboration with Prof. Michael Trauner and senior researcher Peter Fickert in Graz *(http://lipotox.uni-graz.at/P08.html)* has been initiated to evaluate findings from mouse models of PSC in human tissue.

NOPSC

Work package 1
Functional genetics

NoPSC project leader: ***Tom Hemming Karlsen*** • NoPSC affiliated PhD students: ***Espen Melum and Johannes Hov***

BACKGROUND

The etiology of PSC is not known. The risk of PSC is higher *(9-39x)* in first degree relatives than among unrelated individuals. This means that genetic factors are likely to be important in the disease process.

In conditions with a similar degree of heritability *(e.g. Crohn's disease and type 1 diabetes)*, studies have now identified 30-40 disease genes. Whereas these genes have proven of almost no value in the context of "genetic testing" *(predicting disease in healthy individuals)*, they have been able to highlight several distinct, biological systems that are defective in the patients. By studying the disease genes and their function in cell cultures, animal models and of course also in patients and healthy individuals, researchers have defined previously unknown mechanisms by which the diseases develop and eventually may be treated.

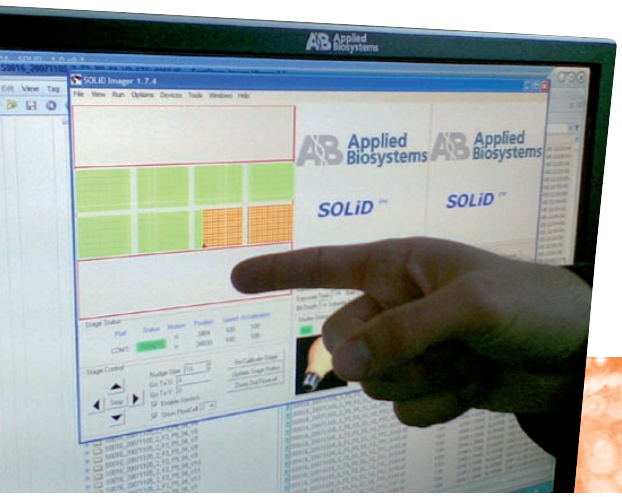
In PSC, an association with genes in the so-called HLA complex has been known since the first genetic study in PSC by Prof. Erik Schrumpf in 1982. PSC genes are likely to exist even outside this genetic region, and the aim of the functional genetics group is to identify these genes and determine their function in the disease process of PSC.

CHALLENGES

- For complex reasons, biologically important disease genes may have a relatively low impact on disease risk. This means that large groups of patients are required to detect as many of the disease genes as possible. For a rare disease like PSC, this requires large scale international collaborations.
- Since the more than 250 genes in the HLA complex are strongly linked, it has proven extremely difficult to define the exact disease gene in this region. In other HLA associated diseases, studies of other ethnicities have helped. However, PSC outside Northern Europe is very rare, and study populations thus equally scarce.
- Detecting disease genes requires technically advanced and expensive equipment *(e.g. microarray SNP genotyping, large-scale "second-generation" sequencing, computer-clusters of up to several hundred processors for data analysis)*.
- Functional studies of the disease genes require a broad repertoire of laboratory methods and biomaterial *(see chapter on NoPSC biobank)* from patients and healthy controls.

PROJECTS

- Finding new disease genes *(international collaboration on genome-wide gene discovery in PSC)*.
- Functional characterization of 2 of 3 new non-HLA disease genes identified by the group in 2008.
- Determining the effect of genetic variants on PSC severity and disease course.
- Determining the effect of genetic variants on risk of cholangiocarcinoma in PSC.
- Further characterization of the HLA association in PSC in Scandinavian and Italian DNA samples.



NOPSC

Work package 2

Molecular biomarkers in early diagnosis of cholangiocarcinoma

NoPSC project leader: ***Kirsten Muri Boberg*** • NoPSC affiliated PhD students: ***Kim Andresen***

BACKGROUND

PSC is strongly associated with the development of cholangiocarcinoma (CCA). This malignancy complicates the disease course in up to 20% of cases. CCA carries a poor prognosis and is an important cause of death among PSC patients. Clinically useful parameters that can identify the patients at highest risk of CCA are, however, lacking. PSC can be cured by liver transplantation, but concurrent CCA significantly reduces survival post transplantation. It is therefore important to:

1) Verify 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.

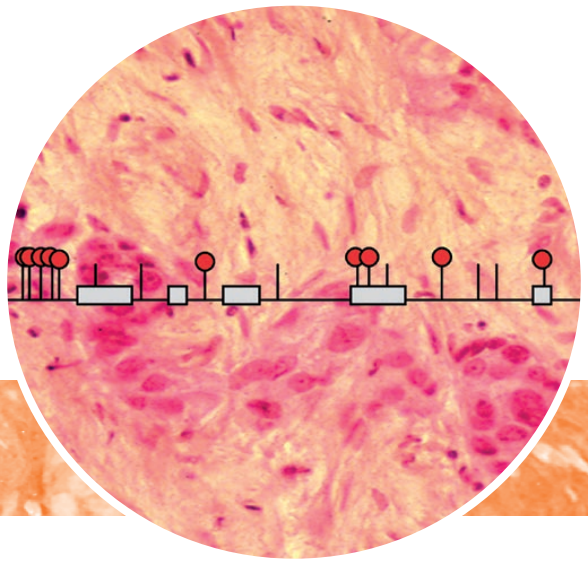
Recent advances in molecular pathogenesis have highlighted the importance of epigenetic changes in carcinogenesis. Epigenetic changes result in changes in gene expression without changes in DNA sequence. DNA methylation is one of the most common epigenetic changes and represents one among several mechanisms that can inactivate tumor suppressor genes.

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. Epigenetic markers that are well suited for early detection of colorectal cancer have previously been identified. The application of corresponding experimental strategies seems relevant 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.
  The promoter methylation status of several genes previously shown to be promising markers of early colon tumorigenesis, has been analyzed by methylation-specific polymerase chain reaction *(MSP)* in CCA- and gallbladder cell lines. We have identified promoter hypermethylation of some of these genes in the cell lines, making them candidates for further study in biological material from patients.



NOPSC

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 is strongly associated with 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 indeterminate colitis. IBD in PSC may be diagnosed at any time during the course of the liver disease.

In the majority of cases, IBD precedes PSC, but IBD may also present after PSC and even after liver transplantation. Moreover, PSC may be diagnosed after colectomy. 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

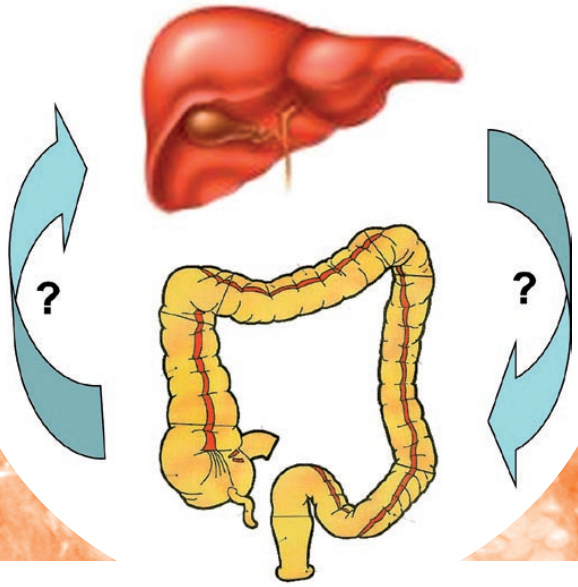
A detailed characterization of the IBD associated with PSC is required as a basis for better understanding of the patho-genetic mechanisms as well as for improved treatment and follow-up. The course of IBD in liver transplanted PSC patients may be complicated and represents a particular challenge.

PROJECTS

- Histopathological characteristics of IBD in PSC.
  The distribution and activity of inflammation in biopsies from the ileum and colon have been systematically assessed. Along with the endoscopic findings, this project will the most detailed description of IBD in PSC carried out until now.

- The clinical disease activity in PSC patients with IBD.
  The clinical disease activity will be described, including a comparison between liver transplanted and non-transplanted patients.

- Colorectal malignancies in IBD associated with PSC.
  By an investigation of colorectal malignancies reported in the entire cohort of PSC patients seen in our departement during several years, we will be able to define the neoplastic potential of IBD in PSC in this group.



NOPSC

Work package 4
Liver transplantation in PSC

NoPSC project leader: ***Tom Hemming Karlsen*** • NoPSC affiliated PhD students: ***Bjarte Fosby***

BACKGROUND

In lack of effective medical treatment, liver transplantation is the only available treatment option for PSC patients with advanced liver disease. In Norway, PSC is the most common indication for liver transplantation and constitutes approximately 25% of all liver transplantations performed.

Recurrence of PSC in the new liver occurs in 15-30% of the cases and may require re-transplantation. In contrast to other solid organ transplantations, tissue type compatibility *(HLA matching)* has not been shown to reduce the risk of rejection in liver transplantation.

Acute rejection in liver transplantation occurs in 20-80% of the cases, but can usually be treated with immunosuppressive therapy and rarely *(<10%)* leads to loss of the liver graft. However, over time, immunosuppressive therapy may have serious side effects.

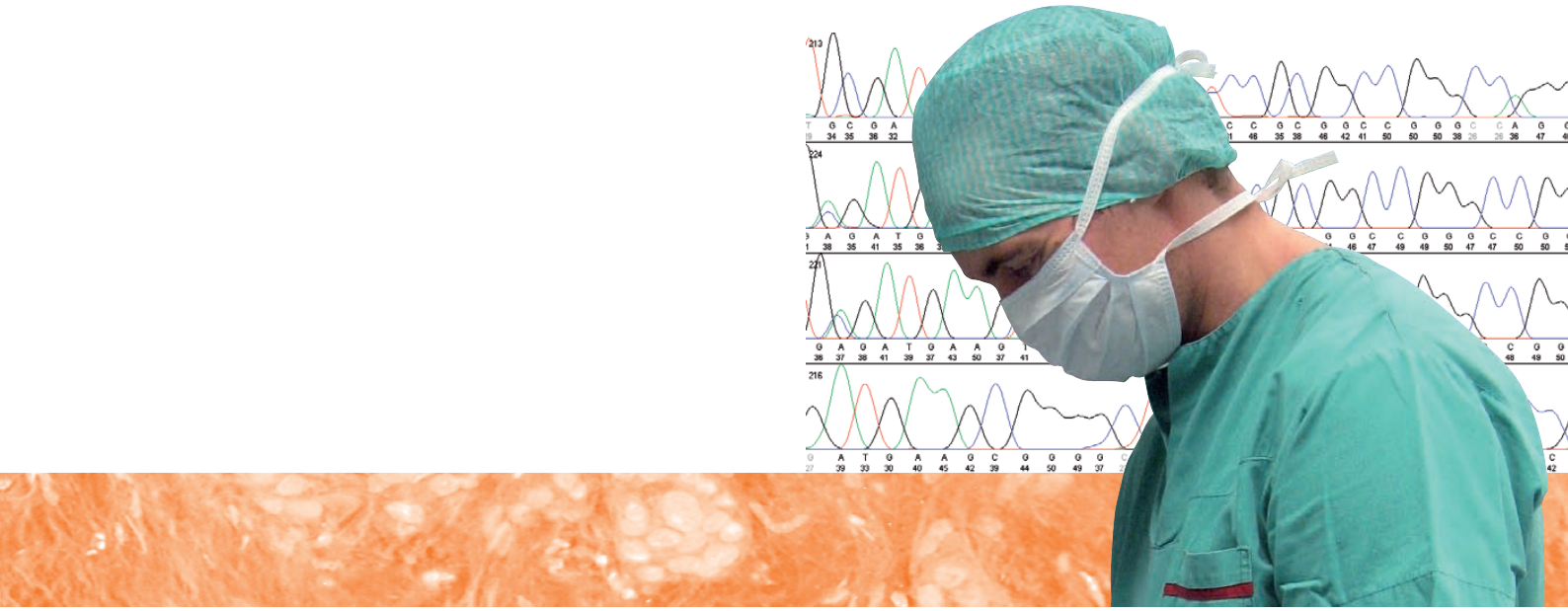
In patients with PSC, the risk of rejection is particularly high. Moreover, rejection episodes seem to predispose to recurrence of PSC in the transplanted liver. On this background it is of great interest to clarify risk factors for rejection in liver transplantation, with a particular emphasis on the high risk in patients with PSC.

CHALLENGES

- The definition of the disease states *("phenotypes")* under study in this work package is difficult. In particular, mild rejection-like immune responses may represent normal adaption to the "foreign" liver in the recipient and should not be treated or considered as such.
- In patients with PSC, the definition of disease recurrence relies on extensive exclusion of other causes of "PSC-like" changes in the bile ducts of the liver graft *(e.g. insufficient blood flow)*.

PROJECTS

- Define the immunological differences between mild and severe rejections.
- Define the immunological characteristics of acute rejection in PSC.
- Identify genetic risk factors *(in donor as well as recipient)* for rejections and graft loss.
- Investigate the risk factors identified in the genetic studies in a rat model of liver transplantation.



Publications

Publications 2008

Melum E, Karlsen TH, Schrumpf E, Bergquist A, Thorsby E, Boberg KM, et al.
Cholangiocarcinoma in primary sclerosing cholangitis is associated with NKG2D polymorphisms.
Hepatology 2008; 47(1): 90-6.

Karlsen TH, Schrumpf E, Boberg KM.
Gallbladder polyps in primary sclerosing cholangitis: not so benign.
Curr Opin Gastroenterol 2008; 24(3): 395-9.

Hov JR, Boberg KM, Karlsen TH.
Autoantibodies in primary sclerosing cholangitis.
World J Gastroenterol 2008; 14(24): 3781-91.

Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, Krawitt EL, et al.
Simplified criteria for the diagnosis of autoimmune hepatitis.
Hepatology 2008; 48(1): 169-76.

Eike MC, Nordang GB, Karlsen TH, Boberg KM, Vatn MH, Dahl-Jorgensen K, et al.
The FCRL3 -169T>C polymorphism is associated with rheumatoid arthritis and shows suggestive evidence of involvement with juvenile idiopathic arthritis in a Scandinavian panel of auto-immune diseases.
Ann Rheum Dis 2008; 67(9): 1287-91.

Bjornsson E, Olsson R, Bergquist A, Lindgren S, Braden B, Chapman RW, et al.
The natural history of small-duct primary sclerosing cholangitis.
Gastroenterology 2008; 134(4): 975-80.

Franke A, Balschun T*, Karlsen TH*, Sventoraityte J, Nikolaus S, Mayr G, et al.*
Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility.
Nat Genet 2008; 40(11): 1319-23.

Franke A, Balschun T*, Karlsen TH, Hedderich J, May S, Lu T, et al.*
Replication of signals from recent studies of Crohn's disease identifies previously unknown disease loci for ulcerative colitis.
Nat Genet 2008; 40(6): 713-5.

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*

Publications 2007

Karlsen TH, Schrumpf E, Boberg KM.
Genetic epidemiology of primary sclerosing cholangitis.
World J Gastroenterol 2007; 13(41): 5421-31.

Karlsen TH, Hampe J, Wiencke K, Schrumpf E, Thorsby E, Lie BA, et al.
Genetic polymorphisms associated with inflammatory bowel disease do not confer risk for primary sclerosing cholangitis.
Am J Gastroenterol 2007; 102(1): 115-21.

Karlsen TH, Boberg KM, Vatn M, Bergquist A, Hampe J, Schrumpf E, et al.
Different HLA class II associations in ulcerative colitis patients with and without primary sclerosing cholangitis.
Genes Immun 2007; 8(3): 275-8.

Karlsen TH, Boberg KM, Olsson M, Sun JY, Senitzer D, Bergquist A, et al.
Particular genetic variants of ligands for natural killer cell receptors may contribute to the HLA associated risk of primary sclerosing cholangitis.
J Hepatol 2007; 46(5): 899-906.

Aabakken L, Bretthauer M, Line PD.
Double-balloon enteroscopy for endoscopic retrograde cholangiography in patients with a Roux-en-Y anastomosis.
Endoscopy 2007; 39(12): 1068-71.

Wiencke K, Karlsen TH, Boberg KM, Thorsby E, Schrumpf E, Lie BA, et al.
Primary sclerosing cholangitis is associated with extended HLA-DR3 and HLA-DR6 haplotypes.
Tissue Antigens 2007; 69(2): 161-9.

Franke A, Ruether A, Wedemeyer N, Karlsen TH, Nebel A, Schreiber S.
No association between the functional CARD4 insertion/deletion polymorphism and inflammatory bowel diseases in the German population.
Gut 2006; 55(11): 1679-80.

AWARDS 2008

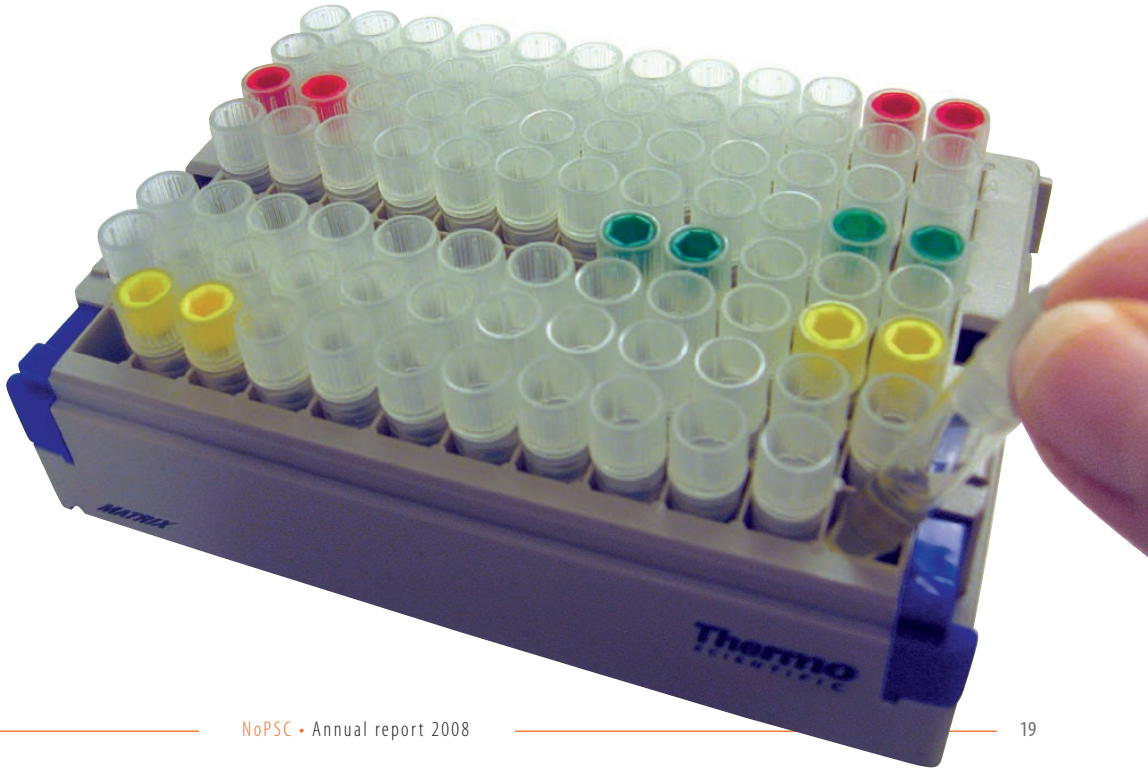
Helge Bell´s price for good clinical research in hepatology for 2008 was awarded to PhD student Espen Melum at the Norwegian PSC research center. The price is given on an annual basis for the best Norwegian article published in the area of clinical or translational basic research in hepatology. Espen Melum was awarded the price for the article *"Cholangiocarcinoma in primary sclerosing cholangitis is associated with NKG2D polymorphisms"* published in Hepatology *(see reference list)*. The work was done in close collaboration with several researchers at the center and Institute of Immunology.

Accounting 2008

The Norwegian PSC Research Center

	RIKSHOSPITALET		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2007			12.500.000	
Accounted expenses 2007		350.000		
Canica funds 2008			10.000.000	
Gift reinforcement funds 2008			2.500.000	
Wages 2008		1.403.744		707.387
Wage related expenses 2008		450.491		260.585
Overhead 2008		200.663		145.196
Infrastructure/equipment 2008		1.328.008		0
Other operating expenses 2008		2.545.109		13.495
Transfer from UiO 2008	7.454.500			7.454.500
Transfer to 2009 budget		**1.176.485**		**16.418.837**

All sums are in Norwegian kr.



The Norwegian PSC research center

www.rikshospitalet.no/nopsc

RIKSHOSPITALET

Rikshospitalet University Hospital, The Norwegian PSC research center
Address: NO-0027 Oslo • Tel: +47 23 07 00 00 • E-mail: nopsc@rikshospitalet.no • www.rikshospitalet.no/nopsc