Oslo University Hospital

UiO : University of Oslo

Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2016

RIIM

ANNUAL REPORT

2016

Pages

RIIM ANNUAL REPORT 2016

More information at the web pages:
http://ous-research.no/riim/

TEXT: RIIM
PUBLISHER: Oslo University Hospital
COVER PHOTOS: Øystein H. Horgmo, UiO
LAYOUT og TRYKK: Møklegaard Print Shop AS
SAMPLES: 150

Photo: Øystein H. Horgmo, University of Oslo

Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

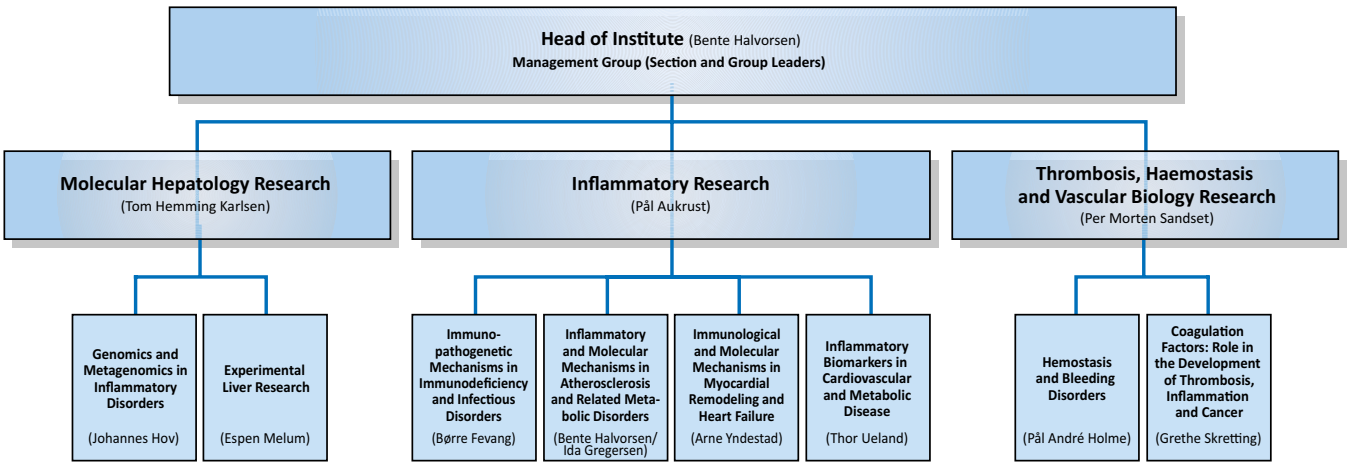
It is a great pleasure for me to look back on our achievements in 2016. Last year, RIIM succeeded in growing and reaching great scientific accomplishments. We published more papers than previous years, and a large proportion of those were published in high impact journals. Like the year before, we received several large external grants, emphasizing our success. Further, three of our scientists; Prof. Pål Aukrust, Dr. Johannes R. Hov and Dr. Espen Melum received prestigious awards for their research in 2016. In addition we have educated several PhDs and master students, and held a series of lectures for students, patient organizations and scientific communities. RIIM is an established and active partner in the scientific society, and houses young talents and researchers of world class.

Oslo University Hospital (OUH) is in the process of becoming a more efficient high quality health care center and so are we. Since RIIM was established in the mid 1950's, the Institute has been under constant reorganization. We work to look upon such structural changes as a room of possibilities. To improve as a research Institute, it is important that we are willing and capable of facing the challenges that may come. In spite of sparse long term funding we manage to keep an active, attractive and creative research milieu. This is a great achievement. However, it is of the utmost importance that the owners of the Institute, Oslo University Hospital and the University of Oslo, gives us the economic framework and infrastructure to secure a more predictable research arena where tomorrow's medicine is given the ability to develop. Together with my leader group, and the rest of RIIM, I am ready to work hard to achieve a more robust Institute, prepared for the future.

Altogether, RIIM is an authoritative research arena nationally and internationally. We recruit young research talents from almost every corner of the world, creating a fruitful, world-leading academic environment. But RIIM has ambitions to improve even further. My job is to maneuver the "ship" the best way in that direction. By that, I will congratulate all employees, across all occupational groups at RIIM, with a successful 2016.

March 15th, 2017
Bente Halvorsen

Organization



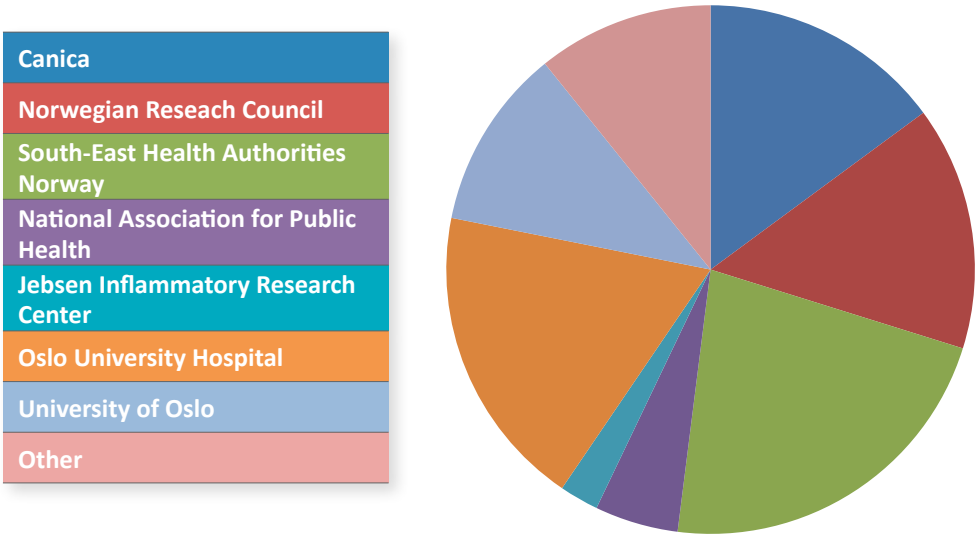
TOM HEMMING KARLSEN
Leader of Molecular Hepatology Research

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 67 million in 2016.
NOK 47 million were money from external sources, while the rest, NOK 20 million, came from Oslo University Hospital and University of Oslo.



Focus area

DNA – The old, the new and the still unsolved

ARNE YNDESTAD

In 2003, the 50th anniversary of the discovery of the double-helical structure of DNA coincided with the completion of the Human Genome project. A project initiated in 1990 culminated with the presentation of a high-quality, comprehensive sequence of the human genome. This massive achievement provided a roadmap that is the foundation of today's biomedical research. In the years that have passed since 2003, we have seen incredible advances in technologies that have hugely increased our understanding of the relationship between DNA, our genes and disease.
The roadmap given by the Human Genome project and also the subsequent HapMap project have given us tools that enable us to link genetic variation to disease. This is for example the basis for genome-wide association studies (GWAS). At the Research Institute of Internal Medicine (RIIM), GWAS has in a number of studies, published in high-ranking journals, been applied to dissection of the genetic susceptibility to complex disorders such as autoimmune liver disease (e.g., PSC) and common variable immunodeficiency. However, researchers at RIIM are working with DNA also at other levels and some of these are highlighted in this Focus area.
Our genome is constantly at threat. Knut Husø Lauritzen and Maria Belland Olsen discuss the importance of our DNA damage repair mechanisms in protecting against disease and whether enzymes involved in DNA repair also could be regulators of epigenetics, i.e., changes to the genome that do not involve a change in the nucleotide sequence. Moreover, it is not only our own genome that is relevant for disease. Johannes R. Hov uses metagenomics to study the composition and the function of gut microbiome and how it can affect human health and disease. Finally, in genomic medicine, the goal is not only to characterize disease-causing mutations, but also to cure the disease. Grethe Skretting describes how this can be achieved through genome editing that takes advantage of the CRISPR/Cas9 system.

DNA damage and repair in cardiovascular disease

KNUT HUSØ LAURITZEN &
MARIA BELLAND OLSEN

Every day, a human cell will need to handle at least 10 000 damages to its DNA. With a number of one trillion cells in a body, that is a decent amount of work. The list of diseases in which accumulation of DNA damage has been implicated is long and diverse, with examples as neurodegenerative diseases, cancer and rheumatoid arthritis. An increasing body of evidence indicates that DNA damage also is of importance in metabolic and cardiovascular disease.
Maintenance of the genome is crucial for life. Against this backdrop, both exogenous and endogenous stress presents a constant threat to the integrity of the DNA in living cells. Three main causes generate diverse DNA lesions. First, exogenous stress, such as the ultraviolet (UV) component of sunlight, ionizing radiation and numerous genotoxic chemicals can damage DNA by altering its chemical properties (Hoeijmakers, Nature 2001). Second, byproducts of normal cellular metabolism, including reactive oxygen species (ROS) derived from oxidative respiration, may damage DNA, and thus constitute an ever-present danger. ROS alone can create single-strand breaks and generate more than 70 oxidative base and sugar products in DNA that destabilize the genome and threaten the viability of the cell. Third, all biological macromolecules inevitably decompose, and some of the chemical bonds in DNA tend to spontaneously disintegrate under physiological conditions (Lindahl, Nature 1993).

At the cellular level, unrepaired DNA damage can cause genomic instability that can lead to apoptosis or senescence, which can disrupt development or accelerate the aging process. DNA damage that leads to genome instability is also the hallmark of all forms of cancer. In addition to the damage to the DNA molecule itself, additional complications can be linked to time-dependent and semi-permanent changes in the epigenome (Hoeijmakers, N Engl J Med 2009).

To preserve the integrity of the genome, cells have an arsenal of repair proteins that detect different forms of DNA damage and initiate the appropriate repair pathway or, if irreparable, induce cell cycle arrest or apoptosis. The 2015 Nobel Prize in Chemistry was awarded to Tomas Lindahl, Paul Modrich, and Aziz Sancar for their work on the molecular mechanisms of these DNA repair processes. The DNA repair machin-

ery can be divided into six major mechanisms: (i) direct reversal, (ii) homologous recombination, (iii) nonhomologous end-joining (NHEJ), (iv) mismatch repair (MMR), (v) nucleotide-excision repair (NER) and (vi) base-excision repair.

The study of the involvement of DNA repair processes in the development of cardiovascular disease is a central focus area for research groups at RIIM. This is in close collaboration with Prof. Magnar Bjørås at Department of Cancer Research and Molecular Medicine, NTNU. We are particularly interested in the role of DNA glycosylases involved in base-excision repair (BER) (Krokan & Bjørås, Cold Spring Harb Perspect Biol 2013). BER is involved in DNA base-damage that could otherwise cause mutations by mispairing or lead to breaks in DNA during replication. BER is mostly concerned with endogenous DNA damage generated by cellular metabolism, and BER substrates are generally small base alterations that typically do not distort the DNA helix. This type of damage is repaired by a multistep process initiated by a damage-specific DNA glycosylase, which recognizes and removes the damaged base. This removal of the base lesion leaves an abasic-site that is both cytotoxic and mutagenic, and must be further processed. This is done by a series of enzymes, including an AP nuclease that nicks the DNA backbone, a DNA polymerase that process the nicked DNA and fills the gap with the correct nucleotide and, finally, a DNA ligase that completes the repair process by sealing the nick and restoring the integrity of the DNA helix. There are several different types of DNA-glycosylases that recognize one or a small group of specific base lesion(s), but there seem to be a degree of overlapping specificity and function between several of the DNA-glycosylases.

Researchers at RIIM have recently published two papers implicating the DNA glycosylase Neil3 in cardiovascular disease. In atherosclerosis, deficiency of Neil3 causes accelerated formation of atherosclerotic plaques, potentially through effects on lipid metabolism and macrophage phenotype (Skarpengland, Sci Rep 2016). Neil3 was also shown to be centrally involved in the healing process following myocardial infarction; mice lacking Neil3 had increased mortality caused by myocardial rupture. What is puzzling, is that the effects of Neil3 do not seem to involve effects on DNA damage repair (Olsen, Cell Rep 2017). There are no overall differences in DNA damage comparing Neil3 knockout and wild type mice in these studies, indicating that Neil3 has effects that go beyond that of "classical" DNA repair. Lack of Neil3 results in altered epigenetic signature, thus the DNA glycosylase seems to be involved in epigenetic modulation important for gene regulation. In line with this, it was recently demonstrated, in vitro, that a DNA glycosylase could initiate epigenetic regulation inducing gene expression (Fleming, PNAS 2017). Thus, we are now seemingly entering a new and exciting era where alternative roles of the DNA repair machinery will emerge.
The next years, researchers at RIIM will try to point out how DNA damage is involved in development of inflammatory diseases and also how the DNA repair machinery through epigenetic regulation could regulate stress responses, for example in an atherosclerotic plaque. Increased understanding of the involvement of these enzymes in epigenetic regulation, opens a new potential for modulating pathological processes.

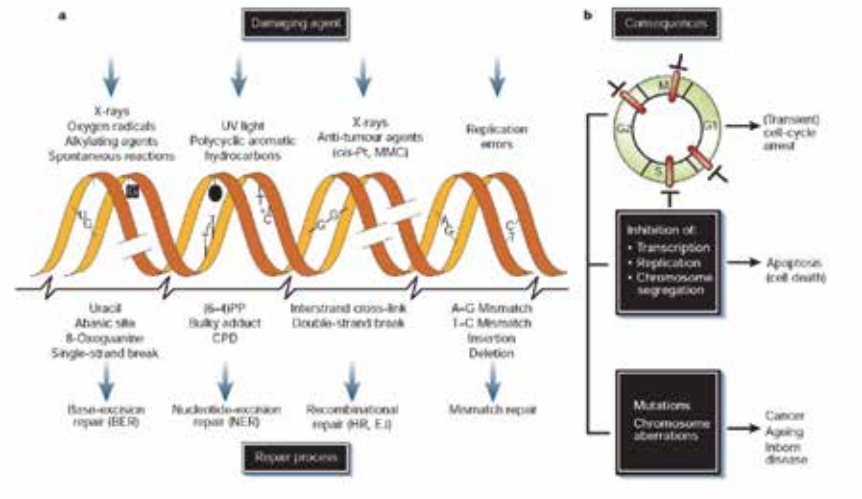


Figure 1: *DNA damage, repair mechanisms and consequences. a, Top: common DNA-damaging agents; middle: examples of DNA lesions induced by these agents; bottom: the most relevant DNA repair mechanism responsible for the removal of the lesions. b, Top: acute effects of DNA damage on cell-cycle progression lead to transient arrest in G1, S, G2 or M phase; middle: acute effects of DNA damage on DNA metabolism; bottom: long-term consequences of DNA injury include permanent changes in the DNA sequence (e.g., point mutations that affect single genes, or chromosome aberrations that may involve multiple genes) and their biological effects (from; Hoeijmakers, Nature, 2001).*

Focus area

Metagenomics

JOHANNES R. HOV

The human gut microbiome comprise between 10,000 and 100,000 billion bacteria and an unknown number of viral and fungal components. State of the art DNA sequencing technology and bioinformatics now allow us to characterize the composition of the gut microbiome, but also to determine what these microbes are doing and how they may promote or protect against disease

Metagenomics is traditionally studies of genetic material in environmental samples. In human disease research the term describes studies of the microbial communities that inhabit the body. The largest of these communities is the gut microbiome. The gut microbiota is a highly active organ, which seems to have a major impact on human health and development, most likely through interaction with metabolical pathways and the immune system.

Modern studies of the metagenomics of human disease involve high-throughput sequencing-based analyses of microbial DNA. The gut microbiome is typically characterized in samples from stool, biopsies of the intestinal mucosa, lavage or swabs. The sampled communities are complex, with a large number (hundreds or even thousands) of different species present. To illustrate the challenges in the analysis, the most recent catalogue of gut microbial genes based on studies from the USA, Europe and Asia now comprise almost 10 million different genes, about 500 times the extent of the human genome.

When introducing new methods it is important to consider the following: Which new questions can be answered by applying it? How is the case for metagenomics? Classic microbiology relied on cultures – and were focused on a low number of bacteria - and on the concept of infection (one bug – one disease). The new microbiome-based science embraces the microbial community, and the gut community is hard to characterize since most gut microbes are difficult to culture. This is where a metagenomic approach has its main advantage.

Key question 1: Who is there?
Metagenomics can efficiently provide an overview of the gut microbial community by performing high-throughput sequencing of marker genes. The most common targeted approach utilizes the presence of the 16S rRNA gene in all bacterial genomes. The 16S rRNA is a structural RNA and is part of the small subunit of the bacterial ribosome. In metagenomic studies we exploit the extensive variability of this gene, which makes it possible to use databases of microbial genomes to classify the origin of a specific read. A modern strategy is to amplify a part of the gene by using primers targeting conserved stretches surrounding one or more highly variable regions. To fully use the capacity of high-throughput sequencers, each sample is amplified with primers with unique barcodes: We can then mix e.g. 192 samples in one sequencing library and run it on our Illumina MiSeq which has a run-time of about 56 hours (when providing 300 bp long reads). Our bioinformatician controls the quality of the reads (sequences) and maps them to microbial databases, providing tables of relative abundances of different taxa. It should be noted that a parallel approach in fungi uses sequencing of the variable internal transcribed spacer (ITS) region to generate relative fungal abundances in metagenomic samples.

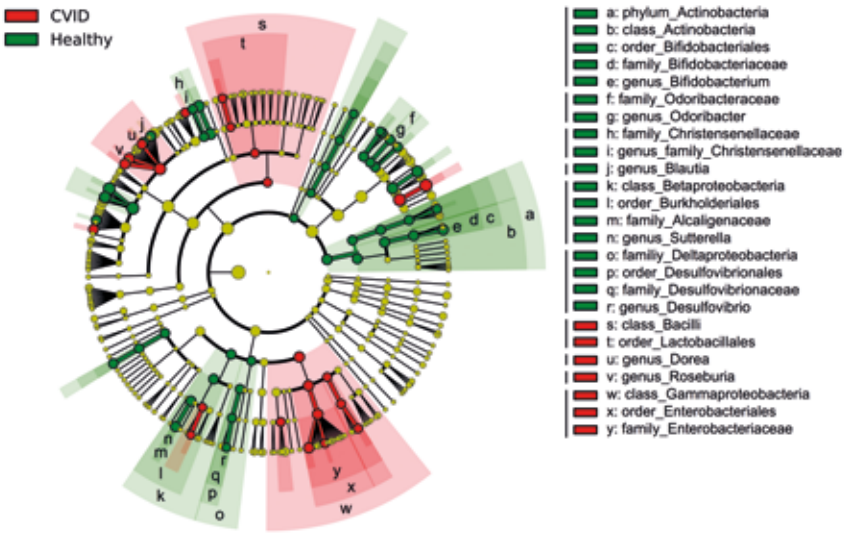


Figure: *A so-called "cladogram" which gives an overview of taxa or clades (in principle "bacteria") different in cases and controls, i.e. a typical representation of question 1: Who is there. The inner circle represent analyses on phylum level and the outermost ring the genus level. Only differences that were robust to multiple statistical methods are named in the legend. (Facsimile from Jørgensen et al. Mucosal Immunology 2016).*

Key question 2: What do the microbes do?
The taxonomic composition says little about the functional capabilities of the microbiome. Do the bugs transform bile acids, generate branched-chain amino acids or metabolize kynurenine? When performing so-called unbiased shotgun (or complete metagenomic) sequencing, DNA in the sample is randomly fragmented and sequenced. In a recent experiment performed in our group with about 150 samples and an aim of yielding 5-6 gigabytes of sequence data per sample – the total unfiltered data closes up on one terabyte size. By mapping the sequences to databases of microbial genes, the relative abundance of genes categorized according to functions can be calculated. In addition, the taxonomic composition can be defined to even higher resolution by identifying species specific marker genes.

Key question 3: When and how do we ask questions 1 and 2?
In the Genomics and Metagenomics group, the overarching theme is to establish clinical microbiota medicine in inflammatory diseases. The rationale in each individual phenotype has been established by asking Is the gut microbiota different in patients and controls? Deriving from this, do opportunities of gut microbial profiles as diagnostic or prognostic tools appear? Should particular metagenomic compositions be treated in specific ways? Can we monitor treatment by following the taxonomic composition? The role of individual bacteria may however be less important than the functional content. This is where shotgun sequencing becomes important. Are particular microbial metabolic functions altered in disease? Do these provide clues to the pathogenesis or to circulating metabolites which could serve as biomarkers or even targets of therapy?

Photo: Øystein Horgmo, University of Oslo

Focus area

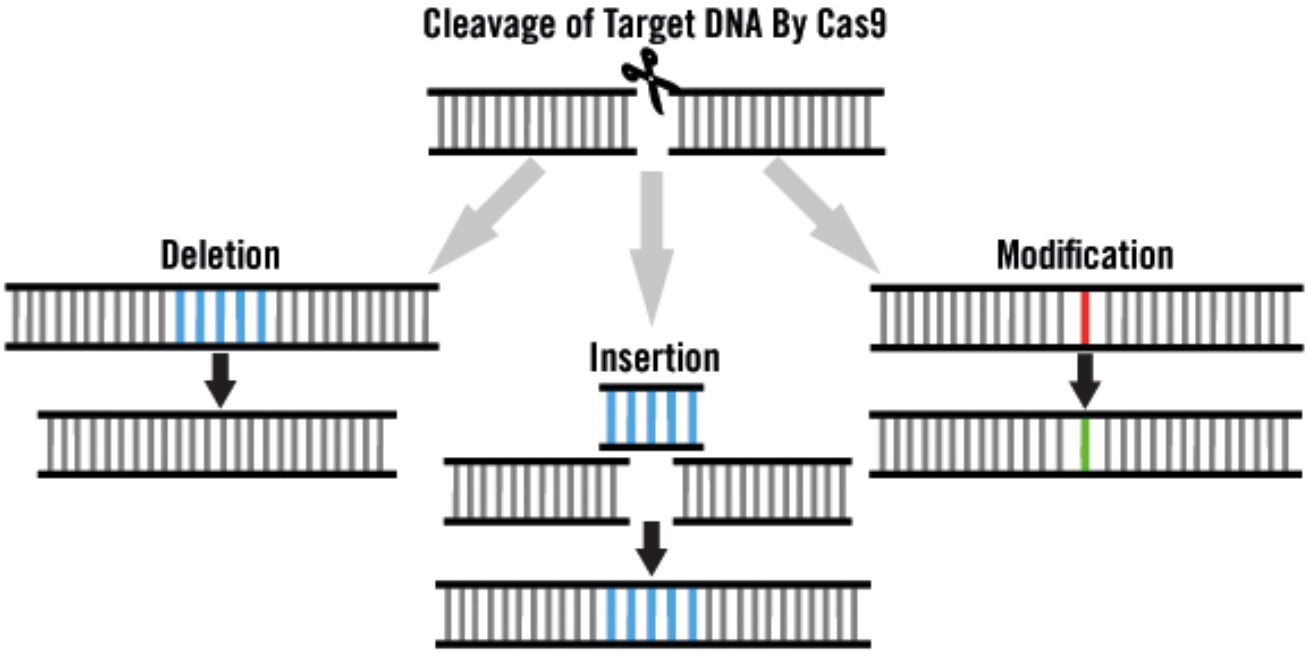
The CRISPR/Cas9 system- genome editing in inherited hematological diseases

GRETHE SKRETTING

The CRISPR/Cas9 system is an extensively used technology for genome editing. CRISPR stands for "Clustered Regularly Interspaced short Palindromic Repeats". These repeats are found in the genomes of bacteria and other microorganisms and are crucial components of their immune system[1] by destroying the genome of infecting virus. The spacers between the repeats are derived from virus DNA and serve as genetic memory of previous infections so that if the bacterium is attacked by the same virus again, the CRISPR system will digest any viral DNA matching the spacer sequences and thus protect the bacterium from viral attack. These spacers are transcribed into RNAs, which are cut into short sequences called CRISPR RNAs that guide the bacteria to destroy the viral material with the help of the Cas enzymes. Lately, the scientists have taken advantage of the CRISPR system to make precise changes in genes of various organisms, including human cells. The CRISPR/Cas9 system enables genetic editing by removing, adding or altering sections of the DNA sequence. It consists of two key molecules; i) the enzyme Cas9 that can cut the two DNA strands at specific locations so that DNA can be removed or new DNA can be added or modified (see figure below), ii) guide RNA (gRNA) that is a pre-designed short RNA sequence within a longer RNA scaffold. The gRNA part guides Cas9 to the correct part of DNA and ensures that Cas9 cuts at the right side of the genome.

Thus, since the CRISPR/Cas9 system can be tailored to target any set of DNA sequences it has caused an upheaval within the biomedical field giving enormous possibilities to further advance the human health and well-being. However, this technology, which is being used for research in a variety of human diseases, with its benefits, is followed by equally huge risks from potential misuses, but also unpredicted consequences. Therefore, ethical and safety concerns are very important issues and are being addressed. In June 2016 the first clinical trial using the CRISPR/Cas9 system was approved in the US. It is a small trial which is designed to test whether the system is safe for use in humans. The researchers will remove T cells from 18 patients with several types of cancers. Three editing will be performed using CRISPR/Cas9. One edit will insert a gene for a protein engineered to detect cancer cells and instruct the T cells to target them, and a second edit will remove a natural T-cell protein that could interfere with this process. The third will remove the gene for a protein that identifies the T cells as immune cells and prevent the cancer cells from disabling them. The researchers will then infuse the edited cells back into the patient.

The CRISPR/Cas9 tool has been successfully used to manipulate the genome in human cells obtained from patients with various inherited



Cas9 can make double-stranded breaks at specific locations in DNA enabling genetic editing by deleting DNA, inserting new DNA or modify DNA.

hematological disorder. Patient-specific induced pluripotent stem cells (iPSCs) are a type of pluripotent stem cells that can be generated directly from adult cells by the introduction of four specific genes encoding transcription factors[2]. One example is the β-thalassemia, which is one of the most common genetic diseases in the world resulting from more than 200 different mutations in the β-globin gene. iPSCs were generated from a patient with a homozygous point mutation in the gene and CRISPR/Cas9 was used to correct one allele[3]. CRISPR/Cas has also been used to correct mutations in iPSCs from patients suffering from hematological disorders, such as sickle cell disease[4], thrombocytopenia[5] and hemophilia. Hemophilia A (HA) is caused by deficiency in coagulation factor VIII (FVIII) and hemophilia B (HB) is caused by coagulation factor IX (FIX). A majority of HA is caused by two different types of DNA inversions in the *F8* gene[6]. A CRISPR/Cas system has been developed to revert these inversions back to normal orientation in iPSCs derived from a HA patient[7]. For HB, the CRISPR/Cas9 system has been used to generate a distinct genetically modified mouse model carrying a novel Y371D mutation resulting in a severe HB phenotype and the same system was used to target the mutation for correction to the wild-type again[8].

Inherited deficiencies of coagulation factors or their inhibitors are clinically associated with either bleeding diathesis or increased risk of thrombosis, and the clinical phenotype is related to the plasma levels of these proteins. Such deficiencies can be caused by protein misfolding, resulting in reduced protein levels in plasma. As part of our research focus, we are studying some mutants of the coagulation factor VII (FVII) that cause FVII deficiency. This is a rare congenital bleeding disorder and the patients have abnormal plasma FVII levels. Current treatment of bleeding episodes in these patients is based on replacement therapy using FVII concentrate, an approach that still has several limitations due to short half-life, adverse events, and high costs. There is thus a large unmet medical need for the development of alternative therapies that allow easier administration, better tolerance and less expense. We aim to uncover the molecular mechanisms implicated in the FVII mutations responsible of FVII deficiency in order to identify possible therapeutic targets. For this we are trying to introduce the various mutations in the endogenous gene for FVII (F7) of the human hepatocyte derived cellular carcinoma cell line Huh7 using the CRISPR/Cas9 system. When succeeded these new cell lines will be used to verify in vivo results obtained by in vitro studies in cell culture. To further verify in vivo, we will also generate human normal (non-cancerous) hepatocytes carrying each specific FVII mutation using the CRISPR/Cas9 system methodology by generating homozygous F7 gene mutations in human embryonic stem cells (hESCs) that will be differentiated into hepatocytes. At this point we will have a model system mimicking the hepatocytes of the patients.

In conclusion, genome editing technology, such as the CRISPR/Cas9 tool, is promising for inherited hematological disorders since they represent ideal targets for gene therapy because only partial restoration of gene functions are sufficient to ameliorate the symptoms of the diseases.

References

1. Barrangou, R. et al., CRISPR provides acquired resistance against viruses in prokaryotes. Science 2007 315, 1709-12.
2. Takahashi, K., Yamanaka, S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006 126, 663–76.
3. Song B., Fan Y., He W., Zhu D., Niu X., Wang D., Ou Z., Luo M., Sun X. Improved hematopoietic differentiation efficiency of gene-corrected beta-thalassemia induced pluripotent stem cells by CRISPR/Cas9 system. Stem Cells Dev. 2015 24, 1053-65.
4. Huang X., Wang Y., Yan W., Smith C., Ye Z., Wang J., Gao Y., Mendelsohn L., Cheng L. Production of Gene-Corrected Adult Beta Globin Protein in Human Erythrocytes Differentiated from Patient iPSCs After Genome Editing of the Sickle Point Mutation. Stem Cells. 2015 33, 1470-9.
5. Zhang Y., Yin C., Zhang T., Li F., Yang W., Kaminski R., Fagan P.R., Putatunda R., Young W.B., Khalili K., Hu W. CRISPR/gRNA-directed synergistic activation mediator (SAM) induces specific, persistent and robust reactivation of the HIV-1 latent reservoirs. Sci Rep. 2015 5, 16277.
6. Bagnall R.D., Waseem N., Green P.M., Giannelli F. Recurrent inversion breaking intron 1 of the factor VIII gene is a frequent cause of severe hemophilia A. Blood 2002 99, 168-74.
7. Park C.Y., Kim D.H., Son J.S., Sung J.J., Lee J., Bae S., Kim J.H., Kim D.W., Kim J.S. Functional Correction of Large Factor VIII Gene Chromosomal Inversions in Hemophilia A Patient-Derived iPSCs Using CRISPR-Cas9. Cell Stem Cell. 2015 17, 213-20.
8. Guan Y., Ma Y., Li Q., Sun Z., Ma L., Wu L., Wang L., Zeng L., Shao Y., Chen Y., Ma N., Lu W., Hu K., Han H., Yu Y., Huang Y., Liu M., Li D. CRISPR/Cas9-mediated somatic correction of a novel coagulator factor IX gene mutation ameliorates hemophilia in mouse. EMBO Mol Med. 2016 8, 477

DISSERTATIONS

MSc Huda Omar Ali

"Molecular mechanisms underlying the effects of oestrogens on tissue factor pathway inhibitor (TFPI) expression in breast cancer cells"
October 13th 2016

Committee:
1. opponent: Senior scientist Lucy Norris, Department of Obstetrics and Gynaecology, Trinity College, The University of Dublin, Ireland
2. opponent: Professor Agneta Siegbahn, Department of Medical Sciences, Coagulation Science, Uppsala University Hospital, Sweden
3. member of the Committee: Professor Kåre Birkeland, Department of Endocrinology, Morbid Obesity and Preventive Medicine, Division of Medicine, Institute of Clinical Medicine, University of Oslo, Norway

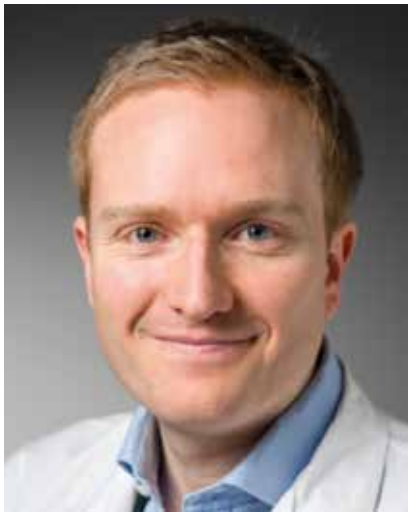
Main supervisor: Grethe Skretting
Co-supervisors: Benedicte Stavik, Per Morten Sandset

Oestrogens can influence the progression of hormone-sensitive cancers, such as breast, ovarian and endometrial cancers. Tissue factor (TF) pathway inhibitor (TFPI) is an inhibitor of TF induced coagulation and has been associated with breast cancer pathogenesis and development. Recently, reduced circulating TFPI levels were detected in healthy post-menopausal women receiving hormone replacement therapy, placing these women in higher risk group for thrombosis.

The aim of the thesis was to examine if oestrogens affected TFPI expression in breast cancer cells and to elucidate the molecular mechanism behind. Treatment with oestrogens, such as 17β-estradiol (E2) or 17α-ethynylestradiol (EE2) lead to reduced TFPI levels in oestrogen sensitive MCF7 cells, an effect that was mediated through the oestrogen receptorα (ERα), which was found to bind three oestrogen responsive element half-sites located in the 5' upstream flanking region of the TFPI gene using techniques such as electrophoretic mobility shift assay, chromatin immunoprecipitation analysis and luciferase reporter gene assay.

Furthermore, we found that the TFPI expression was regulated by oestrogens also at the post-transcriptional level by microRNAs (miRNAs). In silico analysis of the TFPI 3' untranslated region identified potential binding sites for miRNAs, in particular miR-27a, miR-27b and miR-494. All these three miRNAs were upregulated by oestrogen and TFPI mRNA levels were significantly downregulated following transfection with miR-27a/b and miR-494 mimics and upregulated by inhibitors (anti-miRs). Overall, in MCF7 cells, oestrogens repress the TFPI expression through the ERα both at the transcriptional and post-transcriptional level.

Thereby, we have identified potential therapeutic targets to prevent thrombosis in women belonging to higher risk groups.



MD Martin Kummen

"Primary sclerosing cholangitis and the gut microbiota – a study on mice, man and microbes"
October 4th 2016

Committee:
1. opponent: Associate Professor Bernd Schnabl, Division of Gastroenterology, School of Medicine, University of California, San Diego, USA
2. opponent: Senior Scientist Merete Eggesbø, Environmental exposure assessment & -epidemiology, Norwegian Institute of Public Health, Oslo

DISSERTATIONS

3. member of the Committee: Professor John-Anker Zwart, Division of Clinical Neuroscience, Institute of Clinical Medicine, University of Oslo

Main supervisor: Johannes R. Hov
Co-supervisors: Tom H. Karlsen, Pål Aukrust

Primary sclerosing cholangitis (PSC) is a liver disease of unknown aetiology, mostly affecting young adults with concurrent inflammatory bowel disease (IBD). No medical treatment is available, making it the most common indication for liver transplantation in Norway. Both autoantibodies and mouse models suggest a link to the gut microbiota, which the last decade has been implicated as an important contributor in a range of metabolic and inflammatory diseases.

The aim of the thesis was to explore the role of the gut microbiota in PSC, through characterisation of the gut microbiota in human PSC. One sought to complement this by investigating the gut microbiota-dependant metabolite trimethylamine-N-oxide (TMAO) in PSC, and explore the role of the gut microbiota in a mouse model with spontaneous bile duct inflammation (NOD.c3c4).

The gut microbiota of PSC patients differs from both healthy controls and patients with IBD, but is similar in PSC with and without IBD. The Veillonella genus, which is also associated with other inflammatory and fibrotic conditions, is enriched in PSC. Using only a few bacteria one were able to differentiate PSC from controls.

In PSC patients with normal liver function, elevated TMAO is associated with shorter transplantation-free survival, potentially reflecting metabolic changes resulting from gut microbiota-diet interactions.

NOD.c3c4 mice show marked differences in the gut microbiota compared to control mice (NOD). When raised germ free these mice develop a milder biliary disease compared with conventionally raised mice.

Overall, these results implicate the gut microbiota in the pathogenesis of PSC and bile duct inflammation, providing a strong basis and rationale for further studies of the microbiota both related to pathophysiology and clinical utility in PSC, with the potential to improve patient care through development of better diagnostic tools and novel treatments targeting the gut microbiota.

MD Tonje Skarpengland

"Impact of oxidative DNA base excision repair in atherosclerotic disease"
February 19th 2016

Committee:
1. opponent: Professor Jan Borén, Dept of Molecular and Clinical Medicine, University of Gothenburg, Sweden
2. opponent: Professor Hilde Nilsen, Department of Clinical Molecular Biology, Epigen, Institute of Clinical Medicine, University of Oslo, Norway
3. member of the Committee: Professor Kåre-Olav Stensløkken, The Heart Physiology Group, Institute of Basic Medical Sciences, University of Oslo, Norway

Main supervisor: Pål Aukrust
Co-supervisors: Bente Halvorsen

Atherosclerosis is characterized by oxidative stress, possibly leading to cellular DNA damage within the atherosclerotic lesions. NEIL3 is a DNA repair enzyme that recognizes oxidative DNA damage and initiates base excision repair (BER), which is the most important cellular DNA repair mechanism for removal of oxidative DNA damage. By using several experimental approaches, including samples from patients with atherosclerosis, studies of Neil3-deficient murine knockout-models and in vitro experiments in relevant cell lines, the aim of the study was to assess the role of BER, and the BER enzyme Neil3 in particular, in atherosclerosis. Skarpengland and coworkers found increased gene expression of BER genes, including NEIL3, in human atherosclerotic plaques, as well as maintained nuclear, but not mitochondrial DNA integrity. Several BER proteins were also increased in human atherosclerosis. A genetic variant of NEIL3 was associated with increased risk of myocardial infarction, supporting their theory of a role for NEIL3 in atherosclerotic

disease. Neil3-deficiency accelerated murine atherosclerosis by altering hepatic lipid metabolism independently of genome-wide canonical repair of DNA damage. Their study suggests that the upregulation of NEIL3 and the other BER genes in human plaques is a counteracting response to DNA-damaging events in atherogenesis, protecting nuclear, but not mitochondrial DNA integrity. Also, their murine data suggest an involvement of Neil3 in regulation of transcriptional network(s) responding to lipid stress, through removal of oxidative lesions at gene-specific sequences of importance for promoter activity.

MD Karolina Skagen

"Carotid athersoclerosis: imaging and indicators of plaque instability"
June 16th 2016

Committee:
1. opponent: Professor Rolf Salvesen, Department of Neurology, Nordlandssykehuset HF, Bodø and Institute of Clinical Medicine, University of Tromsø, Norway
2. opponent: Head Consultant Bente Thommessen, Department of Neurology, Akershus University Hospital, Lørenskog, Norway
3. member of the Committee: Associate Professor John K. Hald, Department of Radiology and Nuclear Medicine, Institute of Clinical Medicine, University of Oslo, Norway

Main supervisor: David Russel
Co-supervisors: Bente Halvorsen
In this PhD thesis "Carotid atherosclerosis: Imaging and indicators og plaque instability" Karolina Skagen and co-workers investigated whether different imaging methods; PET (Possitron Emission Tomography) and MRI (Magnetic Resonance Imaging) can be of value in the estimation of carotid atherosclerotic plaque content (amount of fat and inflammation), thereby aiding the estimation of patient stroke risk. Serum levels of carnitin, γBB, TML (trimethyllysine) og TMAO (trimelthylamine-N-oxide) in patients were measured and association with cardiovascular mortality was examined.

Both PET and MR images showed higher fat and inflammatory content in patients who had suffered a stroke as compared with images of symptom-free patients. Blood analysis showed levels of γBB to be higher in patients with carotid atherosclerosis as compared to healthy controls and to be associated with cardio-vascular mortality.

Photo: Øystein Horgmo, University of Oslo

SECTION OF MOLECULAR HEPATOLOGY

Genomics and Metagenomics in Inflammatory Disorders

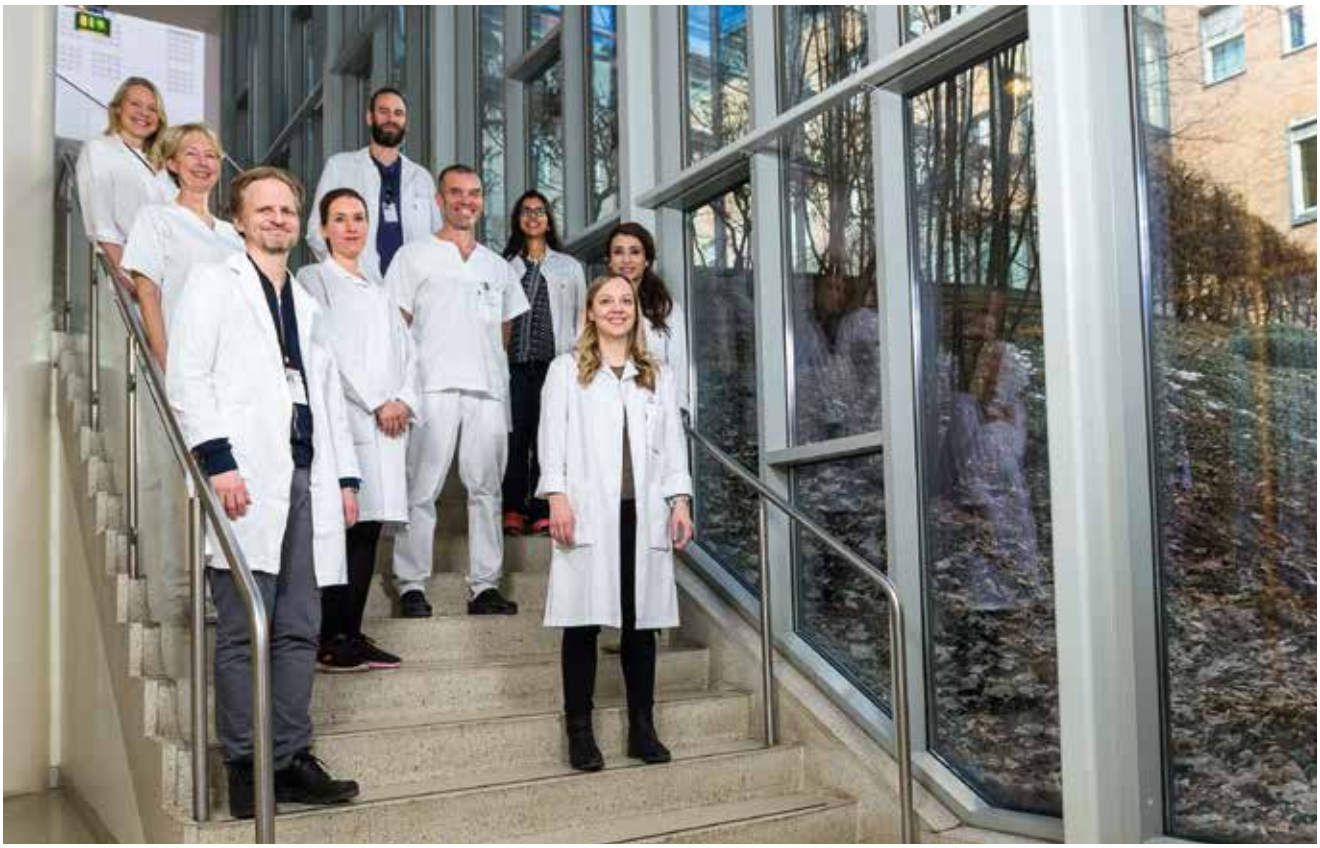


Photo: Øystein H. Horgmo, University of Oslo

From front left: Johannes R. Hov, Beate Vestad, Liv Wenche Thorbjørnsen, Hanne Guldsten (from 2017), Marius Trøseid, Amandeep Kaur Dhillon, Trine Folseraas, Kristian Holm and Cristiane Mayerhofer

GROUP MEMBERS

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

RESEARCHER
Marius Trøseid, MD, PhD (associated)
troseid@hotmail.com

POST DOCS
Martin Kummen, MD, PhD
martin.kummen@medisin.uio.no
Trine Folseraas, MD, PhD (associated)
trine.folseraas@medisin.uio.no

PHD STUDENTS
Cristiane Mayerhofer, MD
cristiane.mayerhofer@rr-research.no
Amandeep Kaur Dhillon, MD
amandeepkaurmahli@hotmail.com
Beate Vestad, MSc
beate.vestad@studmed.uio.no
Silje F Jørgensen, MD (associated)
s.f.jorgensen@medisin.uio.no

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

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

BIOENGINEER
Liv Wenche Thorbjørnsen, BSc
liv.wenche.thorbjørnsen@ous-hf.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) and intestinal diseases, immunodeficiencies (HIV and common variable immunodeficiency) as well as cardiovascular diseases. In 2016, the group has further turned its focus 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.

Cross-sectional studies represent starting points for further studies into the role of gut microbiota in all the diseases, answering the basic question: Is the gut microbiota altered? Several major studies on the gut microbiome in "our" diseases of interest were published in 2016, meaning that we now have strong rationale for further work on the clinical impact of the gut microbiome in both immunodeficiencies (both primary and acquired conditions) as well as PSC. The first PhD thesis focusing primarily on the gut microbiome in a disease was also defended with great success in 2016 (Martin Kummen, now post doc in the group. See details in separate section). Similar efforts are ongoing in the context of heart failure with plan for publication in 2017.

The cross-sectional studies primarily represents starting points for further studies into the role of gut microbiota either in clinical or experimental settings. Several interventional studies targeting the gut microbiota have already been performed. Currently ongoing, driven by the cardiology department, is a randomized controlled trial in heart failure, with antibiotics or probiotics in different study arms. Such studies may represent proof-of-concept of a direct involvement of the gut microbiota in the disease development. A key aspect of clinical microbiota medicine is also the application of gut microbial profile or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity.

Locally, the group is collaborating actively with several groups with expertise within the relevant disease groups. 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 is the opening of a germ-free research animal unit at the hospital, which has been developed by the experimental groups together with the animal facility.

Regionally, 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 third national conference on gut microbiota in November 2016 with about 100 participants and more than 20 abstracts submitted.

Photo: Øystein H. Horgmo, University of Oslo

Amandeep Kaur Dhillon in the lab.

SECTION OF MOLECULAR HEPATOLOGY

Experimental Liver Research

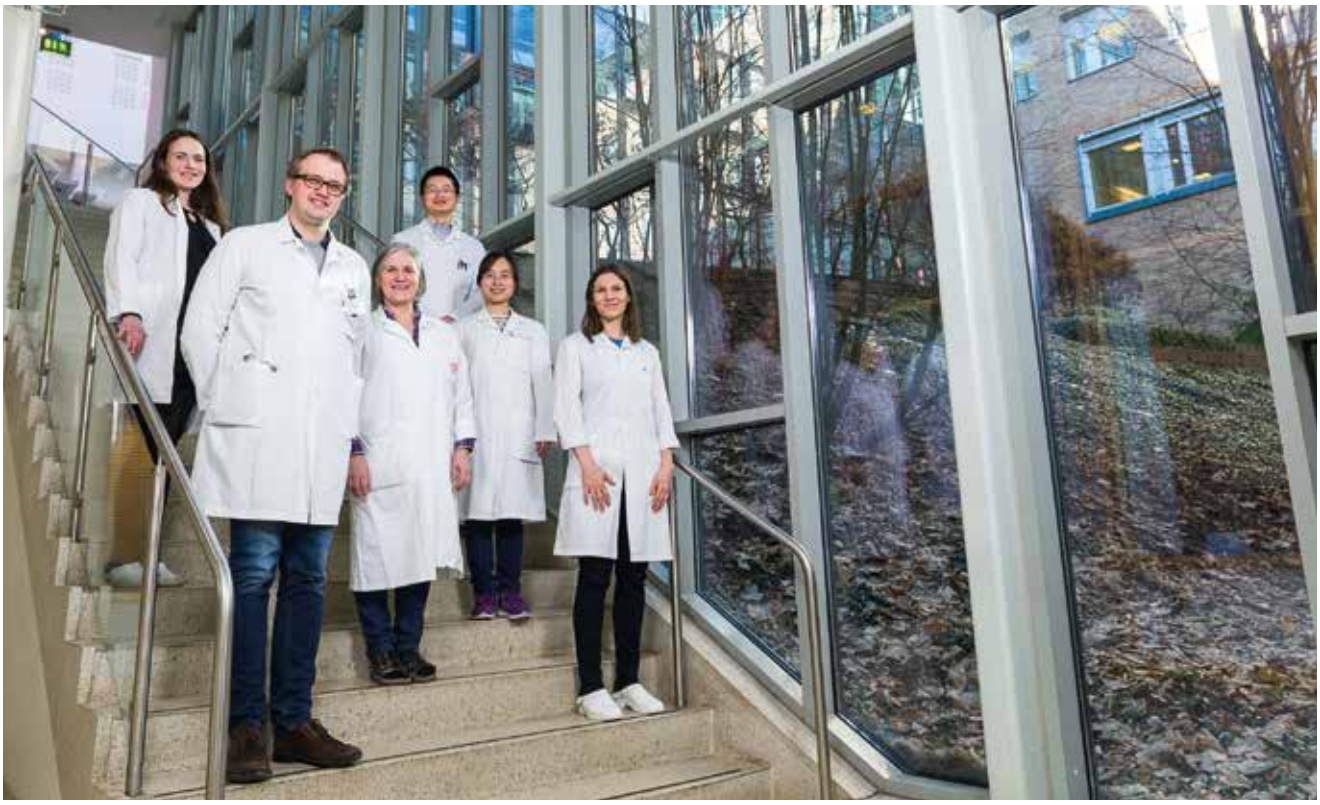


Photo: Øystein H. Horgmo, University of Oslo

From front left: Espen Melum, Anne Pharo, Xiaojun Jiang, Laura Valestrand, Natalie Lie Berntsen and Zheng Fei (Freeman)

GROUP MEMBERS:

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

LAB MANAGER
Anne Pharo, Cand. mag
anphar@ous-hf.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 Hendriksen, MSc
evak.klemsdal@gmail.com
Laura Valestrand, MD
lauravalestrand@gmail.com
Zheng Fei, MD
freemanzheng@163.com

RESEARCH PROFILE

The experimental liver research group is part of both the Norwegian PSC research center and the Research institute for Internal Medicine. All of our laboratory activities take place at the RIIM lab. In 2016 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 and mucosal associated invariant T (MAIT)-cells. NKT and MAIT cells 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 the chronic bile duct disease primary sclerosing cholangitis (PSC).

The most important tools in our research are mouse models that model aspects of cholangitis development. The mouse models we use are immune driven and inspired by the fact that most genes associated with PSC are involved in the immune response. In 2016 we published results showing how the microbiome affects the disease process in mice with bile duct inflammation by using germ-free animals and antibiotics treatment. We also clarified the role of NKT-cells in murine cholangitis to complement previous results where we had demonstrated that cholangiocytes activate NKT-cells.

In September 2016 Zheng Fei (Freeman) started as a scientific assistant in the group and was rapidly recruited as a PhD student. He will work on the role of MAIT-cells in bile duct inflammation. At the end of 2016 Elisabeth Schrumpf and Eva Kristine Klemsdal Henriksen finished their PhD's and their theses will be defended in 2017.

Photo: Øystein H. Horgmo, University of Oslo

From left: Anne Pharo, Laura Valestrand and Zheng Fei (Freeman) discussing lab results.

SECTION OF INFLAMMATORY RESEARCH

Immunopathogenetic Mechanisms in Immunodeficiency and Infectious Disorders

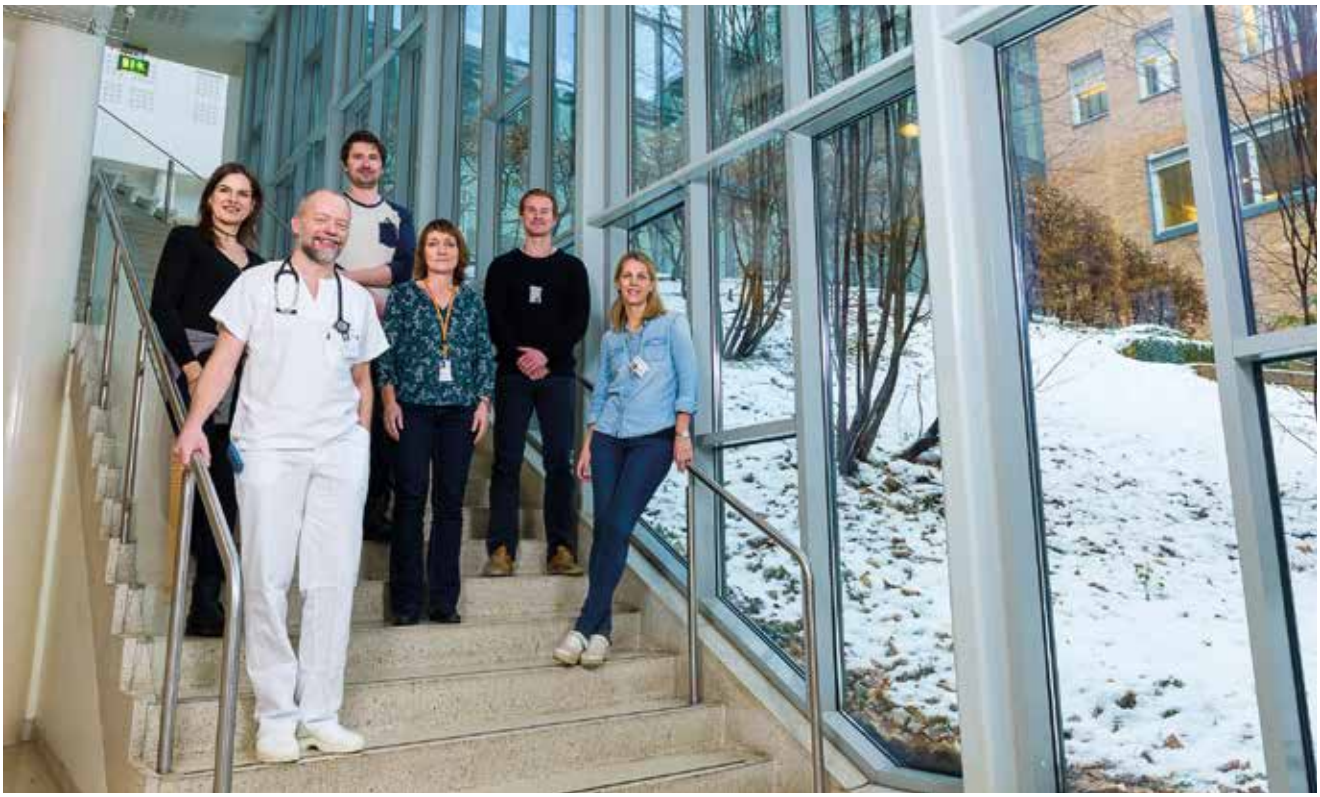


Photo: Øystein H. Horgmo, University of Oslo

Front from left: Børre Fevang, Kari Otterdal, William Siljan, Hedda Hoel. Back from left: Elisabeth Astrup, Jan Cato Holter.

GROUP MEMBERS

GROUP LEADER
Børre Fevang, Assist. Professor, MD, PhD
borre.fevang@ous-hf.no

RESEARCHER
Kari Otterdal, MSc, PhD
kari.otterdal@rr-research.no

SENIOR CONSULTANT
Ingvild Nordøy, MD, PhD
inordoy@ous-hf.no

PHD STUDENTS
Silje F Jørgensen, MD
s.f.jorgensen@medisin.uio.no
Jan Cato Holter, MD
j.c.holter@medisin.uio.no
Magnhild Eide Macpherson, MD
magnhild.eide@studmed.uio.no
Liv Hesstvedt, MD
uxzhcl@ous-hf.no
William Siljan, MD
williasi@ulrik.uio.no
Hedda Hoel, MD
hedhoe@ous-hf.no
Kristine Lillebø Holm, MSc
kristine.lillebo.holm@medisin.uio.no
Eli Taraldsrud, MD
eli.taraldsrud@medisin.uio.no

ASSOCIATED RESEARCHERS
Marius Trøseid, MD, PhD
troseid@medisin.uio.no
Elisabeth Astrup, MD, PhD
elisabeth.astrup@fhi.no
Lars Heggelund, MD, PhD
Lars.heggelund@medisin.uio.no

PROFESSOR EMERITUS
Stig S. Frøland, MD, PhD
s.s.froland@medisin.uio.no

RESEARCH PROFILE

The research group focuses 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 collaboration 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 patients 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, and more particular 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 delivered her PhD thesis in 2016 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 as he is about to deliver his PhD-thesis it is up to William Siljan to pick up the thread 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 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.

SECTION OF INFLAMMATORY RESEARCH

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders

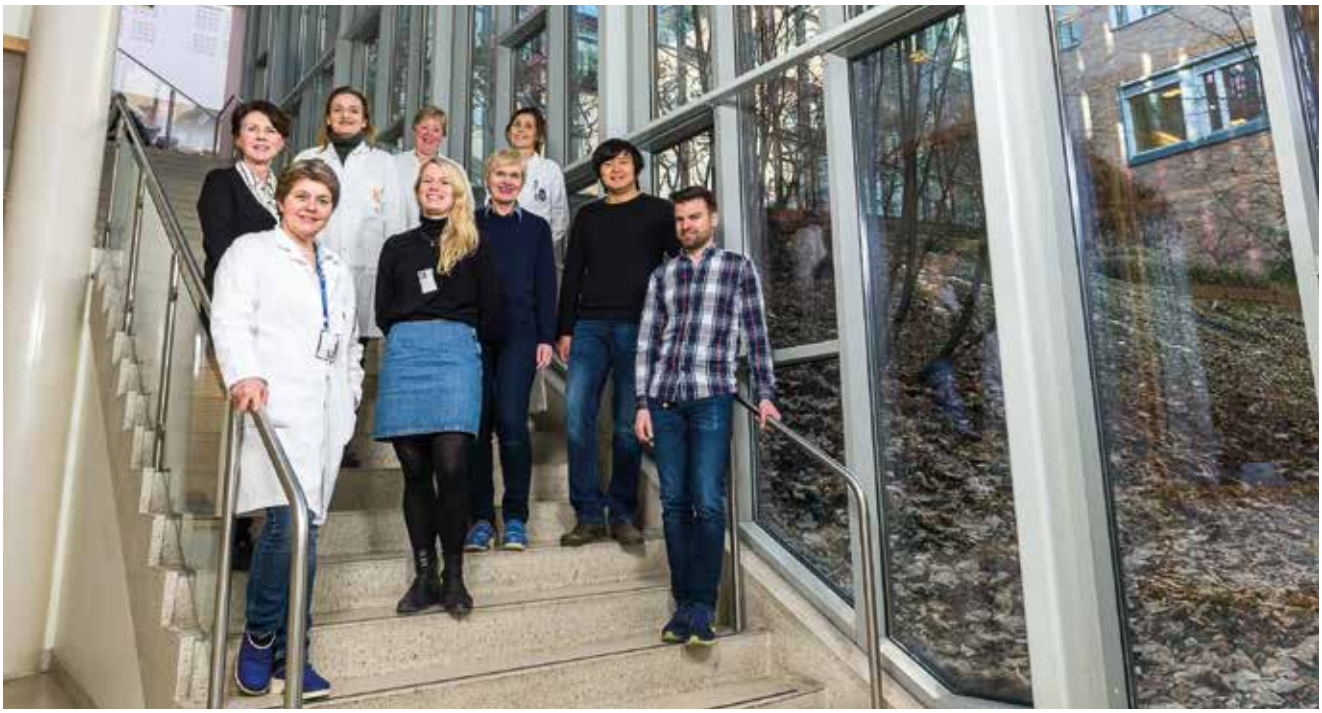


Photo: Øystein H. Horgmo, University of Oslo

From front left: Bente Halvorsen, Ida Gregersen, Ellen Lund Sagen, Xiang Yi Kong, Filip Segers, Turid Margrethe Pedersen, Karolina Ryeng Skagen, Vigdis Bjerkeli and Mona Skjelland.

GROUP MEMBERS

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

POST DOCS
Sverre Holm, MSc, PhD
sverre.holm@rr-research.no
Tuva Børresdatter Dahl, MSc, PhD
tuva.borresdatter.dahl@rr-research.no
Ida Gregersen, MSc, PhD
ida.gregersen@rr-research.no
Filip Segers, MSc, PhD
filip.segers@rr-research.no
Xiang Yi Kong, MSc, PhD
x.y.kong@medisin.uio.no

ASSOCIATED RESEARCHERS
Azhar Abbas, MD, PhD
azhabb@ous-hf.no
Mona Skjelland, MD, PhD
moskje@ous-hf.no
Karolina Ryeng Skagen, MD, PhD
kskagen@ous-hf.no

PHD STUDENTS
Nina Solheim, MD
solnina@hotmail.com
Kjell Torp-Joakimsen, MD
k.a.m.torp-joakimsen@studmed.uio.no
Ana Quiles Jimenez, MSc
anquil@rr-research.no
Tonje Skarpengland, MD, PhD
tonje.skarpengland@gmail.com

SENIOR ENGINEERS
Turid Margrethe Pedersen, BSc
turid.margrethe.pedersen@rr-research.no

Vigdis Bjerkeli, BSc
Vigdis.bjerkeli@medisin.uio.no
Ellen Lund Sagen, BSc
ellen.lund.sagen@rr-research.no

MASTER STUDENT
Lene Løvdahl, BSc
leneloevdahl@gmail.com

RESEARCH PROFILE

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. Atherosclerosis is a leading cause of death and disabilities worldwide. 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 15 years.

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. Valuable access to clinical material from well characterized patients with atherosclerotic lesions and metabolic disease such as obesity and type 2 diabetes is a great strength of our research group. In the last years our group has focused on expanding the repertoire of methodology that is important in this kind of research. We have now established several methods for inducing and monitoring atherosclerosis and metabolic disease in mouse models and also methods for ex vivo culturing of tissues and concomitant cell extractions.

Inflammation in atherosclerosis
We have studied the role of inflammatory mediators in development of atherosclerosis for many years. Together with Dr. Hanne Scholz we have now included IL-22 into our list of interleukins of particular interest.

Nonresolving inflammation is a major driver of atherosclerosis and metabolic disease and recent research has pointed to the lipid mediators, resolvins, as important players in the resolution of inflammation. We have found the resolving E1 (RvE1) receptors and an enzyme in the RvE1 biosynthesis to be upregulated in atherosclerotic plaques from the carotid artery. The consequence of this regulation is still an important issue of our research.

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 newest 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. Our project will include studies on transgenic mice with altered T cell function, as well as blood, adipose tissue and immune cells from patients with metabolic healthy and unhealthy obesity.

NAMPT and macrophage polarization
Our group was the first to link the protein Nicotinamid Phosphoribosyl transferase (NAMPT), a rate limited enzyme in generation of NAD, to atherosclerosis. Since our discovery ten years ago, we have continued working with this relationship. In the plaque, NAMPT is primarily located to lipid loaded macrophages and has been found to modulate lipid accumulation and inflammatory status in these cells. Recently it has become evident that macrophages are a diverse population of cells with different functions and effects. Based on our in vivo and in vitro findings we suggest that NAMPT could contribute to systemic and local plaque inflammation in atherosclerotic disorders, at least partly through effect on macrophages. Together with Dr. Arne Yndestad and his group we have established a common research platform to get further insight into the role of NAMPT in metabolic triggered inflammation.

Oxidative DNA damage and repair enzymes in atherosclerosis
The recent years, a main focus of the research group has been on oxidative DNA damage and 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 DNA is not counteracted, it may promote cellular damage and apoptosis within the atherosclerotic lesion leading to plaque instability. Using several transgenic mouse models, as well as cell lines and primary human cells and clinical material, we, in partnership with Prof Magnar Bjørås`s and his group (NTNU/UiO/OUS), seek to unravel the exact mechanisms through which these enzymes have impact on the development of atherosclerosis. Dr. Tonje Skarpengland was the first PhD student in our research group to defend her thesis on the role of DNA repair in atherogenesis, with the focus on the DNA glycosylase Neil3. Further studies on Neil3 will be our main research focus next 5 years.

SECTION OF INFLAMMATORY RESEARCH

Immunological and Molecular Mechanisms in Myocardial Remodeling and Heart Failure

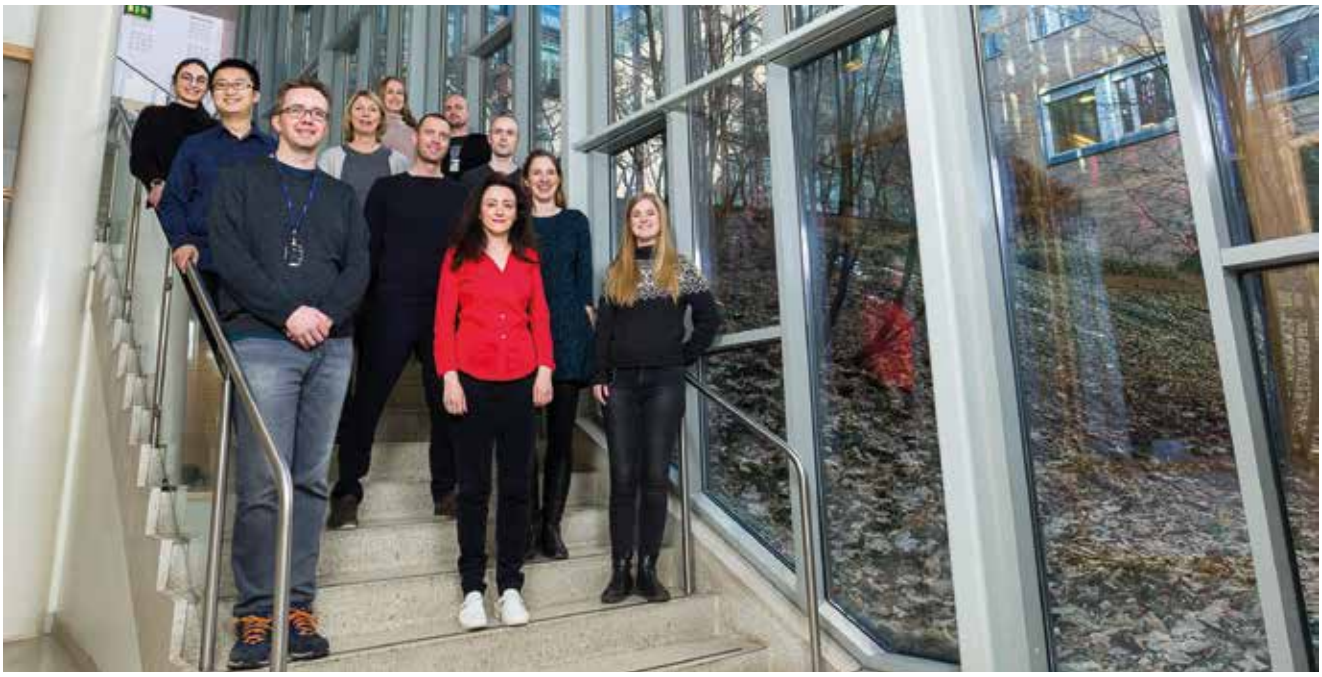


Photo: Øystein H. Horgmo, University of Oslo

From front left: Arne Yndestad, Azita Rashidi, Maria Belland Olsen, Kuan Yang, Jonas Øgaard, Mieke Louwe, Negar Shahini, Trine Ranheim, Øystein Sandanger, Alexandra Finsen and Knut Husø Lauritzen.

GROUP MEMBERS:

GROUP LEADER
Arne Yndestad, MSc.Pharm, PhD
arne.yndestad@rr-research.no

RESEARCHERS
Alexandra V. Finsen, MD, PhD
a.v.finsen@medisin.uio.no
Trine Ranheim, MSc, PhD
trine.ranheim@rr-research.no
Leif Erik Vinge, MD, PhD (associated)
l.e.vinge@medisin.uio.no
Erik Øie, MD, PhD (associated)
erik.oie@medisin.uio.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
staale.nymo@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
Katrine Alfsnes, MSc (Jan-March 2016)
katrine.alfsnes@rr-research.no
Azita Rashidi, BSc
arashid@ous-hf.no
Jonas Øgaard, BSc
jonas.ogaard@rr-research.no

RESEARCH PROFILE

Heart failure is a clinical syndrome caused by the heart's inability to maintain a blood flow that meets the body's requirements. Heart failure represents a major cause of cardiovascular, and also total, morbidity and mortality worldwide. The incidence and prevalence of this disorder is rising and the prognosis is poor. Our group has the ambitious objective to uncover novel mechanisms involved in myocardial infarction and development of heart failure that can form a basis for the development of new therapy with clinical benefit for the patient.

There are many causes of heart failure. Commonly heart failure develops as a consequence of a myocardial infarction or due to valvular heart disease or hypertension, that make the heart pump against increasing pressures. We use experimental mouse models to mimic these conditions and characterize pathogenic processes involved. Since myocardial infarction is a direct consequence of atherosclerosis, we have a growing interest in characterizing mechanisms involved in atherosclerotic plaque development and destabilization.

An increasing cause of heart failure is related to obesity and the metabolic syndrome leading to changes in the heart's ability to relax (i.e., diastolic dysfunction). Importantly, there is currently no effective treatment for these patients. We use a model of diet-induced obesity in mice to mimic the changes observed in obese patients developing diastolic heart failure. In addition to different mouse models of heart failure and atherosclerosis, our research approach includes in vitro studies in primary isolated cardiac myocytes, fibroblasts and macrophages, as well as clinical studies in well characterized patients with heart failure, examining samples from peripheral blood as well as tissue samples from the failing myocardium.

PROJECTS

A main interest of the research group is the study of how innate immune responses are involved in cardiovascular disease development. We focus on 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, we have projects where we investigate how the inflammasome is activated, (2) the role of the complement system in clinical and experimental heart failure, and (3) toll-like receptor 9, a receptor activated by bacterial DNA, but also mitochondrial DNA.

Currently, we are very interested in uncovering novel mechanisms for immune activation in cardiovascular disease. In these studies, we aim to elucidate how different forms of cellular stress and damage to DNA lead to mitochondrial dysfunction, how these induce inflammation and how these thereby promote development of cardiovascular disease. This work also includes the investigation of novel means of modulating inflammatory processes.

FUNDING

Our work in 2016 is based on funding from Helse Sør-Øst RHF, Research Council of Norway, Nasjonalforeningen for folkehelsen (the National Association for Public Health), UNIFOR-FRIMED, Anders Jahres fond til vitenskapens fremme, Eckbos Legat, Familien Blix fond for fremme av medisinsk forskning, Odd Fellow Medisinsk-Vitenskapelig Forskningsfond, and Freia Chocolade Fabriks Medisinske Fond.

In addition we are part of and receive funding through the K.G. Jebsen Inflammation Research Centre.

Photo: Øystein H. Horgmo, University of Oslo

SECTION OF INFLAMMATORY RESEARCH

Inflammatory Biomarkers in Cardiovascular and Metabolic Disease

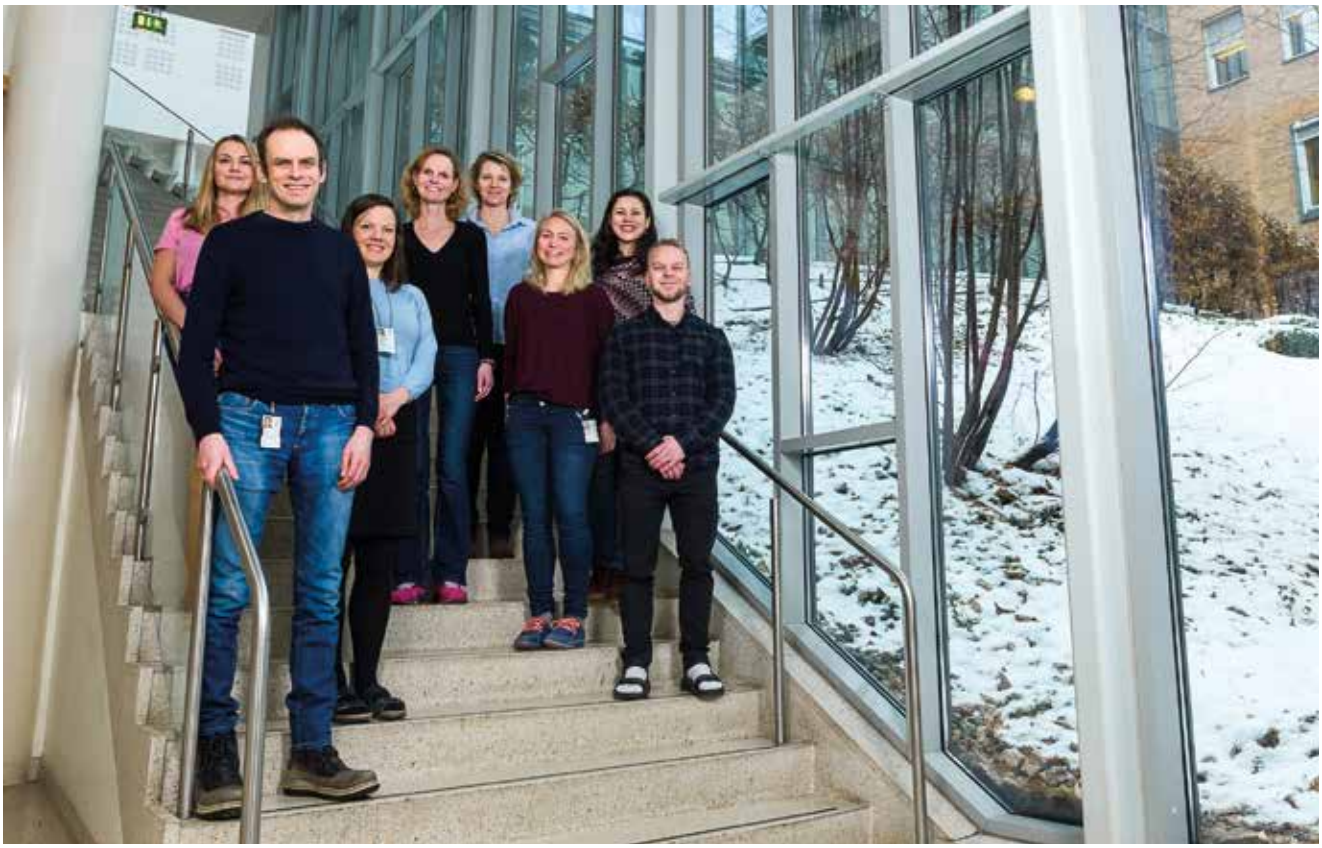


Photo: Kristin Ellefsen, University of Oslo

From left: Camilla Maria Falch, Thor Ueland, Kristin Astrid Beiland Øystese, Hilde M. Norum, Annika E. Michelsen , Kjersti R. Normann, Cristina Olarescu and Alexander Kirkeby Eieland

GROUP MEMBERS

GROUP LEADER
Thor Ueland, MSc, PhD
thor.ueland@rr-research.no

RESEARCHER
Annika Elisabeth Michelsen, MSc, PhD
annika.michelsen@rr-research.no

POST DOCS
Tove Lekva, MSc, PhD
tove.lekva@rr-research.no
Cristina Olarescu, MD, PhD
nicola@ous-hf.no

PHD STUDENTS
Hilde Margrethe Norum, MD
hildenorum@yahoo.com
Aurelija Abraityte, Msc
Aurelija.abraityte@rr-research.no
Kristin Astrid Beiland Øystese, MD
kroeys@ous-hf.no

MEDICAL STUDENT RESEARCHERS
Fizza Arain
fizara@ous-hf.no
Camilla Maria Falch
camfal@ous-hf.no

ENGINEERS
Alexander Kirkeby Eieland, BSc
aleeie@ous-hf.no
Kjersti R. Normann, BSc
kjnorm@ous-hf.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 be 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 endocrine group focuses on the molecular characterization of non-functioning pituitary adenomas with the objective to find biomarkers for growth that can be used for follow-up. Some of these tumors express hormones without secreting them and our aim is to characterize what factors determine this lack of secretion.

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

We have a close collaboration with the department of cardiology and analyzing 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). We also have a tight 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 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 have strong collaborations with other clinical research, national and international.

Photo: Øystein H. Horgmo, University of Oslo

Hilde Norum and Annika Michelsen discussing in the lab.

SECTION OF THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY

Haemostasis and Bleeding Disorders

Photo: Øystein H. Horgmo, University of Oslo

From left: Ragnhild J. Måseide, Pål André Holme, Stine Bjørnsen, Nina Haagenrud Schultz, Adelheid Holm and Christian Qvigstad

GROUP MEMBERS

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

RESEARCH PROFILE

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 1250 persons with bleeding disorders. Several research projects are ongoing besides clinical activity.

Age related comorbidities 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, 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. First publication from the cross sectional study was recently published (Haemophilia 2016; 22:228-255) and now further followed up in the longitudinal prospective study. Christian Qvigstad is working as a PhD student on this project.

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 effects are 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. Two papers from this project have been submitted for publication.

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. 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 and individual variability when it comes to 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.

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 coordinating the study.

Immune thrombocytopenia
Parts of the group is also involved in studies on immune thrombocytopenia ITP and we published a paper where 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. (The RITP trial) (Lancet 2015; 385: 1653–61).
The follow up study PROLONG a prospective randomized study has been initiated to evaluate the long-term effect of rituximab and immunological changes. The study also includes a PhD project on the immunological aspects - candidate to be appointed.

In addition the group also participates in several other international and Nordic investigator initiated research projects on bleeding related disorders.

SECTION OF THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY

Coagulation Factors: Role In The Development of Thrombosis, Inflammation and Cancer

Photo: Kristin Ellefsen, University of Oslo

In front-from left: Christiane Filion Myklebust, Marie-Christine Mowinckel, Grethe Skretting, Maria Eugenia Chollet and Benedicte Stavik.
Back- from left: Huda Omar Ali, Sandra Espada Serrano, Elisabeth Andersen, Marianne S. Andresen, Xue-Yan Cui and Ann Døli.

GROUP MEMBERS

GROUP LEADER:
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
Sandra Espada Serrano, MSc, PhD
s.e.serrano@medisin.uio.no

PHD STUDENTS
Huda Omar Ali, MSc, PhD
huda.o.ali@googlemail.com
Elisabeth Andersen, MSc
elisabeth.andersen@medisin.uio.no

SENIOR 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

RESEARCH PROFILE

Coagulation factors and their inhibitors are important regulators of coagulation activation, and deficiencies in any of these alter the threshold for activation of coagulation and increase the risk of thrombosis. Some may also influence inflammatory pathways, and thus play an important role in

the development of atherosclerosis. Finally, considerable evidence now suggests that certain coagulation factors and inhibitors also play a role in cell proliferation, apoptosis and angiogenesis indicating a role in cancer development.

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. During 2016, one of our post-docs was on maternity leave from January until mid-September. The first half of 2016, a scientist from the University in Ferrara, Italy, worked in our group.

MAIN PROJECTS:

-Estrogens and coagulation inhibitors
We are focusing on the effect of estrogens on TFPI and its homologue TFPI-2. The majority of human breast cancers are estrogen dependent and the cancer cells express the estrogen receptor (ER). Using breast cancer cell lines, we demonstrated that estrogens downregulate TFPI expression in a process dependent on the presence of ERα. This was partly due to binding of ERα to specific elements in the 5' flanking region of the TFPI gene. In collaboration with a research group in Murcia, Spain, we revealed that in addition to this, microRNAs participate in the estrogenic regulation of the TFPI expression. 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. Methylation of the TFPI-2 gene promoter is associated with reduced transcription of the gene. The methylation process is regulated by DNA methyltransferases whose expression is controlled through methylation/demethylation of lysine residues by a specific methylase and a specific demethylase. We found that estrogens induced the TFPI-2 expression in ER positive breast cancer cells in a process mediated by ERα and the specific lysine demethylase.

-Hypoxia and TFPI
Hypoxia is a hallmark of several pathophysiological conditions including cancer, atherosclerosis and ischemic cardiovascular disease, conditions characterized by activation of coagulation and increased risk of thromboembolism. We have investigated the role of hypoxia in the regulation of the TFPI expression in breast cancer cells. Both hypoxia and overexpression of the hypoxia inducible factor (HIF)-1α caused downregulation of TFPI expression. This was caused by binding of HIF-1α to DNA within the TFPI promoter. In tissue samples from breast cancer patients, gene expression analyses showed a positive correlation between the mRNA levels of TFPI and HIF-1α. This study suggests that a hypoxic microenvironment inside a breast tumor may induce a procoagulant state in breast cancer patients. Similar results have been obtained for another factor that mediates the cellular response to hypoxia, namely HIF-2α.

Hypoxia is also evident in advanced atherosclerotic plaques. The extrinsic coagulation activator TF and its inhibitor TFPI are expressed by endothelial cells overlaying the plaques. Plaque rupture leads to activation of coagulation and the formation of a thrombus, which is the main contributor to acute manifestations, morbidity, and mortality in atherosclerotic disease. We used endothelial cells to investigate the impact of hypoxia on TF and TFPI expression. Hypoxic conditions resulted in increased TF and reduced TFPI levels accompanied by increased pro-coagulant activity of the endothelial cells, a situation that might promote atherogenesis in addition to clinical events and thus the severity of atherosclerotic disorders.

-Atherothrombosis and TFPI
In this project we want to examine whether TFPI might represent a novel therapeutic target in atherosclerosis related cardiovascular disease (CVD). We have available carotid plaque material removed from patients during surgery and control carotids. Elevated levels of TFPI have been found in human atherosclerotic plaques, but it is not known which

isoform of TFPI is important and what regulates TFPI levels in the atherosclerotic plaque. We found that both TFPI isoforms were upregulated in the plaques with TFPIα as the major isoform. In polarized human macrophages, TFPI mRNA levels were elevated in M2 compared to M1 and the procoagulant activity was decreased. TFPI was present in early foam cell formation and treatment with the atherogenic inducer cholesterol crystals (CCs) increased TFPI mRNA levels even further in M2 macrophages. So far, our data indicate that both isoforms of TFPI are present in advanced plaques and that the anti-inflammatory M2 macrophages may be a potential source of TFPI. We have also investigated the potential role of endoplasmic reticulum (ER) stress and the function of TFPI in cells treated and the results suggest that the presence of TFPI in the plaques might be a mechanism to protect against ER stress with CCs. The project is a collaboration between our group and the group of Halvorsen at RIIM.

-TFPI and migration of leukemia stem cells

Acute myeloid leukemia (AML) is the most prevalent acute leukemia in adult age. It is a disease with a poor outcome, mainly due to disease relapse which most likely is caused by the inability to eliminate leukemia stem cells (LSCs) with conventional therapies. A key factor of LSCs maintenance is the protective role of the bone marrow (BM) microenvironment. TFPI can inhibit dipeptidyl peptidase-4 (CD26). This inhibition enhances the chemotactic activity of the chemokine and suppresses the spread of leukemia suggesting that TFPI could play a role in migration of LSCs and thereby affect the spread. In this project we will map the expression of TFPI isoforms, LSC markers and adhesion related factors in the AML patients. We will study the migration of LSCs in vivo in mice models. Since there is an increased need for new methods which eliminate the LSCs hidden in the BM microenvironment, the results from this study may lead to innovations and create novel and unique therapeutic targets for treatment of leukemia.

-FVII deficiency

FVII deficiencies are caused by reduced circulating protein levels resulting from a broad spectrum of gene mutations. In collaboration with a research group in Ferrara, Italy, and several groups at the University of Oslo, we are investigating the intracellular fate of a group of FVII mutations previously reported, in order to elucidate the cellular mechanisms implicated in these mutations. Patients with these mutations have bleedings and the present treatment is replacement therapy, which has several limitations. 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 strongly indicate that the FVII mutant proteins evoke ER stress when overexpressed in cells and that UPR is activated. By these studies we hope to envisage possible therapeutic approaches that can substitute the present replacement therapy.

Photo: Øystein H. Horgmo, University of Oslo

AWARDS

Oslo University Hospital's Award for outstanding article 2nd half of 2015 was recieved by Johannes Hov and Mette Vesterhus for the article "Enhanced liver Fibrosis Score Predicts Transplant-Free Survival in Primary Sclerosing Cholangitis"

The annual meeting of the Norwegian Gastroenteorological Society in February 2016 awarded Laura Valestrand with a price for the best experimental work.

In May 2016 Pål Aukrust received Oslo University Hospital's Excellent Researcher Award for his research work in in several fields and lately within inflammation and immunological mechanisms. In the same hospital event Espen Melum received the high ranking Early Career Award for his research on processes that regulate inflammation in the bile ducts.

At Conference on Molecular Mechanisms of Inflammation, Trondheim, June 2016, Mieke Louwe received the Price for best oral abstract presentation:, "NLRP3 aggravates survival, but not cardiac remodeling after myocardial infarction in mice".

Johannes Hov and Marius Trøseid received "Stabsmøteprisen på Rikshospitalet" a price for best lecture during hospital Grand rounds for spring 2016, for a lecture on the gut microbiome and personalized medicine.

American Heart Association Scientific Sessions, Orlando, November 2016 awarded Mieke Louwe with a International travel award for the presentation: "Absence of the NLRP3 Inflammasome Improves Survival but Not Cardiac Remodeling Following Myocardial Infarction".

Photo: Oslo University Hospital

Pål Aukrust receiving Oslo University Hospital's prestigious Excellent Researcher Award for 2016, surrounded by Therese Seiersted and Espen Melum who both received Early Career Awards.

Publications 2016

1. *Christensen JJ, Osnes L, Halvorsen B, Retterstøl K, Bogsrud MP, Wium C, Svilaas A, Narverud I, Ulven SM, Aukrust P, Holven KB (2016)*
Data on circulating leukocyte subpopulations and inflammatory proteins in children with familial hypercholesterolemia and healthy children
Data Brief, 10, 587-592

2. *Hov JR, Kummen M (2016)*
Intestinal microbiota in primary sclerosing cholangitis
Curr Opin Gastroenterol 33 (2), 85-92

3. *Ji SG, Juran BD, Mucha S, Folseraas T, Jostins L, Melum E, Kumasaka N, Atkinson EJ, Schlicht EM, Liu JZ, Shah T, Gutierrez-Achury J, Boberg KM, Bergquist A, Vermeire S, Eksteen B, Durie PR, Farkkila M, Müller T, Schramm C, Sterneck M, Weismüller TJ, Gotthardt DN, Ellinghaus D, Braun F, Teufel A, Laudes M, Lieb W, Jacobs G, Beuers U, Weersma RK, Wijmenga C, Marschall HU, Milkiewicz P, Pares A, Kontula K, Chazouillères O, Invernizzi P, Goode E, Spiess K, Moore C, Sambrook J, Ouwehand WH, Roberts DJ, Danesh J, Floreani A, Gulamhusein AF, Eaton JE, Schreiber S, Coltescu C, Bowlus CL, Luketic VA, Odin JA, Chopra KB, Kowdley KV, Chalasani N, Manns MP, Srivastava B, Mells G, Sandford RN, Alexander G, Gaffney DJ, Chapman RW, Hirschfield GM, de Andrade M; UK-PSC Consortium; International IBD Genetics Consortium; International PSC Study Group, Rushbrook SM, Franke A, Karlsen TH, Lazaridis KN, Anderson CA (2016)*
Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease
Nat Genet 49 (2), 269-273

4. *Malenicka S, Ericzon BG, Jørgensen MH, Isoniemi H, Karlsen TH, Krantz M, Naeser V, Olausson M, Rasmussen A, Rönnholm K, Sanengen T, Scholz T, Fischler B, Nemeth A (2016)*
Impaired intention-to-treat survival after listing for liver transplantation in children with biliary atresia compared to other chronic liver diseases: 20 years' experience from the Nordic countries
Pediatr Transplant 21 (2)

5. *Jørgensen SF, Macpherson ME, Bjøro K, Karlsen TH, Reims HM, Grzyb K, Fosby B, Fevang B, Aukrust P, Nordøy I (2016)*
Liver transplantation in patients with primary antibody deficiency
J Allergy Clin Immunol 6749 (16), 31431-2

6. *Kiani AN, Aukrust P, Ueland T, Hollan I, Barr E, Magder LS, Petri M (2016)*
Serum osteoprotegrin (OPG) in subclinical atherosclerosis in systemic lupus erythematosus
Lupus (in press) (Epub ahead of print)

7. *Taraldsrud E, Aukrust P, Jørgensen S, Lingjærde OC, Olweus J, Myklebust JH, Fevang B (2016)*
Patterns of constitutively phosphorylated kinases in B cells are associated with disease severity in common variable immunodeficiency
Clin Immunol, 175, 69-74

8. *Vesterhus M, Melum E (2016)*
Prognostic biomarkers and surrogate end points in PSC
Liver Int, 36 (12), 1748-1751

9. *Christensen JJ, Osnes LT, Halvorsen B, Retterstøl K, Bogsrud MP, Wium C, Svilaas A, Narverud I, Ulven SM, Aukrust P, Holven KB (2016)*
Altered leukocyte distribution under hypercholesterolemia: A cross-sectional study in children with familial hypercholesterolemia
Atherosclerosis, 256, 67-74

10. *Maroni L, Agostinelli L, Saccomanno S, Pinto C, Giordano DM, Rychlicki C, De Minicis S, Trozzi L, Banales JM, Melum E, Karlsen TH, Benedetti A, Baroni GS, Marzioni M (2016)*
Nlrp3 Activation Induces Il-18 Synthesis and Affects the Epithelial Barrier Function in Reactive Cholangiocytes
Am J Pathol, 187 (2), 366-376

11. *Lunde NN, Holm S, Dahl TB, Elyouncha I, Sporsheim B, Gregersen I, Abbas A, Skjelland M, Espevik T, Solberg R, Johansen HT, Halvorsen B (2016)*
Increased levels of legumain in plasma and plaques from patients with carotid atherosclerosis
Atherosclerosis 257, 216-223

12. *Sokolova M, Vinge LE, Alfsnes K, Olsen MB, Eide L, Kaasbøll OJ, Attramadal H, Torp MK, Fosshaug LE, Rashidi A, Lien E, Finsen AV, Sandanger Ø, Aukrust P, Ranheim T, Yndestad A (2016)*

Palmitate promotes inflammatory responses and cellular senescence in cardiac fibroblasts
Biochim Biophys Acta, 1862 (2), 234-245

13. *Eide IA, Åsberg A, Svensson M, Ueland T, Mollnes TE, Hartmann A, Bjerve KS, Michelsen A, Aukrust P, Christensen JH, Schmidt EB, Jenssen T (2016)*
Plasma Levels of Marine n-3 Fatty Acids Are Inversely Correlated With Proinflammatory Markers sTNFR1 and IL-6 in Renal Transplant Recipients
J Ren Nutr 2276(16)30141-8

14. *Tavoly M, Utne KK, Jelsness-Jørgensen LP, Wik HS, Klok FA, Sandset PM, Ghanima W (2016)*
Health-related quality of life after pulmonary embolism: a cross-sectional study
BMJ Open, 6 (11), e013086

15. *Chung BK, Guevel BT, Reynolds GM, Gupta Udatha DB, Henriksen EK, Stamataki Z, Hirschfield GM, Karlsen TH, Liaskou E (2016)*
Phenotyping and auto-antibody production by liver-infiltrating B cells in primary sclerosing cholangitis and primary biliary cholangitis
J Autoimmun, 77, 45-54

16. *Melleby AO, Strand ME, Romaine A, Herum KM, Skrbic B, Dahl CP, Sjaastad I, Fiane AE, Filmus J, Christensen G, Lunde IG (2016)*
The Heparan Sulfate Proteoglycan Glypican-6 Is Upregulated in the Failing Heart, and Regulates Cardiomyocyte Growth through ERK1/2 Signaling
PLoS One, 11 (10), e0165079

17. *Wang J, Thingholm LB, Skiecevičienė J, Rausch P, Kummen M, Hov JR, Degenhardt F, Heinsen FA, Rühlemann MC, Szymczak S, Holm K, Esko T, Sun J, Pricop-Jeckstadt M, Al-Dury S, Bohov P, Bethune J, Sommer F, Ellinghaus D, Berge RK, Hübenthal M, Koch M, Schwarz K, Rimbach G, Hübbe P et al. (2016)*
Genome-wide association analysis identifies variation in vitamin D receptor and other host factors influencing the gut microbiota
Nat Genet, 48 (11), 1396-1406

18. *Santilli F, Liani R, Di Fulvio P, Formoso G, Simeone P, Tripaldi R, Ueland T, Aukrust P, Davì G (2016)*
Increased circulating resistin is associated with insulin resistance, oxidative stress and platelet activation in type 2 diabetes mellitus
Thromb Haemost, 116 (6), 1089-1099

19. *Schrumpf E, Kummen M, Valestrand L, Greiner TU, Holm K, Arulampalam V, Reims HM, Baines J, Bäckhed F, Karlsen TH, Blumberg RS, Hov JR, Melum E (2016)*
The gut microbiota contributes to a mouse model of spontaneous bile duct inflammation
J Hepatol, 66 (2), 382-389

20. *Stiksrud B, Lorvik KB, Kvale D, Mollnes TE, Ueland PM, Trøseid M, Taskén K, Dyrhol-Riise AM (2016)*
Plasma IP-10 Is Increased in Immunological NonResponders and Associated With Activated Regulatory T Cells and Persisting Low CD4 Counts
J Acquir Immune Defic Syndr, 73 (2), 138-48

21. *Niyonzima N, Halvorsen B, Sporsheim B, Garred P, Aukrust P, Mollnes TE, Espevik T (2016)*
Complement activation by cholesterol crystals triggers a subsequent cytokine response
Mol Immunol 84:43-50

22. *Pihlstrøm HK, Mjøen G, Mucha S, Haraldsen G, Franke A, Jardine A, Fellström B, Holdaas H, Melum E (2016)*
Single Nucleotide Polymorphisms and Long-Term Clinical Outcome in Renal Transplant Patients: A Validation Study
Am J Transplant, 17 (2), 528-533

23. *Henriksen EK, Jørgensen KK, Kaveh F, Holm K, Hamm D, Olweus J, Melum E, Chung BK, Eide TJ, Lundin KE, Boberg KM, Karlsen TH, Hirschfield GM, Liaskou E (2016)*
Gut and liver T-cells of common clonal origin in primary sclerosing cholangitis-inflammatory bowel disease
J Hepatol, 66 (1), 116-122

24. *Sorte HS, Osnes LT, Fevang B, Aukrust P, Erichsen HC, Backe PH, Abrahamsen TG, Kittang OB, Øverland T, Jhangiani SN, Muzny DM, Vigeland MD, Samarakoon P, Gambin T, Akdemir ZH, Gibbs RA, Rødningen OK, Lyle R, Lupski JR, Stray-Pedersen A (2016)*
A potential founder variant in CARMIL2/RLTPR in three Norwegian families with warts, molluscum contagiosum, and T-cell dysfunction
Mol Genet Genomic Med, 4 (6), 604-616

25. *Christensen JJ, Retterstøl K, Godang K, Roland MC, Qvigstad E, Bollerslev J, Ueland T, Henriksen T, Holven KB (2016)*
LDL cholesterol in early pregnancy and offspring cardiovascular disease risk factors
J Clin Lipidol, 10 (6), 1369-1378.e7

26. *Narverud I, Myhrstad MC, Herzig KH, Karhu T, Dahl TB, Halvorsen B, Ulven SM, Holven KB (2016)*
Lack of Effects of a Single High-Fat Meal Enriched with Vegetable n-3 or a Combination of Vegetable and Marine n-3 Fatty Acids on Intestinal Peptide Release and Adipokines in Healthy Female Subjects
Front Nutr, 3, 38

27. *Hov JR, Boberg KM, Taraldsrud E, Vesterhus M, Boyadzhieva M, Solberg IC, Schrumpf E, Vatn MH, Lie BA, Molberg Ø, Karlsen TH (2016)*
Antineutrophil antibodies define clinical and genetic subgroups in primary sclerosing cholangitis
Liver Int 37 (3), 458-465

28. *Normann KR, Øystese KA, Berg JP, Lekva T, Berg-Johnsen J, Bollerslev J, Olarescu NC (2016)*
Selection and validation of reliable reference genes for RT-qPCR analysis in a large cohort of pituitary adenomas
Mol Cell Endocrinol, 437, 183-189

29. *Jørgensen SF, Reims HM, Frydenlund D, Holm K, Paulsen V, Michelsen AE, Jørgensen KK, Osnes LT, Bratlie J, Eide TJ, Dahl CP, Holter E, Tronstad RR, Hanevik K, Brattbakk HR, Kaveh F, Fiskerstrand T, Kran AB, Ueland T, Karlsen TH, Aukrust P, Lundin KE, Fevang B (2016)*
A Cross-Sectional Study of the Prevalence of Gastrointestinal Symptoms and Pathology in Patients With Common Variable Immunodeficiency
Am J Gastroenterol, 111 (10), 1467-1475

30. *Tinholt M, Sandset PM, Mowinckel MC, Garred Ø, Sahlberg KK, Kristensen VN, Børresen-Dale AL, Jacobsen AF, Skretting G, Iversen N (2016)*
Determinants of acquired activated protein C resistance and D-dimer in breast cancer
Thromb Res, 145, 78-83

31. *Garabet L, Gilboe IM, Mowinckel MC, Jacobsen AF, Mollnes TE, Sandset PM, Jacobsen EM (2016)*
Antiphospholipid Antibodies are Associated with Low Levels of Complement C3 and C4 in Patients with Systemic Lupus Erythematosus
Scand J Immunol, 84 (2), 95-9

32. *Knudsen A, Christensen TE, Thorsteinsson K, Ghotbi AA, Hasbak P, Lebech AM, Nielsen SD, Hov JR, Berge R, Ripa RS, Kjær A, Trøseid M (2016)*
Microbiota-Dependent Marker TMAO is Not Associated With Decreased Myocardial Perfusion in Well-Treated HIV-Infected Patients as Assessed by 82Rubidium PET/CT
J Acquir Immune Defic Syndr, 72 (4), e83-5

33. *Siljan WW, Holter JC, Nymo SH, Schjalm C, Müller F, Jenum PA, Husebye E, Ueland T, Aukrust P, Mollnes TE, Heggelund L (2016)*
Circulating cell-free DNA is elevated in community-acquired bacterial pneumonia and predicts short-term outcome
J Infect, 73 (4), 383-6

34. *Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, Erichsen HC, Forbes LR, Gu S, Yuan B, Jhangiani SN, Muzny DM, Rødningen OK, Sheng Y, Nicholas SK, Noroski LM, Seeborg FO, Davis CM, Canter DL, Mace EM, Vece TJ, Allen CE, Abhyankar HA, Boone PM, Beck CR, Wiszniewski W, Fevang B, Aukrust P, Tjønnfjord GE, Gedde-Dahl T, Hjorth-Hansen H, Dybedal I, Nordøy I, Jørgensen SF, Abrahamsen TG, Øverland T, Bechensteen AG, Skogen V, Osnes LT, Kulseth MA, Prescott TE, Rustad CF, Heimdal KR, Belmont JW, Rider NL, Chinen J, Cao TN, Smith EA, Caldirola MS, Bezrodnik L, Lugo Reyes SO, Espinosa Rosales FJ, Guerrero-Cursaru ND, Pedroza LA, Poli CM, Franco JL, Trujillo Vargas CM, Aldave Becerra JC, Wright N, Issekutz TB, Issekutz AC, Abbott J, Caldwell JW, Bayer DK, Chan AY, Aiuti A, Cancrini C, Holmberg E, West C, Burstedt M, Karaca E, Yesil G, Artac H, Bayram Y, Atik MM, Eldomery MK, Ehlayel MS, Jolles S, Flatø B, Bertuch AA, Hanson IC, Zhang VW, Wong LJ, Hu J, Walkiewicz M, Yang Y, Eng CM, Boerwinkle E, Gibbs RA, Shearer WT, Lyle R, Orange JS, Lupski JR(2016)*
Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders
J Allergy Clin Immunol, 139 (1), 232-245

35. *Halvorsen B, Santilli F, Scholz H, Sahraoui A, Gulseth HL, Wium C, Lattanzio S, Formoso G, Di Fulvio P, Otterdal K, Retterstøl K, Holven KB, Gregersen I, Stavik B, Bjerkeli V, Michelsen AE, Ueland T, Liani R, Davi G, Aukrust P (2016)*
LIGHT/TNFSF14 is increased in patients with type 2 diabetes mellitus and promotes islet cell dysfunction and endothelial cell inflammation in vitro
Diabetologia, 59 (10), 2134-44

36. *Arain F, Gullestad L, Nymo S, Kjekshus J, Cleland JG, Michelsen A, McMurray JJ, Wikstrand J, Aukrust P, Ueland T (2016)*
Low YKL-40 in chronic heart failure may predict beneficial effects of statins: analysis from the controlled rosuvastatin multinational trial in heart failure (CORONA)
Biomarkers, 12, 1-7

37. *Jendrek ST, Gotthardt D, Nitzsche T, Widmann L, Korf T, Michaels MA, Weiss KH, Liaskou E, Vesterhus M, Karlsen TH, Mindorf S, Schemmer P, Bär F, Teegen B, Schröder T, Ehlers M, Hammers CM, Komorowski L, Lehnert H, Fellermann K, Derer S, Hov JR, Sina C (2016)*
Anti-GP2 IgA autoantibodies are associated with poor survival and cholangiocarcinoma in primary sclerosing cholangitis
Gut, 66 (1), 137-144

38. *Karlsen TH (2016)*
Primary sclerosing cholangitis: 50 years of a gut-liver relationship and still no love?
Gut, 65 (10), 1579-81

39. *Lekva T, Lyle R, Roland MC, Friis C, Bianchi DW, Jaffe IZ, Norwitz ER, Bollerslev J, Henriksen T, Ueland T (2016)*
Gene expression in term placentas is regulated more by spinal or epidural anesthesia than by late-onset preeclampsia or gestational diabetes mellitus
Sci Rep, 6, 29715

40. *Skarpengland T, Dahl TB, Skjelland M, Scheffler K, de Sousa MM, Gregersen I, Kuśnierczyk A, Sharma A, Slupphaug G, Eide L, Segers FM, Skagen KR, Dahl CP, Russell D, Folkersen L, Krohg-Sørensen K, Holm S, Bjørås M, Aukrust P, Halvorsen B (2016)*
Enhanced base excision repair capacity in carotid atherosclerosis may protect nuclear DNA but not mitochondrial DNA
Free Radic Biol Med, 97, 386-97

41. *Holter JC, Ueland T, Norseth J, Brunborg C, Frøland SS, Husebye E, Aukrust P, Heggelund L (2016)*
Vitamin D Status and Long-Term Mortality in Community-Acquired Pneumonia: Secondary Data Analysis from a Prospective Cohort
PLoS One, 11 (7), e0158536

42. *Dhondup Y, Ueland T, Dahl CP, Askevold ET, Sandanger Ø, Fiane A, Ohm IK, Sjaastad I, Finsen AV, Wæhre A, Gullestad L, Aukrust P, Yndestad A, Vinge LE (2016)*
Low Circulating Levels of Mitochondrial and High Levels of Nuclear DNA Predict Mortality in Chronic Heart Failure
J Card Fail, 22 (10), 823-8

43. *Skarpengland T, Holm S, Scheffler K, Gregersen I, Dahl TB, Suganthan R, Segers FM, Østlie I, Otten JJ, Luna L, Ketelhuth DF, Lundberg AM, Neurauter CG, Hildrestrand G, Skjelland M, Bjørndal B, Svardal AM, Iversen PO, Hedin U, Nygård S, Olstad OK, Krohg-Sørensen K, Slupphaug G, Eide L, Kuśnierczyk A, Folkersen L, Ueland T, Berge RK, Hansson GK, Biessen EA, Halvorsen B, Bjørås M, Aukrust P (2016)*
Neil3-dependent base excision repair regulates lipid metabolism and prevents atherosclerosis in Apoe-deficient mice
Sci Rep, 6, 28337

44. *Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, Viktil E, Henriksen M, Hovde Ø, Huppertz-Hauss G, Høie O, Høivik ML, Monstad I, Solberg IC, Jahnsen J, Karlsen TH, Moum B, Vatn M, Negård A (2016)*
Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease
Gastroenterology, 151 (4), 660-669.e4

45. *Tiscia GL, Dørum E, Myklebust CF, Grandone E, Sandset PM, Skretting G (2016)*
Functional characterization of annexin A5 gene promoter allelic variants
Thromb Res, 144, 93-9

46. *Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, McEvoy LK, Witoelar A, Chen CH, Holland D, Brewer JB, Franke A, Dillon WP, Wilson DM, Mukherjee P, Hess CP, Miller Z, Bonham LW, Shen J, Rabinovici GD, Rosen HJ, Miller BL, Hyman BT, Schellenberg GD, Karlsen TH, Andreassen OA, Dale AM, Desikan RS; Alzheimer's Disease Neuroimaging Initiative (2016)*
Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease
JAMA Neurol, 73 (6), 691-7

47. *Ahmed A, Hollan I, Curran SA, Kitson SM, Riggio MP, Mikkelsen K, Almdahl SM, Aukrust P, McInnes IB, Goodyear CS (2016)*
Brief Report: Proatherogenic Cytokine Microenvironment in the Aortic Adventitia of Patients With Rheumatoid Arthritis
Arthritis Rheumatol, 68 (6), 1361-6

48. *Otterdal K, Portillo A, Astrup E, Ludviksen JK, Schjalm C, Raoult D, Olano JP, Halvorsen B, Oteo JA, Aukrust P, Mollnes TE, Nilsson PH (2016)*
Rickettsia conorii is a potent complement activator in vivo and combined inhibition of complement and CD14 is required for attenuation of the cytokine response ex vivo
Clin Microbiol Infect, 22 (8), 734.e1-6

49. *Paramel Varghese G, Folkersen L, Strawbridge RJ, Halvorsen B, Yndestad A, Ranheim T, Krohg-Sørensen K, Skjelland M, Espevik T, Aukrust P, Lengquist M, Hedin U, Jansson JH, Fransén K, Hansson GK, Eriksson P, Sirsjö A (2016)*
NLRP3 Inflammasome Expression and Activation in Human Atherosclerosis
J Am Heart Assoc, 5 (5)

50. *Palm Ø, Ueland T, Garen T, Michelsen AE, Reiseter S, Aukrust P, Aaløkken TM, Molberg Ø (2016)*
Endostatin is higher and associated with pulmonary involvement in primary Sjögren's syndrome
Clin Exp Rheumatol, 34 (4), 690-3

51. *Husebø GR, Bakke PS, Grønseth R, Hardie JA, Ueland T, Aukrust P, Eagan TM (2016)*

Macrophage migration inhibitory factor, a role in COPD
Am J Physiol Lung Cell Mol Physiol, 311 (1), L1-7

52. *Bernuzzi F, Marabita F, Lleo A, Carbone M, Mirolo M, Marzioni M, Alpini G, Alvaro D, Boberg KM, Locati M, Torzilli G, Rimassa L, Piscaglia F, He XS, Bowlus CL, Yang GX, Gershwin ME, Invernizzi P (2016)*
Serum microRNAs as novel biomarkers for primary sclerosing cholangitis and cholangiocarcinoma
Clin Exp Immunol, 185 (1), 61-71

53. *Pilely K, Rosbjerg A, Genster N, Gal P, Pál G, Halvorsen B, Holm S, Aukrust P, Bakke SS, Sporsheim B, Nervik I, Niyonzima N, Bartels ED, Stahl GL, Mollnes TE, Espevik T, Garred P (2016)*
Cholesterol Crystals Activate the Lectin Complement Pathway via Ficolin-2 and Mannose-Binding Lectin: Implications for the Progression of Atherosclerosis
J Immunol, 196 (12), 5064-74

54. *Otterdal K, Portillo A, Astrup E, Ludviksen J, Davì G, Holm S, Santilli F, Vitale G, Raoult D, Olano JP, Schjalm C, Halvorsen B, Oteo JA, Mollnes TE, Aukrust P, Nilsson PH (2016)*
High serum CXCL10 in Rickettsia conorii infection is endothelial cell mediated subsequent to whole blood activation
Cytokine, 83, 269-74

55. *Kleveland O, Kunszt G, Bratlie M, Ueland T, Broch K, Holte E, Michelsen AE, Bendz B, Amundsen BH, Espevik T, Aakhus S, Damås JK, Aukrust P, Wiseth R, Gullestad L (2016)*
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
Eur Heart J, 37 (30), 2406-13

56. *Ali HO, Arroyo AB, González-Conejero R, Stavik B, Iversen N, Sandset PM, Martínez C, Skretting G (2016)*
The role of microRNA-27a/b and microRNA-494 in estrogen-mediated downregulation of tissue factor pathway inhibitor α
J Thromb Haemost, 14 (6), 1226-37

57. *Barratt-Due A, Fløisand Y, Orrem HL, Kvam AK, Holme PA, Bergseth G, Tjønnfjord GE, Mollnes TE (2016)*
Complement activation is a crucial pathogenic factor in catastrophic antiphospholipid syndrome
Rheumatology (Oxford), 55 (7), 1337-9

58. *Tinholt M, Sandset PM, Iversen N (2016)*
Polymorphisms of the coagulation system and risk of cancer
Thromb Res, 140 Suppl 1, S49-54

59. *Hestad KA, Engedal K, Whist JE, Aukrust P, Farup PG, Mollnes TE, Ueland T (2016)*
Patients with depression display cytokine levels in serum and cerebrospinal fluid similar to patients with diffuse neurological symptoms without a defined diagnosis
Neuropsychiatr Dis Treat, 12, 817-22

60. *Norum HM, Kolberg ES, Solhaug V, Nordal K, Aukrust P (2016)*
Rhabdomyolysis and capillary leak syndrome in a patient treated with topical imiquimod
Int J Dermatol, 55 (9), 1030-2

61. *Zimmer S, Grebe A, Bakke SS, Bode N, Halvorsen B, Ulas T, Skjelland M, De Nardo D, Labzin LI, Kerksiek A, Hempel C, Heneka MT, Hawxhurst V, Fitzgerald ML, Trebicka J, Björkhem I, Gustafsson JÅ, Westerterp M, Tall AR, Wright SD, Espevik T, Schultze JL, Nickenig G, Lütjohann D, Latz E (2016)*
Cyclodextrin promotes atherosclerosis regression via macrophage reprogramming
Sci Transl Med, 8 (333), 333ra50

62. *Sikkeland LI, Johnsen HL, Riste TB, Alexis NE, Halvorsen B, Søyseth V, Kongerud J (2016)*
Sputum neutrophils are elevated in smelter workers, and systemic neutrophils are associated with rapid decline in FEV1
Occup Environ Med, 73 (7), 459-66

63. *Lekva T, Norwitz ER, Aukrust P, Ueland T (2016)*
Impact of Systemic Inflammation on the Progression of Gestational Diabetes Mellitus
Curr Diab Rep, 16 (4), 26

64. *Ali HO, Stavik B, Myklebust CF, Andersen E, Dahm AE, Iversen N, Sandset PM, Skretting G (2016)*
Oestrogens Downregulate Tissue Factor Pathway Inhibitor through Oestrogen Response Elements in the 5'-Flanking Region
PLoS One, 11 (3), e0152114

65. *Hoffmann-Vold AM, Tennøe AH, Garen T, Midtvedt Ø, Abraityte A, Aaløkken TM, Lund MB, Brunborg C, Aukrust P, Ueland T, Molberg Ø (2016)*
High Level of Chemokine CCL18 Is Associated With Pulmonary Function Deterioration, Lung Fibrosis Progression, and Reduced Survival in Systemic Sclerosis
Chest, 150 (2), 299-306

66. *Jørgensen SF, Trøseid M, Kummen M, Anmarkrud JA, Michelsen AE, Osnes LT, Holm K, Høivik ML, Rashidi A, Dahl CP, Vesterhus M, Halvorsen B, Mollnes TE, Berge*

RK, Moum B, Lundin KE, Fevang B, Ueland T, Karlsen TH, Aukrust P, Hov JR (2016)
Altered gut microbiota profile in common variable immunodeficiency associates with levels of lipopolysaccharide and markers of systemic immune activation
Mucosal Immunol, 9 (6), 1455-1465

67. *Zweers SJ, Shiryaev A, Komuta M, Vesterhus M, Hov JR, Perugorria MJ, de Waart DR, Chang JC, Tol S, Te Velde AA, de Jonge WJ, Banales JM, Roskams T, Beuers U, Karlsen TH, Jansen PL, Schaap FG (2016)*
Elevated interleukin-8 in bile of patients with primary sclerosing cholangitis
Liver Int, 36 (9), 1370-7

68. *Ellinghaus D, Jostins L, Spain SL, Cortes A, Bethune J, Han B, Park YR, Raychaudhuri S, Pouget JG, Hübenthal M, Folseraas T, Wang Y, Esko T, Metspalu A, Westra HJ, Franke L, Pers TH, Weersma RK, Collij V, D'Amato M, Halfvarson J, Jensen AB, Lieb W, Degenhardt F, Forstner AJ, Hofmann A; International IBD Genetics Consortium (IIBDGC); International Genetics of Ankylosing Spondylitis Consortium (IGAS); International PSC Study Group (IPSCSG); Genetic Analysis of Psoriasis Consortium (GAPC); Psoriasis Association Genetics Extension (PAGE), Schreiber S, Mrowietz U, Juran BD, Lazaridis KN, Brunak S, Dale AM, Trembath RC, Weidinger S, Weichenthal M, Ellinghaus E, Elder JT, Barker JN, Andreassen OA, McGovern DP, Karlsen TH, Barrett JC, Parkes M, Brown MA, Franke A (2016)*
Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci
Nat Genet, 48 (5), 510-8

69. *Hofsø D, Bollerslev J, Sandbu R, Jørgensen A, Godang K, Hjelmesæth J, Ueland T (2016)*
Bone resorption following weight loss surgery is associated with treatment procedure and changes in secreted Wnt antagonists
Endocrine, 53 (1), 313-21

70. *Waagsbø B, Svardal A, Ueland T, Landrø L, Øktedalen O, Berge RK, Flo TH, Aukrust P, Damås JK (2016)*
Low levels of short- and medium-chain acylcarnitines in HIV-infected patients
Eur J Clin Invest, 46 (5), 408-17

71. *Kummen M, Holm K, Anmarkrud JA, Nygård S, Vesterhus M, Høivik ML, Trøseid M, Marschall HU, Schrumpf E, Moum B, Røsjø H, Aukrust P, Karlsen TH, Hov JR (2016)*
The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls
Gut, 66 (4), 611-619

72. *Mørch RH, Dieset I, Færden A, Hope S, Aas M, Nerhus M, Gardsjord ES, Joa I, Morken G, Agartz I, Aukrust P, Djurovic S, Melle I, Ueland T, Andreassen OA (2016)*
Inflammatory evidence for the psychosis continuum model
Psychoneuroendocrinology, 67, 189-97

73. *Åsberg A, Humar A, Rollag H, Jardine AG, Kumar D, Aukrust P, Ueland T, Bignamini AA, Hartmann A (2016)*
Lessons Learned From a Randomized Study of Oral Valganciclovir Versus Parenteral Ganciclovir Treatment of Cytomegalovirus Disease in Solid Organ Transplant Recipients: The VICTOR Trial
Clin Infect Dis, 62 (9), 1154-60

74. *Rashidi M, Esmaily S, Fiane AE, Gude E, A Tønseth K, Ueland T, Gustafsson F, Eiskjær H, Rådegran G, Dellgren G (2016)*
Wound complications and surgical events in de novo heart transplant patients treated with everolimus: Post-hoc analysis of the SCHEDULE trial
Int J Cardiol, 210, 80-4

75. *Skagen K, Trøseid M, Ueland T, Holm S, Abbas A, Gregersen I, Kummen M, Bjerkeli V, Reier-Nilsen F, Russell D, Svardal A, Karlsen TH, Aukrust P, Berge RK, Hov JE, Halvorsen B, Skjelland M (2016)*
The Carnitine-butyrobetaine-trimethylamine-N-oxide pathway and its association with cardiovascular mortality in patients with carotid atherosclerosis
Atherosclerosis, 247, 64-9

76. *Holter JC, Ueland T, Jenum PA, Müller F, Brunborg C, Frøland SS, Aukrust P, Husebye E, Heggelund L (2016)*
Risk Factors for Long-Term Mortality after Hospitalization for Community-Acquired Pneumonia: A 5-Year Prospective Follow-Up Study
PLoS One, 11 (2), e0148741

77. *Lekva T, Michelsen AE, Bollerslev J, Norwitz ER, Aukrust P, Henriksen T, Ueland T (2016)*
Low circulating pentraxin 3 levels in pregnancy is associated with gestational diabetes and increased apoB/apoA ratio: a 5-year follow-up study
Cardiovasc Diabetol, 15, 23

78. *Haissman JM, Knudsen A, Hoel H, Kjær A, Kristoffersen US, Berge RK, Katzenstein TL, Svardal A, Ueland T, Aukrust P, Lebech AM, Nielsen SD, Trøseid M (2016)*
Microbiota-Dependent Marker TMAO Is Elevated in Silent Ischemia but Is Not Associated With First-Time Myocardial Infarction in HIV Infection
J Acquir Immune Defic Syndr, 71 (2), 130-6

79. *Cui XY, Tinholt M, Stavik B, Dahm AE, Kanse S, Jin Y, Seidl S, Sahlberg KK, Iversen N, Skretting G, Sandset PM (2016)*
Effect of hypoxia on tissue factor pathway inhibitor expression in breast cancer
J Thromb Haemost, 14 (2), 387-96

80. *Stavik B, Espada S, Cui XY, Iversen N, Holm S, Mowinkel MC, Halvorsen B, Skretting G, Sandset PM (2016)*
EPAS1/HIF-2 alpha-mediated downregulation of tissue factor pathway inhibitor leads to a pro-thrombotic potential in endothelial cells
Biochim Biophys Acta, 1862 (4), 670-8

81. *Trøseid M, Hov JR, Nestvold TK, Thoresen H, Berge RK, Svardal A, Lappegård KT (2016)*
Major Increase in Microbiota-Dependent Proatherogenic Metabolite TMAO One Year After Bariatric Surgery
Metab Syndr Relat Disord, 14 (4), 197-201

82. *Stylianou E, Ueland T, Borchsenius F, Michelsen AE, Øvstebø R, Mollnes TE, Skjønsberg OH, Aukrust P (2016)*
Specific allergen immunotherapy: effect on IgE, IgG4 and chemokines in patients with allergic rhinitis
Scand J Clin Lab Invest, 76 (2), 118-27

83. *Gabrielsen IS, Viken MK, Amundsen SS, Helgeland H, Holm K, Flåm ST, Lie BA (2016)*
Autoimmune risk variants in ERAP2 are associated with gene-expression levels in thymus.
Genes Immun. 2016 17(7), 406-411

84. *Zenouzi R, Weismüller TJ, Jørgensen KK, Bubenheim M, Lenzen H, Hübener P, Schulze K, Weiler-Normann C, Sebode M, Ehlken H, Pannicke N, Hartl J, Peiseler M, Hübener S, Karlsen TH, Boberg KM, Manns MP, Lohse AW, Schramm C (2016)*
No Evidence That Azathioprine Increases Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis
Clin Gastroenterol Hepatol, 14 (12), 1806-1812

85. *Kummen M, Vesterhus M, Trøseid M, Moum B, Svardal A, Boberg K M, Aukrust P, Karlsen T H, Berge R K, Hov JR (2016)*
Elevated trimethylamine-N-oxide (TMAO) is associated with poor prognosis in primary sclerosing cholangitis patients with normal liver function
United European Gastroenterology J, DOI: 10.1177/2050640616663453

86. *D'Agnolo HM, Kievit W, Andrade RJ, Karlsen TH, Wedemeyer H5, Drenth JP (2016)*
Creating an effective clinical registry for rare diseases.
United European Gastroenterol J. 2016 Jun;4(3):333-8. doi: 10.1177/2050640615618042.

87. *Gabrielsen IS, Amundsen SS, Helgeland H, Flåm ST, Hatinoor N, Holm K, Viken MK, Lie BA (2016)*
Genetic risk variants for autoimmune diseases that influence gene expression in thymus
Hum Mol Genet, 25 (14), 3117-3124

88. *Saadati HR, Wittig M, Helbig I, Häsler R, Anderson CA, Mathew CG, Kupcinskas L, Parkes M, Karlsen TH, Rosenstiel P, Schreiber S, Franke A (2016)*
Genome-wide rare copy number variation screening in ulcerative colitis identifies potential susceptibility loci
BMC Med Genet, 17, 26

89. *Gregersen I, Holm S, Dahl TB, Halvorsen B, Aukrust P (2016)*
A focus on inflammation as a major risk factor for atherosclerotic cardiovascular diseases
Expert Rev Cardiovasc Ther. 2016; 14(3):391-403

90. *Gregersen I and Halvorsen B*
Epigenetic and atherosclerosis – challenges and potential
JSM Atherosclerosis. 2016:1(1):1010

91. *Nesset C, Kong X, Damme M, Schjalm C, Roos N, Løberg EM and Eskild W (2016)*
Age-dependent development of liver fibrosis in Glmp gt/gt mice
Fibrogenesis & Tissue Repair20169:5

92. *Schurgers LJ, Burgmaier M, Ueland T, Schutters K, Aakhus S, Hofstra L, Gullestad L, Aukrust P, Hellmich M, Narula J, Reutelingsperger CP (2016)*
Circulating annexin A5 predicts mortality in patients with heart failure
J Intern Med., 279(1), 89-97

93. *Norum HM, Gullestad L, Abraityte A, Broch K, Aakhus S, Aukrust P, Ueland T (2016)*
Increased Serum Levels of the Notch Ligand DLL1 are Associated with Diastolic Dysfunction, Reduced Exercise Capacity, and Adverse Outcome in Chronic Heart Failure
J Card Fail., 22(3), 218-23

94. *Hoseth EZ, Westlye LT, Hope S, Dieset I, Aukrust P, Melle I, Haukvik UK, Agartz I, Ueland T, Ueland T, Andreassen OA (2016)*
Association between cytokine levels, verbal memory and hippocampus volume in psychotic disorders and healthy controls
Acta Psychiatr Scand., 133(1), 53-6

95. *Olarescu NC, Heck A, Godang K, Ueland T, Bollerslev J.*
The Metabolic Risk in Patients Newly Diagnosed with Acromegaly Is Related to Fat Distribution and Circulating Adipokines and Improves after Treatment.
Neuroendocrinology, 6;103(3-4), 197-206

96. *Laugsand LE, Åsvold BO, Vatten LJ, Janszky I, Platou C, Michelsen AE, Arain F, Damås JK, Aukrust P, Ueland T (2016)*
Soluble CXCL16 and risk of myocardial infarction: The HUNT study in Norway
Atherosclerosis, 244:188-94

97. *Nymo SH, Ueland T, Askevold E, Dahl CP, Gullestad L, Aukrust P, Yndestad A (2016)*
Circulating nucleosomes in chronic heart failure
Int J Cardiol., 15;203, 742-3

98. *Halvorsen B (2016)*
Cyclodextrin – ny behandling av aterosklerotisk hjerte- og karsykdom?
Best Practice, No. 20, 40-41

Photo: Øystein H. Horgmo, UiO

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