Oslo University Hospital

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Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2018

RIIM

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

Looking back at 2018 as **head of RIIM** makes me glad in many ways**.**
Firstly, RIIM maintains its role as an international top milieu for translational medicine. The scientific production is strong. We continue high quality education of PhD`s, MSc`s, and BSc`s. Two of RIIMS group leaders received prestigious prize and funding; Dr. Espen Melum received "*Andres Jahres pris for yngre forskere*" and Dr. Johannes R. Hov accepted an *ERC Starting grant. Secondly,* the visit of director of Health Authority South East (HSØ), Dr. Loftshus, and the chairman of HSØ board, Mr. Gjedrem, together with the Director of OUS Dr. Eriksstein underscores RIIMs position as an important research unit in OUS and in the health region. *Thirdly*, we have highly skilled technical personnel with long lasting expertise, symbolized by one of RIIMs technicians, Ellen Lund Sagen, who this year won a national pipetting competition. All three points are important for RIIMs reputation as a strong research arena.

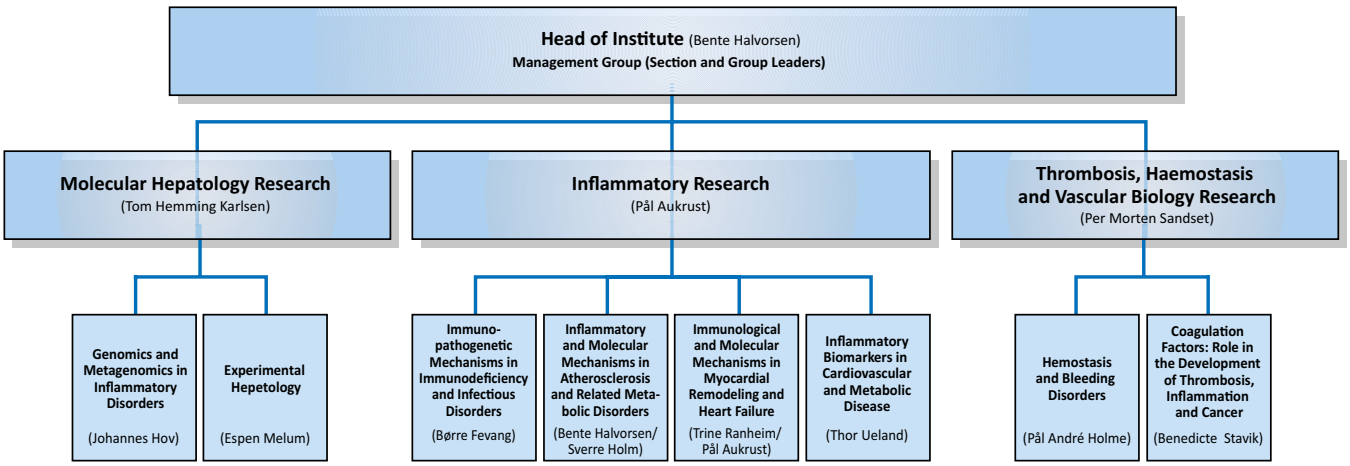
Both the economic and areal situation at RIIM is, like in the hospital in general, under pressure. As shown by the chart illustrating the economy of the institute (page 4), RIIM manages to keep up high levels of external funding, which is extremely important. 2018 was particularly successful for several of RIIMs group leaders and scientists who received large funds. My most important job as head of the Institute is still to work for more stable long term internal funding in appropriate laboratory facilities close to clinical activities. The "*konseptfase*" and "New OUS" has flavored 2018`s discussions at lunch tables for months. 2018 did not give any answers on where and when RIIM will be located in the "New OUS". But I am convinced that RIIM, as a major translational research arena in the years that come, will be an important cornerstone also in the new hospital.

During 2018, **Arne Yndestad,** my deputy head and closest collaborator for 20 years, transitioned from his position at RIIM to a new job in the pharmaceutical industry. I am very grateful for all the work Arne has invested at RIIM, it has been impactful both on the research and the environment at RIIM.. We wish him all the best in his future carrier. Since August this year, **Espen Melum** has been my deputy head with particular focus on improving integration and collaboration with the clinical departments. To equip the institute for the future, we must invest in becoming even better at **translational actives**. To reach this goal we are dependent on good collaboration and **convergence** with the clinical departments and collaborators with complementary skills. RIIM must also continue to take an active role in the development of **personalized medicine**, integrating multiomics with computational science in patient`s healthcare. As to be read further in this report – precision medicine is in our focus.

Looking into 2019, we have important work to do; better work flow in the lab, more collaboration and convergence with clinical departments and institutions, and to find our way on the map in the "new OUS". With these milestones for 2019, I would thank everyone at RIIM including our collaborators at UoO and OUH for an inspiring and fruitful 2018.

Oslo, April 2019
Bente Halvorsen

ORGANIZATION

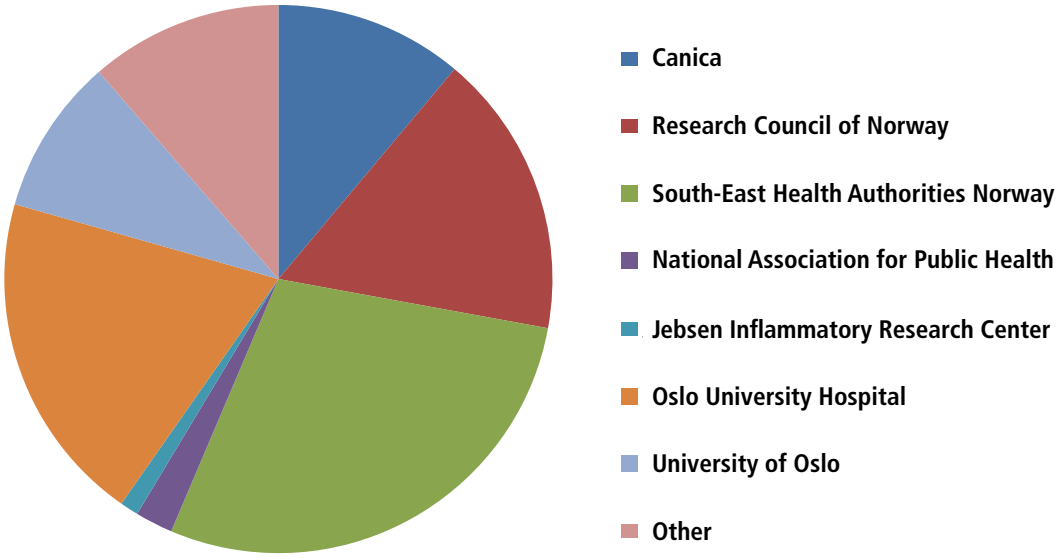


TOM HEMMING KARLSEN
Leader of Molecular Hepatology Research

PÅL AUKRUST
Leader of Inflammatory Research

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

ECONOMY



The institute's total expenditures amounted to NOK 57 million in 2018. NOK 38 million were funds from external sources, while 19 million came from Oslo University Hospital and University of Oslo.

FOCUS AREA

Personalized medicine – introduction

BØRRE FEVANG

Personalized medicine has become a hot topic in medicine in the last few years, and even if buzzwords come and go there is little doubt that we in many parts of medicine are in the midst of a major change in our therapeutic approach. Large scale clinical trials with standardized treatment have been crucial to the radical improvement in health care we have seen over the last 50 years but are not always able to predict the response (or possible side effect) in the individual patient. The implementation of methods to personalize and tailor the treatment of the individual patient is therefore a necessary and much anticipated step forward. Translational research environments like RIIM are ideal for bringing necessary and effective biomedical tools from the laboratory to clinical practice. The following reports from our three sections of research demonstrate that RIIM can make substantial contributions to the further development of personalized medicine.

Personalized approach to detect and treat cholangiocarcinoma in primary sclerosing cholangitis

JOHANNES R. HOV AND TRINE FOLSERAAS

In personalized cancer medicine understanding of the molecular alterations involved in the disease process is used to tailor monitoring and treatment of the individual patient. Primary sclerosing cholangitis (PSC) is a chronic inflammatory disease of the bile ducts with unknown aetiology and no effective medical treatment available. A major clinical problem in PSC is cancer of the bile ducts, cholangiocarcinoma (CCA), which occurs in up to 20% of the patients. Due to difficulties in distinguishing benign from malignant biliary changes in PSC, CCA diagnosis is often made late with limited treatment options available. The CCA-related care is clinically the most critical challenge in this patient group, and may profit from a personalized approach. The critical steps to better CCA care in PSC are 1) to identify PSC patients at increased risk for CCA 2) to establish tools for surveillance and early detection of CCA and 3) to provide novel molecular based treatment options of CCA.

Identification of PSC patients at increased risk for CCA.

How to identify PSC patients at increased risk of CCA for further detailed work-up during decades of follow-up? In stable periods, a PSC patient is typically seen by a specialist twice a year with blood samples and ultrasound and/or MRI annually. Currently PSC is mainly referred to CCA diagnostics based on clinical, biochemical or radiological deterioration, but these are not sensitive or specific tools. Are there molecular markers separating PSC patients at high risk of developing CCA from low risk individuals? Ideally, we would

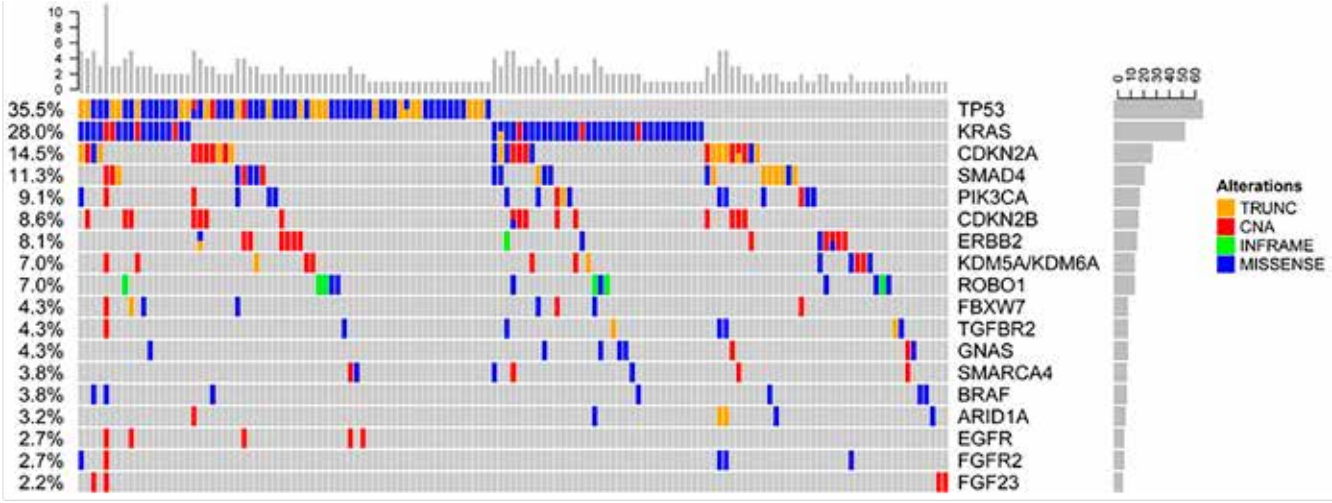


Figure 1

have a simple and sensitive tool to stratify patients according to high or low risk of CCA, and then perform personalized surveillance according to risk. One example is anti-GP2 IgA antibodies, which we recently found in about half of the patients with PSC. Anti-GP2 negative patients only had 3-4% CCA occurrence compared with 13-20% in the anti GP2 positive (1), suggesting that there is potential to identify predictive biomarkers providing a molecular map to guide personalized care in the future.

Tools for surveillance and early detection of CCA.

Tools for surveillance and diagnosis should be accurate, i.e. sensitive and specific. In addition, simplicity, availability and costs are essential for effective surveillance. Personalization may be less relevant for these tools. Still, the currently most common marker, circulating carbohydrate antigen 19-9 (CA19-9) is in part genetically determined (2), but the specificity of CA19-9 is too low to warrant genetic testing to personalize CA19-9 based follow-up. Other important work at NoPSC focuses on diagnostic tests based on epigenetic changes in DNA obtained from biliary brush material and bile (3).

Novel molecular based treatment options.

CCA is the most frequent cause of PSC-associated death. Only one-third of the patients are candidates for radical surgery at time of CCA diagnosis and even after surgery with curative intent there is a high recurrence rate. Benefit of current palliative chemotherapy regimens is limited. Traditionally, choice of cancer treatment is based on tumor origin and distribution. However, it has become evident that a wide range of molecular alterations may be important drivers of neoplasia in different cancers, and some of these may be inhibited by specific drugs, i.e. tyrosin kinase inhibitors in chronic myeloid leukemia and human epidermal growth factor 2 (HER2) antibodies in breast cancer. While programs like Cancer Genome Atlas have increase insight into cancer biology and opportunities for targeted therapy in many other cancers, CCA from PSC patients are missing from these programs. Could personalized cancer therapy be an option also in PSC-CCA? In an international project driven in a collaboration between NoPSC and the University Hospital in Heidelberg, molecular characterization has been performed by sequencing candidate genes in tumor DNA extracted from formalin-fixed PSC-CCA tissue obtained from clinical biobanks. At least one candidate gene mutation was identified in about 78% of the tumors (Figure 1). When reviewing these according to the TARGET (tumor alterations relevant for genomics-driven therapy) database (http://archive.broadinstitute.org/cancer/cga./target), 62 % could potentially be relevant for specific therapy. Keeping in mind that this was only a retrospective study utilizing archived material, it does suggests that there may be a potential for clinical testing of specific drugs in CCA in PSC.

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2. Wannhoff A, Hov JR, Folseraas T, Rupp C, Friedrich K, Anmarkrud JA, Weiss KH, Sauer P, Schirmacher P, Boberg KM, Stremmel W, Karlsen TH, Gotthardt DN. FUT2 and FUT3 genotype determines CA19-9 cut-off values for detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol. 2013;59(6):1278-84.

3. Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen O, Aabakken L, Schrumpf E, Lothe RA, Lind GE. Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma. Hepatology. 2015;61(5):1651-9.

Personalized treatment in haemostasis and bleeding disorders

PÅL ANDRÉ HOLME

Personalized treatment for bleeding disorders and thromboembolic disorders is essential to optimise the treatment outcome and our group is constantly working to achieve such personalised treatment.

Optimising bypassing agents and non-factor replacement therapy.
One of our main objectives has been to tailor the treatment with bypassing agents (BPA) for haemophilia patients with inhibitors. Development of inhibitors is the most serious complication of haemophilia treatment today. High titre inhibitors to factor VIII develop in approximately 30% of haemophilia A patients and less often to factor FIX (3-5%). This represent a major challenge in the treatment of haemophilia A and B as conventional factor concentrates cannot be used to achieve haemostasis and these patients suffer from increased morbidity and mortality. The treatment of bleeds in haemophilia patients with this represents a relies on the use of the bypassing agents, factor eight bypassing activity (FEIBA) or recombinant factor rVIIa. While both therapies are effective in the majority of bleeding episodes and postoperative prophylaxis, there is a significant amount of inter individual variability responding to each product and major bleeds will still occur in 10% of the cases.
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 when using bypassing treatment, and there is no established laboratory assay to monitor efficacy and optimal dosing. We have established methods (thromboelastometry (TEG/ROTEM) and thrombin generation test (TGA) to predict the haemostatic outcome

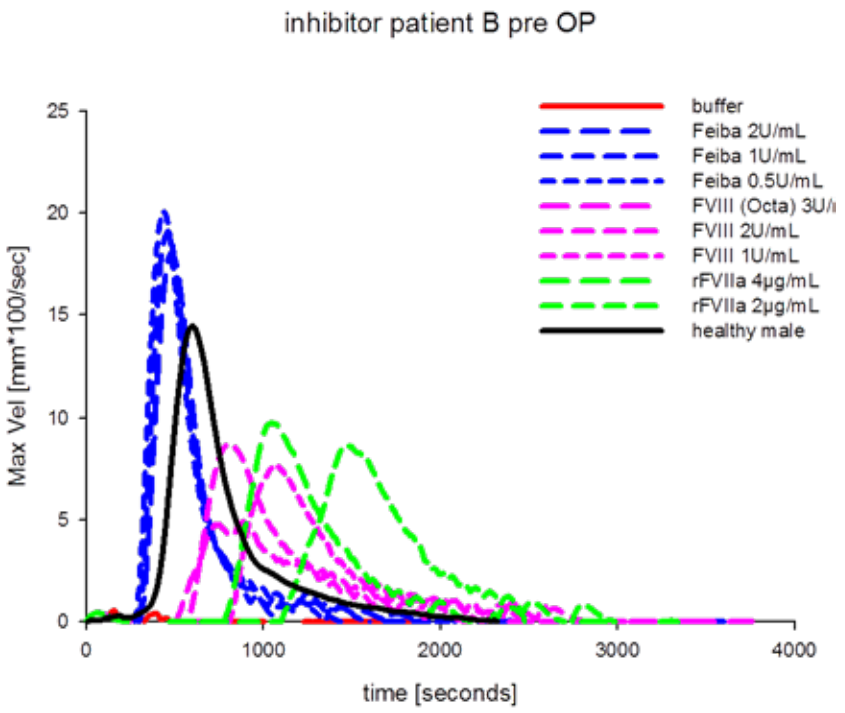


Figure 1: ROTEM analysis (preoperative in vitro studies) in a non-responding man to rFVIIa but showing a normalized response to aPCC, 1U/mL. Major surgery was performed using aPCC with an excellent haemostatic outcome.

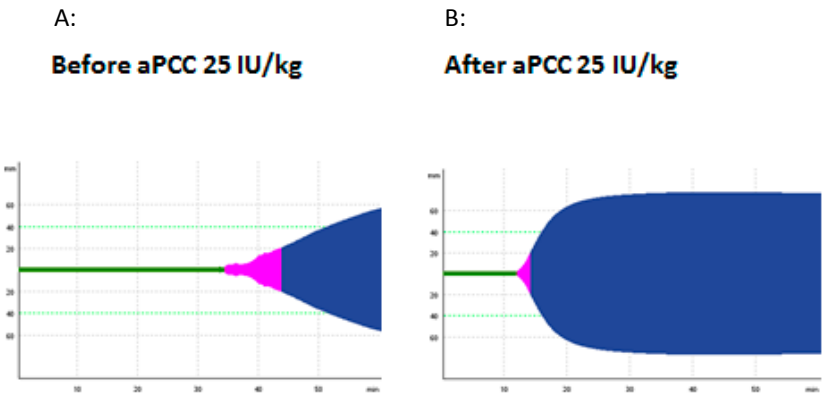


Figure 2: Thromboelastometry curves of a patient under treatment with apixaban 5 mg twice daily due to atrial fibrillation. He was hospitalized after rapidly developing symptoms of heart failure. He had taken his morning dose of apixaban and presented with respiratory distress, fever, and hypotension. An echocardiography revealed an extreme aorta stenosis and a left ventricle dysfunction. His condition deteriorated rapidly, and surgery to replace the aortic valve was needed immediately. There was no time to await the wash-out effect of apixaban. Surgery was performed successfully without excessive bleeding or thromboembolic complications. Hence, administering aPCC improved hemostasis, which was assessed clinically by the surgeon and measured by global coagulation tests. A Thromboelastometry curves before administering activated prothrombin complex concentrate.
B Thromboelastometry curves after administering activated prothrombin complex concentrate 3000 IU.

when using bypassing agents. These methods have been evaluated to be helpful in predicting the haemostatic outcome thereby helping us find the optimal bypassing product and dosing for each individual. This is done by in vitro spiking experiments, in vivo confirmation and thorough testing/monitoring in the post-surgery/bleeding period.
These methods have in our hands also shown to be helpful to optimise treatment on individual basis when non-factor replacement therapy as emicizumab is used in inhibitor patients and additional treatment with bypassing agents is needed for bleeds to avoid adverse event like thromboembolic events.

Reversal of factor Xa inhibitors (DOAC)
Today there is no evaluated effective treatment to reverse the effect of FXa-inhibitors (direct oral anticoagulants (DOAC)). As a PhD project (Nina Haagenrud Schultz), we have studied prothrombin complex concentrate PCC, activated prothrombin complex concentrate aPCC and recombinant factor VIIa (rFVIIa) to reverse the effect of FXa in vitro using thromboelastometry (TEG/ROTEM) and thrombin generation test (TGA).
Furthermore aPCC has been found to be effective to reverse the anticoagulation effect of FXa-inhibitors in vivo before acute cardiovascular surgery. Haemostasis was markedly improved, as assessed clinically and by coagulation tests after administering aPCC 25 IU/kg. None of these surgeries was complicated by excessive bleeding during surgery. The safety of the treatment where demonstrated, as in none of the cases did thromboembolic complications occur.

Personalized medicine in inflammatory and immunological disease

PÅL AUKRUST, BENTE HALVORSEN AND BØRRE FEVANG

In 2018 it was 25 years since the first Norwegian patient was diagnosed with AIDS and in the shadows of that devastating disease we have seen a revolution of immunological insight – an insight that now comes to the aid of patients with a wide variety of not only immunological and inflammatory disease, but also malignancy and metabolic diseases. Moreover, the development of new drugs in cancer and autoimmune disorders targeting specific molecules in complex signaling pathways are also of major interest in other disorders like cardiovascular disease. In fact, new drugs originally design for cancer therapy (e.g., JAK inhibitor), are now widely used in autoimmune and inflammatory disorders and may also have a potential in cardiovascular disorders.

The Section of Inflammatory Research at RIIM has contributed to an increased understanding of the inflammatory and immunological processes underlying diseases like atherosclerosis, heart failure, HIV and primary immunodeficiencies, preparing for the next step in immunomodulating therapy; tailoring effective treatment for the individual patient.
The term personalized medicine was first coined in the treatment of malignancies where the genomic characterization of tumors in individual patients with e.g. breast cancer led to specifically designed chemotherapy regimens. However, the growing arsenal of immunomodulating therapies targeting soluble cytokines, cytokine receptors, cellular surface markers

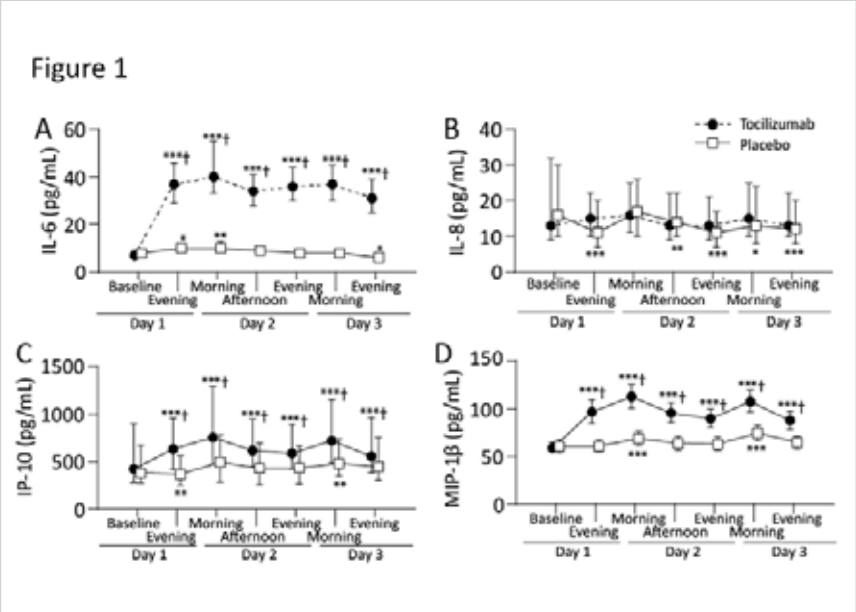


*Figure 1. Interleukin-6 (IL-6), interferon gamma-inducible protein/CXCL10 (IP-10), macrophage inflammatory protein-1β (MIP-1β) (all placebo n = 59, tocilizumab n = 58), and IL-8 (placebo n = 49, tocilizumab n = 46) during hospitalisation in patients with non-ST-elevation myocardial infarction. *p< 0.05, **p < 0.01, ***p< 0.001 vs baseline within group. †p< 0.001 for between-group differences in changes from baseline at separate timepoints. Kleveland, et al, 2018.*

and intra-cellular signaling pathways makes the concept of personalized medicine highly relevant also to inflammatory and immunological disease including cardiovascular diseases. Clinicians can apply a broad or pin-pointed approach and frequently use older regimens like corticosteroids in combination with new monoclonal antibodies like rituximab (anti-CD19), anakinra (anti-IL-1RA) and adalimumab (anti-TNF). This wide selection of potential drugs has implications not only for the choice of drugs in the individual patient, but for the process of selecting drugs in itself. The standard treatment of a specific disease can and must be individualized and we need to develop the tools for making this individualized and personalized medicine both effective and safe.

The first step in this process will be to identify the inflammatory characteristics of a specific disease, ideally at the molecular level, and our section has through many years explored the tangle of inflammatory networks in diseases like atherosclerosis and heart failure as well as immunodeficiency like HIV and CVID. Thus, whereas we through a proof of concept study showed that targeting IL-6 in patients with myocardial infarction could be beneficial, we need in the future to select those patients that could be of particular benefit of such therapy (e.g., those with high CRP and IL-6 levels) (Figure 1). Moreover, recent studies have suggested that patients with particular mutation in genes related to epigenetic modification have a high risk for develop cardiovascular disease (even higher risk than those with hyperlipidemia), and in the future we could select these individuals for targeted therapy. Moreover, inflammatory lung disease is a common and severe complication in CVID patients, and in the future we need better molecular characteristics of these disorders in order to give more targeted therapy.

Thus, while tests of bone marrow, liver and kidney function has been part of the standard work-up new, methods like high-throughput genetic sequencing will push this part of the diagnostics to new frontiers. Currently, whole-exome sequencing of human genome is used routinely in our hospital for the diagnoses of genetically based disease but as our understanding of the genome increase, these analyses will be likely to predict both effects and side-effects of a treatment in question. Excitingly, these methods will not only include a characterization of the patients own DNA but also the DNA of our faithful companions, the microbiota. The relevance of our own genetics to disease and treatment is quite obvious but in the last years the importance of our microbiota, both to the risk of developing disease and to the response to treatment, has also been appreciated. The gut microbiota is by far the largest and - in terms of disease and treatment - probably the most important part of our microbiota. At present we know that gut microbiota is of major importance not only in the intestine, but also systemically in cardiovascular and related metabolic disorders and both primary and secondary immunodeficiency like CVID and HIV. At the RIIM there are several ongoing projects that explore the effects of gut microbiota on systemic disorders like heart failure, liver disorders and CVID and HIV (Figure 2 and 3), but so far, the main question is how to modulate this bacterial community in a beneficial way for the host. Most probably, each disorder and even each person will have their own signature that needs to be modulated by a personalized approach. Importantly, gut microbiota will also have influence on the effects of other drugs such as cancer drugs and this will have to clarified in order to develop real personalized medicine.

The final step in the personalization of immunomodulating therapy will be to describe an immunopathogenetic profile of the individual patient, including levels of inflammatory markers, activity of signaling networks and composition of immune cell compartments. These analyses are performed routinely in research laboratories like ours

Figure 2

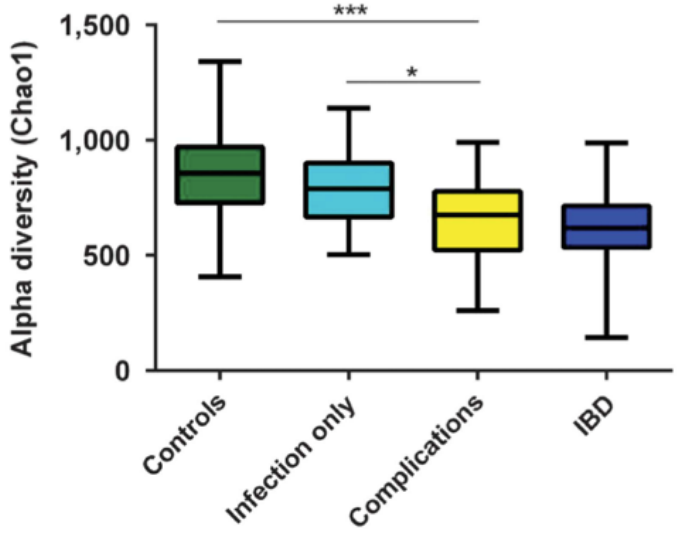
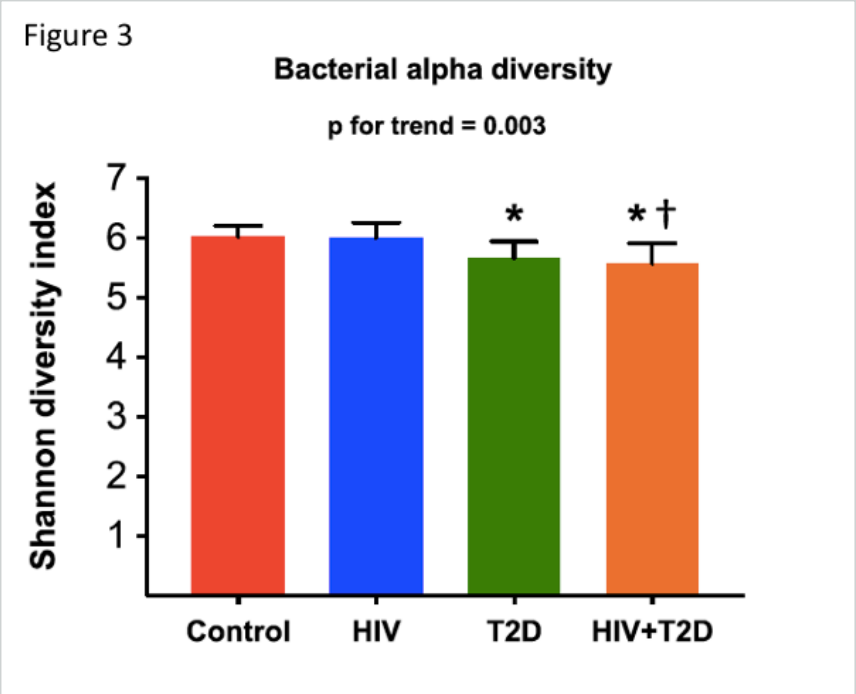
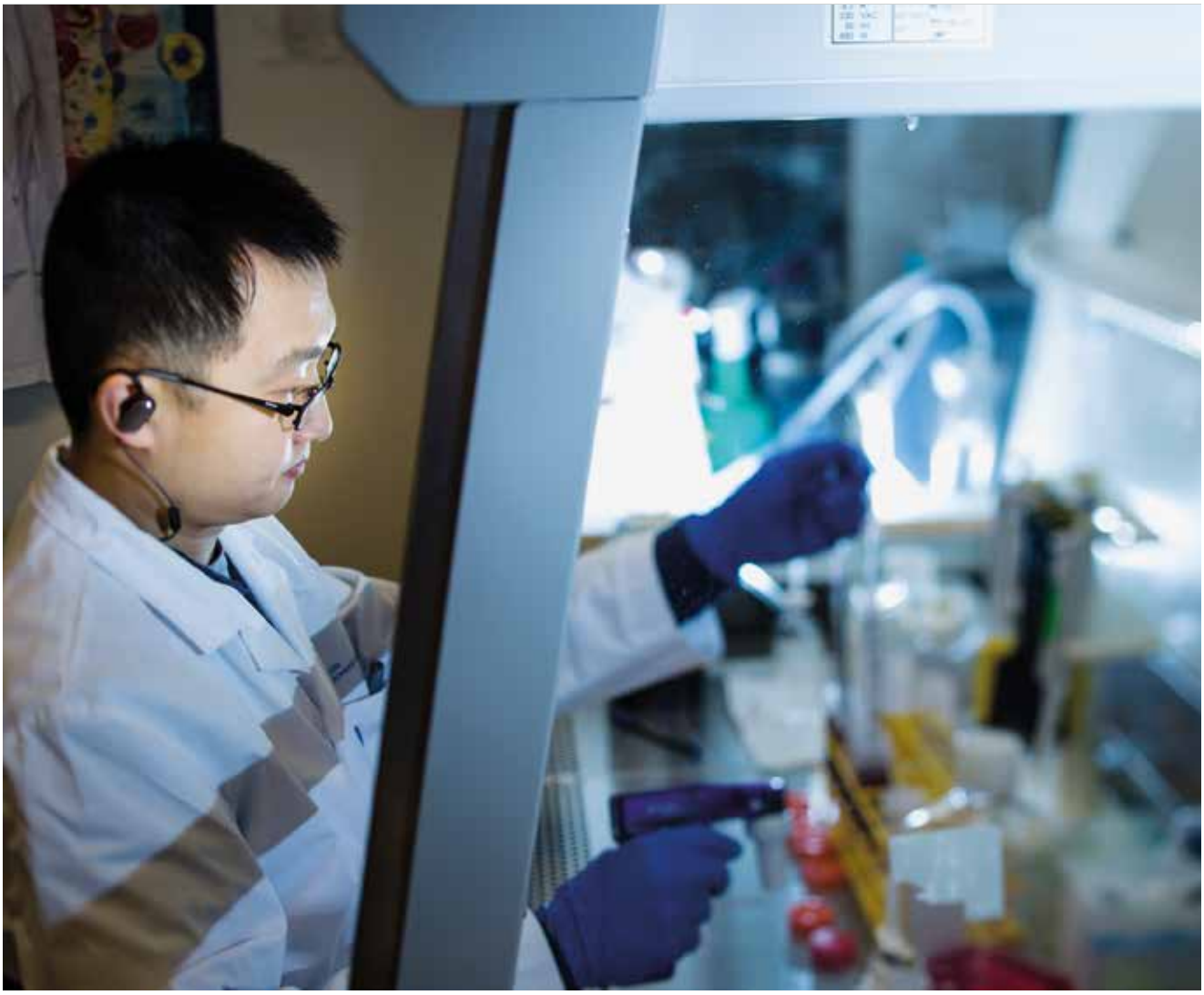


*Figure 2. Gut microbiota diversity in CVID patients with infection only, CVID patients with inflammatory complications and inflammatory bowel disease (IBD). associates with CVID patients with complications. *p<0.05, ***p<0.001. Jørgensen, et al, 2016.*



today and the major challenge is to implement their use in clinical laboratories for the benefit of the single patient. Oslo University Hospital has all means necessary to be a leader in this field, and our Section of Inflammatory Research will continue to identify markers and drivers of inflammation in human disease to that end.

*Figure 3. The impact of HIV, type 2 diabetes (T2D) and both on gut microbiota diversity. *p<0.05, †p<0.05 vs. HIV only. Hoel, et al, 2018*



DISSERTATIONS 2018

Yangchen Dhondup, MD

"Toll-like receptor 9 signalling in heart failure"
February 7, 2018

Main supervisor: Leif Erik Vinge, Diakonhjemmet Hospital, Oslo

Co-supervisor(s): Arne Yndestad and Pål Aukrust, RIIM, Institute of Clinical Medicine, University of Oslo

Summary of PhD project:
Every 10th Norwegian over the age of 70 has heart failure, and as we get older, more people are affected, and the risk of dying earlier is increased.
We have studied the relationship between heart failure (HF) and the mitochondrial DNA (mtDNA).
mtDNA comes from bacteria, and they are necessary for cells to live. However, we found that in people with heart failure, both mtDNA and nuclear DNA (nDNA) were elevated, while levels were lower for healthy people.
Based on the findings that showed increased mtDNA in the patients compared to healthy controls, we expected to find that increased mtDNA levels lead to increased mortality. However, we found the opposite: high levels of mtDNA gave better survival. It is surprising that high levels gave better survival because several studies have shown that under stress, mtDNA from cells leak into the blood, causing inflammation in the body.
To explain this, we wanted to look more closely at Toll-like receptor 9 (TLR9), since previous research has shown that mtDNA can activate TLR9 and cause inflammation. We investigated the effect of over-stimulation and no stimulation of TLR9 on heart failure mice, and found that both gave increased mortality. This is in contrast to the findings in the human study, where we found that high levels of mtDNA gave better survival. Perhaps the favorable level in humans lies between the corresponding levels we tested in the mice. It will therefore be interesting to investigate several levels of stimulation to find where the favorable level lies. This is one of the many interesting questions to investigate further. In the long run, this could contribute to the development of better treatment options for heart failure.

DISSERTATIONS

Marina Sokolova, MD

"Pathogenic consequences of NLRP3 inflammasome activation in metabolic disturbances"
October 18, 2018

Main supervisor: Arne Yndestad; Institute of Clinical Medicine, University of Oslo

Marina Sokolova presenting her thesis on October 18th 2018.

Co-supervisor(s): Trine Ranheim and Pål Aukrust, RIIM, Institute of Clinical Medicine, University of Oslo

Summary of PhD project:
The incidence of obesity is increasing dramatically. Modern dietary patterns, such as nutritional transition to processed foods rich in saturated fats and high calorie diets, and an increasingly sedentary lifestyle fuel the global epidemic of obesity and related metabolic disorders, such as insulin resistance, Type II diabetes, fatty liver disease and hypertension, i.e., cardiometabolic diseases. Chronic low-grade inflammation in general, and nod-like receptor family, pyrin-containing domain 3 (NLRP3) inflammasome activation in particular, has been suggested to be central features of their pathogenesis, involving a dynamic cross-talk between sensing of excess nutrients, the immune system and metabolic tissues. However, the mechanisms linking metabolic dysfunction with innate immunity are undoubtedly complex and far from being fully understood.
The main aim of this thesis was to characterize potential pathogenic effects of NLRP3 inflammasome in metabolic disorders. We were in particular interested in the impact of NLRP3 inflammasome activation within the heart during metabolic dysregulation as well as its role in pancreatic islet β-cells during oxidative stress-induced diabetes with the aim to identify new targets for therapy in these and related metabolic disorders. To address these questions, NLRP3 and ASC deficient mice and cells were used in both in vitro and in vivo experimental models.

Saturated fatty acid Palmitate induced inflammatory responses in cardiac fibroblasts via NLRP3 inflammasome activation. Palmitate exposure also affected cardiac fibroblast functionality. NLRP3 inflammasome deficiency prevented development of obesity-induced left ventricle concentric remodeling and dysfunction via inhibition of systemic inflammation and metabolic dysregulation. NLRP3 inflammasome deficiency was also protective against oxidative stress-induced pancreatic islet dysfunction.

In summary, the results presented in this Thesis indicate that NLRP3 inflammasome can play a pathogenic role in the progression of highly prevalent metabolic diseases, such as diabetes and obesity-related cardiac disease.

Colleagues and friends celebrating the successful dissertation.

Negar Shahini, MSc

"Dysregulation of the complement system in cardiac disease – Clinical and experimental studies"
December 10, 2018

Main supervisor: Arne Yndestad, RIIM, Institute of Clinical Medicine, University of Oslo

Co-supervisor(s): Mieke Louwe and Tom Eirik Mollnes, RIIM, Department of Immunology, University of Oslo

Summary of PhD project:
Heart failure (HF) is an important and increasing cause of cardiovascular morbidity and mortality. The development of HF is characterized by chronic low-grade activation of the immune system; however, the exact underlying molecular mechanisms remain to be understood. The complement system, a central arm of the innate immune system, is activated in HF. This thesis focuses on the role of different complement system components in both HF and severe symptomatic aortic stenosis and their associations with severity of the disease. We hypothesized that complement activation in these patients is mediated through changed levels of amplification loop components such as promoters of the alternative pathway i.e. properdin and factor D (FD), the alternative pathway inhibitor factor H (FH) and FB, an essential component for entire system activation. In addition, we investigated the role of C3 and CD14, bottleneck molecules of pattern recognition systems, in progression of cardiac remodelling in mouse model of angiotensin II-induced cardiac pressure overload.

Taken together, our main findings were that HF patients had significantly increased circulating levels of FD, TCC, and FB with particularly high levels in patients with the more advanced disease. Moreover, decreased circulating levels of FH and properdin were associated with adverse clinical outcome in these patients. Our research has demonstrated that patients with symptomatic aortic stenosis have increased complement activation indicated by elevated circulating levels of TCC. Notably, elevated levels of FB were significantly associated with increased risk of major cardiovascular events and all-cause mortality. Furthermore, our murine model revealed that deficiency in C3 and CD14 did not affect cardiac remodelling in cardiac pressure overload model. Our findings suggest that while C3 and CD14 might not be directly involved in cardiac remodelling, essential complement system components are elevated during symptomatic aortic stenosis and chronic HF, and FB could potentially represent a novel marker for risk stratification in these patients.

SECTION OF MOLECULAR HEPATOLOGY RESEARCH

Genomics and metagenomics in inflammatory diseases

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

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how alterations in the human genome and the gut microbial flora influence disease. We do this by applying modern genotyping and sequencing technologies, as well as metabolomics.
The main current interest of the group is the role of the gut microbiota in multiple inflammatory disease phenotypes, including primary sclerosing cholangitis (PSC) and intestinal diseases, immunodeficiencies (HIV and common variable immunodeficiency) as well as cardiovascular diseases. After an initial phase of defining the gut microbiota in inflammatory diseases, the main focus is now directed towards "Clinical microbiota medicine", that is, studies of the gut microbial content and function gut in human disease – and how the new knowledge can be applied clinically.
Locally, the group is integrated with the clinical microbiology and microbiota medicine group (leader Marius Trøseid) and 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.
A regional research network for clinical microbiota science (ReMicS) was finally funded late 2018, providing financial support to a collaborative research network that has been active the last five years.
In addition, the group hosted the fifth national conference on gut microbiota in November 2018 with about 110 participants and more than 20 abstracts submitted.
A major achievement in 2018 was the ERC Starting Grant awarded to group leader Hov and the project *StopAutoimmunity* (Recurrent disease in the liver transplant: window to identify and stop gut signals driving autoimmunity). Total funding is 1.5 million euros over 5 years, securing the major research axis on the gut microbial influence on PSC and post-transplant PSC for years to come.

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 or circulating markers of microbial activity (i.e. metabolites) as biomarkers of disease or disease activity and severity. Our first full metagenome sequencing project is now being finalized, a tool to identify altered microbial functions in disease and guiding metabolomics efforts.
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:

- 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
- National association for public health: CM
- Norwegian PSC Research Center: KH, SHH

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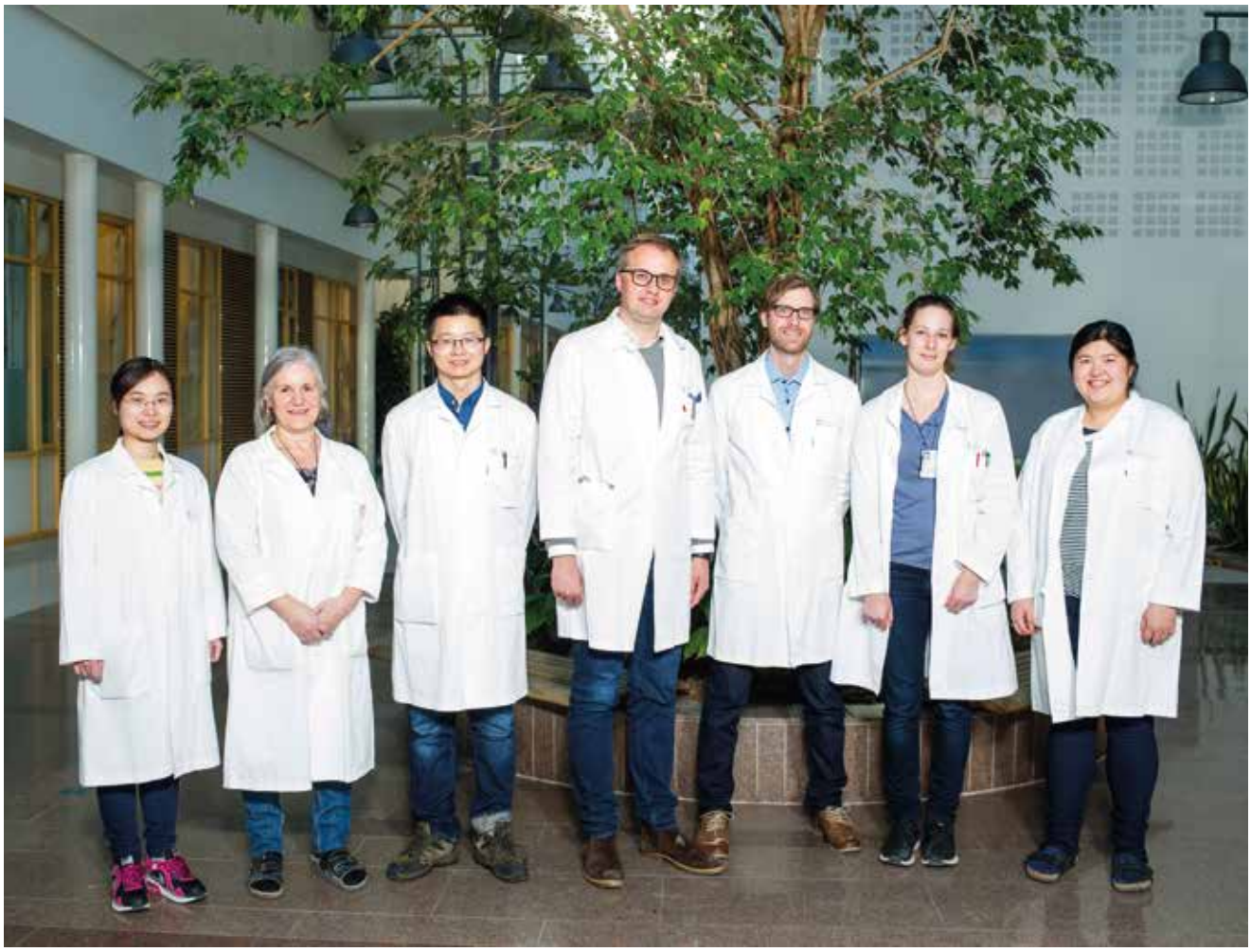
SECTION OF MOLECULAR HEPATOLOGY RESEARCH

The Experimental liver research group



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

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RESEARCH PROFILE

The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). The most important tools in our research are mouse models that model aspects of cholangitis development. The group represents one of the three research group at the Norwegian PSC research center. All of our laboratory activities take place at the Research institute for Internal Medicine. In 2018, the group consisted of the group leader, one post.doc., four PhD students, and a lab manager. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology but also now incorporating aspects of regenerative medicine. In addition to the cholangitis focused studies, we are also doing basic research related to the function natural killer T-cells, mucosal associated invariant T (MAIT)-cells and other immune subsets. NKT and MAIT cells represents unconventional T-cells that are especially interesting in the context of liver diseases since they are abundantly present in the liver. The ultimate goal of our research is to understand the pathology of and uncover potential novel treatment target for PSC.

The mouse models we use are immune driven which is in concordance with the leading theories on PSC pathogenesis. In 2018, we demonstrated for the first time that NKT cells can drive experimental cholangitis that can be treated by monoclonal antibodies.

These results corroborate our earlier results on the role of cholangiocytes as antigen-presenting cells. As part of a collaboration with our guest professor Frank Tacke from Aachen Anna Frank worked in the group as a visiting PhD student during 2018. As part of her project she established protocols for generating biliary organoids from both murine livers, human livers and brush samples acquired during ERCP. These techniques are now being used in studies aiming to understand PSC cholangiocyte biology as well as the role of the cholangiocyte in immunology.

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 and local (intestinal) and systemic inflammation. Magnhild Eide Macpherson is continuing this work with her PhD that includes both the modulation of gut microbiota with rifaximin in CVID-patients and an exciting investigation into the anti-inflammatory effect of HDL in the same patients. This latter work is extended into a Post doc project for Silje Fjellgård Jørgensen that will start up in 2019.
- Community-acquired pneumonia: a prospective observational study to explore etiology, risk factors and potential novel predictors of severe course and mortality. In close cooperation with Vestre Viken HA and Drammen Hospital the project applies new diagnostic methods to assess etiology and risk factors for severe course and mortality of pneumonia. In his PhD-project, William Siljan has been delving into the vast amount of data and samples previously collected, and his thesis will be defended in the spring of 2019.
- Study of immunological mechanisms in malaria. Kari Otterdal has a solid background in platelet research but has received a 4 year researcher grant from HSØ on a project looking at malaria in cooperation with University of Bergen and Stavanger University Hospital. In this exciting project we will take advantage of the institute's extensive knowledge of inflammation and among other things look at inflammatory properties of the Plasmodium produced hemozoin crystal.
- Liv Hesstvedt has through 2018 finished the work on her thesis "Candidemia in Norway and the Nordic countries" and a defense is planned in the early months of 2019. The thesis is partly based a national collaboration where data has been collected from laboratories and medical records from most Norwegian hospitals. Partly it is based on a Nordic collaboration using national epidemiological data. Supervisors are Ingvild Nordøy, Peter Gaustad and Fredrik Müller.
- Targeting the NLRP3 inflammasome in HIV infection. The research institute has a strong track record on HIV-research and this continues with Hedda Hoel's PhD project that looks at the NLRP3 inflammasome as a driving force of the systemic inflammation seen in HIV-infected patients. The NLRP3 inflammasome has been studied in cardiovascular disease by other groups at our institute, and the current project is an excellent example of how immunological insight gained from the study of one disease can be applied to new diagnoses. The project is led by Marius Trøseid who is also the main supervisor.
- Functional consequences of novel genetic variations in primary immunodeficencies and immune dysregulation (FUNPID). High-throughput sequencing has revolutionized the diagnostics of primary immunodeficiencies, giving a definite genetic diagnosis in complicated clinical cases. However, novel genetic variations of uncertain significance tend to show up and in close collaboration with established partners at Oslo University Hospital and the University of Oslo we have established a research-based diagnostic pipeline for these patients. These findings give us an extraordinary opportunity to characterize both new disease entities and new immunologic mediators. We are currently looking into a family with a possible gain-of-function mutation in IL-1R8 and have received funding for a Post doc from 2019.

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 and the Odd Fellow foundation.

INFLAMMATORY RESEARCH

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders

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

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Master student **Baoan Marianne Tran** from school of pharmacy, UoO, finished her work in 2018, with the thesis "Hyperactive T-cells in mice give obesity without metabolic disturbances" for the degree MPharm. Defended her Master thesis June 14th, 2018

Two bachelor students from Oslo MET; Frida Perry and Al Per Gursel; finished their work in 2018 «The role of Endonuclease V in atherosclerosis».

RESEARCH PROFILE

Atherosclerosis is a leading cause of death and disabilities worldwide. Atherosclerosis is a slowly progressing chronic disorder of large and medium-sized arteries that becomes clinically

manifest when it causes thrombosis, leading to complications such as myocardial infarction and ischemic stroke. The interaction between lipids, extra-cellular matrix and inflammation is a characteristic hallmark of atherosclerotic plaque development. The inflammatory mechanisms in atherosclerosis and closely related metabolic disorders have been the cornerstone of the research group's activity for the last 19 years.

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

Inflammation in atherosclerosis
We have studied the role of inflammatory mediators in development of atherosclerosis for many years. In 2018, one of our inflammatory focuses has been on the cysteine protease legumain. We have shown that legumain is increased in both plasma and plaques of patients with carotid stenosis and that legumain is produced by macrophages, and colocalized to macrophages in the plaque. We are currently elucidating the function and role of legumain in macrophage-induced inflammation in clinical atherosclerosis.

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

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

FUNDING

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

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

INFLAMMATORY RESEARCH

Immunological and molecular mechanisms in myocardial remodeling and heart failure

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

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RESEARCH PROFILE

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

PROJECTS

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

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

FUNDING

Our work in 2018 was based on funding from Helse Sør-Øst RHF, Research Council of Norway, UNIFOR-FRIMED, Anders Jahres fond til vitenskapens fremme. In addition we are partners in an EU supported project *ERA-NET in CVD.*

INFLAMMATORY RESEARCH

Inflammatory biomarkers in cardiovascular and metabolic disease

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

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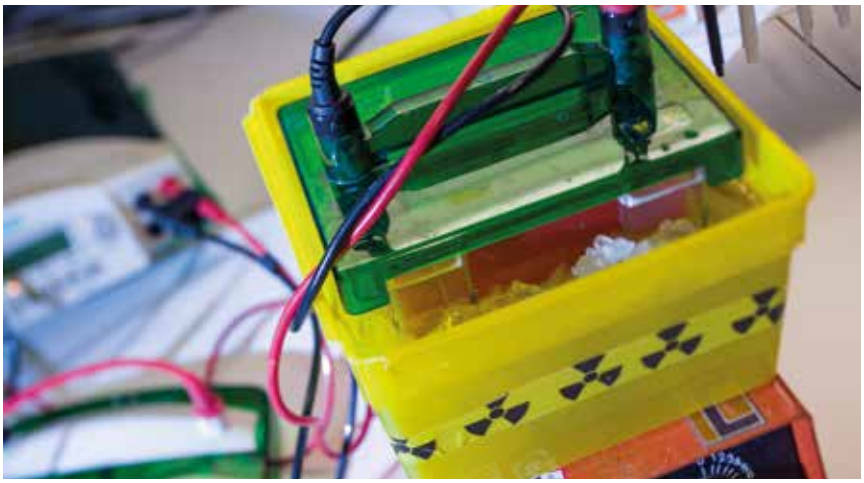
RESEARCH PROFILE

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

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

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

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



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

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

In May 2018 Aurelija Abraityte defended her thesis “Notch and wnt signaling pathways in heart failure”, and in June 2018 Kristin Astrid Øystese defended her thesis “Growth and Aggressiveness in Clinically Non-Functioning Pituitary Adenomas”.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

Haemostasis and bleeding disorders

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

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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 outcome of patients with moderate haemophilia A and B (factor level 1-<5 IU/dL) in the Nordic region (Iceland, Sweden, Denmark, Finland and Norway) and our group is the coordinating centre.

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

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

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

Immune thrombocytopenia
Parts of the group is also involved in studies on immune thrombocytopenia ITP and in the RITP trail we aimed to assess the efficacy of rituximab as compared with placebo as a splenectomy-sparing treatment in patients who were previously treated with corticosteroids. (Lancet 2015; 385: 1653–61). The follow up study PROLONG has now been ongoing for 3 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.

THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY RESEARCH

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

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

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RESEARCH PROFILE:

The main goal of this research group is to identify and uncover important molecular mechanisms of coagulation proteins contributing to or preventing disease.
Anomalies in the blood coagulation system can cause pathological bleeding or thrombosis but also participate in the manifestation of numerous other diseases such as infarctions in the heart or brain, sepsis (a systemic inflammatory reaction), and cancer. For instance, arterial thrombosis is in many cases the direct cause of cardiovascular disease-related deaths, which is the primary cause of death globally, and thrombotic complications are the secondary cause of death among cancer patients. Thus, regulation of the coagulation system is important not only in preventing clinical events related to hemostatic disorders, but also in preventing the morbidity and mortality of other common diseases. We conduct basic research with a translational potential focusing on several aspects of blood coagulation related to thrombosis, bleeding disorders, inflammation and cancer. The coagulation inhibitor tissue factor pathway inhibitor (TFPI) is of special interest as it has been implicated in the development of several non-hemostatic diseases in addition to being the primary inhibitor of coagulation initiation.

PROJECTS:

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

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

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

-TFPI-2 regulation by microRNAs
Although TFPI-2 is structurally similar to TFPI, it has a different, non-hemostatic function and is considered a tumor suppressor involved in regulating tumor progression, invasion and metastasis in breast cancer cells. Clinically, TFPI-2 expression is positively correlated to the survival of breast cancer patients, and thus the molecular mechanism behind the regulation of TFPI-2 expression

is of great interest. Micro-RNAs (miRNAs) have been increasingly Using the GOBO database, we found that the TFPI-2 mRNA levels were significantly increased in patients with ERα+ tumors compared to patients with ERα- tumors and that increased levels of TFPI-2 were associated with increased survival in patients with ERα+ tumors. We have demonstrated that estrogens induced TFPI-2 expression in ER positive breast cancer cells in a process mediated by ERα and a specific lysine demethylase. A continuation of this project is in progress where potential effects on TFPI-2 expression by miR-RNAs are being examined.

-TFPI regulation by transcription factor FOXP3

Previously, we have seen that the -287T/C single nucleotide polymorphism (SNP) of the tissue factor pathway inhibitor (TFPI) gene promoter region exerts differential impact on TFPI mRNA expression, with the C allele being associated with higher TFPI expression than the T allele. Increased expression of TFPI is in turn associated with reduced risk of thrombosis, and the SNP may therefore play an important role in the occurrence of thrombosis in the carriers. In the current project, we aimed to reveal the underlying molecular mechanisms of the differential gene regulation of TFPI caused by the SNP. Using bioinformatics, three potential candidate transcription factors for binding to the two -287 alleles were predicted, of which one, FOXP3, showed increased binding to the T allele compared to the C allele in various analyses. Furthermore, knock down or overexpression of FOXP3 resulted in increased or decreased TFPI levels, respectively, showing a repressor function of FOXP3. In conclusion, this study indicated that FOXP3, a transcription factor initially identified as a functional marker of T regulatory cells, may be the underlying cause to the increased levels of TFPI observed with the -287C allele.

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AWARDS 2018

Espen Melum (left) and Martin Roelsgaard Jakobsen from Århus University recieving Anders Jahres prize for your researches in the Univeristy Aula 11th of October 2018.

Anders Jahres prize for young researchers

- Dr. Espen Melum received in 2018 the prestigious Anders Jahres prize for young researchers. Dr. Melum got the prize for his research on the PSC (Primary Sclerosing Cholangitis). The prize ceremony was at held the University Aula in Oslo 11th of October 2018, followed by a gala dinner
- November 19th 2018, during the Fifth National Microbiota Conference, post doc Martin Kummen received the Tore Midtvedt's Award for the best abstract.
- During the 60th American Society of Hematology (ASH) Annual Meeting i San Diego, USA, in December 2018, postdoc Xue-Yan Cui got a high score on her abstract and received an Abstract achievement award.

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