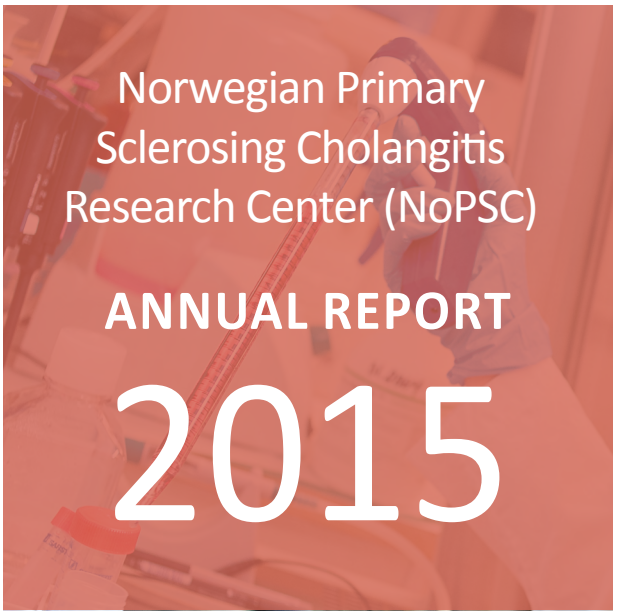
Oslo University Hospital

UiO : University of Oslo

Norwegian PSC Research Center

ANNUAL REPORT 2015

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



Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2015

Content:

NOPSC ANNUAL REPORT 2015

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

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What is PSC?

Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.

PSC 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 one of the most common indications 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 median time from diagnosis to liver transplantation is 10-15 years.

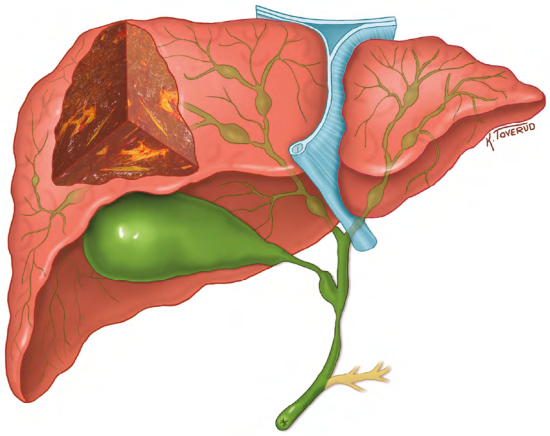
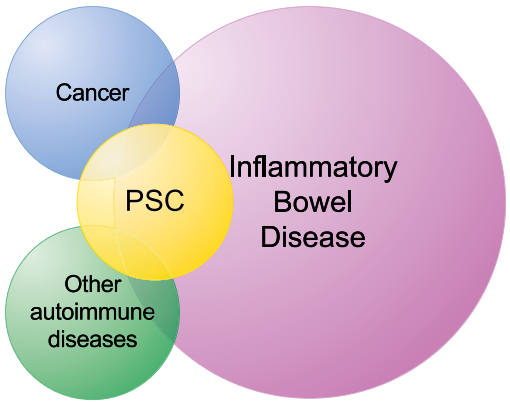


Illustration: © Kari C. Toverud, CMI (Certified Medical Illustrator)



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.

NO PSC
Norwegian PSC Research Center

Aims of the PSC Research Center

- 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

The Leader´s Corner

Professor Tom Hemming Karlsen

The year of 2015 was a special year in many aspects. As can be seen, the publication list harbors a record number of 38 publications, with no less than 6 articles in Hepatology (for many years the leading journal in Hepatology with an impact factor of more than 11). Many other publications in top journals prove success of the ambition we have had within NoPSC: to concentrate on quality – but still be able to deliver a considerable quantity of articles. It is important to recognize that a publication list already constitutes the past, and that the articles of 2015 represent work already performed. We therefore have to continue working hard and not rest on the laurels of these accomplishments.

For this reason, it is reassuring to note that the year of 2015 has been a year of consolidating the research group structure within NoPSC. Importantly, the leaders of the genomic and experimental groups (Johannes Roksund Hov and Espen Melum) have obtained high-profile, independent funding for themselves and key personnel in their groups.
The Norwegian Research Council "young talented researcher" and the Helse Sør-Øst "career stipend" grants, respectively, provide the basis for which these groups can continue to develop into productive independence from the core center funding. For the clinical group, a similar development has been seen, with in 2015 the establishing of a formal working structure within the Section for Gastroenterology, headed by Kirsten Muri Boberg. Multiple ongoing grant application initiatives aim to strengthen these activities.

Toward the end of 2015, the clinical group of NoPSC has made an important outreach to establish a national, collaborative network for autoimmune liver diseases, of which PSC represents an important entity. Autoimmune liver diseases provide significant challenges for the practicing clinicians. In addition to the scientific value of such a network, a closer collaboration at the clinical level will help the implementation of new developments into everyday practice at Norwegian hospitals. The Norwegian patient association for autoimmune liver diseases is closely involved in the initiative, providing important directions for further clinical research. Furthermore, the clinical collaborations represent the national branch of a European initiative to enhance quality of care in rare diseases (European Reference Networks), in which the involvement of PSC is anticipated.

The international standing of Norwegian gastroenterology is exceptionally strong right now, as evidenced by formal positions in key medical associations. This includes Prof. Lars Aabakken (Oslo) serving as president of ESGE (European Society of Gastroenterological Endoscopy), Prof. Odd Helge Gilja (Bergen) serving as president of EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) and myself serving as vice secretary ("president elect") of EASL (European Association for the Study of the Liver). The special situation is a reflection of the many excellent research environments in gastroenterology within Norway, and we should use the opportunity to establish closer collaborations at this strong national arena.

The international collaborations are a hallmark of NoPSC and still as active as ever. Whilst imposing a significant travel burden to maintain and sometimes relatively complex project organizations, the close and friendly collaborations within the International PSC study group (IPSCSG) are absolutely crucial for significant advances in a rare disease like PSC to be made. In 2015, a major accomplishment within the IPSCSG was the conclusion of the Delphi consensus process on endpoints for clinical trials in PSC. The process led to a close collaboration between regulators and scientists and formed the basis of the decision by AASLD to host a 2 days joint conference in Maryland together with the FDA in March 2016 on the subject. These processes are important for the appropriate interpretation of the many ongoing clinical trials in PSC, from which the first data are anticipated to arrive throughout 2016 and 2017.

We are approaching "cruising altitude" with the NoPSC initiative. With now close to 25 researchers and supporting personnel, we should only carefully grow the center size further. There is an ongoing process of consolidating the immunogenetics initiatives, particularly those focusing on the strong HLA association in PSC, within its own structure. Inherent to this is a strengthening of our relationship with the world-leading celiac disease environment in Oslo, led by Prof. Ludvig Sollid. This collaboration is an example of how questions deriving from PSC-specific research can be taken onward in novel constellations as projects dealing with general and fundamental biological issues. Similar directions can be seen for several areas of research within NoPSC at present (e.g. for the gut microbiota).

All taken together, we have a healthy situation for NoPSC at present, forming the best possible platform for our embarking on the next 10-year period of research in 2017.

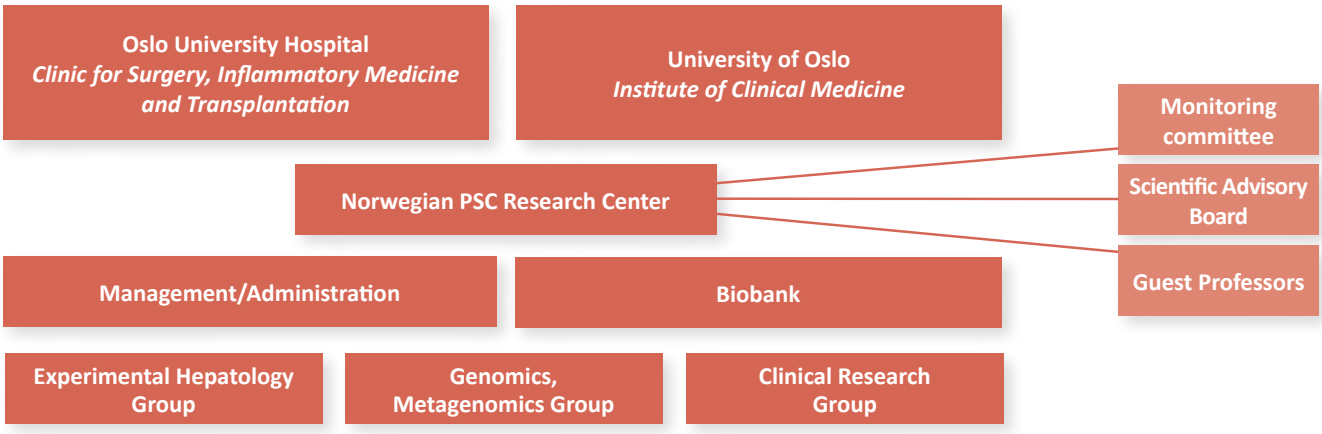
Overview of the Norwegian PSC Research Center

NoPSC was established May 2008 at the Medical Department, Rikshospitalet, upon signing the 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 millions made in September 2007 to substantially strengthen research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis. Approaching the end of this donation period the Center is proud to announce that Canica A/S has provided another NOK 50 millions for a new ten-year period starting in 2017 on the basis of a contractual agreement between Canica A/S and the University of Oslo as of December 2014.

ORGANIZATION

NoPSC has "center status" at the Medical Faculty, University of Oslo and is organized within Oslo University Hospital as a section (level 4 unit) within the Department of Transplantation Medicine at the Clinic for Surgery, Inflammatory Medicine and Transplantation. To maximize the translational opportunities of NoPSC, two of the three research groups comprising NoPSC is organized at the Research Institute of Internal Medicine, Oslo University Hospital (OUS) and one within the Section for Gastroenterology and Hepatology at the Department of Transplantation Medicine.

Internally, NoPSC is organised with an external Monitoring Committee, a Scientific Advisory Board (SAB), a Management, three Research groups and a Biobank.



On October 20th Tom H. Karlsen, together with a PSC patient representative, participated in the morning programme of the Norwegian 2nd Channel (TV2) and explained how PSC occurs and how this uncurable disease effects the lives of all concerned.

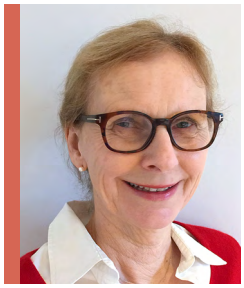
Photo: TV2

MONITORING COMMITTEE

The Committee is supervising all official agreements and financial documents of the Center, and meets twice a year. Apart from presenting all activities, next year's budget is discussed on the autumn meeting while the Annual report and the accounting are reviewed during the meeting in the summer.

Leader
Prof. Ivar Prydz Gladhaug
Head of the Institute of Clinical Medicine, University of Oslo

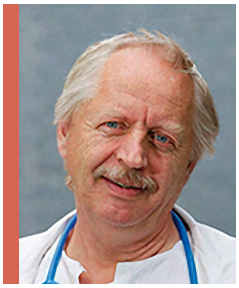
Hans Mossin
Adm. Head of the *Institute of Clinical Medicine, University of Oslo*



Nina Paulsen
Canica A/S

Daniel Sørli
Canica A/S

Prof. Kristian Bjøro
Div. of Surgery, Inflammatory Medicine and Transplantation, OUS Rikshospitalet



Prof. Pål Aukrust
Div. of Surgery, Inflammatory Medicine and Transplantation, OUS Rikshospitalet

***WE AT CANICA** are proud of all the work which had been performed by both the management and the researchers at the Norwegian PSC Research Center in 2015. The number of published articles is quite unique, but what is even more important that the research which is performed is innovative and of the highest international standard. The fact that numerous international scientists are affiliated with the Center bears witness of this. We are also impressed by the management's ability to receive substantial external funding and hence secure the Center's existence for a long time. We are looking forward to the continuation of this important work for the benefit of patients with primary sclerosing cholangitis.* **By Daniel Sørli.**

SCIENTIFIC ADVISORY BOARD

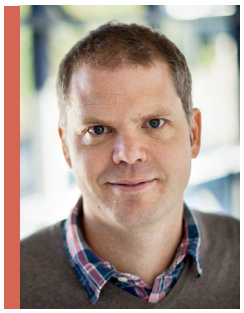
In 2015 the Scientific Advisory Board (SAB) was formally established. The Center has great expectations regarding this highly competent board to evaluate the research being performed and the advice our scientists will receive on their professional development and career perspectives.

Prof. Herbert Tilg
University of Innsbruck, Austria

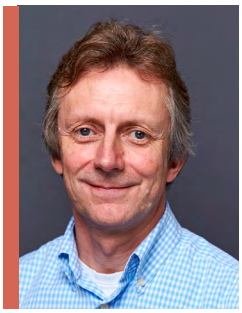
Prof. Terje Espevik
University of Science and Technology (NTNU), Trondheim, Norway

Prof. Tore Kvien
University of Oslo, Norway

GUEST PROFESSORS



Fredrik Bäckhed
Institute of Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden



David Adams
College of Medical and Dental Sciences, University of Birmingham, UK

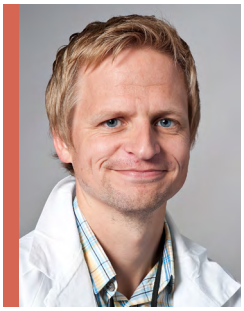
MANAGEMENT

It consists of the three research group leaders and the head of the Center. The Management, together with the Center´s administration, has the overall responsibility for the day-to-day work performed at the Center. Apart from all scientific and academic obligations, the Management, in close contact with the Monitoring Committee, the SAB and the guest professors, continuously plans all future activities and makes sure that all administrative routines are in place for the optimal functioning of the Center.

Prof. Tom Hemming Karlsen
Center leader
t.h.karlsen@medisin.uio.no

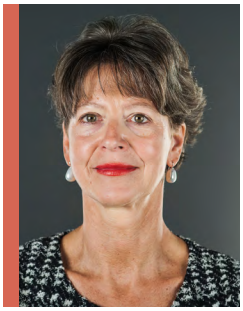
Prof. Kirsten Muri Boberg
Group leader
kboberg@ous-hf.no

Researcher Espen Melum
Group leader
espen.melum@medisin.uio.no

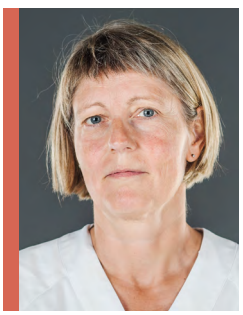


Researcher Johannes Roksund Hov
Group leader
j.e.r.hov@medisin.uio.no

Hege Dahlen Sollid
MSc, Administrative coordinator, until Sept 2015
hegesol@ous-hf.no



Julia Ferkis
Cand.Philol, MHA, Administrative coordinator, Since Sept 2015
julfer@ous-hf.no



Merete Gunvor Gedde-Dahl
MSc, Project coordinator, Since Sept 2015
merged@ous-hf.no

ACCOUNTING

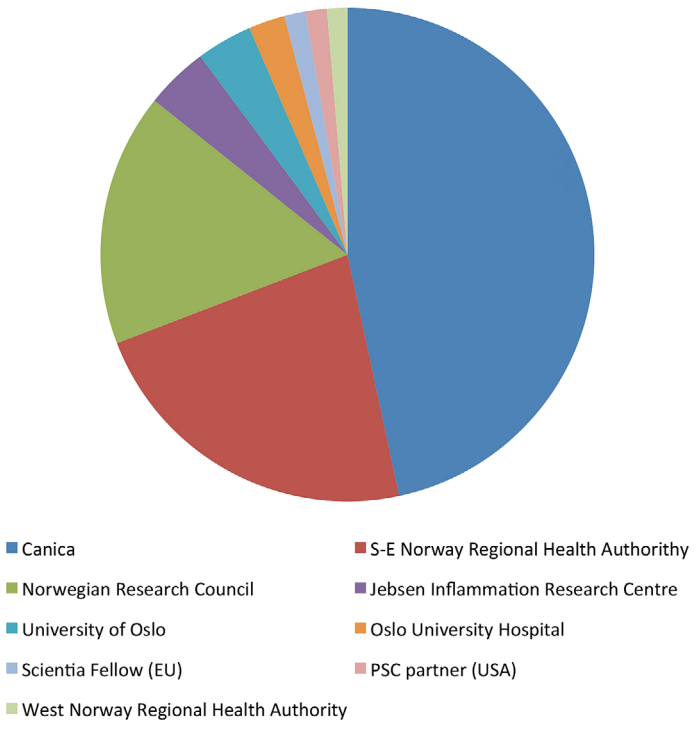
The core expenditures of the Center amounted to 18.728 mill NOK. Out of these 8.735 mill NOK wer from the Canica donation and 2.184 mill NOK were gift reinforcement provided by the Norwegian Research Council, adding to a total of 10.919 mill NOK of Canica-related expenditures in 2015. The remaining expenses of the 2015 budget were covered by a rapidly increasing number of independent grants (also including additional funds from the Norwegian Research Council), in accordance with our goal to build on the Canica funding to increase the external fraction of the overall Center funding which today amounts to somewhat more than 50%.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENSES	INCOME	EXPENSES
TRANSFER FROM 2014	1 817 246		34 566 620	
INTEREST			306 626	
OTHER INCOME	532 237		262 699	
TRANSFER FROM UiO	9 589 673			9 589 673
WAGES		4 585 898		1 810 139
OVERHEAD		284 781		232 116
INFRASTRUCTURE		731 076*		
OTHER OPERATING EXPENCES		3 003 716		118 910
TRANFER TO 2016		**3 333 685**		**23 385 107**

**Additional expenses of NOK 353 054,-for Germ Free Mouse Facility equipment will be presented in the 2016 budget.*

Canica	8 735
S-E Norway Regional Health Authorithy	4 217
Norwegian Research Council	3 103
Jebsen Inflammation Research Centre	770
University of Oslo	686
Oslo University Hospital	445
Scientia Fellows (EU)	262
PSC Partners (USA)	260
West Norway Regional Health Authority	250
Thousand NOK	**18 728**

This pie chart shows the expenditure distribution between the different funds:



Highlights 2015

DISSERTATION OF SIGRID NÆSS

On December 15th Sigrid Næss defended her thesis "The major histocompatibility complex association in Primary Sclerosing Cholangitis". The trial lecture carried the title "Autoimmune leversykdommer: epidemiologi, diagnostikk og behandling". The opponents, Professor Flemming Pociot, Herlev University Hospital, University of Copenhagen, Dr. Magnhild Gangsøy Kristiansen, Institute of Clinical Medicine, University of Tromsø and Professor Jørgen Jahnsen, Institute of Clinical Medicine, University of Oslo contributed to an interesting and fruitful scientific discussion with the candidate. Tom H. Karlsen, Johannes E. R. Hov and Benedicte A. Lie were Næss' supervisors.

SCIENTIA FELLOWS

NoPSC participates in this international postdoctoral fellowship programme in health sciences funded jointly by EU's Marie Curie programme and the Faculty of Medicine, University of Oslo. Candidates are to spend time at the collaborating institutions, where NoPSC is one of the hosts. Dr. Brian Chung, has started his fellowship at the University of Birmingham on June 1st 2015 and will spend two years there and finish his fellowship at NoPSC in the following year. Dr. Schneditz has joined the University of Cambridge on July 1st 2015 and will stay there until June 30th 2017. As with Dr. Chung, Dr. Schneditz will finish his fellowship at NoPSC. For both candidates there is the long-term ambition of subsequent grant applications based upon the Scientia Fellowship period to further the work and enhance the groups at NoPSC with new expertise.

GUEST PROFESSOR MEETINGS

These annual events are one of the most important scientific highlights in the life of NoPSC.
During these visits all scientific projects are critically reviewed in relevant sub-groups under the leadership of a post doc or PhD candidate to enlarge the effect of knowledge transfer between these experienced

Photo Øystein H. Horgmo, University of Oslo

Guest Professor Bäckhed with PhD students Laura Valestrand and Elisabeth Schrumpf, Group Leader Espen Melum and post. doc. Georg Schneditz

scientists and the young researchers of the Center. David Adams from the University of Birmingham and Fredrik Bäckhed from the University of Gothenburg are both internationally renowned experts of their respective fields of immunology and microbiology, and have been serving as guest professors the past few years. Fredrik Bäckhed´s term as visiting professor ended in 2015, leaving a highly flourishing portfolio of research related to the gut microbiota as proof of the usefulness of the activity.

VISITS FROM COLLABORATING SCIENTISTS

With increasing international profile, we experience a great interest in visiting the Norwegian PSC Research Center, both for strategic and collaborative discussions. Visitors from 2015 include:

March 24th: Professor Sebastian Zeisig, University clinic, Dresden
June 16th: Professor Andre Franke, Christian Albrecht University, Kiel
June 30th – July 1st: Dr. Sebastian Jendrek, University Clinic Schleswig – Holstein, Lubeck, Germany
November 3rd: Jean-Michel Pawlotsky, Hospital Henri Mondor, Paris, France

FUNDING FROM HORIZON2020

The project "DYNAFLOW: Dynamic bile flow modeling and cellular sensing in primary sclerosing cholangitis" has received funding within the 1st Joint Transnational Call for Proposals for "European Research Projects to demonstrate the feasibility and benefits of systems medicine" within the Horizon2020 programme. The consortium is headed by Professor Jochen Hampe, University Clinic Dresden, Germany. Beside NoPSC leader, Professor Tom H. Karlsen the members are Professor Michael Trauner, University of Vienna, Austria, Professor Marino Zerial, Max Planck Institute of Cell Biology and Genetics, Dresden, Germany, Professor Josue Sznitman, Israel Institute of Technology, Dr. Patrick Delmas, CNRS AMU, Marseilles, France. The total funding of the project is EURO 1,721,000 and serves to strengthen key aspects of our research and the biobank collaborations with the Department of Pathology.

SECOND NATIONAL MICROBIOTA CONFERENCE

NoPSC Group Leader Johannes R. Hov co-hosted the second national conference on "Gut Microbiota in Health and Disease" at Gardermoen on November 3rd 2015. The conference again became a success with 94 participants and 21 accepted abstracts for oral or poster

Photo: Johannes E. R. Hov

Interested participants on the 2nd National Microbiota Conference

presentation. The first "Tore Midtvedt-price" for best abstract was also presented at the meeting.

NOPSC SCIENTIFIC RETREAT

In September, the third annual NoPSC Scientific Retreat was held at Hadeland Hotel. All members of NoPSC contributed with short presentations of their ongoing work and in depth discussions on the respective projects followed in smaller groups. The management used this opportunity to present its strategies for the coming year. The retreat gave also an excellent possibility to socialize and build relations.

EXPERIMENTAL LIVER IMMUNOLOGY WORKSHOP

There has for many years been a close collaboration between Karolinska Huddinge and Rikshospitalet starting with Erik Schrumpf and the late Ulrika Broomé. In the more recent years this collaboration evolved further focusing on clinical studies headed by Annika Bergquist and Kirsten Muri Boberg. To further strengthen this collaboration, the Experimental Group visited the group of Niklas Björkström at Huddinge for the first joint Experimental Liver Immunology Workshop. There were approximately 20 participants that took active part in the informal discussions. We already have one joint post.doc. working on a familial PSC disease (Xiaojun Jiang) and a new project focusing on MAIT -cells were discussed and formed during the workshop. During the spring of 2016 we will host the second Experimental Liver Immunology workshop in Oslo.

K.G. JEBSEN INFLAMMATION RESEARCH CENTRE (JIRC)

The year of 2015 was an important year for the JIRC, in which NoPSC leader Tom H. Karlsen serves as one of the Principal Investigators, since the evaluation done would form the basis for a potential application of prolonged activities. The evaluation of the Center´s activities was excellent, in line with a general perception of JIRC leader Guttorm Haraldsen being successful in bringing together the various inflammatory research environments at Oslo University Hospital. Several new, local collaborations have been established as a result of JIRC, in particular for topics related to the gut microbiota and immunology, and NoPSC greatly appreciates participating in the well-run network platform of JIRC.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

In 2015, Tom H. Karlsen was elected vice secretary for the steering committee of the European Association for the Study of the Liver as the first Norwegian possessing this position. More importantly, the election is a recognition of the importance of the autoimmune liver disease field within EASL, where the emphasis for many years have been predominantly concerned with hepatitis C drug development. The engagement into international liver research and health care politics is important, given the generally weaker standing of hepatology compared with other medical disciplines. EASL provides a key platform for engagement in European Union priorities as to both research funding programs and regulations.

INTERNATIONAL PSC STUDY GROUP (IPSCSG)

The engagement at the international arena resulting from many years of research collaborations led to the formation of the International PSC study group and made the large genetics studies of NoPSC feasible.
As in previous years, 2015 saw two official meetings of the International PSC Study Group. The first one in conjunction with the International Liver Congress (ILC/EASL) in Vienna on April 25th and the second one in connection with the American Association of the Study of Liver Diseases (AASLD) annual Congress in San Francisco on November 15th. In Vienna the 5th anniversary of this international, team-based and cutting-edge cooperation was celebrated. We sincerely hope that the network will continue its most valuable work and collaboration in the years to come.
For more information on the IPSCSG, please see the separate section on the IPSCSG on page 26 or the www.ipscsg.org webpages.

Project portfolio // Research groups

EXPERIMENTAL HEPATOLOGY GROUP

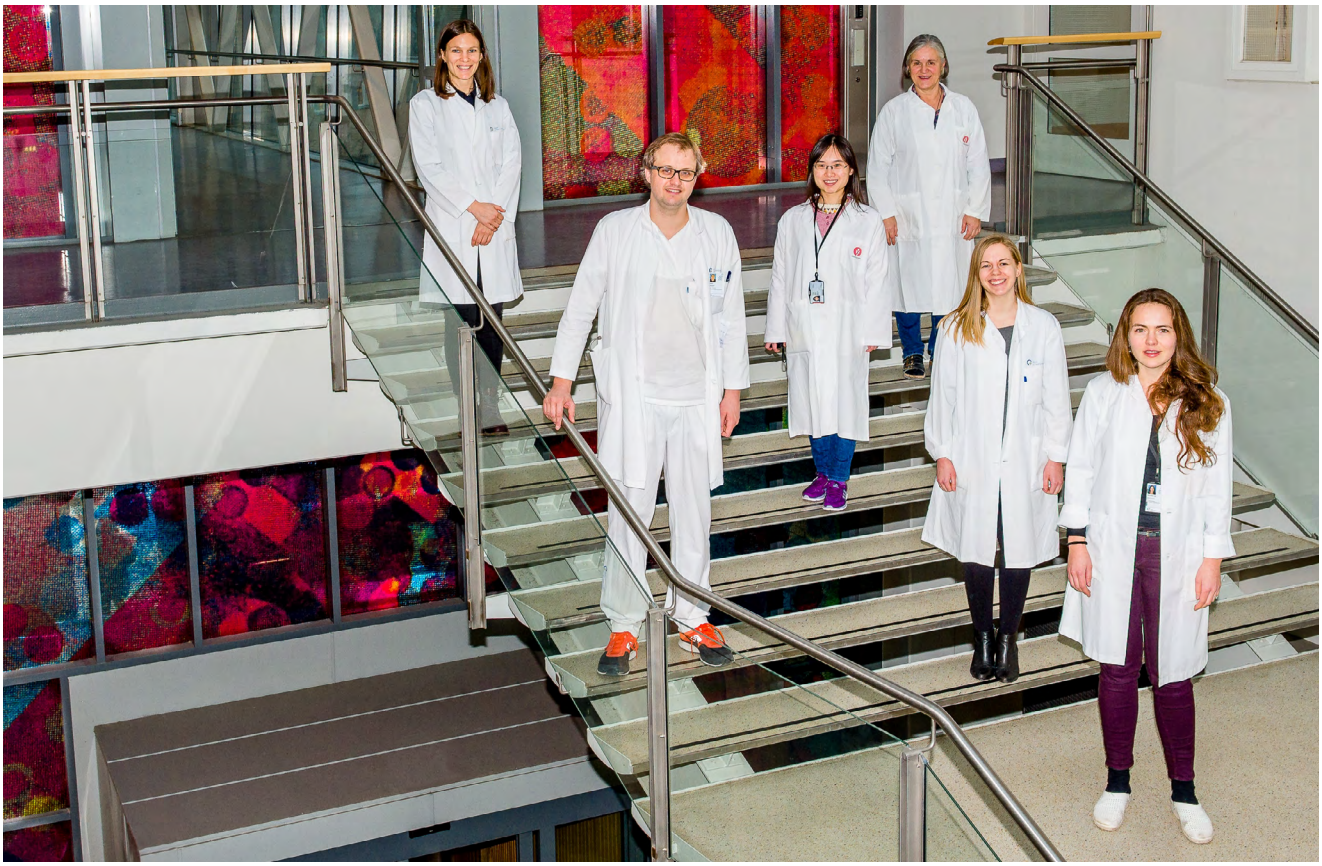


Photo Øystein H. Horgmo, University of Oslo

From left to right: Laura Valestrand, Espen Melum, Xiaojun Jiang, Anne Pharo, Eva Kristine K. Henriksen (middle) and Natalie L. Berntsen (in the front)

GROUP LEADER:
Espen Melum

LAB MANAGER:
Tonje Bjørnetrø (Jan-July 2015)
Anne Pharo
anne.pharo@rr-research.no

POST DOC:
Jiang Xiaojun
xiaojun.jiang@medisin.uio.no

PHD STUDENTS:
Elisabeth Schrumpf
elisabeth.schrumpf@medisin.uio.no
Natalie Lie Berntsen
n.l.berntsen@medisin.uio.no
Eva Kristine Klemsdal Henriksen
evak.klemsdal@gmail.com
Laura Valestrand
lauravalestrand@gmail.com

In 2015 several large projects that have been ongoing in the Research Group for Experimental Hepatology saw completion and publication in or submission to scientific journals. The main focus of the Group for Experimental Hepatology is to understand the regulatory mechanisms involved in bile duct inflammation by using different *in vitro* and *in vivo* assays. In January 2015 Anne Pharo started in a permanent position as a lab manager in our group. Anne has extensive experience from the Institute of Immunology and we were very fortunate that she wanted to join us. In August 2015 Laura Valestrand, who is trained as an MD, started as a PhD student working on the role of the immune system during cholestasis with a particular focus on NKT cells.

In a project involving a familiar form of PSC we have performed lymphocyte RNAseq studies in collaboration of Niklas Björkstöm at Karolinska and revealed mutation expression in patients' T cells at the mRNA level and found several mutation specific signal proteins. Further signaling pathway analysis is ongoing. Furthermore, functional assays to evaluate these functions in T-cell has been set-up. We have also acquired knock-out mice and generated a knock-in mouse.

Using a unique collection of paired patient material, we have studied the T-cell receptor repertoires of PSC-IBD affected livers and intestines. Our findings suggest that a high proportion of the patients' liver and gut memory T cells are able to recognize the same antigen(s) or antigen(s) that share sequence or structural similarities. With this, we provide evidence in humans supporting the hypothesis that memory T cells migrate between the inflamed gut and liver of PSC patients. The development of a surgical model of bile duct inflammation was completed in 2014 and this model now constitutes a unique asset for the group. Using this model, we have in 2015 demonstrated that installation of the NKT cell activating hapten Oxazolone into the biliary tree induces bile duct inflammation that is likely driven by NKT cells. Mice that lack NKT cells (CD1d knockout mice) and mice that are treated with antibodies blocking NKT cell activation seem to be partly protected from disease. Current studies are aimed at further understanding the role of different lymphocyte subsets and the characteristics of the inflammatory process. To investigate the role of the immune system during cholestasis we will use a well-established mouse model of cholestasis, where we induce cholestasis by bile duct ligation. The surgical technique is now up and running, and we will start with descriptive studies before we aim to more closely investigate the role of NKT cells. Using a model of spontaneous bile duct inflammation (NOD.c3c4) we have thoroughly investigated the role of NKT cells in this model by using bone marrow transplantation and knock-out animals. In the same model we have also demonstrated that the gut microbiota is altered in mice with bile duct disease compared to mice with no bile duct disease. Furthermore, we have shown that the bile duct disease is not as pronounced when the mice are rederived into and house in a germ-free environment.

Following the finding that cholangiocytes activate NKT-cells we have investigated bile collect at the time of liver transplantation. These studies have demonstrated that biliary lipids activate NKT-hybridomas with a diverse range of antigen specificities. Of note, we have demonstrated a clear dose-relationship between the grade of bile sample dilution and the activation of the NKT-hybridomas. Further experiments are planned to elaborate the results and to characterise the lipid acting as an antigen.

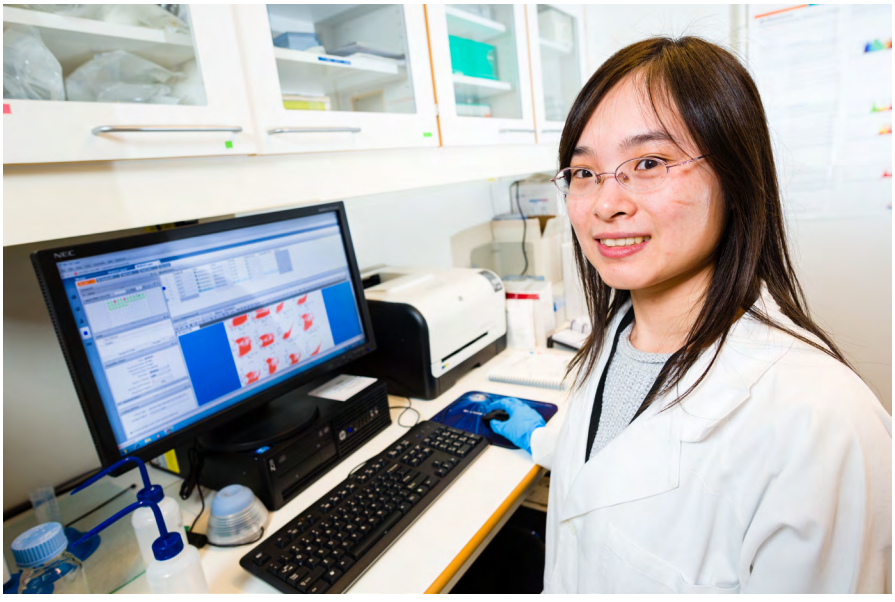


Photo Øystein H. Horgmo, University of Oslo

Post. doc. Xiaojun Jiang during one of her experiments in the lab

New Achievements 2015

- We have demonstrated that Oxazolone cholangitis is CD1d restricted;
- Accomplished successful development of our first CRISPR/Cas9 mouse model together with Applied StemCell;
- Found differences in the microbiota in a murine model of bile duct inflammation and reduced inflammation in germ-free animals;

GENOMICS AND METAGENOMICS GROUP

Photo Øystein H. Horgmo, University of Oslo

From front and to the left: Silje Jørgensen, Johannes R. Hov, Cristiane Mayerhofer, Martin Kummen, Amandeep Kaur Dhillon, Gupta Udatha, Christopher Storm-Larsen, Kristian Holm and Liv Wenche Thorbjørnsen

GROUP LEADER:
Johannes R. Hov

RESEARCHERS:
Marius Trøseid (associated)
troseid@hotmail.com

POST DOCS:
Trine Folseraas (associated)
trine.folseraas@medisin.uio.no
Gupta Udatha
gupta.udatha@outlook.com

PHD STUDENTS:
Martin Kummen
martin.kummen@medisin.uio.no
Sigrid Næss
sigrid.nass@medisin.uio.no
Amandeep Kaur Dhillon
amandeepkaurmahli@hotmail.com
Silje Jørgensen (associated)
s.f.jorgensen@medisin.uio.no
Cristiane Mayerhofer (associated)
cristiane.caroline.mayerhofer@ous-hf.no

BIOINFORMATICIAN:
Kristian Holm
k.holm@ous-hf.no

ENGINEER:
Tonje Bjørnetrø
bjornetro@gmail.com
(February-August 2015)

The PhD dissertation of Sigrid Næss on December 15th was a major event in the Genomics and Metagenomics Group in 2015. Her thesis ”The major histocompatibility complex association in primary sclerosing cholangitis” comprised important studies focusing on the strong genetic associations within the HLA complex in PSC, as well as in acute rejection after liver transplantation.

The group contributed to a large number of publications in 2015. In genetics, the first genetic study on the intriguing subgroup of PSC patients with increased IgG4 was accepted in Gastroenterology, the

top-ranking journal in the field, with Natalie Lie Berntsen as first author (now moved on to full PhD studies in the Experimental Group). Besides this, the first definite reports using sequencing-based gut microbiota profiling were published in 2015. These include the first paper from our group on the microbiota of the intestinal mucosa in PSC (collaboration with the Silverberg group in Toronto), and contributions to two papers characterizing and treating the gut microbiota in HIV, important collaborations in the context of the Research Institute of Internal Medicine and the K.G.Jebsen Inflammation Research Center. Several major studies based entirely on our in-house microbiota analysis pipeline were also finished and submitted in 2015, with expected publication early 2016.

The Norwegian Research Council funded project "NORGUT" was initiated in April 2015 and will run for four years, providing funding for the Group Leader, one PhD student and several studies investigating the gut microbiota in conditions affecting the intestine with a strong focus on PSC. At the end of 2015 we were also happy to receive post. doc. funding from the South-Eastern Norway Regional Health Authority for projects focusing on the clinical application of gut microbiota in PSC.

Research projects related to the concept "clinical microbiota medicine" will be a major strategic goal of the group in the years to come. The starting point is the ongoing in-depth characterisation of the gut microbiota in PSC using modern genetic methods, which will include detailed studies of the mucosal microbes and the functional content of the gut. Bacterial functions will also be characterised using profiling of microbial metabolites in peripheral blood. The next step is application of gut microbiota profiles and metabolomics profiles in biomarker studies of disease activity and severity. Finally, clinical interventions targeting the gut microbiota in PSC may provide important evidence for a role of gut manipulation in the treatment of PSC.

On the basic level, we have an important collaboration with the Experimental Group regarding the gut microbiota of mouse models of biliary disease, which may hopefully translate into clinical applications. In addition, the group is involved in a series of cross-sectional and interventional studies in population controls or other inflammatory conditions like immunodeficiencies and heart disease, aiming to understand the relationship between gut microbiota and markers of inflammation and microbial metabolism, and how diet or drugs may manipulate this system. Finally, following last year's success, the second national conference on gut microbiota was organized in November 2015. The event was once more a great success, with more than twenty abstracts submitted and a fully booked venue.

New Achievements 2015

- Finalization of our first papers of gut microbiota profiling in human diseases based entirely on in-house methodology, from sampling, lab preparations, bioinformatic and statistical analyses.
- Identification of a low diversity gut microbiota in PSC, distinct from the microbiota of healthy individuals and patients with ulcerative colitis without liver disease.
- Identification of the gut microbial metabolite TMAO as a prognostic factor in PSC

EDITORIAL

The gut microbiota appears to play a role in a number of diseases. «Gut profiling» and «gut cocktails» may become standard diagnostic tests and treatments in everyday clinical practice

Personalised medicine targeting the gut microbiota?

The recent national report on personalised medicine (1) devotes little space to microbiomics, that is, studies of the normal microbiota and its genes, owing to a limited existing knowledge base. It is implied, however, that the field will acquire clinical significance. What form might this take?

The gut microbiota varies greatly and has significant metabolic activity. The bacteria constitute a manipulable organ and therefore represent a potential therapeutic target. As more and more diseases are linked to disturbances of the gut microbiota, many of us will find ourselves faced with the option of gut microbiota-directed diagnostics or therapy.

Cross-sectional studies have revealed differences between diseased and healthy individuals in the composition of their gut microbiota, for example in type 2 diabetes (2). Whether it is single bacteria or the entire intestinal environment that plays a role, or whether the observed changes are secondary to disease, is unclear. The studies show, however, that the gut microbiota profile in itself has potential as a diagnostic tool and may become clinically relevant.

A better understanding of the relation between gut microbiota and disease will enable the use of personalised therapy. Trimethylamine-*N*-oxide (TMAO), a product of bacterial metabolism of choline and carnitine (in eggs and meat), is directly involved in atherosclerosis, and is moreover a marker for cardiovascular events (3). We have recently shown that plasma levels of this oxide are also related to survival in patients with heart failure (4). Identification of specific environment-gut microbiota interactions such as these could lead to novel therapeutic recommendations and lifestyle advice, based on either the gut microbiota profile or bacteria-related metabolites.

The efficacy and toxicity of drugs is affected by the gut microbiota. Digoxin, for example, is inactivated in 10% of us by the bacterium *Eggerthella lenta*, while adverse effects of cytostatics can be reduced by bacterial enzymes (5). Pharmacomicrobiomics may therefore become part of personalised medicine.

The condition for which most progress has been made in this regard is *Clostridium difficile* colitis, in which faecal transplantation for recurrent disease can be regarded as established (6). A Dutch group recently showed that faecal transplantation also improved insulin sensitivity in metabolic syndrome (7). Such data give rise to hopes that targeted treatment of the gut microbiota can provide health benefits also for conditions outside the intestines.

In Norway, there has been research into the relation between intestinal bacteria and health for some time (8). The gut microbiota has become a major field of research internationally, driven by new genetic methods that allow culture-independent analyses of the microbiota, and by publicly funded projects in Europe (MetaHIT) and the USA (the Human Microbiome Project). In addition, pioneering work in germ-free mice has directly linked the composition of the gut microbiota to factors such as obesity and behaviour (9, 10).

There are many challenges remaining before terms like «gut microbiota medicine» or «gut microbiota disease» can become part of clinical practice. The gut microbiota is affected by many known and unknown confounding factors, including diet and age. It is important that methods are standardised, as the conditions used can greatly affect the results obtained. In Norway, optimal methods have been established to only a limited degree, and the lack of facilities for research on germ-free animal models is a particular challenge.

Who will claim ownership of this new organ? Gastroenterologists will be in a unique position, with endoscopic access to diagnosis and treatment, but it is difficult to envisage the development of a modern gut microbiota medicine without microbiologists and infectious disease specialists. In order to conduct high quality studies of conditions such as obesity, diabetes and rheumatic diseases, to name but a few, interdisciplinary collaboration will be required. The first national microbiota conference, held in 2014, was a step in that direction, as was the foundation of a Norwegian Microbiota Society.

It is important not to get carried away. A thorough understanding of the gut microbiota in different diseases is needed, and clinical trials will be required before implementation in clinical practice. The risk of transmission of infectious diseases and a more theoretical risk of transmission of a deleterious microbiota must be monitored and weighed up against presumed health benefits. We know little about whether probiotics, for example, have positive effects in the long term, such that one can usefully refrain from such treatment given that the benefits are not proven. All in all, there is still legitimate cause for optimism. By means of high- quality scientific studies of the gut microbiota, we can achieve better understanding of disease, diagnosis and treatment in a personalised manner.

Johannes Espolin Roksund Hov
j.e.r.hov@medisin.uio.no
Marius Trøseid

Johannes Espolin Roksund Hov (born 1977), PhD, speciality registrar in the Section of Gastroenterology and postdoctoral researcher at the Norwegian Primary Sclerosing Cholangitis Research Center at Oslo University Hospital, Rikshospitalet and the University of Oslo. He is head of a research group studying genetics and the gut microbiota in inflammatory diseases at the Research Institute for Internal Medicine.
The author has completed the ICMJE form and declares no conflicts of interest.

Marius Trøseid (born 1972), PhD, specialist in infectious diseases and senior consultant at Oslo University Hospital, Rikshospitalet. His research examines the significance of inflammation and the gut microbiota in HIV infection and cardiovascular disease.
The author has completed the ICMJE form and declares no conflicts of interest.

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CLINICAL RESEARCH GROUP IN OSLO AND BERGEN

Photo Øystein H. Horgmo, University of Oslo

From front and to the left: Kristine Wiencke, Kirsten Muri Boberg, Trine Folseraas, Kristian Bjøro, Erik Schrumpf and Liv Wenche Thorbjørnsen

GROUP LEADER:
Kirsten Muri Boberg

POST DOCS
Mette Vesterhus
mette.vesterhus@helse-bergen.no
Trine Folseraas
trine.folseraas@medisin.uio.no

RESEARCHERS:
Kristine Wiencke (associated)
kwiencke@ous-hf.no
Erik Schrumpf
erik.schrumpf@medisin.uio.no
Kristin Kaasen Jørgensen (associated)
krikjo@online.no
Kristian Bjøro (associated)
kbjoro@ous-hf.no

CORE STAFF:
Mona Bjørnstad
(until Sept)
mona.bjornstad@ous-hf.no
Liv Wenche Thorbjørnsen
liv.wenche.thorbjornsen@ous-hf.no
Jorunn Bratlie
(affiliated engineer; until Oct)
Aud Sissel Hjartholm (associated)

BIOMARKERS FOR PROGNOSIS IN PSC

PSC is usually a slowly progressive disorder. Consequently, the design of clinical trials of drugs that improve prognosis is hampered by the relatively low rate of clinically relevant endpoints. Appropriate surrogate endpoints are lacking. An expert panel appointed by the IPSCSG and including members from NoPSC, has reviewed potential endpoints and performed a consensus process to assess the currently available candidates (Ponsioen CY el al, Hepatology 2015). It is evident that novel, preferably non-invasive, biomarkers as surrogate endpoints are urgently needed. The identification of such markers is a current focus of activities within the IPSCSG, as is the search for more potent prognostic markers. The Mayo risk score has been the most widely used model for prediction of the disease course in PSC patients, but novel biomarkers are also urgently needed to assess disease stage and activity as well as prognosis in PSC. A variety of potential prognostic markers are under study. PSC is characterized by a fibrotic process involving the bile ducts. In a study of the noninvasive, serum-based enhanced liver fibrosis (ELF) score in Norwegian patients, our group concluded that the ELF score was a potent prognostic marker in PSC, independent of the Mayo risk score (Vesterhus et al, Hepatology 2015). These findings will now be tested in independent patient cohorts from other IPSCSG centers. Furthermore, based on previous reports indicating that imaging of liver fibrosis by ultrasound elastography might predict clinical outcome, we are investigating ultrasound elastography as a prognostic biomarker in an ongoing prospective study as well as exploring the evaluation of liver fibrosis by a novel multimodal MRI method. Further search for novel serum markers of PSC prognosis is also ongoing.

TREATMENT OF PSC

Whereas endoscopic treatment of strictures in PSC and transplantation of selected patients are well established treatment modalities, no drug has so far been shown to improve the prognosis. This is partly due to the lack of appropriate surrogate endpoints making drug trials difficult to perform. Nevertheless, some studies are ongoing - some are aiming at changing the bile composition, some are directed against the development of fibrosis, whereas some are directed against inflammation or potential infectious components. Our group has participated in a drug trial with norursodeoxycholic acid. The study has been completed, but results are so far unknown.

EARLY DETECTION OF CHOLANGIOCARCINOMA

PSC is strongly associated with cholangiocarcinoma (CCA) development, which complicates the disease in 10 – 15% of patients. The pathogenesis of PSC-related CCA is poorly understood. The lack of diagnostic methods for early detection and the limited therapeutic options once the tumor is diagnosed by available techniques, constitute major challenges in the current handling of PSC patients. A main research focus is to detect biomarkers for diagnosis of PSC-CCA at an early stage that might be curable by radical surgery. DNA methylation analyses in biliary brush samples could potentially serve as supplement to conventional brush cytology. Building on our previous identification of methylated DNA biomarkers in CCA tissue samples, we have now tested biliary brush specimens for specific methylation patterns in 4 genes (CDO1, CNRIP1, SETP9, and VIM) and demonstrated a sensitivity of 85% and specificity of 98% for CCA detection. Methylation profiling of this gene panel outperformed the diagnostic accuracy of conventional brush cytology (Andresen K et al, Hepatology 2015). Analysis of methylation profiles in bile samples are currently ongoing.

TARGETED MUTATION PROFILING IN PSC-ASSOCIATED CHOLANGIOCARCINOMA AND GALLBLADDER CARCINOMA

In personalized medicine, screening for clinically relevant genetic tumor alterations is increasingly used to aid in prognostication and stratification of patients into targeted cancer therapy. Mutations in different tumor suppressor genes and oncogenes have been detected in non-PSC CCA and gallbladder carcinoma (GBC), but dedicated genetic studies in PSC-associated CCA and GBC are missing. NoPSC, in collaboration with the Department of Pathology, University Hospital of Heidelberg, Germany, is leading a study in which genomic DNA extracted from archived formalin fixed, paraffin embedded (FFPE) PSC-associated CCA and GBC specimens is

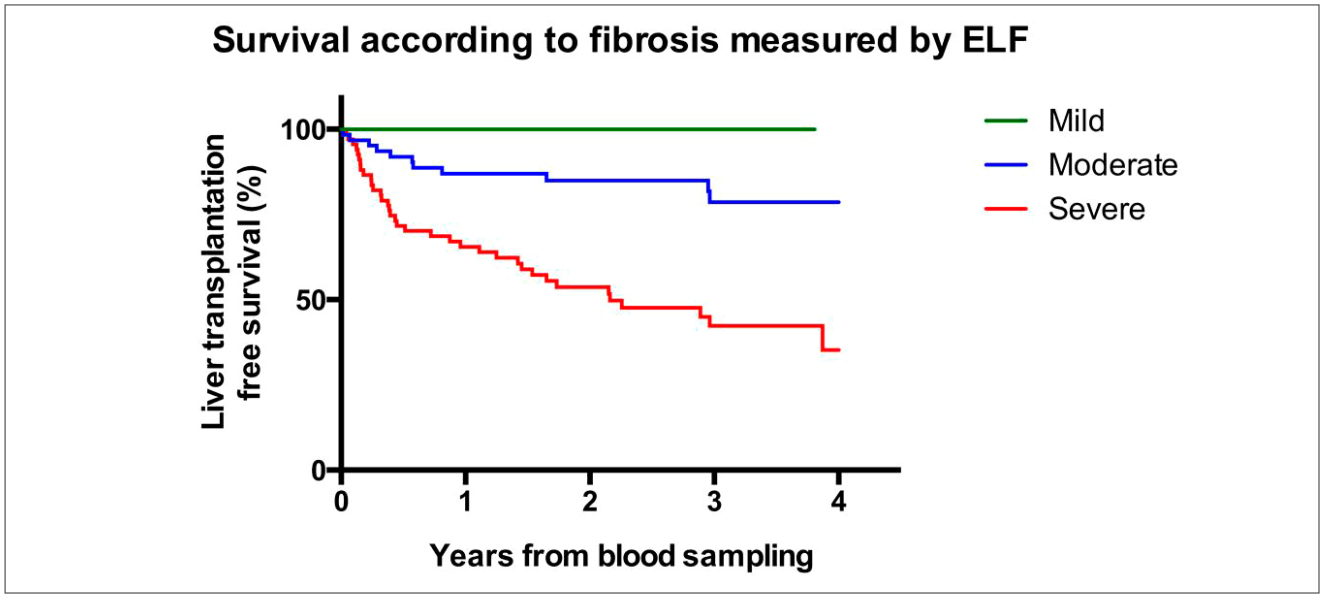
analysed by targeted, massive parallel sequencing covering hotspot mutations in cancer related genes. Preliminary results are interesting, indicating several druggable targets. In 2016 the study will be extended by the inclusion of CCA and GBC specimens from several centers within the IPSCSG.

REGIONAL RESEARCH AND REFERENCE NETWORK IN AUTOIMMUNE LIVER DISEASE (AILD)

PSC is commonly designated an autoimmune liver disease (AILD), along with primary biliary cirrhosis (PBC) and autoimmune hepatitis (AIH). These are all rare and complex disorders with significant impact on patient health and with important areas of unmet needs. Apart from ongoing efforts to improve the understanding of etiopathogenesis, there are challenges related to diagnostic difficulties, the definition of relevant prognostic markers, performance of clinical trials as well as better handling of patient symptoms, for all three conditions. Furthermore, there is a need to ensure quality and equality in patient care.

During 2015 NoPSC has taken the initiative to organize a regional research- and reference network for AILD in the South-Eastern Norway Health Region with a further aim to extend this network to a national undertaking. A systematic, prospective follow-up of PSC patients has already been implemented at Haukeland University Hospital (led by post doc Mette Vesterhus) and at Oslo University Hospital, Rikshospitalet (led by prof. Erik Schrumpf). Colleagues at all major hospitals in South-Eastern Norway have responded positively to the invitation to join this collaborative effort. A similar action has also been asked for by patient organizations. We aim to follow patients prospectively on a regular basis, with registration of predefined and standardized clinical, biochemical and radiological parameters at each visit. Data will be entered into a common database, with the prospect of having a web-based version available by the end of 2016. We also intend to prospectively collect biological material and will make the NoPSC sampling procedures available, including the option to store samples in the NoPSC biobank at Oslo University Hospital.

Providing a potential for improved diagnosis, treatment and follow-up, this network will be useful for both clinicians and patients. It will also be an important resource for future clinical studies. A European Reference Network (ERN) program with the goal of improving clinical care in rare, complex liver diseases (including AILD) across Europe, will be launched during 2016. We will be prepared to join the ERN, thereby contributing to and benefiting from this European joint action.



The figure shows the cumulative liver transplantation free survival in n=138 Norwegian PSC patients classified according to their enhanced liver fibrosis score, confirming its predictive potential. The figure is based on data from the study by Vesterhus et al. published in Hepatology 2015

Awards

- The annual meeting of the Norwegian Gastro-enteorological Society in February 2015 awarded ***Martin Kummen*** for best clinical work presented at the meeting that was perfomed at a university hospital. Kummen has stated that the gut microbiota is different in patients with PSC from healthy controls or patients suffering from inflammatory bowel disease.

- On the same meeting ***Natalie Lie Berntsen*** was awarded with the prize for best presentation for her work in establishing a new surgical animal model for cholangitis.

- On October 16th ***Tom Hemming Karlsen*** was awarded the International Hans Popper Award for his outstanding achievements in the study of the liver. This prestigious prize is awarded once in every third year, and this years' jury underlined Dr. Karlsen's meaningful results in basic and experimental hepatology related to PSC.

- ***Elisabeth Schrumpf*** was awarded the first ever "Tore Midtvedt-Prize" for her presentation of the gut microbiome in the NOD.c3c4 biliary disease model on the Second Microbiota Congress.


29 NYTT FRA FAGMILJØENE

HANS POPPER AWARD

Tom Hemming Karlsen har fått Hans Popper Award som deles ut av Falk Foundation. Prisen er doteret med € 25.000. Seremonien fant sted under Falk Symposium nr. 200: Highlights from Hepatology 2015, 14.-15. oktober, Freiburg, Tyskland.

- Jeg ser på prisen som en anerkjennelse av det gode fagmiljøet ved Norsk senter for PSC, sier prisvinner Tom Hemming Karlsen.

Juryen trekker frem Karlsens fremragende bidrag til basal og eksperimentell hepatologi relatert til sykdommen Primær skleroserende cholangitt (PSC).

Members of the Prize Committee:
M. Colombo, Mailand (Italy)
M. Trauner, Vienna (Austria)
M. Houghton, San Francisco (USA)
M. Omata, Tokyo (Japan)
P. Ginès, Barcelona (Spain)
R. Perrillo, Dallas (USA)

Hans Popper Award Winners 1989-2012:
1989 - H. C. Thomas, London (Great Britain)
1992 - M. Rizzetto, Turin (Italy)
1995 - M. P. Manns, Hannover (Germany)
1999 - M. Houghton, Emeryville (USA)
2003 - S. L. Friedman, New York (USA)
2006 - P. Ginès, Barcelona (Spain)
2012 - J. Bruix, Barcelona (Spain) / J. M. Llovet, Barcelona (Spain)

Anders Jahres Medisinske Pris 2015

NGF-nytt 4 • 2015

Facsimile from the Journal of the Norwegian Gastro-Forum

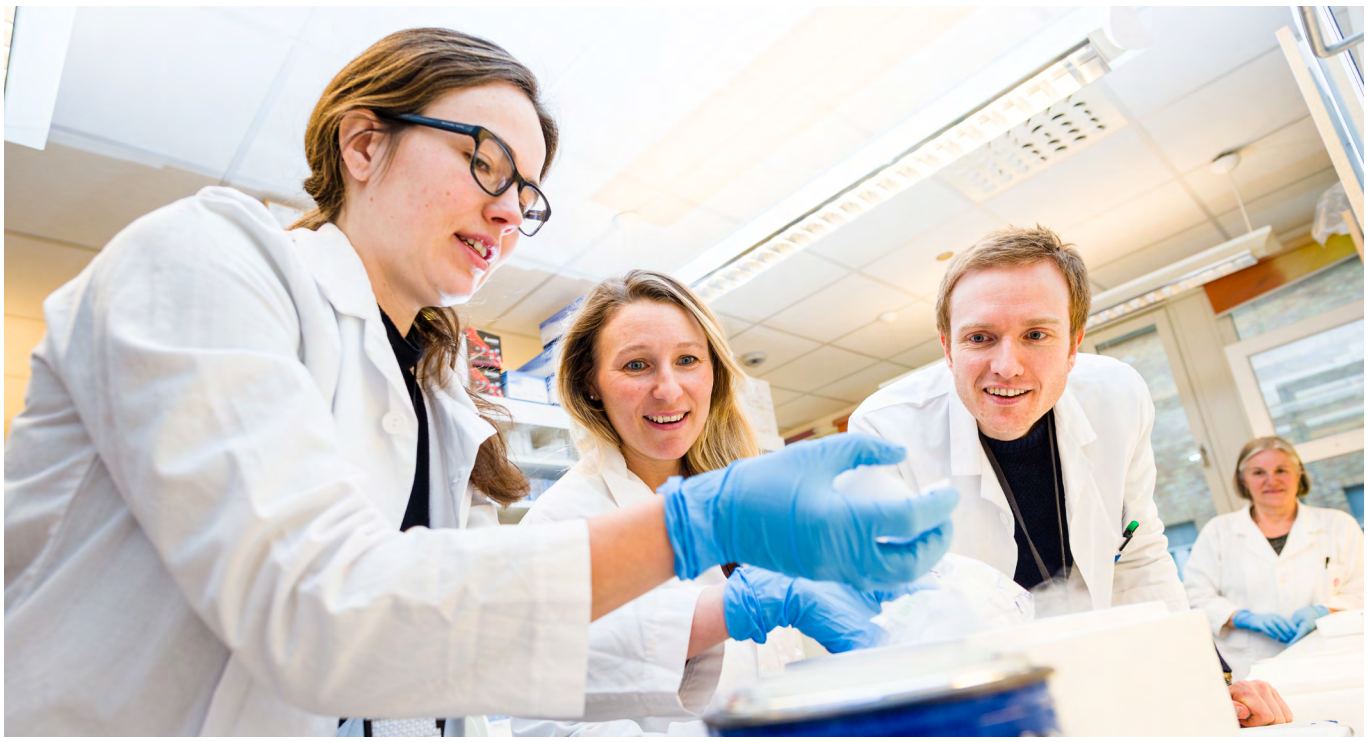


Photo Øystein H. Horgmo, University of Oslo

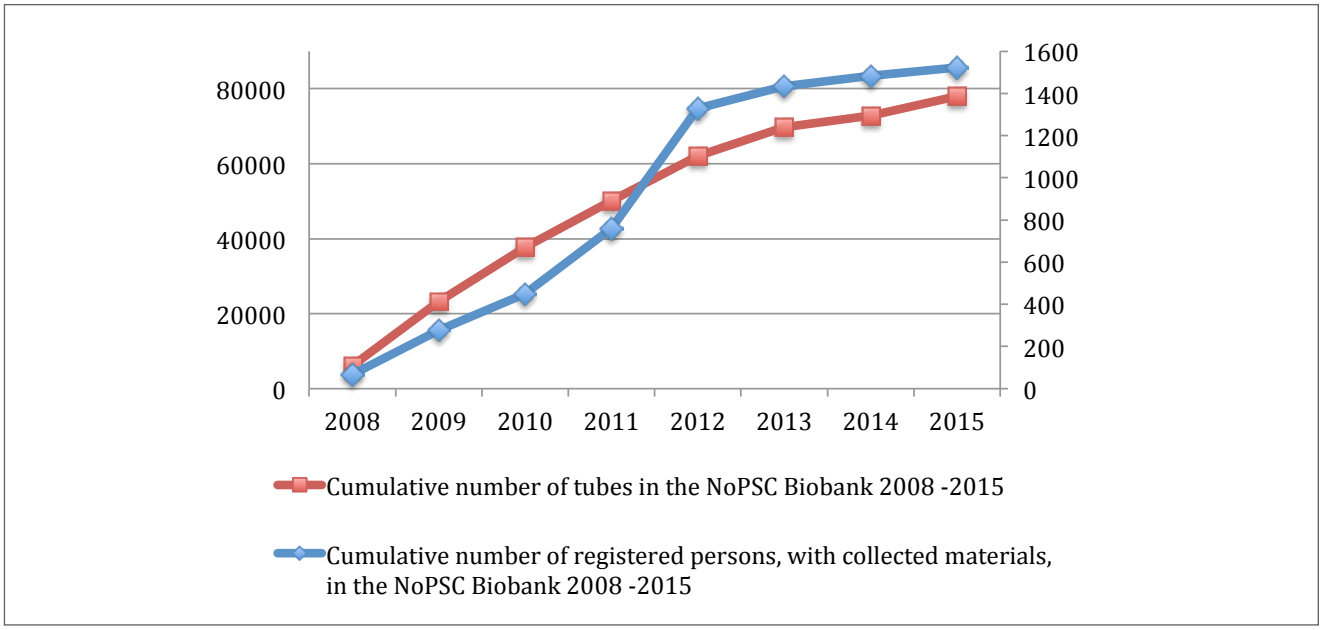
Natalie L. Berntsen, Benedicte Stavik (Institute of Internal Medicine), Martin Kummen and Anne Pharo in the lab

Updates from the NoPSC Biobank

Liv Wenche Thorbjørnsen,
Biobank Manager

By the end of 2015, a total of 1926 individuals were registered in the NoPSC Biobank.

The material amounts to approximately 80 000 tubes of different types of material (e.g. blood, bile, DNA, RNA etc.). The total number of individuals comprises patients with several types of liver diseases (autoimmune liver diseases in particular) and various types of controls (including healthy controls). Patients with PSC have always been the "core business" of the biobanking activities. From 2010, this emphasis was strengthened and we introduced prospective follow-up with annual biobanking from a subgroup of the PSC patients. For some patients we are now also able to collect new material up to five years after the first sample. Such long-term follow samples are extremely important for longitudinal biomarker assessments.



Unit for Experimental Gnotobiology

Henrik Rasmussen,
Head of the Departement of Comparative Medicine, OUS

ORGANISATION

- EG is a research unit for breeding and experimental use of gnotobiotic mice, located at Comparative Medicine (KPM) at Rikshospitalet. The collaboration between NoPSC and KPM was initiated in 2015 and the formal agreement between NoPSC and KPM was signed in February 2016.
- NoPSC funded the isolators while UiO research funds from NoPSC, the Clinic for Cancer, Surgery and Transplantation and KPM funded the building of the animal room. KPM will be responsible for the daily operation, that is to be initiated at the beginning of 2016.

- The facility will be open to all users. Projects will be prioritized by a Scientific Advisory Committee, focusing on NoPSC projects during startup (at least first year). User fees will be charged per isolator per week. The EG unit is approved by the Ministry of Agriculture and the Ministry of Health for housing of genetically modified mice.

CAPACITY

- 4 breeding (5'x2'2') and 4 experimental (3'x'2x2') isolators in a 14 m^2 animal room.

REMAINING ISSUES

- Defining a sterilant that can be readily used in our facility has emerged as an unexpected challenge. Clidox (formerly used in Sweden) is no longer available. While peracetic acid is a very effective sterilant, practical use is a challenge with respect to HMS in the KPM facility.
- Validating optimal programs and chemical/biological indicators for autoclaving of diet, bedding and water.
- Optimal routines for regular confirmation of sterility (monthly bacterial culture/16S PCR, quarterly fungal culture, yearly virology).

Networks

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)
The Institute is headed by Professor Bente Halvorsen and the research groups led by Espen Melum and Johannes E.R. Hov respectively are operational at RIIM. Several collaborative projects are established with the other research groups.

Department of Transplantation Medicine
Department Head, Prof. Pål-Dag Line, Prof. Aksel Foss, Dr. Einar Martin Aandahl and Head of the Section for Transplantation Surgery, Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Pathology
Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models. Through the K.G. Jebsen Inflammation Research Centre (JIRC) we have several ongoing projects with Prof. Guttorm Haraldsen.

Department of Medical Genetics
The Immunogenetics group, led by Prof. Benedicte A. Lie is involved in several projects related to the further characterization of the HLA association in PSC. The Norwegian Sequencing Center hosts the NoPSC MiSeq next generation sequencing machine.

Institute of Immunology
NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular, the good collaborations with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, and the research group of Fridtjof Lund-Johansen, are important in the activities of NoPSC.

Department of Medical Biochemistry
In conjunction with the establishment of the NoPSC Biobank quality control Project the collaboration with Dr. Yngve Thomas Bliksrud is highly appreciated.

Center for Cancer Biomedicine
A collaboration with Prof. Ragnhild Lothe and Prof. Guro Lind at the Department of Cancer Prevention, OUS Radiumhospitalet is the basis for epigenetics-centered projects on early diagnosis of cholangiocarcinoma in PSC.

Department of Radiology
The involvement of the Department of Radiology at OUS Rikshospitalet in the prospective follow-up of PSC patients has been crucial for the success of the initiative. We are particularly grateful to Dr. Andreas Abildgaard and Dr. Knut Brabrand for their active contributions.

KEY NATIONAL COLLABORATORS

The IBSEN study group
The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is important for several of the basic genetic and meta-genomic studies at NoPSC. Blood samples of patients undergoing magnetic resonance cholangiography (MRC) at the 20 years follow-up consultation are deposited in the NoPSC Biobank. Dr. Anne Nergård and Dr. Aida Kapic Lunder are performing the MRCs at Akershus University Hospital. Dr. Kristin Kaasen Jørgensen has entered a combined consultant–researcher position at Akershus University Hospital and continues her collaboration on PSC with the Center.

Haukeland University Hospital and University of Bergen
For the prospective PSC cohort and advanced imaging modalities there is a close collaboration with Prof. Odd Helge Gilja and several other researchers at the Section for Gastroenterology and the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography at the Medical

Department at Haukeland University Hospital in Bergen. For the bile acid and microbiota projects, Prof. Rolf Berge at the University of Bergen provides the serum lipid measurements.

KEY INTERNATIONAL COLLABORATORS

Institute for Clinical and Molecular Biology Christian-Albrechts University, Kiel, Germany
Several co-workers of Prof. Stefan Schreiber and Prof. Andre Franke's group in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and metagenomic projects. Prof. Andre Franke has served as a loyal and dedicated guest professor at NoPSC for 5 years. In addition, Prof. John Baines (joint position at Christian-Albrechts University and the Max Planck Institute of Evolutionary Biology in Plön) is an important collaborator in the metagenomic projects.

Universitätsklinikum Dresden Dresden, Germany
There is a growing collaborative activity with Professors Jochen Hampe and Sebastian Zeissig. With Professor Hampe there is a system biology project under initiation, for which EU funding within the Horizon2020 program has been obtained. Professor Zeissig is participating in the NKT-related projects that are being performed in the Experimental Group.

Cambridge Institute for Medical Research Cambridge, UK
The HLA association in PSC poses particular challenges, and the collaboration with Prof. John Trowsdale and senior researcher James Traherne and Vasilis Kosmoliaptsis in Cambridge is invaluable for the progress of several of our functional genetic projects.

Dept of Medicine, University of Cambridge Addenbrooke's Hospital, Cambridge, UK
Prof. Arthur Kaser is Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK. He served for 3 years as a NoPSC guest professor and is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes. This project is funded within the Scientia Fellows' program of the University of Oslo and involves post.doc. Georg Schneditz and his daily supervisor Dr. Nicole Kaneider-Kaser.

University of Birmingham, Birmingham, UK
Prof. David Adams, a Guest Professor at NoPSC since 2013, and Dr. Gideon Hirschfield at the Center for Liver Research at the Institute of Biomedical Research, University of Birmingham collaborate on several projects related to the further characterization of the HLA related immune response in PSC. Post.doc. and Scientia Fellow Brian Chung participates actively in these projects under the daily supervision of Dr. Evaggelia Liaskou.

The Mayo Clinic, Rochester, USA
Collaboration with Dr. Konstantinos Lazaridis at the Mayo Clinic in Rochester has been established within our projects on the genetics of PSC. Via infrastructure at the Mayo Clinic, DNA from PSC patients in USA and Canada are collected and utilized in local projects as well as for verification of findings in genetic studies at NoPSC.

Brigham and Women's Hospital Harvard Medical School, Boston, USA
Prof. Richard Blumberg is an important collaborator in Dr. Espen Melum's projects related to NKT cells. He is also the co-supervisor of PhD student Elisabeth Schrumpf.

Medical University of Vienna and Medical University of Graz, Austria
In collaboration with Prof. Michael Trauner and Prof. 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

Photo: Tom Henning Karlsen

Participants on the spring International PSC Study Group meeting in Vienna.

the development of a bile duct specific Cre mouse.

The Nordic Liver Transplant Group
Collaborators in Helsinki (Prof. Krister Höckerstedt, Prof. Helena Isoniemi), Stockholm (Prof. Bo-Göran Ericzon), Gothenburg (Prof. William Bennet) and Copenhagen (Dr. Allan Rasmussen) are involved in several projects where data from the Nordic Liver Transplant Registry are required.

Photo: Tom Henning Karlsen

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and has also participated in the genetics projects. Associate Professor Niklas Björkström is involved in projects relating to human immunology in PSC.

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Fredrik Bäckhed and Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed, being a guest professor at NoPSC since 2012 is an expert on gut microbiota, metabolism and gnotobiotic animals and has been an advisor and collaborator on gut microbiota studies in mice, while hepatologist Hanns-Ulrich Marschall contributes with bile acids expertise.

Sapienza, Università di Roma, Italy
Professors Eugenio Gaudio, Domenico Alvaro and co-workers are experts on stem-cells in biliary tree, and the NoPSC Biobank material is used to explore these in PSC.

NoPSC International lectures 2015

Karlsen TH.
Genome-wide association studies in hepatology
48th Annual Meeting of the Italian Association for the Study of the Liver (A.I.S.F.)
Rome, February 17th – 19th 2015

Karlsen TH.
Primary Sclerosing Cholangitis – Where are the Treatment Targets?
Grand Rounds, Beaujon Hospital
Paris, March 6th 2015

Karlsen TH.
Evolution of the genetics of PSC and PBC
Cholestasis: Past, Present and Future
Medical University of Vienna
Vienna, April 15th 2015

Karlsen TH.
Are there common genetic factors among the three autoimmune liver diseases?
Falk Symposium "Autoimmune Diseases of the Liver"
Lisbon, May 8th – 9th 2015

Karlsen TH.
MHC risk mapping – a holy grail of complex disease genetics?
6th International Workshop on Genomic Epidemiology
London, May 14th – 16th 2015

Karlsen TH.
Approach to the cholestatic patient
ASSA SAGES annual meeting
Durban, South Africa, August 8th 2015

Karlsen TH.
Management and treatment failures in autoimmune hepatitis ansd cholestatic liver disease
ASSA SAGES annual meeting
Durban, South Africa, August 8th 2015

Karlsen TH.
GWAS in hepatology – What did we learn?
Department of Biology, Henri Mondor University Hospital
Paris, September 14th 2015

Karlsen TH.
Cholestatic and autoimmune liver disease – from genetics to environment and back
Falk Symposium "Therapeutic strategies in diseases of the digestive tract – 2015 and beyond"
Freiburg, Germany, October 16th – 17th 2015

Karlsen TH.
Predicting susceptibility in cholestatic liver diseases and gall stones
United European Gastroenterology Week
Barcelona, Spain, October 24th – 28th 2015

Karlsen TH.
State of the art introduction: Insights into cholestatic liver disease
United European Gastroenterology Week
Barcelona, Spain, October 24th – 28th 2015

Karlsen TH.
Controversies in management of PSC
American Association for the Study of Liver Diseases
San Francisco, USA, November 13th – 17th 2015

Karlsen TH.
Genetic factors in autoimmune liver diseases
American Association for the Study of Liver Diseases
San Francisco, USA, November 13th – 17th 2015

Karlsen TH.
State of the art in primary schlerosing cholangitis
2nd Swiss Hepatology postgraduate Course
Ermatingen, Switzerland, November 26th – 28th 2015

Karlsen TH.
Cholestatic and metabolic liver diseases
EASL Masterclass
Pavia, Italy, December 3rd – 5th 2015

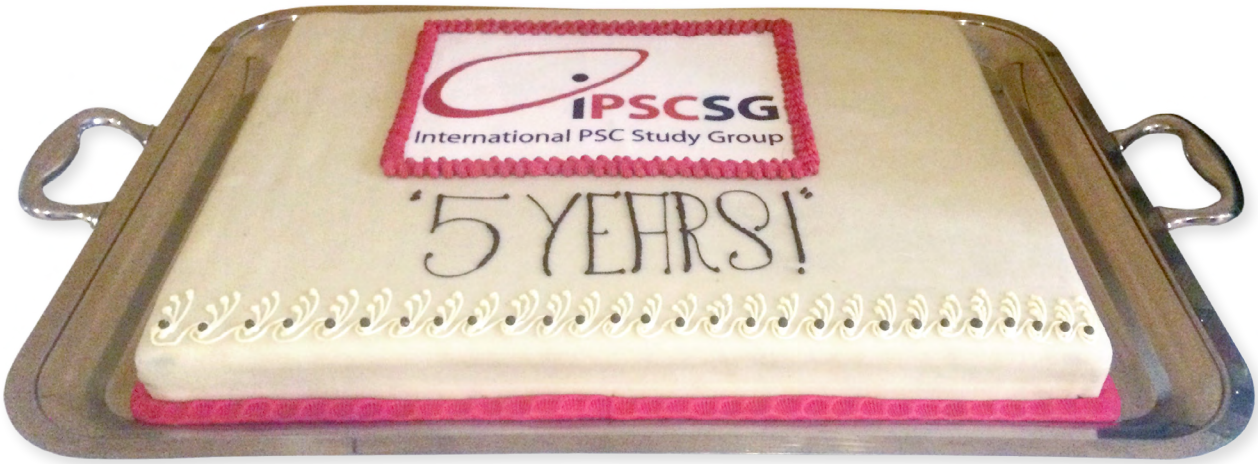
Boberg KM.
Overlap syndromes between PSC or PBC and AIH
24th Conference of the Asian Pacific Association for the Study of the Liver (APASL)
Istanbul, March 12th – 15th 2015

Boberg KM.
AIH-PSC variant syndromes
EASL Monothematic Conference on Autoimmune Hepatitis
London, September 4th – 5th 2015

Boberg KM.
The experience of the Norwegian PSC Research Center
Morning GI Seminar Meeting, Mayo Clinic
Rochester, USA, November 19th 2015

International PSC Study Group (IPSCSG) Annual report

In June 2010, a total of 45 active PSC researchers from Norway, Sweden, Finland, Germany, Switzerland, Austria, Italy, Spain, France, Belgium, the Netherlands, UK, Ireland, US and Canada met in Oslo and established the International PSC Study Group (IPSCSG). Entering 2016 the network consists of renowned scientists and clinicians from more than 57 different institutions in 22 countries working with autoimmune liver diseases.



Representation in the network is based on active participation in at least one ongoing study, but intentionally kept low, informal- and interest-driven. Every second year, a two-day meeting is hosted by one of the participating institutions, in 2012 in Hamburg, and in 2014 in Amsterdam. Two hour update meetings are held twice a year during the International Liver Congress™ (ILC) organized by the European Association for the Study of the Liver (EASL) and the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

In 2015 the first meeting took place in conjunction with the EASL International Liver Congress in Vienna on April 25th where the 5th anniversary of this international, team-based and cutting-edge cooperation was celebrated. In addition to the project updates, a key point for this meeting was to bring the group closer to joint grant applications within major funding bodies like the EU/Horizon2020 and NIH. One step in this direction is the leadership role taken within the autoimmune liver disease arena (IPSCSG included) to enter into an application of a "European Reference Network" for rare liver diseases. Whilst a clinical initiative, a platform of an EU accredited clinical network is also anticipated to be important when reaching out for research funding (e.g. within Horizon 2020).

The second meeting was organized in connection with the AASLD Liver Meeting in San Francisco on November 15th. The update meeting was concerned with the completion of several major undertakings in the international PSC study group, for which papers are expected to appear in 2015. These include the genome-wide association study meta-analysis (almost 5,000 patients), the Immunochip cross-disease analysis (including more than 85,000 individuals and in addition to PSC patients with inflammatory bowel disease, psoriasis and ankylosing spondylitis), the clinical database paper with clinical data from more than 7,000 patients, the cholangiocarcinoma sequencing project, and the Immunochip sub-

phenotype paper (more than 3,000 patients). Furthermore, several clinical biomarker and intervention studies are underway, including the IPSCSG anchored FICUS study (elastography, Olivier Chazouillieres) and DILSTENT2 study (endoscopic therapy, Cyriel Ponsioen).

Both meetings attracted a full auditorium and the group has all reason to be proud of its achievements and most valuable work and collaboration. Planning is now ongoing for the 4th biennial meeting in New Haven, for which Yale holds the organizing responsibilities. Further details on projects and updated meeting details can be found at www.ipscsg.org.

The IPSCSG Delphi consensus process on clinical endpoints

A key deliverable of the IPSCSG in 2015 was the publishing of the Delphi consensus process on endpoints in clinical trials in PSC in Hepatology (see facsimile). The process resulted in the furthering of the topic by the American Association for Liver Diseases (AASLD) by the joint organizing of a workshop together with the FDA in Maryland in March of 2016. There are now many ongoing clinical trials in PSC, targeting a broad range of potentially relevant targets (ranging from novel bile acid derivatives, immune-targeted therapeutics, antibiotics and antifibrotics). To be able to compare the results of all these trials, robust endpoints and the consensus initiative is sorely needed.

MEMBERS OF THE STEERING COMMITTEE

Prof. **Ulrich H. Beuers**, Amsterdam, the Netherlands
Dr. **Luca Fabris**, Padua, Italy
Prof. **Martti Färkkilä**, Helsinki, Finland
Prof. **Chris Bowlus**, Sacramento, USA
Prof. **Olivier Chazouilleres**, Paris, France
Dr. **Gideon Hirschfeld**, Birmingham, UK
Prof. **Tom Hemming Karlsen**, Oslo, Norway
(coordinator/secretary)

PLANNED MEETINGS IN 2016:

Barcelona in April 14th
New Haven in June 26th – 27th
Boston in November

INTERNATIONAL PSC STUDY GROUP NETWORK

Australia
Austria
Belgium
Canada
Denmark
Finland
France
Germany
Greece
Ireland
Iceland
Israel
Italy
Japan
Norway
Poland
Spain
Switzerland
Sweden
The Netherlands
UK
US

More information on:
www.ipscsg.org

Publications 2015

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Genetic Risk and the Development of Autoimmune Liver Disease
Dig Dis, 33 Suppl 2, 13-24

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Transplantation With Livers From Deceased Donors Older Than 75 Years
Transplantation, 99 (12), 2534-42

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The First European Evidence-Based Consensus on Extra-Intestinal Manifestations in Inflammatory Bowel Disease
J Crohns Colitis 10 (3), 239-54

4. Stiksrud B, Nowak P, Nwosu FC, Kvale D, Thalme A, Sonnerborg A, Ueland PM, **Holm K**, Birkeland SE, Dahm AE, Sandset PM, Rudi K, **Hov JR**, Dyrhol-Riise AM, Trøseid M (2015)
Reduced Levels of D-dimer and Changes in Gut Microbiota Composition After Probiotic Intervention in HIV-Infected Individuals on Stable ART
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Gut microbiota diversity predicts immune status in HIV-1 infection
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Characterization of Intestinal Microbiota in Ulcerative Colitis Patients with and without Primary Sclerosing Cholangitis
J Crohns Colitis, 10 (3), 330-7

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Cancer Risk and Surveillance in Primary Sclerosing Cholangitis
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Inherited determinants of Crohn's disease and ulcerative colitis phenotypes: a genetic association study
Lancet, 387 (10014), 156-67

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Imputation of KIR Types from SNP Variation Data
Am J Hum Genet, 97 (4), 593-607

10. Ponsioen CY, Chapman RW, Chazouillères O, Hirschfield GM, **Karlsen TH**, Lohse AW, Pinzani M, **Schrumpf E**, Trauner M, Gores GJ (2015)
Surrogate endpoints for clinical trials in primary sclerosing cholangitis; review and results from an International PSC Study Group consensus process
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Inflammation But Not Biliary Obstruction Is Associated With Carbohydrate Antigen 19-9 Levels in Patients With Primary Sclerosing Cholangitis
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Nucleic Acids Res, 43 (11), e70

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Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma
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Association Between HLA Haplotypes and Increased Serum Levels of IgG4 in Patients With Primary Sclerosing Cholangitis
Gastroenterology, 148 (5), 924-927.e2

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Differences in long-term survival among liver transplant recipients and the general population: a population-based Nordic study
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Transplantation Direct 2015;1: e39

38. Wannhoff A, **Folseraas T**, Brune M, Rupp C, Friedrich K, Knierim J, Weiss KH, Sauer P, Flechtenmacher C, Schirmacher P, Stremmel W, **Hov JR**, Gotthardt DN (2015)
A common genetic variant of fucosyltransferase 2 correlates with serum carcinoembryonic antigen levels and affects cancer screening in patients with primary sclerosing cholangitis
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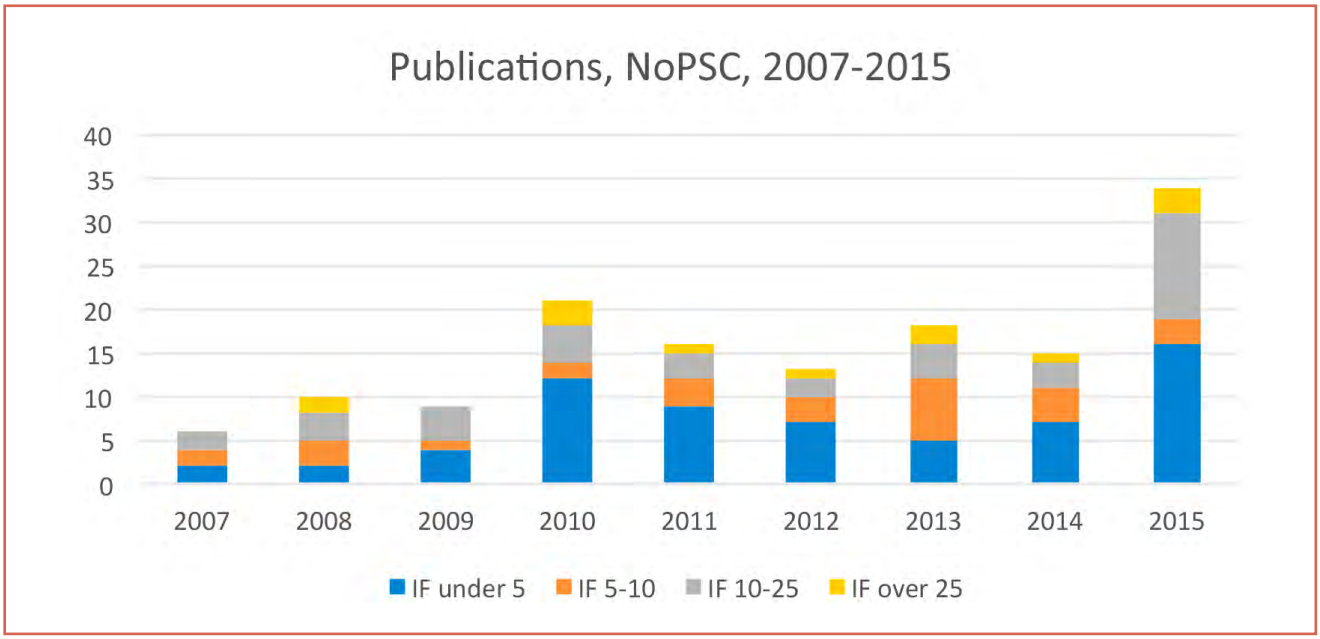

The diagram shows the Center's publication development including Impact factor (IF). Publications are registered in the year they were first published.


NOPSC

NOPSC
Norwegian PSC
Research Center

Clinic For Surgery, Inflammatory Medicine and Transplantation
Oslo University Hospital, Rikshospitalet
P.O. Box 4950 Nydalen, 0424 Oslo, Norway

Tel: +47 23 07 00 00
Email: nopsc@ous-hf.no

www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/
www.oslo-universitetssykehus.no

UiO : University of Oslo

Oslo
University Hospital

Oslo University Hospital is Norway's largest hospital, and conducts a major portion of medical research and education of medical personnel in Norway. Post: Oslo University Hospital, P O Box 4950 Nydalen, NO-0420 Oslo, Norway.
Switchboard: +47 91 50 27 70