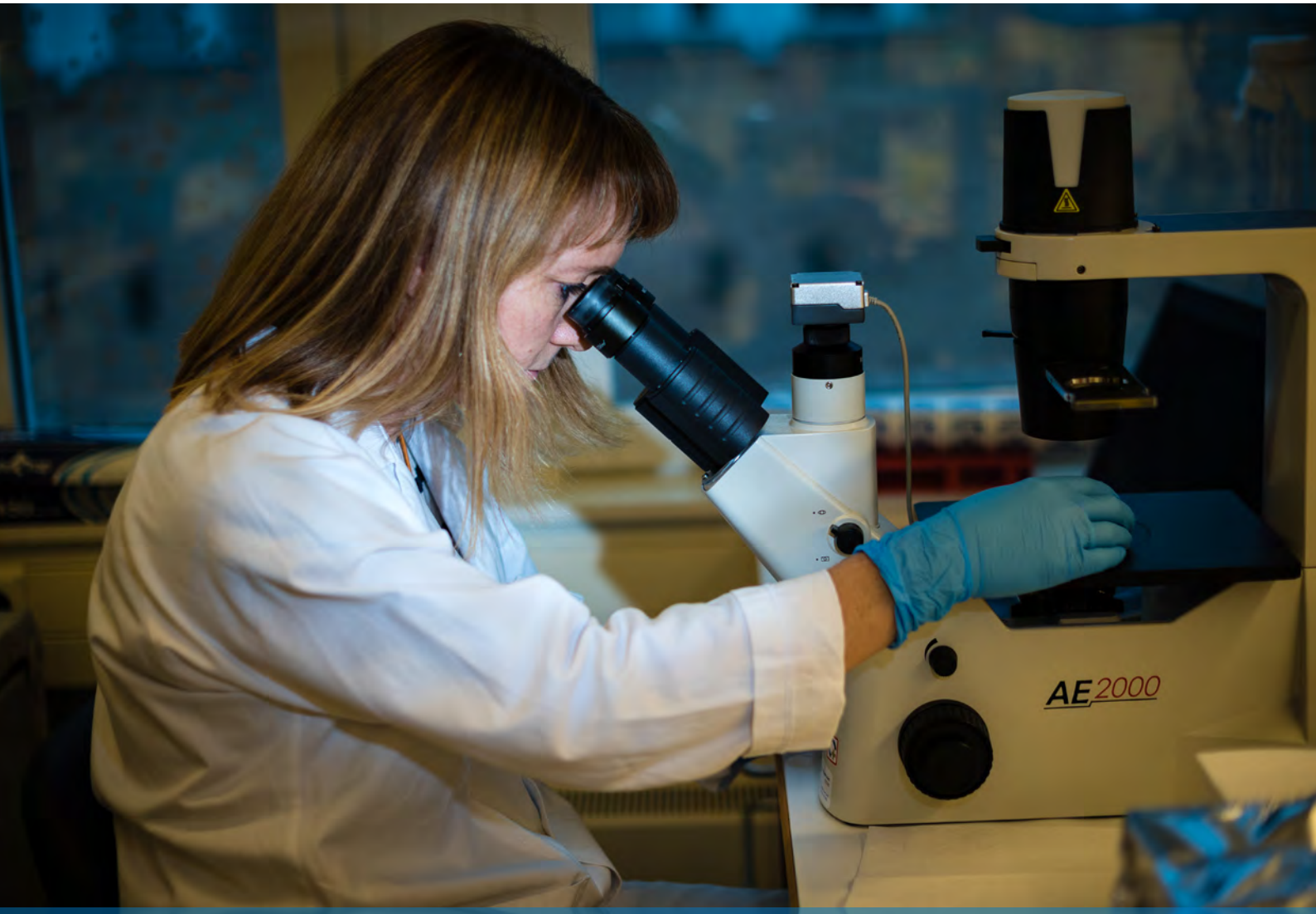
Oslo University Hospital

UiO : University of Oslo



Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2017

RIIM

ANNUAL REPORT

2017

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RIIM ANNUAL REPORT 2017

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

2017, is like the year before, a successful year to look back on. RIIM`s scientific activities, measured by publications, text books, presentations, prizes and and success in getting external funding, increases. The scientific production is at a level which makes RIIM one of the most productive milieus at Oslo University Hospital (OUH) and among the top national, as well as international translational research milieus. We manage to keep up the recruitment of top international researchers, which is important for our success. Also, RIIM scientists received important national (HSØ grants and NRC funding), as well as international funding (such as ERA – CVD grants) in 2017. Moreover, Dr. Espen Melum received the prestigious NRCs early career grant. RIIM is established as a robust research arena in OUH.

In spite of crowded office space and lab benches and queues on the laboratory equipment, RIIM continues to mature into a more robust organization. My most important job as leader is to secure better long-term and predictable funding and to ensure a fruitful/productive and healthy working environment. After two years of hard work we finally received more office space. Getting brand new office space for 5-6 people, underscores that the Head of Division sees and believes in what we are doing. This is an important and encouraging "victory".
In 2017 new colleagues were hired, PhD candidates dissertated, and colleagues rotated to other positions. RIIM is a dynamic milieu. In December one of our group leaders, Dr. Grethe Skretting, retired after many years in science. With that we lost a brick of knowledge in molecular biology and a good and colorful colleague. We thank Grethe for all she has done for RIIM.

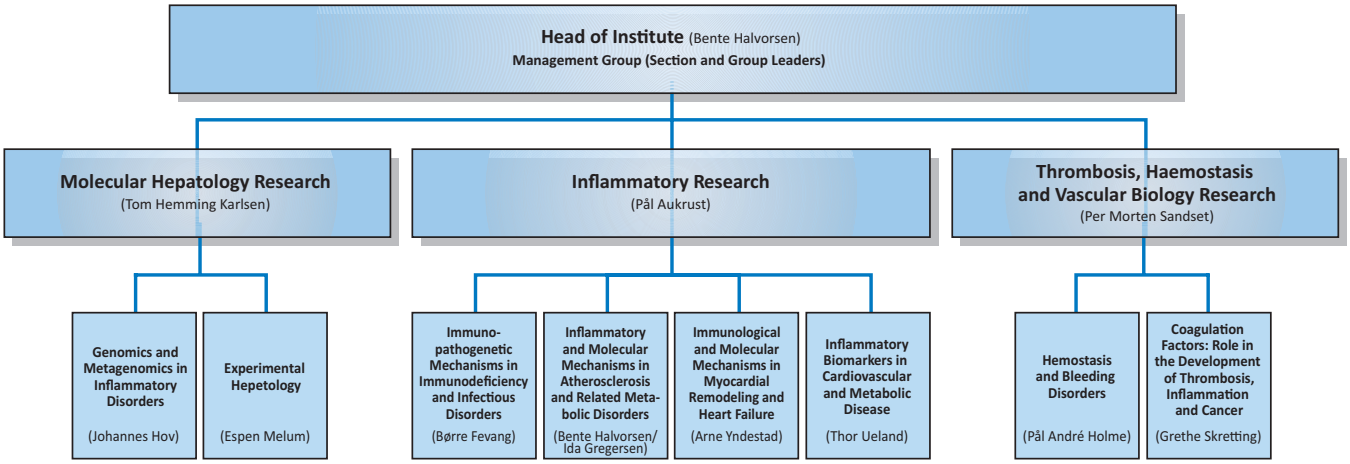
We embrace the dynamics of the Institute, but RIIM also acknowledges and focuses on its status and robustness as a translational research arena, built up of inflammation-oriented projects. A focus area in 2017 and particular goal for the coming years, is to strengthen translational research projects with a focus on giving something back to the patients, such as intervention studies and proof of concept studies.

With enthusiasm I look into 2018 and the concept phase of Oslo University Hospital 2030 with two RIIM scientists (Dr. Annika Michelsen and Dr. Sverre Holm) on board. This is a phase with positivism and abilities for RIIM to secure the infrastructure for next generation researchers at OUH. In the meantime it will be important to seek opportunities to organize RIIM into a more functional structure and research environment, ensuring better robustness.
I would like to present a flower and a special thanks to our fantastic collaborator, Merete Tysdahl, whom initiated a physical activity program at our Institute. With her enthusiasm and together with enormous team spirit among our employees, we have implemented 10 minutes of physical activity ("sirkeltrening"), twice a week. This is an important initiative to improve the wellbeing, health and camaraderie of the personnel at RIIM.

To all employees and colleagues - thank you all for a fruitful collaboration in 2017. We will meet 2018 with vision and enthusiasm to strengthen RIIMs translation research profile.

Oslo, March 2018
Bente Halvorsen

ORGANIZATION

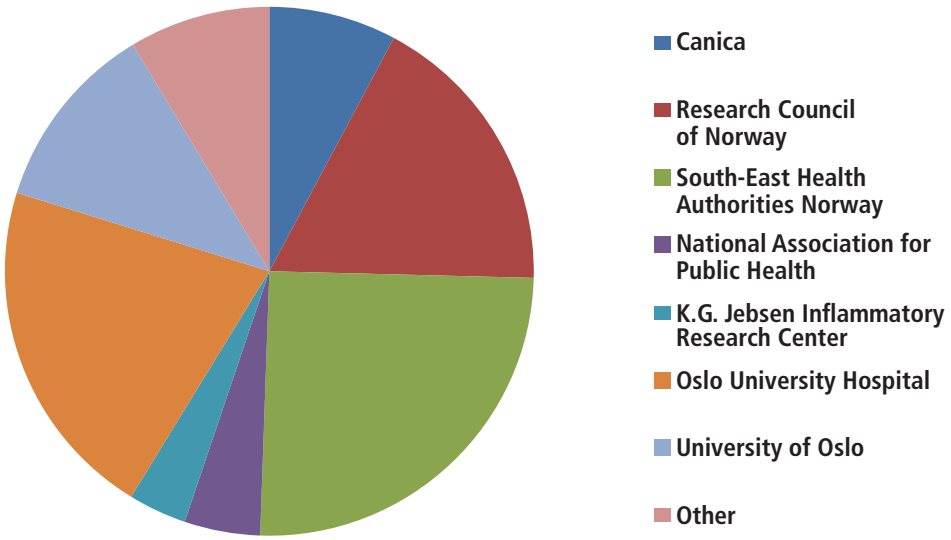


TOM HEMMING KARLSEN
Leader of Molecular Hepatology Research

PÅL AUKRUST
Leader of Inflammatory Research

PER MORTEN SANDSET
Leader of Thrombosis, Haemostasis and Vascular Biology Research

ECONOMY



The institute's total expenditures amounted to NOK 64 million in 2017. NOK 43 million were funds from external sources, while 21 million came from Oslo University Hospital and University of Oslo.

FOCUS AREA

Translational research at Research Institute of Internal Medicine – from bed to bench and back

JOHANNES R. HOV AND
PÅL AUKRUST

Research Institute of Internal Medicine (RIIM) has a wide research focus, currently harboring eight research groups organized into sections on Inflammation, Hematology and Hepatology. The institute is uniquely situated close to the clinical departments, only one hundred footsteps from the hallway to the closest medical ward. A large proportion of the affiliated researchers are also working in the clinic, with the shared philosophy of collecting patient materials in the clinical departments and performing the molecular biology studies in the institute labs – to understand the diseases and advance medicine.

The European Society of Translational Medicine defines translational research as an "interdisciplinary branch of the biomedical field with three main pillars: benchside, bedside and community" aiming to combine "…resources, expertise, and techniques within these pillars" to promote disease prevention and patient care (1). Typically, this is seen as a process translating basic science to the clinic. In contrast, at RIIM the research questions arise in the clinic, i.e. bedside, with a final aim of improving of patient care based on molecular knowledge.

In this section of the year report, the three sections of RIIM describe examples of the research process from bed – to bench – and back. The long-term collaboration between the inflammation groups and the Cardiology department resulted in a proof-of-concept intervention trial to modify inflammatory pathways in myocardial infarction. In the hematology groups, the clinical challenge of factor VII deficiency related bleeding disorder has inspired research into how molecular chaperones may improve folding and activity of Factor VII mutants, which could be a new therapeutic strategy in these patients. Finally, in the gastroenterology department, proteomic analysis of bile sampled from primary sclerosing cholangitis patients admitted for endoscopic therapy of strictured bile ducts was utilized to identify disease-related proteins which eventually could be measured in peripheral blood and used as biomarkers of disease outcome. These stories are quite different but all show that molecular characterization of clinical challenges may provide new opportunities in patient care and therapy.

1. *Cohrs RJ, Martin T, Gharhamani P, Bidaut L, Higgins PJ, Shahzad A. Translational Medicine definition by the European Society for Translational Medicine. N Horizons in Translat Med 015;2:86-88.*

From bedside to bench and back - targetting inflammation in myocardial infarction

PÅL AUKRUST

For the past 20 years, immunopathogenic and inflammatory mechanisms in various forms of cardiovascular disease has been a subject of intense research in the inflammatory research groups at RIIM. This has been and is a close collaboration between RIIM, Department of Cardiology and Section of Clinical Immunology and Infectious Diseases at OUS Rikshospitalet and this collaboration across disciplines has the last 10 years also included Department of Neurology. Our ambitious goal is to develop new treatment modalities in atherosclerotic disorders, based on clinical studies as well as in vitro studies and studies in experimental models of atherosclerosis – i.e., from bed to bench and back to bed, where the last step is the most challenging, such as coronary artery disease (CAD) *(Figure 1).*

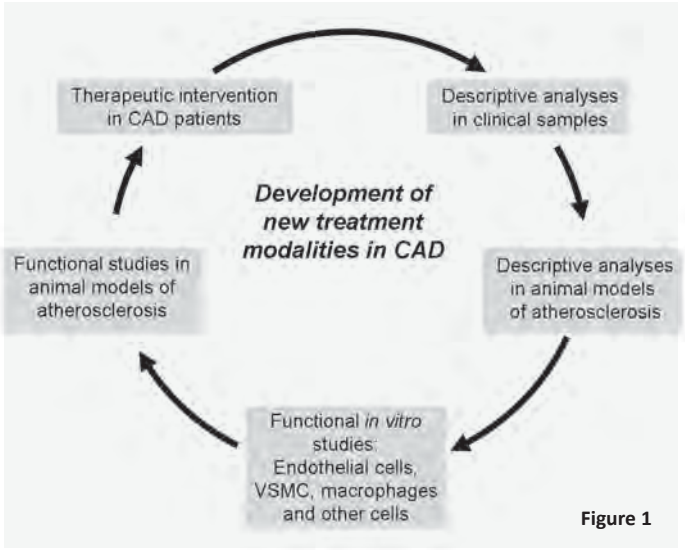


Figure 1

We and others have shown in numerous studies that patients with coronary and carotid atherosclerosis are characterized by a state of chronic inflammation with raised levels of various inflammatory mediators both systemically and within the atherosclerotic lesion despite state-of-art treatment. We and others have also shown relevant effects of these inflammatory molecules in vitro such as promoting lipid accumulation in macrophages, increasing matrix degradation and inducing platelet and endothelial cell activation. During the recent years we have through international and national collaborators also been involved in studies in experimental atherosclerosis among others showing that NLRP3 inflammasome, a potent inflammatory factory and a major cellular source of the prototypical inflammatory cytokine interleukin-1 (IL-1), could play a major role in atherosclerosis progression. Importantly, this was very recently taken back to the bed through the important CANTOS study (>10,000 patients) that showed that neutralization of IL-1β by canakinumab for 48 months, a medication used in various auto-inflammatory disorders, reduces the rate of recurrent cardiovascular events in patients with previous myocardial infarction (MI). However, the cost of this drug is high, and based on the current prize in Norway, the study drug must have cost >10 billion NOK.

A downstream mediator of IL-1 is IL-6, and several of the beneficial effects of IL-1 inhibition in cardiovascular disease could in fact be mediated through IL-6. We and others have shown an early and marked rise in IL-6 in patients with MI, in particular after reperfusion with percutaneous coronary intervention (PCI). This is accompanied by a rise in CRP and markers of complement activation (Figure 2). Thus, an additional approach in immunomodulating therapy in atherosclerotic disorders could be short-term intervention during MI to attenuate myocardial damage and dampen plaque inflammation and thereby destabilization. We hypothesized that one dose of tocilizumab, a medication that blocks the IL-6 receptor and has been used in autoimmune disorders for several years, would attenuate the acute inflammatory response and reduce myocardial damage in patients with non-ST-elevation MI (NSTEMI). This study was initiated by the collaborators at OUS Rikshospitalet and collaborators at St. Olav's Hospital in Trondheim. This randomized double-blind placebo-controlled trial showed that IL-6 inhibition in NSTEMI patients significantly attenuates inflammation (i.e., CRP) and myocardial damage as assessed by troponin release in NSTEMI patients (Figure 3). This latter effect was primarily seen in those who underwent PCI, illustrating that whereas revascularization procedures through PCI is mainly beneficial in MI it may also have some harmful effects through induction of ischemia/reperfusion damage. This study is one of the first to show a potential beneficial effect of anti-inflammatory intervention beyond that of state-of-art treatment in MI patients. However, there is still a way to go. Whereas too much inflammation could be harmful, too little could also be injurious with impaired repair of the infarcted area as a consequence. This may be particularly relevant in patients with ST-elevation MI (STEMI) who mostly have larger MI's than NSTEMI patients. Accordingly, a new study with IL-6 inhibition is currently being performed in STEMI patients that in addition to the collaborators in the NSTEMI study

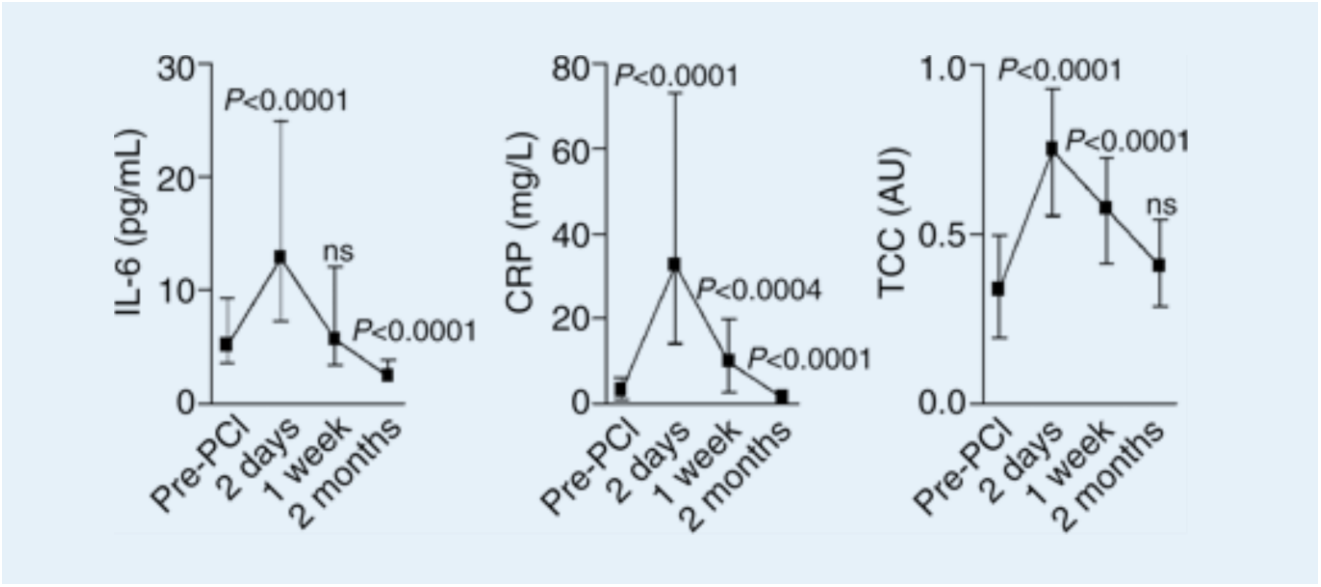


Figure 2. *Time profiles of interleukin (IL)-6, C-reactive protein (CRP), and terminal complement complex (TCC) in 42 patients with ST segment elevation myocardial infarction before and 2 days, 1 week, and 2 months following primary percutaneous coronary intervention. From S Ørn et al. Eur Heart J. 2009;30(10):1180-1186.*

also include Department of Cardiology, OUS Ullevål. If successful, this treatment modality will have to be tested in larger multicenter studies with clinical events including mortality as endpoints.

Although several studies are still needed, this research could potentially change the clinical management of MI patients, introducing the first new therapeutic approach for several years in this common and severe disorder. These studies also illustrate the need for collaboration across disciplines including research groups with strong expertise in cardiovascular disease and research groups with expertise in basic immune mechanisms, molecular biology and cell metabolism. In our opinion, translational research, i.e., to link clinical and basic research, is a prerequisite to bring the results not only from the bed to the bench, but also back to the bed.

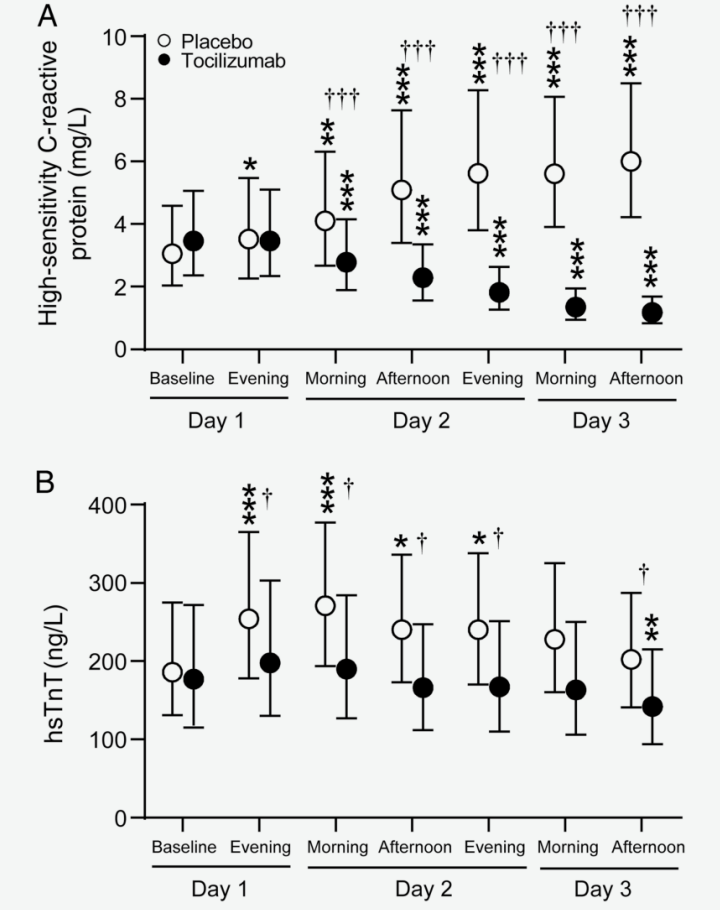


Figure 3. *Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. From O Kleveland et al. Eur Heart J. 2016;37(30):2406-2413.*

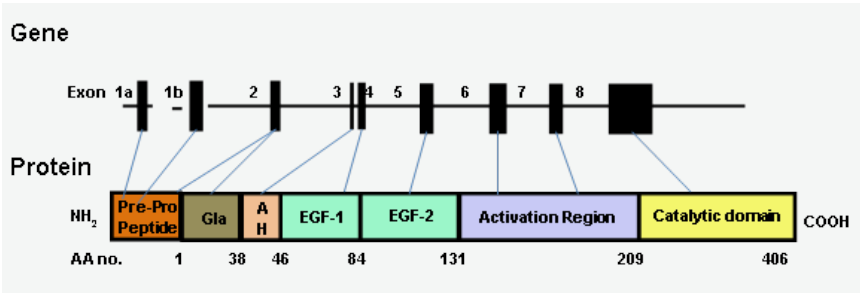
From bedside to bench and back- in clotting factor deficiency

GRETHE SKRETTING AND ELISABETH ANDERSEN

Clotting factor deficiencies are a group of inherited bleeding disorders which are caused by a problem with one or several clotting factors. The Clotting factors are proteins in the blood that control bleeding and several different clotting factors work together in a series of chemical reactions to stop bleeding in a process called clotting. One of these clotting factors is factor (F) VII.

Factor VII deficiency

FVII is a vitamin K-dependent glycoprotein that is synthesized in the liver. Native FVII comprises 406 amino acids and consists of an N-terminal γ-carboxyglutamic acid domain followed by two epidermal growth factor-like domains (EGF1 and EGF2) and a C-terminal protease domain. The human FVII gene (F7) is located on chromosome 13q34 and comprises nine exons. Inherited FVII deficiency is the most common of rare congenital clotting disorders and has an autosomal recessive pattern of inheritance. Individuals with FVII deficiency can experience prolonged, uncontrolled bleeding episodes due to low levels of FVII or an abnormally functioning FVII protein.



Organization of the human F7 gene and the FVII protein (modified from Perry)(1).

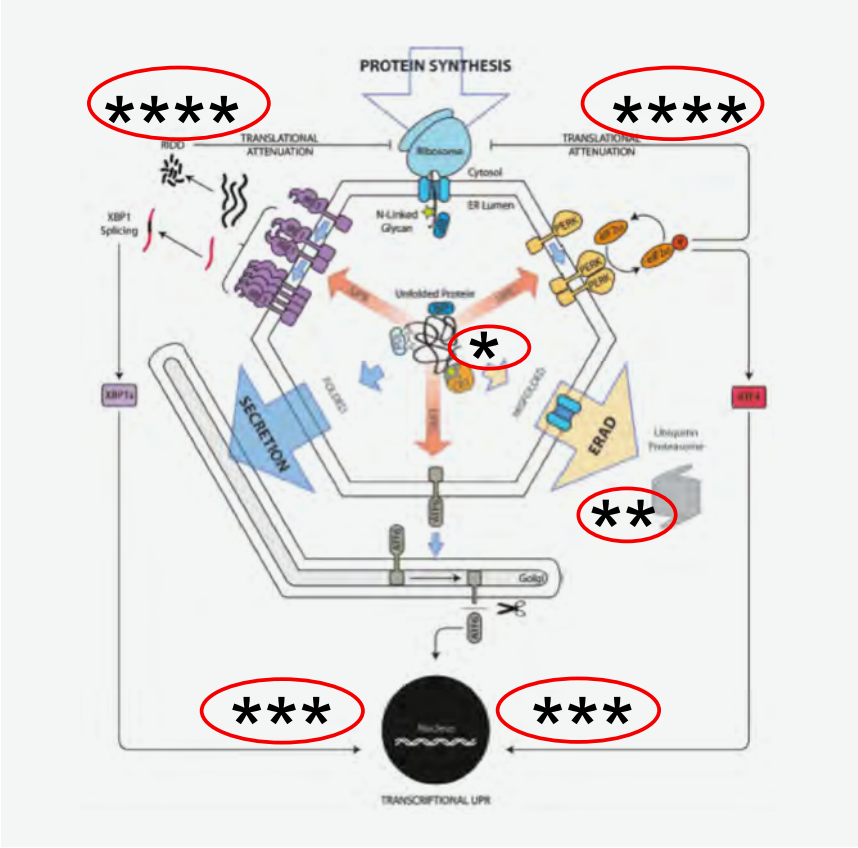
The F7 gene mutational pattern is extremely heterogeneous(2). Studies have indicated a common pathogenic mechanism for several mutations, namely defective folding of the mutant proteins, causing retention in the endoplasmic reticulum resulting in very low levels of FVII in blood plasma.

Clinical phenotypes and current treatment

The clinical phenotypes for FVII deficiency range from severe to mild or even asymptomatic forms. No strict correlation between a mutation in the F7 gene and the residual FVII activity has been demonstrated. The current treatment of these patients is based on replacement therapy using FVII concentrate, an approach that still has several limitations due to short half-life of FVII, a risk of adverse events, and high costs. Thus, there is a large need for development of alternative therapies allowing easier administration, better tolerance and fewer expenses. It is essential that in FVII and other clotting factor deficiencies, even a modest increase of functional protein levels will ameliorate the bleeding phenotype, and would be of major impact for individual patients.

Modulation of protein folding by chemical chaperones

Based on the knowledge we have on endogenous protein complexes called molecular chaperones and their ability to stabilize newly synthesized peptides in the cytosol and in the endoplasmic reticulum, chemical chaperones have been developed. These molecules are able to modulate the protein folding and potentially to restore the biosynthesis of misfolded proteins(3). As such, betaine was shown to improve both protein secretion and trafficking of a defective FVIII mutant in vitro and in a hemophilia A mice model(4). Furthermore, sodium 4-phenylbutyrate (PBA), which is an orally available hydrophobic compound that has been approved by the Food and Drug Administration (FDA) for treatment of urea cycle disorders, has shown effects in vitro and in vivo in mice models in degenerative disorders, such as Parkinson's, Huntington's and Alzheimer's diseases that are all caused by accumulation of protein aggregates (5). In our group we have shown that 4-PBA is able to increase the secretion and trafficking of a clotting factor protein C mutant (6) and at present, preliminary results indicates that 4-PBA has a positive effect of the secretion and activity of FVII mutants (manuscript in preparation). This suggests that the chemical chaperone 4-PBA might represent a promising therapeutic approach for the treatment of congenital FVII deficiency caused by protein misfolding.



Protein folding and misfolding in ER. *Proteins must fold into 3-D structures to attain functionality. Failure to fold or to remain correctly folded can result in misfolding and aggregation. The stars denote processes, which are affected by misfolded proteins. *, retention in ER; **, increased proteasomal degradation; ***, reduced transcription; ****, translational attenuation (from Chambers & Marciniak3).*

1. *Perry DJ. Factor VII Deficiency. Br J Haematol 2002; 118: 689-700.*
2. *Mariani G, Bernardi F. Factor VII Deficiency. Semin Thromb Hemost 2009; 35: 400-406.*
3. *Chambers JE, Marciniak SJ. Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 2. Protein misfolding and ER stress. Am J Physiol Cell Physiol 2014; 307: C657-670.*
4. *Cohen FE. Kelly JW. Therapeutic approaches to protein-misfolding diseases. Nature 2003; 426: 905-909.*
5. *Roth SD, Schuttrumpf J, Milanov P, et al. Chemical chaperones improve protein secretion and rescue mutant factor VIII in mice with hemophilia A. PLoS One 2012; 7: e44505.*
6. *Chollet ME, Skarpen E, Iversen N, et al. The chemical chaperone sodium 4-phenylbutyrate improves the secretion of the protein CA267T mutant in CHO-K1 cells trough the GRASP55 pathway. Cell Biosc 2015; 5:57.*

From bedside to bench and back – in liver disease

JOHANNES R HOV AND
METTE VESTERHUS

Primary sclerosing cholangitis is a chronic inflammatory disease of the large bile ducts leading to strictures, scarring and often end stage liver disease with a need for liver transplantation (1).

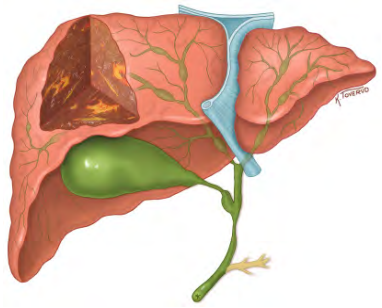


Figure 1: *Primary sclerosing cholangitis is characterized by inflammation, strictures and dilatation of the biliary tree.*

The clinical problem
Very little is known about the pathogenesis of PSC. There are no tools to measure or predict disease activity or prognosis, (Figure2) and still no effective medical treatment. These challenges are interdependent, since tools to identify patients who need treatment, select their treatment and measure treatment effects are necessary to establish new therapy

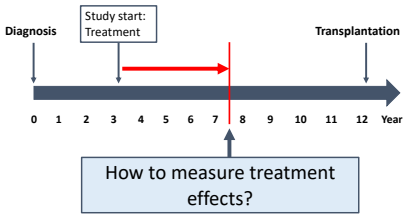


Figure 2: *One challenge in primary sclerosing cholangitis is how to measure the effect of treatment in "short" studies, since progression to hard endpoints, like transplantation, may take years.*

Sometimes there is uncertainty regarding the diagnosis or a clinical deterioration with suspicion of obstructed bile ducts, in which case there is an indication to perform an endoscopic retrograde cholangiography (ERC), i.e. an intubation of the bile ducts aiming to visualize, diagnose and treat complications. At NoPSC, bile is sampled for the general research biobank during most ERCs.

Profiling of the biliary proteome
Bile is the bodily fluid closest to the pathological process and a probable hot spot for disease relevant substances. In an attempt to understand the disease and identify new biomarkers, we characterized the proteome of the bile (2), using antibody-covered beads, a method developed and available in a collaborating lab (Figure 3). The bile proteome was largely unknown and extensive time and resources were needed to optimize methodology and choose a reasonable collection of targets. After testing 1570 targets, a core set of 63 were chosen for a final array.

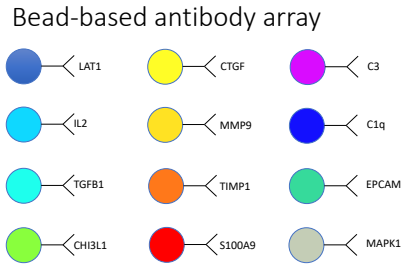


Figure 3: *In the custom antibody array multiple antibody-coated beads with different sizes and colors are used. The heterogeneity of the beads allows flow-based separation and the detection of multiple protein targets in one sample.*

The biliary proteome in PSC
We applied the final protein array in a Norwegian discovery set and a Finnish validation set. To understand PSC we compared PSC bile with bile from patients with other conditions, and early PSC with late PSC, as determined by the extent of pathology identified in the cholangiogram (Figure 4). A large number of proteins had different concentrations in PSC compared with controls and early and late PSC, constituting possible biomarkers. These proteins belonged to pathways like innate immunity and fibrosis.

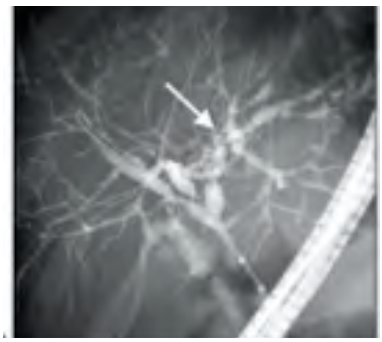


Figure 4: *Cholangiogram; X-ray of contrast-filled bile ducts in a PSC patient, illustrating advanced disease with strictures and dilatations.*

Clinical relevance?
Bile is only sampled with invasive methods, while a clinical biomarker should be easily accessible. The first step was to investigate the most promising markers in serum. The innate immunity cytokine interleukin-8 was a strong predictor in bile, and highly elevated in PSC serum compared with controls, with high levels predicting disease outcome (Figure 5). However, it did not outperform a prognostic score based on clinical observations.

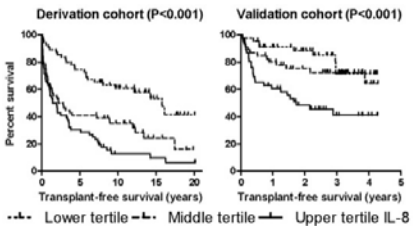


Figure 5: *In a study of a discovery panel of 167 and a validation panel of 138 PSC patients, increasing serum IL-8 was associated with reduced liver transplantation free survival in both panels, as shown separated in tertiles of IL-8 (2).*

Clinical translation
The identification of TIMP1 as a strong biliary marker, led to the investigation of the enhanced liver fibrosis (ELF™) test in serum, an already commercially available composite score consisting of TIMP1 and two other fibrosis markers. ELF was associated with clinical outcome in two independent cohorts in the first paper

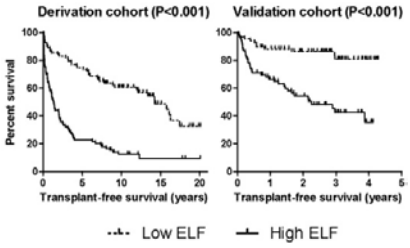
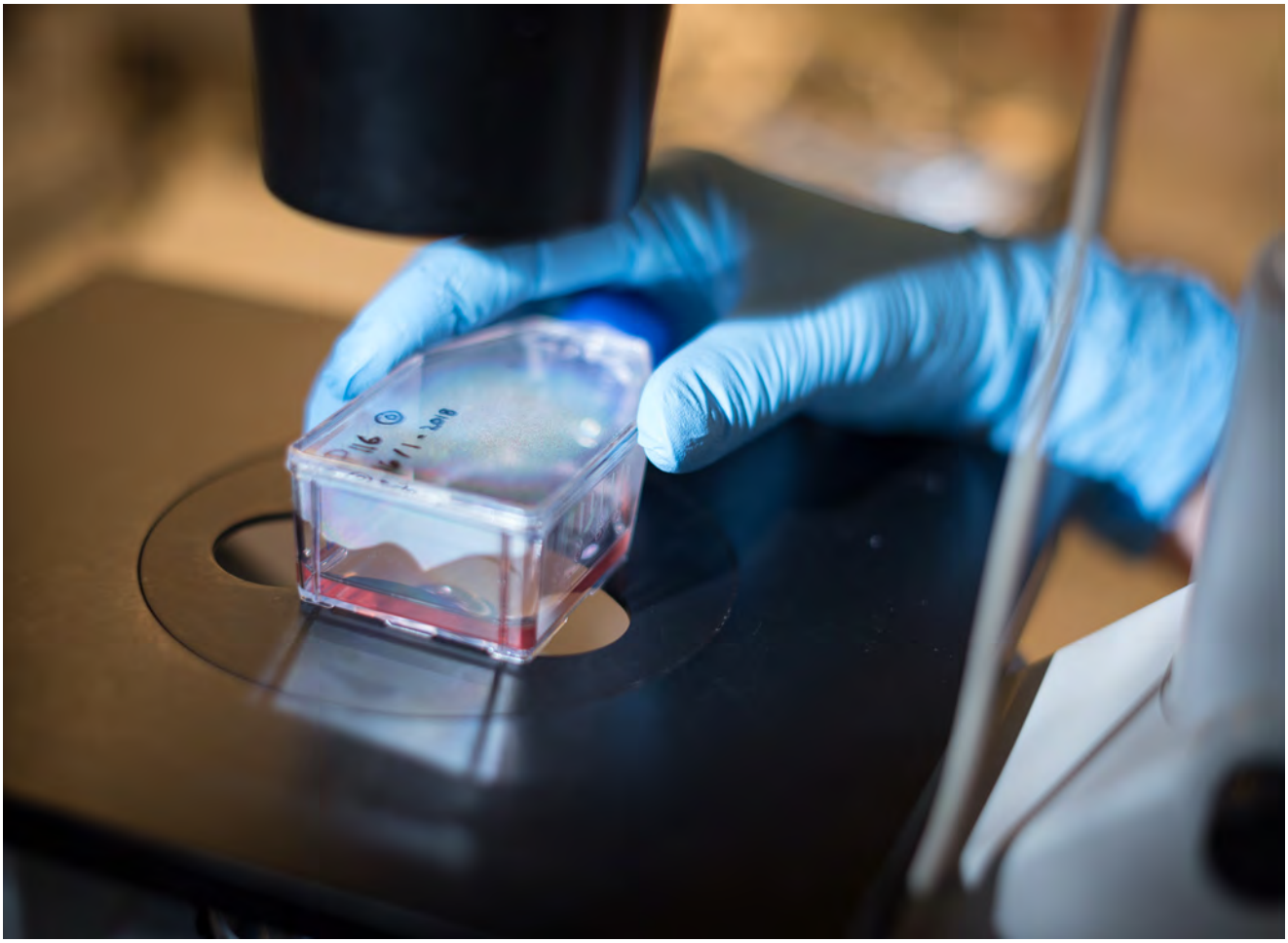


Figure 6: *In a study of the same patients as in Figure 5, the level of the enhanced liver fibrosis test (TM) clearly associated with liver transplantation free survival.*

(Figure 6) (3). Later papers focus on further clinical validation including the possible role in cancer identification (4), and ELF test is now part of the typical biomarker panels in clinical trials. In collaboration with Nordic Biosciences, further circulating fibrosis markers with possibly better characteristics are explored and validated.

Overall, the *clinical deterioration* and *ERCP* examination was the starting point for *basic characterization of pathophysiology in bile,* followed by *blood tests* identifying severe disease, hopefully adequate to measure the effects of novel treatments.

1. *Karlsen TH, Folseraas T, Thorburn D, et al. Primary sclerosing cholangitis - a comprehensive review. J Hepatol 2017;67:1298-1323.*
2. *Vesterhus M, Holm A, Hov JR, et al. Novel serum and bile protein markers predict primary sclerosing cholangitis disease severity and prognosis. J Hepatol 2017;66:1214-1222.*
3. *Vesterhus M, Hov JR, Holm A, et al. Enhanced liver fibrosis score predicts transplant-free survival in primary sclerosing cholangitis. Hepatology 2015;62:188-97.*
4. *de Vries EMG, Farkkila M, Milkiewicz P, et al. Enhanced liver fibrosis test predicts transplant-free survival in primary sclerosing cholangitis, a multi-centre study. Liver Int 2017;37:1554-61.*



DISSERTATIONS

Silje Fjellgård Jørgensen, MD

Immunogenetic susceptibility, gut microbiota profile and gastro-intestinal disease in common variable immunodeficiency
February 2nd 2017

Main supervisor: Pål Aukrust
Co-supervisors: Tom Hemming Karlsen and Børre Fevang

Summary of PhD project:
Patients with the primary immuno-deficiency Common variable immunodeficiency (CVID) are characterized by both increased susceptibility to infections and a hyperactive immune system. This project showed that CVID patients have a reduced diversity of their gut microbiota compared to healthy controls, in particular the CVID patients with signs of chronic inflammation. Gut biopsies showed that although many CVID-patients present with coeliac-like disease they have a very different genetic profile, suggesting that chronic immune activation rather than gluten allergy is the cause of this disease. There is a high prevalence of immune-driven disease in CVID and in a genome-wide association study the known autoimmune susceptibility gene CLEC16A was found to be associated with CVID and linked to B-cell development.

Ståle Haugset Nymo, MD

Inflammatory Biomarkers in Cardiovascular diseases
March 17th 2017

Main supervisor: Arne Yndestad
Co-supervisors: Thor Ueland and Pål Aukrust

Summary of PhD project:
Cardiovascular disease affects a lot during life, and although many survive the acute disease, cardio-vascular disease has high mortality and morbidity also after the onset. Heart failure is in particular associated with many hospitaliza-tions and a low 5-year survival rate. Multiple studies have shown that patients with heart failure or acute coronary disease show signs of activation of the immune system. It has also been speculated whether this immune activation may be one of the causes of the bad prognosis of many of these patients. In this dissertation Nymo and colleagues have looked into mediators that are usually associated with the immune system, and if the concentration of these in blood can indicate some-thing about long-term survival. Their findings clearly show that levels of many known mediators in the immune system are increased in patients with heart failure, but that they are not likely to say anything about the prognosis. Even when combining several of these biomarkers into panels describing different parts of the disease development, the prognostic strength of the models does not increases remarkably.

DISSERTATIONS

Elisabeth Schrumpf

The role of natural killer T cells and gut microbiota in biliary inflammation
June 6th 2017
Main supervisor: Espen Melum
Co-supervisors: Tom Hemming Karlsen and Richard Blumberg, Harvard Univeristy, Boston USA

Summary of PhD project:
Biliary inflammation is one of the key features of the diseases primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). The etiologies of these diseases are unclear and the treatment options are limited. The aim of this research has been to better understand which underlying factors contribute to biliary inflammation, as seen in these diseases. In the thesis Schrumpf and colleagues explored the role of the innate-like lymphocytes natural killer T (NKT) cells and the antigen presenting molecule CD1d in biliary inflammation. They further investigated whether the gut microbiota contributes to inflammation in the bile ducts. With flow cytometry, western blotting and immunofluorescence it was demonstrated that the biliary epithelial cells expressed CD1d, a molecule presenting lipid antigens to NKT cells. They demonstrated that the CD1d expression on the biliary epithelium is down-regulated in diseased livers. Further they found, in vitro and ex vivo assays, that the biliary epithelium can present lipid antigens to and activate NKT cells. Exploring the role of NKT cells in a mouse model with biliary disease (NOD.c3c4) and saw that the proportion of NKT cells was higher and the NKT cells were more activated in NOD.c3c4 mice compared to control mice, but activation or pharmacological and genetically removal of NKT cells did not affect the disease of these mice.
Finally they explored the role of the gut microbiota in NOD.c3c4 mice and saw that NOD.c3c4 mice harbored a different gut microbiota compared to control mice. It was also demonstrated that NOD.c3c4 mice born and raised in a germ free facility or antibiotic treated NOD.c3c4 mice develop a milder biliary disease phenotype compared to conventionally raised mice.
In summary their findings implicate NKT cells and the gut microbiota as possible modulators of biliary inflammation, and can be considered as possible therapeutic targets in human biliary disease if their role is clarified.

Eva Kristine Klemsdal Henriksen, MSc

T-cell receptors and human leukocyte antigens in primary sclerosing cholangitis
October 4th 2017

Main supervisor: Tom Hemming Karlsen
Co-supervisors: Espen Melum, Benedicte A. Lie and Evaggelia Liaskou, University of Birmingham, UK

Summary of PhD project:
The focus of the thesis was to characterize the T-cell repertoire of patients with PSC using high-throughput sequencing of their T-cell receptors (TCRs), and further investigate whether studying admixed or multi-ethnic populations might aid in fine mapping the human leukocyte antigen (HLA) association in PSC. They further observed a diverse, polyclonal T-cell repertoire in PSC-affected livers, and detected eight PSC-associated amino acid clonotypes with signs of antigen-driven clonal selection. Henriksen and colleagues further confirmed the presence of gut and

liver T cells of common clonal origin in patients with concurrent PSC and IBD. Finally, their data support efforts to systematically collect samples from PSC patients of admixed or non-European ancestry for the purpose of pinpointing the causative HLA alleles in PSC in genetic association analyses.

Jan Cato Holter, MD

Etiology and outcome in adults hospitalized with community-acquired pneumonia. Observations from a prospective cohort study.
October 10th 2017
Main supervisor: Lars Heggelund, Drammen Hospital, Norway

Co-supervisors: Pål Aukrust, Einar Husebye, Drammen Hospital and Fredrik Müller, Department of Microbiology, Oslo University Hospital

Summary of PhD project:
Community-acquired pneumonia is a significant cause of morbidity and mortality and a precise etiologic diagnosis is essential for providing the patients with the right treatment. This project combined traditional methods of microbial diagnostics with modern gene based analyses in a prospective cohort study of nearly 270 patients admitted to Drammen Hospital with pneumonia. It was possible to identify an etiologic agent in 4 out of 5 patients, and the bacteria *Streptococcus pneuomonie* was the most common cause of pneumonia, followed by influenza virus and rhinovirus. Viral infections and combined infections with both bacteria and virus were common, in particular in winter. There was a 5-year survival rate of 70% and mortality was associated with known risk factors as age and comoribity, but also low levels of albumin and vitamin D.

Maria Belland Olsen, MSc

To the Heart of NEIL3 –Experimental studies on NEIL3 DNA glycosylase in cardiac disease
October 13th 2017

Main supervisor: Alexandra V. Finsen
Co-supervisors: Pål Aukrust and Magnar Bjørås, Department of Clinical and Molecular Medicine, NTNU

Summary of PhD project:
Our DNA is damaged every day and to repair this we are equipped with a DNA repair system. NEIL3 is a DNA glycosylase recognizing oxidized bases in DNA, removing them and initiating repair though the base excision repair pathway. To evaluate the importance of NEIL3 in cardiac disease we have used a mouse devoid of Neil3 and applied three models of cardiac disease; (1) myocardial infarction, (2) pressure-overload hypertrophy and (3) cardiac remodeling caused by dyslipidemia. After myocardial infarction mouse lacking NEIL3 had dysregulated tissue repair causing increased number of animals to die. Furthermore, mice lacking NEIL3 showed increased hypertrophy in response to pressure-overload but decreased hypertrophy in response to dyslipidemia.
How the DNA repair initiator, NEIL3, operates to produce these responses we do not know. Although NEIL3 initiates DNA repair, we did not find increased DNA damage in hearts lacking NEIL3. What we did find by analyzing the DNA, however, was a different pattern of epigenetic markers. These markers work as coded messages and NEIL3 is thought to be a reader of these. We hypothesize that NEIL3 is involved in the decoding process of these epigenetic markers and that lack of NEIL3 halts the decoding process resulting in altered gene expression. Thus, even though NEIL3 does not seem to be an essential DNA repair enzyme in the diseased heart, it is involved in the cardiac disease response, possibly through epigenetic regulation.

SECTION OF MOLECULAR HEPATOLOGY RESEARCH

Genomics and Metagenomics in Inflammatory Disorders

From front left: Johannes R. Hov, Martin Kummen, Lise Katrine Engesæter, Liv Wenche Thorbjørnsen, Christopher Storm-Larsen, Magnhild Eide Macpherson, Brain Chung, Silje Jørgensen, Beate Vestad, Hanne Guldsten and Amandeep Kaur Dhillon

GROUP MEMBERS IN 2017

GROUP LEADER
Johannes R. Hov, MD, PhD
j.e.r.hov@medisin.uio.no

POST DOCS
Martin Kummen, MD, PhD
martin.kummen@medisin.uio.no
Brian Chung, PhD
b.k.chung@medisin.uio.no
Murat Gainullin, M.D, PhD
murat.gainullin@medisin.uio.no

PHD STUDENTS
Cristiane Mayerhofer, MD
cckm@uol.com.br
Amandeep Kaur Dhillon, MD
a.k.dhillon@medisin.uio.no
Lise Katrine Engesæther, MD
lisek78@hotmail.com
Beate Vestad, MSc
beate.vestad@studmed.uio.no

MEDICAL STUDENT RESEARCHER:
Christopher Storm Larsen
christopher@storm-larsen.no

BIOINFORMATICIAN
Kristian Holm, Cand. scient
kristian.holm@medisin.uio.no

ENGINEERS:
Hanne Guldsten, MSc
hanne.guldsten@medisin.uio.no
Liv Wenche Thorbjørnsen, BSc
(associated)
liwtho@ous-hf.no

ASSOCIATED RESEARCHERS:
Marius Trøseid, MD, PhD
troseid@hotmail.com
Trine Folseraas, MD, PhD
trine.folseraas@medisin.uio.no
Silje Jørgensen, MD, PhD
s.f.jorgensen@medisin.uio.no
Magnhild Eide Macpherson, MD
m.e.macpherson@studmed.uio.no

RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how alterations in the human genome and the gut microbial flora influence disease. We do this by applying modern genotyping and sequencing technologies, as well as metabolomics.

The main current interest of the group is the role of the gut microbiota in multiple inflammatory disease phenotypes, including primary sclerosing cholangitis (PSC), intestinal diseases and immunodeficiencies (HIV and common variable immunodeficiency), as well as cardiovascular diseases. After an initial phase, defining the nature of the altered gut microbiota in inflammatory diseases, the main focus is now directed towards "Clinical microbiota medicine", that is, studies of the microbial content of the gut in human disease – and how the new knowledge can be applied clinically.

Locally, the group has extensive collaborations ongoing within the Research Institute of Internal Medicine, with clinical research group as well as pathology. A strong link to the experimental groups is also important, providing opportunities to understand disease mechanisms in more detail. Of particular importance for the gut microbiome field was the opening of a germ-free research animal unit at the hospital in 2017, which has been developed by the experimental group together with the animal facility.

The group has continued its work with a collaborative research network centered on the meetings in the regional interest group Oslo microbiota forum. In addition, the group hosted the fourth national conference on gut microbiota in November 2017 with an all-time high of about 110 participants and more than 20 abstracts submitted.

PROJECTS

The major project axes center around the following:

- Clinical implications of the functional microbial alterations in PSC
- The microbiome of recurrent PSC
- Identifying exogenous drivers of autoimmunity in the gut microbiome
- Pharmacomicrobiomics and interventions targeting the gut microbiome
- The microbiome in heart failure
- The microbiome in immundeficiencies and their co-morbidities

The cross-sectional studies primarily represents starting points for further studies into the role of gut microbiota either in clinical or experimental settings. An important development in 2018 will be the strengthening of the clinical microbiome research in a new research group in the rheumatology and infectious disease department, led by Marius Trøseid.
A key aspect of clinical microbiota medicine is the application of gut microbial profile or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity. Our first full metagenome sequencing data were generated in 2017, serving as a tool to identify altered microbial functions in disease and guiding metabolomics efforts. Several interventional studies targeting the gut microbiota have already been performed or are ongoing. Such studies may represent proof-of-concept of a direct involvement of the gut microbiota in the disease development and also speed up the process of clinical translation.

FUNDING

The main group members are currently funded as follows:

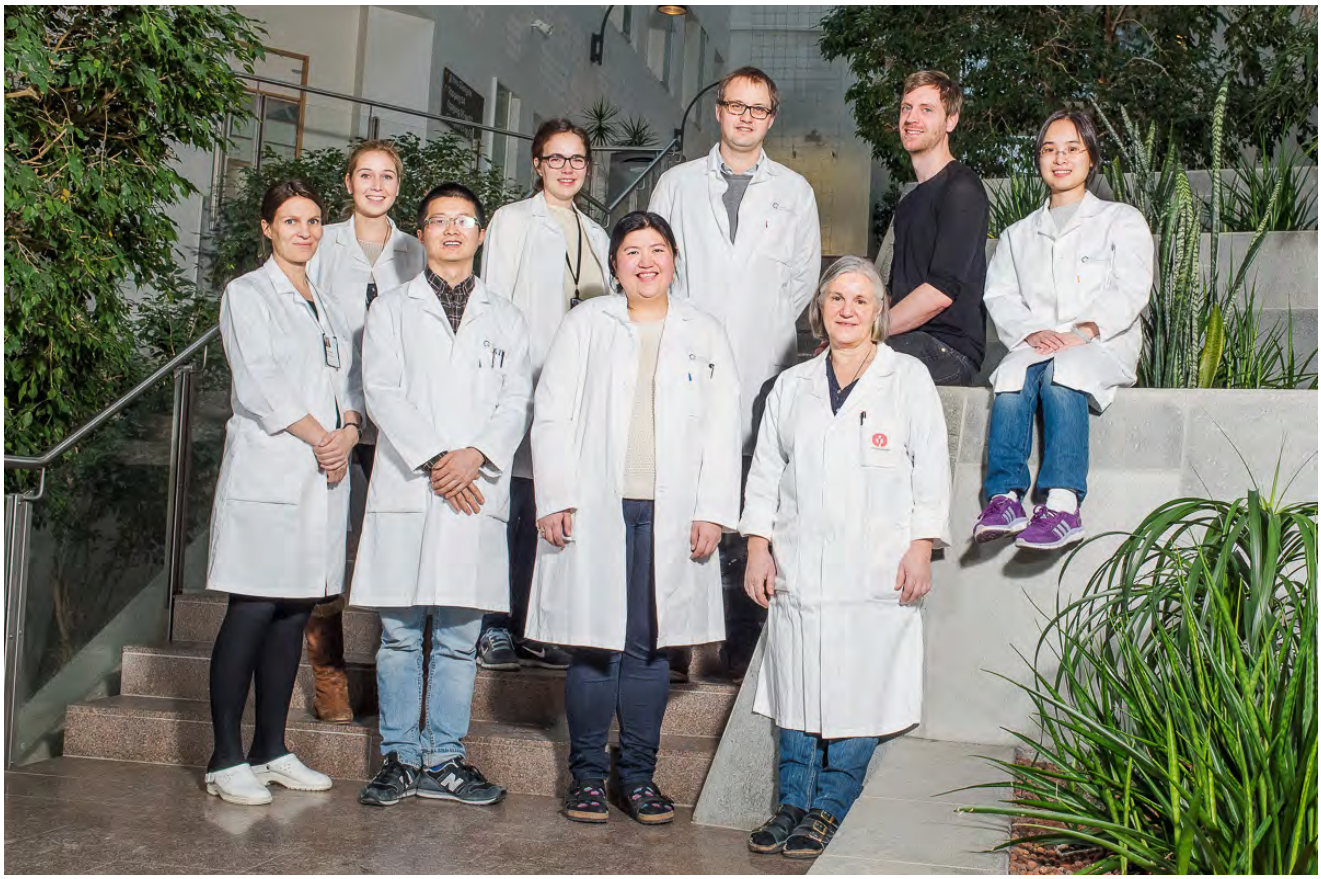
- Research Council of Norway, NORGUT project (young research talent grant): JRH and AKD
- Regional Health Authorities of South Eastern Norway. Postdoc grants: MK, MG. PhD grants: BV, LKE
- National association for public health: CM
- Norwegian PSC Research Center: KH and BC
- K.G.Jebsen Inflammation Research Centre: HG

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Prof. Rolf Berge, University of Bergen
Hanns-Ulrich Marschall, Wallenberg Laboratory, Göteborg
Prof. Andre Franke, Christian-Albrechts University, Kiel
Kostas Lazaridis, Mayo Clinic, Rochester
International PSC Study Group

SECTION OF MOLECULAR HEPATOLOGY RESEARCH

The Experimental Hepatology group



From front left: Laura Valestrand, Anna Frank, Freeman (Fei) Zheng, Natalie Lie Berntsen, Lisa Yuen Løvold, Espen Melum, Anne Pharo, Jonas Øgaard and Xiaojun Jiang

GROUP MEMBERS IN 2017

GROUP LEADER
Espen Melum, MD, PhD
espen.melum@medisin.uio.no

POST DOC
Xiaojun Jiang, PhD
xiaojun.jiang@medisin.uio.no

PHD STUDENTS
Elisabeth Schrumpf, MD
elisabeth.schrumpf@medisin.uio.no
Natalie Lie Berntsen, MD
n.l.berntsen@medisin.uio.no
Eva Kristine Klemsdal Henriksen, MSc
evak.klemsdal@gmail.com
Laura Valestrand, MD
lauravalestrand@gmail.com
Fei (Freeman) Zheng, MD
zheng.fei@medisin.uio.no

CORE ENGINEERS
Anne Pharo, Lab. Manager
anphar@ous-hf.no
Lisa Yuen Løvold, MSc
l.y.lovold@medisin.uio.no

The experimental hepetology group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The most important tools in our research are mouse models that model aspects of cholangitis development. The group represents one of the three research group at the Norwegian PSC research center. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2017, the group consisted of the group leader, one post.doc., five PhD students, and a lab manager. The main aim

of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology. In addition to the cholangitis focused studies, we are also doing basic research related to the function of natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subset. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment target for PSC.

The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2017, we published results clarifying the role of NKT cells in a mouse model with spontaneous cholangitis. We have also done extensive method development to be able to challenge the bile ducts with antigens and this methodological work was also finished and published in 2017. As part of the PhD of Eva Kristine Klemsdal Henriksen work on the HLA in PSC and clonal similarities of T-cells in the gut and liver were finished. The work on unconventional T-cells is planned to be expanded and the group leader received a young research talent grant from the Norwegian Research Council in 2017 involving integrated murine and human studies.

In 2017 the two first PhD students from the group defended their theses, which both represented major events. Elisabeth Schrumpf defended her thesis in June with Agnes Lehuen from Paris as the first opponent and Eva Kristine Klemsdal Henriksen defended her thesis in October with Steven Lee as the first opponent.

INFLAMMATORY RESEARCH

Clinical immunology and infectious diseases

From left: Silje Fjellgård Jørgensen, Børre Fevang, Hedda Hoel, Kari Otterdal, Ingvild Nordøy, Magnhild Eide Macpherson and William Siljan

GROUP MEMBERS IN 2017

GROUP LEADER
Børre Fevang, MD, PhD
borre.fevang@rr-research.no

RESEARCHERS
Kari Otterdal, MSc, PhD
kari.otterdal@rr-research.no
Ingvild Nordøy, MD, PhD
ingvild.nordoy@ous-hf.no

PHD STUDENTS
Silje Fjellgård Jørgensen, MD
s.f.jorgensen@studmed.uio.no
Jan Cato Holter, MD
j.c.holter@studmed.uio.no
Magnhild Eide Macpherson, MD
m.e.machperson@studmed.uio.no
William Siljan, MD
wsiljan@gmail.com
Hedda Hoel, MD
hedda_hoel@hotmail.com
Liv Hesstvedt, MD
liv.hesstvedt@ous-hf.no

ASSOCIATED RESEARCHERS:
Stig S Frøland, MD, PhD
s.s.froland@medisin.uio.no
Marius Trøseid, MD, PhD
marius.troseid@medisin.uio.no

RESEARCH PROFILE

The research group focus on immunopathogenesis in primary and secondary immunodeficiency such as Common variable immunodeficiency (CVID) and HIV and selected infectious diseases, in particular the study of chronic inflammation characterising these disorders. The aim is to improve the understanding of disease mechanisms and to discover new targets for therapeutic intervention. The group works in a translational setting combining close contact to the clinic, in particular Section of Clinical Immunology and Infectious Diseases at OUS, with access to a wide range of immunological methods through extensive collabo-ration with other groups.
Chronic inflammation is a common feature of both immunodeficiencies

and many infectious disorders. While inflammation is vital to the clearance of both invading microbes and potentially malignant cells a continued or exaggerated response will further compromise the patient's health. Identifying the factors leading to such an exaggerated response will potentially enable clinicians to modify the inflammatory response of the single patient with agents targeting anything from intracellular signalling pathways to intercellular cytokine networks and microbiota. The group is currently working with several projects, including:

- Immunopathogenic mechanisms in CVID – a disease model for autoimmunity and persistent inflammation. In close collaboration with Johannes Hov's group at our institute this project will use CVID as a model disease to study potentially novel aspects of autoimmune and autoinflammatory disorders in more general terms, in particular for the study of the interaction between gut microbiota and local (intestinal) and systemic inflammation. The project has involved proof-of-concept study for the use of the antibiotic rifaximin in modulating gut microbiota and systemic inflammation, and an extensive endoscopic study of gut pathology in CVID patients. Silje Jørgensen did an excellent job defending her PhD thesis this year but will keep working on the project in close cooperation with Magnhild Eide Macpherson who started her PhD in 2015.
- Community-acquired pneumonia: a prospective observational study to explore etiology, risk factors and potential novel predictors of severe course and mortality. In close cooperation with Vestre Viken HA and Drammen Hospital the project applies new diagnostic methods to assess etiology and risk factors for severe course and mortality of pneumonia. Jan Cato Holter has done a tremendous job collecting and organizing samples in a hectic clinical setting, and did a splendid defence of his PhD this autumn. William Siljan is further exploring the vast amount of data and samples collected in his PhD-project.
- Study of immunological mechanisms in malaria. Kari Otterdal has a solid background in platelet research but has received a 4 year researcher grant from HSØ on a project looking at malaria in cooperation with University of Bergen and Stavanger University Hospital. In this exciting project we will take advantage of the institutes extensive knowledge of inflammation and among other things look at inflammatory properties of the Plasmodium produced hemozoin crystal.
- Cand. med. Liv Hesstvedt is finishing her work on her thesis "Candidemia in Norway and the Nordic countries". The thesis is partly based on a national collaboration where data has been collected from laboratories and medical records from most Norwegian hospitals. And partly based it is based on a Nordic collaboration using national epidemiological data. Supervisors are Ingvild Nordøy, Peter Gaustad and Fredrik Müller.
- Targeting the NLRP3 inflammasome in HIV infection. The research institute has a strong track record on HIV-research and we are very pleased that it will continue with this exciting new project. In close collaboration with Arne Yndestad's group that has studied the role of the NLRP3 inflammasome in cardiovascular disease, this project aims to look at the inflammasome as a driving force of the systemic inflammation seen in HIV-infected patients. The project is led by Marius Trøseid and forms the basis of Hedda Hoel's PhD project.
- Functional consequences of novel genetic variations in primary immunodeficencies and immune dysregulation (FUNPID). High-througput sequencing has revolutionized the diagnostics of primary immunodeficiencies, giving a definite genetic diagnosis in complicated clinical cases. However, novel genetic variations of uncertain significance tend to show up and in close collaboration with established partners at Oslo University Hospital and the University of Oslo we have established a research-based diagnostic pipeline for these patients. These findings give us an extraordinary opportunity to characterize both new disease entities and new immunologic mediators.

FUNDING

The group is currently mainly funded through grants from the South-East Regional Health Authorities in Norway but has also funding from the Anders Jahre and the Odd Fellow foundations.

INFLAMMATORY RESEARCH

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders

From left: Turid Margrethe Pedersen, Mona Skjelland, Karolina Ryeng Skagen, Ana Quiles Jimenez (in front), Xiang Yi Kong, Tom Rune Karlsen, Ellen Lund Sagen, Vigdis Bjerkeli, Ida Gregersen, Bente Evy Halvorsen (in front), Tuva Børresdatter Dahl, Baoan Marianne Tran and Sverre Holm

GROUP MEMBERS IN 2017

GROUP LEADER
Bente Evy Halvorsen, MSc, Dr Philos, Professor
bente.halvorsen@rr-research.no

RESEARCHERS
Sverre Holm, MSc, PhD
sverre.holm@rr-research.no

POST DOCS
Filip Segers, MSc, PhD
filip.segers@rr-research.no
Tuva Børresdatter Dahl, MSc, PhD
tuva.Borresdatter.Dahl@rr-research
Ida Gregersen, MSc, PhD
ida.gregersen@rr-reseach.no
Xiang Yi Kong, MSc, PhD
x.y.kong@medisin.uio.no
Karolina Ryeng Skagen, Senior consultant, MD, PhD
kskagen@ous-hf.no

PHD STUDENTS
Tom Rune Karlsen, MD
tom.rune.karlsen@rr-research.no
Ana Quiles Jimenez, MSc
ana.quiles.jimenez@rr-research.no
Nina Solheim, MD
nina.solheim@lds.**no**
Kjell Torp-Joakimsen, MD
kjto@lds.no

MASTER STUDENT:
Baoan Marianne Tran, BSc
marianne.t94@hotmail.com

SENIOR ENGINEERS:
Turid Margrethe Pedersen, BSc
turid.margrethe.pedersen@rr-research.no
Ellen Lund Sagen, BSc
ellen.lund.sagen@rr-research.no
Vigdis Bjerkeli, BSc
vigdis.bjerkeli@rr-research.no

SENIOR CONSULTANT
Mona Skjelland, MD, PhD
moskje@ous-hf.no

RESEARCH PROFILE

Atherosclerosis is a leading cause of death and disabilities worldwide. Atherosclerosis is a slowly progressing chronic disorder of large and medium-sized arteries that becomes clinically manifest when it causes thrombosis, leading to complications such as myocardial infarction and ischemic stroke. The interaction between

lipids, extracellular matrix and inflammation is a characteristic hallmark of atherosclerotic plaque development, and atherosclerosis is now regarded as an inflammatory condition. The inflammatory mechanisms in atherosclerosis and closely related metabolic disorders have been the cornerstone of the research group's activity for the last 17 years.

Valuable access to clinical material from well characterized patients with atherosclerotic lesions and related metabolic disease, such as obesity and type 2 diabetes, is a great strength of our research group. Through a translational approach, combining human clinical material with in vivo studies in animal models and in vitro work in cell cultures, we seek to find novel mechanisms important for the development of these conditions. In the last years our group has focused on expanding the repertoire of methodology that is important in this kind of research. We have established several methods for inducing and monitoring atherosclerosis and metabolic disease in mouse models and also methods for ex vivo culturing of tissues and cell extractions. The last year we have had a particular focus on establishing robust collaborations and methods for state of the art technologies for characterization of our patient material, such as advanced DNA methylation sequencing and mass spectrometry.

Inflammation in atherosclerosis

We have studied the role of inflammatory mediators in development of atherosclerosis for many years. In 2017, one of our inflammatory focuses has been on the cysteine protease legumain. We have shown that legumain is increased in both plasma and plaques of patients with carotid stenosis and that legumain is produced by macrophages, and colocalized to macrophages in the plaque. We are currently elucidating the function and role of legumain in macrophage-induced inflammation in atherosclerosis.

Obesity

Obesity increases the risk of several metabolic conditions, with type 2 diabetes as one of its most devastating consequences. The term "metabolic healthy obese" has emerged the last years, describing those who develop severe obesity without metabolic sequela. Understanding the underlying mechanism for metabolic healthy and unhealthy obesity is of great interest to develop better treatment for this patient group. One of our major research projects is the study of T cell function in metabolic regulation during obesity development. Circulating and tissue resident T cells can modulate macrophage function and adipocyte differentiation, and thereby affect energy storage and utilization, resulting in healthy or dysregulated metabolism. This will further result in metabolic health or disease. To study this interaction we use a transgenic mouse with altered T cell function, as well as blood, adipose tissue and immune cells from patients with metabolic healthy and unhealthy obesity. We will also address the relationship between metabolic healthy and unhealthy obesity and atherosclerotic risk.

Oxidative DNA damage and repair enzymes in atherosclerosis

The recent years, a main focus of the research group has been on oxidative DNA repair enzymes and their role in atherosclerosis. Enhanced generation of reactive oxygen species (ROS) is an important feature of atherosclerosis, induced by etiologic risk factors such as smoking and metabolic disturbances as well as their common final pathway, inflammation. Although ROS generation is a fundamental component of cellular metabolism and signal transduction, enhanced ROS generation may induce increased inflammation, cellular damage and apoptosis as well as DNA instability. If the ROS-induced damage on cellular DNA is not counteracted, it may promote cellular damage and apoptosis within the atherosclerotic lesion leading to plaque instability. Preliminary data from our group indicate that the DNA glycosylase Neil3 could serve as a sensor of metabolic stress, linking metabolic disturbances to atherosclerotic plaque development. Our hypothe-sis is that Neil3 modulates the development of atherosclerosis through epigenetic mechanisms, and the last year we have started a new major animal study to explore this hypothesis. In 2016, Tom Rune Karlsen started on his PhD on a NRC funded project and we got Sverre Holm back in our "Mannschaft".

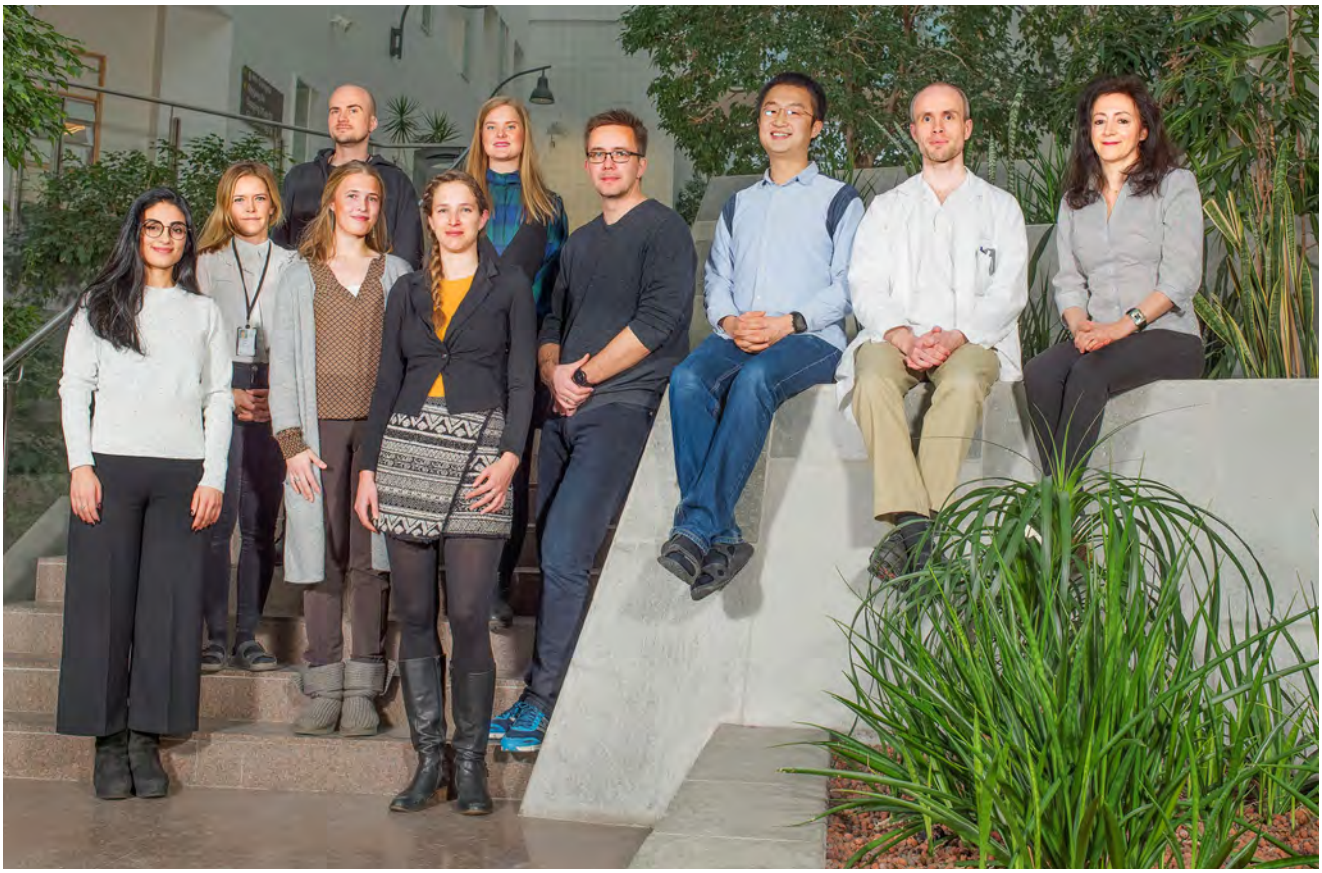
FUNDING

Our major external foundings are from:

- Norwegian Research Council
- South-East Regional Health Authorities
- Odd Fellow Medisink Vitenskapelig Forskningsfond
- Unifor

INFLAMMATORY RESEARCH

Immunological and molecular mechanisms in myocardial remodeling and heart failure



From left: Negar Shahini, Linn E. Fosshaug, Margrethe Flesvig Holt (in front) Knut Husø Lauritzen, Mieke Louwe, Maria Belland Olsen, Arne Yndestad, Kuan Yang, Øystein Sandanger and Azita Rashidi

GROUP MEMBERS IN 2017

GROUP LEADER
Arne Yndestad, MSc.Pharm., PhD
arne.yndestad@medisin.uio.no

RESEARCHERS
Alexandra V. Finsen, MD, PhD
alexandra@finsen.no
Trine Ranheim, MSc, PhD
trine.ranheim@rr-research.no

POST DOCS
Knut Husø Lauritzen, MSc, PhD
knut.huso.lauritzen@rr-research.no
Mieke Louwe, MSc, PhD
mieke.louwe@rr-research.no
Øystein Sandanger, MD, PhD
oystein.sandanger@rr-research.no

PHD STUDENTS
Yangchen Dhondup, MD
yangched@gmail.com
Linn E. Fosshaug, MD
l.e.lillerud@medisin.uio.no
Ståle Haugset Nymo, MD
staalenymo@gmail.com
Maria Belland Olsen, MSc
maria.belland.olsen@rr-research.no
Negar Shahini, MSc
negar.shahini@rr-research.no
Marina Sokolova, MD
marina.sokolova@rr-research.no
Kuan Yang, MPhil
kuan.yang@rr-research.no

MEDICAL STUDENT RESEARCHER
Margrethe Flesvig Holt
margrethe.flesvig.holt@
rr-research.no

ENGINEERS:
Azita Rashidi, BSc
arashidi@ous-hf.no
Jonas Øgaard, BSc
jonas.ogaard@rr-research.no

RESEARCH PROFILE

Cardiovascular disease (CVD) is the leading cause of death globally. Most forms of CVD are associated with inflammation. Atherosclerosis and chronic heart failure are conditions characterized by a chronic non-resolving inflammatory phenotype, while myocardial infarction and stroke, the direct consequences of atherosclerosis, are acute inflammatory conditions. Our main hypothesis is that these inflammatory processes, chronic or acute, directly contribute to the pathogenesis of CVD. The main focus on our research is on heart failure, myocardial infarction and atherosclerosis. By studying how specific components of the inflammatory response affects CVD progression and also how inflammation is initiated, maintained and terminated, our group has the ambitious aim to develop novel strategies for preventing, identifying and treating different forms of CVD. Our group has a translational research profile. We use experimental mouse models to mimic CVD development and characterize the pathogenic processes involved. In addition, our research approach includes in vitro studies in primary isolated cells from man and mouse, as well as clinical studies in well characterized patients with CVD, examining samples from peripheral blood as well as tissue samples.

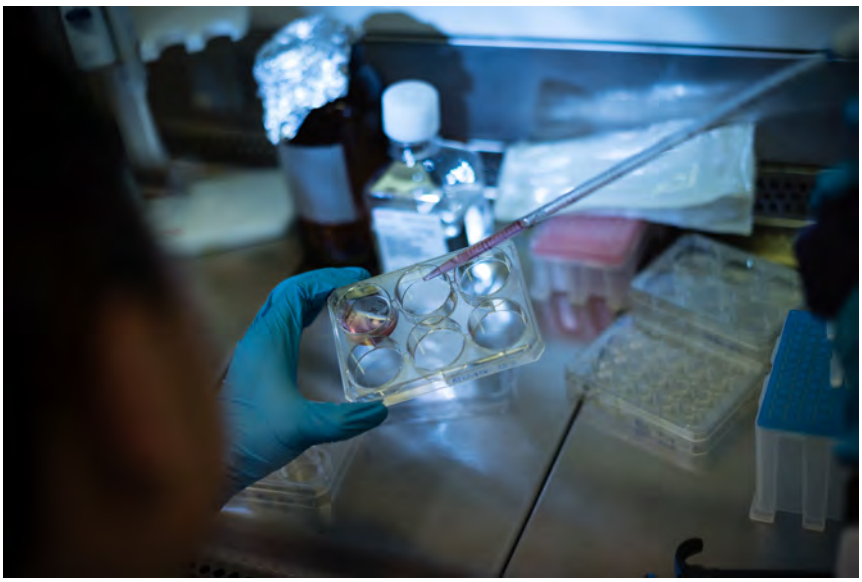
PROJECTS

Innate immune responses in cardiac injury and heart failure development. We study three arms of the innate immune system: (1) The NLRP3 inflammasome, a platform for the post-translational activation of IL-1β. In addition to studies on the pathogenic consequences of activation of the NLRP3 inflammasome in CVD, we have projects where we investigate how the inflammasome is activated. (2) Toll-like receptor 9, a receptor activated by bacterial DNA, but also mitochondrial DNA. (3) The role of the complement system in clinical and experimental heart failure, and (3). In addition, effective resolution of inflammation is important to prevent progression of acute inflammation to non-resolving chronic inflammation. Inflammation resolution is a coordinated and active process, and we are currently examining how this is regulated in different forms of CVD.

DNA damage and repair in atherosclerosis and heart failure. Aging, reactive oxygen species and chronic stress cause damage to both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) and this is proposed to contribute to development of non-communicable disease such as CVD. We believe that DNA damage and the associated DNA repair mechanisms are centrally involved in the pathogenesis of both atherosclerosis and heart failure by promoting non-resolving inflammation. We are currently examining this hypothesis experimentally, using mouse models that are deficient in DNA repair enzymes or have increased DNA repair activity.

FUNDING

Our work in 2017 was based on funding from South-Reat Regional Health Autorities, Research Council of Norway, the Norwegian Health Association, UNIFOR-FRIMED, Anders Jahres fond til vitenskapens fremme. In addition we have been part of and received funding through the K.G. Jebsen Inflammation Research Centre.



INFLAMMATORY RESEARCH

Inflammatory Biomarkers in Cardiovascular and Metabolic Disease

From left: Thor Ueland, Alexander Kirkeby Eieland, Annika E. Michelsen, Tove Lekva, Kristin Astrid Beiland Øystese, Kjersti R. Normann and Hilde M. Norum

GROUP MEMBERS IN 2017

GROUP LEADER
Thor Ueland, PhD
thor.ueland@medisin.uio.no

RESEARCHERS
Annika E. Michelsen, PhD
annika.michelsen@rr-research.no

POST DOCS
Tove Lekva, PhD
tove.lekva@rr-research.no

PHD STUDENTS
Aurelija Abraityte, MSc
aurelija.abraityte@rr-research.no
Hilde Margrethe Norum, MD
hildenorum@yahoo.com

ASSOCIATED RESEARCHERS
Cristina Olarescu, MD, PhD
nicoleta.cristina.olarescu@rr-research.no
Kjersti Ringvoll Normann, MSc
k.r.normann@medisin.uio.no
Alexander Kirkeby Eieland, MSc
alexander.kirkeby.eieland@rr-research.no
Camilla Maria Falch, MD
cafal14@student.sdu.dk
Kristin Astrid Berland Øystese, MD
k.a.b.oystese@studmed.uio.no

RESEARCH PROFILE

Many disease states are associated with low-grade chronic inflammation that may result in detectable changes in inflammatory

proteins that can be measured in biological fluid such as serum and plasma, making them valuable biomarkers. Measurement of these biomarkers may therefore be useful for detecting diseases before they present and/or offer information on the mechanisms of disease, they may represent treatment targets or be helpful in evaluating treatment responses and predicting outcomes.

Our research focuses on measurement and use of inflammatory markers in different populations characterized by low-grade systemic inflammation focusing on cardiovascular disease and risk, neuropsychiatric disorders and metabolic endocrine disease.

Together with the endocrine unit we have analyzed inflammatory markers in blood and tissue in well characterized cross-sectional cohorts and clinical trials in patients with heart failure, acute coronary syndromes and aortic stenosis. In these studies we evaluate biomarkers, reflecting a wide range of inflammatory processes, as predictors of adverse outcome and treatment responses. A focus in these studies is investigating the impact of Wnt signaling and secreted Wnt antagonist in these conditions.

We have a close collaboration with the endocrine unit, analyzing inflammatory markers in patients characterized by growth hormone deficiency (GHD) and excess (acromegaly) as well as glucocorticoid excess (Cushing syndrome).
In collaboration with the women and children center evaluating the impact of systemic inflammation in pregnancy on future cardiovascular and metabolic risk. These studies investigate the association between hormones and inflammatory mediators and impact on metabolic disturbances in different target tissues such as adipose tissue and bone with special focus on glucose metabolism.

We also have a tight collaboration with the Psychosis Research Centre Thematically Organized Psychosis Research (TOP) group, analyzing inflammatory biomarkers in patients with schizophrenia and bipolar disorder. In these studies we focus on markers in serum/plasma as well as mRNA levels in circulating immune cells that may reflect neuroinflammation and further, investigate associations with immune-related candidate risk genes within the major histocompatibility complex, identified by genome-wide association studies (GWAS).

In addition, we collaborate with other clinical research, nationally and internationally.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

Haemostasis and Bleeding Disorders

In front-from left: Adelheid Holm, Stine Bjørnsen, Ragnhild J. Måseide, Pål Andre Holme, Nina Haagenrud Schultz and Christian Qvigstad.

GROUP MEMBERS 2017

GROUP LEADER
Pål André Holme, Professor, MD, PhD
pholme@ous-hf.no

PHD STUDENTS
Nina Haagenrud Schultz, MD
nisc@ahus.no
Ragnhild J. Måseide, MD
ragmas@ous-hf.no
Christian Qvigstad, MD
chrqvi@ous-hf.no

ENGINEERS
Stine Bjørnsen, BSc
stine.bjornsen@medisin.uio.no

STUDY COORDINATOR
Adelheid Holm
adholm@ous-hf.no

ASSOCIATED
Geir E. Tjønnfjord, Professor, MD, PhD
gtjonnfj@ous-hf.no
Heidi Glosli, MD, PhD
hglosli@ous-hf.no

Our scientific interests are focused on clinical and basic aspects of normal and disturbed haemostasis in particular bleeding disorders like hereditary and acquired coagulation disorders.

Oslo University hospital, Rikshospitalet is the only Haemophilia Comprehensive Care Centre in Norway and is one of the biggest haemophilia centres in the Nordic region taking care of more than 1200 persons with bleeding disorders. Several research projects are ongoing besides clinical activity.

Moderate haemophilia
Current treatment of haemophilia is predominantly guided by the severity classification. While patients with severe haemophilia are closely monitored and receive early prophylaxis, moderate and mild patients are monitored less frequently and mostly receive treatment on-demand. The group of moderate haemophilia, however, is heterogeneous with a wide variation in clinical phenotype, with some of the patients having a considerable need for factor substitution. Bleeding phenotype is not strictly correlated to the coagulation factor level, but also influenced by physical activity, presence of target joints and synovial hypertrophy, degree of arthropathy and adherence to a prophylactic regime. According to

more recent thinking, haemophilia care and treatment therefore should be tailored individually. The aim of the initiated PhD project (Ragnhild J Måseide) is to study and evaluate the treatment and outcome of patients with moderate haemophilia A and B (factor level 1-<5 IU/dL) in the Nordic region (Iceland, Sweden, Denmark, Finland and Norway) and our group is the coordinating centre.

Age related comobidities in haemophilia
Rates of hypertension and renal disease, as with other cardiovascular risk factors and comorbidities, are known to rise with age. In haemophilia, it appears from some reports that there is an even stronger association with hematuria and hypertension. Our group is the coordinating centre for an epidemiologic European multicentre study on behalf of the ADVANCE (Agerelated-DeVelopments-ANd-Comorbidities-in-hemophilia Working Group). The group is interested in determining, among consecutively screened people with haemophilia (> 800 pts.), aged ≥40 years with a follow up period of 10 years, whether rates of hypertension and renal disease vary according to a previous history of hematuria and whether rates of hypertension/renal disease/ and other cardiovascular and malignant comorbidities vary with specific influencing factors in haemophilia. Two papers form the cross sectional study have already been published and now further followed up in the longitudinal prospective study. Christian Qvigstad is working as a PhD student on this project.

Optimizing bypassing agents.
During the last years we have studied and published papers on how to optimize and tailor treatment in persons with haemophilia with or without inhibitors to FVIII and in persons with FVII deficiency.
One of main objectives has been tailoring of treatment with bypassing agents (BPA) for haemophilia patients with inhibitors. Development of inhibitors is the most serious complications of haemophilia treatment today, High titre inhibitors to factor VIII and less often to factor FIX, represent a major challenge in the treatment of haemophilia A and B. The treatment of bleeds in haemophilia patients with inhibitors relies on the use of the bypassing agents, factor eight bypassing activity (FEIBA) or recombinant factor VIIa. While both therapies are effective in the majority of bleeding episodes and postoperative prophylaxis, there is a significant amount of inter individual variability when it comes to the response to therapy. In haemophilia patients without inhibitors, there is a close relationship between the level of FVIII or FIX measured ex vivo and the haemostatic outcome of the patients. However, in inhibitor patients there is no such relationship using bypassing treatment as there is no established laboratory assay to monitor efficacy and optimal dosing. We are studying the effect of bypassing agents using thromboelastography (TEG/ROTEM) and thrombin generation test (TGA) to individualize coagulation factor concentrate usage and dosing in the home treatment program, individualize coagulation factor concentrate usage and dosing prior to and in the postoperative period, address the issue of minimum effective dose during surgery and apply these assays in the evaluation of the critically ill patient with concomitant haemostatic insufficiency. In addition we have published that adjunct use of tranexamic acid (TXA) to BPA significantly increased the clot stability without increasing the thrombin generation and may be superior to standard treatment with BPA alone.

Reversal of factor Xa inhibitors
Today there are no evaluated effective treatments to reverse the effect of FXa-inhibitors (direct oral anticoagulants (DOAC)). As a PhD project (Nina Haagenrud Schultz) we are performing studies where the objectives are to detect the most effective haemostatic agent and appropriate dose for reversal of bleeds caused by FXa inhibitors extensively used in the clinic for atrial fibrillation and treatment of venous thromboembolism. The effect will be assessed mainly by the two global coagulation methods thromboelastography (TEG) and thrombin generation assay (TGA) since conventional coagulation assays such as aPTT and INR are not capable to measure the effect of DOAC accurately. Studies are also performed to investigate the effect of FXa inhibitors on platelet function and endothelium.

Immune thrombocytopenia
Parts of the group is also involved in studies on immune thrombocytopenia ITP and in the RITP trail we aimed to assess the efficacy of rituximab as compared with placebo as a splenectomy-sparing treatment in patients who were previously treated with corticosteroids. (Lancet 2015; 385: 1653–61). The follow up study PROLONG has now been ongoing for a year where we want evaluate the long-term effect of rituximab and immunological changes also including a PhD project on the immunological.

The group also participates in several other international and Nordic investigator initiated research projects on bleeding disorders.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

Coagulation factors: role in the development of thrombosis, inflammation and cancer

In front from left: Maria Eugenia Chollet, Benedicte Stavik, Grethe Skretting, Ann Døli, Elisabeth Andersen and Marie-Christine Mowinckel, from left back: Marianne Seierstad Andersen, Christiane Filion Myklebust and Xue-Yan Cui

GROUP MEMBERS 2017

GROUPLEADER:
Grethe Skretting, MSc, PhD
grethe.skretting@medisin.uio.no

POST-DOCS:
Benedicte Stavik, MSc, PhD
benedicte.stavik@rr-research.no
Maria Eugenia Chollet, MD, PhD
mechollett@yahoo.com
Xue-Yan Cui, MD, PhD
x.y.cui@medisin.uio.no

PHD-STUDENTS:
Elisabeth Andersen, MSc
elisabeth.andersen@medisin.uio.no

ENGINEERS:
Marianne Seierstad Andresen, MSc, PhD
marianne.andresen@rr-research.no
Christiane Filion Myklebust, MSc
christiane.filion.myklebust@rr-research.no
Marie-Christine Mowinckel, MSc
UXMAOW@ous-hf.no

ADMINISTRATIVE COORDINATOR:
Ann Døli
UXNNDL@ous-hf.no

ASSOCIATED RESEARCHERS:
Nina Iversen, MSc, PhD
UXNAIV@ous-hf.no
Mari Tinholt, MSc, PhD
matinh@ous-hf.no

RESEARCH PROFILE:

Our research focuses on the molecular mechanisms underlying the role of coagulation inhibitors in thrombosis, inflammation and cancer. Of special

interest is the coagulation inhibitor tissue factor (TF) pathway inhibitor (TFPI). Additionally, we are interested in the functional consequences of mutations in the factor VII (FVII) gene in order to find novel therapeutic targets. The group is also involved in a number of clinical studies and responsible for analysis of biochemical markers in these studies.

MAIN PROJECTS:

-Estrogens and TFPI-2

TFPI-2 is a matrix-associated protein inhibiting the activation of matrix metalloproteinases involved in tumor progression, invasion and metastasis. Using the GOBO database, we found that the TFPI-2 mRNA levels were significantly increased in patients with ERα+ tumors compared to patients with ERα- tumors and that increased levels of TFPI-2 were associated with increased survival in patients with ERα+ tumors. We have demonstrated that estrogens induced TFPI-2 expression in ER positive breast cancer cells in a process mediated by ERα and a specific lysine demethylase. A continuation of this project is in progress where potential effects on TFPI-2 expression by miR-RNAs are being examined.

-Atherothrombosis and TFPI

In this project we want to examine whether TFPI might represent a novel therapeutic target in atherosclerosis related cardiovascular disease (CVD). TFPI is known to circulate in plasma in complex with cholesterol transporting proteins such as LDL, and elevated levels of TFPI have previously been found in human atherosclerotic plaques. Our data indicate that the anti-inflammatory M2 macrophages may be a potential source of TFPI in the atherosclerotic plaque, possibly promoted by the presence of cholesterol crystals. Apparently, endoplasmic reticulum (ER) stress is involved in the upregulation of TFPI in the macrophages and the presence of TFPI in the plaques reduced the inflammatory response advocated by the cholesterol crystals.

-Hypoxia and TFPI

We have previously demonstrated that TFPI expression was transcriptionally repressed by the activation of hypoxia inducible factor (HIF)-1α under hypoxic conditions. In addition, we have examined the role of HIF-2α, also known as endothelial PAS domain-containing protein 1 (EPAS1), on TFPI expression and found an inverse correlation between the expression of HIF-2α/EPAS1 and TFPI in the breast cancer cell line MCF7. Using gene expression analysis it was observed a positive correlation between HIF-2α/EPAS1 and total TFPI mRNA expression in breast cancer patients. This might suggest that the activation of coagulation and increased risk of thrombosis observed in breast cancer patients may correlate with local hypoxic regulation of coagulation factors and their inhibitors.

-TFPI and migration of leukemia stem cells

It is known that TFPI affects healthy bone marrow cells ability to migrate. In an attempt to find new therapeutic approaches to eliminate leukemia stem cells (LSCs) hidden in the bone marrow microenvironment of patients with acute myeloid leukemia, we are studying the role of TFPI in the migration of LSCs.

-FVII deficiency

To envisage possible therapeutic approaches that can substitute the present replacement therapy we are investigating the intracellular fate of a group of FVII mutations previously reported to give FVII deficiency. The project includes both studies by overexpressing the FVII variants in a non-FVII expressing cell line, but also genomic editing using a hepatic cell line Huh7, and human embryonic stem cells, which will be differentiated into hepatocytes being the main site of FVII expression. Accumulation of misfolded proteins within the ER might cause ER stress and can trigger the unfolded protein response (UPR) and apoptosis. Our results demonstrate that the FVII mutant proteins evoke ER stress when overexpressed in cells and that UPR is activated.

FUNDING

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KEY COLLABORATORS

Prof Bernardi Francesco and his group in Ferrara, Italy
Dr Bernt Thiede, Section for Biochemistry and Molecular Biology, University of Oslo
Dr. Gareth Sullivan, Norwegian Stem Cell Centre, University of Oslo
Ellen Skarpen, Stig Ove Bøe and Anna Lång, Core facility for Advanced Light Microscopy, Oslo University Hospital
L. Vijaya Mohan Rao, Department of Cellular and Molecular Biology, University of Texas at Tyler. USA
Ling Sun, Department of hematology, Zhengzhou University, China
Mitchell Ho, National Cancer Institute, USA
Ulla Randen and Hiep Phuc Dong, Department of Pathology, Oslo University Hospital, Radiumhospitalet, Confocal microscope
Dr. Anders EA Dahm, Department of Haematology, Ahershus University Hospital
Prof. Sandip Kanse, Institute of Basal Medical Sciences, University of Oslo
Prof. Terje Espevik, Centre of Molecular Inflammation Research and Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.
Mona Skjelland, Department of Neurology, Oslo University Hospital, Rikshospitalet

AWARDS 2017

Best poster at K.G. Jebsen Inflammation Research Centre Scientific Retreat, February 2017 to Maria Belland Olsen: "Neil3-dependent regulation of cardiac fibroblast proliferation prevents myocardial rupture".

The annual meeting of the Norwegian Gastroenterological Society in February 2017 awarded Laura Valestrand with a scientific award and a research grant.

In May 2017 Johannes Hov received Oslo University Hospital's high ranking Early Career Award. The evaluation committee stated: "Johannes Espolin Roksund Hov defended his PhD thesis in 2011 and has been most productive in the immediate post-doc period, with high profile publications. His field of research is gut microbiota in human disease. He has established a research group within the field that has produced several scientific papers and the first PhD student defended his thesis in 2016. Dr. Hov is driving and developing the field of the gut microbiome and has excellent communication skills that he uses to spread knowledge of the area."

Benedicte Stavik recieved a Young investigator award for a highly rated abstract at the XXVI International Society on Thrombosis and Haemostasis Congress i Berlin in July 2017.

The National Societies Committee and the UEG Scientific Committee jointly select 6-8 emerging clinical scientists as Rising Stars every year, based on a track record of international quality research and developing scientific independence. At the United European Gastroenterology Week (UEGW) in Barcelona, October 2017, Johannes R. Hov received this prestigious award.

Photo: UEG

Johannes R. Hov accepting the Rising Star Award.

Photo: Oslo University Hospital

Johannes R. Hov recieving Oslo Univeristy Hospital's Early Career Award together with Tor Paaske Utheim (to the left). In the center Kirsten Sandvig who recieved the Exellent Researcher Award for 2017.

Publications 2017

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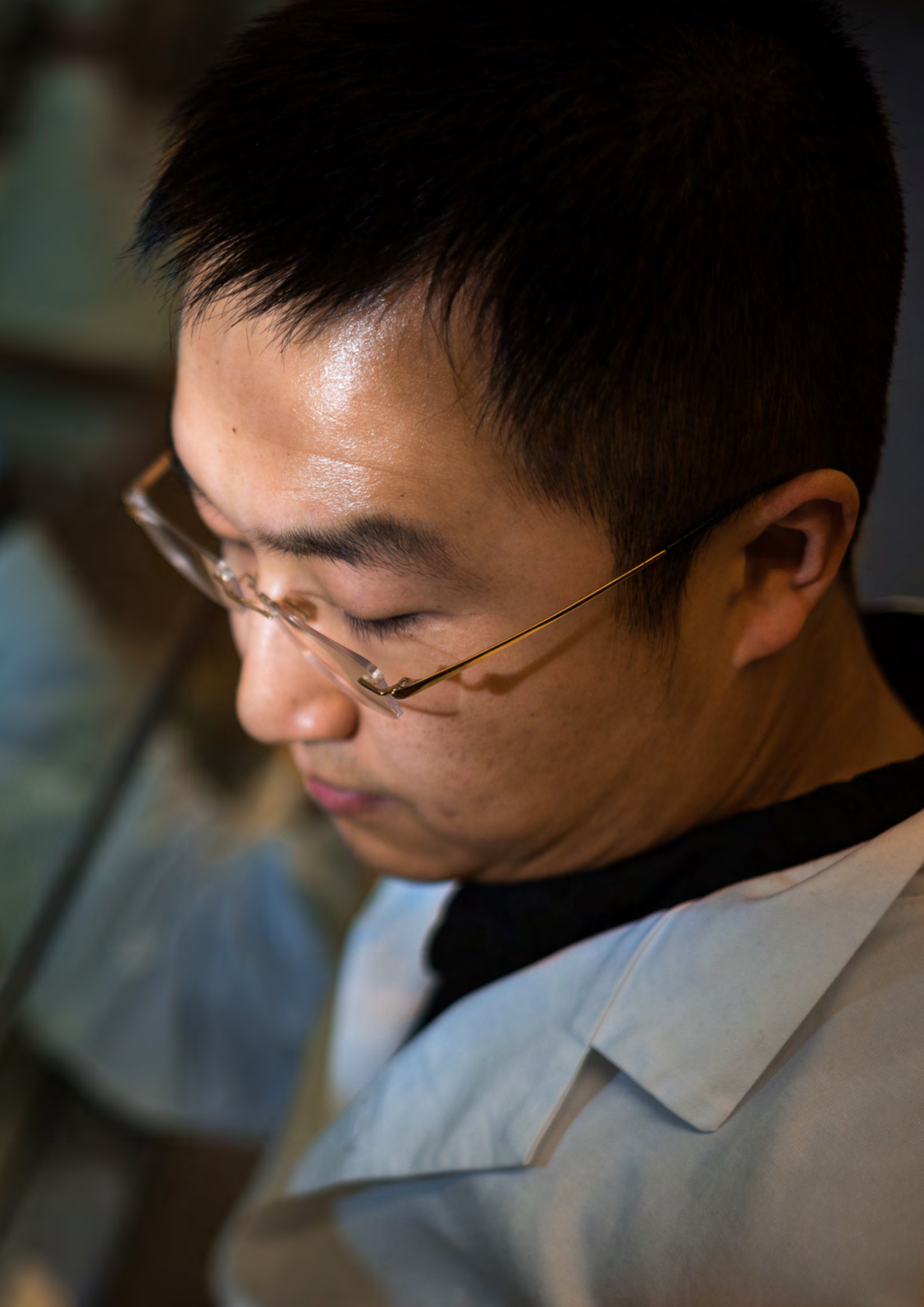

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The Research Institute of Internal Medicine

Oslo University Hospital, Rikshospitalet
P.O. Box 4950 Nydalen, 0424 Oslo, Norway

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

http://ous-research.no/riim/

Oslo University Hospital

UiO : University of Oslo

www.oslo-universitetssykehus.no

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