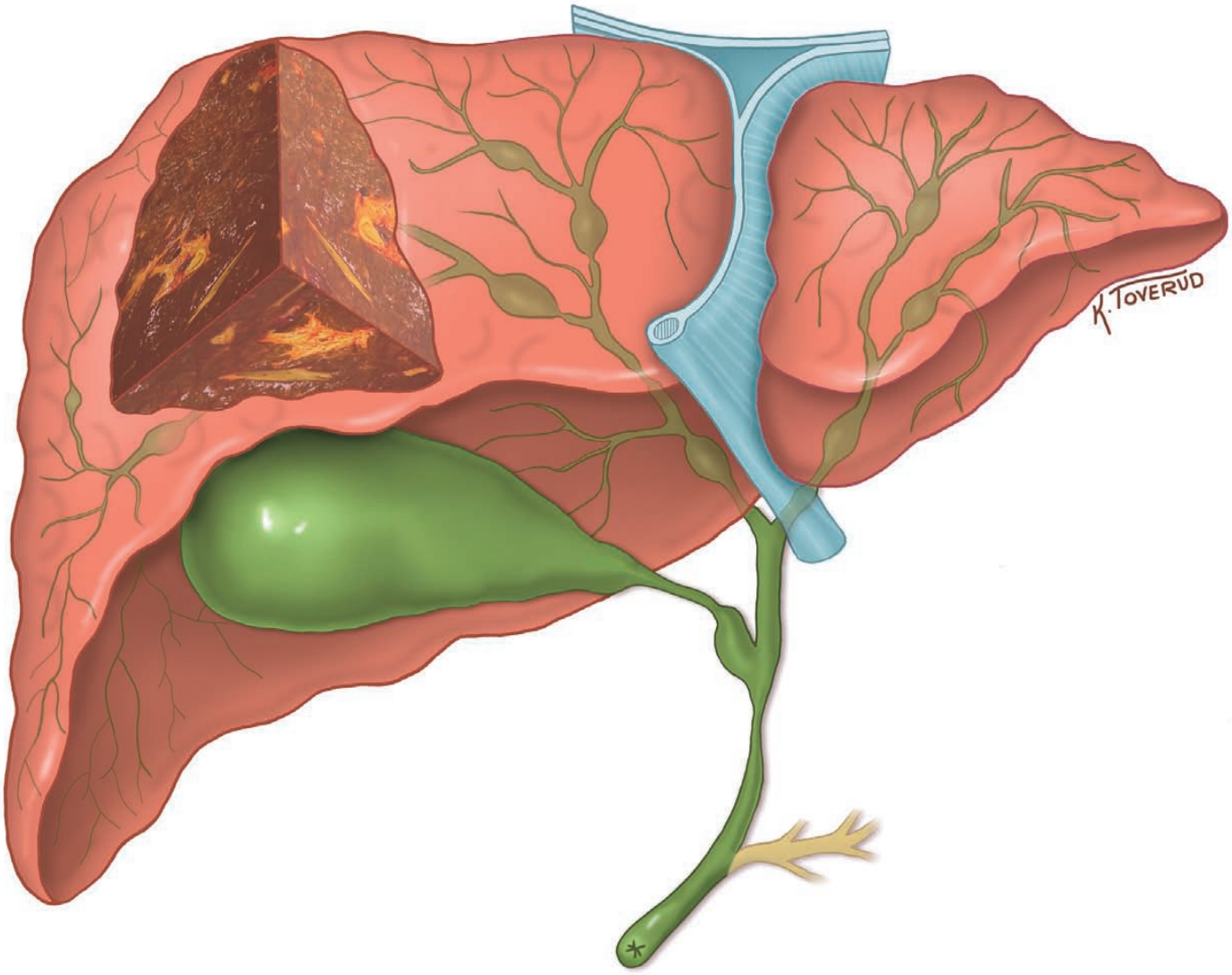

Annual report 2011

Norwegian PSC Research Center

NOPSC

Visit the NoPSC web pages: *www.ous-research.no/nopsc* and *www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/*

Oslo University Hospital

Annual report 2011

NoPSC ANNUAL REPORT 2011

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

TEXT: Hege Dahlen Sollid and Tom Hemming Karlsen, NoPSC
PUBLISHER: Oslo University Hospital
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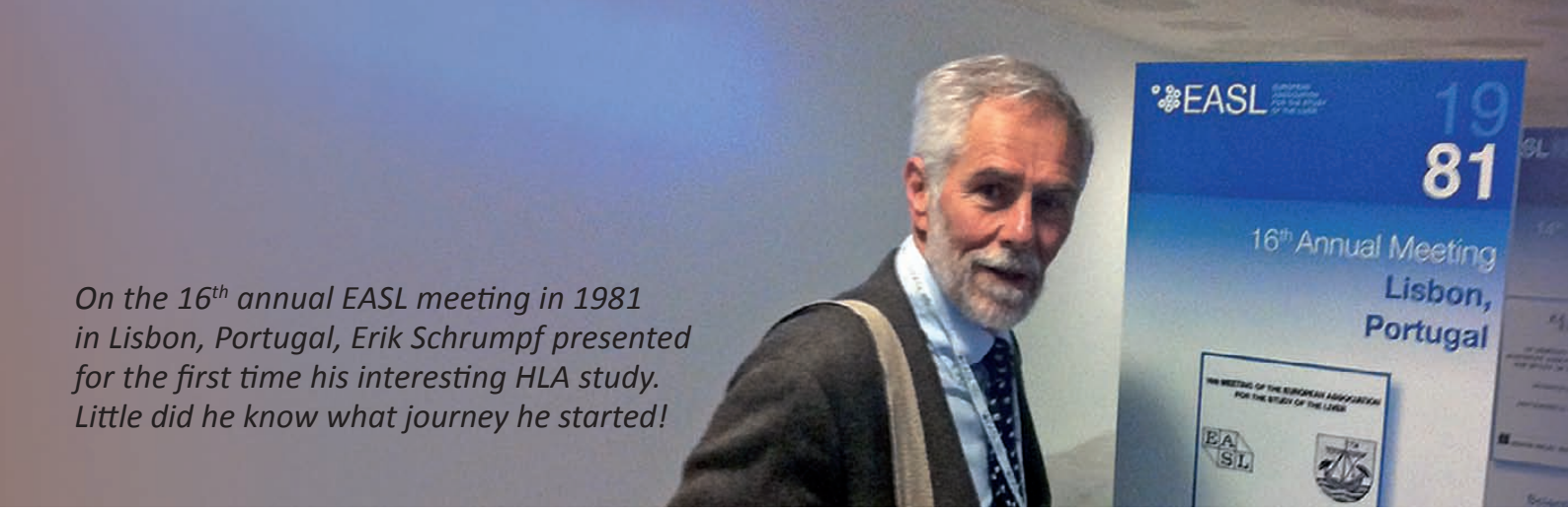
Leader´s comments

2011 was the 5th year with the very generous financial support of 10 million NOK annually for 10 years from Canica AS *(Stein Erik Hagen)* to Norwegian PSC Research Center *(NoPSC)*. As a matter of fact the establishment of NoPSC was a direct consequence of this donation. The formal start of the group took place in the spring 2008. As the money was given via The University of Oslo, *"Gift reinforcement"* of 25 % of the donated amount was released from the Norwegian Research Council. During 2011 the Norwegian Government decided to end this arrangement. This was a disappointment and surprise to many researchers for whom this *"Gift reinforcement"* had been of major importance. Representatives from the Government had the view that this arrangement was undemocratic; the distribution of money should be decided by government people exclusively. From recent unveiling we know that this may often give very undemocratic results. Anyway, thanks to considerable flexibility from Canica we managed to get hold of the gift reinforcement also for the remaining 5 years of the 10 year donation.

It is now time to ask where we stand. What are our critical measures of success and what are our challenges?

1. **The staff.** We have a well established core facility *(5 persons)* including laboratory and research support and informatics expertise. Three post docs *(one of them is presently in Boston)* are employed in addition to 6 research fellows. Two associate professors from abroad are linked to our group as are also 4 persons being presently in full time clinical job including the three members of the management group. One of the research fellows *(Johannes R. Hov)* defended his thesis during 2011; we expect the remaining 5 to do so during 2012-2013. It is now a challenge to recruit more research fellows to replace those who end their projects.

2. **Room facilities.** We have sufficient laboratory and office space within The Department of Transplantation Medicin and the Research Institute for Internal Medicine at Rikshospitalet.



On the 16th annual EASL meeting in 1981 in Lisbon, Portugal, Erik Schrumpf presented for the first time his interesting HLA study. Little did he know what journey he started!

Due to the Oslo University Hospital process this situation is clearly unstable.

3. **Network.** Since the start of NoPSC a substantial network has been established both nationally but most of all; internationally. As Tom H. Karlsen has been awarded a professorship at the University of Bergen, priority will be given to increase the collaboration between the Universities of Bergen and Oslo. Maintaining the international network is as important as establishing it; a continuous ongoing scientific activity is the key to success.

4. **Scientific production.** Science of high quality and within the fields that have been defined as important, are the most obvious measures of success. We regard ourselves to be in the international forefront of research related to PSC. During 2011 our research fellows received prizes for best abstracts at all the major congresses: EASL, DDW and UEGW. Johannes R. Hov from our group was awarded the Helge Bell price for best Norwegian publication within hepatology 2011. To keep up the pace we need not only to recruit more research fellows, but we must also take onboard new technology which is being developed all the time, and to some extent modify the focus of our research. We must admit that our scientific results, so far, have not been of importance for the practical handling of the patients i.e. diagnosis and treatment. This is a challenge.

Ahead of us we see substantial challenges in keeping our scientific momentum. From January 1st, 2012 Tom H. Karlsen has taken over as leader of the Management group. During a few years time he has demonstrated extraordinary qualifications as scientist and scientific leader. I'm sure he will handle the forthcoming challenges as well as opportunities
for NoPSC in the best possible way.

Professor Erik Schrumpf
Leader of Management Group
Oslo, 2012 May 2

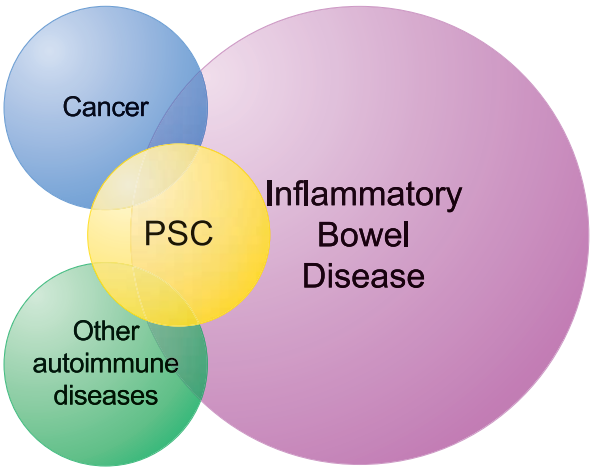
NO PSC
Norwegian PSC
Research Center

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 Scandinavia.

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



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

2011 in brief

Photo: © NoPSC

M.D. Johannes R. Hov defended his thesis in an excellent way.

In 2011, the high activity in both the research projects and the core facility continued. In total, members of NoPSC published 15 publications in high impact peer-reviewed journals. The projects were awarded 5 prizes during national and international conferences.

The present size of NoPSC is efficient and productive, and there was no expansion of the scientific team or core facility in 2011. Bente Woldseth left for other challenges after being at the center since the start, and was replaced by PhD Jarl Andreas Anmarkrud, who has valuable experience for many of the projects.

KEY NoPSC EVENTS IN 2011

- **Major scientific achievements**
  Multiple important scientific achievements were made during 2011 and will become evident by the publishing of several major articles throughout 2012. The work partly concludes the genetics agenda of NoPSC that has been performed with the intention of setting the stage for the ongoing translational efforts *(see project description on pages 8-12 for further details).* NoPSC also acquired funding for these ongoing efforts through external sources *(Helse-Sør Øst and EU-ESGI)*, an important first step taken toward establishing a future financial basis of the research activities.

- **Dissertation of Johannes R. Hov**
  On the 20th of September M.D. Johannes R. Hov defended his thesis *"Functional genetics in primary sclerosing cholangitis: Studies of the bile acid receptor TGR5 and genes in the HLA complex"* in an outstanding manner. The trial lecture was entitled *"Next generation genetics in inflammatory diseases".* The opponents, Professor David H. Adams from University of Birmingham and Researcher Stefan Johansson from Haukeland University Hospital contributed to an exceptional good scientific discussion with the candidate. Following his dissertation, Johannes R. Hov was assigned a 50 % post doc position at the center and a 50 % position as recident at the Gastroenterology department at Oslo University Hospital Rikshospitalet.

IMMUNOCHIP PROJECT UPDATE

In 2009, the Wellcome Trust Sanger Institute, Hinxton, UK *(www.sanger.ac.uk/)* initiated the Immunochip project. The project aims at identifying the genetic similarities and differences in a large number of immune mediated diseases, and represents a historic opportunity to map the genetic relationship in between these diseases. For more information, please see the annual report 2010.

During 2010 and 2011 more that 4000 DNA samples from PSC patients, along with more than 26 000 DNA samples from healthy controls were included world wide for the purpose of the Immunochip analysis in PSC. *See table to the right of this article.*

The majority of PSC samples were quality controlled and plated in Oslo, – a collaborative effort including several persons here at NoPSC, in particular Trine Folseraas, Bente Woldseth and Sigrid Næss.

Genotyping of the PSC samples were performed at the Institute of Clinical Molecular Biology, Christian-Albrechts-University (CAU) in Kiel, Germany and at the Department of Medical Genetics, Groningen, The Netherlands.

In 2011, the processing of the genotyping data was finally started. The finalizing steps of processing and analysis of the PSC Immunochip data will be performed in 2012 with main contributions to the analysis and manuscript preparation from NoPSC, CAU Kiel, Germany and the Sanger Institute, UK.

- **The 46th International Liver Congress™ by EASL**
  The congress was held in Berlin in March, and Tom H. Karlsen, together with Michael Trauner and Peter L. M. Jansen, directed the two-day long postgraduate course *"Cholestatic disease of the liver and bile ducts"* with more than 3,000 attendees. During the course, Dr. Kirsten Muri Boberg gave a presentation entitled *"Current consensus on the management of primary sclerosing cholangitis".* PhD students Johannes R. Hov and Trine Folseraas were chosen for oral presentation of their abstracts. In addition, Folseraas was given the prize for Best Clinical Abstract. She presented her findings during a general session.

Photo: © Silke Helmerdig, EASL 2011

Trine Folseraas is accepting her Best Clinical Abstract award at the International Liver Meeting in Berlin in March from Mark Thurz, Secretary General of European Association for the Study of the Liver.

- **Annual Guest professor meeting 2011**
  The annual guest professorship seminars were held in April, and all scientific projects at NoPSC underwent critical discussion. The guest professorship meetings serve as an important *"benchmarking"* of the NoPSC research projects that underwent critical evaluation and expansion. During these meetings, all post docs and Ph.D. students discuss their projects head-to-head with both Prof. Andre Franke and Prof. Arthur Kaser *(separately).* This allows for reflection of project content according to the highest possible international standards.

Photo: © NoPSC

Guest professor Arthur Kaser and post doc Anders Holm during their one-to-one meeting, discussing the next steps forward.

- **International PSC Study Group**
  NoPSC organized two meetings for the International PSC Study Group throughout 2011. Multiple projects are performed within this group *(see separate presentation at page 18)*, not only those driven and financed by NoPSC. The group has attracted some of the leading scientists in the field of liver diseases and is now being considered the main international arena for development and discussion of PSC projects in need of collaborative efforts.

- **NoPSC biobank**. The NoPSC biobank logistics has some capacity in excess of PSC. The efficient routines tightly linked with clinical patient care are now supporting also collaborating research groups within the Department of Organ Transplantation *(e.g. the group of Børre Fevang working on immunodeficiency).* Quite often the biobank also has visitors from other research groups planning to establish a state-of-the-art biobank. Hege Dahlen Sollid is now part of the working group set down to establish a broader biobank system at Oslo University Hospital, and Tom Hemming Karlsen is member of the Biobank Council of Oslo University Hospital; a recognition of the quality of the efforts put down in establishing the NoPSC biobank.

- **Home page**. In addition to the research websites of Oslo University Hospital (*www.ous-research.no/nopsc*) Norwegian PSC Research Center is now presented on the University of Oslo websites as well.

  Please visit us at:
  www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/index.html

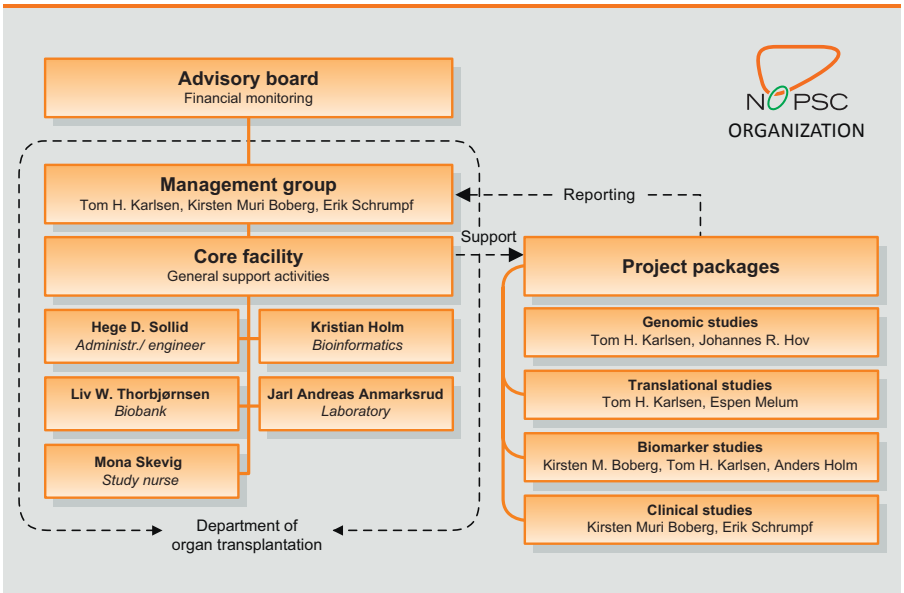
SAMPLE NUMBERS PSC IMMUNOCHIP PROJECT

ORIGIN	CASES	CONTROLS	TOTAL
Belgium	163	1425	1588
Canada	323	0	323
Canada/USA	0	1340	1340
Finland	308	504	812
France	45	0	45
Germany	852	5435	6287
Italy	0	299	299
Italy/Greece	69	0	69
The Netherlands	255	3421	3676
Norway	504	1412	1916
Poland	43	541	584
Spain	27	284	311
Sweden	282	2665	2947
UK	1121	8970	10091
USA	533	681	1214
Grand total	**4525**	**26977**	**31502**

Norwegian PSC Research Center (NoPSC)

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 PSC.

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



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

The Management group is continuously staking out the future plans of the center, and is of great support for the Executive Manager, Tom Hemming Karlsen. From January 1st 2012, Tom Hemming Karlsen is taking over as leader of the Management group.

The Core facility runs support functions of general importance for the project units and the research center in general. This includes a state-of-the-art biobank and data registry in the MEDinsight database *(clinical, technical and biological information).* In addition, all projects are given laboratory assistance and the technical level in e.g. HLA typing is world class.

We also have a dedicated bioinformatician who is providing computer support on all levels. Administrative support is also given by personnel in the core facility.

The Project units of NoPSC are defined by priorities of the Managment group *(see project description on pages 8-12).*

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

NoPSC ORGANIZATIONAL AIMS

- **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

- **Genomic studies**
- **Translational studies**
- **Biomarker studies**
- **Clinical studies**

See pages 8–12

THE ADVISORY BOARD

Ivar Prydz Gladhaug *(Leader)*
Institute of Clinical Medicine, University of Oslo

Randi Stene*
Institute of Clinical Medicine, University of Oslo

Unn-Hilde Grasmo-Wendler*
Institute of Clinical Medicine, University of Oslo

Kristian Bjøro
Div. of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Pål Aukrust
Div. of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital, Rikshospitalet

Nina Paulsen
Canica A/S

Peter Ruzicka
Canica A/S

** Unn-Hilde Grasmo-Wendler replaced Randi Stene in the Fall of 2011*

Team work

– a critical success factor to efficient patient inclusion and blood sampling

Two of the most important and central functions of the core facility are the recruitment of patients and the collection of biological material. This function is dependent on the every day collaboration between our study nurse, Mona Bjørnstad and our biomedical laboratory scientist (bioengineer), Liv Wenche Thorbjørsen.

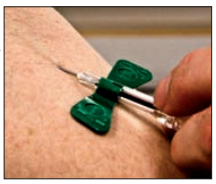


Photo: © Tone Thorbjørnsen

So far, the NoPSC state-of-the-art biobank has collected biological material from more that 900 individuals, stored in more than 60 000 2D barcoded tubes. Blood, bile, urine, feces and brush cytology samples are kept at -80 °C, while tissue biopsies from liver and bowel are stored in the gas phase of nitrogen tanks.

In order to include as many patients as possible, the tight collaboration between study nurse Mona Bjørnstad and biomedical laboratory scientist Liv Wenche Thorbjørnsen is crucial. They are our face towards the patient, and a link between the NoPSC research and the clinical activity at the Section of Gastroenterology. Mona and Liv Wenche have worked together since august 2009 and are now a well functioning team. Due to their team work, their advanced planning and flexibility, we are able to perform highly efficient patient inclusion and blood sampling.

Weekly, Mona receives lists over next week's patients and their planned activities during their stay. Together, Mona and Liv Wenche plan how and when the inclusion and blood sampling should take place. It must fit into the often tight schedule of the patient, and they are focused on not stressing the patient more than outmost necessary. All patients are given thorough information, both written and oral, regarding participation in our studies from Mona. They are given time to read through the information before she asks the patient if he/she would like to participate. Mona always stresses that participation is voluntary, and that participation does not alter their planned clinical examination/treatment. If the patient agrees, he/she signs an informed consent form. Liv Wenche is then notified, and she performs blood sampling at a convenient time.

Liv Wenche does all blood sampling personally as an effort to minimize pre-analytical variations, resulting in a standardized sampling procedure. Two patients are also sampled consecutively to further rationalize the sampling. In such event, according to NoPSC biobank standard operating procedures (SOP's), the sampling must be conducted within 30 minutes. This poses challenges and both Mona and Liv Wenche often arrive early in the morning to include and perform the blood sampling before the patient starts off on their planned examinations.

Photo: © NoPSC

Study nurse Mona Bjørnstad (left) and Biomedical Laboratory Scientist Liv Wenche Thorbjørnsen.

Quite often they experience changes in the planned clinical examinations, both related to location, extent and schedule. Sometimes, the patient also needs more time to decide whether to participate or not. Nonetheless, our experience so far is that the collaboration with doctors and nurses in the different wards are running smoothly. And even more important; most patients are positive when we approach them, and taking an extra blood sample is no problem!

Following sampling, the blood samples are brought to the biobank facilities and Liv Wenche prepares them following our SOP's. Some are frozen as is and some are, following centrifugation, aliquoted into a large number of 2D barcoded tubes. In average, more than 90 barcoded tubes are registered per patient. All tubes are scanned into the MEDinsight database, and information regarding e.g. sample type and date, SOP and volume follows each tube. The tubes are placed in boxes and positioned in the freezer. The procedures from sampling to the tubes are securely positioned takes approximately half a day.

Blood samples from healthy controls are also of our interest, and during 2009-2010 Liv Wenche included samples from more than 100 individuals. In addition, the NoPSC Biobank is turning out to be a valuable resource for several other ongoing projects at Oslo University Hospital and collaborating research groups throughout the world.

Genomic studies

NoPSC

Principal Investigator: **Tom Hemming Karlsen**
Affiliated post docs: **Espen Melum, Johannes R. Hov**
Affiliated Ph.D. students: **Trine Folseraas, Sigrid Næss, Bjarte Fosby**

During 2011 major fruits of the extensive work performed in the genetics group became evident in terms of the publication of a PSC genome-wide association study in Nature Genetics. Several other projects were published as part of the PhD thesis of Johannes R. Hov. The group also contributed to the meta-analysis of genome-wide association studies in ulcerative colitis which also was published in Nature Genetics. Several other large-scale projects were completed throughout 2011 and will be published throughout the first half of 2012. In addition to an extended analysis of the Nature Genetics dataset and a direct comparison between the genetics of PSC and ulcerative colitis, the Immunochip project was completed at the logistical and technical level. The project includes more than 4,000 PSC patients and 26,000 healthy controls and compares the genetics of PSC with multiple other immune mediated diseases. The three projects will make up the PhD thesis of Trine Folseraas.

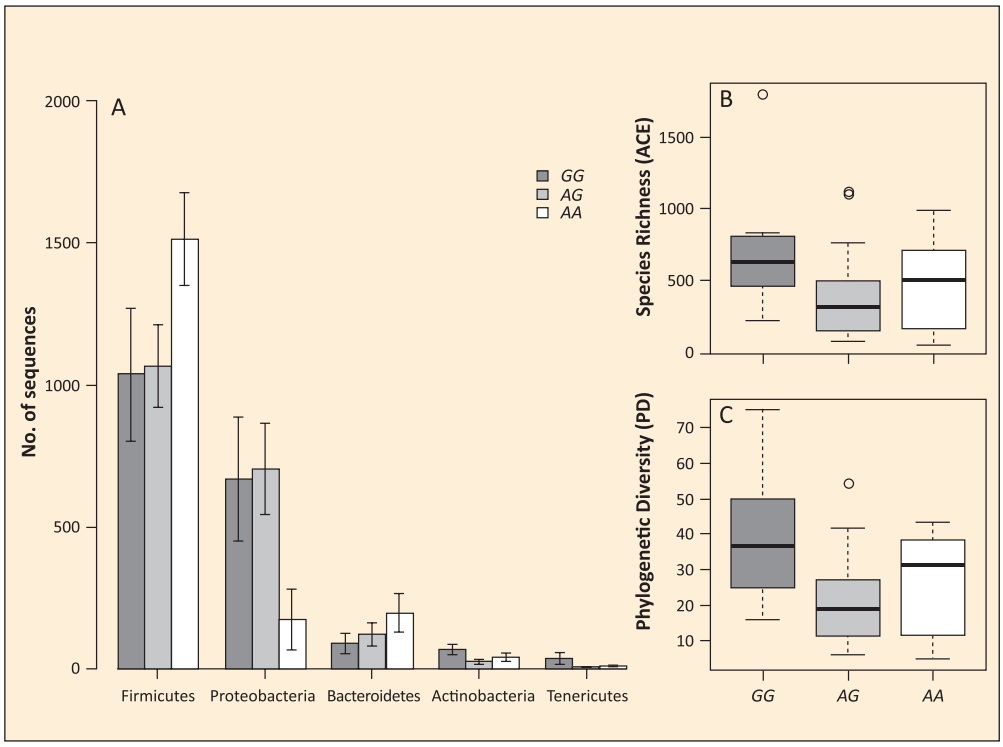
Three main directions are taken for the onward genomics work at the Norwegian PSC Research Center.

First, a heavy focus will be put on resolving the genetic details of the HLA association. This facilitated by the group being awarded a 200,000 Euro grant from the ESGI EU program *(www.esgi-infrastructure.eu/)* for the development of novel HLA typing technologies. The work also involves characterization of antigens binding the PSC associated HLA molecules as well as the corresponding T-cell response.

While the group is strongly involved in ongoing genome-wide association studies in PSC in the US and the UK, there will be a shift in the existing skills in human genomics to relevant applications in microbiomics. There is good reason to believe that the gut microbial community composition is of importance in shaping the immune response in PSC and several projects have been initiated.

Finally, Norwegian PSC Research Center contributes to several ongoing studies aimed at detecting genetic risk factors for clinical complications of PSC *(e.g. itching/pruritis, cholangiocarcinoma and disease progression).*

The publication *"Electrostatic modifications of the human leukocyte antigen-DR P9 peptide-binding pocket and susceptibility to primary sclerosing cholangitis"* by Hov JR et al. was featured on the cover of the June 2011 issue of Hepatology. The study explored the HLA-DRB1 gene, encoding parts of the HLA-DR molecule, which is important for presenting antigen to the immune system. It was shown that the characteristics of the antigen-binding part of HLA-DR molecule, in particular the so-called P9 pocket, was associated with PSC susceptibility. These molecular characteristics of HLA-DR could influence which antigens are presented to the immune system in PSC, possibly predisposing to disease-causing immune responses.



The figure shows analyses of the composition of the microbiota in bile according to the genotype (AA, AG or GG) of the FUT2 (Secretor) gene in the individuals. FUT2 is a gene associated with PSC susceptibility and has previously been shown to affect the microbiota composition of the intestine.

The close relationship between PSC and IBD and the presence of interactions between PSC risk genes and microbial composition make further investigation of gut and bile microbiota a strong priority of the genomics group. Given the possibility of changing gut microbial composition through dietary and other means, understanding the impact of microbiota on immune responses in the bowel and bile duct of the PSC patients may easily have therapeutic implications.

The data from n=39 PSC patients are included in Folseraas T et al. "Extended Analysis of a Genome-Wide Association Study in Primary Sclerosing Cholangitis Detects Multiple Novel Risk Loci" which will be published in Journal of Hepatology in 2012.

Translational studies

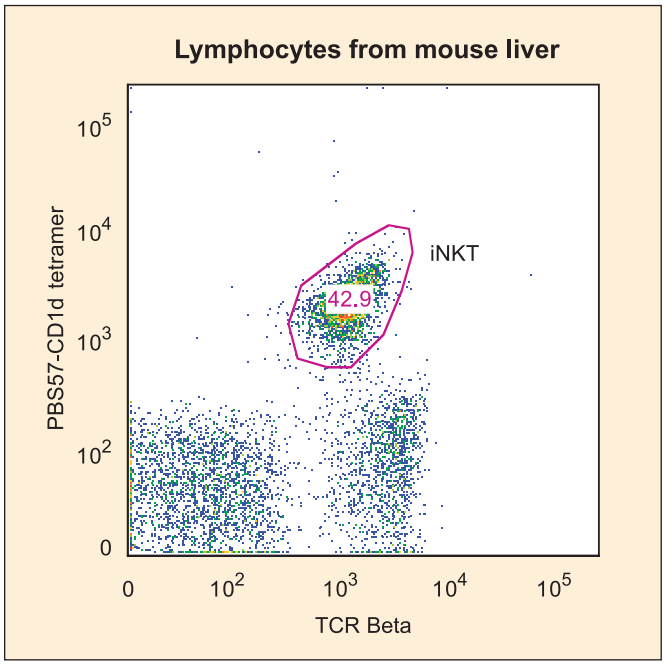
NoPSC

Principal Investigator: **Tom Hemming Karlsen**
Affiliated post docs: **Espen Melum, Alexey Shiryaev, Johannes R. Hov**
Affiliated Ph.D. students: **2 new PhD students fall 2012**

Based on findings from the genetic studies, a three-fold approach is being taken. First, the overall impression of the genetics of PSC is that it represents a polygenic pro-inflammatory state with large similarities as to the genetics of many other autoimmune and immune-mediated conditions. This makes it of interest to make the NOD.c3c4 mouse the first dedicated in vivo model system at Norwegian PSC Research Center. It is a polygenic model system for autoimmunity and features spontaneous biliary inflammation with similarities to PSC. A large number of experiments have been defined to characterize the pathophysiologic mechanisms that make these changes arise. The group was awarded a PhD fellowship grant for this project, meaning the first PhD student to be paid from "external funds".

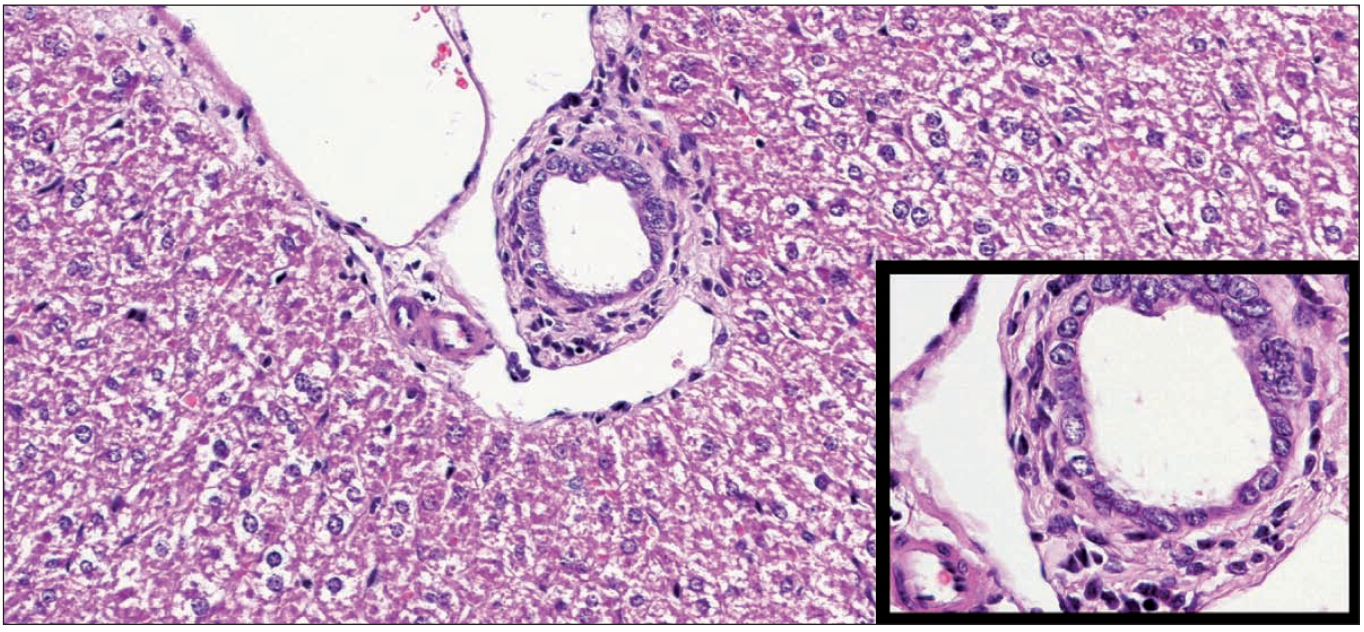
There is also a basis for working on single genes coming from the genetic analysis of PSC, and an extensive work package has been initiated for one of the risk genes from the genetic studies. The work includes in vitro characterization *(cell line system, functional assays)*, in vivo characterization *(knock-out mouse is already available and will be studied extensively and crossbred with strains relevant to the molecular mechanism involved)* as well as clinical characterisation in biomaterial available in the NoPSC biobank and from patients at collaborating hospitals.

Finally, as an extension of the post doc stay of Espen Melum at Harvard Medical School, a work package on the function of natural killer T cells *(NKT cells)* has been defined. The work aims at elucidating basic mechanisms of importance to studies in the NOD.c3c4 mouse and is related to the genomics efforts on gut and biliary microbiota.



Dot plot demonstrating the relative percentage of invariant NKT cells in the liver of a B6 mouse. Lymphocytes were stained with a PBS57-Cd1d tetramer and a TCR beta antibody. The double positive cells represent the invariant NKT cells. NKT cells will be the focus of a novel project package at NoPSC that was granted additional support from Helse-Sør Øst (3 year's salary for a PhD student). The known interaction between NKT cells and microbiota links this work package closely to the activities of the genomics package.

Microscopic picture of the liver in mice lacking the PSC associated Bcl2l11 gene. The picture demonstrates an increased presence of immune cells suggesting that this gene plays a role in regulation of immune cells in the liver and bile ducts. Several mouse models are under study at NoPSC to understand the biological function of the proteins that are encoded by the PSC susceptibility genes.



Biomarker studies

NoPSC

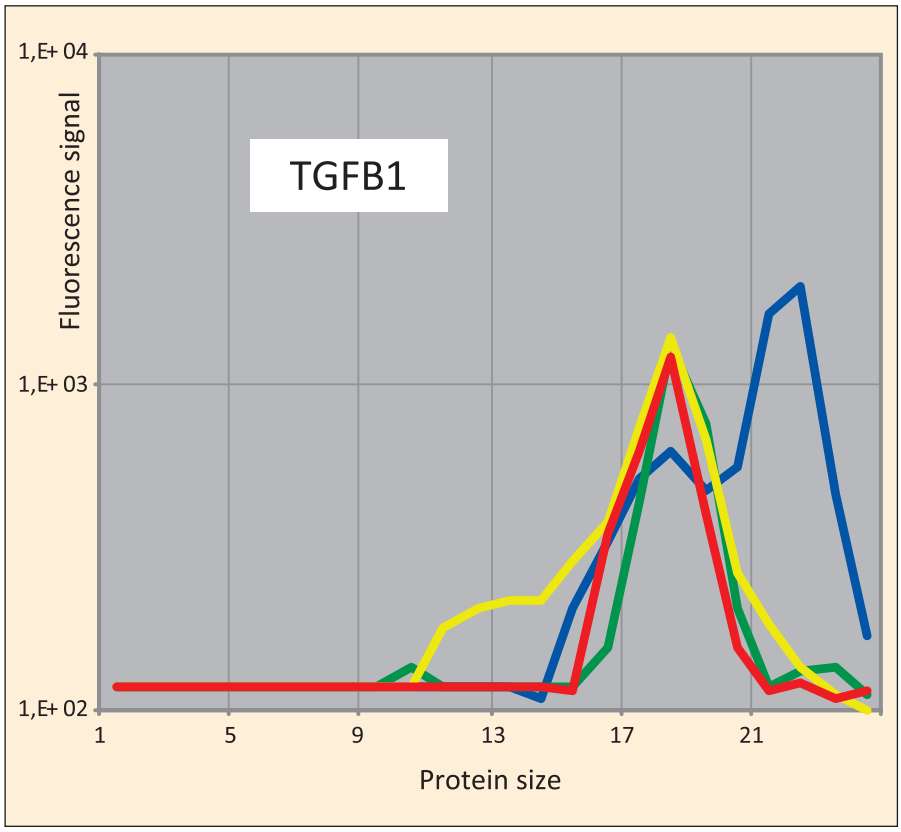
Principal Investigator: **Tom Hemming Karlsen and Kirsten Muri Boberg**
Affiliated post docs: **Anders Holm, Alexey Shiryaev, Johannes R. Hov**
Affiliated Ph.D. student: **Kim Andresen**

The biomarker studies rely on the availability of two technological advantages accessible within the research center. First, NoPSC post doc Anders Holm has made the large scale multiplex proteomics platform *(array based)* in the group of Fridtjof Lund-Johansen at the Institute of Immunology at OUS Rikshospitalet applicable to bile and serum samples from PSC patients. Throughout 2011 a protein panel of almost 2,000 different proteins aimed at measuring disease activity has been established. This panel is now being applied to carefully selected patient populations to define biomarkers suitable to predict disease stage and disease progression in PSC. This will be of great importance for the clinical management of the patients as well as for evaluating the effects of novel drugs in PSC.

Not only disease activity will be measured, also the presence and absence of PSC will be evaluated using the protein biomarker panel. As a prerequisite for future treatments of PSC, it is of importance to establish the diagnosis prior to the development of too much scar tissue in the liver. Mainly this applies to patients with inflammatory bowel disease, where collaboration with the Inflammatory Bowel in South Eastern Norway *(IBSEN)* group has been established.

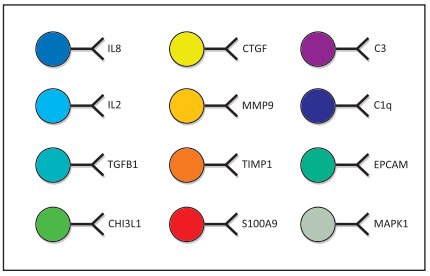
At 20-years follow up, approximately 500 patients will undergo magnetic resonance cholangiography *(MRC)* to define presence/absence of biliary changes. Applying the multiplex proteomics platform on this study population will yield a subset of proteins that later can be measured prospectively.

A major challenge in PSC is the development of cholangiocarcinoma. The multiplex protein array will be applied also to define differences in protein composition from patients with and without cholangiocarcinoma. In 2011, the biomarker activities were targeted at the development of a biomarker panel at the epigenetic level, in close collaboration with the group of Ragnhild Lothe at OUS Radiumhospitalet. The results from these efforts will be published throughout 2012 together with epigenetic analyses of brush cytology specimens from bile ducts to define early stages of cancer in PSC *(dysplasia)*. The Norwegian PSC Research Center also contributed to an effort aimed at detecting specific protein degradation products in urine from patients with cholangio carsinoma. The results will be publised in 2012.



◀ This plot shows the TGFB1 protein expression in bile from 4 different PSC patients. TGFB1 is present in all 4 samples and an additional cleaved form is present in the patient represented by the blue line. *(Protein size is indicated on the x-axis where large proteins elute early and small proteins late. The amount of protein is represented by the fluorescence emmission on the y-axis).*

▼ The multiplexed immunoprecipitation – flow cytometry (MIP-FCM) platformconsists of 1500+ color-coded beads each coated with an antibody against a specific target. Combined with flow-cytometric detection this enables simultaneous detection of the presence and context of hundreds of preselected proteins in a given sample. This unique technology allows for efficient screening of large numbers of patient samples (serum, bile, cell samples etc.), and will become important for efficiently establishing novel prog-nostic and diagnostic markers in PSC.



Clinical studies
NoPSC

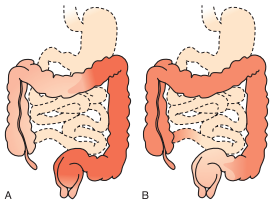
Principal Investigator: **Kirsten Muri Boberg**
Affiliated Ph.D. student: **Kristin Kaasen Jørgensen**

PhD student Kristin Kaasen Jørgensen completed most of the work related to her PhD thesis throughout 2011. This is evident from several papers to be published in 2012.

The work has shed new light on the clinical characteristics of PSC patients as well as on the impact of liver transplantation on inflammatory bowel disease behavior in patients with PSC. The work has detected multiple risk factors for worsening of inflammatory bowel disease in PSC, amongst other the type of immunosuppressive regimen used following transplantation. The work has also detected several important risk factors for the development of cancer of the large bowel in patients with PSC.

In sum the work is an important contribution to the clinical management of patients with PSC; pre- and post-liver transplantation. A large volume of biomaterial has been collected as part of the project and serves as a resource for several projects throughout 2012, amongst other related to the microbiomics agenda within the genomics project package.

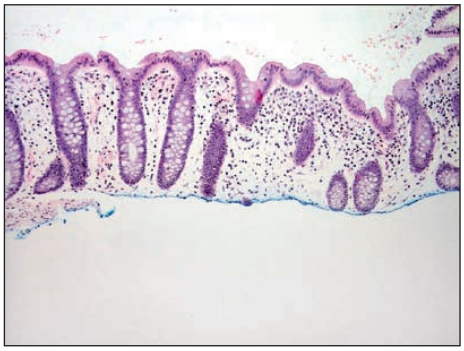
NoPSC participates in a multicenter study aimed at evaluating which type of endoscopic treatment is preferable for PSC patients with strictures of the main bile ducts *(balloon dilatation with or without concomitant stenting)*. Throughout 2012, NoPSC will also contribute to a large multicenter *(>30 centers)* trial of a new drug in PSC, norursodeoxycholic acid. The trial is managed by the FALK pharmaceutical company, and patients from Oslo will be included and followed up by Erik Schrumpf as one of many tasks to be continued after retirement.



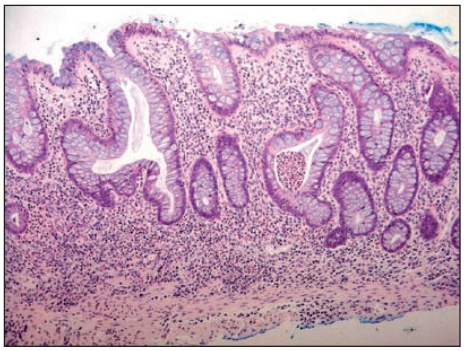
Most of the focus of the clinical studies has so far been put on precisely determining the characteristics of IBD in PSC before and after liver transplantation. Compared with regular UC (A), colitis in PSC (B) is usually mild with a right-sided predominance. Many of the patients have rectal sparing and backwash ileitis.

In a prospective study of 110 consecutive PSC-IBD patients, we found that 86% of patients had histopathologic signs of inflammation involving the right colon. Although the general level of inflammation was low, the degree of inflammation was higher in the right compared to the left colon. Backwash ileitis was demonstrated in 20% of patients and rectal sparing in 65%. (Jørgensen KK et al., Inflamm Bowel Dis, 18 (3), 536-45, 2012).

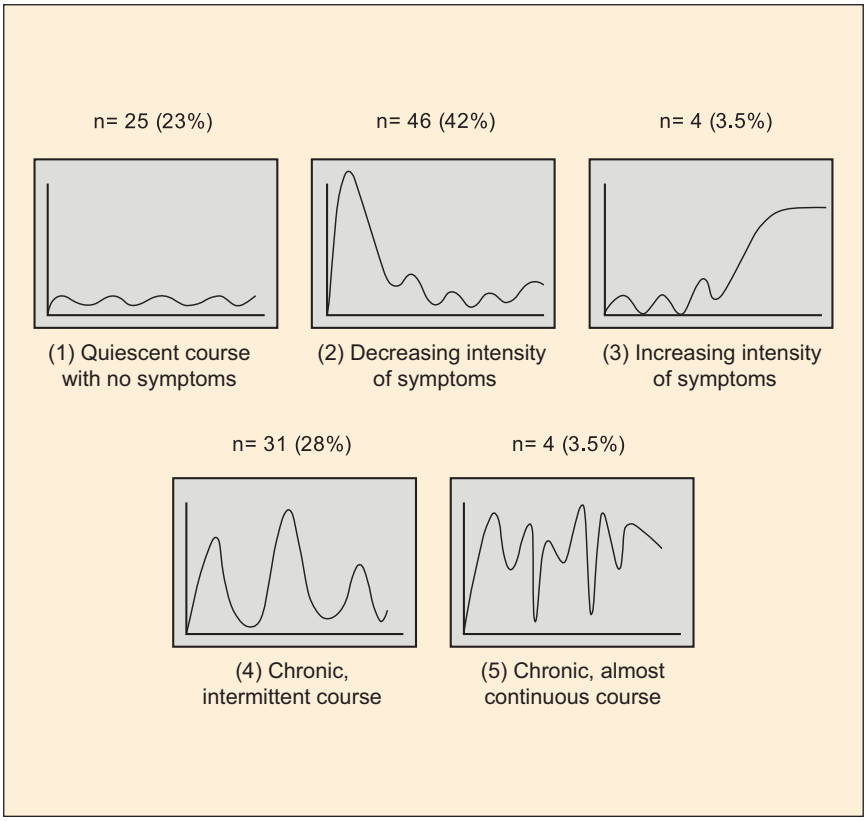
HISTOLOGY OF NORMAL AND INFLAMED COLONIC MUCOSA



A) Normal colonic mucosa



B) Chronic active inflammation with moderately increased number of inflammatory cells in the lamina propria with cryptitis and cryptabcesses



Five different curves depicting the course of IBD from diagnosis until last follow-up in 110 PSC-IBD patients *(based on the patients' own opinion)*. The majority *(65%)* of patients reported non or sparse symptoms in their course of IBD. (Jørgensen KK et al., Inflamm Bowel Dis, 18 (3), 536-45, 2012).

People at NoPSC

Management group

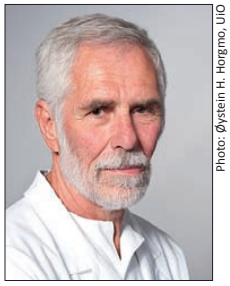


Photo: Øystein H. Horgmo, UiO

Prof. Erik Schrumpf
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Leader

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

Ragnhild A. Lothe
Professor / Head of Dep.

Dept. of Cancer Prevention
Oslo University Hospital

Presentation of post docs at NoPSC


Photo: Øystein H. Horgmo, UiO

Espen Melum
MD, Ph.D.
Post doc (Boston)

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Espen Melum studied medicine at the University of Oslo and graduated in 2006. While in medical school he started doing research on PSC genetics, and after finishing his clinical internship he joined the group as a Ph.D. student with Prof. Tom H. Karlsen as his main supervisor. His motivation for starting PSC research was the largely unknown pathogenesis of PSC and the opportunity to work within a highly motivated research group.
Following his Ph.D. thesis defense in 2010 he joined the laboratory of Prof. Richard S. Blumberg at Harvard Medical School in Boston as a post-doctoral research fellow to work on genetically modified mouse models. During his time in Boston he has been working on mechanisms related to activation of Natural Killer T (NKT)-cells, a subset of lymphocytes particularly abundant in the liver (up to 30%), that are likely to play a regulatory role in PSC. Espen Melum will return to Oslo and NoPSC in June 2012 and will continue to work on NKT-cell activation together with a PhD student.


Photo: Øystein H. Horgmo, UiO

Alexey Shiryaev
MD, Ph.D.
Post doc

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Alexey Shiryaev received his medical diploma (summa cum laude) in 2004 from the Northern State Medical University, Arkhangelsk, Russia. During graduate- and post-graduate studies he was continuously involved in several collaborative Norwegian-Russian research projects in the fields of immunology and infectious diseases. This activity was noted with several awards and scholarships including a scholarship of President of Russian Federation for excellence in research and studies. After completing internship he proceeded with a Ph.D. fellowship in molecular medicine at Tromsø University Hospital with focus on intracellular signaling. In November 2010, after defending his theses, he joined our research center.
Alexey Shiryaev supplements and expands on findings from genetic studies at the molecular and cellular level. Throughout 2012 and 2013 he will be responsible for collaboration with Prof. Arthur Kaser's group at Cambridge University, United Kingdom, characterizing and expanding our knowledge of a particularly interesting molecular pathway shown to be strongly associated with PSC in the genetic studies.

Scientific personnel


Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Oslo University Hospital

NoPSC Guest professors


Photo: Thea Tønnessen, OUS HF

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Professor
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Div. of Cancer Medicine, Surgery and Transplantation
Oslo University Hospital


Photo: © CAU

Andre Franke
Professor in Genetics
Institute of Clinical Molecular Biology, Christian-Albrechts-University (CAU)
Kiel, Germany


Photo: © Addenbrooke's Hospital

Arthur Kaser
Prof. of Gastroenterology
Div. of Gastroenterology and Hepatology, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK


Photo: Øystein H. Horgmo, UiO

Anders Holm
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Post doc
anders.holm@rr-research.no

Anders Holm obtained his Ph.D. in analytical chemistry in 2004 at the Department of Chemistry, University of Oslo and has since then acquired broad knowledge in the field of proteomics. Holm spent 4 years working with mass spectrometry based proteomics at the Proteomics Core Facility, Institute of Immunology (IMMI) at OUH. In April 2008 Holm joined the affinity proteomics group of Dr. Fridtjof Lund-Johansen, also at IMMI, to contribute in the build-up of an antibody array platform to be used for human cell lines and freshly isolated cells.

Early 2011 Holm was employed by NoPSC with the aim to apply this technology in the search for biomarkers of diagnostic and prognostic utility in PSC. The array technology enables simultaneous detection of over 1500 predefined proteins and the strategy is to generate proteomic *"biomarker profiles"* using a large panel of markers rather than trying to identify one single marker. During 2011 Anders Holm has optimized the technology platform for the analysis of bile samples from PSC patients that will be performed throughout 2012.


Photo: Øystein H. Horgmo, UiO

Johannes Roksund Hov
MD, Ph.D. student/
Post doc from October 1st.
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Johannes Roksund Hov graduated as an M.D. from the University of Oslo in 2003. He joined the Norwegian PSC Research Center as it was founded, late 2007, and received his Ph.D. in genetics in 2011 with the thesis *"Functional genetics in primary sclerosing cholangitis: Studies of the bile acid receptor TGR5 and genes in the HLA complex"*.

He is currently 50% post doc. fellow at NoPSC with a particular focus on further genomic studies in PSC. One research axis is the further genetic characterization of the HLA complex and T cell reactivity, as well as investigations of B and T cell antigens in PSC. In addition, Johannes R. Hov is responsible for projects related to genomic characterization of the microbiota in gut and bile ducts of patients with PSC. He combines his research activity with a 50% position as resident at the Section of Gastroenterology at Oslo University Hospital, Rikshospitalet.

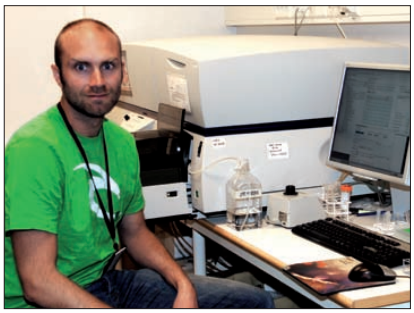
2011 snap shots

Espen Melum is accepting his Best Abstract award at Digestive Disesase Week in Boston in November.

Kristin Kaasen Jørgensen is accepting her Top Abstract Prize at United European Gastroenterology Week (UEGW) in Stockholm in October from Rolf Hultcrantz, president of United European Gastroenterology Federation.

Jarl Andreas Anmarkrud has taken over the lab management in an excellent way.

The management group: Tom Hemming Karlsen, Erik Schrumpf and Kirsten Muri Boberg.



Anders Holm is running bile samples on the LSRII flow cytometer instrument at IMMI, OUH.

Post doc Espen Melum and Ph.D. student Kim Andresen were not present.

Photo: Foto- og videotjenesten, Oslo University Hospital

Kristian Holm is working together with guest researcher Michael Wittig from CAU, Kiel, Germany.

Sigrid Næss is registering samples from a liver transplantation into the MEDinsight database.

Mona Bjørnstad is administering the distribution of questionnaires to patients and controls in the Pruritus project.

Kim Andresen is discussing his projects with guest professor Andre Franke from CAU, Kiel, Germany.

Liv Wenche Thorbjørnsen is making sure our samples are safely stored.

On top of full clinical duties as liver transplant surgeon, Bjarte Fosby is working on the genetics of liver graft rejection.

Kirsten Muri Boberg and Tom Hemming Karlsen at the annual NoPSC boat trip.

Johannes R. Hov, Jarl Andreas Anmarkrud, Kristian Holm, Sigrid Næss, Alexey Shiryaev, Hege Dahlen Sollid and Erik Shrumpf are enjoying the annual NoPSC boat trip.

Network

KEY LOCAL COLLABORATORS

RESEARCH INSTITUTE FOR INTERNAL MEDICINE

NoPSC is affiliated with Research Institute for Internal Medicine (*www.ous-research.no/riim*) as a separate research group (*www.ous-research.no/karlsen/*), and is now well intergrated at the institute.

SECTION FOR ORGAN TRANSPLANTATION

Head of Department of Transplantation, Pål-Dag Line, MD Ph.D., Head of Section of Organ transplantation Aksel Foss, MD prof., and Ph.D. student Bjarte Fosby, MD, at the Institute for Surgical Research (*www.surgicalresearch.net/*) collaborate with NoPSC on projects related to liver transplantation in PSC.

Photo: © Tone Thorbjørnsen

DEPARTMENT OF PATHOLOGY

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

DEPARTMENT OF MEDICAL GENETICS

The Immunogenetics group, led by professor Benedicte A. Lie (*www.ous-research.no/home/lie/home/6630*), is involved in several projects related to the further characterization of the HLA association in PSC.

INSTITUTE OF IMMUNOLOGY

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

DEPARTMENT OF MEDICAL BIOCHEMISTRY

In conjunction with post doc Hov's IgG4 project and the establishment of a quality control cohort for the NoPSC biobank, collaboration with respectively Olav Klingenberg, MD and Ph.D. student Yngve Thomas Bliksrud, MD, were established during 2011.

CENTER FOR CANCER BIOMEDICINE

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

THE IBSEN STUDY GROUP

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

CENTRE FOR MOLECULAR BIOLOGY AND NEUROSCIENCE

The collaboration with Jon K. Lærdal, PhD within the Bioinformatics group (*www.cmbn.no/group-rognes.php*) at the CMBN on structural modeling has been a great resource and inspiration for the genetic projects.

KEY INTERNATIONAL COLLABORATORS

THE UK PSC GROUP

JOHN RADCLIFFE HOSPITAL, OXFORD

(*www.oxfordradcliffe.nhs.uk/forpatients/departments/gastro_i/gastroenterology/consultants.aspx*)
Prof. Roger Chapman has set up a consortium of key hepatologists in the UK with financial and infrastructural (database and protocols) support from NoPSC. The initiative is managed by several co-workers at Addenbrooke's Hospital and the Wellcome Trust Sanger Institute in Cambridge (including Dr. George Mells, Dr. Simon Rushbrook, Dr. Graeme Alexander, Dr. Richard Sandford, Dr. Brijesh Srivastava and Dr. Carl Anderson).

CAMBRIDGE INSTITUTE FOR MEDICAL RESEARCH, CAMBRIDGE

The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale and senior researcher James Traherne in Cambridge (*www.cimr.cam.ac.uk/investigators/trowsdale/index.html*) are invaluable for the progress of several of our functional genetic projects.

DEPT OF MEDICINE, UNIVERSITY OF CAMBRIDGE, ADDENBROOKE'S HOSPITAL, CAMBRIDGE

In conjunction with the transformation of project activity from gene identification to translational efforts, Prof. Arthur Kaser (*www.immunology.cam.ac.uk/directory/profile.php?ak729*) is assigned as guest professor for 3 years and will help guide the establishment of novel methodologies. In 2011 he took up his appointment as Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK.

INSTITUTE FOR CLINICAL AND MOLECULAR BIOLOGY, CHRISTIAN-ALBRECHTS-UNIVERSITY, KIEL, GERMANY

Several co-workers of Prof. Stefan Schreiber in the German excellence cluster *"Inflammation at interfaces"* (*www.inflammation-at-interfaces.de/en_startseite.phtml*) are involved in technically advanced projects within the genetic and translational projects. Prof. Andre Franke is assigned as guest professor to participate in these projects (*www.ikmb.uni-kiel.de/cms/ueber-uns/mitarbeiter/mitarbeiterseite/andre-franke/*).

THE MAYO CLINIC, ROCHESTER, USA

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

HEINRICH-HEINE-UNIVERSITY DÜSSELDORF, GERMANY

Functional characterization of genetic variation of the bile acid receptor TGR5 is performed together with Prof. Dieter Häussinger and senior researcher Verena Keitel in Düsseldorf (*www.uniklinik-duesseldorf.de/englisch/departments/departmentofgastroenterologyhepatologyandinfectiology/page.html*).

MEDICAL UNIVERSITY OF VIENNA AND MEDICAL UNIVERSITY OF GRAZ, AUSTRIA

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

THE NORDIC LIVER TRANSPLANT GROUP

Collaborators in Helsinki (*Prof. Krister Höckerstedt, Dr. Helena Isoniemi*), Stockholm (*Prof. Bo-Göran Ericzon*), Gothenburg (*Prof. Michael Olausson*) and Copenhagen (*Dr. Allan Rasmussen*) are involved in several projects 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 at NoPSC. The clinical data and blood samples that were collected by Dr. Ulrika Broomé over more than a decade, still serve as a valuable resource for these collaborative projects.

IRCCS ISTITUTO CLINICO HUMANITAS MILAN, ITALY

Dr. Pietro Invernizzi and co-workers Carlo Selmi and Ana Lleo in Milan (*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, as well as evaluating serum biomarkers for cholangiocarcinoma in PSC.

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

The collaboration with Prof. Mario Strazzabosco and Dr. Luca Fabris (*www.celiver.org/index.php?option=com_content&task=view&id=19&Itemid=29&lang=english*) is important for several of the genetic projects. In particular, the experience in cholangiocyte biology of this group has proven essential in the establishing of the cholangiocyte isolation protocols.

International PSC Study Group (IPSCSG) Annual report

In Oslo June 2010 a total of 45 active PSC researchers from Norway, Sweden, Finland, Germany, Switzerland, Austria, Italy, Spain, France, Belgium, the Netherlands, the UK, Ireland, the US and Canada met and established the International PSC Study Group (IPSCGS, *www.ipscsg.org*, password required).

MEMBERS OF THE STEERING COMMITTEE

Prof. **Michael Manns**, Hannover, Germany
Prof. **Keith Lindor**, Rochester, MN, US *
Prof. **Konstantinos Lazaridis**, Rochester, MN, US *
Prof. **Peter Jansen**, Amsterdam, The Netherlands
Prof. **Michael Trauner**, Vienna, Austria
Prof. **Roger Chapman**, Oxford, UK
Dr. **Tom Hemming Karlsen**, Oslo, Norway
(coordinator/secretary)

* *Prof. Keith Lindor was replaced in November 2011 by Prof. Konstantinos Lazaridis, Rochester, MN, US.*

Representation in IPSCSG is based on active participation in ongoing studies and meetings are held biannually at the International Liver Congress™ by the European Association for the Study of the Liver (*EASL*) and the American Association for the Study of Liver Diseases (*AASLD*) annual conferences. During 2011 the group first met in Berlin during the International Liver Congress™ March 30th and then in San Francisco during AASLD November 7th.

DURING 2011 THE GROUP HAS MADE PROGRESS ON SEVERAL TOPICS:

- In the Immunochip project a preliminary analysis was presented and the further strategy was discussed. Working groups for each individual subproject with a specified leader was proposed.
- The IPSCSG database format was sent to all study groups in April, and most groups have now modified their database according to the final IPSCSG format. A summary article on the total IPSCSG study population of 4,500-5,000 PSC patients is in the planning. In the Dilstent2 project the first patients have been included.
- Questionnaires were completed in the *"itching"* (*cholestatic pruritus*) genetics project, and answers from parts of the UK and Canadian PBC and German and Norwegian PSC populations are presently available and analysis presently being performed.
- Regarding the cholangiocyte Cre project the ASBT is now done (*Prof. Arthur Kaser*) and under evaluation. The cholangiocyte transcriptome sequencing is ongoing and will be completed in 2012.
- Different funding opportunities have been discussed, like EU FP7/FP8 and HEALTH program 2013, but so far there has been no call perfectly matching the needs of the group.

Ill: © Anton Balazh / Shutterstock.com

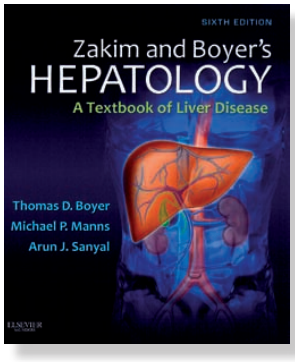
PLANNED MEETINGS IN 2012:

During the International Liver Meeting™ in Barcelona Friday April 20th, in Hamburg 11th-12th for the second focus group meeting and during the AASLD in Boston in November.

INTERNATIONAL PSC STUDY GROUP NETWORK

COUNTRY, CITY	INSTITUTION
Austria	
Graz	Medical University of Graz
Vienna	Medical University of Vienna
Belgium, Leuven	University Hospital Gasthuisberg
Canada	
Alberta	University of Alberta
Calgary	Health Research and Innov. Centre/Univ. of Calgary
Toronto	Toronto Western Hospital/University of Toronto
Finland, Helsinki	Helsinki University Central Hospital
France, Paris	Université Pierre et Marie Curie
Germany	
Düsseldorf	University Medical Center Düsseldorf
Hamburg	University Medical Center Hamburg-Eppendorf
Hannover	Hannover Medical School
Heidelberg	University Hospital of Heidelberg
Kiel	Christian-Albrechts-University of Kiel
Tübingen	University Hospital of Tübingen
Ireland, Dublin	St. Vincent's University Hospital
Iceland, Reykjavik	The National University Hospital of Iceland
Italy	
Ancona	Università Politecnica delle Marche
Rozzano (Milan)	IRCCS Istituto Clinico Humanitas
Padua	University of Padua
Japan, Tokyo	Teikyo University School of Medicine
Norway, Oslo	Oslo University Hospital/University of Oslo
Poland	
Szczecin	Pomeranian Medical University
Warsaw	Maria Skłodowska-Curie Memorial Cancer Center
Spain, Barcelona	Hospital Clínic i Provincial
Switzerland, Zurich	University Hospital Zurich
Sweden	
Stockholm	Karolinska University Hospital
Uppsala	Uppsala University Hospital
Gothenburg	Sahlgrenska University Hospital
Linköping	University of Linköping
The Netherlands	
Amsterdam	Academic Medical Center/University of Amsterdam
Groningen	University Medical Center Groningen
Rotterdam	Erasmus University Medical Centre
UK	
Birmingham	University of Birmingham
Cambridge	Addenbrooke's Hosp./The Wellcome Trust Sanger Inst.
London	Univ. Col. London/Royal Free Hosp./Imp. Col. Hosp.
Newcastle	Newcastle University
Norwich	Norfolk and Norwich University Hospital
Oxford	John Radcliffe Hospital
US	
California	University of California Davis Medical Center
Connecticut	Yale University
Minnesota	Mayo Clinic College of Medicine
Pennsylvania	University of Pennsylvania
Tennessee	Memphis Medical Center

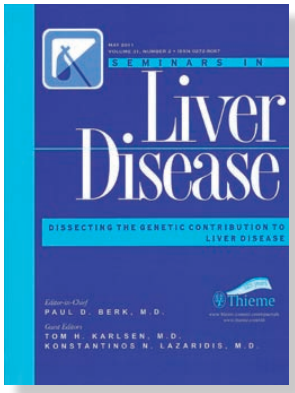
General contributions 2011



CONTRIBUTION TO ZAKIM AND BOYER: A TEXTBOOK OF HEPATOLOGY, 6TH EDITION

Karlsen TH, Boberg KM, Schrumpf E.
Primary Sclerosing Cholangitis.

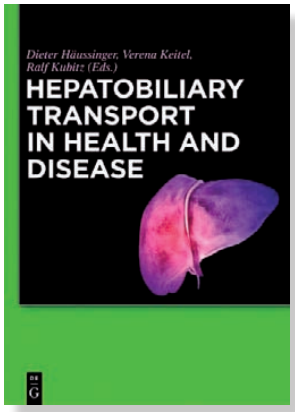
The book was released in July 2011.
See annual report 2010
for more information.



CONTRIBUTION TO SEMINARS IN LIVER DISEASE, VOLUME 31

Karlsen TH, Kaser A.
Deciphering the genetic predisposition to primary sclerosing cholangitis.

Released in May 2011.
See annual report 2010
for more information.



HEPATOBILIARY TRANSPORT IN HEALTH AND DISEASE

De Gruyter, Berlin, to be released in 2012

Editors: *Häussinger D, Keitel V, Kubitz R, Hov JR, Schrumpf E, Karlsen TH.*
Molecular basis of primary sclerosing cholangitis.

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

Recent advances in PSC have shown that genetic defects affecting T cell activity and tolerance are important and taken together; the biliary tract seems to be a *"weak spot"* among the mucosal surfaces, critically dependent on T cell mediated immune tolerance. Genetic variants affecting innate immune responses could also contribute to a pro-inflammatory hepatic environment. The close relationship between inflammation in the gut and liver could be caused by shared genetic susceptibility, influx of bacterial products from the intestine and/or gut activated T cells entering the liver.

Defects related to bile acid homeostasis and the protective measures against toxic bile are also likely to be of importance, but whether these are primary or only modifying event is an open question. In addition, bile acid toxicity and chronic inflammation influence the neoplastic process in PSC, but host factors like cancer immunosurveillance is likely to take part.

In conclusion, several disease mechanisms contribute to the bile duct injury in PSC. Autoimmunity is highlighted in this text, but other pathogenetic mechanisms are also likely to be important, and may in some patient subgroups represent the initiating events.

Communications

NoPSC international lectures by invitation 2011

Karlsen TH.
Pathogenesis and management of primary sclerosing cholangitis.
Meetings of gastroenterology
Padua University, Padua, Italy, March 15th.

Karlsen TH.
The clinical utility of genome-wide association studies *and*
Basic Research Symposium: "Genetics".
EASL International Liver Congress
Berlin, Germany, March 30th - April 4th.

Boberg KM.
Current consensus on the management of primary sclerosing cholangitis.
EASL International Liver Congress
Berlin, Germany, March 30th.

Folseraas T.
Novel susceptibility loci identified in primary sclerosing cholangitis.
EASL International Liver Congress
Berlin, Germany, March 30th - April 4th.

Melum E.
New PSC Genes – What Should We Do with Them?
PSC partners meeting
Sacramento, CA, USA, April 30th.

Karlsen TH.
Clinical and pathophysiological implications of genome-wide analysis studies in PSC.
Réunion centres de compétence des maladies inflammatoires des voies biliaires.
Paris, France, May 26th.

Hov JR.
Progress and prospects in genetics of primary sclerosing cholangitis
Sig. K. Thoresen Foundation Symposium "Gene diversity in historical Norway and its present day applications".
The Norwegian Academy of Science and Letters, Oslo, Norway, November 2nd.

Karlsen TH.
Genetics in PSC
The American Association for the Study of Liver Diseases, The Liver Meeting
San Francisco, CA, USA, November 4th - 8th.

Karlsen TH.
Do genetics explain the mystery of primary sclerosing cholangitis?
Hepatology 2011 and Beyond.
Hannover, Germany, December 2nd.

Publicity 2011

In conjunction with the publication of the PSC genome-wide association study in Nature Genetics the study was presented several places

"Norsk artikkel i Nature Genetics"

Norsk Gastroenterologisk forening
NBS-nytt, issue 2/2011, page 22

"Ny kunnskap om patogenesen ved sjelden gallegangssykdom"

Tidsskrift for Norsk Legeforening, issue 6/2011, page 533

"Ny kunnskap om sjelden gallegangssykdom"

Official web pages of Oslo University Hospital, online February 2nd

www.oslo-universitetssykehus.no/aktuelt/nyheter Sider/ny-kunnskap-om-sjelden-gallegangsykdom.aspx

Other NoPSC headlines

"Fant nye ledetråder ved gallegangsbetennelse"

Dagens Medisin, online September 21st

www.dagensmedisin.no/nyheter/ fant-nye-ledetrader-ved-gallegangsbetennelse/

"Bioingeniører i høyspesialisert forskningsmiljø"

Bioingeniøren, issue 8/2011 page 11-14

http://viewer.zmags.com/ publication/85728978#/85728978/1

"Rimi-Hagens milliondonasjon gir resultater"

Uniforum, online December 16th

www.uniforum.uio.no/nyheter/2011/12/ rimi-hagens-milliondonasjon-gir-resultater.html

Publications 2011

1. ***Folseraas T, Melum E,*** *Franke A,* ***Karlsen TH***
   Genetics in primary sclerosing cholangitis
   Best Pract Res Clin Gastroenterol, 25 (6), 713-26 (Impact 2.2)

2. ***Boberg KM, Lind GE***
   Primary sclerosing cholangitis and malignancy
   Best Pract Res Clin Gastroenterol, 25 (6), 753-64 (Impact 2.2)

3. *Wiencke K,* ***Boberg KM***
   Current consensus on the management of primary sclerosing cholangitis
   Clin Res Hepatol Gastroenterol, 35 (12), 786-91

4. *Naalsund A, Lund MB, Mynarek G, Aakhus S,* ***Boberg KM****, Nordøy I*
   A man in his 60s with severe respiratory failure
   Tidsskr Nor Laegeforen, 131 (17), 1654-7

5. ***Folseraas T, Karlsen TH***
   To MMP or not to MMP: a role for matrix metalloproteinase 3 in primary sclerosing cholangitis?
   Liver Int, 31 (6), 751-4 (Impact 3.8)

6. ***Hov JR****, Keitel V,* ***Schrumpf E****, Häussinger D,* ***Karlsen TH***
   TGR5 sequence variation in primary sclerosing cholangitis
   Dig Dis, 29 (1), 78-84 (Impact 1.0)

7. *Janse M, Lamberts LE, Franke L, Raychaudhuri S, Ellinghaus E, Muri Boberg K,* ***Melum E****,* ***Folseraas T****,* ***Schrumpf E****, Bergquist A, Björnsson E, Fu J, Jan Westra H, Groen HJ, Fehrmann RS, Smolonska J, van den Berg LH, Ophoff RA, Porte RJ, Weismüller TJ, Wedemeyer J,Schramm C, Sterneck M, Günther R, Braun F et al.*
   Three ulcerative colitis susceptibility loci are associated with primary sclerosing cholangitis and indicate a role for IL2, REL, and CARD9
   Hepatology, 53 (6), 1977-85 (Impact 10.9)

8. ***Hov JR****, Kosmoliaptsis V, Traherne JA, Olsson M,* ***Boberg KM****, Bergquist A,* ***Schrumpf E****, Bradley JA, Taylor CJ, Lie BA, Trowsdale J,* ***Karlsen TH***
   Electrostatic modifications of the human leukocyte antigen-DR P9 peptide-binding pocket and susceptibility to primary sclerosing cholangitis
   Hepatology, 53 (6), 1967-76 (Impact 10.9)

9. ***Karlsen TH, Kaser A***
   Deciphering the genetic predisposition to primary sclerosing cholangitis
   Semin Liver Dis, 31 (2), 188-207 (Impact 5.3)

10. ***Karlsen TH****, Lazaridis KN*
    At the end of the beginning. Foreword
    Semin Liver Dis, 31 (2), 111-3 (Impact 5.3)

11. ***Boberg KM***
    Current consensus on the management of primary sclerosing cholangitis
    Karlsen TH and Lasaridiz K, editors. Proceedings from Postgraduate course of meeting of The European Association for the Study of the Liver, Berlin, Germany, 2011. p. 81-85.

12. *Moghaddam A,* ***Melum E****, Reinton N, Ring-Larsen H, Verbaan H, Bjøro K, Dalgard O*
    IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection
    Hepatology, 53 (3), 746-54 (Impact 10.9)

13. *Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, Lagacé C, Scott R, Amininejad L, Bumpstead S, Baidoo L, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Colombel JF, Denson LA, De Vos M, Dubinsky M, Edwards C et al.*
    Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47
    Nat Genet, 43 (3), 246-52 (Impact 36.4)

14. *Friman S, Foss A, Isoniemi H, Olausson M, Höckerstedt K, Yamamoto S,* ***Karlsen TH****, Rizell M, Ericzon BG*
    Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results
    Scand J Gastroenterol, 46 (3), 370-5 (Impact 2.0)

15. ***Boberg KM****, Chapman RW, Hirschfield GM, Lohse AW, Manns MP,* ***Schrumpf E****, International Autoimmune Hepatitis Group*
    Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue
    J Hepatol, 54 (2), 374-85 (Impact 9.3)

16. ***Melum E****, Franke A, Schramm C, Weismüller TJ, Gotthardt DN, Offner FA, Juran BD, Laerdahl JK, Labi V, Björnsson E, Weersma RK, Henckaerts L, Teufel A, Rust C, Ellinghaus E, Balschun T,* ***Boberg KM****, Ellinghaus D, Bergquist A, Sauer P, Ryu E,* ***Hov JR****, Wedemeyer J, Lindkvist B, Wittig M et al.*
    Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci
    Nat Genet, 43 (1), 17-9 (Impact 36.4)

17. ***Boberg KM***
    Managing the patient with features of overlapping autoimmune liver disease
    Hirschfield GM, Heathcote EJ, editors. Autoimmune Hepatitis: A Guide for Practicing Clinicians. Clinical Gastroenterology. Springer, New York, 2011, DOI 10.1007/978-1-60761-569-9_12.

THESES:

Hov JR
Functional genetics in primary sclerosing cholangitis: Studies of the bile acid receptor TGR5 and genes in the HLA complex
University of Oslo, Institute for Clinical Medicine, 2011.

Photo: © Oslo University Hospital

Awards

AWARDED HELGE BELL´S PRICE FOR GOOD CLINICAL RESEARCH IN HEPATOLOGY FOR 2010

National Liver Meeting, Oslo, March 2011

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.

Mutational Characterization of the Bile Acid Receptor TGR5 in Primary Sclerosing Cholangitis

Published in PLoS ONE

Hov JR**, Keitel V, Laerdahl JK, Spomer L, Ellinghaus E, ElSharawy A, **Melum E**, **Boberg KM**, Manke T, Balschun T, Schramm C, Bergquist A, Weismüller T, Gotthardt D, Rust C, Henckaerts L, Onnie CM, Weersma RK, Sterneck M, Teufel A, Runz H, Stiehl A, Ponsioen CY, Wijmenga C, Vatn MH*, for the IBSEN study group, *Stokkers PCF, Vermeire S, Mathew CG, Lie BA, Beuers U, Manns MP, Schreiber S, **Schrumpf E**, Haüssinger D, Franke A, **Karlsen TH

SELECTED FOR BEST OF DIGESTIVE DISEASE WEEK (DDW)

Chicago, USA, May 2011, and:

BEST CLINICAL ABSTRACT AT INTERNATIONAL LIVER MEETING™ (EASL)

Berlin, Germany, March 2011

Novel susceptibility loci for primary sclerosing cholangitis identified by genome-wide association and replication analysis.

Melum E**, **Folseraas T**, Juran B, Weersma RK, Schramm C, Weismüller TJ, Gotthardt DN, **Boberg KM**, Janse M, Buchert E, Björnsson E, Henckaerts L, Rust C, Teufel A, Bergquist A, Ryu E, **Hov JR**, **Holm K**, Ponsioen CY, Runz H, Sterneck M, Vermeire S, Wijmenga C, Beuers U, **Schrumpf E**, Manns MP, Lazaridis K, Schreiber S, Franke A, **Karlsen TH

AWARDED ONE OF TOP SIX OUTSTANDING ORIGINAL PAPERS

Jan-July 2011 at Oslo University Hospital

This award is given to papers that have achieved great impact internationally or have otherwise distinguished themselves in particular. The price of NOK 50 000 is given as an inspiration and is of free disposal for the research group.

Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci

Published in Nature Genetics

Melum E**, **Franke A**, Schramm C, Weismüller TJ, Gotthardt DN, Offner FA, Juran BD, Laerdahl JK, Labi V, Björnsson E, Weersma RK, Henckaerts L, Teufel A, Rust C, Ellinghaus E, Balschun T, **Boberg KM**, Ellinghaus D, Bergquist A, Sauer P, Ryu E, **Hov JR**, Wedemeyer J, Lindkvist B, Wittig M, Porte RJ, **Holm K**, Gieger C, Wichmann HE, Stokkers P, Ponsioen CY, Runz H, Stiehl A, Wijmenga C, Sterneck M, Vermeire S, Beuers U, Villunger A, Schrumpf E, Lazaridis KN, Manns MP, Schreiber S, **Karlsen TH

AWARDED TOP ABSTRACT PRIZE AT UNITED EUROPEAN GASTRO-ENTEROLOGY WEEK (UEGW)

Stockholm, Sweden, Oct 2011, and:

AWARDED BEST CLINICAL ABSTRACT FROM A NORWEGIAN UNIVERSITY HOSPITAL

Annual Meeting of the Norwegian Gastroenterology Association, Lillehammer, Norway, February 2011

Colorectal neoplasia in PSC patients undergoing liver transplantation: a Nordic multicenter study

Gut 2011;60 (Suppl 3) A1

Jørgensen KK**, Lindstrom L, Cvancarova M, Castedal M, Friman S, **Schrumpf E**, Foss A, Isoniemi H , Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, **Boberg KM

Accounting 2011

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2010	2.220.633		18.749.914	
Canica funds 2011			54.000.000	
Gift reinforcement funds 2011			13.500.000	
Interest			487.278	
Own share			152 727	
Transfer from UiO	14.156.574			14.156.574
Wages		3.143.783		2.236.183
Wage related expenses		934.207		811.002
Overhead		466.505		457 078
Infrastructure/equipment		768.353		
Other operating expenses		8.026.846		19.998
Award money	50.000			
Transfer to 2012 budget		**3.087.513**		**69.209.085**

UiO accounting revised by Riksrevisjonen. OUH accounting revised by PricewaterhouseCoopers.

All sums are in Norwegian kr.

Photo: © Per Marius Didriksen / Oslo University Hospital

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www.ous-research.no/nopsc

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

Oslo University Hospital

www.oslo-universitetssykehus.no