Oslo University Hospital

UiO : University of Oslo

Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2020

RIIM

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2020

Pages

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

The year 2020 will forever be historical; the world was hit by the Covid-19 pandemic. RIIM had its first quarantines in February and faced a 4 weeks full look down in March-April, with home offices, and closed laboratories. All these restrictions have challenged the research projects and working environment. Despite this, RIIM personnel kept on producing good science; scientific papers, and funding applications. Importantly, RIIM supplied the OUS health care with first line personnel, as well as personnel for biobanking of the first hospitalized Covid-19 patients in Norway. RIIM was also a central lab in the biobanking and assessment of the WHO sponsored NOR-Solidarity lead by OUS clinicians (Prof. Aukrust and Dr. Barratt –Due).

Prof. Tom Hemming Karlsen and Prof. Johannes Hov, together with other RIIM scientists, Dr. Trine Folseraas and Dr. Marit M. Grimsrud, were among the first in the world to identify genetic characteristics of risk alleles in severe Covid-19 patients. This important work was published in New England Journal of Medicine already in October 2020. During 2020, RIIM scientists have produced several groundbreaking publications on Covid-19. Throughout this extraordinary year, RIIM really showed the importance of being a front-line translational research institute, situated next to clinical activities, making it easy to adapt our activities to the needs of our health care system (i.e., rapid assessment, test capacity, updated lab apparatuses and specialized biobanking). Importantly, we continued our normal activities and the education of our PhD`s, and had three dissertations in 2020. In addition, two of the group leaders at RIIM received prestigious funding (Dr. Melum [large research grant, NRC] and Prof. Halvorsen [large research grant, HSØ]). RIIM maintains its role as an international top milieu for translation medicine.

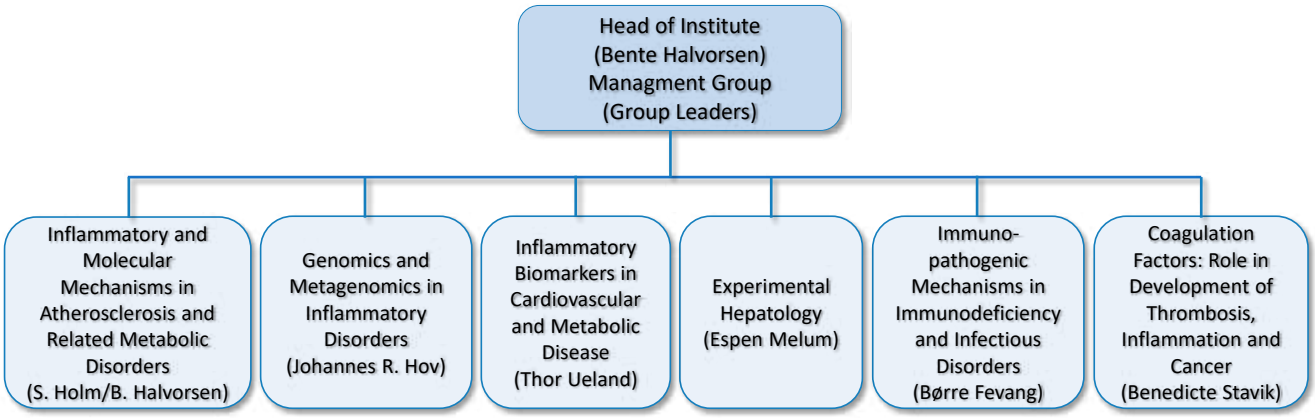
Both the economical and areal situation at RIIM are, like in the hospital in general, under pressure and particular the shortage of offices is a daily challenge for us. As shown by the chart illustrating the economy of the institute (page XX), RIIM manages to keep up high levels of external funding, which is extremely important. Still, my most important job as head of the Institute is to work for more stable long term internal funding in appropriate laboratories close to clinical activities. The “Forprosjekt” and “New OUS” processes are in progress and a large job needs to be done to keep RIIM situated at the hospital when the “C1 Rokade” process starts in 2021. Everything we have achieved in 2020 has strengthened RIIM`s position as a major translational research arena also in the years to come and RIIM will be an important cornerstone in the new hospital, hopefully situated close to “New OUS” in 2030.

During 2020, Prof. Pål Aukrust, our previous head and my closest collaborator for more than 20 years, retired from his position as Professor at RIIM. I will thank Pål for everything he has done and meant for all of us scientifically and personally - and luckily, he will still be around us as Prof. Emeritus and senior consultant.

To further gear the institute for the future, we have reorganized RIIM to make the organization more like the hospital`s organization, which will give the head direct leadership of the group leaders which will hopefully have a powering effect on RIIM. In addition, RIIM needs to further strengthen the translational activities. To reach this goal we depend on good collaboration with clinical departments and collaborations with complementary skills. Importantly, RIIM must take a more active role in clinical intervention studies and in the establishing of centers (i.e., K.G. Jebsen Center, SFF etc.), and most importantly, RIIM scientist must work hard in order to compete for ERC grants and EU funding.

Looking into 2021, we have important work to do; the pandemic is still around, and we need better work flow in the lab, upgrade of equipment, better implementation of collaboration and convergence with clinical departments and institutions, and we still need to find our position on the map in the “new OUS”. With these milestones for 2021, I would like to thank everyone at RIIM including our collaborators at UiO and OUS for all the patience and loyalty you have shown in 2020, and last, but not least – thanks for an inspiring and productive year..

ORGANIZATION

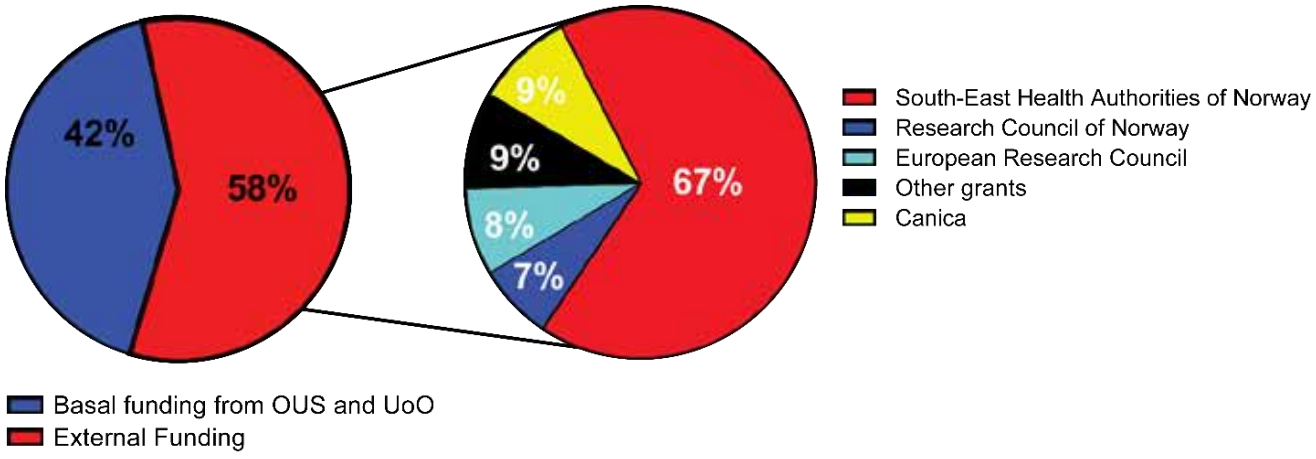


TOM HEMMING KARLSEN
Leader of Molecular Hepatology Research

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 63,4 mill in 2020. NOK 36,6 mill (58%) was funds from external sources, while NOK 26,8 mill (42%) was from Oslo University Hospital and University of Oslo. The contributions from external sources are shown in the chart to the right.

FOCUS AREA

RIIM participating in the Nor Solidarity trial

When the Covid pandemic hit the world early in 2020 it was an urgent need for good treatment options and to know what is effective and what is not. In February 2020, a WHO expert group recommended that four drugs approved for other indications, hydroxychloroquine (HCQ), remdesivir, ritonavir-boosted lopinavir and interferon (IFN) should be evaluated in an international adaptive open label randomized clinical trial, and compared with standard of care (SoC) in the treatment of hospitalized patients with SARS-CoV-2 infection. This initiative resulted in the initiation of the WHO Solidarity trial.

NOR-Solidarity is an independent add-on trial to WHO Solidarity trial where the participants in NOR-Solidarity were recruited from 23 Norwegian hospitals. Eligibility criteria were adult patients, with confirmed SARS-2-CoV-2 infection, admitted to the hospital ward or the intensive care unit (ICU). NOR-Solidarity started recruiting patients on March 28th 2020, as the first study site within the WHO Solidarity Trial. Patients were initially randomized to HCQ or SoC, and randomization to remdesivir started on April 7th. In late April 2020 **RIIM** started bio banking immune cells from patients recruited from 5 of the hospitals located in the eastern part of Norway. PBMC, monocytes and T-cells were isolated at 4 different time points, at inclusion to the study, 3 to 5 days after intervention, 7 to 10 days after intervention and 3 months after intervention. In addition all plasma and serum from the complete Nor Solidarity trial were collected, organized and stored at RIIM.

On June 8th 2020 HCQ was removed as a treatment arm after advice from the NOR-Solidarity steering committee due to lack of evidence of its effectiveness, confirmed both in internal WHO interim analyses and an external report from the Recovery study. Thus, from June 8th 2020, NOR-Solidarity allocated patients only to SoC and remdesivir. On October 4th 2020, the WHO Solidarity trial consortium published interim results, reporting that HCQ and remdesivir, as well as the other repurposed drugs in the trial, had little or no effect on in-hospital mortality. Whereas the remdesivir arm was continued in the WHO Solidarity trial, it was stopped in the NOR-Solidarity study, on October 5th due to 1) general low mortality in hospitalized patients in Norway, 2) the potential for untoward effects in ventilated patients, and 3) potentially little, if any, effect of remdesivir in patients with mild disease. Similarly to the WHO Solidarity study, the Nor Solidarity trial found no effects of remdesivir or HCQ on the rate of ICU admission, or the use of mechanical ventilation during hospitalization. The most important secondary outcome in the NOR-Solidarity trial was viral load in oropharynx. There was a general marked decrease in SARS-CoV-2 oropharyngeal load during the first week after randomization, with a similar decrease and levels after 10 days in both the remdesivir and HCQ groups and the SoC groups. The difference between the treatment groups regarding the decrease rate during the first week and at Day 10 were nominally in favor of SoC, excluding major effects on viral clearance for both active treatments.

Although disappointing results from the Nor Solidarity trial so far, there is yet a lot of in-depth analysis planned at **RIIM** on the materiel bio-banked in the Nor Solidarity trial evaluating remdesivir and HCQ. In addition, to fight the SARS-CoV-2 infection, new treatment strategies need to be tested in new random clinical trials in the Solid Act trial, and again **RIIM** will be an important participant in biobanking of leukocytes.

Genome-wide association study to define genetic risk of severe Covid-19 infection

JOHANNES R. HOV

Covid-19 has unveiled the fantastic potential of science and molecular medicine, from the early publication of the SARS-CoV-2 DNA sequence to finalization and approval of highly effective vaccines in less than a year. In contrast, research areas requiring really large-scale, multi-national collaborations (e.g. large drug trials) have been more slow growing. In the PSC groups of RIIM, large-scale international collaborations on genetic studies have been one of the important starting points for new discoveries in a rare liver disease, while the SARS-CoV-2 virus itself had limited relevance for the ongoing PSC projects. However, as COVID-19 hit Norway early March 2020, Tom H. Karlsen, the leader of the PSC groups, realized that we based on our expertise and international network could make a meaningful contribution to better understand the severe disease outcomes of the virus. By activating friends and collaborators within hepatology (in Italy and Sweden) and genetics (in Germany) we were able to set up a team that could perform all steps of a genome-wide association study from patient inclusion to genotyping, statistics, writing and publication with high speed.

The key question was; Do genetic risk factors explain why some patients with Covid-19 develop severe pulmonary disease while some do not? From seven hospitals in Northern Italy and Spain, we included around 2000 patients with severe pulmonary COVID-19, as defined by respiratory failure, i.e. the need for oxygen supply or respiratory support like a ventilator. DNA samples were genotyped in Kiel, and an analysis and writing group was established with participants from Kiel and Oslo.

The final results uncovered two regions (loci) of the genome where some genetic variants were more common in patients with severe pulmonary disease compared to the control population. The strongest risk factor was seen at chromosome 3, where several genes may be involved either as mediators of inflammation or they may change how the virus enters host cells. The chromosome 3 risk has later been identified as remnants from the Neanderthal genome, and the frequency varies extensively around the globe, which could potentially influence the overall disease severity in different countries. The other risk factor was blood group status, where blood group O seems to be protective, and which has later been proven to primarily protect against the viral infection itself. The study was published in the highest-ranking medical journal in the world, New England Journal of Medicine (1), in June, less than 3 months after the project was initiated.

1. Ellinghaus D, Degenhardt F, Bujanda L, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med 2020;383;1522-34

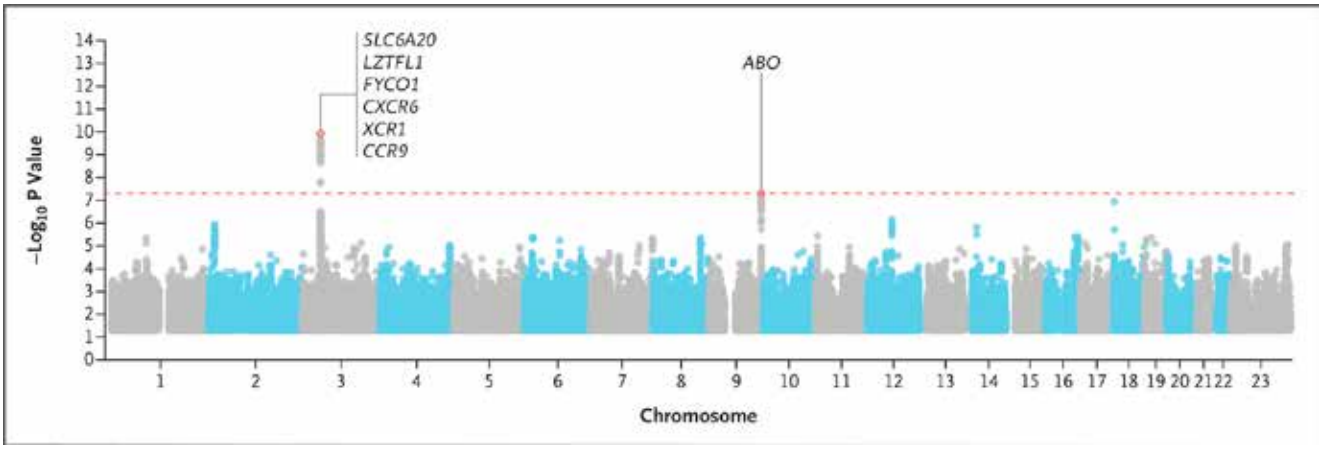


Figure legend:
Here is shown a classical genome-wide association study Manhattan plot, where the p-value (y-axis) of the associations of genetic variants (the individual dots along the chromosomes at the x-axis) are shown, highlighting the 2 “towers” representing the main findings at chromosome 3 and 9.

DISSERTATIONS 2020

Photo: Øystein H. Horgmo, University of Oslo

Ana M.T. Quiles-Jiménez, MSc

Molecular mechanisms of atherosclerotic disease. Studies on the role of the DNA glycosylase NEIL3 and the epitranscriptome in the development of atherosclerosis
Nov. 18th 2020

Committee
1. opponent: Professor Allan Sirsjö, School of Medicine, Örebro University, Sweden
2. opponent: Associate Professor Vivian de Waard, Amsterdam UMC, The Netherlands
3. opponent: Associate Professor Thomas Sæther, Institute of Basic Medical Sciences, University of Oslo

Main supervisor: Filip Segers

Co-supervisors: Bente Halvorsen and Ida Gregersen

Summary of the project
Cardiovascular diseases are one of the top causes of mortality worldwide, and the main underlying cause is atherosclerosis. Atherosclerosis is a multifactorial and progressive arterial disease where lipid accumulation and a low-level inflammatory response are at play. This leads to the formation of a plaque, which upon rupture can trigger thrombosis and artery occlusion, causing myocardial infarction or stroke.

Numerous studies have shown that cells within atherosclerotic plaques, like vascular smooth muscle cells (VSMCs), accumulate DNA damage. If left unrepaired, DNA damage can promote plaque instability leading to the fatal consequences of atherosclerosis. NEIL3 is a canonical DNA glycosylase involved in oxidative stress-damaged DNA base lesion repair, which seems to have functions beyond DNA repair, e.g., in cell proliferation. Yet, the role of NEIL3 in atherosclerosis is not well understood. The aim of this thesis was to examine the role of NEIL3 deficiency in atherosclerosis with a focus on VSMCs, using mouse- and cell-based models. Our results show that NEIL3 could be a new player in atherosclerosis affecting VSMC phenotypic identity.

Moreover, epitranscriptomics has emerged as a novel research field investigating the role of post-transcriptional RNA modifications on gene expression. Epitranscriptomics is previously shown to function in diseases like cancer, but a possible role in atherosclerosis is not known. The aim of this thesis was also to explore the role of RNA modifications in human atherosclerosis. Our results show that the well-studied RNA modification N6-methyladenosine is decreased in human atherosclerotic lesions, with dysregulated levels of several RNA modification enzymes.

Overall, this work intends to refine the understanding of the molecular mechanisms involved in atherosclerosis, where targeting NEIL3 or RNA modification-related proteins could help creating new prognosis tools and treatment strategies.

Photo: Øystein H. Horgmo, University of Oslo

Beate Vestad, M.Sc.

Gut microbiota, extracellular vesicles and comorbidities in HIV infection; Exploring the drivers of metabolic disease risk and microbe-host crosstalk

October 30, 2020

Committee:
1. opponent: Section Chief Roger Paredes, Institut de Recerca de la Sida IrsiCaixa, Barcelona, Spain

2. opponent: Professor An Hendrix, University of Gent, Belgium

3. opponent: Professor Marit Inngjerdingen, Institute of Clinical Medicine, University of Oslo

Main supervisor: Marius Trøseid

Co-supervisor(s): Reidun Øvstebø, Department of Medical Biochemistry, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo. Johannes R. Hov

Summary of PhD project:
Despite effective antiretroviral treatment, people living with HIV (PLWH) have reduced life

DISSERTATIONS 2020

expectancy. Gut microbiota alterations, chronic inflammation and increased risk of cardiometabolic disorders have been reported. Extracellular vesicles (EVs) have emerged as important modulators of intercellular communication and microbe-host crosstalk and gut microbes may utilize EVs to transfer toxic components from the gut to the circulation.
In Beate Vestad's thesis she explored the interplay between the HIV-related gut microbiota and risk of comorbidities. We found that reduced Enterobacteriaceae after probiotic intervention in PLWH support a local anti-inflammatory effect in the gut. She also identified an HIV-related microbiota signature (specific composition of microbes), independently of confounders, which correlated closely with higher risk of metabolic syndrome and abdominal obesity. Furthermore, EVs were explored as disease biomarkers, both in a methodology paper evaluating analytical variation in analysis of EVs, and subsequently showing that PLWH and T2D had elevated plasma EV levels, which strongly correlated with plasma LPS and a risk score for cardiovascular disease, but not with gut microbiota alterations. The proteomic content of plasma EVs was largely related to cardiometabolic disease genes and inflammatory pathways. Several bacterial proteins were identified.

Photo: Øystein H. Horgmo, University of Oslo

Christian Qvigstad, MD, PhD

Age-related health and comorbidities in haemophilia
7 December 2020

Committee:
1. opponent: Professor Michael Makris, MA, MB BS, MD, FRCP, FRCPath
Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK
2. opponent: Professor John-Bjarne Hansen, MD, PhD
K.G. Jebsen – Thrombosis Research and Expertise Center (TREC), Department of clinical medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway
3. opponent: Professor Ingebjørg Seljeflot, MD, PhD
Department of Cardiology, Oslo University Hospital, Institute of Clinical Medicine, University of Oslo

Main supervisor: Professor Pål André Holme, MD, dr.med.
Co-supervisor(s): Professor Robert Campbell Tait, MbChB
Royal Infirmary, Glasgow, UK
Professor Geir Erland Tjønnfjord, MD, dr.med.

Summary of PhD project:
In the not too distant past, until around 1960, haemophilia was a disease experienced only by young people. The reason was that few survived past adolescence as it proved impossible to prevent fatal haemorrhages. In this period, when haemophilia caused death before old age, comorbidities were a secondary concern. With the advent of factor replacement treatment, however, life expectancy for people with haemophilia (PWH) is now approaching that of the general male population.
For the first time, we now have a large ageing haemophilia population. Unfortunately, the longevity comes with a cost. As the number of ageing PWH increases, so does the number of age-related diseases and comorbidities. These are now a primary concern, causing new clinical challenges.
In this thesis, we investigated possible causes of comorbidities in PWH and possible consequences of treatment options. As all data were obtained from an observational study, we deliberately tried to avoid causal language and instead discussed associations discerned from cross-sectional data.
In Paper I, we examined risk factors for chronic liver disease (CLD). CLD progresses through several stages, and in our view, we have not yet seen the peak of deaths due to CLD. We documented that the main risk factors for CLD were hepatitis C virus (HCV), human immunodeficiency virus (HIV), and diabetes, and showed that the same risk factors were responsible for the CLD deteriorating.
On a brighter note, we discussed and recommended new promising treatments, in particular direct-acting antivirals, specifically targeted at combating HCV, the most significant risk factor for CLD.
Papers II and III share a common focus on macroscopic haematuria, which is defined as visible blood in the urine. Macroscopic haematuria

has often been considered a less serious comorbidity, but in this thesis, we considered the possibility of more sinister effects, and hence a desire to avoid the condition. In the final two papers, we discussed possible ways to limit macroscopic haematuria and possible adverse effects of bleeding episodes. Paper II focused on the relation between treatment and macroscopic haematuria. We documented that frequent prophylaxis with coagulation factor concentrates appeared to limit haematuria and argued that this was likely due to frequent prophylaxis ensuring factor levels above a critical threshold. In Paper III, we showed that macroscopic haematuria seemed to be a risk factor for hypertension, but only when a family history of hypertension was present. We discussed why this may be plausible and pointed to recent empirical evidence.

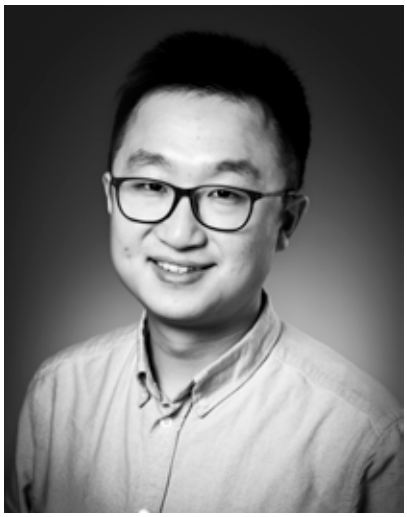


Photo: Amalie Huth Hovland, UiO

Kuan Yang, MSc

Regulation of TLR4 and NLRP3 Activities
Nov. 25th 2020

Committee:
1. opponent: Professor Ines Heiland, UiT – The Arctic University of Norway, Tromsø
2. opponent: Researcher Pablo Pelegrin, BioMedical Research Institute of Murcia, Spain
3. opponent: Associate Professor Thomas Sæther, Institute of Basic Medical Sciences, University of Oslo

Main Supervisor: Øystein Sandanger

Co-Supervisors: Pål Aukrust and Arne Yndestad

Summary of the project:
Inflammation depends on pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) which sense molecular patterns associated by microbes and cellular damage. TLR4 and NLRP3 are two well-characterized PRRs. TLR4 induces transcription of pro-inflammatory cytokines while NLRP3 forms inflammasomes that mediate activation and release of IL-1β. Inflammation is closely linked to metabolism as it requires both energy and synthesis of new molecules. The studies presented in this thesis addressed the following questions: Does NAD+ levels affect TLR4 function? Does autophagy regulate TLR4/NLRP3-dependent IL-1β secretion from cardiac fibroblasts? Is CD38 (a NAD+ dependent Ca2+mobilizing enzyme) implicated NLRP3 activation in monocytes and macropahges?

Human primary monocytes were treated with FK866, a NAD+ synthesis inhibitor, leading to a NAD+ depletion which significantly down-regulated TLR4-depednent cytokine synthesis. Further proteomic analysis showed that FK866 inhibited phosphorylation of several proteins involved in the TLR4 signal pathway, which could be rescued by replenishing NAD+ with nicotinamide riboside (NR). Serum starvation of cardiac fibroblasts profoundly reduced TLR4-induced pro-IL-1β protein levels while TNF, IL-6 and inflammasomes proteins were not affected. Surprisingly, the mTOR inhibitor rapamycin increased pro-IL-1β protein levels while the autophagy inhibitor chloroquine induced pro-IL-1β protein degradation. Both serum starvation and chloroquine increased general protein ubiquitination, suggesting that mTOR regulates pro-IL-1β degradation in cardiac fibroblasts through proteasomes but not autophagy.

Human monocytes and macrophages were treated with CD38 inhibitors which significantly attenuated IL-1β release upon NLRP3 inflammasome activation and suppressed Ca2+ flux induced by NLRP3 activators. These findings support that CD38 promote NLRP3 activity by increasing cytosolic Ca2+ levels.

DISSERTATIONS 2020

Photo: Øystein H. Horgmo, University of Oslo

Magnhild Eide Macpherson, MD, PhD

Gut microbiota, lipid metabolism and systemic inflammation in common variable immunodeficiency - A translational research approach
Sep. 16, 2020

Committee:
1. opponent: Professor Vanda Friman, University of Gothenburg, Sweden

2. opponent: Senior Consultant Torgun Wæhre, Oslo University Hospital, Norway

3. opponent: Associate Professor Are Martin Holm, Institute of Clinical Medicine, University of Oslo

Main supervisor: Senior consultant Børre Fevang, Oslo University Hospital

Co-supervisor(s): Senior consultant Silje Fjellgård Jørgensen and Professor Tom Hemming Karlsen

Summary of PhD project:
Patients with common variable immunodeficiency (CVID) have a dysfunctional immune system leading to recurrent infections while also frequently suffering non-infectious autoimmune and inflammatory complications. These non-infectious complications are connected with higher mortality rates.

The aim of this thesis was to explore the gut microbiome and novel molecular mechanisms involved in the underlying pathogenesis of systemic inflammation in CVID in order to identify therapeutic targets to reduce autoimmune and inflammatory manifestations.

Through a randomized controlled trial, we tested if the oral antibiotic rifaximin would alter gut microbial composition and thereby modulate systemic inflammation in CVID patients. Indeed, rifaximin decreased their gut microbial diversity, but did not significantly change any markers of systemic inflammation or gut leakage.

Gut microbes also interact with the regulation of lipids and we found reduced HDL cholesterol levels in the plasma of CVID patients. Low HDL correlated with raised inflammatory markers CRP and sCD25. Important HDL functions, related to reverse cholesterol transport, were significantly impaired in CVID patients.

Dietary nutrients are metabolized by gut microbes to form the organic compound TMAO. In CVID patients, we found an abundance of gut *Gammaproteobacteria* to be associated with raised plasma levels of TMAO, inflammatory markers TNF and IL-12 and lipopolysaccharide. This indicates a connection between gut leakage, TMAO and inflammation in CVID.

Overall, gut microbial dysbiosis in CVID patients appears linked to systemic inflammation through the metabolite TMAO and altered lipid metabolism via reduced reverse cholesterol transport. Modulating the gut microbiota using a short-term course of oral antibiotic rifaximin is not sufficient to affect systemic inflammation in CVID. HDL levels and function and gut microbial composition emerge as novel therapeutic targets to reduce sterile systemic inflammation in CVID.

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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Facebook: Centre of Thrombosis and Haemostasis Research (CTHR) at Oslo Univ Hospital

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 haemostatic 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-haemostatic diseases in addition to being the primary inhibitor of coagulation initiation. Our group is part of the Centre of Thrombosis and Haemostasis Research (CTHR), which is an initiative to unite researchers and clinicians working in the field of thrombosis and haemostasis at OUH and Akershus University Hospital.

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 leukaemia (CLL) is the most common leukaemia 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 tumour. However, the role of TFPI in the progression of solid tumours is still controversial and the effect of TFPI on leukaemia 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.

-Oestrogens regulate Coagulation factor (F) V expression

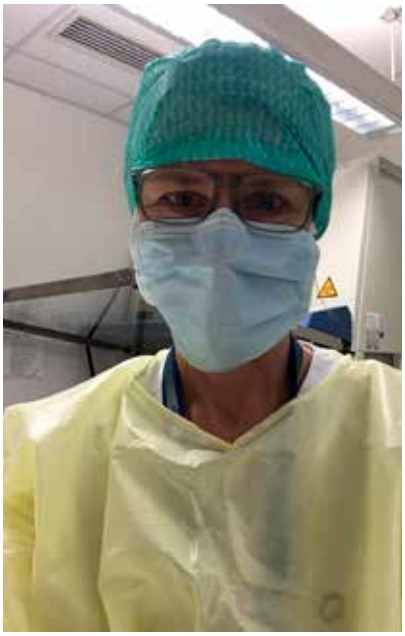
We have in previous settings shown that oestrogens regulate the expression of several proteins involved in blood coagulation. In oestrogen responsive breast tumours, oestrogen signalling plays an important role in the development of the disease. We know that breast cancer patients have increased risk of developing thrombosis and that pro-thrombotic proteins are elevated in some breast tumours. In this project we are investigating whether oestrogen can affect the expression of coagulation factor V (FV) in an oestrogen responsive breast cancer cell line. Results show that both natural and synthetic oestrogen increase FV production in the cells. To look further into the mechanism, we use siRNA technology receptor antagonist to inhibit oestrogen receptor signalling. Bioinformatic analyses of the promoter sequence of the factor V gene (F5) reveal several binding sites for the oestrogen receptor and their involvement are investigated by cloning the promoter sequence in reporter gene vectors and using site-directed mutagenesis to destroy the bindings sites. Furthermore, by mining public databases online, we find that patients with oestrogen responsive breast cancers that have high levels of FV in the tumour, are associated with prolongs survival.

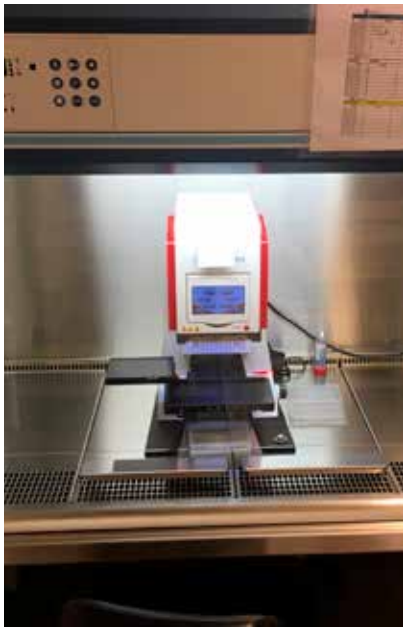
-Characterization of coagulation markers in clinical samples

The group 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.

FUNDING

Oslo University Hospital; The South-Eastern Norwegian Regional Health Authority; Fondsstiftelsen; Norwegian foundation for bleeders.





INFLAMMATORY RESEARCH

Immune regulation in atherosclerosis and other cardio metabolic diseases

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

About the group

In the past year, the two research groups «Atherosclerosis and related metabolic disorders» and «Immunological and molecular mechanisms in myocardial remodeling and heart failure» at the institute have merged into a larger group which in turn is divided into smaller project groups.

Our overall focus in is on cardiovascular disease and related metabolic diseases such as diabetes, obesity and fatty liver which are major causes of morbidity and mortality worldwide. More specifically, atherosclerosis is a condition characterized by a chronic inflammatory phenotype, while myocardial infarction and stroke, the direct consequences of atherosclerosis, are acute inflammatory conditions. These disorders have many common features, such as dyslipidemia and inflammation. By studying these processes using a translational approach, where we connect basic research and clinic, we want to build a foundation for the development of new diagnostics and treatment for these diseases. Our research group works at the intersection between molecular biology and biochemistry, and cardiovascular, cerebrovascular and endocrine medicine. Our overall goal is to uncover new therapeutic goals and biomarkers. The group uses a wide range of methods, ranging from analysis of blood and tissue samples from patients, to studies in genetically modified mice using advanced cell and molecular biology. The group consists of people with different backgrounds and includes doctors, nutritionists, biochemists, molecular biologists and engineers. This interdisciplinary competence is a great strength of our research group.

Activity in 2020

As for all other parts of society, also our research has been highly affected by the Covid-19 pandemic. We have been fortunate to be able to maintain activity in the lab throughout this challenging situation, but some of our projects have been suffering, as we allocated people to the collection and biobanking of clinical materials

from Covid-19 patients from several hospitals in Norway. We are involved in the analysis of NorSolidarity study, the Norwegian part of the WHO-initiated treatment study of Covid-19 patients, where sequencing and metabolic mapping of the patients are key tasks for personnel in our group. Moreover, the biobank with material for further analysis of follow-up and complications in critically ill Covid-19 patients will in the coming years prove to be valuable for further understanding of the pandemic. Despite much focus and effort has been dedicated to these tasks, we have also been able to pursue our regular research ranging from work on human mutations in the Sigirr genes, the role of complement in atherosclerosis, and deciphering the role of ENDOV. Below are listed some of our main projects in 2020:

Methodology We are constantly seeking to expand our methodology repertoire. During the last year, a focus in our research group has been on establishing an in-house workflow for analysis of complex multi-omic data. Include both the infrastructure and the competence to perform advanced bio-informatic analyses. We performed several different large-scale analyses on both human and murine samples, such as RNA sequencing, mass spectrometry and bisulfite sequencing. The major goal is to be able to integrate the generated data in a useful manner.

T cells in obesity We investigate T cell function in metabolic regulation during obesity development to seek new treatment options. T cells can modulate macrophage function and adipocyte differentiation, which affects energy storage and utilization, leading to healthy or dysregulated metabolism. In 2020 we have performed several advanced animal studies leading us closer to pinpoint important mechanisms of how T cells affect whole body metabolism.

NLRP3 inflammasome The NLRP3 protein is essential for inflammasome formation and inflammation itself. In 2020 we published 2 articles in relation to NLRP3, both products

of our long-term research on this protein. The first revealed the role NLRP3 plays in cardiac remodeling after a myocardial infarction. The second article supported a role for NLRP3 in the interface between metabolic and inflammatory stress, involving an altered gut microbiota composition.

The role of DNA repair enzymes in atherogenesis Recently we showed that Neil3, a DNA glycosylase, modulates vascular smooth muscle cell proliferation and transdifferentiation. This is a vital feature in atherogenesis, suggesting that Neil3 might have an important role in atherosclerosis development, possibly independent of its role as a DNA repair enzyme. Moreover, we are exploring role of the enzyme Mutyh in atherosclerosis development and metabolic disturbances in a similar manner as for Neil3. The main finding so far is that Mutyh is involved in maintaining metabolic homeostasis in mice. Furthermore, vascular cells lacking Mutyh are more prone to acquire a pathological phenotype, possibly due to genomic instability.

EU- projects We actively participating in two EU projects. The first, AtheroMacHete, aims to decipher the heterogeneity of macrophages in atherosclerotic plaques and to determine different functions of the cell types their contribution to disease development. The second project, PainFact, has the objective to investigate the connection of chronic pain, pain sensitivity and development of cardiovascular disease. In 2020 we contributed with methodological development as well as piloting animal studies in these projects.

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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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 analysed and 2 publications have publiched in Haemophilia and a 3rd manuscript 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 defended his thesis entiteled: "Age-related health and comorbidities in haemophilia". November 2020 and now work as a Post doc.

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 all patients are included in the study and manuscript preparation is in progress.

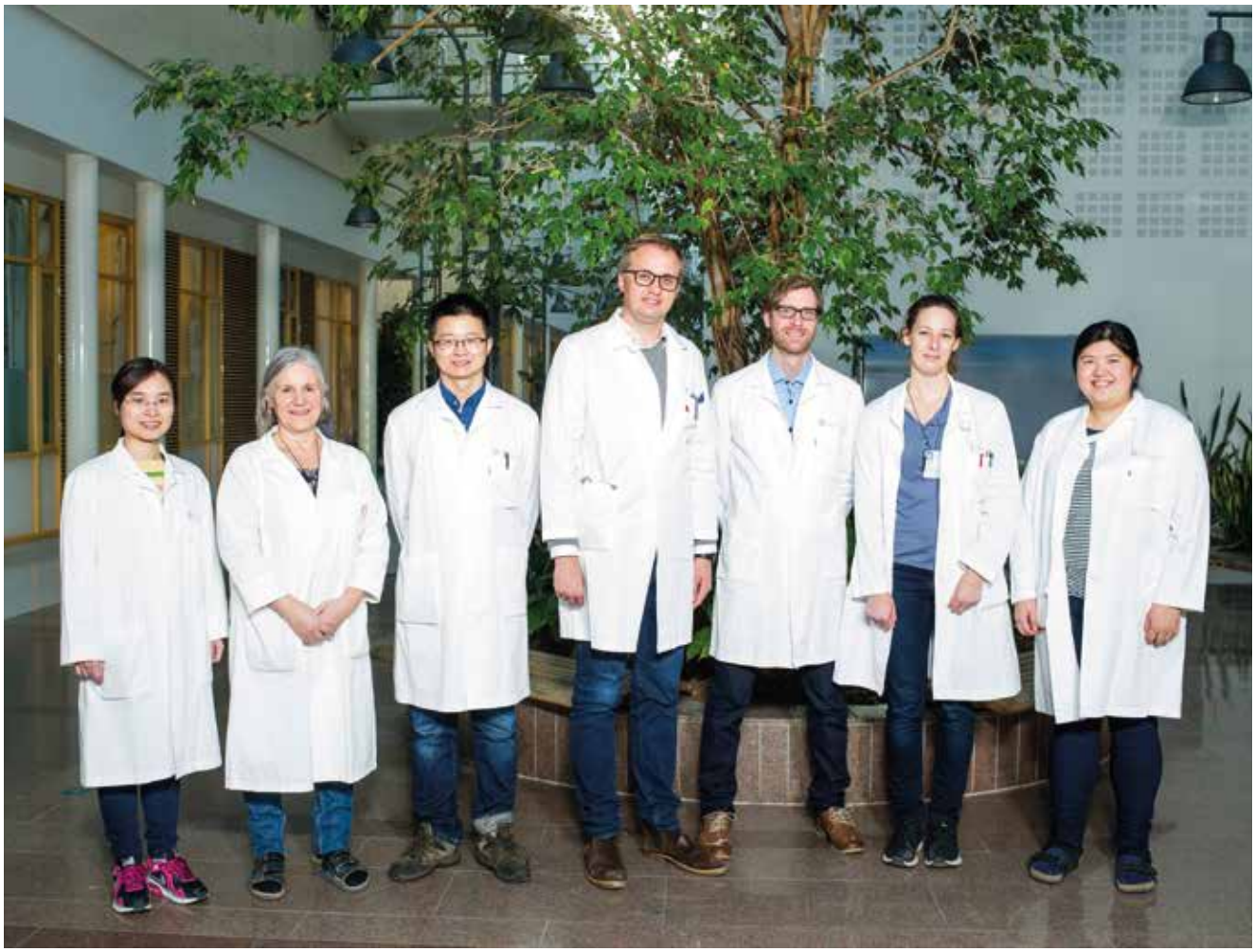
Immune thrombocytopenia

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 5 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.

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 group represents one of the three research group at the Norwegian PSC research center. Our laboratory activities take place at the Research institute of Internal Medicine. In 2020, the group consisted of the group leader, two senior researchers, two postdocs, four PhD students, the lab manager and one part-time technician. The 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. Recently, we have also started to incorporate aspects of regenerative medicine. Our tools to achieve this aim is to use patient material, animal models, advanced cell-culture in terms of organoid technology and recently organ-on-a chip systems.

During the last years one of our major lines of research has been to clarify the regulatory role of unconventional T-cells in bile duct inflammation and in 2020 we published a report demonstrating the presence of antigens activating natural killer T (NKT)-cells in bile. Similarly, we also demonstrated in another project that antigens for mucosal associated invariant T (MAIT)-cells are also present in bile and are defined by the microbiome. Extensive animal experiments clarifying the role of NKT-cells during cholestasis were also performed in 2020 focusing on CD1d on the bile

duct epithelium and the contribution of type 1 vs type 2 NKT cells. Another major topic of our immunology studies has been the role of CD100, which we have found to regulate cholangitis in a familiar form of PSC, and in 2020 we have expanded our molecular understanding on how CD100 affect immunological function. In our studies using germ-free animals we have continued the work on clarification on how the timing of introduction of the microbiome affects the development of bile duct inflammation in the NOD.c3c4 model that we have previously shown to be partly dependent upon the presence of bacteria. We have also performed ground-work using ***in vitro*** studies on metabolites in fecal material that will form the basis for ***in vivo*** mechanistic studies in 2021.

In 2020 we also generated the first prototypes for a bile duct on a chip together with the rest of the team at the center of excellence Hybrid-technology-hub. This work was facilitated by the recruitment of Anna Frank as a Scientia Fellows postdoc that will work on the collaborative projects between the Norwegian PSC research center and the Hybrid technology hub. We also continued research on the basic properties of organoids by doing single-cell sequencing of cholangiocyte organoids generated from brushings of the bile ducts from patients with PSC. As part of the expansion on the activities related to organoids, senior researcher Kari Otterdal has also been engaged in this project.

Our RNA-based sequencing technology approaches were also expanded in 2020 with the establishment of spatial sequencing, which will be used by several projects in the experimental hepatology group and also by other projects at NoPSC. Jonas Øgaard, who has been in the group for several years as a technician, started his master project where he will investigate the spatial and temporal transcriptomic landscape of cholestasis using this technology.

Besides a little downtime in March-April 2020, the ongoing COVID-19 pandemic has not led to any major delays or reduction in scientific productivity for the group.

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

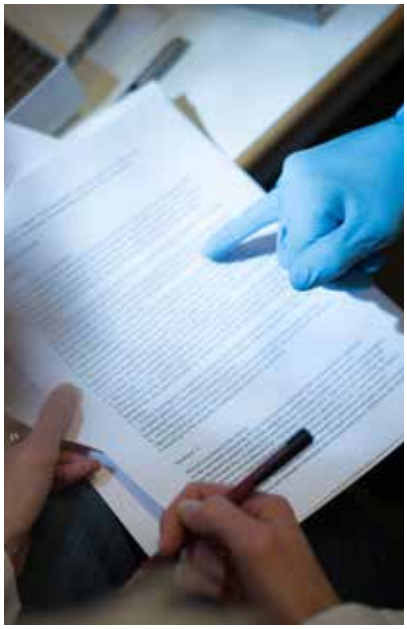
The research group focus on immunopathogenesis in primary and secondary immunodeficiency such as Common variable immunodeficiency (CVID) and HIV and selected infectious diseases, in particular the study of chronic inflammation characterizing these disorders. The aim is to improve the understanding of 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 has defended her PhD thesis 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. We have started a new project focusing on granulomatous-lymphocytic interstitial lung disease (GLILD) in CVID where Mai Sasaki Aanensen Fraz has looked into differences between patients with stable and progressive disease. This project will include collaboration with several Nordic centers with our research group leading the network.

- 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 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.

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. The main focus of the group 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. Our group is spearheading a regional research network for clinical microbiota science (ReMicS) ReMicS together with the clinical microbiology and microbiota medicine group at the RHI (leader Marius Trøseid), with which are integrated. Hanne Guldsten is a key person as network administrator and laboratory responsible person. In addition, we run a Strategic research area in the hospital called "Personalized microbiota therapy in clinical medicine", aiming to translate microbiota research to clinical practice as biomarkers and target of interventions. Significant progress towards a donor bank for fecal microbiota transplants were made in 2020, lead by external part-time expert Peter Holger Johnsen. 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 is important to strengthen our research agenda, although the Covid-19 situation has been challenging in 2020. Still, we were able to host the sixth national conference on gut microbiota in November 2020 as a screening event with more than 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 immundeficiencies 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. SHH. Regional research network: HG
- National association for public health: CM
- Norwegian PSC Research Center: KH
- Nordforsk (NordTreat trial): AG

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

Prof. Rolf Berge, University of Bergen
Fredrik Bäckhed and Hanns-Ulrich Marschall, Wallenberg Laboratory, Göteborg
Prof. Andre Franke, Christian-Albrechts University, Kiel
Kostas Lazaridis, Mayo Clinic, Rochester

Awards to members of the group in 2020

Best article in Oslo University Hospital, first half of 2020:
The group contributed to the New England paper "Genomewide Association Study of Severe Covid-19 with Respiratory Failure", which investigated genetic risk factors for severe Covid-19 with respiratory failure in a collaboration with Italian, Spanish, German and Norwegian investigators. Senior author Tom H. Karlsen.

N Engl J Med. 2020 Oct 15;383(16):1522-1534.

PUBLIC OUTREACH

38 Viten — Aftenposten, Torsdag 7. mai 2020

Immunforsvaret kan være både venn og fiende

Viten

Maria Belland Olsen, Post Doc, Institutt for indremedisinsk forskning, Oslo Universitetssykehus Rikshospitalet

Ida Gregersen, forsker, Institutt for indremedisinsk forskning, Oslo Universitetssykehus Rikshospitalet

Et overaktivt immunforsvar vil bidra til sykdom og skade i stedet for å beskytte. Det hele handler om balanse.

Vi har et helt arsenal av ulike typer immunceller, med ulike egenskaper og dermed ulik «personlighet». Noen er mer opptatt av å hisse opp stemningen, andre jobber for å roe ned. Her illustreres en virusinfeksjon, der hvite blodceller angriper viruset. Foto: Yurchanka Siarhein Shutterstock / NTB scanpix

FAKTA: Forskning på immunforsvaret

40 Viten — Aftenposten, Torsdag 10. september 2020

Åreforkalkning er drevet av betennelse

Viten

Ida Gregersen, forsker, Institutt for indremedisinsk forskning, Rikshospitalet, OUS

Maria Belland Olsen, post.doc., Institutt for indremedisinsk forskning, Rikshospitalet, OUS

Åreforkalkning er hovedårsaken til hjerte- og karsykdom, som er en de vanligste årsakene til død i Norge og i verden. Her blokkerer plakk åreveggen. Illustrasjon: Shutterstock/NTB Scanpix

FAKTA: Aterosklerose

Den vanligste årsaken til hjerte- og karsykdommer, og er en kronisk prosess der immunceller, kolesterol og andre fettstoffer samles i åreveggen.

Selv om intensjonen er god, kan resultatet bli noe helt annet – en ond sirkel av betennelse som driver sykdom

44 Viten — Aftenposten, Torsdag 3. desember 2020

Den mindre kjente delen av immunforsvaret

Viten

Mieke Louwe, postdoktor, Institutt for indremedisinsk forskning, Oslo Universitetssykehus Rikshospitalet

En patruljecelle gjenkjenner sitt offer. Foto: Shutterstock/NTB

I mage og tarm må inntrengerne passere potensielt dødelige syrer, som mage- og gallesyre

BAKGRUNN: Forskning på det medfødte immunforsvaret

AWARDS 2020

Oslo University Hospital awards outstanding research articles twice a year. In spring 2020 the article “Genomewide Association Study of Severe Covid-19 with Respiratory Failure” in the New England Journal of Medicine received the prestigious award of NOK 50.000. Marit Mæhle Grimsrud received the prize on behalf of the authors from NoPSC; Marit Mæhle Grimsrud, Johannes R. Hov, Trine Folseraas and Tom Hemming Karlsen.

At the Norwegian Gastroenterology Associations annual meeting at Lillehammer 6th to 8th of February 2020 our PhD student Mikal J. Hole received an award of NOK 25.000 for his project “Gut mucosal Klebsiella pneumoniae is a disease modifier in PSC”.

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