Oslo University Hospital

Annual report 2010

Norwegian PSC Research Center

NO PSC

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Annual report 2010

NOPSC ANNUAL REPORT 2010

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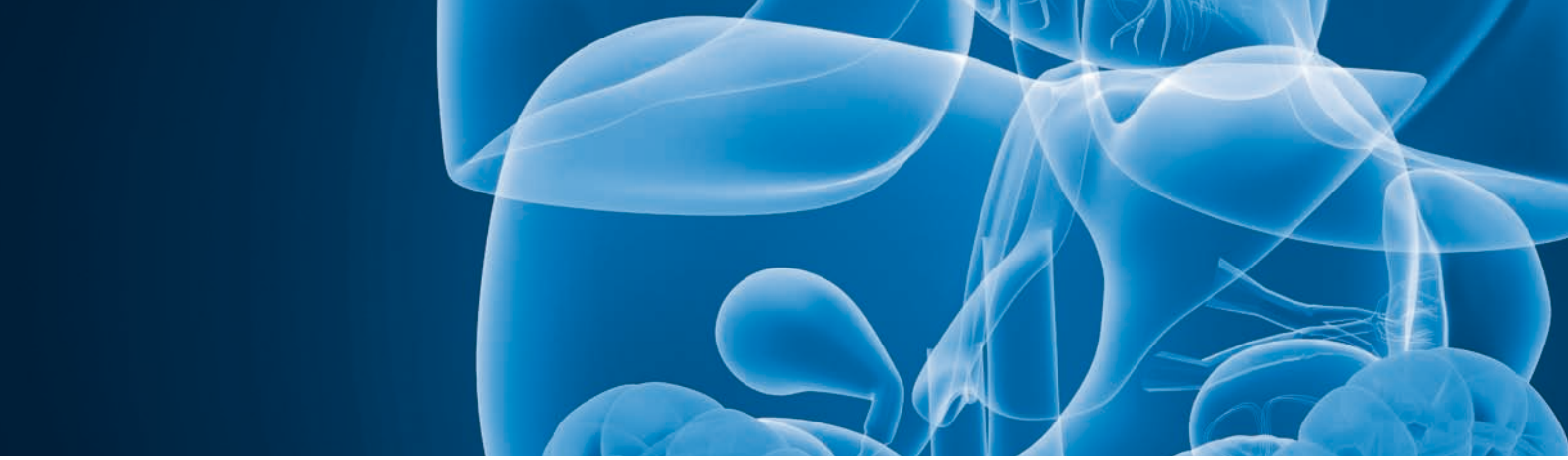
Leader´s comments

Norwegian PSC Research Center (NoPSC) has now existed for more than 3 years. This period has been demanding in building-up the activities to a level corresponding to our favourable financial situation. We have aimed at a process characterized by a certain speed but also *"full control"*. We feel that we have succeeded in recruiting a group of people covering all skills needed the most, we have access to adequate research areas, and we have established contact with important groups for future collaboration – both nationally and internationally. Our main projects during 2010 have been:

1. Optimize the distribution of working tasks among our employees, and the spending of their time. Tom Hemming Karlsen went into clinical work from September 1st and most of the administrative job is now taken care of – on a part time basis – by Hege Dahlen Sollid and also Kristian Holm and Mona Bjørnstad.

2. Our main focus has obviously been on research activities. We have been through a building-up period e.g., the construction of the biobank and database and further strengthening of collaboration with other researchers. Nevertheless, we have now started a period of *"harvesting"* i.e. we are now able to see results of the work invested during the first years of NoPSC *(see Publications page 22).*

3. Our 3rd goal has been to achieve as much attention as possible around PSC. This is partly done by providing new information based on scientific studies of high quality. Most of this was achieved by the acceptance of the publication "Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci", published online in Nature Genetics December 12th, 2010, with Espen Melum as first author and Tom Hemming Karlsen as last author.



Several other highquality publications from our group *(see Publications)* have also contributed significantly to this. The fact that Johannes Hov was awarded the Helge Bell price as best Norwegian paper within hepatology 2010, also deserves mentioning.

Equally important it has been to have PSC on the agenda at international meetings and to have representatives from our group in central positions in PSC related activities. Kirsten Muri Boberg has been co-author of both the European and American guidelines for handling of PSC patients. Several presentations dealing with PSC have been given at different meetings by members of our group *(see Communications page 21)*, and the group has also contributed on a large scale in writing reviews on PSC *(see Publications).*

In June 2010 we had an important meeting in Oslo where the International PSC Study Group was established *(see separate description page 18).* Representatives from all centers involved in major PSC research were present. Tom Hemming Karlsen was elected secretary of the group, and we had a fruitful 2nd meeting in connection with the American liver congress in Boston *(AASLD)* in October 2010.

We are still optimistic for the future. There is an ongoing, and quite disturbing, process involving all hospitals in the Oslo region. The final result of this process is difficult to foresee. However, we have reason to believe that science on high international level will be given possibilities to evolve also in the future.

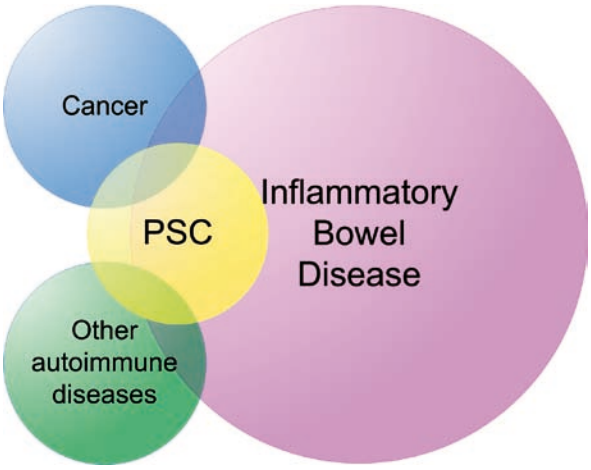
Oslo 2011-05-04
Professor Erik Schrumpf
Leader of Management Group

NO PSC
Norwegian PSC Research Center

What is PSC?

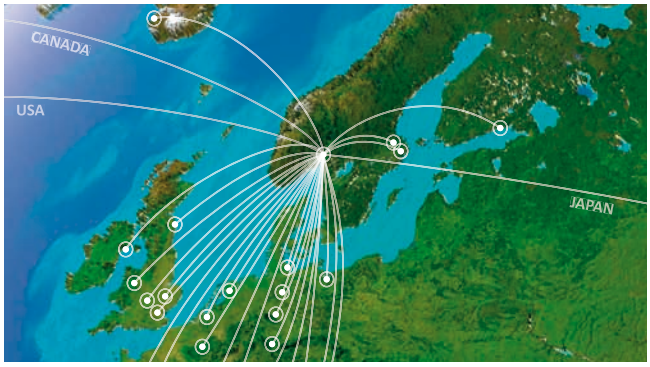
PSC, *primary sclerosing cholangitis*, is a chronic inflammatory disorder of the bile ducts. PSC leads to progressive strictures of the bile ducts and ultimately to liver cirrhosis.

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 Norway. Affected individuals are typically young *(30–40 years old)* and have concurrent inflammatory bowel disease *(IBD)* in 60–80% of the cases. Disease course is highly variable from patient to patient. However, given an average time from diagnosis to liver transplantation of 10–15 years, PSC should be considered a serious and important condition.



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

2010 in brief



In 2010, NoPSC became a well functioning research center with high activity in both the research projects and the core facility, thus reaching the critical first milestone. 17 publications during 2010 have lead to both national and international recognition, especially since a majority was published in high impact peer-reviewed journals.

Since September 2010, Executive Manager Tom Hemming Karlsen has been working full time in the clinic, and Hege Dahlen Sollid has in an excellent manner taken over parts of the administrative tasks. One new PhD student *(Sigrid Næss)* and one new post doc *(Alexey Shiryaev)* were added to the team, thus expanding the scientific personnel in line with the growing activities of NoPSC.

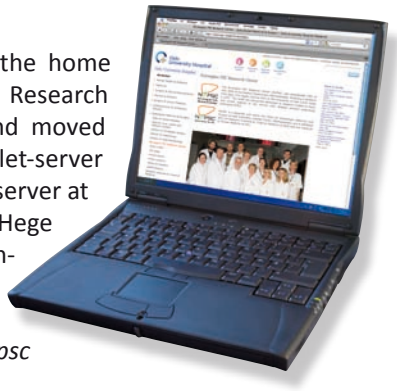
KEY NOPSC EVENTS IN 2010

- **Establishment of the International PSC Study Group**
  See separate presentation on page 18.

- **Guest professor meeting**
  The annual guest professorship seminars were held in February, and all scientific projects at NoPSC underwent critical discussion. *See separate presentation of Prof. Andre Franke and Prof. Arthur Kaser on page 13.*

- **The inclusion of 100 healthy controls in the NoPCS biobank sample collection**
  During 2009 and 2010 more than 100 healthy controls were recruited to donate a large panel of different blood samples to the NoPSC biobank. This was an important contribution to the biobank resource, and a major collaborative project involving several persons at NoPSC, Liv Wenche Thorbjørnsen in particular.

- **Home page**
  During the fall of 2010 the home pages of Norwegian PSC Research Center were updated and moved from the old Rikshospitalet-server to the common research server at Oslo University Hospital. Hege Dahlen Sollid was responsible for the process.
  Please visit us at:
  www.ous-research.no/nopsc

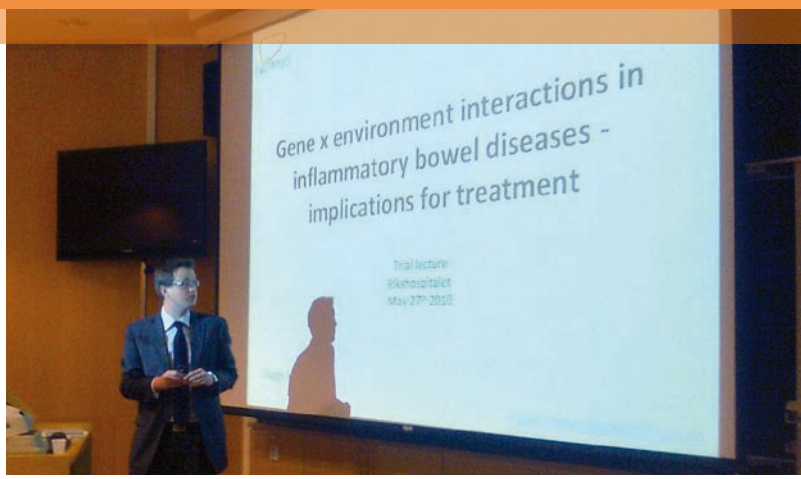


IMMUNOCHIP PROJECT

In 2009, the Wellcome Trust Sanger Institute, Hinxton, UK (*www.sanger.ac.uk/*) initiated the Immunochip project; a project that aim at identifying the genetic similarities and differences in a large number of immune mediated diseases.

More than 210 000 DNA samples are collected worldwide, and will be genotyped for approx. 200 000 genetic variants that have previously been shown to confer risk in either one of these diseases. A new genotyping platform (*Immunochip, Illumina®*) was designed for this purpose. More than 20 different disease groups are included in the project, among these also PSC. A separate consortium (*The Immunochip Consortium*) has been established for coordination of data analysis. The project represents a historic opportunity to map the genetic relationship between different immune-mediated diseases. The PSC part of the project is lead by Tom Hemming Karlsen and PhD student Trine Folseraas.
The preparation and quality control check of several thousand samples was performed as a collaborative effort during fall 2010. More than 4000 PSC samples will be included in the project, approx. 1000 from Scandinavia and Finland, 750 from Germany, 1000 from the UK, 1000 from the US and Canada, 500 from the Netherlands and Belgium, and 200 from Southern Europe.

- **Integration of NoPSC at the Research Institute for Internal Medicine** *(RIIM, http://ous-research.no/riim/)* During 2010 NoPSC has gradually found its place at RIIM. The institute, lead by Prof. Pål Aukrust, has six highly active research groups *(Tom Hemming Karlsen's group being one of them).* The main focus of the institute is inflammation and immune activation in cardio vascular and related metabolic disorders *(e.g., atherosclerosis and heart failure)*, and now, following the inclusion of Tom Hemming Karlsen's group, also gastrointestinal and liver disorders. The research groups comprise platelet researchers, coagulationists, immunologists, gastro-enterologists, nutrition researchers and cardiologists. RIIM's primary goal is to combine clinical medicine and molecular biology to establish a bridge between bench and bedside. Taken together, the researchers at the institute hold an impressive variety of methods, from (i) high through-put studies of biomarkers in large patient populations; (ii) a wide range of advanced molecular and biochemical methodology for studies in various cells and cell lines; (iii) animal models with relevance to the actual disorders that also include genetically modified mice. The institute also has large experience in performing *"proof of concept"* studies on clinical samples. In 2010, the institute had 3 professors, 6 research scientists including 3 group leaders, 4 post docs, 20 PhD students and 1 master student, in addition to 10 bioengineers, research engineers, study nurse and administrative personnel. Most of the laboratory activity of NoPSC is now located at RIIM, the only exception being HLA typing, which is still performed at IMMI.



M.D. Espen Melum defended his thesis in an excellent way.

- **First dissertation**
  On the 28th of May M.D. Espen Melum defended his thesis *"From single markers to genome-wide association – A study of Primary Sclerosing Cholangitis genetics"* in an excellent manner. This was the first dissertation in the history of Norwegian PSC Research Center. The trial lecture was entitled *"Gene x environment interactions in inflammatory bowel diseases – implications for treatment".* Following his dissertation, Espen Melum was assigned a post doc in the Functional genetics group at NoPSC. He is currently working on non-PSC projects in Prof. Richard Blumbergs' lab at Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston to acquire skills that upon return are expected to enrich the research activity at NoPSC.

- **PSC patient information folder**
  In December, study nurse Mona Bjørnstad finished her work on an information folder regarding PSC. This folder is meant for PSC patients and their relatives, and it has been warmly welcomed among the patients as well as the nurses and doctors at the Section of Gastroenterology.

CONTRIBUTORS WITH REGARD TO PSC SAMPLES

LOCALIZATION	INSTITUTION	MAIN CONTACT
Oslo, Norway	Oslo University Hospital	Tom Hemming Karlsen
Stockholm, Sweden	Karolinska University Hospital	Annika Bergquist
Helsinki, Finland	Helsinki University Central Hospital	Martti Färkkilä
Szczecin, Poland	Pomeranian Medical University	Piotr Milkiewicz
Heidelberg, Germany	University Hospital of Heidelberg	Daniel Gotthard
Hannover, Germany	Hannover Medical School	Tobias Weismüller
Hamburg, Germany	University Clinic of Hamburg-Eppendorf	Christoph Schramm
München, Germany	University Clinic of München	Christian Friedrich Rust
Kiel, Germany	Christian-Albrechts-University	Andre Franke
Berlin, Germany	Charité Campus Virchow	Tobias Müller
Leuven, Belgium	University Hospital Gasthuisberg	Liesbet Henckaerts
Groningen, the Netherlands	Medical Center Groningen	Rinse K Weersma
Paris, France	Hôpital Saint-Antoine	Olivier Chazouillères
Barcelona, Spain	Hospital Clínic, University of Barcelona	Albert Pares
Milan, Italy	IRCCS Istituto Clinico Humanitas	Pietro Invernizzi
Larissa, Greece	University of Thessaly	Georgios Dalekos
Cambridge, UK	Addenbrooke's Hospital, Cambridge	Carl Anderson
Rochester, MN, USA	Mayo Clinic	Kostas Lazaridis
Sacramento, CA, USA	University of California at Davis	Christopher Bowlus
Toronto, Canada	Toronto Western Hospital/University of Toronto	Peter Durie

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 PSC. NoPSC is now a separate unit within the Clinic for Specialized Medicine and Surgery 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.

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, see page 8).*
- Molecular biomarkers in early diagnosis of cholangiocarsinoma *(work package 2, see page 10).*
- Inflammatory bowel disease in PSC *(work package 3, see page 11).*

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.

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 *(see next page)* and data registry in the MEDinsight database *(both 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. Since the fall of 2010, administrative support is also given by personnel in the core facility.

The Project units of NoPSC are built around work packages defined by priorities of the Management group. At present, 3 work packages are established within the context of NoPSC *(each work package is presented separately on pages 8-11)*.

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

Present members of the advisory board are:

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

NoPSC Biobank

The NoPSC Biobank is a state-of-the-art biobank, where every sample is traceable throughout the system. Our study nurse includes patients and make sure they are well informed when written consent is given, and both clinical parameters and biological materials are then collected.

Photo: © Tone Thorbjørnsen

A sample set of 8 blood samples gives us plasma *(with and without protease inhibitors)*, serum, DNA and RNA *(including micro RNA)*. Bile and surplus tissue samples are stored in conjunction with various procedures *(e.g. ERCP, liver transplantation)*. Tissue sampling from diseased liver during transplantation is performed on a 24 hour voluntary basis by medically educated scientific personnel at NoPSC. Samples are stored in tubes with a two-dimensional barcode *(Matrix®)* and scanned into the MEDinsight database *(programmed by Odd Røyne at the Department of Medical Informatics, OUH)*.

In MEDinsight, each and every tube is connected to a unique form where information regarding e.g., sample date, preparation procedure, volume and position is registered. Standard operation procedures *(SOP's)* are established for each material, and are written in the *"Book of procedures for Biobank at Norwegian PSC Research Center"* (*www.ous-research.no/nopsc/NoPSC%20biobank/10846*). There is a 1:1 relationship between a stored sample and a SOP. After being positioned in the system, all samples are stored at either - 20 °C, - 80 °C or in the gas phase of liquid nitrogen. The MEDinsight database has a unique system of sample deposition, position and retrieval, and is connected to the clinical database. Retrieval from the biobank can thus be coupled to a wide variety of both clinical, technical and biological parameters.

The biobank has now samples from 336 patients with PSC and related liver diseases, in addition to 100 healthy controls. The total amount of tubes is 41 738! During 2010 there have been 23 withdrawals from all different material types *(including clinical data)*, and material from the biobank has been used in several different projects, both locally and internationally. Standardized withdrawal procedures have been established by Liv Wenche Thorbjørnsen, and Odd Røyne has finalized the programming of the biobank module of MEDinsight. The high quality of the biobank has also been recognized elsewhere, it has in several occasions been looked upon as a model biobank. When the International PSC Study Group was standardizing their biobank procedures, the NoPSC's *"Book of Procedures"* was used as a reference. Several other researchers at OUH have contacted us to learn about our biobank, and the SECA2 study, conducted by Dr. Aksel Foss and Dr. Svein Dueland, will use the NoPSC biobank logistics. In addition, blood samples collected in the IBSEN20 follow-up study, administered by Prof. Morten H. Vatn, will be stored in the NoPSC biobank. Since 2008, Tom Hemming Karlsen has been in the Biobank Advisory Board at OUH. In addition, the previous manager of the biobank, Hege Dahlen Sollid, was involved as an advisor in the planning of the OUH/ Health region South East regional biobank center *(RBS)* at *"Myren's verksted"* during fall 2010.

Photo: © Tone Thorbjørnsen

Work package 1
Functional genetics

NoPSC project leader: ***Tom Hemming Karlsen*** • NoPSC affiliated PhD students: ***Espen Melum*** (now post doc), ***Johannes R. Hov*** (now post doc), ***Trine Folseraas, Sigrid Næss, Bjarte Fosby***
NoPSC affiliated post docs: ***Anders Holm, Alexey Shiryaev*** • Research group website: ***www.rr-research.no/karlsen/***

BACKGROUND

The etiology of PSC is not known. Genetic factors are likely to play an important role in disease development, as shown by an increased risk of disease in first degree relatives of patients with PSC. By studying disease genes and their function, the mechanisms by which PSC develop and eventually may be treated can be defined. This has been the basis for the first 3-year work package in the functional genetics group at the Norwegian PSC Research Center *(2008-2011)*. Since 80% of the patients with PSC also have ulcerative colitis *(UC)*, both diseases are studied in parallel. Alongside the genetic studies, targeted biobanking and establishing of new laboratory methods *(required for the subsequent "translational" work packages)* have been performed *(see Figure 1)*. Several milestones have been accomplished and the studies performed so far have revealed a surprising large overlap of PSC genes with various autoimmune diseases. The primary bile duct injury in PSC is thus likely to be "autoimmune", but infectious and toxic *(i.e. bile)* factors may also play a role.

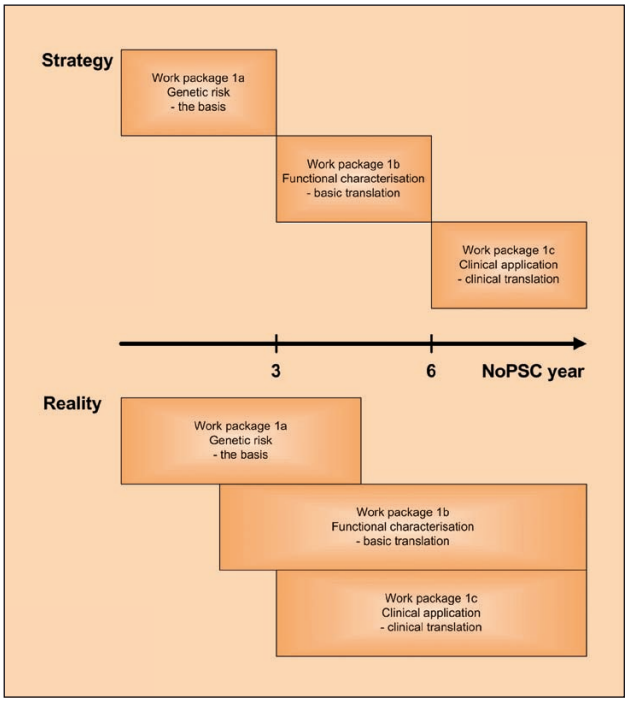


Figure 1. An overview of the strategy of the functional genetics group. The "ideal" plan (upper panel) with three subsequent 3-year work packages in reality means that activities need to overlap. The main message is that a shift from genetic studies to functional and clinical applications is intended and ongoing. Likely, most of the "pure" genetic studies in the first work-package will be completed late 2011 and early 2012. Output from the activity is evident from the publication lists.

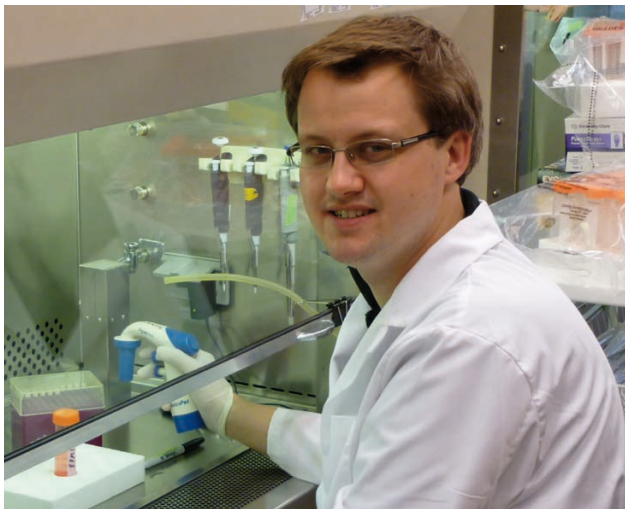
CHALLENGES AND STRATEGY

- There has been a systematic focus at establishing new methods in the group throughout 2010. Of particular importance in 2010 were a transcriptome analysis pipeline, refinement of next-generation sequencing data analysis, human and mice cholangiocyte isolation protocols as well as the initiation of a project aimed at generating transgenic mice that allows for targeted knock-out of genes in the cholangiocytes *("cholangiocyte specific Cre")*.

- To expand further on methodology in preparation for the next steps of the program of the group, two new post docs have been employed: Anders Holm *(cellular proteomics and high-throughput biomarker detection, started 01.01.11)* and Alexey Shiryaev *(intracellular signaling, ex vivo cellular biology)*. After his dissertation, Espen Melum was *"sent"* to Harvard to acquire skills required for work in the upcoming mice models.

- Large groups of patients are required to detect as many of the disease genes as possible. Much effort in the group therefore goes into supporting the collection of DNA samples in other countries for collaborative projects *(in 2010 mainly the US and the UK)* and more than 4,000 DNA samples are now available world-wide.

- Genes in the HLA complex are strongly linked, and it has proven extremely difficult to define the exact disease gene(-s) in this region. Several ongoing projects in the group are aimed at refining the HLA association in PSC and the hitherto unknown molecular targets of the *"auto-immune"* reactions.



MAIN PROJECTS COMPLETED IN 2010

The acceptance of the joint Scandinavian/German genome-wide association study *(GWAS)* of PSC in Nature Genetics was a major accomplishment of the group. Also, the ulcerative colitis GWAS program was completed with the acceptance of the fourth ulcerative colitis-related Nature Genetics article to which the group had contributed *(meta-analysis finding 47 robust ulcerative colitis genes)*. Both these articles were published early 2011.

- The first translational studies were completed, reporting on the influence of genetic variation in the bile acid receptor TGR5 on ex vivo expression and function *(published in PLoS One in 2010)* and the influence of genetic variation in the HLA molecules on protein structure and electrostatic properties *(published in Hepatology in 2011)*.

- The group also published groundbreaking methodological work of relevance to other diseases, an evaluation of "next-generation" sequencing technologies *(published in Human Mutation in 2010)* and a web-based tool for assessing the influence of genetic variants on gene expression *"in silico" (published in BMC bioinformatics in 2010)*.

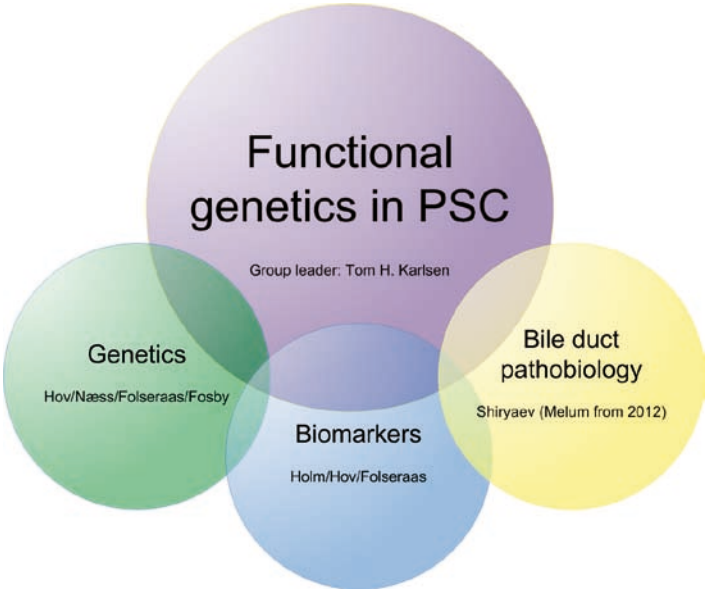


Figure 2. The activities of the functional genetics group were throughout 2010 directed in three directions to expand according to the strategy yet restricting the focus.

MAIN ONGOING PROJECTS AND PROSPECTS

To focus the expansion of activity, the local undertakings in projects of the group were slowly being directed in three major directions throughout 2010 *(see Figure 2):*

Genetic susceptibility: During 2010, PhD students Trine Folseraas and Sigrid Næss took the lead in the genetic studies in PSC following the completion of the PhD projects of Espen Melum and Johannes Hov. Main ongoing projects in 2010 were an extended analysis of the existing GWAS data; the Immuno-chip project *(see Box page 4)*; a collaboration with groups working on primary biliary cirrhosis to detect genetic factors responsible for cholestatic itching as well as several projects refining the genetic associations in the HLA complex in PSC. Throughout 2011 these latter activities will be integrated with activities aimed at defining the specificity of the T-cell reactivity in PSC with Johannes Hov in charge of several of subprojects. During 2010 the genetics sub-group also initiated preparations for whole-exome sequencing projects in families with >3 PSC affected members and the final preparations for the UK and US based GWAS to be performed in 2011 were also performed.

Biomarker discovery: Anders Holm was employed as post doc from 2011 to support proteomic aspects of *"disease activity markers"* in PSC. Disease activity markers may guide prognostic considerations and serve as surrogate markers for effects from interventions *(e.g. therapeutics)*. The protein level work will be integrated with transcriptomic *(Trine Folseraas)* and micro-RNA *(performed by collaborator)* analyses performed throughout 2010 and is partly founded on insights obtained from the genetic studies. Diagnostic aspects will be restricted to the early detection of PSC in inflammatory bowel disease *(IBD)*, and approximately 500 Norwegian patients with a 20 year history of IBD are currently being screened with magnetic resonance cholangiography as part of this.

Bile duct pathobiology: Alexey Shiryaev was employed as post doc in 2010 to facilitate studies into disease mechanisms based on genetic findings. The initial work has gone into establishing tools for in vitro and in vivo experiments, including the establishment of cholangiocyte isolation protocols *(allowing for culturing as well as transcriptome analysis of freshly isolated cholangiocytes)* and activities to support the development of a "cholangiocyte specific Cre" *(a transgenic mouse strain that will allow for deletion of particular genes in cholangiocytes only).* The model will be used to study the influence of selected PSC susceptibility genes on cholangiocyte function. Espen Melum at Harvard is currently performing work in mice not directly related to PSC, but will strengthen the activities of this work package upon return in 2012, including the ultimate establishment of relevant animal facilities in the group.

Work package 2

Molecular biomarkers in early diagnosis of cholangiocarcinoma

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

BACKGROUND

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

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

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

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

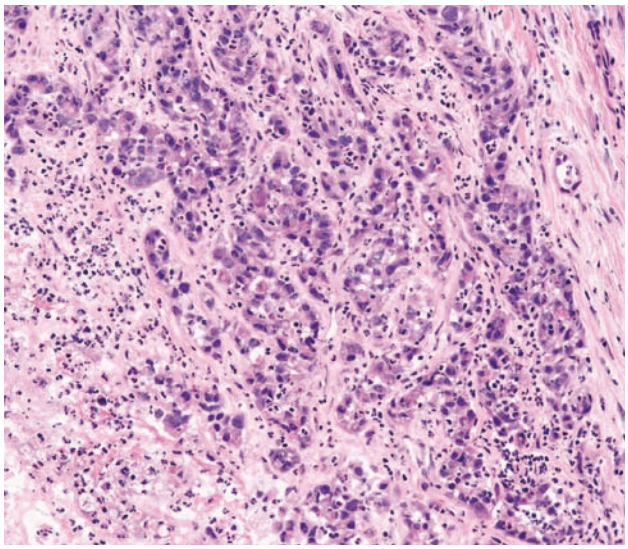


Photo: © Oslo University Hospital

Cryo-sectioned cholangiocarcinoma specimen stained with hematoxylin and eosin. The depicted sample is diagnosed as CCA, and illustrates the infiltration of fibrosis and inflammatory conditions often detected in these samples.

CHALLENGES

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

PROJECTS

- **Identification of novel epigenetic biomarkers in CCA.** Gene expression microarray experiments were performed using CCA cell lines before and after treatment with epigenetic drugs. Genes that responded to epigenetic treatment in the cell lines and simultaneously were down-regulated in primary tumors compared with normal tissue *(previously published expression profiles)* were considered potential epigenetically regulated targets. These candidate genes *(n = 47)* were subject to methylation-specific polymerase chain reaction (MSP). In addition to CCA, cell lines from gall bladder, liver and pancreas were investigated. Seventeen of the genes were frequently methylated in CCA cell lines and are currently being analyzed in CCA tissue samples and normal tissue. Genes frequently methylated in CCA and rarely methylated in normal tissue represent novel epigenetic biomarkers for CCA detection – potentially at an early stage.

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

- **Gene expression signatures of CCAs.** By using exon-based microarrays to analyse CCAs, normal liver samples and liver biopsies from PSC patients we aim at gaining new insight into the development of cholangiocarciomas. Resulting gene signatures might be useful to pinpoint subgroups of PSC patients at high risk of developing CCA.

Work package 3

Inflammatory bowel disease in PSC

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

BACKGROUND

Primary sclerosing cholangitis *(PSC)* is strongly associated with inflammatory bowel disease *(IBD)* with a prevalence of IBD in PSC patients in Northern Europe and North America in the range of 60-80%. IBD in PSC differs from IBD unrelated to hepatobiliary disease in several regards. The patients most often have a total colitis, typically with a quiescent clinical course. The colitis in PSC appears to carry an increased risk of malignancy as compared with colitis without concomitant PSC. The etiopathogenetic relationship between PSC and IBD is largely unknown. Previous studies from our group have suggested that the genetic basis for PSC-IBD differs from that of IBD in general.

CHALLENGES

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

PROJECTS

- **Clinical characterisation of IBD in liver transplanted and non-transplanted PSC patients.** We have carried out colonoscopy with biopsies and a clinical interview in a prospective study of PSC patients admitted to our department during a 3-year period. The results, including a detailed description of the 110 patients *(42 liver transplanted cases)* who had IBD and an intact colon, have now been published: Jørgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, Schrumpf E, Vatn MH, Boberg KM. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver-transplanted and non-transplanted patients. Inflamm Bowel Dis. 2011 Mar 31. doi: 10.1002/ibd.21699.

- **Risk of colorectal neoplasia in liver transplanted PSC patients with IBD.** In a multicenter study within the Nordic Liver Transplant Group, we have reviewed the records of PSC patients undergoing liver transplantation during the period 1984–2006. The cumulative risk of colorectal neoplasia before and after transplantation has been estimated using competing risk regression analysis. The overall cumulative risk of colorectal neoplasia in PSC-IBD patients increases with the time from diagnosis of IBD, and after transplantation, the risk appears to increase more than that expected from the longer duration of IBD. Potential risk factors for development of colorectal neoplasia after liver transplantation will be described.

- **Clinical course of IBD in liver transplanted PSC patients.** As a separate part of the above multicenter study of liver transplanted PSC patients with IBD, the IBD activity before and after liver transplantation will be described.

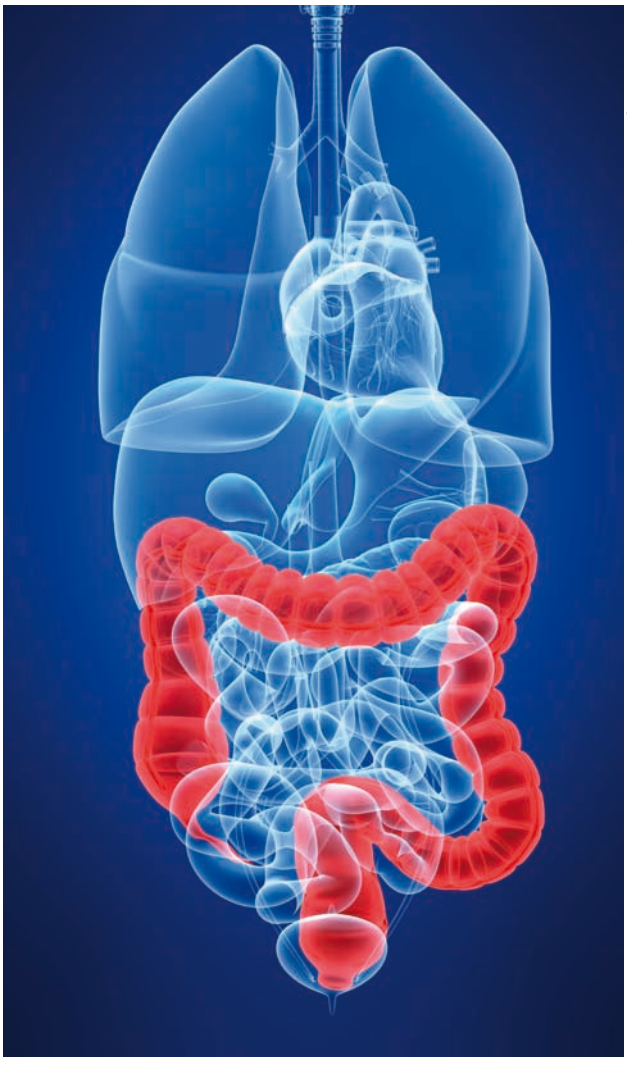


Illustration: © Sebastian Kaulitzki / Shutterstock.com

People at NoPSC

Management group

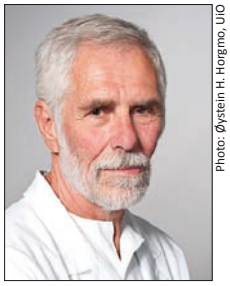


Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Øystein H. Horgmo, UiO

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Photo: Thea Tønnessen, OUS HF

Kristian Bjøro
Professor

Section for Gastroenterology
Division of Specialized Medicine
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Oslo University Hospital

NOPSC GUEST PROFESSORS

GUEST PROFESSOR AT OUR RESEARCH CENTER SINCE APRIL 2008

Andre Franke

is professor in Genetics at the Institute of Clinical Molecular Biology, Christian-Albrechts-University (CAU) in Kiel, Germany. He is a biologist with a PhD from the Institute of Clinical Molecular Biology, CAU under the supervision of Prof. Dr. S. Schreiber and Prof. Dr. Dr. h.c. Thomas C.G. Bosch. Since 2006 he has been leader of the bioinformatics and genetics groups, head of high-throughput core facility ICMB (CAU), and since 2008 he has had a Junior Professorship (W1) for Epithelial Barrier Diseases within the DFG Cluster of Excellence "Inflammation at Interfaces", CAU. In December 2008 he received the Hensel-Prize award (100 000 €) for excellent biomedical research.
Franke's main scientific interests are the development and establishment of novel high-throughput technologies, the inherent bioinformatic integration and the application of both to identify genetic and epigenetic causes of chronic inflammatory diseases like Crohn's disease, ulcerative colitis, psoriasis, primary sclerosing cholangitis, and atopic eczema. During he's work on genome-wide association studies for the last years, Franke's research agenda currently focuses on targeted enrichment strategies, whole-genome and whole-exome resequencing, and copy number variation analyses.

Adapted from: ***www.ikmb.uni-kiel.de/cms/ueber-uns/mitarbeiter/mitarbeiterseite/andre-franke/***

Three representative publications:

Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci.
Melum E, Franke A*, et al.* Nat Genet. 2011 Jan;43(1):17-9. * contributed equally to this work.

Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci.
Franke A, et al. Nat Genet. 2010 Dec;42(12):1118-25.

Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility.
Franke A, Balschun T*, Karlsen TH*, et al. Sventoraityte J, Nikolaus S, Mayr G, Domingues FS,Albrecht M, Nothnagel M, Ellinghaus D, Sina C, Onnie CM, Weersma RK, Stokkers PC, Wijmenga C, Gazouli M, Strachan D, McArdle WL, Vermeire S, Rutgeerts P, Rosenstiel P, Krawczak M, Vatn MH, IBSEN study group, Mathew CG, Schreiber S.*
Nat Genet 2008, 40 (11), 1319-23. * contributed equally to this work.

GUEST PROFESSOR AT OUR RESEARCH CENTER SINCE NOVEMBER 2009

Arthur Kaser

is gastroenterologist with a Univ.-Doz. (professorial thesis, Medical University Innsbruck) from 2003. He is currently Professor of Gastroenterology at the Div of Gastroenterology and Hepatology, Dept of Medicine at the University of Cambridge, Addenbrooke's Hospital. Kaser studied medicine in Innsbruck, Austria. After completing a 6yr fellowship training in internal medicine, he worked at Harvard Medical School for more than 3 years; first as a Max Kade Fellow of the Austrian Academy of Science, later supported by a Schrödinger scholarship from the Austrian Science Fund (FWF). Upon his return to the University Clinic of Internal Medicine II, Innsbruck, he completed his fellowship in Gastroenterology and Hepatology (2008) and continued research on development of intestinal inflammation (ER stress). In 2011 he took up his appointment as University Chair in Gastroenterology at the University of Cambridge. Kaser has received several national and international research awards.
Kaser's main scientific focus is on mucosal immunology, where he has a special interest in inflammatory bowel disease and its closely related conditions like primary sclerosing cholangitis. In particular, Kaser studies the biology of the intestinal (and biliary) epithelium that forms the interface between the body's most abundant and diverse microbial habitat and the sterile host environment. Kaser aims to understand how host genetics, the environment, and the microbiota intersect to lead to pathological inflammation.

Adapted from: ***www.immunology.cam.ac.uk/directory/profile.php?ak729*** and ***www.i-med.ac.at/mypoint/news/2009103001.xml***

Three representative publications:

XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease.
Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, Tilg H, Nieuwenhuis EE, Higgins DE, Schreiber S, Glimcher LH, Blumberg RS.
Cell. 2008 Sep 5;134(5):743-56.

Microsomal triglyceride transfer protein regulates endogenous and exogenous antigen presentation by group 1 CD1 molecules.
Kaser A, Hava DL, Dougan SK, Chen Z, Zeissig S, Brenner MB, Blumberg RS. Eur J Immunol. 2008 Aug;38(8):2351-9.

Increased expression of CCL20 in human inflammatory bowel disease.
Kaser A, Ludwiczek O, Holzmann S, Moschen AR, Weiss G, Enrich B, Graziadei I, Dunzendorfer S, Wiedermann CJ, Mürzl E, Grasl E, Jasarevic Z, Romani N, Offner FA, Tilg H. J Clin Immunol. 2004 Jan;24(1):74-85.

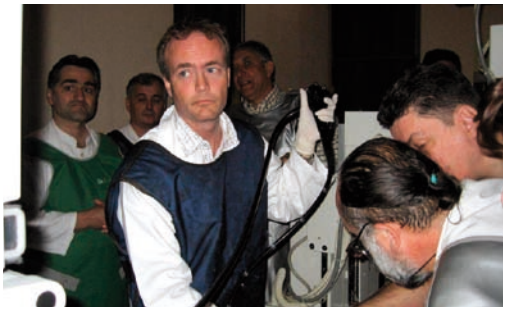
2010 snap shots

PhD student Trine Folseraas is handling Immunochip samples', making sure everything is of high quality before shipment to Kiel.

Post doc Espen Melum and PhD students Trine Folseraas and Bjarte Fosby was not present. Post doc Anders Holm *(second left in back row)* started 01.01.2011.

Bioengineer Liv Wenche Thorbjørnsen is making sure the liver biopsies and cells have enough liquid nitrogen in the storage tank.

Prof. Erik Schrumpf, Dr. Kirsten Muri Boberg and Dr. Kristin Kaasen Jørgensen is discussing new scientific knowledge regarding IBD.



Professor Lars Aabakken is performing Endoscopic Retrograde Cholangiopancreatography (ERCP) on a PSC patient.

Study nurse Mona Bjørnstad is including patients, updating the clinical database and helping out in the daily activities of the center.

PhD students Trine Folseraas and Sigrid Næss are working in tight collaboration on several projects within work package 1.

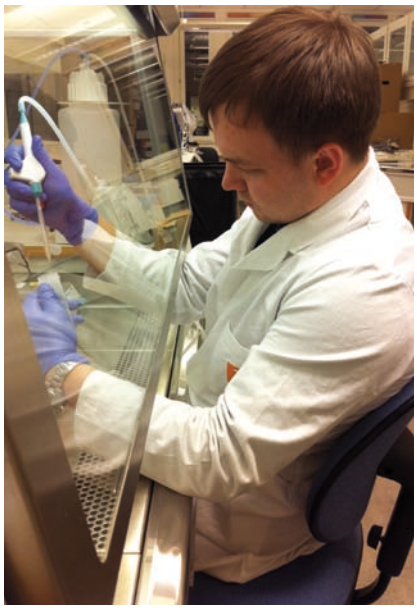
PhD student Johannes Hov delivered his theses in December, and is now looking forward to the dissertation scheduled in September 2011.

Photo: Foto- og videotjenesten, Oslo University Hospital

Kristian Holm is managing the expanding bioinformatic challenges at NoPSC in an excellent manner.

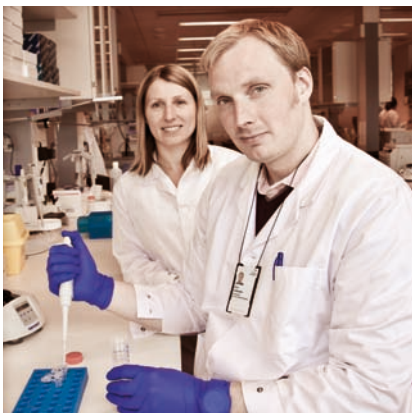
Espen Melum is working in projects of Prof. Richard Blumberg at Harvard up to 2012 in order to gain expertise of relevance to NoPSC projects upon return.

Post doc. Alexey Shiryaev is establishing new laboratory methods at IIF.



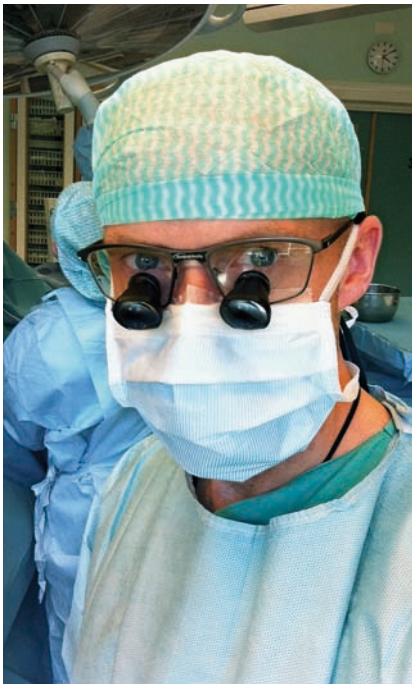
Bioengineer Bente Woldseth is managing the laboratory facilities is an excellent manner.

Hege Dahlen Sollid is managing the everyday administrative tasks at NoPSC.



PhD student Kim Andresen is given good advice on how to proceed from his co-supervisor Guro E. Lind.

◄ Executive manager Tom Hemming Karlsen is giving a lecture at the Falk Symposium, Freiburg, in October 2010.



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

Network

KEY LOCAL COLLABORATORS

RESEARCH INSTITUTE FOR INTERNAL MEDICINE

The integration of NoPSC within the Research Institute for Internal Medicine (RIIM) (*www.ous-research.no/riim/*) was practically accomplished with the building of the new NoPSC biobank and the accompanying laboratories. Formally, work package 1 is now established at RIIM as a separate group (*www.ous-research.no/karlsen/*) and members of this group collaborate closely with the groups of Prof. Pål Aukrust and Prof. Bente Halvorsen.

Photo: © Oslo University Hospital

SECTION FOR ORGAN TRANSPLANTATION

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

DEPARTMENT OF PATHOLOGY

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

INSTITUTE OF IMMUNOLOGY

The Immunogenetics group, led by 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. Lie is now Professor in Genetics at the Department of Medical Genetics, OUH, and moved her research activities to the Ullevål location in November 2010. NoPSC has a longstanding collaboration with the Institute of Immunology in work package 1. 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.

CENTER FOR CANCER BIOMEDICINE

A collaboration with Prof. Ragnhild Lothe's group, and senior researcher and project group leader Guro Lind in particular, at the Department of Cancer Prevention, OUH (*www.ous-research.no/cancerprevention/*) is the basis for work package 2 on diagnosis of cholangiocarcinoma in PSC.

THE IBSEN STUDY GROUP

The infrastructure utilized in work package 3 on IBD in PSC (*biobank, protocols etc.*) is derived from the IBSEN II project. The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is also important for basic studies in work package 1. 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

Recently, the collaboration with Jon K. Lærdal 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 within work package 1.

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 projects on this topic in work package 1.

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

In conjunction with the transformation of activity within work package 1 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 within the work package. 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 work package 1. Prof. Andre Franke is assigned as guest professor to participate in this work package (*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 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.

HEINRICH-HEINE-UNIVERSITY DÜSSELDORF, GERMANY

Functional characterization of genetic variation of the bile acid receptor TGR5 within work package 1 is performed together with Prof. Dieter Häussinger and senior researcher Verena Keitel in Düsseldorf (*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 in work package 1 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 projects in several work packages where data from the Nordic Liver Transplant Registry are required (*see www.scandiatransplant.org*).

KAROLINSKA UNIVERSITY HOSPITAL STOCKHOLM, SWEDEN

Associate professor Annika Bergquist is involved in several projects in work packages 1 and 3 at NoPSC. The clinical data and blood samples that were collected by Dr. Ulrika Broomé over more than a decade, still serve as a valuable resource for these collaborative projects.

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 (*work package 1*), as well as evaluating serum biomarkers for cholangiocarcinoma in PSC (*work package 2*).

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 projects in work package 1. In particular, the experience in cholangiocyte biology of this group has proven essential in the establishing of the cholangiocyte isolation protocols in work package 1.

Tom Hemming Karlsen from NoPSC kept detailed records of all ideas exchanged in the discussions as basis for the extensive minutes from the meeting (found at www.ipscsg.org).

Lars Aabakken from NoPSC and Cyriel Ponsioen (Amsterdam) are instrumental in a study aimed at determining the optimal endoscopic treatment regimen in PSC.

Cyriel Ponsioen (Amsterdam) and Christoph Schramm (Hamburg).

Erik Schumpf from NoPSC during his talk at the dinner.

Establishment of International PSC Study Group

In Oslo June 14th-15th 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 with the purpose of establishing an International PSC Study Group.

The proposal for such a study group was made by prof. Michael Manns (*Dept. of Gastroenterology, Hepatology and Endocrinology Medical School of Hannover*), on the basis of successful collaborations on PSC genetics and experience from similar initiatives in autoimmune hepatitis and hepatitis C. The meeting covered seven topics within eight sessions; constitutional aspects, database issues, biobanking, clinical trials, cholangiocarcinoma, genetic/functional studies and the opportunity for collaborative grant applications within the EU FP7 program.

There was a clear consensus toward the establishing of an International PSC Study Group, with representation based on active participation in ongoing studies. Meetings will be held biannually at the European Association for the Study of the Liver (*EASL*) and the American Association for the Study of Liver Diseases (*AASLD*) annual conferences.

A steering committee and secretariat was set, and will manage the organizational aspects of the group. The committee members are:
Prof. Michael Manns, Hannover, Germany
Prof. Keith Lindor, 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*)

A biobank/database working group was established (*led by Kirsten Muri Boberg and Tobias Weismüller*) and there was consensus on several concrete projects (*of which the most precise conclusions were reached regarding the Immunochip, cholangiocyte cre, protein biomarkers for cholangiocarcinoma in bile, pregnancy in PSC and treatment of PSC with autoimmune features*).

Important priorities for the group was put forward; in particular the establishing of common database/biobanking protocols and the need to systematically work toward the identification of surrogate markers for disease severity/ progression in PSC as a basis for future clinical trials.

Ill: © Anton Balazh / Shutterstock.com

"PSC veterans" Ulrich Beuers (Amsterdam) and Keith Lindor (Rochester, US) exchanges ideas.

Kirsten Muri Boberg from NoPSC and Marco Marzioni (Italy). In the background, Brijesh Srivastava, who was founded as PhD student for 6 months from NoPSC as part of the UK PSC initiative.

Erik Schrumpf from NoPSC and Michael Manns are chairing the conclusive session at the meeting.

Arthur Kaser (Cambridge) in lively discussions during the dinner.

A website was established (*www.ipscsg.org*, password required), and in October the Study Group meet for their second meeting in Boston during the AASLD. The main topics for the meeting were the common database and a general project update. Next meeting will be in Berlin March 2011 during the EASL. The intention of the Berlin workshop is to bring forward projects and ideas of young investigators working on new topics in the field of PSC.

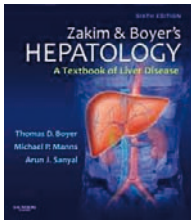
INTERNATIONAL PSC STUDY GROUP NETWORK

COUNTRY, CITY	INSTITUTION
Austria	
Graz	Medical University of Graz
Vienna	Medical University of Vienna
Canada	
Alberta	University of Alberta
Calgary	Health Research and Innovation Centre
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	Medical School of Hannover
Heidelberg	University Hospital of Heidelberg
Kiel	Christian Albrechts University of Kiel
Ireland, Dublin	St. Vincent's University Hospital
Iceland, Reykjavik	The National University Hospital of Iceland
Italy	
Ancona	Università Politecnica delle Marche
Milan	University of Milan
Padua	University of Padua
Japan, Tokyo	Teikyo University School of Medicine
Norway, Oslo	Oslo University Hospital/University of Oslo
Poland, Szczecin	Pomeranian Medical University
Spain, Barcelona	Hospital Clínic i Provincial
Switzerland, Zurich	University Hospital Zurich
Sweden	
Stockholm	Karolinska University Hospital
Uppsala	Uppsala University Hospital
The Netherlands	
Amsterdam	Academic Medical Center/University of Amsterdam
Groningen	University Medical Center Groningen
UK	
Birmingham	University of Birmingham
Cambridge	Addenbrooke's Hosp./The Wellcome Trust Sanger Inst.
London	University College London
Newcastle	Newcastle University
Oxford	John Radcliffe Hospital
US	
California	University of California Davis Medical Center
Connecticut	Yale University
Minnesota	Mayo Clinic College of Medicine
Tennessee	Memphis Medical Center

General contributions in 2010

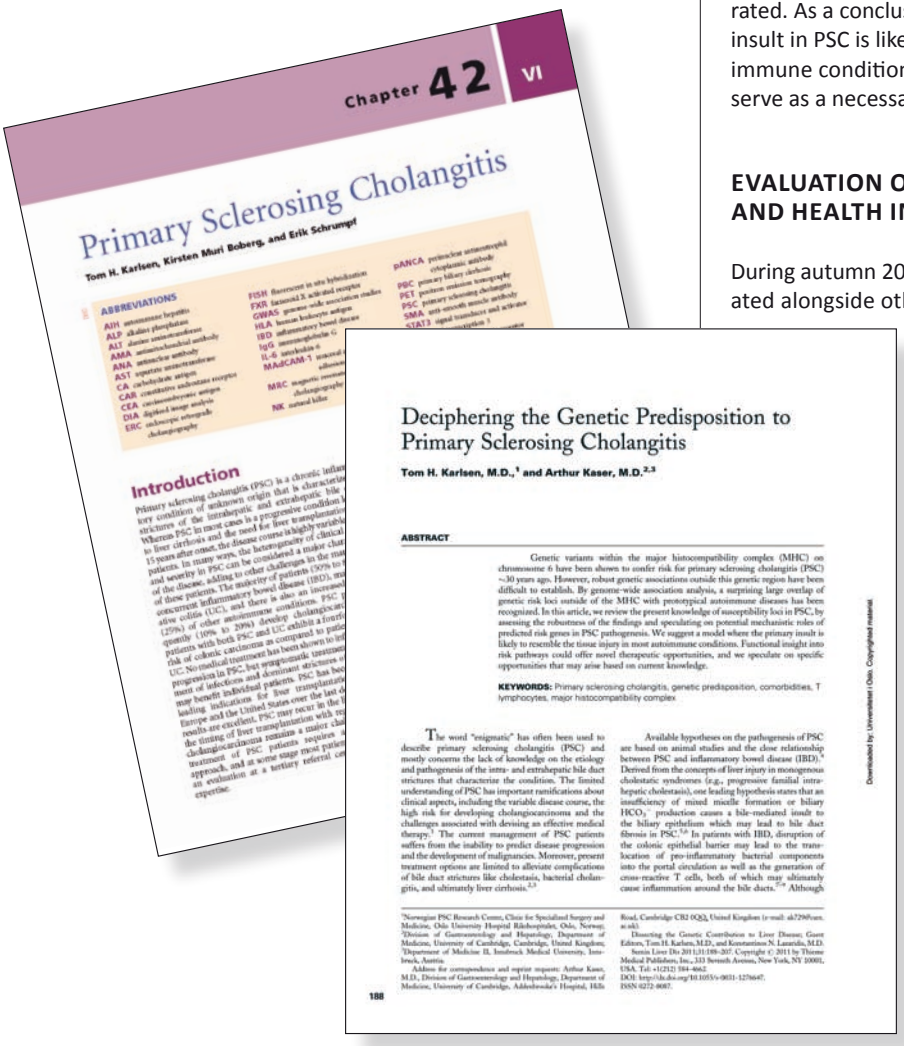
CONTRIBUTION TO ZAKIM AND BOYER: A TEXTBOOK OF HEPATOLOGY, 6TH EDITION

Expected Release in July 2011.



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

Following an invitation from one of the Editors, Prof. Michael Manns, Hannover Medical School, Germany, the management group of NoPSC put much effort during 2009 and 2010 into providing a chapter on primary sclerosing cholangitis for the 6th edition of the well-renowned Zakim and Boyer: A textbook of Hepatology. Almost 500 articles were carefully reviewed and made the basis of the 80 A4 pages of text that constituted the final chapter. All aspects of PSC were represented: epidemiology, pathogenesis, clinical presentation and treatment.
The chapter represents an important summary of the expertise and experience of the management group of NoPSC.


Chapter 42 VI

Primary Sclerosing Cholangitis

Tom H. Karlsen, Kirsten Muri Boberg, and Erik Schrumpf

Introduction

Deciphering the Genetic Predisposition to Primary Sclerosing Cholangitis

Tom H. Karlsen, M.D.,[1] and Arthur Kaser, M.D.[2,3]

ABSTRACT

CONTRIBUTION TO SEMINARS IN LIVER DISEASE, VOLUME 31

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

In 2010, Dr. Tom Hemming Karlsen and Dr. Konstantinos N. Lazaridis were asked to guest editor a Seminars in Liver Disease issue entitled *"Dissecting the Genetic Contribution to Liver Disease"* (*www.thieme-connect.de/ejournals/toc/sld/105475*). They invited world experts on so called *"complex"* genetic liver diseases (*diseases caused by an interplay of multiple genetic and environmental factors*) to provide their speciality contributions. In addition to the processing of these contributions, Dr. Karlsen collaborated with Prof. Arthur Kaser on writing the review *"Deciphering the genetic predisposition to primary sclerosing cholangitis"*. In this article, the status of genetics in PSC is extensively reviewed and compared with other autoimmune diseases. Furthermore, the possible roles of each potential risk gene in PSC pathogenesis, and strategies for translational studies based on the genetic findings, are elaborated. As a conclusion they suggest a model where the primary insult in PSC is likely to resemble the tissue injury in most autoimmune conditions, but where actions of bile elements may serve as a necessary cofactor to cause PSC.

EVALUATION OF RESEARCH IN BIOLOGY, MEDICINE AND HEALTH IN NORWAY

During autumn 2010, the NoPSC research activities were evaluated alongside other research activities in the Division of specialized medicine and surgery as part of the Research Council of Norway´s *"Evaluation of research in Biology, Medicine and Health in Norway"* 2010/2011 (*www.forskningsradet.no/en/Newsarticle/Biology_medicine_and_health_sciences_undergoing_evaluation/1253965762941*).

The self-assessment is a critical review of the research with regard to quality on an international level. Both weaknesses and strengths were reported, in addition to the financial status, future scientific plans and plans for recruitment of new scientists.

The report is reviewed by an international panel of scientists, and the final conclusion of the process (*which is expected in 2011*) is likely to impact on how the financial support is distributed throughout Norway in general and OUH in particular.

Communications

NoPSC international lectures by invitation 2010

Boberg KM.
Primær skleroserende cholangitt.
Dansk gastroenterologisk Selskab og Dansk Selskab for Hepatologi. Hindsgavl Slot, Danmark, September 3.

Boberg KM.
The genetics of PSC
Annual Course in HPB Surgery. Hammersmith Hospital, London, England, October 19.

Boberg KM.
Sclerosing cholangitis and cholangiocarcinoma: When is it time for transplantation?
United European Gastroenterology Week (UEGW). Barcelona, Spain, October 25.

Folseraas T.
Results of PSC Genome Studies in Norway. and **Future Plans for the Norwegian PSC Research Center.**
PSC Partners Seeking A Cure 2010 Conference The Liver Center at Yale School of Medicine, Connecticut, USA, May 14-16.

Karlsen TH.
Genetics at the PSC/IBD Interface.
GIH Research Conference. Mayo Clinic, Rochester, USA, February 8.

Karlsen TH.
New genes for PBC and PSC.
International Liver Congress Clinical Symposium: "EASL highlights on Hepatology: the role of host genetics in the management of liver diseases".
Vienna, Austria, April 14-18.

Karlsen TH.
Outcomes Indicators for Immune-mediated Hepatitis and Cholangiopathies.
Focus Group on Value Based Medicine in Hepatology. Milan, Italy, June 30.

Karlsen TH.
TGR5 sequence variation in primary sclerosing cholangitis.
Falk Symposium 175, XXI International Bile Acid Meeting. Freiburg, Germany, October 7-8.

Karlsen TH.
Update on the genetic susceptibility to primary sclerosing cholangitis.
Symposium: "Hepatobiliary transport and liver diseases". Düsseldorf, Germany, November 10-11.

Karlsen TH.
Deciphering the genetic predisposition to primary sclerosing cholangitis.
Seminars in Gastroenterology and Hepatology, Department of Gastroenterology/Hepatology and the Tytgat Institute for Liver and Intestinal Research. Amsterdam, The Netherlands, December 15.

Prof. Erik Schrumpf was elected into the Executive Committee of United European Gastroenterology Federation for the period 2012-2015.

Publicity in 2010

Karlsen T, Boberg KM, Schrumpf E
Et løft for forskning på primær skleroserende cholangitt.
Norsk Gastroenterologisk forening, NGF-nytt, nr 4/2010 side 15-17

Publications

Publications 2010

1. *Chapman R, Fevery J, Kalloo A, Nagorney DM,* ***Boberg KM****, Shneider B, Gores GJ, American Association for the Study of Liver Diseases*
   Diagnosis and management of primary sclerosing cholangitis
   Hepatology, Feb; 51 (2), 660-78 (Impact factor 10.8)

2. ***Karlsen TH***
   Annual report 2009 for The Nordic Liver Transplant Registry (NLTR)
   March 2010 (*www.scandiatransplant.org*)

3. ***Karlsen TH****, Franke A,* ***Melum E****, Kaser A,* ***Hov JR****, Balschun T, Lie BA, Bergquist A, Schramm C, Weismüller TJ, Gotthardt D, Rust C, Philipp EE, Fritz T, Henckaerts L, Weersma RK, Stokkers P, Ponsioen CY, Wijmenga C, Sterneck M, Nothnagel M, Hampe J, Teufel A, Runz H, Rosenstiel P, Stiehl A, Vermeire S, Beuers U, Manns MP,* ***Schrumpf E****,* ***Boberg KM****, Schreiber S*
   Genome-wide association analysis in primary sclerosing cholangitis
   Gastroenterology, Mar; 138 (3), 1102-11 (Impact factor 12.9)

4. *Franke A, Balschun T, Sina C, Ellinghaus D, Häsler R, Mayr G, Albrecht M, Wittig M, Buchert E, Nikolaus S, Gieger C, Wichmann HE, Sventoraityte J, Kupcinskas L, Onnie CM, Gazouli M, Anagnou NP, Strachan D, McArdle WL, Mathew CG, Rutgeerts P, Vermeire S, Vatn MH, IBSEN study group, Krawczak M, Rosenstiel P,* ***Karlsen TH****, Schreiber S*
   Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL)
   Nat Genet. April; 42 (4), 292-4 (Impact factor 34.3)

5. ***Hov JR****, Lleo A, Selmi C, Woldseth B, Fabris L, Strazzabosco M,* ***Karlsen TH****, Invernizzi P*
   Genetic associations in Italian primary sclerosing cholangitis: heterogeneity across Europe defines a critical role for HLA-C
   J Hepatol. May; 52 (5), 712-7 (Impact factor 7.8)

6. ***Karlsen TH****,* ***Melum E****, Franke A*
   The utility of genome-wide association studies in hepatology
   Hepatology May; 51 (5), 1833-42 (Impact factor 10.8)

7. ***Karlsen TH****,* ***Hov JR***
   Genetics of cholestatic liver disease in 2010
   Curr Opin Gastroenterol. May; 26 (3), 251-8 (Impact factor 4.3)

8. ***Karlsen TH, Schrumpf E, Boberg KM***
   Update on primary sclerosing cholangitis
   Dig Liver Dis. Jun; 42 (6), 390-400 (Impact factor 3.0)

9. ***Melum E****, May S, Schilhabel MB, Thomsen I,* ***Karlsen TH****, Rosenstiel P, Schreiber S, Franke A*
   SNP discovery performance of two second-generation sequencing platforms in the NOD2 gene region
   Hum Mutat. Jul; 31 (7), 875-85 (Impact factor 6.9)

10. *Hollenbach JA, Meenagh A, Sleator C, Alaez C, Bengoche M, Canossi A, Contreras G, Creary L, Evseeva I, Gorodezky C, Hardie RA,* ***Karlsen TH****, Lie B, Luo M, Martinetti M, Navarette C, de Oliveira DC, Ozzella G, Pasi A, Pavlova E, Pinto S, Porto LC, Santos P, Slavcev A, Srinak D, Tavoularis S, Tonks S, Trachtenberg E, Vejbaesya S, Middleton D*
    Report from the killer immunoglobulin-like receptor (KIR) anthropology component of the 15th International Histo-compatibility Workshop: worldwide variation in the KIR loci and further evidence for the co-evolution of KIR and HLA
    Tissue Antigens Jul; 76 (1), 9-17 (Impact factor 2.3)

11. ***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, IBSEN Study Group, Stokkers PC, Vermeire S, Mathew CG, Lie BA, Beuers U, Manns MP, Schreiber S,* ***Schrumpf E****, Häussinger D, Franke A,* ***Karlsen TH***
    Mutational characterization of the bile acid receptor TGR5 in primary sclerosing cholangitis
    PLoS One Aug; 5 (8), e12403 (Impact factor 4.4)

12. *Ponsioen CY, Reitsma JB,* ***Boberg KM****,* ***Aabakken L****, Rauws EA,* ***Schrumpf E***
    Validation of a cholangiographic prognostic model in primary sclerosing cholangitis
    Endoscopy Sept; 42 (9), 742-7 (Impact factor 5.5)

13. *Dolgos S, Hartmann A, Isaksen GA, Simonsen S, Bjørtuft Ø,* ***Boberg KM****, Bollerslev J*
    Osteoporosis is a prevalent finding in patients with solid organ failure awaiting transplantation – a population based study
    Clin Transplant. Sep-Oct; 24 (5), E145-52 (Impact factor 2.0)

14. ***Karlsen TH****,* ***Schrumpf E****,* ***Boberg KM***
    Primary sclerosing cholangitis
    Best Pract Res Clin Gastroenterol. Oct; 24 (5), 655-66 (Impact factor 2.5)

15. *Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, Belouchi M, Fournier H, Reinhard C, Ding J, Li Y, Tejasvi T, Gudjonsson J, Stoll SW, Voorhees JJ, Lambert S, Weidinger S, Eberlein B, Kunz M, Rahman P, Gladman DD, Gieger C, Wichmann HE,* ***Karlsen TH****, Mayr G, Albrecht M, Kabelitz D, Mrowietz U, Abecasis GR, Elder JT, Schreiber S, Weichenthal M, Franke A*
    Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2
    Nat Genet. Nov; 42 (11), 991-5 (Impact factor 34.3)

16. *Bowlus CL, Li CS,* ***Karlsen TH****, Lie BA, Selmi C*
    Primary sclerosing cholangitis in genetically diverse populations listed for liver transplantation: unique clinical and human leukocyte antigen associations
    Liver Transpl. Nov; 16 (11), 1324-30 (Impact factor 3.7)

17. ***Holm K****,* ***Melum E****, Franke A,* ***Karlsen TH***
    SSNPexp - A web tool for calculating and visualizing correlation between HapMap genotypes and gene expression levels
    BMC Bioinformatics Dec; 11, 600 (Impact factor 3.4)

Publications 2009

1. ***Karlsen TH***
   Genome-wide association studies reach hepatology
   J Hepatol. Jun; 50 (6), 1278-80 (Impact 7.8)

2. *Lorentzen AR, **Karlsen TH**, Olsson M, Smestad C, Mero IL, **Woldseth B**, Sun JY, Senitzer D, Celius EG, Thorsby E, Spurkland A, Lie BA, Harbo HF*
   Killer immunoglobulin-like receptor ligand HLA-Bw4 protects against multiple sclerosis
   Ann Neurol. Jun; 65 (6), 658-66 (Impact 9.3)

3. *Forsbring M, Vik ES, Dalhus B, **Karlsen TH**, Bergquist A, **Schrumpf E**, Bjørås M, **Boberg KM**, Alseth I*
   Catalytically impaired hMYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma
   Carcinogenesis, Jul; 30 (7), 1147-54 (Impact 4.8)

4. ***European Association for the Study of the Liver***
   EASL Clinical Practice Guidelines: management of cholestatic liver diseases
   J Hepatol. Aug; 51 (2), 237-67 (Impact 7.8)

5. *Yu X, Wieczorek S, Franke A, Yin H, Pierer M, Sina C, **Karlsen TH**, **Boberg KM**, Bergquist A, Kunz M, Witte T, Gross WL, Epplen JT, Alarcón-Riquelme ME, Schreiber S, Ibrahim SM*
   Association of UCP2 -866 G/A polymorphism with chronic inflammatory diseases
   Genes Immun. Sep; 10 (6), 601-5 (Impact 4.2)

6. ***Melum E**, Franke A, **Karlsen TH***
   Genome-wide association studies – a summary for the clinical gastroenterologist
   World J Gastroenterol. Nov; 15 (43), 5377-96 (Impact 2.1)

7. *Scholz T, **Karlsen TH**, Sanengen T, **Schrumpf E**, Line PD, **Boberg KM**, Jörgensen PF, Fosby B, Bentdal O, Ostensen AB, Osnes S, Riddervold F, Haugaa H, Hausken J, Bergmann JB, Foss S, Björo K, Foss A, Levertransplantasjonsgruppen ved Oslo universitetssykehus, Rikshospitalet*
   [Liver transplantation in Norway through 25 years]
   Tidsskr Nor Laegeforen. Des; 129 (24), 2587-92

Accounting 2010

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENCES	INCOME	EXPENCES
Transfer from 2009	1.878.821		17.898.833	
Canica funds 2010			10.000.000	
Gift reinforcement funds 2010			2.500.000	
Interest			77.296	
Own share			189.282	
Transfer from UiO	8.610.975			8.610.975
Transfer from RIIM*	250.000			
Wages		3.082.074		1.966.943
Wage related expenses		725.076		834.419
Overhead		386.391		470.135
Infrastructure/equipment		585.264		
Other operating expenses		3.740.358		33.024
Transfer to 2011 budget		**2.220.633**		**18.749.914**

** reimbursement of expences during the establishment of the biobank/laboratory (D4.1031) in 2008. All sums are in Norwegian kr.*

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

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