The Research Institute of Internal Medicine (RIIM)

RIIM
ANNUAL REPORT
2013

The Research Institute of Internal Medicine (RIIM)
The Research Institute of Internal Medicine (RIIM) has a proud and long history which is outlined elsewhere in this Annual Report. It started in 1963 as an Institute of Thrombosis Research and several important scientific breakthroughs were achieved during the first years (for example the discovery of coagulation factor V). While research on the complex regulation of thrombus formation is still a main activity at RIIM, the activity has during the last 10–15 years expanded to other and related research areas, i.e., the role of inflammation in cardiovascular and immunodeficiency disorders and molecular and immunologic mechanisms in hepatic disorders.

The changes at the institute have markedly accelerated during the last four years. The fusion process at Oslo University Hospital is often described as troublesome. However, the fusion of RIIM with the Coagulation Laboratory at Ullevål Hospital and with the Primary Sclerosing Cholangitis (PSC) Research Group who had stayed at Institute of Immunology for some years has been a success. There have been some challenges, believe me, but it has most of all resulted in synergy, new collaboration between the research groups and a more inspiring, but also demanding environment.
Today the RIIM consists of 8 research groups which is divided into three sections (i) Section of Inflammatory Research, (ii) Section of Molecular hepatology, and (iii) Section of thrombosis, haemostasis and vascular biology.

During the last year the RIIM has had a large discussion on our research strategy that was approved just before Christmas. The main points in this strategy give insight into the “phenotype” of our research.

Our research primarily involves translational research with “one foot in the bed and one in the bench”, i.e., the experimental research profile is «close to bedside. This research incorporates both experimental, basic, clinical and epidemiological components.

This research profile is also based on a close teamwork between skilled basic and clinical researchers and the institute has a close collaboration with several clinical departments such as Department of Transplantation Medicine, Department of Cardiology, Department of Hematology, Department of Cardio-thoracic Surgery, Department of Neurology and Department of Dermatology, Rheumatology and Infectious Diseases. Although several topics are studied, our main thematic research focus is related to inflammation and hemostasis.

Our aim is to compete at a high international level within our research fields. To obtain this several points are of importance such as collaborations both nationally and internationally, recruitment and carrier building for young talented researchers.

In this regard, we believe that exchange of researchers between foreign research institutions is of major importance. We also believe that more close collaboration between the different research institutes at Oslo University Hospital could strengthen the research at this hospital.

This is the first Annual Report from RIIM in several years. However, we hope to break this “bad tradition” and plan to come back with an updated version next year.

Professor Pål Aukrust | Institute Leader at RIIM
The history
of the Research Institute of Internal Medicine – a brief review

The history of The Research Institute of Internal Medicine (RIIM) started in 1956. At that time the institute was named Institute of Thrombosis Research (Institutt for tromboseforskning) and was a university institute at Rikshospitalet, lead by Paul Arnor Owren. Owren’s research focus was coagulation system and his discovery of Factor V and its role in coagulation system was a milestone in field of coagulation research. This research was also the basis for new coagulation tests to evaluate the coagulation system in a clinical setting.

In 1962 Nils Olav Solum and Holm Holmsen started at the institute and their work on platelet biology and pathophysiology achieved much attention worldwide. Helge Stormorken started at the institute in 1963 and worked on the complex regulation of the coagulation system, and among others he described patients with a complex thrombogenic diseases which was named “Stormorken Syndrome” and very recently the gene mutation causing this syndrome was discovered.

The Faculty of Medicine decided in 1978 that the institute should be an “arena for Internal Medicine Research” and the institute was then named RIIM “Institutt for indremedisinsk forskning” (IIF). This was the start of a broader research activity at the institute.

Frank Brosstad started his carrier at RIIM in 1981 and all his important research was on thrombosis and the coagulation system in close collaboration with Nils Olav Solum underscoring the close interaction between the coagulation system and platelets in health and disease. At the same period Hans Prydz (1980-1989) also worked at RIIM with tissue factor and coagulation system as his main focus.

In 1996 Stig Frøland started at RIIM with his well rebutted HIV and immunodeficiency research. He was the “father” of translational research with one foot in the bed and one in the bench which is now an important part of our research strategy. One year later Christian Hall came to the institute with his research on heart failure. Hall research was focused on biomarkers in cardiovascular research and his work on netriuretic peptides achieved much attention, and one of his tests is now in clinical use world wide and is an example of excellent innovative research.

In 2000 Pål Aukrust, which had also been working together with Frøland, Yndestad, Halvorsen and Ueland, started their research on “Cardioimmunology” which included diseases like heart failure, atherosclerosis and related metabolic disorders. This research also included a close collaboration with Frank Brosstad and Nils Olav Solum focusing on the inflammatory role of platelets in various disorders.

Tom Hemming Karlsen and colleagues came to RIIM in 2008 with their research focus on liver immunology and primary sclerosing cholangitis. They strengthened the research profile at the institute by their high standard methodology, international collaborations and their high expertise in molecular genetics. The “Oslo process” lead to the fusion of “Coagulation laoratory” at Ullevål and RIIM, and as a result of this process Per Morten Sandset and colleagues came to the institute in 2011 with their high standard research on thrombosis and haemostasis that also includes large scale clinical studies. This group together with Pål Andre Holme keeps the “thrombosis arm” of the research profile at RIIM in live.

In 2011 RIIM was formally changed from a university institute into a Department at the Division of Cancer Medicine, Surgery and Transplantation at the Oslo University Hospital.

AUTHOR: Professor Bente Halvorsen
Organization
The Research Institute of Internal Medicine 2013

Research Institute of Internal Medicine

Head of Institute (Pål Aukrust)
Management group (section and group leaders)

Section of thrombosis, haemostasis and vascular biology
(Per Morten Sandset)

Section of Inflammatory Research
(Pål Aukrust)

Section of Molecular Hepatology
(Tom Hemming Karlsen)

Vascular pathophysiology
(Sandip Kansal)

Hemostasis and bleeding disorders
(Pål Andrén Holme)

Coagulation factors: role in the development of thrombosis, inflammation and cancer
(Grøthe Skjellberg)

Immunopathogenetic mechanisms in inflammatory and infectious disorders
(Bjarne Fevang)

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders
(Brente Hakonsen)

Immunological and molecular mechanisms in myocardial remodeling and heart failure
(Arne Ystadstad)

Inflammatory biomarkers in cardiovascular and metabolic disease
(Thor Ueland)

Genomics and metagenomics in inflammatory disorders
(Johannes Hov)

Experimental liver research
(Espen Melum)

Clinical liver research
(Multiple PIs)

Institute of basic medical sciences

Department of transplantation medicine
Research group

SECToN oF TRoMBoSIoN, hAEMoSTASIS ANd VASCuLAR BIoLoGY

Haemostasis and bleeding disorders

GROUP MEMBErs

GROUP LEADER:
Pål André Holme Asc prof., MD, PhD

PHD STUDENTS:
Hoa Thi Tuyet Tran MD
Nina Haagenrud Schultz MD

ENGINEER:
Stine Bjørnsen

STUDY COORDINATOR:
Adelheid Holm

ASSOCIATED:
Geir E. Tjønnfjord Prof., MD, PhD

RESEARCH PROFILE

Our scientific interests are focused on clinical and basic aspects of normal and disturbed haemostasis in particular bleeding disorders like hereditary and acquired coagulation disorders.

Oslo University hospital, Rikshospitalet is the only Haemophilia Comprehensive Care Centre in Norway and is one of the biggest haemophilia centres in the Nordic region taking care of more than 1200 persons with bleeding disorders. Several research projects are ongoing besides clinical activity.

During the last years we have studied and published papers on how to optimize and tailor treatment in persons with haemophilia with or without inhibitors to FVIII and in persons with FVII deficiency.

One of main objectives has been tailoring of treatment with bypassing agents (BPA) for haemophilia patients with inhibitors. High titre inhibitors to factor VIII and less often to factor FIX, represent a major challenge in the treatment of haemophilia A and B. The treatment of bleeds in haemophilia patients with inhibitors relies on the use of the bypassing agents, factor eight bypassing activity (FEIBA) or recombinant factor VIIIa. 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.

Recently, we reported our experience and performed a clinical, prospective, randomized, crossover study of concomitant usage of bypassing agents and tranexamic acid (TXA) in haemophilia A patients with inhibitor and in patients with acquired haemophilia with respect to haemostatic efficacy and safety. These studies showed that adjunct use of TXA to BPA significantly increased the clot stability without increasing the thrombin generation and may be superior to standard treatment with BPA alone.
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 (Age-related-DeVelopments-ANd-Comorbidities-in-hemophilia Working Group).

The group is interested in determining, among consecutively screened people with haemophilia (> 800 pts.), aged ≥40 years, whether rates of hypertension and renal disease vary according to a previous history of hematuria and whether rates of hypertension/renal disease/ and other comorbidities vary with specific influencing factors in haemophilia. A cross sectional part is already performed and will be further followed up in a longitudinal prospective study.

Today there are no evaluated effective treatments to reverse the effect of direct oral anticoagulants (DOAC).

Recently, we have initiated a study where the objectives are to detect the most effective haemostatic agent and appropriate dose for reversal of bleeds caused by DOACs extensively used in the clinic for atrial fibrillation and treatment of venous thromboembolism. The effect will be assessed mainly by means of 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.

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

SECTION OF THROMBOSIS, HAEMOSTASIS AND VASCULAR BIOLOGY

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

GROUP MEMBERS

GROUP LEADER:
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Elisabeth Dørum  MSc

BIOENGINEER:
Marie-Christine Mowinckel

AREAS OF FOCUS

Our research focuses on the molecular mechanisms underlying the role of coagulation inhibitors in thrombosis, inflammation and in cancer. Of special interest is the coagulation inhibitor tissue factor (TF) pathway inhibitor (TFPI). Our main goal is to establish the link between coagulation, inflammation and cancer.

Coagulation inhibitors, such as TFPI, antithrombin, protein C (PC) and protein S (PS), are important regulators of coagulation activation, and deficiencies of these inhibitors alter the threshold for activation of coagulation and increase the risk of thrombosis. The inhibitors also influence inflammatory pathways, and may thus play an important role in inflammation and the development of atherosclerosis. Finally, considerable evidence now suggests that certain coagulation inhibitors also play a role for cell proliferation and apoptosis and for angiogenesis, which indicates a role in cancer development.

PROJECTS

Our group has lately focused on the molecular mechanisms related to the role of coagulation inhibitors for the development of thrombosis and cancer. In particular we have concentrated on the involvement of TFPI and PC in these processes.

TFPI is the physiological inhibitor of TF induced coagulation. Low levels of TFPI in plasma are associated with increased risk of thrombosis and SNPs in the TFPI genes have been shown to influence the TFPI plasma levels. Significantly increased levels of TFPI have been found in plasma from cancer patients and expression of TFPI in many cancer cells has been demonstrated. The mechanism behind this is as yet unknown. We are also studying the role of TFPI in endothelial cell activation and atherosclerosis.

Estrogens can influence the pathological processes of many hormone-dependent cancers such as breast and ovarian cancers. Women using oral contraception or postmenopausal hormone therapy are at increased risk of venous thrombosis. These women have decreased plasma TFPI levels indicating a link between estrogens and TFPI, both in cancer and venous thrombosis. At present we are focusing on the effect of estrogens on TFPI and the underlying mechanisms.

Lately, our group has initiated a project to study the molecular mechanisms underlying hypoxia and coagulation in cancer progress and multidrug resistance. Hypoxia is a hallmark of several pathophysiological conditions including cancer, atherosclerosis and ischemic cardiovascular disease, conditions characterized by activation of coagulation and increased risk of thromboembolism.

Hypoxia is defined as an inadequate oxygen supply to the cells and tissues of the body and hypoxia due to low atmospheric pressure triggers activation of coagulation, most probably...
due to tissue factor (TF) production by intravascular cells. Another phenomenon related to hypoxia is multidrug resistance (MDR), an acquired phenotype of certain cancers that results in inadequate response to chemotherapy (chemoresistance) and reduced survival. To date, the relationship between hypoxia, coagulation and metastasis, particularly chemoresistance, has remained largely unexplored. To develop new targeted therapies towards avoiding thrombotic complications in cancer and to increase the rate of successful treatment of cancer by reducing the rate of MDR, basic knowledge into the underlying mechanisms is essential.

A large number of human diseases are caused by defects in protein folding as a result of genetic mutations or adverse physiological conditions. The maintenance of the protein homeostasis in blood requires regulation of coagulation and fibrinolysis and protein deficiencies in these processes lead to hemorrhagic or thrombotic tendency. Many of the coagulation factor deficiencies are caused by reduced circulating protein levels resulting from a broad spectrum of gene mutations. This can cause impaired secretion due to increased intracellular degradation or accumulation of misfolded proteins, processes that have been reported for some factor VII (FVII) and factor VIII (FVIII) deficiencies, and also in deficiencies of protein C and plasmin inhibitor. For a number of cases of diseases caused by protein misfolding, drugs acting directly on the affected protein have been found to prevent misfolding and restore biosynthesis and function.

A project in our group aims to investigate the intracellular fate of a group of FVII mutations previously reported in both Norwegian patients and also in patients from elsewhere, in order to elucidate the cellular mechanisms implicated in these mutations and thus, to envisage possible therapeutic approaches. In addition, we are extending a previous study from our group on a protein C mutation, now from a therapeutic point of view.
Research group

SECTION OF INFLAMMATORY RESEARCH

Inflammatory and molecular mechanisms in atherosclerosis and related metabolic disorders

GROUP MEMBERS

GROUP LEADER:
Bente Halvorsen Professor, Dr. philos

OVER ENGINEERS:
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Håvard Lorentzen MD

SENIOR CONSULTANT:
Mona Skjelland Dr. med

MASTER STUDENTS:
Lene Løvdal BSc
Andrea Øvergård BSc (nutrition)

RESEARCH PROFILE

Halvorsen’s research group studies the inflammatory and molecular mechanisms involved in the development of atherosclerosis and related metabolic disorders. The research has a clear translational approach. The projects range from analyses of blood and tissue samples from patients with cardiovascular disorders or other metabolic disturbances to studies in preclinical models, as gene modified mice, or cell models using advanced cellular and molecular biology. The group consists of people with different educational background like medical doctors, nutritionists, biochemists and engineers. Such multidisciplinary personal composition is one of strength of the research group.

RESEARCH PROJECTS

- The role of NAMPT/visfatin in atherosclerosis and metabolic disorders
- The role of DNA repair systems in experimental atherosclerosis and metabolic disorders
- The role of chemokines in acute coronary syndromes
- The role of homeostatic chemokines in atherogenesis
- Metabolic effects of IL-10
- Platelet-mediated inflammation
- Inflammatory and metabolic effect of LIGHT
- The role of TNF superfamily related molecules in acute coronary syndromes
- Pain mediated inflammation

SOME IMPORTANT MILESTONES FOR THE GROUP IN 2013

- Filip Segers started in the group. He is a Belgian post doc educated in Prof Erik A Biessen’s lab in Maastricht. Filip has a strong portfolio in experimental atherosclerosis.
- Linda Smedbakken defended her doctoral thesis entitled: “Homeostatic chemokines and adhesion molecules in atherosclerosis – from bed to bench” May 2013 – Faculty of Medicine, University of Oslo
- Martine Z. Espeland defended her Master Thesis entitled: “Nicotinamide phosphoribosyltransferase in macrophage polarization – A possible role in atherosclerosis” in June 2013, Faculty of Medicine, University of Oslo
Research group

SECTION OF INFLAMMATORY RESEARCH

Immunological and molecular mechanisms in myocardial remodeling and heart failure

GROUP MEMBERS FEBRUARY 2014

GROUP LEADER:
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RESEARCHERS:
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Leif Erik Vinge MD, PhD

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ENGINEERS:
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Øystein Sandanger MD, PhD
Erik Øie MD, PhD

Immunological and molecular mechanisms in myocardial remodeling and heart failure

The Research Institute of Internal Medicine (RIIM) • ANNUAL REPORT 2013

Research profile

Our group works on uncovering novel mechanisms involved in the response to myocardial infarction and the development of heart failure (HF), with the objective to form the basis for new treatment modalities as well as for the identification of new biomarkers in this disorder.

HF is defined as a clinical syndrome characterized by dyspnea and fatigue, at rest or with exertion due to impaired structure and/or function of the heart. HF represents a major cause of cardiovascular and also total morbidity and mortality in the western hemisphere. The incidence and prevalence of this disorder is rising and it is estimated that HF affects 1–3% of the population. Moreover, the prognosis is poor. Due to the high prevalence and morbidity, HF also represents a major and increasing socioeconomic burden. Thus, there is an obvious need for new treatment options for this patient group.

The development of HF is characterized by several cellular and molecular processes, referred to as remodeling, leading to important changes in myocardial structure and function. These changes include cardiomyocyte hypertrophy, increased ventricular volume due to dilation of the ventricular cavity, regression to a fetal phenotype characterized by expression of fetal genes and proteins, enhanced apoptosis, as well as the development of fibrosis involving changes in the quantity and quality of the extracellular matrix. Initially the ventricular remodeling is thought to be adaptive and accommodates the increased myocardial wall stress. However, over time, this process turns maladaptive, leading to a progressive decrease in myocardial function.

Our research include experimental in vivo studies in different animal models of HF, in vitro studies in primary isolated cardiac myocytes, fibroblasts and macrophages, as well as clinical studies in well characterized patients with heart failure, examining samples from peripheral blood as well as tissue samples from the failing myocardium.

Research focus

Currently, our research focus is divided in three:

1. Innate immune responses in cardiac injury and heart failure development
2. Oxidative DNA damage repair and stem/progenitor cell proliferation in the pathogenesis of heart failure
3. Pathogenic role of adipose tissue and fatty acids in heart failure
Research group

SECTION OF INFLAMMATORY RESEARCH

Immunopathogenetic mechanisms in immunodeficiency and infectious disorders

GROUP MEMBERS

GROUP LEADER:
Børre Fevang Ass professor
POST DOC:
Kari Otterdal Researcher
PHD STUDENTS:
Elisabeth Astrup
Jan Cato Holter
Silje Jørgensen
ASSOCIATED MEMBERS:
Stig S Frøland Professor emeritus
Ingvild Nordøy Senior consultant, researcher
Kristine Lillebø Holm PhD student
Eli Taraldsrud PhD student

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 characterising these disorders. The aim is to improve the understanding of disease mechanisms and to discover new targets for therapeutic intervention. The group works in a translational setting combining close contact to the clinic, in particular Section of Clinical Immunology and Infectious Diseases at OUS, with access to a wide range of immunological methods through extensive collaboration with other groups.

Chronic inflammation is a common feature of both immunodeficiencies and many infectious disorders. While inflammation is vital to the clearance of both invading microbes and potentially malignant cells a continued or exaggerated response will further compromise the patients health. Identifying the factors leading to such an exaggerated response will potentially enable clinicians to modify the inflammatory response of the single patient with agents targeting anything from intracellular signalling pathways to intercellular cytokine networks and microbiota.

RESEARCH PROJECTS

The group is currently working with several projects, including:

- Immunopathogenetic mechanisms in infection with Rickettsia species. Infections with the vector borne intracellular bacteria Rickettsia conori and Oritenta tsutsugamishu lead to vasculitis and multi-system disease. The project studies the interplay between host and microbe through the Wnt system and chemokine signalling in collaboration with partners in India, France and USA.

- 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.

- Immunopathogenic mechanisms in CVID – a disease model for autoimmune and persistent inflammation. In close collaboration with Johannes Hov’s and Espen Melum’s groups at our institute this project will use CVID as a model disease to study potentially novel aspects of autoimmune and autoinflammatory disorders in more general terms, in particular for the study of the interaction between gut microbiota and local (intestinal) and systemic inflammation. The project also includes a genome wide association study on CVID through an international network of clinical immunologists.

- The role of vitamin A in regulation of B cell immunology: Implications for patients with CVID. In close collaboration with Heidi Kiil Blomhoff’s group at Institute for medical basic science this project aims to look at the modulating effect of vitamin A on TLR9 stimulation of B cells, both in respect to chromosomal instability and proliferation.

- New diagnostic tools to unravel the dysfunctional cell communication in CVID. In close collaboration with Johanna Olweus’ group at Institute of Cancer Research this project will strengthen the diagnosis of CVID through shedding light on intracellular signaling pathways of potential importance in B-, T- and dendritic (DC) cells.
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.
Research group

SECTION OF MOLECULAR HEPATOLOGY

Genomics and metagenomics in inflammatory disorders

GROUP MEMBERS

GROUP LEADER:
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BIOINFORMATICIAN:
Kristian Holm

ASSOCIATED MEMBERS:
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Silje Jørgensen PhD student

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, in particular the susceptibility to primary sclerosing cholangitis (PSC) and cholangiocarcinoma, but also to other inflammatory phenotypes. We do this by applying modern genotyping and sequencing technologies in cross-sectional and interventional study design.

Genetic factors play a role in most inflammatory diseases. By studying disease genes and their function, the mechanisms by which PSC develop and eventually may be treated can be defined. Since many of the patients with PSC have concurrent inflammatory diseases (mainly inflammatory bowel disease, but also prototypical autoimmune diseases like type 1 diabetes and rheumatoid arthritis), these diseases are studied in parallel.

The gut microbiota is an important human organ comprising ten times more cells than the body itself, and likely plays a major role in human disease. Ongoing studies aim to characterize how the gut microbial community composition in patients with PSC or other inflammatory phenotypes interacts with immune regulation, bile acid metabolism and drugs.

An important part of the activities is the standardization of methods related to key challenges in the field; study designs, sample collection and preparation, sequencing technology and bioinformatics.

Lifetime risk of cancer of the bile ducts in patients with PSC is 10–20%. Few inflammatory conditions have an equally high risk of cancer development, and determining the genetic and epigenetic alterations responsible for this is of great importance. In addition to understanding the pathogenesis of cholangiocarcinoma, cancer genetics and epigenetics may serve as diagnostic and prognostic markers.
The Research Institute of Internal Medicine (RIIM) • ANNUAL REPORT 2013

Research group

SECTION OF MOLECULAR HEPATOLOGY

The experimental liver research group

GROUP MEMBERS

GROUP LEADER: 
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RESEARCH ASSISTANT: 
Corey Tan BSc

LAB MANAGER: 
Jarl Andreas Anmarkrud PhD
(temporary on leave)
Kristian Alfnes PhD

RESEARCH PROFILE

The experimental liver research group was formed in June 2013 with three members from the Norwegian PSC research center. During of 2013 we have been through a build-up period and have recruited several talented colleagues. Currently the group consists of the group leader, one post doc, three PhD students, one scientific assistant and a lab manager. The group still remains an integral part of the Norwegian PSC research center, but is a separate group at the Research Institute for Internal medicine.

The main aim of our research is to understand mechanisms regulating cholangitis, which potentially can lead to understanding of the pathology, and identification of novel treatment targets for the chronic bile duct disease primary sclerosing cholangitis (PSC). We do this by using in vivo mouse models of cholangitis development along with genetically modified mice, so called knockout mice that are missing central molecules involved in the immune response. The mouse models used are immune driven and inspired by the fact that most genes associated with PSC are involved in the immune response. One of our models is a mouse strain that spontaneously develops cholangitis while in another model we induce cholangitis through microsurgery. To specifically address the role of an associated PSC gene we use tissue from knockout mice for expression profiling.

To complement the in vivo studies we are also using selected in vitro cellular models to study the role of various cell types in the liver and bile duct immune responses. A special emphasis in our studies is natural killer T-cells, an abundant population of lymphocytes in the liver with regulatory properties. Several ongoing studies aim to clarify the role of these cells in cholangitis development. Along with the cholangitis-centered studies we perform basic studies related to activation and development of NKT-cells.
Publications from The Research Institute of Internal Medicine

PUBLICATIONS IN PRESS

   Prognostic Impact of High-sensitive Troponin T Assessment in Elderly Patients with Chronic Heart Failure: Results from the CORONA Trial
   Circ Heart Fail (in press)

2. Tran HT, Sørensen B, Rea CJ, Bjørnsen S, Ueland T, Pripp AH, Tjønnfjord GE, Holme PA
   Tranexamic acid as adjunct therapy to bypassing agents in haemophilia A patients with inhibitors
   Haemophilia (in press)

3. Nensterer MS, Aukrust P, Ose L, Holven KB
   Low level of inflammatory marker in hyperhomocysteinemic patients on statin therapy

   Common variable immunodeficiency revisited: normal generation of naturally occurring dendritic cells that respond to toll-like receptors 7 and 9
   Clin Exp Immunol (in press)

5. Manhenke C, Ueland T, Jugdutt BI, Godang K, Aukrust P, Dickstein K, Orn S
   The relationship between markers of extracellular cardiac matrix turnover: infarct healing and left ventricular remodelling following primary PCI in patients with first-time STEMI
   Eur Heart J (in press)

   Secreted Wnt Antagonists During Eradication of Cytomegalovirus Infection in Solid Organ Transplant Recipients
   Am J Transplant (in press)

   Colectomy for patients with ulcerative colitis and primary sclerosing cholangitis – What next?
   J Crohns Colitis (in press)

   Differences in insulin sensitivity, lipid metabolism and inflammation between young adult Pakistani and Norwegian patients with type 2 diabetes: a cross sectional study
   BMC Endocr Disord, 13 (1), 49 (in press)

   Microencapsulation of mildronate in bio-degradable and non-biodegradable polymers
   J Microencapsul (in press)

10. Westberg M, Paus AC, Holme PA, Tjønnfjord GE
    Haemophilic arthropathy: Long-term outcomes in 107 primary total knee arthroplasties
    Knee (in press)

11. Andersen IM, Tengesdal G, Lie BA, Boberg KM, Karlsen TH, Hov JR
    Effects of Coffee Consumption, Smoking, and Hormones on Risk for Primary Sclerosing Cholangitis
    Clin Gastroenterol Hepatol (in press)

12. Tran HT, Tjønnfjord GE, Holme PA
    Use of thromboelastography and thrombin generation assay to predict clinical phenotype in patients with severe FVII deficiency
    Haemophilia (in press)

    Inflammatory cytokines in chronic heart failure: interleukin-8 is associated with adverse outcome. Results from CORONA
    Eur J Heart Fail (in press)

14. Iversen PO, Negaard H, Ostenstad B, Sandset PM, Kolset SO
    Evidence for long-term hypercoagulopathy, but normalization of markers of extracellular matrix turnover, in patients with non-Hodgkin lymphoma
    Leuk Lymphoma (in press)

    Anakinra and tocilizumab enhance survival and function of human islets during culture: implications for clinical islet transplantation
    Cell Transplant (in press)


9. Casar-Borota Q, Heck A, Schulz S, Nesland JM, Ramm-Pettersen J, Lekva T, Alafuozoff I, Bollerslev J (2013) Expression of SSTR2a, but not of SSTRs 1, 3, or 5 in Somatotroph Adenomas Assessed by Monoclonal Antibodies Was Reduced by Octreotide and Correlated With the Acute and Long-Term Effects of Octreotide J Clin Endocrinol Metab, 98 (11), E1730-9


The G protein-coupled estrogen receptor 1 (GPER1/GPR30) agonist G-1 regulates vascular smooth muscle cell Ca\(^{2+}\) handling  
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Doctoral theses
The Research Institute of Internal Medicine (RIIM)

**PhD 2010**

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<th>Name</th>
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<td>Arora S</td>
<td>Immunological and non-immunologiscal markers of cardiac allograft vasculopathy amongst heart transplant recipients</td>
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<td>Breland UM</td>
<td>The pathogenic role of chemokines in atherosclerotic disorders: clinical and experimental studies</td>
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<td>Dahl CP</td>
<td>Inflammatory cytokines in heart failure: potential role as mediators and biomarkers</td>
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<td>Dahl TB</td>
<td>Nicotinamide phosphoribosyltransferase: role in atherosclerosis and nonalcoholic fatty liver disease</td>
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<td>Fevang B</td>
<td>Profound perturbation: immunopathological mechanisms in common variable immunodeficiency</td>
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<td>Fougner S</td>
<td>Molecular biological examination of somatotroph pituitary adenomas related to clinical data from patients with acromegaly</td>
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<td>Holm S</td>
<td>Liver X receptor: physiological regulation at the crossroads of glucose and lipid metabolism</td>
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<td>Melum E</td>
<td>From single markers to genome-wide association: a study of primary sclerosing cholangitis genetics</td>
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**PhD 2011**

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<td>Hov JER</td>
<td>Functional genetics in primary sclerosing cholangitis: studies of the bile acid receptor TGR5 and genes in the HLA complex</td>
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<td>Platelet-derived microparticles and biomarkers in atherosclerosis and inflammation</td>
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**PhD 2012**

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<td>Tjeldhorn L</td>
<td>Protein C deficiency-molecular and functional studies on the protein C A267T mutation</td>
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<td>Sandanger Ø</td>
<td>The innate immune system – A paradoxical mediator of host defense, tissue repair and collateral damage</td>
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**PhD 2013**

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<td>Andresen K</td>
<td>Novel epi-markers in cholangiocarcinoma and their clinical potential</td>
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<td>Askevold ET</td>
<td>The Wnt signaling pathway and soluble glycoprotein 130 in heart failure and aortic stenosis. Novel markers and mediators of cardiac disease</td>
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<td>Bergrem A</td>
<td>Hemostatic risk factors for pregnancy-related venous thrombosis</td>
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<tr>
<td>Jørgensen KK</td>
<td>Inflammatory Bowel Disease in Primary Sclerosing Cholangitis: Clinical Characteristics in Liver Transplanted and Non-Transplanted Patients</td>
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<td>Lekva T</td>
<td>Epithelial Mesenchymal Transition in Somatotroph Pituitary adenomas</td>
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<tr>
<td>Smedbakken LM</td>
<td>Homeostatic chemokines and adhesion molecules in atherosclerosis – from bed to bench</td>
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Awards

The Research Institute of Internal Medicine (RIIM)

2010

Johannes Espolin Roksund Hov. Helge Bell’s award for excellent research in hepatology 2010. “Mutational Characterization of the Bile Acid Receptor TGR5 in Primary Sclerosing Cholangitis”.

2011


2012


2013


Pål Aukrust. The research award for University of Oslo 2013.

Tom Hemming Karlsen. Oslo University Hospital’s Early Career Award 2013.

Tom Hemming Karlsen. Researcher of the Month, South-Eastern Norway Regional Health Authority, November 2013.
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