Oslo University Hospital

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Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2019

RIIM

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

The last year has been an important and fruitful year for the Institute. We have made word-leading scientific contributions, with over fifty percent of our publications in high-impact Level 2 journals. Our work is being acknowledged and we have been granted several important external fundings. These include, but are not limited to, a career fellowship (Gregersen) and research network (microbiota –Trøseid/Hov) from the South-Eastern Health Authority (HSØ) and a large Horizon 2020 project grant (Halvorsen and collaborators at NIPH). Oslo University Hospital has appointed "Personalized microbiota therapy in clinical medicine" as a strategic research area led by Johannes Hov. Johannes is also currently implementing his ERC starting grant project, which he received in 2018.

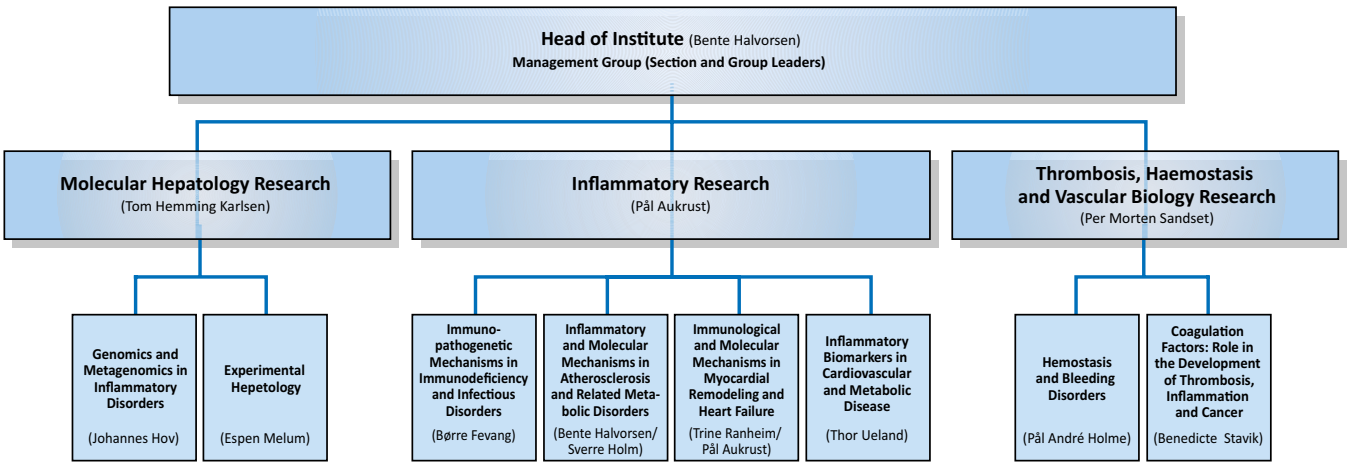
Oslo University Hospital is developing, and 2019 has been colored by great discussions about the organization and building of a new hospital. It is now decided that there will be a large hospital building situated at Gaustad, which will result in extensive reorganizations. It is of great importance that our voices are heard in this process. In the years to come, we will follow this process closely, and convey the message underlining the importance of our position in the hospital building, with proximity to the patients, to be able to pursue our translational research.

In light of this, in the strategy for 2019-2023, the Institute has set the major goal to be the leading translational research milieu at Gaustad. To achieve this, we need to continue to strive to succeed with high-impact publications and major external funding. A very important element to accomplish this goal is collaboration. In 2020 our goal should be to embrace our possibilities for fruitful collaborations in close proximity. Of course, we should still aim to establish and nourish are collaborations abroad, but strive to make the best use of our common competence and research interests both between research groups at the institute and within the clinic. Together, we have what it takes to reach our ultimate goal, to perform translational research of world-leading quality, which will have great impact on and importance for the society.

I hope and believe 2020 will be yet an inspiring and exciting year at RIIM, but at the time of writing we know that the Covid-19 pandemic will be a worldwide "game changer" that probably also will affect RIIM`s reach activity in the year(s) to come.

OUH, Rikshospitalet March 2020,
Bente Halvorsen,
Head

ORGANIZATION

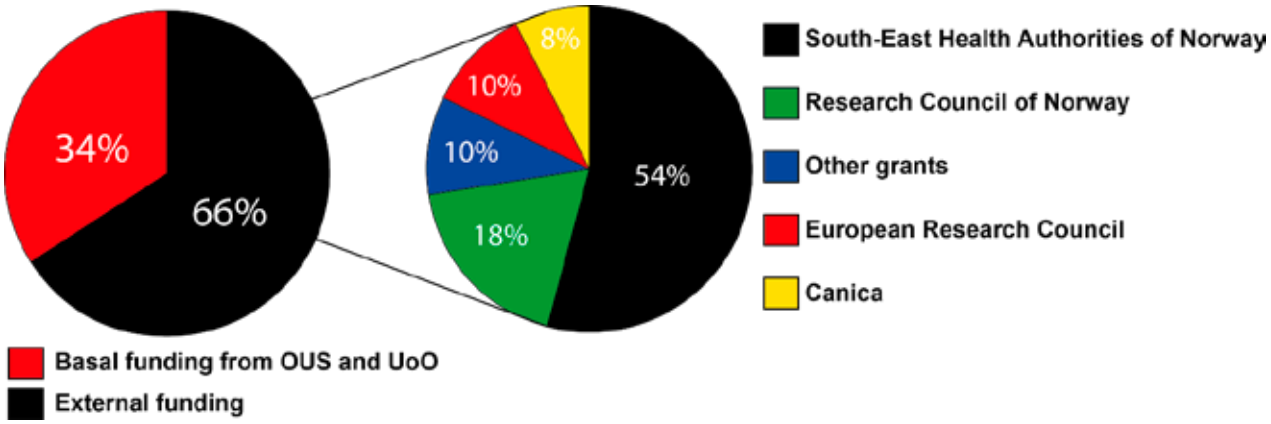


TOM HEMMING KARLSEN
Leader of Molecular Hepatology Research

PÅL AUKRUST
Leader of Inflammatory Research

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

ECONOMY / FUNDING



The institute's total funding amounted to NOK 67 mill in 2019. NOK 44.2 mill (66%) was funds from external sources, while NOK 22.8 mill (34%) was from Oslo University Hospital and University of Oslo. The contributions from the external sources are shown in the chart to the right.

FOCUS AREA

Induced pluripotent stem cells

ØYSTEIN SANDANGER, MD, PhD

Induced pluripotent stem cells (iPSCs) may be invaluable tools when studying the pathogenesis of genetic diseases at the cellular level. They can be made from several cell types, although dermal fibroblasts are often preferred and are easily obtained from patients with a punch biopsy. After a few weeks of in vitro culture, the fibroblasts appear from the biopsy fragments and are ready for reprogramming into iPSCs. Both viral and non-viral strategies are used for reprogramming and kits are commercially available. Then, when your iPSCs are ready, you may differentiate them to a relevant cell type for your experiment. Several different cell types derived from iPSCs have been reported, including monocytes, NK-cells, endothelial cells, keratinocytes, neurons and hepatocyte-like cells. However, these cells will almost certainly differ somewhat from their corresponding primary cells and thus selected key findings should be reproduced in experiments performed on primary cells if possible. The real power of induced stem cells, however, is realized when combined with gene editing. When studying the impact of a particular mutation on some cellular function or behavior, the optimal control cells are made by correcting the mutation by gene editing in a subset of the same iPSCs. Furthermore, with gene editing the mutation can also be introduced in iPSCs made from a healthy donor. The combination of both strategies yields strong evidence for a general causality between the mutation and the observed differences between mutated cells and control cells. Sounds elegant and easy? However elegant it may be, gene editing requires time, effort and patience. Finally, iPSCs may prove useful in gene therapy strategies including transplantation of cells differentiated from gene corrected iPSCs. Again, gene editing is both elegant and personalized but also time consuming. However, in some cases gene editing may be bypassed by transfecting a new healthy gene under the control of a suitable promoter, a one-size-fits-all approach.

FVII deficiency: developing new therapeutic strategies to rescue FVII production and function

ELISABETH ANDERSEN, MSc, PhD,
MARIA EUGENIA CHOLLET, MD, PhD

Congenital factor VII deficiency is a rare bleeding disorder with three times higher frequency in Norway compared to other countries. The current treatment, based on replacement therapy, has considerable limitations. The aim of this project is to develop new therapeutic strategies for FVII deficiency. To this end, we are using human induced pluripotent stem cells coupled with genome editing technology.

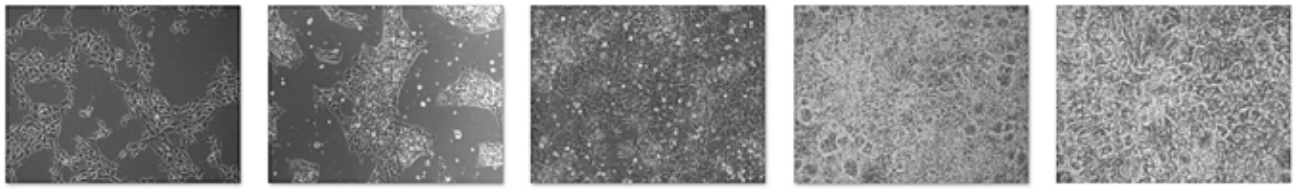
Congenital FVII deficiency

Coagulation factor (F) VII takes part in the cascade of reactions that result in the formation of thrombin, an enzyme that cleaves fibrinogen to form fibrin, which then forms a stable blood clot able to stop the bleeding. Congenital deficiency of blood coagulation FVII is a rare bleeding disorder with a prevalence of approximately 1:300.000-1:500.000 (1). It has an autosomal recessive pattern of inheritance, and the mutational pattern of the *F7* gene is highly heterogeneous (http://www.hgmd.cf.ac.uk/ac/index.php). About 78% of the disease-associated mutations are missense mutations associated with reduced FVII plasma levels and/or decreased biological activity. (2). In Norway the prevalent mutation among the patients with FVII deficiency is the p.Q160R (formerly denoted Q100R). Symptoms range from mild (epistaxis, gum bleeding, easy bruising) to severe (hemarthrosis, gastrointestinal bleeding, central nervous system bleeding) (3). Replacement therapy is the mainstay of treatment both prophylactically and to treat bleeding episodes. However, treatment of FVII deficiency is challenging due to the very short half-life of the FVII protein which might require frequent bolus injections. Additionally, the current therapy has very high costs; 1 mg of recombinant FVII costs approximately 950 euros (4).

Generation of hepatocytes from stem cells

The FVII protein is synthesized by the hepatocytes in the liver and secreted into the plasma. Human induced pluripotent stem cells (hiPSCs) provide a limitless supply of material able to differentiate to any given cell type. In this project, we are using an approach in which

small molecules will drive the differentiation of hepatocyte-like cells (HLCs) from hiPSCs generated from somatic cells isolated from patient blood. We generate hepatocytes from stem cells via the primitive streak to definitive endoderm (DE) using a Wnt agonist (CHIR99021). The small-molecule-derived DE is then differentiated to hepatoblast-like cells which are then differentiated to HLCs using a hepatocyte growth factor agonist (Dihexa,) and dexamethasone (5) (Figure 1).



D0 iPSC (10x) | D1 primitive streak (10x) | D2 DE (10x) | D20 HLCs (10x) | D20 HCLs (20x)

Figure 1: Different stages of iPSC-hepatocyte differentiation.

The hiPSCs are generated from somatic cells (peripheral blood mononuclear cells, PBMCs) by transducing the cells with Sendai virus vectors containing the four Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) that induce pluripotency. In this manner, we are able to generate patient specific hepatocytes with potential for translational research.

Possible therapeutic applications

The aim of the project is to pave the way to the development of new therapeutic strategies directed to stop and prevent the bleeding in patients with FVII deficiency. For this purpose, we are using two different approaches: 1) genome editing by CRISPR/Cas9 to correct the *F7* gene mutation in cells derived from patients. 2) chaperone therapy to rescue the secretion and activity of the FVII mutant protein. For both approaches, we are using hepatocytes generated from hiPSCs. Combining stem cell technology with genome editing techniques has the potential to transform the way we treat disease. Using CRISPR/Cas9 we will attempt to correct the *F7* gene mutation p.Q160R in hiPSCs derived from the patients, replacing the mutant with the wild-type. These cells will subsequently be differentiated into hepatocytes with normal FVII expression. Our long-term goal is to transplant these genetically modified cells into patients as an approach for achieving permanent FVII replacement (Figure 2).

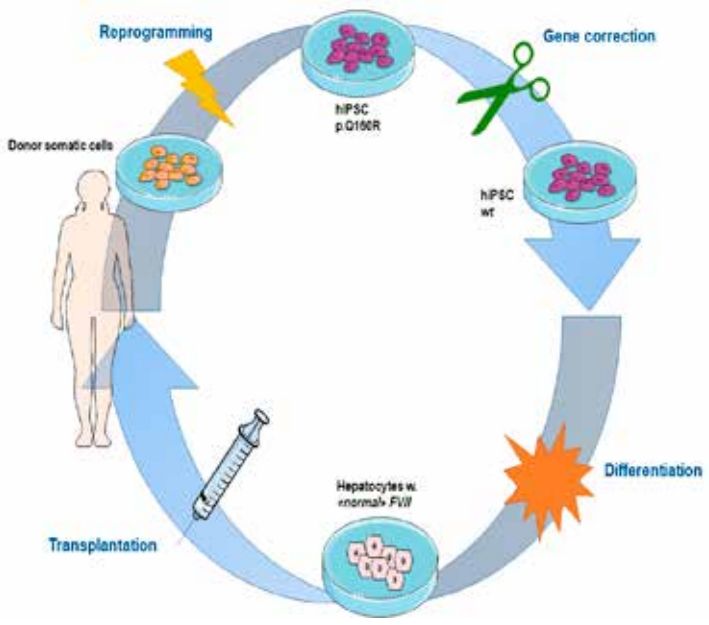


Figure 2: Using stem cells and CRISPR/Cas9 to achieve permanent FVII replacement.

In the short-term, these cells will provide us with a cell disease model for FVII deficiency with high translational potential as they are derived from human donors rather than model species. We will treat these cells with various chemical and pharmacological chaperones that are known to increase the secretion and/or activity of mutant proteins. Additionally, we will use a high-throughput screening approach on these cells to identify FDA-approved compounds that can be repurposed for treatment of FVII deficiency.

The project is supported by grants from South-Eastern Norway Regional Health Authority and the Society for Bleeders in Norway.

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Use of human iPSC-derived brain cells in mechanistic studies of severe mental illness

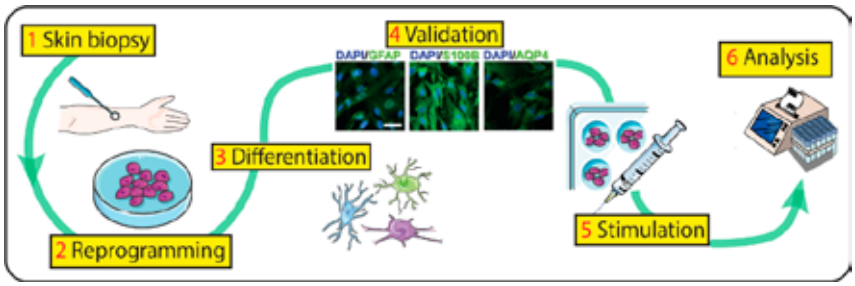
THOR UELAND, PhD

The severe mental disorders schizophrenia (SCZ) and bipolar disorder (BD) are leading causes of morbidity both globally and in Norway, and rank as some of the most costly human disorders [1]. The disease mechanisms are still mostly unknown so there is little expectation of effective treatment alternatives in the nearby future. It is therefore imperative to identify the pathophysiology of the disorders. The heritability for SCZ and BD is estimated to be 60-80% and the disorders are regarded as complex genetic disorders with multifactorial causes [2]. The neurodevelopmental hypothesis of schizophrenia suggests that subtle perturbations in early neurodevelopment, mediated by genetic risk factors, increase later susceptibility for disease, which typically manifests in adolescence to early adulthood [3].

Our group has for >10 years had tight collaboration with the Norwegian Centre for Mental Disorders Research (NORMENT) led by Ole Andreassen, analyzing inflammatory biomarkers in patients with SCZ and BD disorder. Genetic and epidemiological evidence implicates immune factors in SCZ and BD) [4, 5] and we and others have demonstrated dysregulated activation of immune cells in the vasculature, including leukocyte subsets and endothelial cells, as reflected by secreted activation markers preceding [6] and following diagnosis of SCZ and BD [7-9]. The blood-brain barrier (BBB) is not deteriorated as observed in neurological diseases such as stroke, brain trauma or neurodegenerative disorders, and mechanisms for communication between systemic factors and the CNS in severe metal illness are less known. However, we have linked elevated levels of systemic inflammatory molecules, possibly related to atherogenic and metabolic comorbidities, to MRI brain abnormalities, clinical phenotypes and cognitive performances [10-13], suggesting systemic that inflammation may influence neurogenesis and cognitive function. Alternatively, systemic dysregulation is a proxy and mirrors similar processes in the brain.

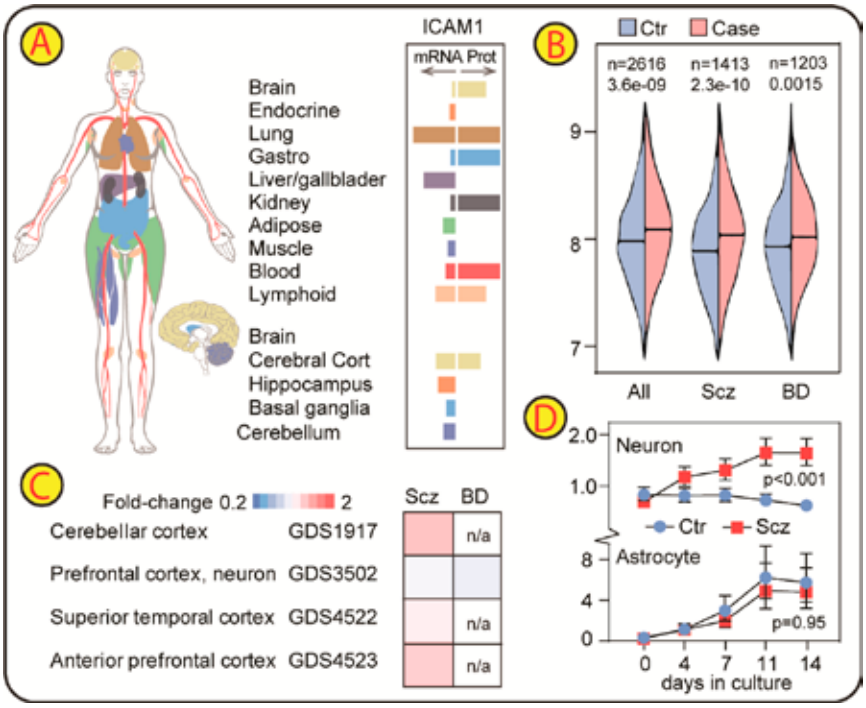
Although these studies further support dysregulated immune activation in the pathogenesis of severe mental disorders, mechanistic studies are needed to bring the field forward and identify viable therapeutic targets. However, obtaining neuronal cells from patients for mechanistic studies is not possible and cell lines fail to capture the significant genetic component in these individuals. The advent of induced pluripotent stem cell (iPSC) technology allows for the *in vitro* analysis of disease-relevant neuronal cell types from the early stages of human brain development. These are artificially made from somatic cells (such as fibroblasts of the skin) and can be differentiated into various cell types. Since iPSCs capture each donor's genotype, comparison between neuronal cells derived from healthy and diseased individuals can provide important insights into the molecular and cellular basis of SCZ and BD. This may in turn lead to major health benefits through better treatment strategies.

Within NORMENT, the group of Srdjan Djurovic focuses on molecular mechanisms



in psychiatry and employs established iPSC culture systems from patients and healthy controls to evaluate the effects of innate immune activation on the biological features of iPSC cell-derived cell types (conducted by post doc's Attila Szabo and Jordi Requena Osete). The group is co-localized at the Norwegian Core Facility for Human Pluripotent Stem Cells. The main stages for iPSC derivation, characterization and study are shown in Figure 1. The first publication from the group explored the global transcriptomic effects of IL-1β modulation on human iPSC-derived astrocytes generated from SCZ and controls [14]. After successfully establishing an in vitro iPSC-astroglia model, the study showed that inflammasome activation, as mimicked by short-term IL-1β treatment, had a reduced up-regulatory effect on CCL20 expression in SCZ. IL-1β activated iPSC-derived astrocytes had a weaker chemotactic effect on Treg cells and blocking experiments suggested that this effect was mediated by astrocyte-derived CCL20. Based on the ability of Treg cells to control inflammation, the findings suggest the attenuated CCL20 response may contribute to a dysregulated brain inflammation in SCZ.

Cell adhesion molecules orchestrate leukocyte trafficking during inflammatory responses and could link peripheral and neuro-inflammation in severe mental disorders [15, 16]. We recently found high circulating levels of soluble intercellular CAM1 (sICAM1) in patients with severe mental disorder (MS in preparation by Mashhood) with particularly high levels in SCZ. However, as shown in Figure 2A, ICAM1 has multiple cellular sources and high levels are linked to risk of cardiovascular disease, a significant burden in severe mental disorders. Thus, it is unknown if the enhanced levels just reflect comorbid conditions, or could play a role in modulating neuro-inflammation in these patients. However, high sICAM1 levels were associated with a higher symptom burden supporting a role for direct role for ICAM1 in disease progression. As shown in Figure 2C, evaluation of post mortem studies from public repositories support upregulation of sICAM1 in the brain in SCZ. Furthermore, sICAM1 is both secreted by [17] and involved in the functional modulation of human astrocytes, thereby influencing cortical microvasculature topology and overall neuroplasticity [18], features closely linked to negative symptoms in SCZ [19, 20]. We therefore assessed the secretion of sICAM1 from iPSC derived neurons and astrocytes from SCZ and heathy controls. As shown in Figure 2D, patients with SCZ had a markedly higher temporal increase in secretion of sICAM1 from neurons, while the trajectories were similar between groups in astrocytes. Thus, the increased systemic sICAM1 in severe mental illness may reflect a similar upregulation in the brain, possibly representing both marker and mediator of deteriorating brain health, and candidate in future pharmacological studies in these patients.



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DISSERTATIONS 2019

Photo: Øystein H. Horgmo, University of Oslo

Hilde Margrethe Norum, MD

Soluble Notch Ligands in Heart Failure
May 27th 2019

Committee:
1. opponent: Professor Truls Myrmel, University of Tromsø
2. opponent: Professor Bjørn Tore Gjertsen, University of Bergen
3. opponent: Professor Ingrid Os, University of Oslo

Main supervisor: Thor Ueland
Co-supervisor(s): Pål Aukrust
Summary of PhD project:
Abstract

Heart failure (HF) is a feared condition, with a five-year survival of only 50%. The life-time risk of developing HF is one in five. The Notch signaling system, whose Notch receptors interact with Notch ligands, is active in myocardial tissue in HF, but little is known about circulating Notch ligands in HF.

We hypothesized involvement of Notch signaling in HF development, as well as in development and progression of cardiac allograft vasculopathy (CAV) after heart transplantation (HTx). We aimed at studying circulating Notch ligands and their relation to clinical and hemodynamic characteristics in four HF and post-HTx populations.

Levels of circulating Notch ligands like DLL1 and periostin from patients and controls, as well as expression of myocardial Notch proteins were measured, and additional experiments were conducted to elucidate potential sources of Notch ligands.

In chronic HF, serum DLL1 was elevated. High levels of DLL1 were associated with diastolic dysfunction, reduced exercise capacity and adverse outcome.

In dilated cardiomyopathy, severely affected patients had increased plasma DLL1 and periostin, associated with indices of diastolic dysfunction. In myocardial biopsies, expression of DLL1 and periostin correlated with indices of more preserved and more impaired cardiac function, respectively.

Plasma DLL1 and periostin were increased in *de novo* and maintenance HTx recipients. Everolimus based immunosuppression, compared to standard regimen, was associated with weakened DLL1 response. In *de novo* recipients, long-term changes in plasma DLL1 correlated with changes in CAV indices. Myocardial DLL1 shared its distribution pattern with T cells, vascular smooth muscle cells and endothelial cells. *In vitro*, these cells secreted DLL1. Everolimus attenuated DLL1 secretion from T cells and endothelial cells.

Notch signaling may thus be involved in development of HF and progression of CAV.

Photo: Øystein H. Horgmo, University of Oslo

Linn Elisabeth Fosshaug, MD

Adipose Tissue and Fatty Acids in Cardiovascular Disease
25.10.19

Committee:
1. opponent: Associate Professor Harry Björkbacka, Lund University, Sweden
2. opponent: Professor Terje Larsen, UiT - The Arctic University of Norway, Tromsø
3. opponent: Researcher Cathrine Rein Carlson; University of Oslo, Norway

Main supervisor: Erik Øie, Diakonhjemmet Hospital, Oslo

Co-supervisor(s): Leif Erik Vinge, Diakonhjemmet Hospital, Oslo and Pål Aukrust

Summary of PhD project:
Cardiovascular disease is the main cause of death globally and addressing risk factors can prevent disease. Obesity is a major risk factor and a growing health problem in both developed and developing countries and adipose tissue produces a variety of biologically active substances relevant in cardiovascular disease.

The main aim of the thesis was to shed light on the biological role of fatty acids in myocardial infarction and remodeling, taking a prime interest in the interactions between the immune system and adipose tissue. Specifically, the aim was to study the effects of omega-3 fatty acids after myocardial infarction during myocardial remodeling in an experimental rat infarction model. Furthermore, we investigated if the levels of fatty acids and cardiovascular mediators are modulated in adipose tissue in patients with heart failure by retrieving tissue samples from adipose tissue in proximity to the heart and to the skin. And last, our aim was to provide "proof-of-concept" that fatty acid-derived pro-resolving lipid mediators are biosynthesized during acute myocardial infarction in humans by sampling blood.

The thesis demonstrate that supplementation with omega-3 fatty acids leads to a proportional increase of omega-3 fatty acids in myocardial tissue and attenuates left ventricle remodeling after myocardial infarction. Second, adipose tissue from the heart and skin displays molecular similarities in patients with heart failure and controls. However, depot-specific differences of possible importance were demonstrated. And third, omega-3 fatty acid derived pro-resolving lipid mediators play a role in acute myocardial infarction and their temporal dynamics in blood provide a potential target for modulation and therapeutic interventions.

Overall, our results suggest a potential role for fatty acids and fatty acid-derived mediators after myocardial infarction and during myocardial remodeling.

Photo: Øystein H. Horgmo, University of Oslo

Liv Hesstvedt, MD

Aspects of candidemia in Norway and in the Nordic countries: A contribution to the understanding of epidemiology, clinical aspects and outcome in patients with candidemia
Feb. 8, 2019

Committee:
1. opponent: Professor Paul Verweij, Nijmegen Medical Center, Radboud University, The Netherlands
2. opponent: Senior Consultant Jannik Helweg-Larsen, Department of Infectious Diseases, Rigshospitalet Copenhagen, Denmark
3. opponent: Associate Professor Anne-Marte Bakken Kran, Faculty of Medicine, University of Oslo

Main supervisor: Associate Professor Ingvild Nordøy, Oslo University Hospital

Summary of PhD project:
Blood stream infection with yeast, candidemia, is a rare, but severe condition with high mortality. Candidemia is diagnosed in immuno-compromised hospitalized patients with underlying illnesses. In Norway the incidence has been low, compared to Denmark, where it is 3 times more common, for reasons we do not fully understand.

There are few reports focusing on the epidemiological differences in candidemia in the Nordic countries, as well as long-term epidemiological follow up in Norway. Risk factors for candidemia, treatment practice and outcome in the Norwegian setting are unknown.

The aims of this thesis were to shed light on the epidemiological development of candidemia in Norway over time and differences between the Nordic countries. Through a Nordic collaboration and 2 multicentre studies they assessed risk factors for candidemia, therapeutic practice and outcome by reviewing medical records and laboratory data.

The incidence of candidemia in Norway is low, but slowly increasing, particular in patients over 65 years. Risk factors for candidemia in the elderly were abdominal surgery and malignancy. Patients below 65 years were more often in Intensive Care Units with a CVC, being mechanically ventilated, receiving chemo- and other immune-suppressive therapies than the elderly. Antifungal treatment was given significantly more often to the younger patients than to the elderly, with a lower mortality at 23.9% vs. 45.5% in the elderly.

Higher incidence of haematological malignancies and more frequent use of antibiotics with anti-anaerobic effect can be part of the reason for the high incidence in Denmark compared to the other Nordic countries.

In conclusion, we observed significant differences regarding candidemia according to age-groups. Overall, despite many elderly patients had an underlying cancer, better knowledge of this treatable

DISSERTATIONS

infection and increased antifungal treatment to the elderly could improve survival.

Photo: Øystein H. Horgmo, University of Oslo

Elisabeth Andersen, M.Sc.

FVII deficiency: from molecular mechanisms to novel therapeutic approaches
18-12.2018

Committee:
1. opponent: Professor Javier Corral, Universitety of Murcia, Spain
2. opponent: Professor Björn Dahlbäck, Lund university, Sweden
3. opponent: Professor Britt Nakstad, University of Oslo, Norway

Main supervisor: Grethe Skretting

Co-supervisor(s): Maria Eugenia Chollet, Per Morten Sandset

Summary of PhD project:
The aim of this study was to obtain a better understanding of the underlying molecular basis of FVII deficiency to eventually be able to find new therapeutic approaches. Congenital deficiency of blood coagulation factor (F) VII is a rare bleeding disorder with a prevalence of approximately 1:300.000-1:500.000. It is caused by mutations in the F7 gene resulting in reduced levels of FVII in the blood and/or decreased biological activity. As of today, bleeding episodes are treated with factor concentrates. However, this therapy requires frequent intravenous administrations and is extremely expensive. In this study, we focused on the four FVII mutations p.G420V, p.I289del, p.Q160R and p.A354Vp.-P464Hfs. They were chosen because they represent different types of mutations with distinct disease pathways. Additionally, the p.Q160R and p.A354V-p.P464Hfs mutations are among the most frequent in the FVII deficient patients. Patients harboring these mutations all experience bleeding symptoms due to both reduced levels and activity of FVII. Both the wild-type and the mutant FVII were expressed in mammalian cell lines and cell studies were performed by different molecular biology techniques.
We found impaired biosynthesis of the mutant FVII proteins and reduced secretion from the cells compared to the wild-type FVII, possibly as a result of misfolding of the FVII protein. Furthermore, we found that the intracellular transport of the FVII mutants was affected. The mutant proteins were not transported to the Golgi apparatus as the wild-type FVII, but were retained inside the endoplasmic reticulum (ER) of the cells causing ER stress. Chemical chaperones are compounds that enhance the stability of misfolded proteins, enabling them to be secreted from the cells. We therefore tested the effect of various chemical chaperones on the FVII mutants. We found that 4-phenylbutyrate was able to increase the biosynthesis and secretion of FVII from the cells and partially restore the biological activity of the FVII mutants.
The results from these studies indicate that correction of protein misfolding or treatment targeting ER stress responses may represent relevant, novel treatment targets for FVII deficiency.

Photo: Øystein H. Horgmo, University of Oslo

Nina Haagenrud Schultz, MD

Oral factor Xa inhibitors: Studies on reversal of their anticoagulant effect and on their influence on primary hemostasis, endothelial function and fibrinolysis
November 8. 2019

Committee:
1. opponent: Professor Sam Schulman, McMaster University, Ontario, Canada
2. opponent: Senior Consultant Fariba Baghaei Borzabadi, Sahlgrenska University Hospital, Gothenburg, Sweden
3. opponent: Professor Bjørn Bendz, Institute of Clinical Medicine, University of Oslo

Main supervisor: Professor Pål Andre Holme

Co-supervisor(s): Carola Henriksson, Dept of Medical Biochemistry, OUS, Eva Jacobsen, Dept of Haematology, OUS, Hoa Thi Tuyet Tran, Department of Haematology, Akershus University Hospital, Professor Per Morten Sandset, University of Oslo

Summary of PhD project:
Direct-acting oral anticoagulants (DOACs) were recently introduced for clinical use before a specific reversal strategy had been developed. In spite of their short half-life, a reversal strategy may be lifesaving in case of major bleeding or when urgent surgery is required. An antidote for activated factor X (FXa) inhibitors is not yet available in Norway.

We have performed in vitro-studies with potential reversal agents of the FXa inhibitors rivaroxaban and apixaban and a case series where the effect of apixaban was reversed with the activated prothrombin complex concentrate (aPCC) FEIBA® in three patients in need of urgent heart surgery. Furthermore, we investigated the effect of rivaroxaban on stages of hemostasis other than the coagulation system. We found that aPCC, in a lower dose than recommended in current guidelines, was more effective in reversing the anticoagulation effect of both rivaroxaban and apixaban than recombinant FVIIa and four-factor prothrombin complex concentrate (PCC). aPCC 25-30 IU/kg also had a good hemostatic effect in two out of three apixaban-treated patients assessed both clinically, and by laboratory assays.

An influence of rivaroxaban on platelet aggregation, von Willebrand factor or markers of endothelial activation was not demonstrated. However, after measurements of fibrinolytic markers, we detected a reduction of plasminogen activator inhibitor (PAI-1) in samples with peak concentrations of rivaroxaban. In conclusion, aPCC may be a potential reversal agent of FXa inhibitors. Furthermore, rivaroxaban may increase fibrinolytic activity by reducing the level of PAI-1.

William Ward Siljan, MD

Title: Immunodeficiencies, immune responses and biomarkers in community-acquired pneumonia
Date: March 29, 2019

Committee:
1. opponent: Senior Consultant Adamantia Liapikou, Sotiria Chest Diseases Hospital, Athens, Greece
2. opponent: Senior Consultant Torgun Wæhre, Department of Infectious Diseases, Oslo University Hospital
3. opponent: Associate Professor Truls Michael Leegaard, Faculty of Medicine, University of Oslo

Main supervisor: Dr.med. Lars Heggelund, Vestre Viken Hospital Trust

Co-supervisor(s):
Professor Pål Aukrust, RIIM
Professor Tom Eirik Mollnes, Department of Immunology, Oslo University Hospital
Jan Cato Holter, RIIM

Summary of PhD project:
Community-acquired pneumonia (CAP) is a common infectious condition, responsible for considerable short- and long-term morbidity and mortality worldwide. Despite advances in diagnosis and care of pneumonia, deaths due to this disease have only slightly decreased over recent decades. Better understanding of the immunological mechanisms underlying CAP could help identify patients at risk of poor outcomes, lead to a reduction in antimicrobial overuse and even reveal new therapeutic targets.
Over a three-year period 267 patients admitted with CAP to Drammen Hospital were included in this study and followed for 5 years after hospital discharge. Patients were assessed at three time points with extensive clinical, laboratory and microbiological testing.
The study aimed to shed light on host immune responses and potential immunodeficiencies in CAP and examine whether these factors were associated with different microbial patterns, disease severity, and outcomes. Further, we aimed to identify new diagnostic and prognostic biomarkers that could help important clinical decisions in CAP.
For most of the immune mediators examined, including complement factors, immunoglobulins, and cytokines, only minor non-significant variations were seen for different microbial patterns, disease severity and outcomes. Additionally, the presence of low levels of mannose-binding lectin, a complement factor deficient in 10-15% of the Nordic population, or low immunoglobulins, a cornerstone of host immunity against invading pathogens, were not associated with differences in endpoints.
However, circulating cell-free DNA, pentraxin 3 and presepsin were markers of short-term prognosis, while calprotectin was both a marker of bacterial CAP, but also of 5-year mortality in this cohort.

Overall, in this CAP study, we did not find major differences in host immune responses compared by microbial patterns, disease severity or outcomes, but several new markers with potential clinical utility were identified and should be investigated in future CAP cohorts.

SECTION OF MOLECULAR HEPATOLOGY RESEARCH

Genomics and metagenomics in inflammatory diseases

From left: Simen Hyll Hansen, Marit Mæhle Grimsrud, Martin Kummen, Alexandra Götz, Georg Schneditz, Lise Katrine Engesæter, Liv Wenche Thorbjørnsen, Brian Chung, Johannes R. Hov, Magnhild Eide Macpeherson, Silje Jørgensen and Murat Gainullin.

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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. After an initial phase of defining the gut microbiota in inflammatory diseases, the main focus is now directed towards "Clinical microbiota medicine", that is, studies of the gut microbial content and function gut in human disease – and how the new knowledge can be applied clinically. This concept has been significantly strengthened in 2019, after receiving funding from Helse Sør-Øst to a regional research network for clinical microbiota science (ReMicS). Our group is spearheading ReMicS together with the clinical microbiology and microbiota medicine group at the RHI (leader Marius Trøseid), with which are integrated. Hanne Guldsten has been employed as the network administrator and laboratory responsible person.
In addition, the OUH scientific board awarded the group Strategic research area status for "Personalized microbiota therapy in clinical medicine", aiming to translate microbiota research to clinical practice as biomarkers and target of interventions.
Locally, the group has extensive collaborations ongoing within the Research Institute of Internal Medicine and with the clinical research groups of the hospital.
A strong link to the experimental groups is also important, providing opportunities to understand disease mechanisms in more detail. The regional network ReMicS will be increasingly important to strengthen our research agenda. Finally, the group hosted the fifth national conference on gut microbiota in November 2019 with about 100 participants.

PROJECTS

The major project axes center around the following:

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

A key aspect of clinical microbiota medicine is the application of gut microbial profile defined by microbial composition or functions, or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity. Several interventional studies targeting the gut microbiota have been performed or are ongoing. Such studies may represent proof-of-concept of a direct involvement of the gut microbiota in the disease development and also speed up the process of clinical translation.

FUNDING

The main group members are currently funded as follows:

- European Research Council, StopAutoimmunity project (ERC Starting Grant): JRH
- Research Council of Norway, NORGUT project (young research talent grant): JRH and AKD
- Regional Health Authorities of South Eastern Norway. Postdoc grants: MK, BC, MG, GS. PhD grants: BV, LKE, MJH. Regional research network: HG
- National association for public health: CM
- Norwegian PSC Research Center: KH, SHH
- Nordforsk (NordTreat trial): AG

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

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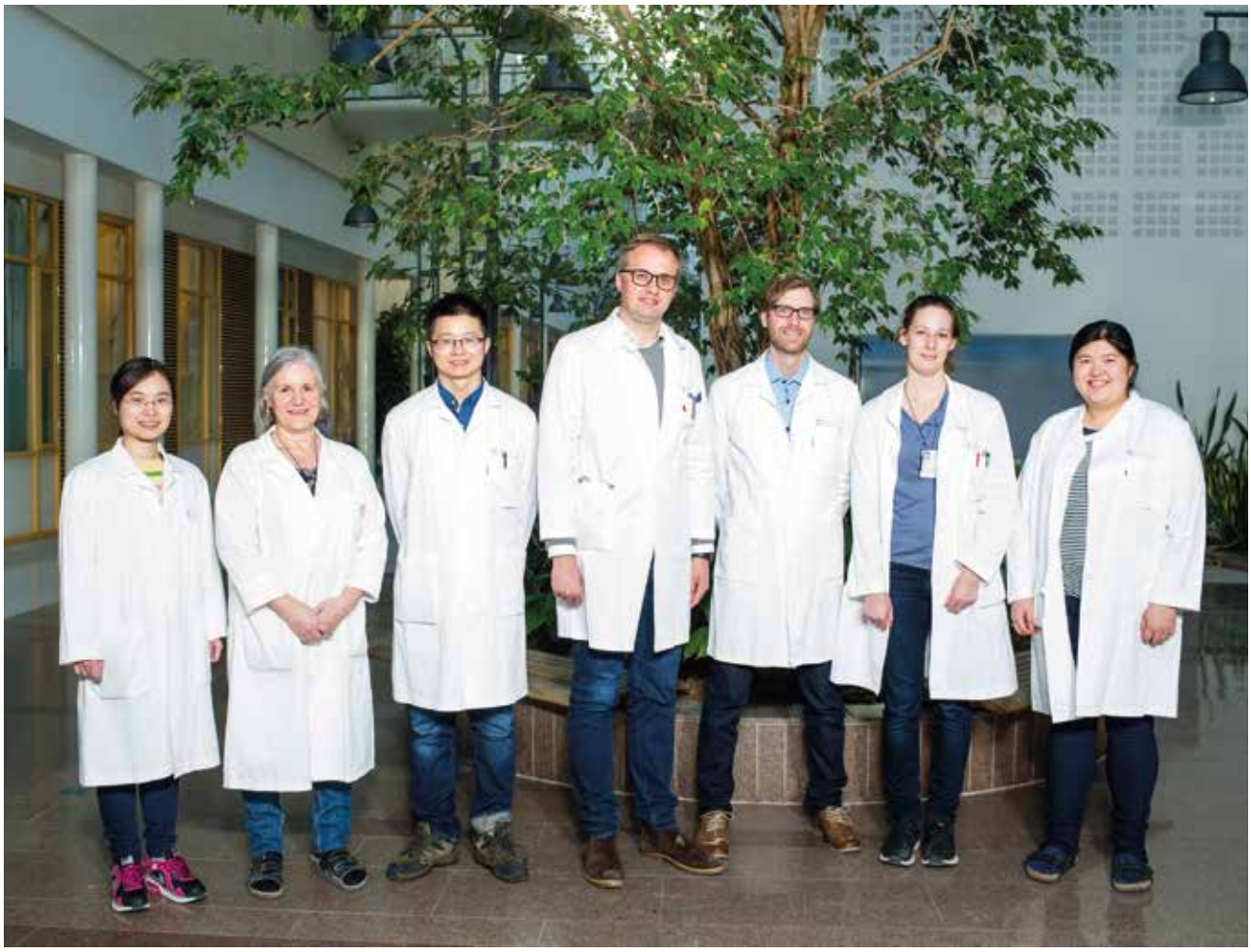
Prof. Andre Franke, Christian-Albrechts University, Kiel
Kostas Lazaridis, Mayo Clinic, Rochester
International PSC Study Group

Awards to members of the group in 2019
Tore Midtvedt's Award to Beate Vestad at the National Microbiota Conference in Oslo, November 19, 2019.

SECTION OF MOLECULAR HEPATOLOGY RESEARCH

The Experimental liver research group



From left: Xiaojun Jiang, Anne Pharo, Fei (Freeman) Zheng, Espen Melum, Jonas Øgaard, Kathrine Sivertsen Åsrud and Lisa Yuen Løvold.

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RESEARCH PROFILE

The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The most important tools in our research are mouse models that model aspects of cholangitis development. The group represents one of the three research group at the Norwegian PSC research center. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2019, the group consisted of the group leader, two postdocs, four PhD students, the lab manager and two part-time technicians. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology but also now incorporating aspects of regenerative medicine. In addition to the cholangitis focused studies, we are also doing basic research related to the function natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment target for PSC.

The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2019, we continued the hunt for antigens for unconventional T cell antigens in bile and discovered that

bile contains antigens for the two major sub-types of unconventional T cells, NKT and MAIT cells. It seems like these antigens are both endogenous and exogenous, and studies are ongoing to determine their molecular identity. As part of the basic studies on the function of NKT cells we published in 2019 that sphingomyelin can block development and activation of NKT cells and affect several disease models. These results were also translatable to the human disease. The team working on unconventional T cells were strengthened in 2019 with Kathrine S. Åsrud who joined as postdoc and will work on the specific role of CD1d on cholangiocytes during bile duct inflammation. Tine Simensen Oldereid started as a new PhD student in the group on a collaborative project with Ass. Prof. Henrik Rasmussen at the animal facility using the germ-free unit to study microbiome regulation of bile duct inflammation and development of the immune system. A new line of collaboration with Prof. Stefan Krauss at the center of excellence Hybrid-technology-hub was started up in 2019 where our competence in bile duct biology will be used together with other groups at the hub. In a collaborative project involving a new Scientia Fellow postdoc we also aim to study the bile ducts using organ-on-a-chip systems.

INFLAMMATORY RESEARCH

Clinical immunology and infectious diseases

From left: Ingvild Nordøy, Børre Fevang, Magnhild Eide Macpherson, Kari Otterdal and Silje Jørgensen.

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RESEARCH PROFILE

The research group focus on immunopathogenesis in primary and secondary immunodeficiency such as Common variable immunodeficiency (CVID) and HIV and selected infectious diseases, in particular the study of chronic inflammation characterizing 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 OUH, 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 patient's health. Identifying the factors leading to such an exaggerated response will potentially enable clinicians to modify the inflammatory response of the single patient with agents targeting anything from intracellular signaling 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. Our group has for a long time used primary immunodeficiency in the form of CVID as a model for studying the immune system. In recent years we have been focusing on the interaction between gut microbiota, gut mucosa and local (intestinal) and systemic inflammation. Magnhild Eide Macpherson is continuing this work with her PhD that includes both the modulation of gut microbiota with rifaximin in CVID-patients and an exciting investigation into the anti-inflammatory effect of HDL in the same patients. This latter work is extended into a Post doc project for Silje Fjellgård Jørgensen that started up in 2019 and will include in-depth studies of epigenetic changes in gut mucosa from CVID-patients.

- 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. In his PhD-project, William Siljan has been delving into the vast amount of data and samples previously collected, and his thesis was successfully defended in March 2019.

- Liv Hesstvedt defended her thesis "Candidemia in Norway and the Nordic countries" in February 2019. The thesis is partly based a national collaboration where data has been collected from laboratories and medical records from most Norwegian hospitals. 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 this continues with Hedda Hoel's PhD project that looks at the NLRP3 inflammasome as a driving force of the systemic inflammation seen in HIV-infected patients. The NLRP3 inflammasome has been studied in cardiovascular disease by other groups at our institute, and the current project is an excellent example of how immunological insight gained from the study of one disease can be applied to new diagnoses. The project is led by Marius Trøseid who is also the main supervisor.

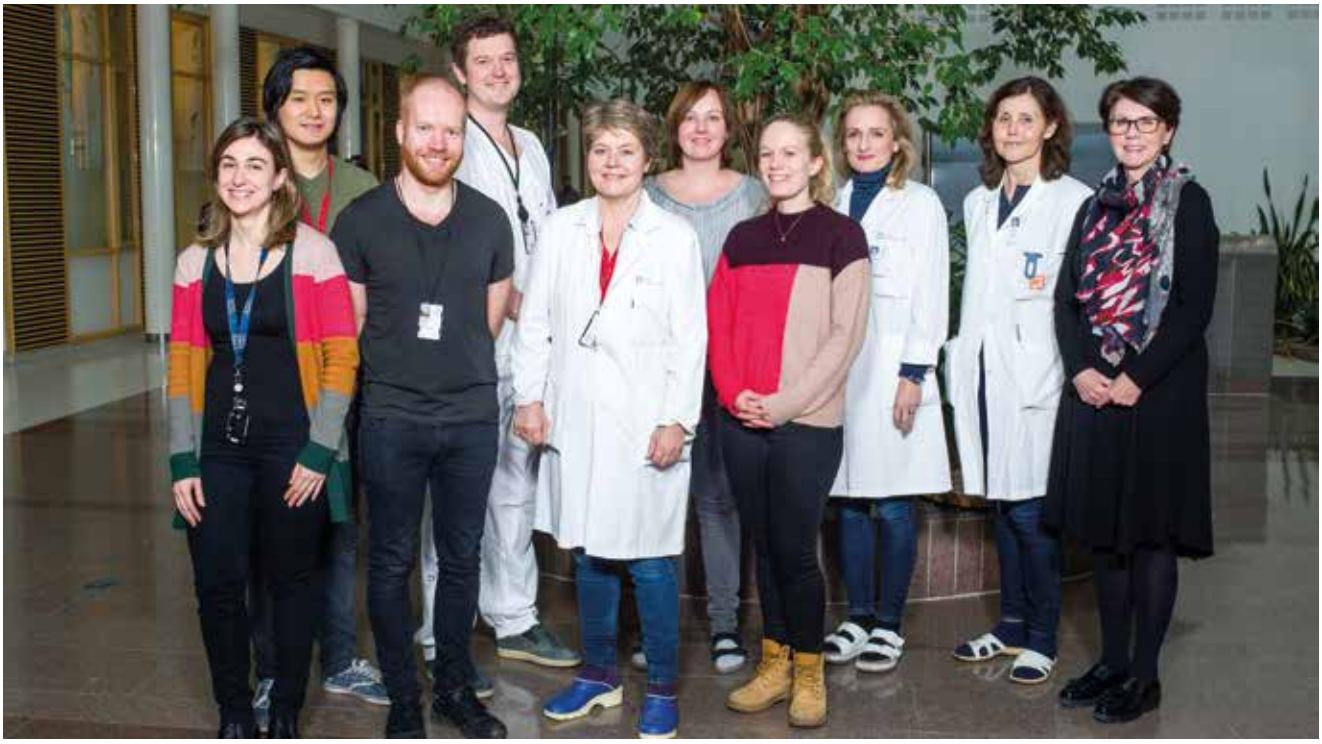
- Functional consequences of novel genetic variations in primary immunodeficencies and immune dysregulation (FUNPID). High-throughput sequencing has revolutionized the diagnostics of primary immunodeficiencies, giving a definite genetic diagnosis in complicated clinical cases. However, novel genetic 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. We are currently looking into a family with a possible gain-of-function mutation in IL-1R8.

FUNDING

The group is currently mainly funded through grants from the South-Eastern Norway Regional Health Authority but has also funding from the Anders Jahre foundation, Unifor and the Odd Fellow foundation.

INFLAMMATORY RESEARCH

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders



From left: Ana Quiles Jimenez, Xiang Yi Kong, Tom Rune Karlsen, Sverre Holm, Bente Evy Halvorsen, Tuva Børresdatter Dahl, Ida Gregersen, Karolina Ryeng Skagen, Mona Skjelland and Turid Margrethe Pedersen.

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TWO BACHELOR STUDENTS
from Oslo MET; Marielle Storbråten and Eivind Skurdal finished their work in 2019 on the project "Human Endonuclease V isoforms"

RESEARCH PROFILE

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

extracellular matrix and inflammation is a characteristic hallmark of atherosclerotic plaque development. The inflammatory mechanisms in atherosclerosis and closely related metabolic disorders have been the cornerstone of the research group's activity for the last two decades.

Access to clinical material from well characterized patients with atherosclerotic lesions and related metabolic disease such as obesity and type II diabetes is a great strength of our research group. Through a translational approach, combining human clinical material with in vivo studies in animal models and in vitro work in cell cultures, we seek to unravel mechanisms important for the development of these conditions. In the recent 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 cell extractions. The last year we have had a particular focus on establishing robust collaborations and methods for state of the art technologies for characterization of our patient material, such as advanced DNA methylation sequencing and mass spectrometry.

During the last year, a special focus in our research group has been on establishing an in-house workflow for analysis of complex multiomic data. This include both the infrastructure and the competence to perform advanced bioinformatic analyses. In our research, we perform several different large-scale analysis on both human and murine samples, such as RNA sequencing, mass spectrometry and bisulfite sequencing, and it is a major goal for us to be able to integrate the data generated from these analyses in a useful manner.

Inflammation in atherosclerosis
We have studied the role of inflammatory mediators in development of atherosclerosis for many years. In 2019, one of our inflammatory focuses has been on the cysteine protease legumain. We have previously shown that legumain is increased in both plasma and plaques of patients with carotid stenosis and that legumain is produced by macrophages, and colocalized to macrophages in the plaque. During the last year, we have further shown that legumain is upregulated in patients with acute cardiovascular disease, associated with improved outcome. Further, legumain was produced from platelets upon activation, and induce anti-inflammatory effects in macrophages, suggesting a possible protective role in cardiovascular disease.

T cells in Obesity
Obesity increases the risk of several metabolic conditions, with type 2 diabetes as one of its most devastating consequences. The term "metabolic healthy obese" has emerged the last years, describing those who develop severe obesity without metabolic sequela. Understanding the underlying mechanism for metabolic healthy and unhealthy obesity is of great interest to develop better treatment for this patient group. One of our major research projects is the study of T cell function in metabolic regulation during obesity development. Circulating and tissue resident T cells can modulate macrophage function and adipocyte differentiation, and thereby affect energy storage and utilization, resulting in healthy or dysregulated metabolism. This will further result in metabolic health or disease. To study this interaction we use a transgenic mouse with altered T cell function, as well as blood, adipose tissue and immune cells from patients with metabolic healthy and unhealthy obesity. We also address the relationship between metabolic healthy and unhealthy obesity and atherosclerotic risk.
Oxidative DNA damage and repair enzymes in atherosclerosis
The recent years, a main focus of the research group has been on oxidative DNA repair enzymes and their role in atherosclerosis. Enhanced generation of reactive oxygen species (ROS) is an important feature of atherosclerosis, induced by etiologic risk factors such as smoking and metabolic disturbances as well as their common final pathway, inflammation. Although ROS generation is a fundamental component of cellular metabolism and signal transduction, enhanced ROS generation may induce increased inflammation, cellular damage and apoptosis as well as DNA instability. If the ROS-induced damage on cellular DNA is not counteracted, it may promote cellular damage and apoptosis within the atherosclerotic lesion leading to plaque instability. Preliminary data from our group indicate that the DNA glycosylase Neil3 could serve as a sensor of metabolic stress, linking metabolic disturbances to atherosclerotic plaque development. Our hypothesis is that Neil3 modulates the development of atherosclerosis through epigenetic mechanisms, and the last year we have started a new major animal study to explore this hypothesis.

FUNDING

Our major external fundings are from
- Norwegian Research Council
- Helse Sør-Øst RHF
- ERA-CVD
- Odd Fellow Medisink Vitenskapelig - Forskningsfond
- Unifor (Freia, Blix, FRIMED, Nansenfondet og de dermed forbundne fond, Wedel Jarlsbergs Fond)

Main Collaborators
Our group has wide range of long lasting collaborators both at the local level: Kåre Birkeland, Hanne Scholz, Kjetil Taskén, Kjetil Retterstøl, Kirsten Holven (Oslo University Hospital and University of Oslo), the national level: Terje Espevik (NTNU), Rolf Berge (University of Bergen), Magnar Bjørås (NTNU and UoO) and Hilde Nilsen (Akershus University Hospital and UoO), as well as important intarnational collaborators: Patrick Rensen (Leiden, The Netherlands), Erik Biessen (Maastricht, The Netherlands), Joachim Schulze (Bonn, Germany)

INFLAMMATORY RESEARCH

Immunological and molecular mechanisms in myocardial remodeling and heart failure

From left: Kuan Yang, Azita Rashidi, Mieke Louwe, Trine Ranheim, Jonas Øgaard, Knut Lauritzen, Maria Belland Olsen and Øystein Sandanger.

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RESEARCH PROFILE

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

PROJECTS

Innate immune responses in cardiac injury, atherosclerosis and related metabolic disorders.
We study three arms of the innate immune system: (1) The NLRP3 inflammasome, a platform for the post-translational activation of IL-1β. In addition to studies on the pathogenic consequences of activation of the NLRP3 inflammasome in CVD, we have projects where we investigate how the inflammasome is activated. (2) The role of the complement system in clinical and experimental atherosclerosis. (3) Effective resolution of inflammation is important to prevent progression of acute inflammation to non-resolving chronic inflammation. Inflammation resolution is a coordinated and active process, and we are currently examining how this is regulated in different forms of CVD.

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

FUNDING

Our work in 2019 was based on funding from Helse Sør-Øst RHF, Research Council of Norway, UNIFOR-FRIMED, Anders Jahres fond til vitenskapens fremme. In addition we are partners in an EU supported project *ERA-NET in CVD.*

INFLAMMATORY RESEARCH

Inflammatory biomarkers in cardiovascular and metabolic disease

From left: Alexander Kirkeby Eieland, Cristina Olarescu, Tove Lekva, Thor Ueland, Mashhood Ahmed Sheik, Annika E. Michelsen and Kjersti R. Normann.

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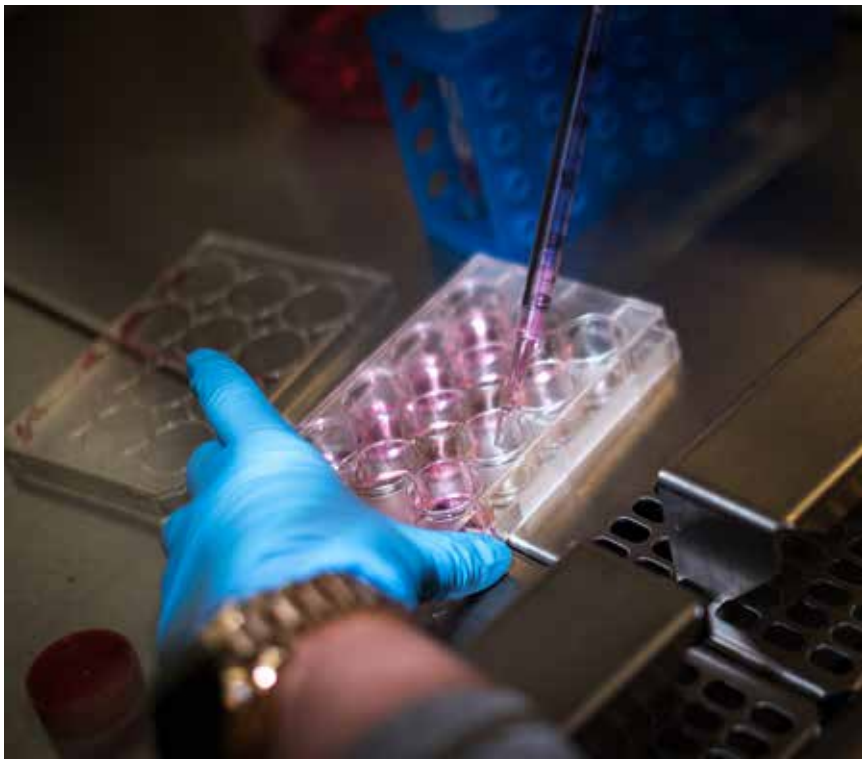
RESEARCH PROFILE

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

We have a close collaboration with the Department of cardiology, 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.

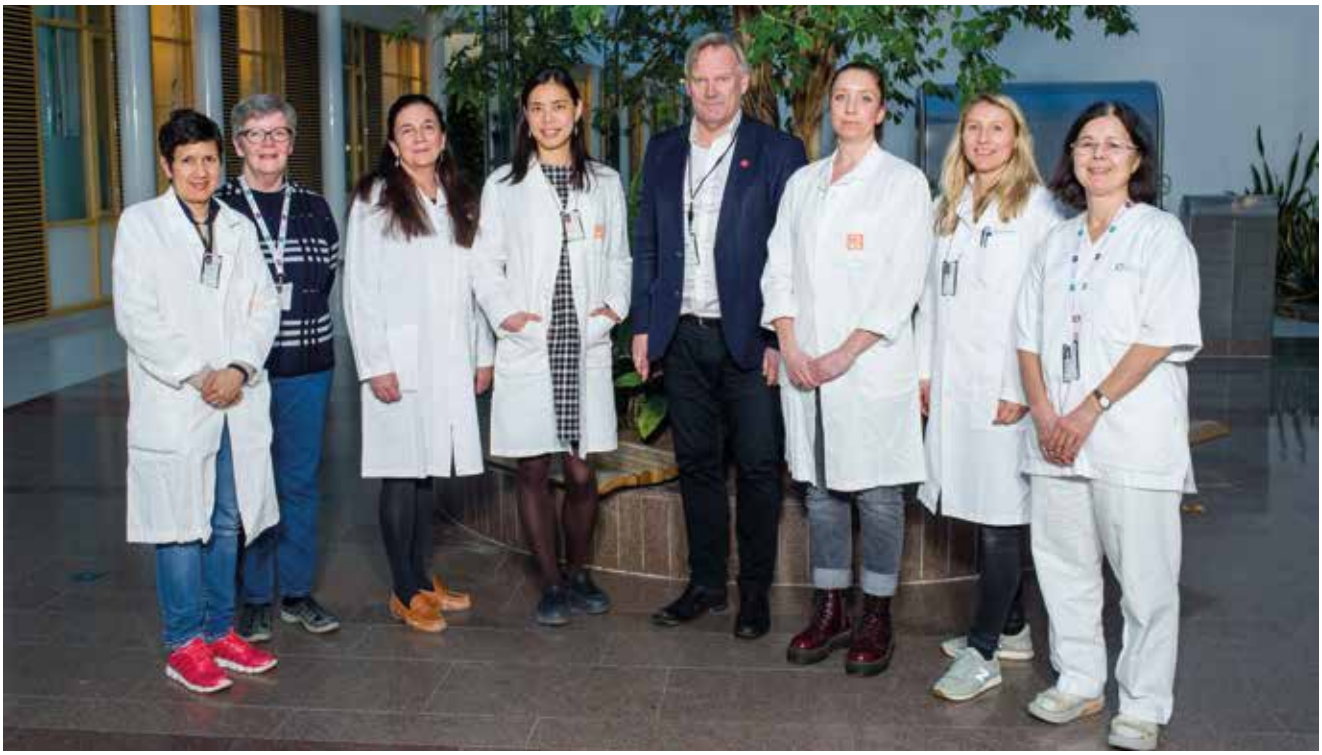
We have a tight collaboration with the Psychosis Research Centre Thematically Organized Psychosis Research (TOP) group, analyzing inflammatory biomarkers in patients with schizophrenia and bipolar disorder. In these studies we focus on markers in serum/plasma as well as mRNA levels in circulating immune 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 projects.

In May 2019 Hilde Margrethe Norum defended her thesis “Soluble Notch Ligands in Heart Failure”.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

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



From left: Maria Eugenia Chollet, Ann Døli, Christiane Filion Myklebust, Xue-Yan Cui, Per Morten Sandset, Marianne Seierstad Andersen, Benedicte Stavik and Marie Christine Mowinckel.

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RESEARCH PROFILE

The main goal of this research group is to identify and uncover important molecular mechanisms of coagulation proteins contributing to or preventing disease.

Anomalies in the blood coagulation system can cause pathological bleeding or thrombosis but also participate in the manifestation of many other diseases such as cardiovascular and inflammatory diseases, and cancer. For instance, arterial thrombosis is in many cases the direct cause of cardiovascular-related deaths, which is the primary cause of death globally, and thrombotic complications are the secondary cause of death among cancer patients. Thus, regulation of the coagulation system is important not only in preventing clinical events related to hemostatic disorders, but also in preventing the morbidity and

mortality of other common diseases. We conduct basic research with a translational potential focusing on several aspects of blood coagulation related to thrombosis, bleeding disorders, inflammation and cancer. The coagulation inhibitor tissue factor pathway inhibitor (TFPI) is of special interest as it has been implicated in the development of several non-hemostatic diseases in addition to being the primary inhibitor of coagulation initiation.

PROJECTS

-Novel treatment options for inherited coagulation factor (F) VII deficiency

Coagulation FVII is produced in the liver and secreted to the blood stream where it circulates as an inactive zymogen. In the event of vascular damage, FVII is activated and fuels the coagulation cascade that is essential for proper clot formation in order to stop the bleeding. Inherited FVII deficiency is caused by mutations in the F7 gene leading to reduced FVII antigen and/or activity levels in the blood and potentially severe bleeding symptoms in the patient. Although the disease is rare, it is the most common of the inherited coagulation factor deficiencies and has a 10-fold higher prevalence in Norway. Factor replacement therapy is the only available treatment for these patients, however, it is not optimal due to a short half-life and high cost. To explore new potential therapeutic approaches that can substitute the present replacement therapy, we are investigating the intracellular fate of different FVII proteins containing mutations previously reported to cause FVII deficiency and bleeding symptoms. The studies are done in physiological relevant liver cell models that express mutated FVII protein, which are generated by genomic editing of immortalized human pluripotent stem cells differentiated into hepatocyte-like cells. Our goal is to use genome editing to correct the FVII mutation in patients-derived cells and to find chemical/pharmacological compounds that can improve the secretion of an active FVII.

-Coagulation factor (F) V and TFPI in atherosclerotic inflammation

A bi-directional relationship between blood coagulation and inflammation has existed for millions of years, and it is clinically evident even today as patients with chronic inflammatory diseases are at higher risk of thrombosis. Atherosclerosis is now recognized as an inflammatory driven disease, where accumulation of immune cells together with lipids causes the artery wall to expand into the vessel lumen, restricting blood flow. Occasionally, these plaques rupture, breaking the protective endothelial lining in the vessel and resulting in thrombus formation, which is the main cause of myocardial infarction and stroke. Using a biobank of human carotid plaques, we are investigating the presence of coagulation factors inside the plaque, and their role in regulating inflammation in the plaque and thus atherosclerotic development. The aim is to identify potential new therapeutic targets that can reduce the inflammatory burden and, potentially, be beneficial in attenuating atherothrombosis.

-TFPI and migration of leukemia cells

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world. Cell trafficking and homing of CLL cells play a critical role in organ infiltration and contribute to the clinical course of CLL. Interaction between CLL cells and endothelial cells affects gene expression in CLL cells and further regulates cell trafficking. Endothelial cells are the main source of tissue factor (TF) pathway inhibitor (TFPI), which is the primary inhibitor of TF. Research showed that TFPI is involved in cell migration in solid tumor. However, the role of TFPI in the progression of solid tumors is still controversial and the effect of TFPI on leukemia progression has not been investigated. In an attempt to find new therapeutic approaches to CLL organ infiltration, we are studying the role of TFPI in the migration of aberrant B cells from patients with CLL.

-TFPI-2 regulation by microRNAs

Although TFPI-2 is structurally similar to TFPI, it has a different, non-hemostatic function and is considered a tumor suppressor involved in regulating tumor progression, invasion and metastasis in breast cancer cells. Clinically, TFPI-2 expression is positively correlated to the survival of breast cancer patients, and thus the molecular mechanism behind the regulation of TFPI-2 expression is of great interest. Micro-RNAs (miRNAs) have been increasingly Using the GOBO database, we found that the TFPI-2 mRNA levels were significantly increased in patients with ERα+ tumors compared to patients with ERα- tumors and that increased levels of TFPI-2 were associated with increased survival in patients with ERα+ tumors. We have demonstrated that estrogens induced TFPI-2 expression in ER positive breast cancer cells in a process mediated by ERα and a specific lysine demethylase. A continuation of this project is in progress where potential effects on TFPI-2 expression by miR-RNAs are being examined.

FUNDING

Oslo University Hospital; The South-Eastern Norwegian Regional Health Authority.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

Haemostasis and bleeding disorders

From left: Adelheid Holm, Nina Haagenrud Schultz, Pål André Holme, Ragnhild J. Måseide, Christian Qvigstad and Ruth Elise Dybvik Matlary.

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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 1200 persons with bleeding

disorders. Several research projects are ongoing besides clinical activity.

Moderate haemophilia
Current treatment of haemophilia is predominantly guided by the severity classification. While patients with severe haemophilia are closely monitored and receive early prophylaxis, moderate and mild patients are monitored less frequently and mostly receive treatment on-demand. The group of moderate haemophilia, however, is heterogeneous with a wide variation in clinical phenotype, with some of the patients having a considerable need for factor substitution. Bleeding phenotype is not strictly correlated to the coagulation factor level, but also influenced by physical activity, presence of target joints and synovial hypertrophy, degree of arthropathy and adherence to a prophylactic regime. According to more recent thinking, haemophilia care and treatment therefore should be tailored individually. The aim of the ongoing PhD project (Ragnhild J Måseide) is to study and evaluate the treatment and joint health in Nordic moderate haemophilia patients (haemophilia A and B) (factor level 1-<5 IU/dL) in the Nordic region to explore if they receive optimal care. The study have enrolled 145 pts and data are now analysed and manuscripts soon submitted for publication.

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

Optimizing bypassing agents.
During the last years we have studied and published papers on how to optimize and tailor treatment in persons with haemophilia with or without inhibitors to FVIII and in persons with FVII deficiency.
One of main objectives has been tailoring of treatment with bypassing agents (BPA) for haemophilia patients with inhibitors. Development of inhibitors is the most serious complications of haemophilia treatment today, High titre inhibitors to factor VIII and less often to factor FIX, represent a major challenge in the treatment of haemophilia A and B. The treatment of bleeds in haemophilia patients with inhibitors relies on the use of the bypassing agents, factor eight bypassing activity (FEIBA) or recombinant factor VIIa. While both therapies are effective in the majority of bleeding episodes and postoperative prophylaxis, there is a significant amount of inter individual variability when it comes to the response to therapy. During the last year emicizumab have been introduced to many of our haemophilia patients with inhibitors as prophylactic treatment. When these persons need to undergo major surgery etc monitoring of the haemostatic effect is essential since we need to use concomitant treatment with BPA.
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 with or without concomitant treatment of emicizumab using thromboelastography (TEG/ROTEM) and thrombin generation test (TGA) to individualize coagulation factor concentrate usage and dosing in the home treatment program, individualize coagulation factor concentrate usage and dosing prior to and in the postoperative period,

address the issue of minimum effective dose during surgery and apply these assays in the evaluation of the critically ill patient with concomitant haemostatic insufficiency. In addition we have published that adjunct use of tranexamic acid (TXA) to BPA significantly increased the clot stability without increasing the thrombin generation and may be superior to standard treatment with BPA alone.

Reversal of factor Xa inhibitors
Today there are no available, evaluated effective treatments to reverse the effect of FXa-inhibitors (direct oral anticoagulants (DOAC)). We have performed studies where the objectives were to detect the most effective haemostatic agent (activated prothrombin complex concentrate (aPCC), prothrombin complex concentrate (PCC) and rFVIIa and appropriate dose for reversal of bleeds caused by FXa inhibitors extensively used in the clinic for atrial fibrillation and treatment of venous thromboembolism. The effect was assessed mainly by the two global coagulation methods thromboelastography (TEG) and thrombin generation assay (TGA). Five papers on this subject have been published and Nina Haagenrud Schultz defended her thesis entiteled: "Oral factor Xa inhibitors: Studies on reversal of their anticoagulant effect and on their influence on primary hemostasis endothelial function and fibrinolysis." November 2019 and further studying new aspects as a post doc.

HemFitBit study- Defining Normal Activity in Hemophilia
There is a lack of knowledge regarding how physically active people with the bleeding disorder haemophilia A are compared to

controls without haemophilia. This project will collect information on physical activity levels in 40 patients with haemophilia A aged 12-30 years over a 3-month period. This will be done using the wearable technology 'Fitbit'. A subgroup of participants will also wear the accelerometer 'ActiGraph' in order to validate the two devices against each other.
The study data will be compared with pre-existing age-, region- and season-matched controls. Additional data will be collected on absence from school/work and on the individuals' experiences of how the bleeding disorder affects daily life. Relevant medical information such as coagulation factor consumption, joint status, bleeding rate and wellbeing will be collected. This information will be analysed to see if there are any relationships between these factors and level and intensity of physical activity. One hypothesis is that the registered physical activity level can be used as a surrogate outcome measure to the number of bleeds per year (annual bleeding rate) which is currently the most utilised outcome measure, although considered an uncertain subjective endpoint. Ruth Elise Dybvik Matlary, MSc is working as a PhD student on this project and already included 30 pts.

Immune thrombocytopenia
Parts of the group is also involved in studies on immune thrombocytopenia ITP and in the RITP trail we aimed to assess the efficacy of rituximab as compared with placebo as a splenectomy-sparing treatment in patients who were previously treated with corticosteroids. (Lancet 2015; 385: 1653–61). The follow up study PROLONG has now been ongoing for 4 years where we want evaluate the long-term effect of rituximab and immunological changes also including a PhD project on the immunological.

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

AWARDS 2019

Beate Vestad, PhD student in the Genomics and Metegenomics group of NoPSV won the Tore Midtvedt Prize for her abstract "Interplay of Gut Microbiota and Immunodeficiency on Excess Metabolic Risk in HIV Infection", at the National Microbiota Conference 19th of November 2019 in Oslo.


Marit Grimsrud fikk 10 000 kr for arbeidet: «Epigenetiske biomarkørar i galle identifiserer kolangiokarsinom hos pasientar med primær skleroserande kolangitt med høg diagnostisk nøyaktigheit.»

Marit Mæhle Grimsrud recieved a prize for her work on «Epigenetiske biomarkørar i galle identifiserer kolangiokarsinom hos pasientar med primær skleroserande kolangitt med høg diagnostisk nøyaktigheit» at Norsk Gastroenterologisk Forening's (NGF) annual meeting at Lillehammer 7-9th of February 2019.

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