Oslo University Hospital

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Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2022

RIIM
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2022

Pages

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Leader´s corner

Professor Espen Melum
Head of the Research Institute of Internal Medicine

2022 marks the first year where RIIM was back to almost normal operations following the pandemic. The good collaborative spirit did not go away, and it has been great to see so many people back in the labs and offices on a regular basis once again. The institute has been very active with regards to COVID research, and many of these papers were finished and published in 2022 which led to an all-time-high number of publications with 125, this is a 30% increase compared to 2019. Among these papers several were published in high-impact journals that received a lot of attention.

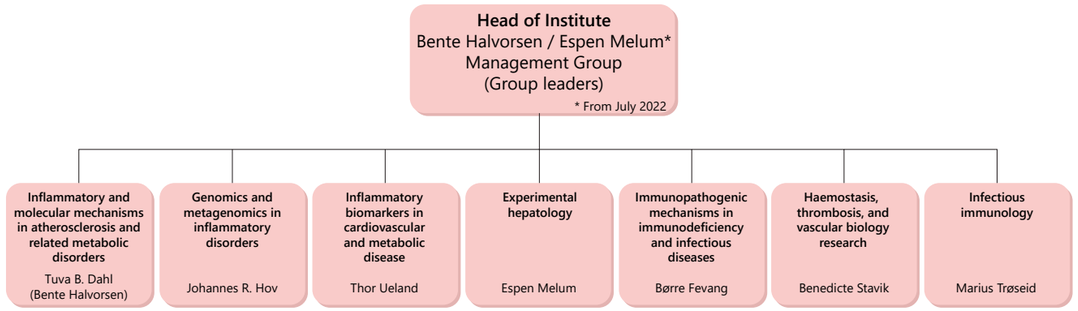
In 2022 Professor Bente Halvorsen received The Nikkilä Memorial Lecture Award, which is prestigious European award within atherosclerosis research. This award is an important acknowledgment for her focus on atherosclerosis research with a range of important discoveries. Post.doc. Silje Fjellgård Jørgensen received the Oslo university hospital early career award for her work on common variable immunodeficiency (CVID) and I hope this will encourage her to continue this important line of research. The institute is extremely proud of these awards and they demonstrate that our research is acknowledged in the wider research community both internationally and locally. The EASL-Lancet Liver Commission on liver diseases led by Professor Tom H. Karlsen was also published in 2022 which is a landmark paper in the field of liver disease and outlines the unmet needs and action points for the years to come.

What we thought was impossible in Europe happened with the Russian invasion of Ukraine in February 2022. Together with the Norwegian PSC research center we reached out to Ukrainian scientists through the #scienceforukraine initiative to fund short research stays. Based on this we had the pleasure of welcoming two new colleagues that integrated very fast into our research environment, one of them later moved on to a prestigious program at the University of Oxford with a full stipend while the other one has continued to work with us.
Oslo University Hospital is currently going through the final stages of planning the new national Hospital at the Gaustad campus. RIIM has actively taken part in multiple committees related to these plans with the aim of getting the best possible solution for the institute within the framework offered to us by the hospital. As it has already been decided that we need to move out of our current location to make room for clinical activities, it is important for us to maintain the proximity to the clinic to enable true translational research and access to key infrastructure like the animal facility. In parallel with participating in these committees, we have also had a central role in a separate process evaluating whether it is possible to place the four research institutes at Oslo University Hospital focusing on translation science in close proximity at the new national hospital. Such co-localization will give us significant synergies both with regards to scientific projects as well as equipment and infrastructure. This initiative has been enthusiastically welcomed by the involved institutes and the report from this initiative is currently under evaluation by the South-Eastern health authorities before potentially moving into a more detailed planning phase. The process with the new hospital has previously been challenging for many of us as it gives uncertainty for our future placement, but with the developments in 2022 this process is now being perceived as something very positive with our options being either moving into new laboratories in the new M building or together with the other research institutes focusing on translational research. In the meantime, it is also extremely important that we develop scientifically in our current location and also adapt these areas according to our needs.

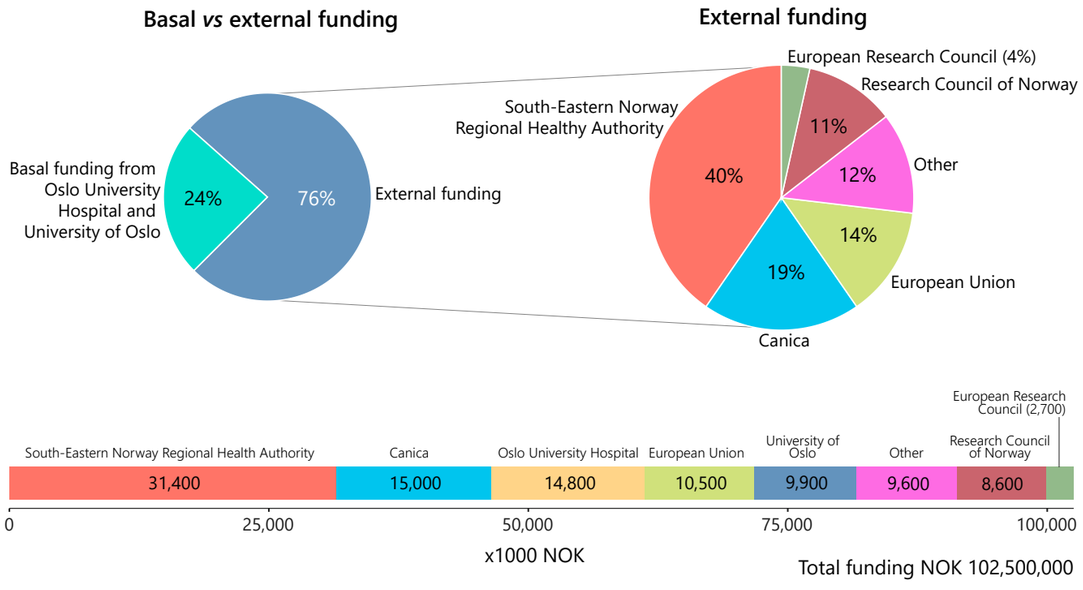
Funding is continued priority and necessity to perform our research. The funding situation in the Norwegian Research Council has received a lot of attention, and will hopefully soon lead to the launch of new and strong grant opportunities. In addition to changes at the research council, we must also acknowledge that our funders are shifting their focus to the utility of the research. This can be challenging for basic and translational projects, but at RIIM with our clear clinical connection our research should remain competitive also in this framework. This was underlined by a record number of grants award by the South-Eastern health authorities at the end of the year.

I have had the privilege of leading the institute as the locum department chair while Professor Bente Halvorsen is on a sabbatical in Boston. It has been a pleasure to get to know the research groups at the institute even better and try to facilitate so they can perform their research in the best possible manner. I am also very grateful to Sverre Holm, Kari Otterdal and Turid Pedersen who has joined me in running the institute and ensured smooth operations in this period. Finally, I want to thank everyone at RIIM for their efforts in 2022 that has enabled high scientific productivity and a fantastic working environment.

ORGANIZATION



ECONOMY / FUNDING



Upper panel: Organizational chart.
Left panel: Funding sources for the institute (basal versus external funding).
Right panel: External funding sources detailed. Lower panel: Amount of funding from all sources in NOK (represented by thousands).

FOCUS AREA

Research theme – Atherosclerosis

Ida Gregersen and Sverre Holm

Atherosclerosis is a pathogenic accumulation of lipid and immune cells in the vessel wall of middle-sized and large arteries, and is the main underlying cause of cardiovascular disease, including myocardial infarction and ischemic stroke (Fig. 1). Atherosclerotic disease was traditionally a disease of high-income countries, but has now spread to the whole world, and is the main cause of death globally. In Norway, one in five adults are currently living with or are at high risk of developing cardiovascular disease; and even though deaths of these diseases is lower than in the rest of Western Europe, it is still the second most important cause of death in Norway. Besides percutaneous angiographic intervention, effective therapeutic options have not improved during the last decade. The traditional risk factors, including high levels of LDL and high blood pressure, has now received significant company of the increasing prevalence of obesity and its subsequent metabolic disease; which are now important drivers of atherosclerotic disease all over the world. As a common mediator of cardiovascular risk factors stands inflammation; and in essence all immune cells are involved in the inflammatory response driving atherogenesis. Inflammation is involved in all stages of atherosclerotic plaque development, and plays a significant role in clinical manifestation, including myocardial infarction and ischemic stroke. A better understanding of the pathogenesis of this complex disorder is a prerequisite for the development of new prevention and treatment modalities in atherosclerosis and its complications.

Recently, a novel risk factor of atherosclerotic disease has emerged, termed Clonal haematopoiesis of indeterminate potential (CHIP). This is a common condition, according with age, characterized by clonal expansion of haematopoietic stem cells bearing mutations in certain genes. CHIP is associated with accelerated atherosclerosis in mice and increased risk of atherosclerotic disease in humans. The increased risk observed with CHIP involves immune cell activation and inflammation, however the exact mechanisms are still not clear. Recent clinical trials have shown potential of anti-inflammatory therapy, however, such treatment also poses an increased risk of infections; indicating that more precise anti-inflammatory treatment is warranted. CHIP carriers are suggested as a target group that would benefit from such therapy, and could thus be a stepping-stone for personalized medicine to treat atherosclerotic disease. This will be an interesting research area to follow the coming years and will hopefully increase or knowledge of atherosclerosis, to improve patient care and reduce death and disabilities.

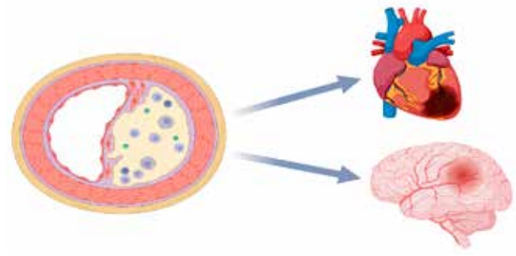


Fig. 1. Cross section of an atherosclerotic artery showing accumulation of lipids and influx of immune cells. This leads to narrowing of the lumen, disturbed blood flow and increased risk of rupture and thrombosis. Altogether, atherosclerosis is the most important underlying factor for the development of myocardial infarction and ischemic stroke.

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Atherosclerosis research in a translational perspective

Ida Gregersen and Sverre Holm

Researchers at RIIM are world leading in the field of translational atherosclerosis research and RIIM is the only milieu in Norway working with atherosclerotic mouse models. The preclinical models used at RIIM to study atherosclerosis includes *ApoE*$^{-/-}$ and *Ldlr*$^{-/-}$ mice, as well as atherosclerotic models driven by adenoviral expression of PCSK9. Use of these models combined with other genetic modifications, through for instance bone marrow transplantations, is a powerful tool to further decipher the underlying mechanisms of atherosclerosis development.
Through close collaboration with clinicians, researchers at RIIM have valuable access to unique patient material and data, ensuring rapid translation from the lab bench to bed, and back again. In-depth studies in immune cells and screening of inflammatory mediators in patient samples, as well as knock out mouse models supplemented with in vitro cell experiments, are essential components in our translational research approach on atherosclerosis (Fig. 1)

The atherosclerosis research focus on RIIM has largely been on the role of inflammation as a driver of disease, as well as studies on DNA repair enzymes, epitranscriptomic regulation, metabolic dysfunction and the interplay between these processes. The last years, the Covid-19 pandemic has also had impact on the atherosclerosis research at RIIM, as several studies indicate that patients suffer an increased risk of cardiovascular disease after recovery from severe Covid-19 disease. At the Institute, several translational research projects to unravel the underlying mechanisms of cardiovascular sequela after Covid-19 are currently ongoing. A recent finding is that patients that have been hospitalized with Covid-19, still 3 months after hospitalization have altered aggregation pattern of LDL particles suggesting a possible contributor for the increased cardiovascular risk observed after severe Covid-19 infections.

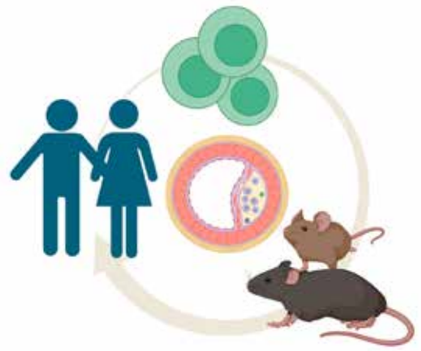

Fig. 1. Translational atherosclerosis research at RIIM combines well-characterized patient materials with *in vitro* studies and advances studies in mice models of atherosclerosis. All aiming at bringing the findings back to the clinic, improve both diagnosis and treatment of atherosclerosis and related cardiovascular diseases.

Institute collaboration – From atherothrombosis to inflammation

By Benedicte Stavik

Even for us researchers in the coagulation field, it is easy to dismiss thrombosis as thrombosis whether it occurs in the venous or arterial system. However, there are substantial differences in the pathophysiology related to these unwanted and potentially serious clinical events. While venous thrombosis has a large genetic component and usually occurs during immobilization, arterial thrombosis is caused by atherosclerotic lesions in the vessel wall and often occurs during stress. In fact, atherosclerosis is the main cause of cardiovascular disease and only cancer kills more people every year. It is the inflammatory driven, progressive development of lipid-filled plaques in the arteries, eventually causing a rupture in the vessel wall, that leads to thrombus formation and clinical symptoms. Blood clots are formed due to exposure of components such as von Willebrand Factor and Tissue Factor (TF) in the sub-endothelial layer of the blood vessel, resulting in platelet binding and coagulation initiation. Pro-coagulant and anti-coagulant proteins circulate in the blood stream and are captured at these initiation sites to perform their function, thus regulating both the strength and localization of the clotting. However, it is well known that components of atherosclerotic plaques can be highly thrombogenic, especially the lipid-filled necrotic core

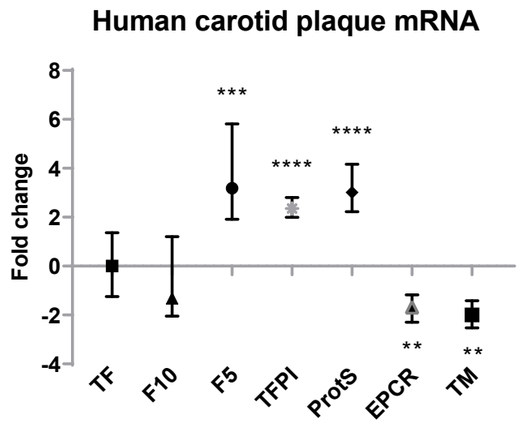

Fig. 1. mRNA expression of different coagulation proteins analysed in human carotid endarterectomies and control arteries (common iliac artery of diseased organ donors) using real-time qPCR. Results are calculated as fold change against control and presented as median ± interquartile range (n = 14; control arteries, n ≥ 159; plaques).

(1), and this is thought to be due to high TF activity (2). Thus, upon rupture, the plaque content can destroy the fine-tuned balance between pro- and anti-coagulant forces in the blood, resulting in a stronger clotting response and pathologic thrombus formation (atherothrombosis). Through a collaboration with the department of neurology, Bente Halvorsen has access to a unique biobank of atherosclerotic plaques collected from patients undergoing carotid endarterectomy here at the hospital. We therefore decided to join forces and together with her group we investigated in greater detail the expression and potential role of different pro- and anti-coagulant proteins in the plaque material to find out more about how they contribute to atherothrombosis. We started with measuring mRNA expression of different coagulation genes, and with the exception of Factor (F) 7 and Protein C, we detected the expression of all other genes tested (Fig. 1). Interestingly, we found no difference in TF mRNA levels in the plaque material compared to non-atherosclerotic control arteries, but the pro-coagulant F5 was upregulated. Of the anti-coagulant genes, Tissue factor pathway inhibitor (TFPI) and its co-factor Protein S (ProtS) were upregulated while Endothelial protein C receptor (EPCR) and Thrombomodulin (TM) was downregulated. FV is a co-factor substantially increasing the activation of FX and the coagulation cascade, while EPCR and TM efficiently inhibits prolonged thrombin activity and clotting, and their levels may contribute to a more thrombogenic plaque. TFPI, however, is the physiological inhibitor of TF and its increased expression made us curious. In addition to being an important anti-coagulant, TFPI also has a to date unknown function as a carrier of lipoproteins in plasma and its levels correlate

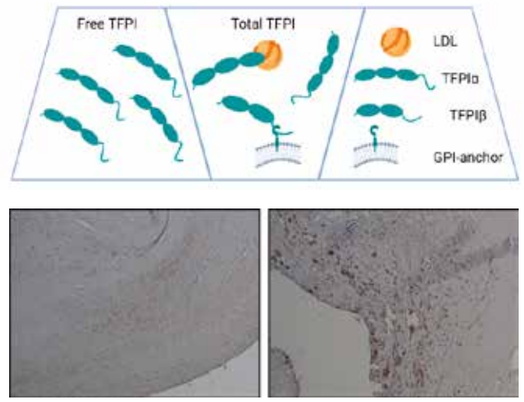

Fig. 2. Immunohistochemistry of plaque sections stained with antibodies against free TFPI (left) or total TFPI (right). 100x.

strongly with LDL cholesterol levels in the blood (3). We therefore went on investigating the presence of TFPI protein in the plaque material. Two isoforms of TFPI are made, TFPIα and TFPIβ. Some TFPIα circulates in a free, full-length form but the majority circulates as a truncated from in complex with lipoproteins that have little anti-coagulant activity. TFPIβ contains a GPI-anchor and is only found on the cell surface. We found evidence for increased mRNA expression of both isoforms of TFPI in the plaque material, though the expression of TFPIβ was marginal, Also, both free (full-length TFPIα) and total (TFPIα in complex with lipids + TFPIβ) TFPI protein was detected (Fig. 2), but total TFPI was more abundant. In patients with echolucent plaques, total TFPI levels were high while free TFPI levels were low, indicating that the majority of TFPI in these lipid-filled plaques were not of the free, anti-coagulant form, but rather the lipid-carrying, non-anticoagulant form. Consistent with this, we detected abundant total TFPI in foam cell structures surrounding cholesterol crystals in the plaque core (Fig. 3). In vitro studies revealed that cholesterol crystals induced TFPI expression in primary monocyte-derived macrophages, but only of the M2 subtype, and TFPI co-localized to a

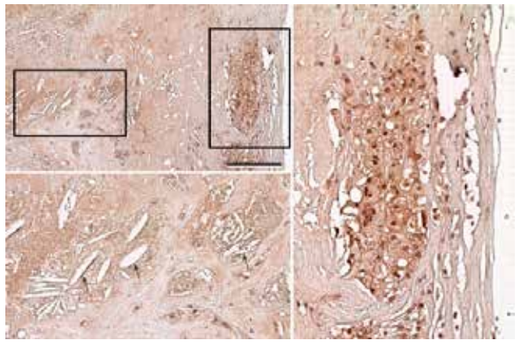

Fig. 3. Immunohistochemistry of human carotid plaque sections stained with antibody against total TFPI. Rectangles of s elected areas are shown in higher magnifications. Arrows indicate CC-clefts. Scale bar=200 µm

greater extent with macrophages of the M2 than the M1 subtype in the human plaques (Fig. 4). Thus, in contrast to what we initially thought, TFPI present in plaque material might not play such a substantial role in atherothrombosis upon plaque rupture but seemed instead to be more involved in the inflammatory process responsible for plaque development. Whether this is a positive or negative thing for disease development in humans remains to be unveiled but it has been shown that mice that overexpress TFPI hardly develop atherosclerosis at all (4). This discovery (5) was the start of a fruitful and productive collaboration between our research groups that has strengthened both our scientific and social bonds.

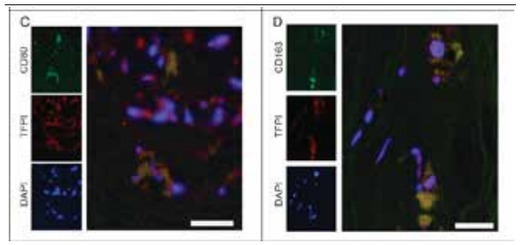

Fig. 4. Co-immunofluorescence staining of human carotid plaques with antibodies against total TFPI, and M1 marker CD80 (left) or M2 marker CD163 (right). Sections were counterstained with DAPI. 400× magnification. Scale bar = 25 µm.

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DISSERTATIONS 2022

Photo: Ine Eriksen, UiO

Camilla Huse, MSc.

"Regulation of immune cells in atherosclerosis and its clinical implications - The role of A-to-I editing and interleukin 6 receptor inhibition"
Nov. 29, 2022

Committee:
1. opponent: Professor Paolo Parini, Karolinska Institutet, Sweden
2. opponent: Researcher Pieter Goossens, Maastricht University, The Netherlands
3. opponent: Professor Marit Inngjerdingen, University of Oslo

Main supervisor: Senior Researcher Tuva Børresdatter Dahl
Co-supervisor(s): Professor Bente Halvorsen, Professor emeritus Pål Aukrust

Summary of PhD project:
Recruitment of immune cells to the developing atherosclerotic plaques is a hallmark in the atherosclerotic process. Immune cell recruitment is also a major factor following acute cardiovascular events in atherosclerosis, such as myocardial infarction and stroke, where there is massive recruitment to the site of injury. To identify treatment targets, there is a need to better understand the immunopathogenic mechanism in the atherosclerotic process and its related clinical implications.
In this thesis, we aimed to: (i) assess the impact of Endonuclease V (EndoV), an enzyme known to cleave adenosine-to-inosine (A-to-I) modified RNA, on the immune cell response in atherogenesis and stroke, and (ii) investigate the effect of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, on the immune cell levels and responses in patients during ST-elevation myocardial infarction (STEMI).
In human carotid atherosclerotic plaques, we found higher levels of EndoV and A-to-I editing than in non-atherosclerotic arteries. Absence of EndoV gave a reduced atherosclerotic plaque burden, both in lipid content and lesion size, with reduced monocyte recruitment in mice. In addition, abolishment of EndoV seemed to have protective effects on brain damage in a murine hypoxia-ischemic stroke model. Inhibition of the IL-6 signaling pathway in STEMI patients is beneficial for the patient outcome. This thesis shows that tocilizumab reduced neutrophil and monocyte counts without affecting lymphocyte counts in the circulation following STEMI. Tocilizumab dampened the inflammatory responses in neutrophils with neutrophil degranulation, while monocytes had an upregulation of several cytokine signaling pathways with potential beneficial effects on myocardial remodeling and inflammation. These changes might contribute to the observed improved outcome for the tocilizumab treated patients.

Photo: Øystein Horgmo, UiO

Tom Rune Karlsen, MD

"Missing NEIL3: a kick in the gut and a punch to the heart"
Nov. 24, 2022

Committee:
1. opponent: Professor Allan Sirsjö, Ørebro University
2. opponent: Professor Tor Gjøen, Faculty of Mathematics and Natural Sciences, University of Oslo
3. opponent: Researcher Cathrine Rein Carlson, University of Oslo

Main supervisor: Professor Bente Evy Halvorsen
Co-supervisor(s): Senior Researcher Ida Gregersen, Researcher Xiang Yi Kong

Summary of PhD project:
Cardiovascular disease (CVD), which includes cerebral stroke and myocardial infarction, comprises a significant risk to public health, in addition to being a major financial burden in society. The most important cause behind CVD is atherosclerosis. Even though we are familiar with several risk factors underlying atherosclerosis, there is a lot we do not know about the

DISSERTATIONS 2022

initiation and progression of the disease.
Endonuclease VIII-like glycosylase 3 (NEIL3) is an enzyme that repairs oxidized (damaged) bases in DNA. Previous research suggests that certain polymorphisms of NEIL3 are associated with increased risk of myocardial infarction. The aim of this thesis is to explore this relationship further, using mouse models prone to atherosclerosis.
It was shown that NEIL3-deficient mice develop more atherosclerosis than control mice. The increased atherosclerosis was not associated with increased lipid levels or inflammatory markers in the blood, nor with increased DNA damage in the cells. However, smooth muscle cells in the arterial wall of NEIL3-deficient mice exhibited a pro-atherogenic and proliferative phenotype.
Furthermore, gut microbiota-dependent metabolites were found at differing levels in the plasma when comparing NEIL3-deficient mice and control mice. Investigations of the bowel showed that the gut microbiota had a different composition between the two groups, and there was increased gut permeability in NEIL3-deficient mice.
Telomeres, DNA-protecting structures which shorten with age, were shorter in NEIL3-deficient than in control mice. Also, hematopoietic cell numbers were decreased both in the bone marrow and in peripheral blood. This suggests that NEIL3 has an essential telomere-protecting function in vivo.
These findings confirm and elaborate on previous research done on NEIL3, and suggest mechanisms linking NEIL3-deficiency and increased atherosclerosis.

Photo: Øystein Horgmo, UiO

Christopher Storm T. Ligaard, MD

"Clinical interventions of the human gut microbiota"
Aug. 26, 2022

Committee:
1. opponent: Professor Max Nieuwdorp, Amsterdam University Medical Centers
2. opponent: Researcher Randi J Bertelsen, University of Bergen
3. opponent: Professor II Mathias Toft, University of Oslo

Main supervisor: Professor II Johannes E. R. Hov, Institute of Clinical Medicine, University of Oslo
Co-supervisor(s): Professor II Marius Trøseid, Research Institute for Internal Medicine, University of Oslo

Summary of PhD project:
Growing evidence suggests that bacteria residing in the intestines have a significant impact on factors related to human health and disease. An increasing number of reports have demonstrated associations between gut microbiota and human diseases; however, most studies have yet to demonstrate causality. Knowledge on how we could induce alterations of gut microbiota through targeted interventions would increase our understanding of the complex interplay within this intricate ecosystem. This thesis includes three clinical trials aiming to induce perturbations in the gut microbial composition of individuals with an altered gut microbiota compared to healthy individuals. Longitudinal research efforts permit the exploration of the dynamics of gut microbiota and increase the functional understanding of its relationship with human health factors.

First, the gut microbiota of people infected with HIV was targeted using a probiotic milk supplement. Second, the effects on the gut microbiota of a common disease-modifying drug used for multiple sclerosis were evaluated with emphasis on the relationship with drug-associated gastrointestinal symptoms. Last, the effect of omega-3 fatty acids on the gut microbiota and blood lipids was tested in a population with familial hypercholesterolemia.

The treatments modulated the gut microbiota to a varying degree, and in this thesis, the author discusses factors related to the observed effects and the clinical relevance of these perturbations. A critical review of the methodology used is provided, with emphasis on the limitations that may have caused clinically relevant effects to be overlooked. Lastly, the author presents the experiences the research team has had after targeting the gut microbiota in three different clinical trials and concerns that should be considered when designing a clinical trial to target the gut microbiota.

Photo: Ine Eriksen, UiO

Ragnhild Johanne Måseide, MD

"Moderate haemophilia A and B in the Nordic countries – The MoHem study"
Feb. 16, 2022

Committee:
1. opponent: Professor John Pasi, Queen Mary University of London
2. opponent: Adjunct Professor Anna-Elina Lehtinen, HUCH Comprehensive Cancer Center, Meilahti Triangle Hospital
3. opponent: Professor II Bjørn Bendz, University of Oslo

Main supervisor: Professor II Pål André Holme, University of Oslo
Co-supervisor(s): Professor Erik Berntorp, Lund University, Professor II Geir E. Tjønnfjord, Oslo University Hospital

Summary of PhD project:
Recurrent joint bleeds lead to progressive arthropathy, which is the main long-term complication for patients with haemophilia. Prophylactic replacement therapy from early age has improved joint health in severe haemophilia (factor VIII/factor IX activity (FVIII/FIX:C) < 1 IU/dL) and is now the standard of care. Patients with moderate haemophilia (1-5 IU/dL) have mainly received episodic treatment, and the prevalence of arthropathy in the group is not well characterised.
The aims of the thesis were to describe current joint health in Nordic patients with moderate haemophilia A (MHA) and B (MHB) in relation to treatment modality, and to explore and compare ultrasound and physical examination to detect early arthropathy. We also explored the role of global coagulation assays to unravel the patients' bleeding phenotype.
The MoHem study was a cross-sectional, multicentre study covering 145 patients with MHA and MHB in Sweden, Finland, and Norway. Median age was 28 years and 38% were on prophylaxis, started at median 10 years of age. Patients with FVIII/FIX:C ≤ 3 IU/dL and those with MHA had experienced their first joint bleed at a younger age, implying more severe bleeding phenotype. Overall, current joint health was good, but 15% had undergone orthopaedic surgery because of haemophilic arthropathy. FVIII/FIX:C ≤ 3 IU/dL was associated with impaired joint health. Ultrasound clarified the origin of subtle clinical findings and detected subclinical pathology. In a study subgroup, thrombin generation and thromboelastometry distinguished between mild or more severe bleeding phenotypes.
In conclusion, we suggested primary prophylaxis to all patients with FVIII/FIX:C ≤ 3 IU/dL according to similar guidelines as for severe haemophilia. Ultrasound improved joint assessment and should be used regularly in clinical practice to detect early arthropathy. Global coagulation assays were able to discriminate between bleeding phenotypes, which may contribute to personalised treatment.

Immune regulation in atherosclerosis and other cardio-metabolic diseases

Photo: Åsne Rambøl Hillestad, UiO

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Immune regulation in atherosclerosis and other cardiometabolic diseases
About the group
Cardiovascular disease and related metabolic disorders such as diabetes, obesity and fatty liver disease are major causes of morbidity and mortality worldwide. They have many common features, such as dyslipidemia and inflammation. In our research group we focus on immune-mediated mechanisms in these conditions. The last years we have also studied these mechanisms in Covid-19, and the association between Covid-19 and risk of cardiovascular disease. By exploring these processes through a translational approach, connecting basic science and the clinic, we wish to build a foundation for the development of new diagnostic and treatment targets for cardiometabolic disease. Our research group works in the cross-section between molecular biology and biochemistry, and cardiovascular, cerebrovascular, and endocrine medicine. Our ambitious goal is to delineate novel therapeutic targets and biomarkers.
The group uses different research approaches, ranging from analyses of blood and tissue samples from patients to studies in genetically modified mice and cell culture systems, using advanced cellular and molecular biology. The group consists of people with different educational background and includes medical doctors, nutritionists, biochemists, and engineers. Such multidisciplinary competence is a great strength of our research group.

Activity in 2022
The group runs a large span of interconnected translational projects to study the immunological and molecular mechanisms in obesity, metabolic disorders, cardiovascular disease and Covid-19, and our main projects during 2022 were:

DNA repair enzymes. The group has finalized a long project to study the role of the DNA repair enzyme Neil3 in atherosclerosis. NEIL3-deficient mice develop increased atherosclerosis compared to control mice, and we have further found that NEIL3 is important for hematopoiesis and telomere maintenance in mice. We have also studied the role of the DNA repair enzyme, SMUG1 in fatty liver disease and found that SMUG1 modulates fat metabolism favoring lipogenesis resulting in development of a fatty liver phenotype in mice.
T cells in obesity and metabolic disease. One of the group's largest projects aims to decipher the role of T cells in development of obesity and metabolic disease. We study a transgenic mouse model with altered T cell activation, which is a unique model to explore this association. In 2022 we have performed extensive immune characterization of our model, including single cell RNA sequencing and CyTOF analysis, as well as adaptive T cell transfer experiments and bone marrow transplantation experiment to determine the role of immune cells in these conditions.

Clinical material and add-on studies to clinical intervention trials. In addition to a wide spectrum of animal models to study cardiometabolic disease, we study molecular mechanisms in patient materials, as a bridge between the lab and the clinic. In 2022 we have published several papers describing altered immune status in patients with cardiovascular disease. Particularly, in blood from patients with acute myocardial infarction, we have found increased potential of circulating factors to active macrophages ex vivo. Further, we have characterized the immune cell profile of STEMI patients receiving anti IL-6 treatment (from the ASSAIL trial) to identify molecular mechanisms for the beneficial effects of tocilizumab in this group.

Covid-19 and Covid-19 sequalae. In several publications, we have in

2022 described different features of altered immune regulation in patients with Covid-19. We have studied DNA repair mechanisms in circulating lymphocytes, and shown that markers of cellular senescence is associated with reduced lung function 3 months after infection. Further, we have measured and found several inflammatory mediators to be associated with mortality and disease severity (CCL19, CCL20), and also cardiac involvement (CXCL16) in hospitalized patients with Covid-19. Further we have studied how the treatment of hospitalized patients with the anti-viral drugs Remdesivir and Hydroxychloroquine, affects the immune response and metabolism.

Other projects – cooperation. Experience and expertise possessed by our group members lead to fruitful collaborations also in 2022. To mention a few, we planned and performed a pre-clinical study in mice in collaboration with NTNU, where a synthetic peptide was used as a potential new treatment after myocardial infarction. In a different collaboration with Nofima and Division of Clinical Nutrition we are now finalizing a pre-clinical study where we found that certain dietary lipids can dampen the development of atherosclerosis in mice. Of clinical collaborations, we are now studying the role of immune cells and inflammation in brain abscesses.

EU-project – Painfact. We are actively participating in an EU-funded project, PainFACT, investigating the link between pain sensation and immune response. The sensation of pain is an evolutionary adaptation for organism to identify danger. It is a hallmark for injury, inflammation and pathogen invasion, and is mediated through nociceptor sensory neurons. A cross-talk between nociceptors and the immune system is well known, especially the capability of immune modulators to sensitize nociceptors, thus increasing an individual's sensation of pain. The PainFACT consortium integrates pre-clinical and clinical data to investigate the correlation between pain sensitivity/threshold and risk of cardiovascular events. In 2022, we have further processed biological material from a large-scale pre-clinical study, and made them suitable for down-stream analysis to be conducted by the consortium.

Clinical immunology and infectious diseases

Photo: Øystein Horgmo, UiO

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

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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. Silje Fjellgård Jørgensens post-doc project include in-depth studies of transcriptomic, proteomic and epigenetic changes in gut mucosa from CVID-patients. The post-doc project will now be continued through a researcher grant from HSØ. Granulomatus-lymphocytic Interstitial lung disease (GLILD) can be a severe complication of CVID and in a new project Mai Sasaki Aanensen Fraz has looked into biomarkers for GLILD as well as differences between patients with stable and progressive disease. This project will include collaboration with several Nordic centers with our research group leading the network. The project was given a PhD grant from HSØ starting in 2023.

- Targeting the NLRP3 inflammasome in HIV infection. The research institute has a strong track record on HIV-research and this has been continued with Hedda Hoel's PhD project that have looked 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.

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

Inflammatory biomarkers in cardiovascular and metabolic disease

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RESEARCH PROFILE

Many disease states are associated with low-grade chronic inflammation that may result in changes in inflammatory proteins in biological fluid such as serum and plasma. Measurement of these biomarkers will therefore be useful for detecting diseases before the diagnosis and/or offer information on the mechanisms of disease and treatment targets, or be helpful in evaluating treatment responses and predicting outcomes.

A cornerstone in our research is the close collaboration with the Department of Cardiology, and evaluation of biomarkers in heart failure, acute coronary syndromes and aortic stenosis. Biomarkers reflect a wide range of inflammatory processes in the patients and can further predict adverse outcome and treatment responses.

We are evaluating the impact of systemic inflammation in pregnancy on future cardiovascular and metabolic risk. The project “Regulation of non-coding RNAs in preeclampsia and impact on future cardiovascular risk” was started in 2020 by Tove Lekva with grants from the Norwegian Health Association in collaboration with the Department of Obstetrics, Norwegian Institute of Public Health, Section of Endocrinology and the Department of Cardiology. Our hypothesis is that non-coding RNA is crucial for both development of preeclampsia and later development of cardiovascular disease. Hopefully our research will lead to an early prediction and better monitoring of this condition, in addition to possible new treatment opportunities, and more understanding of the mechanisms of non-coding RNA in the development of preeclampsia and cardiovascular disease.

The endocrine unit is a part of the research group. The main research focuses on the molecular characterization of the pituitary adenomas and finding novel biomarkers to predict the aggressiveness and recurrence, or the response to medical treatment. In addition, we carry several projects on the role of the adipose tissue and bone on the glucose metabolism and cardiovascular risk in different endocrine diseases.

Severe mental disorders like schizophrenia and bipolar disorders are major contributors of morbidity globally and is associated with both cardiovascular and cancer disease. Together with the Norwegian Centre for Mental Disorders Research (NORMENT) we have for more than 10 years analyzed levels of inflammatory molecules in circulation and demonstrated dysregulation of immune cells and endothelial cells. More recently the use of induced pluripotent stem cell (iPSC) models have enabled more mechanistic studies of how brain cells function in mental disorders.

The newly initiated ALPHA2PREVENT will study if delirium can be prevented in patients undergoing open heart surgery. All five Norwegian heart surgery centers participate and patients will be randomized to receive a_2-adrenergic agonists or placebo. Biomarkers in plasma reflecting neuronal damage will be measured and related to possible development of delirium during the first week postoperatively, but also to declining cognitive and motoric function, and mortality during the next six months.

We have an ongoing strong collaboration with TREC, a translational research center at the University of Tromsø, focusing on patient-oriented and population-based research to reveal new risk factors and mechanisms for the formation of venous thrombosis.

In addition, we have strong collaborations with other clinical research, national and international projects.

EXAMPLES OF ACTIVITY IN 2022

- Also in 2022 our attention has been drawn to the COVID-19 pandemic, resulting in several published papers focusing on biomarkers associated with poor prognosis in hospitalized patients. This work is in collaboration with other research groups at RIIM as well as national and international collaborating hospitals and research units.
- We have continued our effort to identify biomarkers that give useful clinical information on prognosis in patients with cardiovascular disease, but also exciting data in pathophysiological context. Our data suggest that upregulated MMP-9, a matrix degrading enzyme, is a common feature of several subgroups of heritable thoracic aortic disease. In addition, Loeys-Dietz syndrome patients have increased levels of PTX3 reflecting systemic and in particular vascular inflammation.
- In a venous thromboembolism (VTE) study we discovered and validated increased lipopolysaccharide-binding protein (LBP) as a predictive biomarker for deep vein thrombosis (DVT) in women. We found an increased VTE risk for men in the lowest quartile of LBP.
- When investigating plasma extracellular vesicles in women with preeclampsia (PE) using RNA-seq we find the RNA cargo to be differently than in normal pregnancy. A large amount of RNAs and especially non-coding RNAs are differently expressed between PE and normal pregnancy and also from early to late pregnancy in women developing PE.
- We have recently described TGFBR3L - an uncharacterised pituitary specific membrane protein detected in the gonadotroph cells in non-neoplastic and tumour tissue. During the last year, in addition to performing a RNA-seq study in tumour samples from patients, we have carried out in vitro studies in mouse gonadotroph cells to further search for the role of TGFBR3L.
- In the metabolic research project we have measured circulating adipo- and cytokines in patients with acromegaly and identified novel biomarkers of diseases activity. Further, we have shown in a large of patients with acromegaly that mortality was not increased compared to the general population and comparable with recent registry studies from the Nordic countries and Europe. Overall cancer risk was slightly, but not significantly increased in the patients.
- Our results support a systemic and cerebral dysregulation of circulating cell adhesion molecule (sICAM-1) signaling in severe mental disorders (SMI), by possible promoting inflammatory and immune-mediated responses and mediating signals across blood-brain barrier. We also found that intestinal barrier inflammation and dysfunction in SMI could contribute to systemic inflammation through inflammasome activation.

Genomics and metagenomics in inflammatory diseases

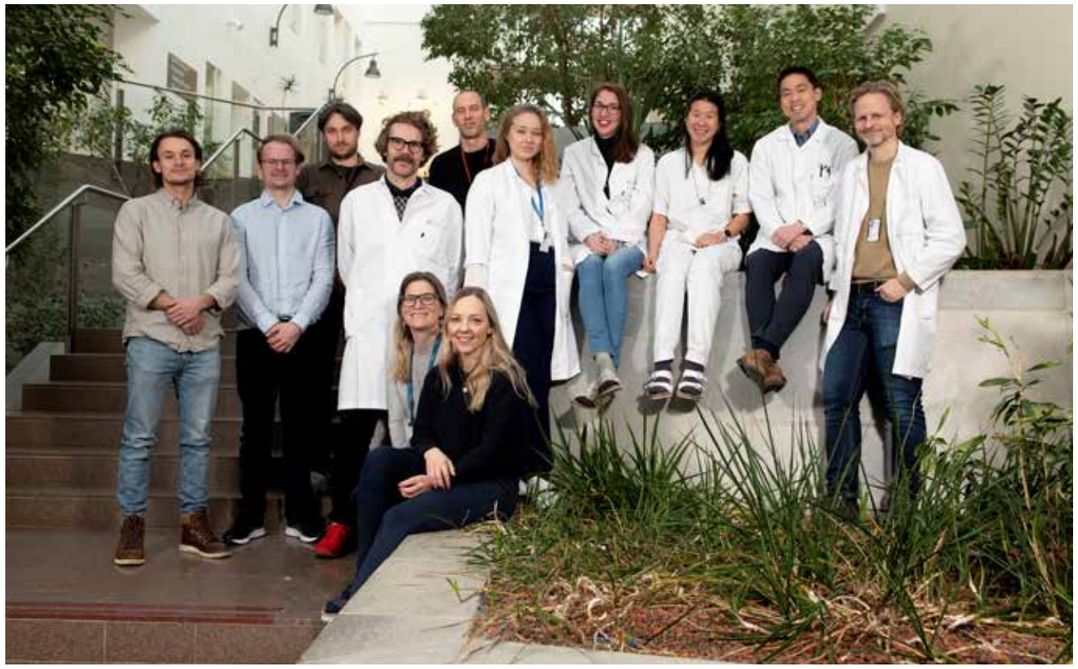

Photo: Åsne Rambøl Hillestad, UiO

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RESEARCH PROFILE

The genomics and metagenomics group aim to characterize and understand how the human genome and the gut microbiome influence inflammatory disease, and how this knowledge can be applied clinically. Our general approach is to used nontargeted high-throughput omics like sequencing and metabolomics, followed by targeted our hypothesis-driven methods, supported by bioinformatics and biostatistics including machine-learning. Increasingly, experimental approaches in vitro and in vivo (mouse models) are important to define cause-or-effect and disease mechanisms.

Our main interest is primary sclerosing cholangitis, a disease of the bile ducts of the liver, but we are also involved in research in multiple other conditions relevant for the institute, including heart failure and immunodeficiencies. Our main human materials are blood and fecal samples, but we are also establishing methodology for microbiota profiling in low-biomass material (blood, tissue, bile), while our experimental agenda involves germ-free and conventional mice with induced biliary or intestinal disease, in collaboration with the Melum group.

Our current main working hypothesis is that biochemical footprints of microbial activity is driving disease. We aim to define altered functional microbial changes using metagenome sequencing (i.e. the study of all microbial genes) and metabolomics. Our first interesting finding was of altered microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 as a potential disease-modifying factor caused by microbiome changes. A clinical trial focusing on translational aspects of vitamin B6 supplementation is on its way. This represents an example on how we work to identify and potential treat altered microbial functions, defining their clinical impact as biomarkers or in therapy. We are applying this methodology also on recurrence of PSC after liver transplantation, which is a significant clinical problem. This is the underlying idea of the ERC Starting Grant project *StopAutoimmunity*, which directs many of the priorities in the group. With growing data size and complexity, we increasingly depend on bioinformatics and statistics.
In our IBD focused projects, now comprising thousands of samples, in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we now apply more advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The groups also work more disease independent with *Clinical microbiota medicine*, as part of a Strategic research area at Oslo University Hospital awarded to the group in 2019. Interventions targeting the gut microbiome to treat disease may provide evidence of causal relationships between the gut microbiome and disease.

In 2022, MD Christopher Storm Ligaard defended his thesis “Clinical Interventions of the human gut microbiota” on this topic. Finally, the annual National Microbiota conference was a success – the ninth consecutive event since 2014.

FUNDING

The people in the group were in 2022 funded by one ERC Starting Grant, five grants from Regional Health Authorities of South Eastern Norway, one PhD student following an industrial PhD scheme (funded by Research Council of Norway), one Strategic research area grant in Oslo University Hospital, one postdoc is funded by a grant from UEG, in addition to Canica, funding one bioinformatician, and Nordforsk. In a collaboration with the Experimental group and partners from the Baltic area (driven from Lithuania) we also have funding from the EEA Baltic research funds, which is funding one post doc.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Locally, the group has extensive collaborations ongoing within NoPSC and the Research Institute of Internal Medicine, multiple clinical research groups (including in particular the IBD group at the Ullevål campus) as well as pathology and radiology.
Regionally and nationally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator.
Internationally, we continue strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish groups in Stockholm, Gothenburg and Uppsala.

The Experimental liver research group

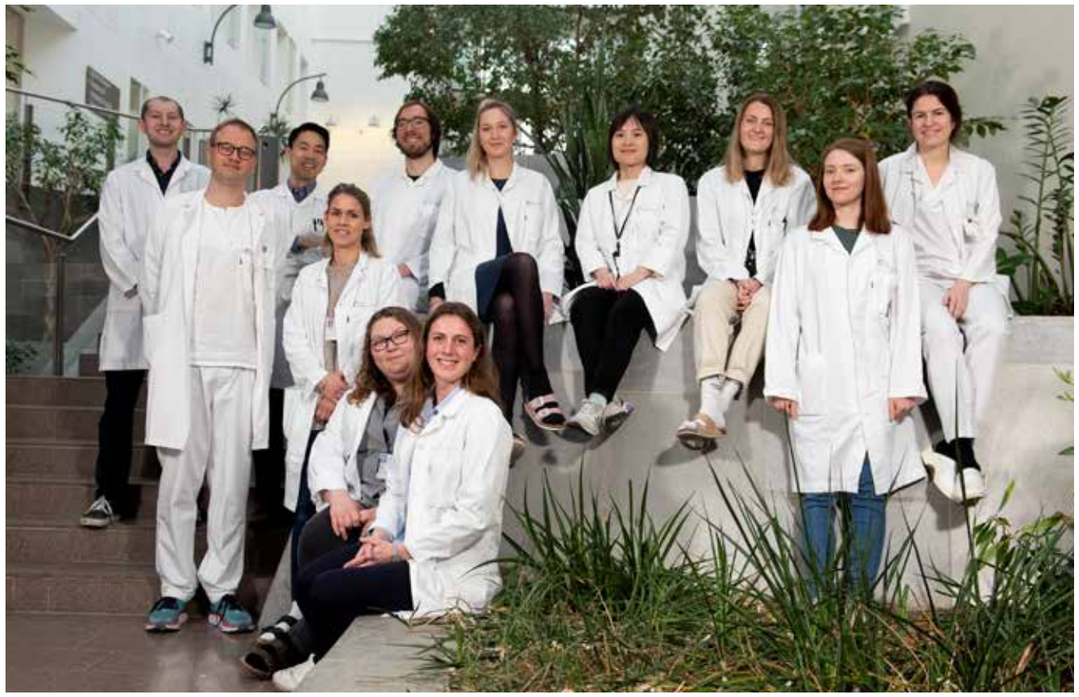

Photo: Åsne Rambøl Hillestad, UiO

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The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2022 the group consisted of the group leader, two senior researchers, four postdocs, five PhD students, the lab manager, one researcher and two technicians. The overall main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and what role the cholangiocytes play in propagation of the inflammatory process.

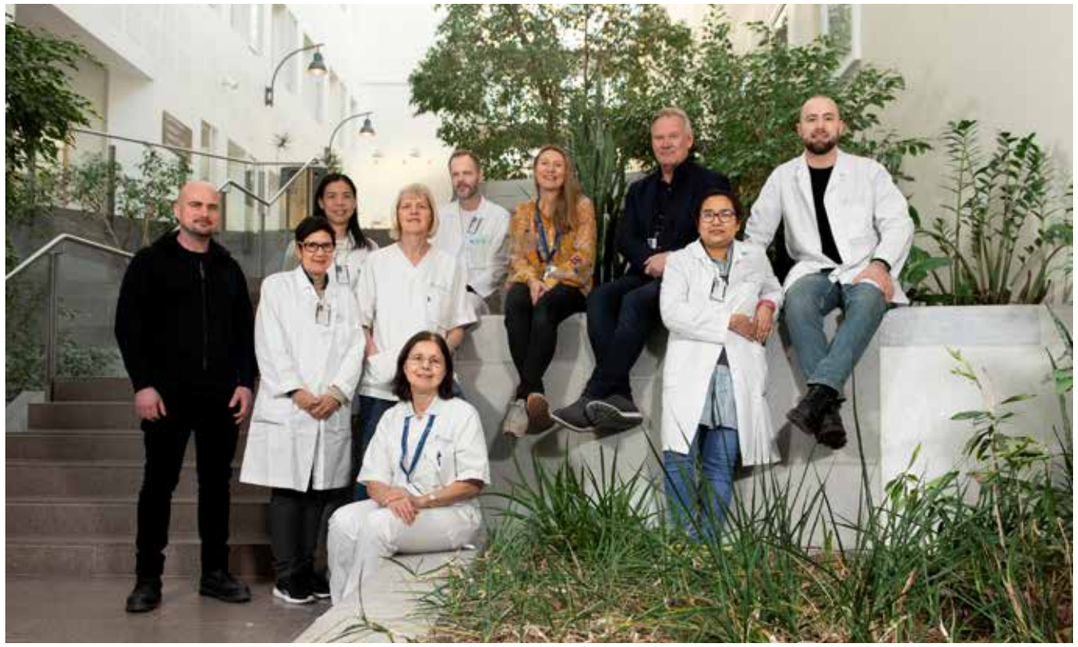
Our strong collaboration with the Hybrid-technology-hub on establishing a bile-bile-duct-on-a-chip was in 2022 strengthened by the recruitment of Henry W. Hoyle who joined the group in June. Henry has an ideal background for the project with a combination of molecular biology and physics. He defended his PhD thesis at the University of Durham before joining NoPSC. His main responsibility will be to improve the chip design and its integration with cholangiocyte organoids and immune cells. The organoid and bile-duct-on-a-chip projects were also strengthened in 2022 by Yuliia Boichuk who contacted us through the Science of Ukraine initiative where NoPSC offered to help Ukrainian scientists. Yuliia was one of the two Ukrainian colleagues that joined NoPSC. She has a solid background in molecular biology and long experience with advanced cell culture and was therefore an ideal fit for the ongoing work on organoids and chip-based technologies. At the end of the year her position was prolonged by a grant from “Fondsstiftelsen” at Oslo university hospital.

In an extensive follow-up study to our 2021 paper on CD100 in Science Translational Medicine we have in 2022 investigated the direct interaction of cells from CD100 mutated mice with cholangiocytes and discovered a clear Th17 profile. These data were presented at the International Liver Congress in London as an oral presentation and was well received. The large projects addressing the timing of introduction of the microbiome in the NOD.c3c4 mouse model was concluded in 2022 with detailed characterization of the immune phenotype using high-dimensional flowcytometry with 25-colors using the BD Symphony located at the flow-cytometry core facility.

In 2022 we published a report demonstrating the presence of antigens for mucosal associated invariant T (MAIT)-cells in the bile of patients with PSC and that these antigens were largely defined by the microbiome. Using organoids as a platform for detailed studies on the role of interaction of NKT cells with cholangiocytes we were able to further dissect the antigen production potential of cholangiocytes themselves. These observations will be followed up in relevant mouse models with genetically altered antigen presentation specifically in the bile ducts.

We have expanded our work on using 10x technology to examine single cells and spatial transcriptomics in two different mouse models that we have used for many years in the group; NOD.c3c4 mice with spontaneous bile duct inflammation and induced bile duct inflammation following direct injection of oxazolone in the bile ducts. These two projects will be part of the PhD work of Markus Jördens and will accompany studies using the same methodologies in a large panel of PSC patients. In new a PhD project, which was awarded funding by The South-Eastern health authorities, we will also use sequencing-based technologies to potentially define antigens for PSC. In this project we have recruited Lisa Bynjulfsen as a PhD student and she will be supervised by senior scientist Brian Chung as the main supervisor.

Haemostasis, Thrombosis, and Vascular Biology Research



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Research profile Sandset/Stavik:

"Coagulation Factors: Role in the Development of Thrombosis, Inflammation and Cancer"

Our main goal is to identify how and why coagulation proteins contribute to or prevent disease, and to utilize this knowledge to improve patient care. To do this, we conduct basic, translational, and clinical research with focus on gene mutations, molecular and biological activities and haemostatic function. Last year, we expanded the group with three new co-workers, Giacomo, Knut and Christian, and we are now one PI, four researchers, two post docs, one PhD student and two engineers. Giacomo is a talented and enthusiastic PhD student from Italy that has previously worked with haemophilia and stem cells. Knut is a productive and highly experienced researcher that is an expert in in vivo mice work. His competence has made it possible for us to finally have our own mice, which is a hallmark for the group. Christian works as a post doc in our group and divides his time between research and the clinic, as a part-time physician at the Dept. of Hematology. His clinical experience and network are invaluable when identifying the regulatory hurdles we will be facing when translating our research from bench to bedside. Needless to say, our three new colleagues perfectly complement the group, both at the social and scientific level, and we are grateful to have them with us.

Activity in 2022:

Coagulation disorders – ex vivo liver cell models and gene therapy

Inherited deficiency in coagulation proteins can cause mild to severe bleeding or thrombosis in affected individuals. The deficiency is caused by a mutation in the corresponding gene that results in reduced or diminished activity of the protein in plasma. Most coagulation proteins are produced in the liver and secreted to plasma and, with help from our collaborator Gareth Sullivan, Maria Eugenia have therefore utilized stem cell differentiation techniques to generate stem cell derived liver cells and organoids in the lab to model coagulation protein production and secretion. In 2022, she completed the characterization of the liver organoids with respect to coagulation protein expression and a major publication on this model is currently under revision. Additionally, she has been investigating the possibility to correct the disease-causing mutation using CRISPR-CAS9 gene editing in patient-derived stem cells. Last year, Giacomo reprogrammed cells from 2 patients with severe factor (F) VII deficiency into induced pluripotent stem cells and optimized protocols for gene editing of this mutation. We also recruited several patients with antithrombin (AT) deficiency in 2022, and Anindita has successfully reprogrammed cells from these patients into stem cells. She has also identified important protocol optimizations for improved expression of coagulation proteins by the liver organoids during the last year. Thus, several important milestones were reached last year, and we are now excited to move into the pre-clinical stage of these projects.

Drug repurposing

Drug repurposing has become a valuable tool to find new treatments to various diseases with low cost and little time. Previous findings in our lab indicated that an approved drug was able to increase the activity of mutated FVII. We therefore performed a larger screen using >1000 FDA approved drugs to identify potential compounds. The screen identified two hits, and Marianne is now in the process of confirming these in *in vitro* and *ex vivo* studies.

Coagulation proteins in atherosclerotic disease

Atherosclerosis is an inflammatory disease that culminates in thrombotic complications. Using a biobank of human carotid plaques, Benedicte is looking into the presence of coagulation factors inside the plaque and investigate their potential role in regulating inflammation and plaque development. The aim is to identify regulatory targets that can reduce the inflammatory burden and, potentially, be beneficial in attenuating atherothrombosis.

Bone marrow microenvironment in Multiple Myeloma

In this project, which was started up in 2021, Xue-Yan is using single cell sequencing to map coagulation protein expression in the bone marrow of patients with different stages of multiple myeloma (MM). These patients are prone to cancer-related thrombosis and she is looking for possible explanations in the tumour microenvironment. Together with orthopaedic department, she established a procedure for collecting normal bone marrow from hip replacement patients to use as controls in the study. With the help of collaborators Fredrik Schjesvold at the Oslo Myeloma Centre and June Myklebust and Ludvig Munthe at the K.G. Jebsen Centre for B cell malignancies she has banked bone marrow cells from MM patients and performed multiple protocol optimizations and in the end of last year single cell sequencing of the first patient and control samples was performed at the genomics core facility.

Coagulation factor V and breast cancer
We have in previous settings shown that oestrogens regulate the expression of several coagulation proteins and in oestrogen responsive breast tumours, oestrogen signalling plays an important role in the development of the disease. We know that breast cancer patients have increased risk of developing thrombosis and that pro-thrombotic proteins are elevated in some breast tumours. In this project, Marianne and Benedicte have been investigating whether oestrogen can affect the expression of coagulation factor V (FV) in an oestrogen responsive breast cancer cell line. We found that oestrogen bind to specific sites in the promotor sequence of the *F5* gene and regulate its expression. Also, through mining public databases online we found that patients with oestrogen responsive breast cancers that have high levels of FV in the tumour, are associated with prolongs survival. These findings were published last year in Thrombosis and Haemostasis.

Characterization of coagulation markers in clinical samples
Marie-Christine is involved in a number of clinical studies in collaboration with local and national/international clinicians and researchers and is responsible for the analysis of coagulation related biochemical markers in these studies. Last year, she participated in a large, national study investigating haematological parameters in health care workers following COVID-19 vaccination, and the results from this study was published in Research and Practice in Thrombosis and Haemostasis last year.

Biobank
We established a general biobank for thrombosis and hemostasis research a few years back, with the intent of collecting samples from patients with bleeding or thrombotic symptoms for future research. In 2022, we recruited the very first patient to this biobank and we are now continuously collecting samples.

Research profile Holme:
"Haemostasis and Bleeding Disorders"

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.

Activity in 2022:

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. PhD student Ragnhild J Måseide has studied and evaluated 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 has enrolled 145 pts. Three papers have been published from the study and she defended her thesis entitled: Moderate haemophilia A and B in the Nordic countries – The MoHem study with dissertation February 16th, 2022. More papers form this cohort are under preparation.

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.

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.

Autologous tolerogenic dendritic cells to treat patients with hemophilia A with neutralizing antibodies.
An open-label, first in human, phase 1/2a to evaluate the safety and efficacy of autologous tolerogenic dendritic cells ex vivo loaded with recombinant factor VIII in adults with congenital hemophilia A with neutralizing antibodies to FVIII and having failed immune tolerance induction has been initiated at our center and first patient world-wide was included Q4, 2022.

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 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. The overarching aim of the HemFitbit study was to investigate aspects related to the habitual physical activity (PA) of young persons with hemophilia A on prophylaxis in Norway. This project has collected information on physical activity levels in 40 patients with haemophilia A aged 12-30 years over a 3-month period using the wearable technology ‘Fitbit’. A subgroup of participants has also wear the accelerometer ‘ActiGraph’ in order to validate the two devices against each other. Through this work we have been able study and (1) to compare PA measurements of the consumer-grade activity tracker Fitbit Charge 3 to the research-grade accelerometer ActiGraph GT3X-BT in young PWH A, (2) to compare objectively measured levels and types of habitual PA among young PWH A on prophylaxis to general population peers over a period of 12 weeks, andto investigate the proportion of study participants meeting the WHO recommendations for weekly MVPA and (3) to investigate factors associated with PA in young people with haemophilia A on prophylaxis. . Ruth Elise Dybvik Matlary, MSc is working as a PhD student on this project and two papers from this project has already been published and another one

submitted for publication. The thesis for PhD dissertation entiteled: Physical activity in young people with haemophilia A in Norway - The HemFitbit study will be submitted Q1 2023.

VITT- Vaccine-induced immune thrombotic thrombocytopenia
From March 2021 the group has worked extensively on the SARS-CoV-2 vaccination-related thrombotic complications and thrombocytopenia giving devastating adverse events. This has been done in close collaboration with other groups here at RIIM and Department of immunology, OUS and the Norwegian National Unit for Platelet Immunology, Division of Diagnostics, University Hospital of North Norway. This work lead to the first main publications: Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med. 2021;384: 2124-30 and Immune Complexes, Innate immunity, and NETosis in ChadOx1 vaccine-induced thrombocytopenia. Eur Heart J. 2021; 42:4064-72. Further work on this and thrombosis associated with SARS-CoV-2 vaccination is ongoing to study causal relationships.

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 7 years where we want to evaluate the long-term effect of rituximab and study immunological aspects including a PhD project .
The group also participates in several other international and Nordic investigator-initiated research projects on bleeding disorders.

PUBLIC OUTREACH

During 2022, Maria Belland Olsen, Ida Gregersen and Xiang Yi Kong have successfully continued producing the podcast “Labprat”. The podcast was started with a desire to reach out with research and knowledge dissemination to the general public, and that it can be used as an advertising or recruitment method for scientific and medical studies. At the same time, parts of research life and research in general that do not always appear in public is presented. It’s rarely just scandals or just magical discoveries, but also a lot of trial and errors and hidden bureaucracy. More than 40 episodes of the podcast is now available for download from most platforms, and “Labprat” is established among the most popular podcasts in its field here in Norway.

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