Oslo University Hospital

UiO : University of Oslo

Research Institute of Internal Medicine (RIIM)

ANNUAL REPORT 2015

RIIM

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2015

Pages

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Leader´s corner

Professor Bente Halvorsen
Head of the Research Institute of Internal Medicine

On July 1st 2015 I took over the relay baton after Pål Aukrust who had chaired our institute since 2010. With that, a new era in RIIM's history started.

I hereby would like to thank Pål for the thorough job he has done for the Institute and its scientific reputation. For safe and secure guidance through fusions and other organizational changes both at the Institute and in Oslo University Hospital.

With respect for RIIM´s history, and humbled by duties the leader role encompasses, I started this job with enthusiasm. To be honest, I like it. It is so inspiring to lead an Institute consisting of so many eminent and talented scientists from all continents every day. Besides, I am also very glad that I have Tom Hemming Karlsen as Deputy Head. Together with Turid Margrethe Pedersen, Ann Døli and Julia Ferkis in the Leader group we secure the daily management of the Institute.

After many years at RIIM, I know the Institute very well. Most functions are formed in an optimal manner. However, my sincere intention is to secure a more predictable and generous funding for RIIM. As you will see in this year's Annual report, the Institute's existence is fully dependent on external funds. My primary duty for the coming years is to ensure RIIM better long-term funding.

With that in mind, it is important that we all are aware of the importance of "branding ". It is like elections; the politicians use slogans. We should do that too! Every student we teach, every lecture we hold, every talk we give, every article we publish should be an ambassador for this Institute.

2015 was an extremely good scientific year, and RIIM lived up to the manifestation as a top international research institute. Our researchers have produced more scientific publications than in the previous years. This is impressing. It is challenging and motivating to keep up with such high standards. 2015 has also shown that we are able to secure large external funding, and as mentioned above, it is a work we need to keep up with in the future.

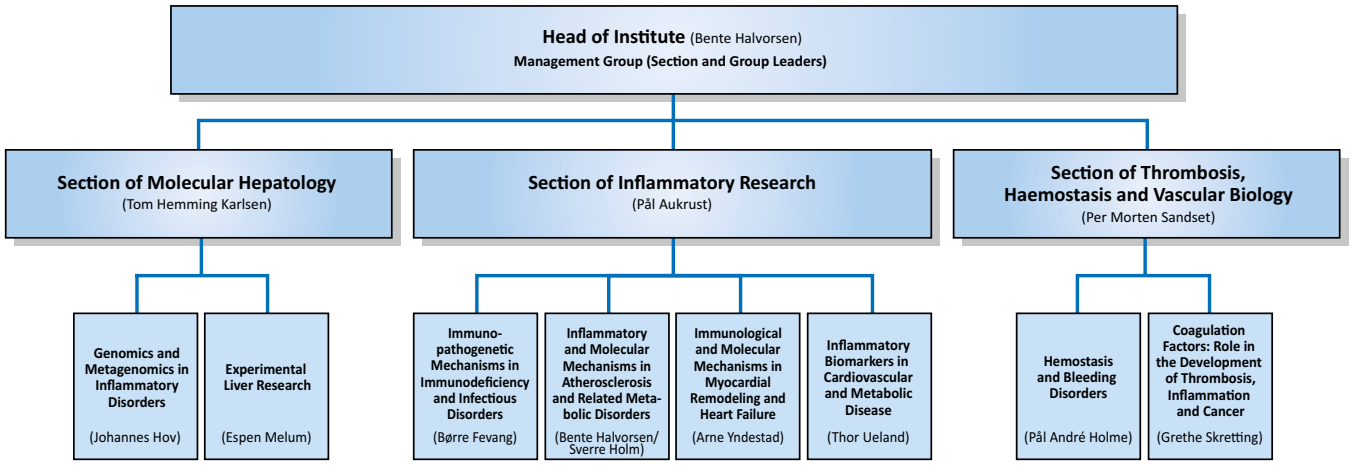
2015 was also a year of contemplation regarding research ethics. Scientific misconduct is a threat against all academic environments and we as researchers and academic leaders will have to do our utmost to prevent it. Through our strategy and action plan we have created a transparent environment to enable all researchers to work according to the highest possible ethical standards.

2015 was also the end of the "KKT" clinic/division. From January 1st 2016 we are in the Division of Surgery, Inflammatory Medicine and Transplantation (KIT clinic/division).

I am very enthusiastic and positive to the new division and all the possibilities that lie in this small division consisting of departments mostly situated at Rikshospitalet.

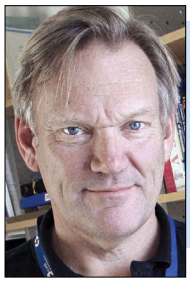
March 1st, 2016
Bente Halvorsen

Organization



TOM HEMMING KARLSEN
Leader of Section of Molecular Hepatology

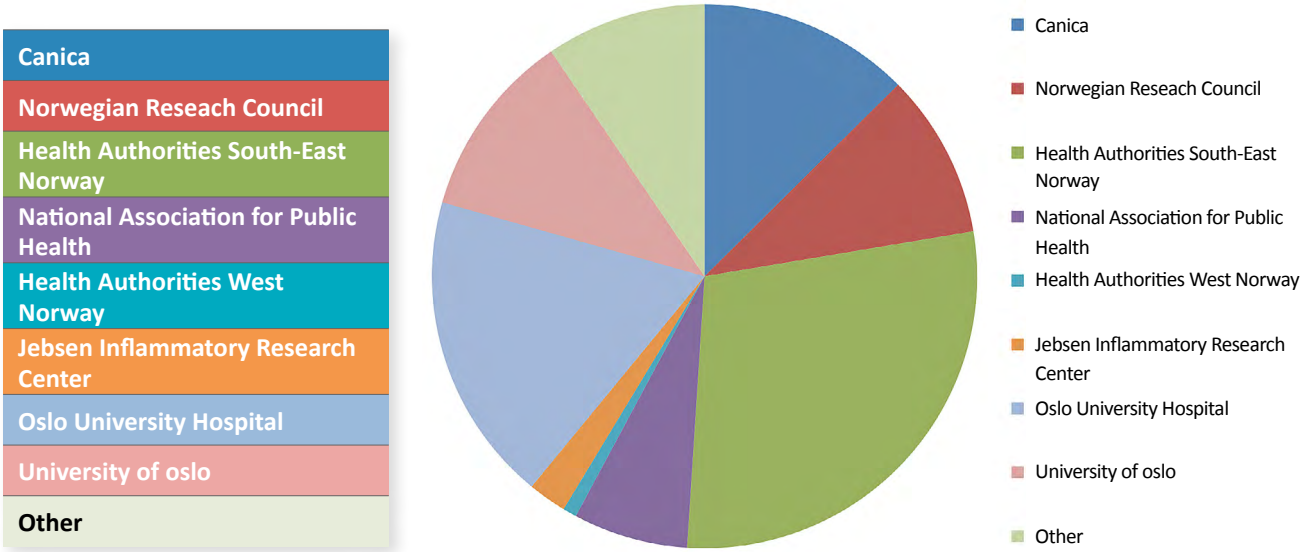
PÅL AUKRUST
Leader of Section of Inflammatory Research



PER MORTEN SANDSET
Leader of Section of Thrombosis, Hemostasis and Vascular Biology

Economy

The Institute's total expenditures amounted to NOK 69 millions in 2015.
NOK 49 millions were money from external sources while the rest, NOK 20 millions, came from funding from Oslo University Hospital and the University of Oslo.



Dissertations

Cand.med. Elisabeth Astrup
"Inflammation in rickettsial infections. Role of Wnt-signaling and innate immunity in Mediterranean spotted fever and scrub typhus"
March 20th 2015

Committee:
1. opponent: Dr. Bjørn Blomberg, Faculty of Medicine and Dentistry, University of Bergen

2. opponent: Dr. Helge Røsjø, Clinic for Internal and Laboratory Medicine, Akershus University Hospital, Institute of Clinical Medicine, University of Oslo

3. member of the Committee: Dr. Anne-Marte Bakken Kran, Clinic of Diagnostics and Intervention, Institute of Clinical Medicine, University of Oslo

Main supervisor: Prof. Pål Aukrust

Infectious diseases, and among them rickettsial infections, remain a major factor in sustaining poverty, causing nearly 9 million deaths yearly and an enormous burden of disability. We need better understanding of the host response to these infections to improve treatment modalities, identify prognostic markers and not least develop vaccines. Our aim was to explore immunopathogenic mechanisms in Mediterranean spotted fever (MSF), caused by Rickettsia conorii, and scrub typhus, caused by Orientia tsutsugamushi, based on a thoroughly characterized clinical material.
In MSF, we explored the Wnt-signaling pathway and found that R. conorii down-regulate endothelial-derived DKK-1, and silenced DKK-1 attenuate R. conorii-induced inflammation in endothelial cells. This may reflect a mechanism by which R. conorii escapes the immune response through DKK-1 and Wnt-signaling.
We also found that the CCL19/CCL21/CCR7 axis is up-regulated in R. africae- and particularly R. conorii infection. We suggest these "homeostatic" chemokines may contribute to the pathogenesis of these diseases.
In scrub typhus, our findings suggest a specific cytokine profile that includes dysregulated levels of a wide range of mediators, and this enhanced inflammation may contribute to disease severity and outcome. In particular, we identified IL-8 as a potential biomarker for disease severity and prognosis.
Toll-like receptors play an essential role in innate immune responses, but the signaling pathways in rickettsial infections are only partially known. We found significant correlation between the presence of heterozygous TLR4 Asp299Gly and the incidence of scrub typhus. This mutation has been reported to cause LPS hyporesponsiveness. Although O. tsutsugamushi lacks LPS, it may also have a role in susceptibility to O.

Cand.med. Azhar Abbas
"Carotid artery atherosclerosis- The role of inflammation in ischemic stroke"
June 26th 2015

Committee:
1. opponent: Professor Ellisiv Mathiesen, Institute of Clinical Medicine, University of Tromsø, Norway's Arctic University

2. opponent: Dr. Line Mariann Grønning-Wang, Institute of Basic Medicine, University of Oslo

3. member of the Committee: Professor Lars Eide, Institute of Clinical Medicine, University of Oslo

Main supervisor: Senior consultant Mona Skjelland

Stroke is one of the leading causes of death and disability. The aim of this thesis was to identify novel inflammatory mediators that contribute to atherosclerotic plaque destabilization leading to ischemic stroke, and to identify potential biomarkers in patients with carotid artery atherosclerosis. The thesis focused on the role of three inflammatory mediators (S100A12, MMP-7 and IL-23). These mediators were studies in blood samples and atherosclerotic lesions taken from patients with symptomatic and non-symptomatic atherosclerotic carotid stenosis. Totally 182 patients were included as well as 24 healthy controls. The mediators were studied in vitro regarding their biological role in atherosclerosis.
We demonstrated a pro-inflammatory role for these mediators and a relation to recent symptoms as well as a relationship between high plasma levels of MMP-7, IL-23 and mortality.
Our findings suggest an important role for these mediators in atherosclerotic disease progression and plaque destabilization, supporting a potential role for these mediators as disease markers. Our finding suggests that these mediators should be investigated in larger studies in patients with atherosclerosis.

Cand.Scient. Ida Gregersen
"Immunomodulatory cytokines in atherosclerotic disease. Possible pathogenic role of interleukin-9, -23 and -27"
December 11th 2015

Committee:
1. opponent: Dr. Harry Björkbacka, Experimental Cardiovascular Research, Faculty of Medicine, University of Lund, Sweden

2. opponent: Professor Tor Gjøen, Section of Pharmaceutical Bioscience, Institute of Pharmacy, University of Oslo

3. member of the Committee: Professor Benedicte Paus, Department of Medical Genetics, Clinic for Diagnostics and Intervention, Institute of Clinical Medicine, University of Oslo

Main supervisor: Prof. Bente Halvorsen

Cardiovascular disease is the major cause of death in the world and is mainly caused by underlying atherosclerosis, a dynamic process characterized by accumulation of lipids and immune cells in the arterial wall. Inflammation has a central role in atherosclerotic disease development, through close interaction with lipid metabolism. It is extremely important to understand the inflammatory mechanisms in atherosclerosis to develop better diagnostics and treatment for these patients. The main objective of this thesis was to improve our knowledge of inflammatory mediators in atherosclerotic disease.
With the use of a translational research approach, combining basal research with clinical material, the role of three cytokines in atherosclerotic disease was explored. Interleukin-9, -23 and -27 are known to be involved in inflammation and in the pathogenesis of inflammatory diseases, however their importance in atherosclerosis is not fully understood. Circulating levels of all three were increased in patients with atherosclerotic disease compared to healthy controls. For interleukin-23, levels were especially increased in patients with the most recent clinical symptoms, such as acute ischemic stroke, and levels were also associated with increased mortality in patients. Gene expression levels of interleukin-9, -23 and -27 were also elevated in atherosclerotic carotid plaques compared to healthy vessels. Interleukin 9 and interleukin 23 gave a higher inflammatory response in leucocytes from patients, compared to leucocytes from healthy controls, measured by interleukin-17 release. Interleukin-27 stimulation of monocytes increased NLRP3 inflammasome activation and IL-1β release, possibly through increased response to lipopolysaccharide (endotoxin). Thus, all three mediators have inflammatory effects with relevance to atherosclerotic disease. As their levels are increased in patients with atherosclerosis, this may have an impact on atherosclerotic plaque development and disease progression.

Cand.med. Sigrid Næss
"The major histocompatibility complex association in primary sclerosing cholangitis"
December 15th 2015

Committee:
1. opponent: Professor Flemming Pociot, Institute of Cliniical Medicine, University of Copenhagen, Denmark

2. opponent: Dr. Magnhild Gangsøy Kristiansen, Institute of Clinical Medicine, University of Tromsø

3. member of the Committee: Professor Jørgen Jahnsen, Clinic for Internal and Laboratory Medicine, Akershus University Hospital, Institute of Clinical Medicine, University of Oslo

Main supervisor: Prof. Tom Henning Karlsen

Primary sclerosing cholangitis (PSC) causes chronic inflammation of the bile ducts. The majority of these patients will eventually develop liver failure and the need for liver transplantation as there is no effective medical therapy for this disease. The cause of the disease is unknown, however a strong genetic predisposition is indicated by several studies.
The strongest genetic risk identified for PSC is located on chromosome 6, in the major histocompatibility complex (MHC) region. This is a complex genetic region with more than 250 described genes and it is difficult to pinpoint which genes that are of major importance, however the antigen presenting HLA genes are strong candidates. The main aim of this thesis was to further characterize the MHC association in PSC, with particular focus on HLA genes.
Nine MHC haplotypes were found to be associated with PSC in a Scandinavian study population. HLA genes and variants of these seemed to be of superior importance, especially variants located at HLA-B and HLA-DRB1. However, contribution from non-HLA genes could not be excluded. Further, variants of HLA genes known to be associated with risk and protection of classic PSC, did not show the same association in a clinically distinct subgroup of PSC with affection of only the smallest bile ducts, so-called "small duct PSC". This genetic diversity may be driven by the proportion of small duct patients without co-existing inflammatory bowel disease. In the third and last study we found that the same variants of HLA genes that are associated with PSC also predispose to risk and protection of acute rejection of the liver after liver transplantation, irrespective of the underlying liver condition. This can perhaps indicate a similar pathogenic mechanism in PSC development and acute rejection of liver grafts.
Studies of the most important genetic risk for PSC, the MHC, are necessary and an important step towards identifying the cause of this disease.

Photo: Øystein H. Horgmo, University of Oslo

Project portfolio

SECTION OF MOLECULAR HEPATOLOGY

Genomics and Metagenomics in Inflammatory Disorders

Photo: Øystein H. Horgmo, University of Oslo

From front and to the left: Silje Jørgensen, Johannes R. Hov, Cristiane Mayerhofer, Martin Kummen, Amandeep Kaur Dhillon, Gupta Udatha, Christopher Storm-Larsen, Kristian Holm and Liv Wenche Thorbjørnsen

GROUPS MEMBERS

GROUP LEADER
Johannes R. Hov, MD, PhD
j.e.r.hov@medisin.uio.no

RESEARCHER:
Marius Trøseid, MD, PhD (associated)
troseid@hotmail.com

POST DOCS
Trine Folseraas,MD, PhD (associated)
tine.folseras@medisin.uio.no
Gupta Udatha, MSc, PhD
gupta.udatha@outlook.com

PHD STUDENTS
Martin Kummen, MD
martin.kummen@medisin.uio.no
Sigrid Næss, MD
sigrid.nass@medisin.uio.no
Amandeep Kaur Dhillon, MD
amandeepkaurmahli@hotmail.com
Silje Jørgensen, MD
s.f.jorgensen@medisin.uio.no
Cristiane Mayerhofer, MD
cristiane.mayerhofer@rr-research.no

BIOINFORMATICIAN
Kristian Holm
k.holm@ous-hf.no

BIOENGINEER
Liv Wenche Thorbjørnsen, MSc
liv.wenche.thorbjornsen@rr-research.no
Tonje Bjørnetrø (Jan-July 2015)
bjornetro@gmail.com

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), an inflammatory disease of the bile ducts, but also to other phenotypes characterized by inflammation. 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 disease phenotypes, including PSC and inflammatory intestinal diseases, immunodeficiencies (HIV and common variable

immunodeficiency) as well as cardiovascular diseases. In 2015, the group published the first papers based on the recently established complete in-house gut microbiota analytical pipeline. Several major cross-sectional studies characterizing the disease associated gut microbiota have also been submitted, with expected publication early 2016.
The cross-sectional studies primarily represents starting points for further studies into the role of gut microbiota either in clinical or experimental settings. Several interventional studies targeting the gut microbiota using e.g. probiotics or antibiotics have already been performed/are ongoing/are in a planning phase in different diseases. Such studies may represent proof-of-concept of a direct involvement of the gut microbiota in the disease development. Application of gut microbiota characteristics as biomarkers may be another strategy to develop "Clinical microbiota medicine", which is the main aim of the group. Still, a strong collaboration with the experimental liver group regarding the role of the gut microbiota in experimental disease models should be mentioned.
There has also been an increasing interest in the association of microbial metabolites with the pathogenesis of common diseases. This may also be important for clinical microbiota medicine since such metabolites may both represent harmful or protective substances and good biomarkers. The group has been involved in a series of papers related to one particular metabolic pathway (choline/carnitine - trimethylamine-N-oxide) in conditions like heart failure, carotid atherosclerosis, HIV, PSC and bariatric surgery.
In 2015 the group continued the regional collaborative research network centered on the meetings in the regional interest group Oslo microbiota forum. In addition, the group hosted the second national conference on gut microbiota in November 2015. The meeting was highly successful, fully booked and with and a large number of submitted abstracts presented. .

Photo: Øystein H. Horgmo, University of Oslo

One of many deep freezers at RIIM

SECTION OF MOLECULAR HEPATOLOGY

Experimental Liver Research

Photo: Øystein H. Horgmo, University of Oslo

From left to right: Laura Valestrand, Espen Melum, Xiaojun Jiang, Anne Pharo, Eva Kristine K. Henriksen (middle) and Natalie L. Berntsen (in the front)

GROUPS MEMBERS

GROUP LEADER
Espen Melum, MD, PhD
espen.melum@medisin.uio.no

LAB MANAGER
Tonje Bjørnetrø, MSc (Jan-July 2015)
bjornetro@gmail.com
Anne Pharo, Cand. mag
anne.pharo@rr-research.no

POST DOC
Xiaojun Jiang, PhD
xiaojun.jiang@medisin.uio.no

PHD STUDENTS
Elisabeth Schrumpf, MD
elisabeth.schrumpf@medisin.uio.no
Natalie Lie Berntsen, MD
n.l.berntsen@medisin.uio.no
Eva Kristine Klemsdal Hendriksen, MSc
evak.klemsdal@gmail.com
Laura Valestrand, MD
lauravalestrand@gmail.com

RESEARCH PROFILE

The experimental liver research group is part of both the Norwegian PSC research center and the Research institute for Internal Medicine. All of our laboratory activities take place at the RIIM lab.

Currently the group consists 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. In addition to the cholangitis focused studies, we are also doing basic research related to the function of natural killer T (NKT)-cells. NKT cells are especially interesting in the context of liver diseases as 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

Photo: Øystein H. Horgmo, University of Oslo

Lab. manager A. Pharo while at work in the lab

the chronic bile duct disease primary sclerosing cholangitis (PSC).

The most important tools in our research are mouse models that model aspects of cholangitis development. The mouse models we use are immune driven and inspired by the fact that most genes associated with PSC are involved in the immune response. One of these mouse models is a spontaneous model that develops cholangitis without any intervention, while others are based on surgical induction of inflammation by manipulation and injections in the biliary tree. In 2015 we have successfully generated a knock-in mouse model for as PSC-related genetic variant together Applied StemCell in California that will be subjected to intense investigations. 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.

In January 2015 Anne Pharo started as a lab-manager and manages the day-to-day operations of the lab and administers our mouse colonies. Dr. Laura Valestrand started as PhD student in August 2015 and will work on the interplay between cholestasis and immune function.

SECTION OF INFLAMMATORY RESEARCH

Immunopathogenetic Mechanisms in Immunodeficiency and Infectious Disorders

Photo: Øystein H. Horgmo, University of Oslo

From left: Kari Otterdal, Jan-Cato Holter, Børre Fevang, Elisabeth Astrup, William Siljan, Magnhild Eide Macpherson, Liv Hesstvedt, Silje Jørgensen, Ingvild Nordøy

GROUP MEMBERS

GROUP LEADER
Børre Fevang, Asst. Professor, MD, PhD
borre.fevang@ous-hf.no

POST-DOC
Kari Otterdal, Researcher, MSc, PhD
kari.otterdal@rr-research.no

PHD-STUDENTS
Silje Jørgensen, MD
siljor@ous-hf.no
Jan Cato Holter, MD
jacoho@vestreviken.no
Magnhild Eide Macpherson, MD
magnei@ous-hf.no
Liv Hesstvedt
liv.hesstvedt@ous-hf.no
William Siljan
wilsil@vestreviken.no
Kristine Lillebø Holm (associated)
k.l.holm@medisin.uio.no
Eli Taralsrud (associated)
eli.taralsrud@medisin.uio.no

RESEARCHERS
Ingvild Nordøy, MD, PhD
ingvild.nordoy@ous-hf.no
Elisabeth Astrup, MD, PhD
Stig S. Frøland, Prof. Emeritus

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.

The group is currently working with several projects, including:

• **Immunopathogenic mechanisms in CVID – a disease model for autoimmunity and persistent inflammation**.

In close collaboration with Johannes Hov's group 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 includes a genome wide association study on CVID through an international network of clinical immunologistis that was published in 2015, and more articles are in progress. Silje Jørgensen keeps a steady pace towards her PhD title and will now hand over the torch to Magnhild Eide Macpherson who started her PhD-study in September 2015.

• **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. Elisabeth Astrup defended her PhD-thesis on this project in 2015 but we are happy to announce that she still has both motivation and energy to keep the project moving forwards.

• **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. Jan Cato Holter is approaching his Ph-dissertation but we are lucky to have William Siljan to pick up any loose ends in this extensive clinical project.

• **Study of immunological mechanisms in malaria.** Kari Otterdal has a solid background in platelet research but now 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 institutes extensive knowledge of inflammation and among other things look at inflammatory properties of the Plasmodium produced hemozoin crystal.

• **"Candidemia in Norway and the Nordic countries".**

Cand. med. Liv Hesstvedt is in her third year working on her thesis which is partly based on 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. Supervisers are Ingvild Nordøy, Peter Gaustad and Fredrik Müller.

Photo: Øystein H. Horgmo, University of Oslo

SECTION OF INFLAMMATORY RESEARCH

Inflammatory and Molecular Mechanisms in Atherosclerosis and Related Metabolic Disorders

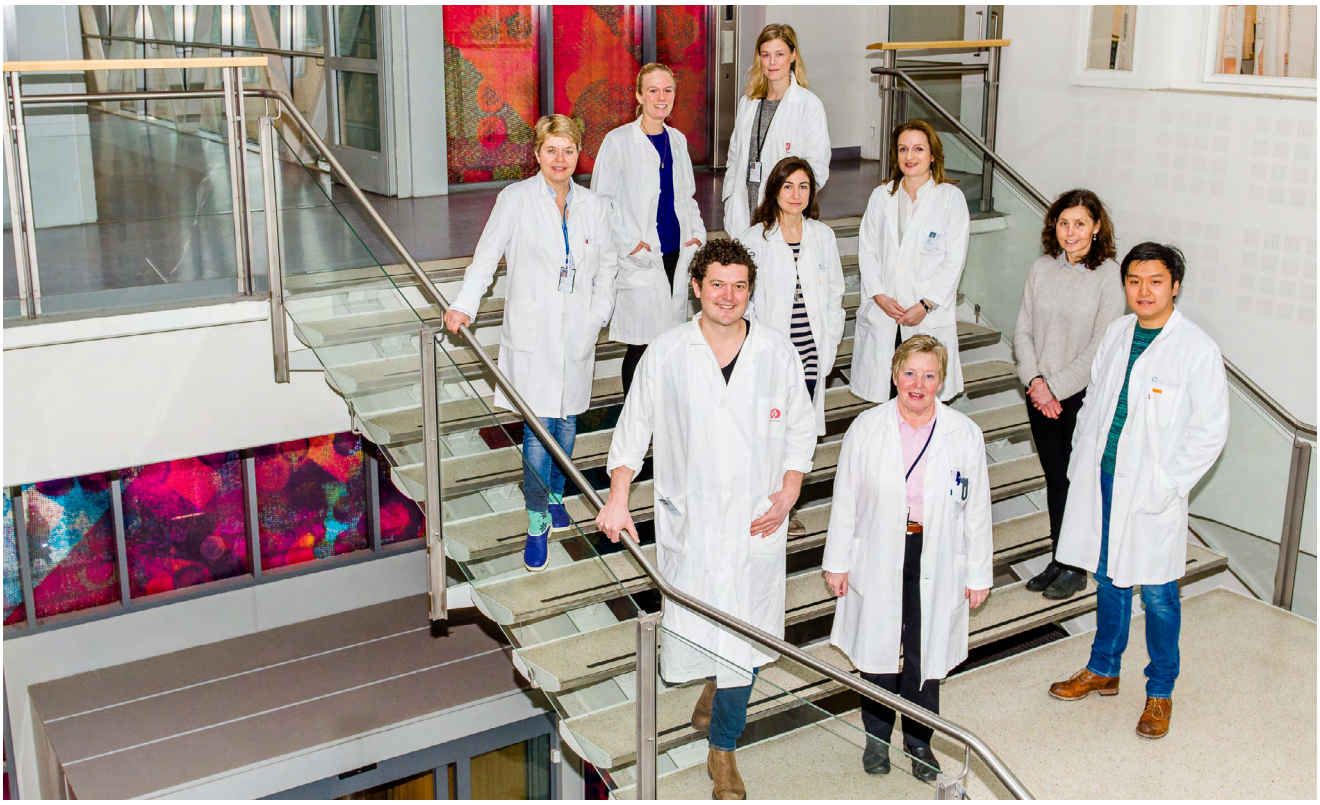


Photo: Øystein H. Horgmo, University of Oslo

From left: Bente Halvorsen, Ida Gregersen, Tonje Skarpengland, Sverre Holm ,Ana Quiles Jimenes, Karolina Ryeng Skagen, Vigdis Bjerkeli, Mona Skjelland and Xiang Yi Kong.
Not present: Ellen Lund Sagen, Turid M Pedersen, Filip Segers, Tuva Børresdatter Dahl, Kjell Torp-Joakimsen, Nina Solheim and Azhar Abbas

GROUP MEMBERS:

GROUP LEADER:
Bente Halvorsen, Professor, Dr. Philos
bente.halvorsen@rr-research.no

ASS. GROUP LEADER:
Sverre Holm, MSc, PhD
sverre.holm@rr-research.no

POST-DOCS
Tuva Børresdatter Dahl, MSc, PhD
tuva.borresdatter.dahl@rr-research.no
Filip Segers, MSc, PhD
filip.segers.filip.segers@rr-research.no
Ida Gregersen, MSc, PhD
ida.gregersen@medisin.uio.no
Xiang Yi Kong, MSc, PhD
x.y.kong@medisin.uio.no

PHD STUDENTS
Kjell Torp-Joakimsen, MD
k.a.m.torp-joakimsen@studmed.uio.no
Nina Solheim, MD
solnina@hotmail.com
Tonje Skarpengland, MD
tonje.skarpengland@rr-research.no
Karolina Ryeng Skagen, MD
kskagen@ous-hf.no
Ana Quiles Jimenes, MSc
anquil@rr-research.no

SENIOR CONSULTANTS
Mona Skjelland, MD, PhD
moskje@ous-hf.no
Azhar Abbas, MD, PhD
azhabb@ous-hf.no

MASTER STUDENTS
Lene Løvdal, MSc
Andrea Øvergård, MSc

OVER ENGINEERS
Ellen Lund Sagen
ellen.lund.sagen@rr-research.no
Turid Margrethe Pedersen
turid.margrethe.pedersen@rr-research.no

CHIEF ENGINEER
Vigdis Bjerkeli
vigdis.bjerkeli@medisin.uio.no

RESEARCH PROFILE

Atherosclerosis is a chronic disease of the arterial wall and a leading cause of death and loss of productive life years 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. Today, atherosclerosis is being thought of as a chronic inflammatory disease with interactions between lipids, extracellular matrix and inflammation as a characteristic hallmark, leading to the growth of an atherosclerotic plaque. The inflammatory mechanisms in the atherosclerotic process and closely related metabolic disorders have been the cornerstone of the research group's activity for the last 15 years. By using clinical material from well characterized patients with atherosclerotic lesions we seek to find novel mechanisms important in the development of atherosclerosis. To manage this we have a translational approach, where we combine the human clinical material with in vivo studies in animal models and in vitro work in cell cultures. The last two years, our group has particularly focused on expanding the methodological repertoire in order to be in the front of the field of atherosclerosis research. We have now established several front-line technologies for inducing and monitoring atherosclerosis in mouse models and also methods for ex vivo culturing of tissues and concomitant cell extractions from atherosclerotic material.

CYTOKINE NETWORK

For many years we have had interest in cytokines and their role in atherosclerotic disease. Recently the particular focus has been on the group of cytokines and receptors comprising Interleukin 9, -23 and -27. These cytokines possess both pro- and anti-inflammatory properties and their effects have been described in several inflammatory conditions. We have shown that these three cytokines are present in atherosclerotic plaques, and are upregulated in patients with atherosclerosis and have inflammatory effects relevant for the atherosclerotic process.

NAMPT AND MACROPHAGE POLARIZATION

Our group was the first to link the protein Nicotinamid Phosphoribosyl Transferase (NAMPT) to atherosclerosis ten years ago. Since then we have continued working with this relation, and NAMPT and its role in atherosclerosis is still one of the group`s major research interests. We know from plaque studies that NAMPT is primarily located to lipid loaded macrophages, and it has been found to modulate lipid accumulation and inflammatory status in these cells. Recently it has become evident that macrophages are a diverse population of cells with different functions and effects. NAMPT is increased both intracellularly and extracellularly in inflammatory M1 macrophages compared to the anti-inflammatory M2 macrophages. When the enzymatic activity of NAMPT is inhibited, also the polarization of M1 macrophages is inhibited, linking NAMPT to a central role in the shift between macrophage populations in atherosclerosis. Our research group has the ambition to increase the knowledge of macrophage plasticity in atherosclerosis.

NON-RESOLVING INFLAMMATION IN ATHEROSCLEROSIS- REGULATION OF THE RESOLVING E1 PATHWAY

Nonresolving inflammation is a major driver of disease. Since atherosclerosis is a chronic inflammatory disease, we are interested in mechanisms by which the inflammation can be resolved. Recent research has pointed to the resolvins (endogenous compounds synthesized from omega -3 fatty acids) as important players in the resolving of inflammation. Our focus is to characterize the RvE1 receptors and enzymes in the RvE1 biosynthesis in atherosclerotic disease. We find these components to be present in atherosclerotic plaques, indicating that this resolving apparatus is operating in clinical atherosclerosis. The impact of resolvins on the atherosclerotic process will be perused further in the years to come.

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. The atherosclerotic plaque is abundant in ROS, as the inflammatory milieu is a source of intracellular ROS generated through NADPH oxidase and also by conversion of molecular oxygen to superoxide from the mitochondrial respiratory chain. 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. Using several transgenic mouse models as well as cell lines and primary human cells and clinical material we seek to unravel the exact mechanisms through which these enzymes have impact on the development of atherosclerosis.

SECTION OF INFLAMMATORY RESEARCH

Immunological and Molecular Mechanisms in Myocardial Remodeling and Heart Failure

Photo: Øystein H. Horgmo, University of Oslo

From left: Kuan Yang, Øystein Sandanger, Arne Yndestad, Maria Belland Olsen, Marina Sokolova, Mieke Louwe, Linn Fosshaug, Katrine Alfsnes, Trine Ranheim, Knut Husø Lauritzen, Negar Shahini, Jonas Øgaard, Alexandra Finsen, Margrethe Holt, Azita Rashidi

GROUPS MEMBERS

GROUP LEADER
Arne Yndestad, MSc. Pharm, PhD
arne.yndestad@rr-research.no

RESEARCHERS:
Alexandra V Finsen, MD, PhD
a.v.finsen@medisin.uio.no
Trine Ranheim, MSc, PhD
trine.ranheim@rr-research.no

POST-DOCS
Knut Husø Lauritzen, PhD
knut.huso.lauritzen@rr-research.no
Mieke Louwe, PhD
m.c.louwe@medisin.uio.no

Øystein Sandanger, MD, PhD
oystein.sandanger@rr-research.no

PHD STUDENTS:
Linn E Fosshaug, MD
l.e.lillerud@medisin.uio.no
Yangchen Dhondrup, MD
yandho@ous-hf.no
Ståle Haugest Nymo, MD
s.h.nymo@studmed.uio.no
Maria Belland Olsen, MSc
maria.belland.olsen@rr-research.no
Negar Shahini, MSc
negar.shahini@studmed.uio.no
Marina Sokolova, MD
marina.sokolova@rr-research.no
Kuan Yang, MPhil
kuan.yang@rr-research.no

MEDICAL STUDENT:
Margrethe Flesvig Holt
m.f.holt@studmed.uio.no

ENGINEERS:
Katrine Alfsnes, BSc
katrine.alfsnes@rr-research.no
Azita Rashidi, BSc
arashidi@ous-hf.no

RESEARCH ASSISTANT
Jonas Øgaard
jonas@ogaard.no

ASSOCIATED RESEARCHERS:
Leif Erik Vinge, MD, PhD
leif.erik.vinge@rr-research.no
Erik Øie, MD, PhD
erik.oie@rr-research.no

RESEARCH PROFILE

Our group has the ambitious aim to uncover novel mechanisms involved in myocardial infarction and development of heart failure that can form a basis for the development of new therapy with clinical benefit for the patient. Heart failure is a clinical syndrome caused by the heart's inability to maintain a blood flow that meets the body's requirements. Heart failure represents a major cause of cardiovascular and also total morbidity and mortality worldwide. The incidence and prevalence of this disorder is rising and the prognosis is poor. Due to the high prevalence and morbidity, heart failure also represents a major and increasing socioeconomic burden.

Heart failure may have many causes. Commonly, heart failure develops as a consequence of loss of pump function after a myocardial infarction or due to valvular heart disease or, making the heart pump against increasing pressures. We use experimental mouse models to mimic these conditions and characterize pathogenic processes involved. An increasing cause of heart failure is related to obesity and the metabolic syndrome leading to changes in the heart's ability to relax (i.e., diastolic dysfunction). Importantly, there is currently no effective treatment for these patients. We use a model of diet-induced obesity in mice to mimic the changes observed in obese patients developing diastolic heart failure. In addition to different mouse models of heart failure, our research approach includes 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.

PROJECTS

A main interest of the research group is the study of how innate immune responses are involved in the response to cardiac stress and heart failure development. We focus in particular on 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, we have projects where we investigate how the inflammasome is activated. Our work on innate immune responses also includes Toll-like receptor 9, a receptor activated by bacterial DNA, but also mitochondrial DNA. More recently, we have initiated projects on the role of the complement system in clinical and experimental heart failure.
Currently, we are very interested in uncovering novel mechanisms for immune activation in cardiovascular disease. In these studies, we aim to elucidate how different forms of cellular stress and damage to DNA lead to mitochondrial dysfunction, how these induce inflammation, and how these thereby promote disease development. Importantly, this work also includes the investigation of novel means of modulating inflammatory processes.

FUNDING

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Helse Sør-Øst RHF
Research Council of Norway
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Odd Fellow Medisinsk-Vitenskapelig Forskningsfond
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In addition we are part of and receive funding through the K.G. Jebsen Inflammation Research Centre

Photo: Øystein H. Horgmo, University of Oslo

SECTION OF INFLAMMATORY RESEARCH

Inflammatory Biomarkers in Cardiovascular and Metabolic Disease

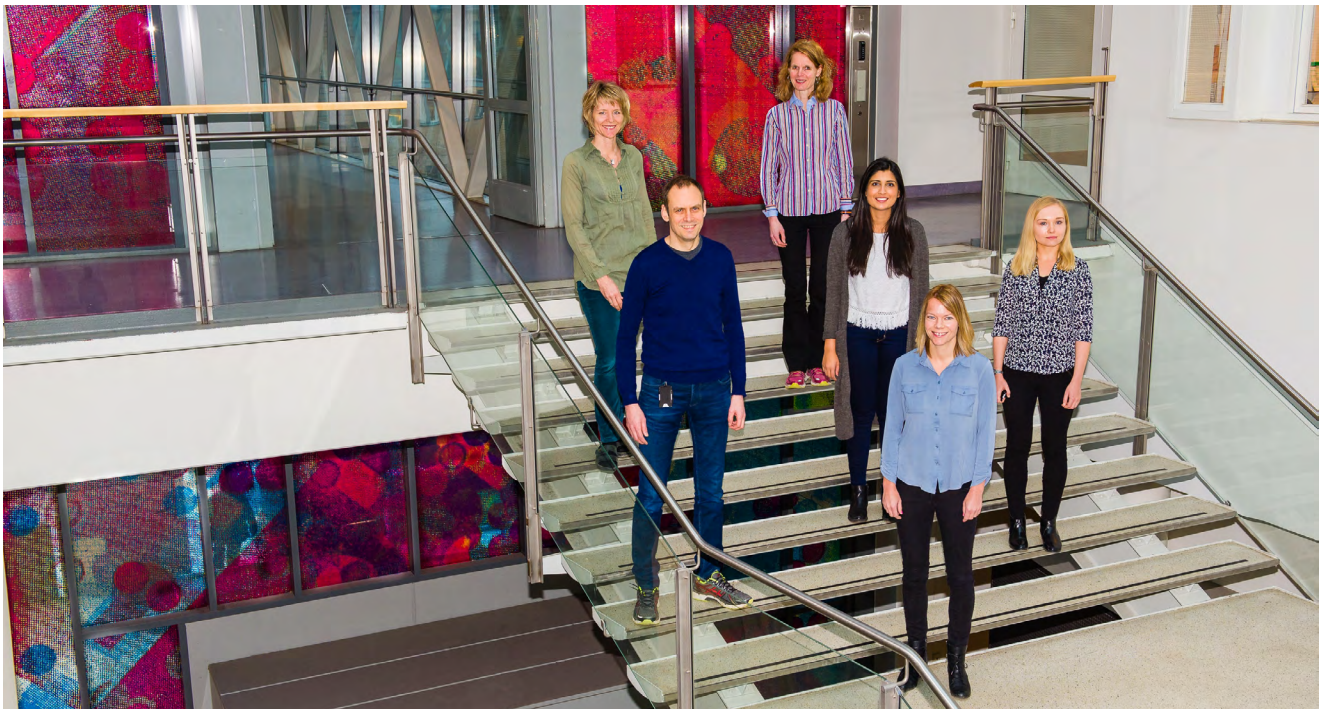

Photo: Øystein H. Horgmo, University of Oslo

Fra venstre mot høyre: Annika Elisabeth Michelsen, Thor Ueland, Hilde Margrethe Norum, Fizza Arain, Tove Lekva, Aurelija Abraityte

GROUPS MEMBERS

GROUP LEADER
Thor Ueland, Research Scientist, PhD
thor.ueland@rr-research.no

RESEARCHER
Annika Elisabeth Michelsen, PhD
annika.michelsen@rr-research,no

POST-DOC
Tove Lekva, PhD
tove.lekva@rr-research.no

PHD STUDENTS
Hilde Margrethe Norum, MD
hildenorum@yahoo.com
Aurelija Abraityte
aurelija.abraityte@rr-research.no

MEDICAL STUDENT
Fizza Arain
fizara@ous-hf.no

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 and Notch signaling and secreted Wnt antagonist and Notch ligands in these conditions.

We have a close collaboration with the endocrine unit, analyzing inflammatory markers in patients characterized by growth hormone deficieny (GHD) and excess (acromegaly) as well as gluccocorticoid 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.

Photo: Øystein H. Horgmo, University of Oslo

Researcher K. Otterdal using the microscope in the lab

SECTION OF THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY

Haemostasis and Bleeding Disorders

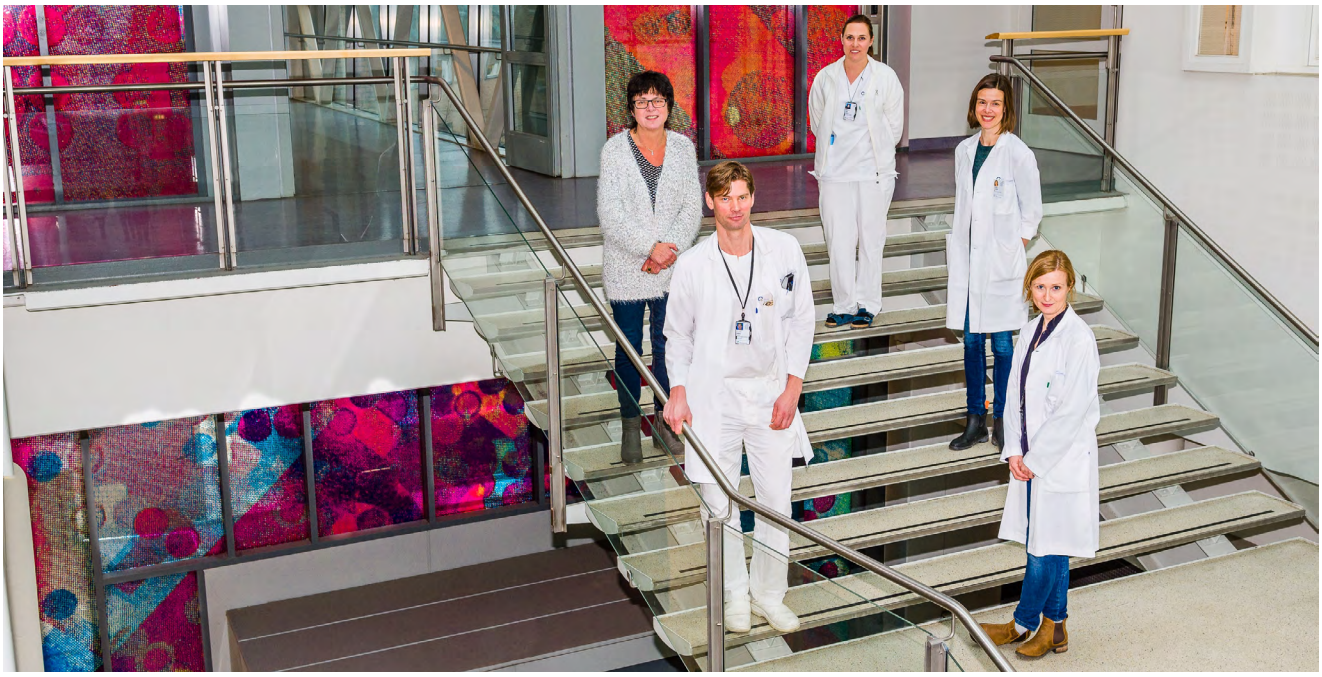

Photo: Øystein H. Horgmo, University of Oslo

From left: Stine Bjørnsen, Pål Andre Holme, Adelheid Holm, Ragnhild J Måseide and Nina Haagenrud Schultz

GROUP MEMBERS:

GROUP LEADER
Professor
Pål André Holme, MD, PhD
pholme@ous-hf.no

POST DOC
Hoa Thi tuyet Tran, MD, PhD
htra@ahus.no

PHD STUDENT
Nina Haagenrud Schultz, MD
Email:nisc@ahus.no
Ragnhild J. Måseide, MD
ragmas@ous-hf.no

ENGINEER
Stine Bjørnsen
stine.bjornsen@medisin.uio.no

STUDY COORDINATOR:
Adelheid Holm
adholm@ous-hf.no

ASSOCIATED
Professor
Geir E. Tjønnfjord, MD, PhD
gtjonnfj@ous-hf.no

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.

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. 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 individ-

ual 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 recently 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.

AGE RELATED COMORBIDITIES 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, 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. First publication from the cross sectional study was recently published (Haemophilia 2015,1-8, first published online: 16 Dec 2015) and will be further followed up in the longitudinal prospective study.

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 initiated 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.

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 will be 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 recently we published a paper where 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. (the RITP trial) (Lancet 2015; 385: 1653–61). Follow up studies to evaluate the long-term effect of rituximab and immunological changes are now initiated.

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

SECTION OF THROMBOSIS, HEMOSTASIS AND VASCULAR BIOLOGY

Coagulation Factors: Role In The Development of Thrombosis, Inflammation and Cancer

Photo: Kristin Ellefsen, University of Oslo

In front-from left: Christiane Filion Myklebust, Marie-Christine Mowinckel, Grethe Skretting, Maria Eugenia Chollet and Benedicte Stavik.
Back- from left: Huda Omar Ali, Sandra Espada Serrano, Elisabeth Andersen, Marianne S. Andresen, Xue-Yan Cui and Ann Døli.

GROUPS MEMBERS

GROUP LEADER:
Grethe Skretting, Senior Scientist, MSc, PhD
grethe.skretting@medisin.uio.no

POST-DOCS:
Benedicte Stavik, MSc, PhD
benedicte.stavik@rr-research.no
Maria Eugenia Chollett, MD, PhD
mechollett@yahoo.com
Xue-Yan Cui, MD, PhD
x.y.cui@medisin.uio.no
Sandra Espada Serrano, MSc, PhD
sandra.espada.serrano@rr-research.no

PHD-STUDENTS
Huda Omar Ali, MSc
h.o.ali@medisin.uio.no
Elisabeth Andersen, MSc
elisabeth.andersen@medisin.uio.no

SENIOR ENGINEERS
Marianne Seierstad Andresen, MSc, PhD
marianne.andresen@rr-research.no
Christiane Filion Myklebust, MSc
christiane.filion.myklebust@rr-research.no
Marie-Christine Mowinckel, MSc
uxmaow@rr-research.no

ADMINISTRATIVE COORDINATOR:
Ann Døli
uxnndl@ous-hf.no

Research Profile

Areas of focus:
Our research focuses on the molecular mechanisms underlying the role of coagulation inhibitors in thrombosis, inflammation and 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.
The group is also involved in a number of clinical studies and responsible for analysis of biochemical markers in these studies. During 2015, two of our post-docs were partly on maternity leave.

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 gene 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. The majority of human breast cancers are estrogen dependent and the cancer cells express the estrogen receptor (ER). Using breast cancer cell lines, both ER expressing and non-expressing, we have demonstrated that estrogens can downregulate the expression of TFPI in a process dependent on the presence of the estrogen receptor ERα. By studying the 5' flanking region of the TFPI gene, we found that this effect partly was due to binding of the receptors to specific elements in the DNA. In collaboration with a research group in Murcia, Spain, we have revealed that in addition to the direct transcriptional regulation of the TFPI gene by estrogens, microRNAs also participate in the regulation of the TFPI expression. A homologue to TFPI named TFPI-2 is a matrix-associated protein inhibiting the activation of matrix metalloproteinases involved in tumor progression, invasion and metastasis as a tumor suppressor. Methylation of the TFPI-2 gene promoter is associated with reduced transcription of the gene. Estrogens have been shown to regulate the expression of DNA methyltransferases (DNMT) in ER positive cells. Our data strongly indicates that like TFPI, the TFPI-2 expression is also affected by estrogens, evidenced by increased TFPI-2 mRNA levels in breast cancer cells after treatment with estrogens. This is also an ERα dependent process. We are now whether this effect is due to changes in methylation of the TFPI-2 promoter. 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. In a study we have investigated the role of hypoxia in the regulation of the TFPI expression in breast cancer cells on the transcriptional level. We found that both hypoxia and overexpression of the hypoxia inducible factor (HIF)-1α caused a strong repression of the TFPI promoter activity. This was caused by binding of HIF-1α to a hypoxia response element (HRE)

within the TFPI promoter located at -1065 to -1060 relative to the transcriptional start point. In tissue samples from breast cancer patients, gene expression analyses showed a positive correlation between the mRNA expression of TFPI and HIF-1α. This study has thus demonstrated that HIF-1α is involved in the transcriptional regulation of the TFPI gene and suggests that a hypoxic microenvironment inside a breast tumor may induce a procoagulant state in breast cancer patients. A similar study on another factor that mediates the cellular response to hypoxia, namely HIF-2α, is on-going and the results so far, indicate that HIF-2α can affect the TFPI expression. Hypoxia is also evident in advanced atherosclerotic plaques most likely due to thickness and level of oxidative burden within the plaques when they are growing. The extrinsic coagulation activator TF and its inhibitor TFPI are expressed by endothelial cells overlaying the plaques, and plaque rupture leads to activation of coagulation and the formation of a thrombus, which is the main contributor to acute manifestations, morbidity, and mortality in atherosclerotic disease. In a project (collaboration with Bente Halvorsen, RIIM), we have used endothelial cells to investigate the impact of hypoxia on the expression of TF and TFPI, which is important for the initiation of coagulation. Hypoxic conditions resulted in an increased TF expression and a reduced TFPI expression accompanied by an increased pro-coagulant activity of the endothelial cells, a situation that might promote atherogenesis in addition to clinical events and thus the severity of atherosclerotic disorders.
In the same project, we have available carotid plaque material removed from patients during surgery and control carotids. Since both TF and TFPI previously have been shown to be present in atherosclerotic lesions where they are expressed by macrophages, smooth muscle cells, and endothelial cells overlaying the plaques, we want to examine the expression of TFPI, which is expressed as two different isoforms, TFPIα and TFPIβ, in atherosclerotic plaques and associated cells. For this we are using the monocytic cell line THP-1 differentiated into macrophages and further polarized into M1 and M2 macrophages. Recently, we have extended this project to studies on endoplasmic reticulum (ER) stress since this is associated with atherosclerosis. The objective for this part is to investigate the expression of TFPI in response to ER stress and which role TFPI plays in foam cell formation and plaque stability.
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.
In collaboration with a research group in Ferrara, Italy and several groups at the University of Oslo, we are investigating 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. Patients with these mutations have bleedings and the present treatment is replacement therapy, which has several limitations. The project includes both studies by overexpressing the FVII variants in a non-FVII expressing cell line, but also genomic editing using a hepatic cell line Huh7, and human embryonic stem cells, which will be differentiated into hepatocytes being the main site of FVII expression. Accumulation of misfolded proteins within the ER might cause ER stress and can trigger the unfolded protein response (UPR) and apoptosis. We have results strongly indicating that the FVII mutant proteins indeed evoke ER stress when overexpressed in cells. We are now investigating the functional consequences of ER stress by mapping affected pathways, apoptosis etc. By these studies we hope to envisage possible therapeutic approaches that can substitute the present replacement therapy. In addition, we are extending a previous study from our group on a protein C mutation, now from a therapeutic point of view.

Photo: Øystein H. Horgmo, University of Oslo

Focus area - Biomarkers

Basics on Biomarkers

THOR UELAND

The idea of using information about a subject to detect subclinical disease states and to predict future health events has great appeal, and the search for such markers has been blooming for many years. A biomarker may be defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention” [1]. Biomarkers are anything that could be measured objectively and consistently and may consist of measurements in a biologic specimen (e.g. blood or urine sample), from recording of parameters (e.g. ECG), or data from imaging tests. Biomarkers have several potential functions, which can roughly be divided into indicators of disease trait (e.g. risk factors), disease state (e.g. preclinical or clinical) or disease rate (progression of disease) [2]. Some are antecedent, i.e., measured before development of a disease. Such biomarkers can give clues on the risk of developing the disease, work as screening methods recognizing subclinical disease states, be diagnostic and recognize what disease causes the overt symptoms, be used in staging the disease, and finally aid in estimating prognosis of a patient with known disease.

Morrow and deLemos have proposed three criteria a good biomarker needs to fulfill [3]. Clinically, these criteria boil down to three key questions: (1) Can the clinician measure the biomarker? This question relates to the accuracy and reproducibility of the analytical method, the accessibility of the assay and cost-effectiveness. (2) Does the biomarker add new information? The marker needs to display consistent and solid association to the disease or outcome of interest (in multiple studies); the information the marker provides must add to or improve on existing tests. Lastly, (3) will the biomarker help the clinician to manage patients? In order to impact the latter aspect, the marker needs to either surpass performance of other diagnostic tests, provide evidence that associated risk is modifiable with specific therapy or give evidence that implementation of biomarker-guided triage or monitoring enhances care of the patient.

These benchmarks were proposed for assessment of novel cardiovascular biomarkers but could be relevant for any disease. Implicitly, these are tough criteria to meet for any biomarker and despite an abundance of biomarker publications in recent years, particularly since the emergence of omics technology, only few clinically useful biomarkers have been successful validated for routine clinical practice [4]. Thus, clinical translation remains a major challenge in the biomarker field. However, although a biomarker may display poor analytical characteristics, it could still be worth pursuing if it expands our current understanding of pathophysiology, potentially representing a mediator rather than a viable marker of disease. Furthermore, while subjecting potential new biomarkers to comparisons with “gold-standard” markers using rigorous statistical risk models makes sense from a clinical standpoint, it may pose a threat to a broadening of mechanistic insight if the new markers are dismissed solely on account of lower statistical power. The research groups at the Research Institute for Internal Medicine study a wide range of patient populations with diverse scientific approaches to investigate these. Collaboration between these groups holds promise for biomarker discovery as major increments in predictive value and new insight might be gained by searching outside of established pathological pathways.

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Focus area - Biomarkers

Biomarkers in Immunodeficiency and Infectious Disease

BØRRE FEVANG

Biomarkers as tools for diagnosis and prognosis have a long history in infectious diseases, with CRP and leukocyte number in peripheral blood being a central part of any clinical evaluation of a patient with a suspected infection. So much in fact, that CRP, leukocytes and other biomarkers in hospitals often go under the obvious misnomer of ”infection parameters”, instead of the more correct and precise name of ”inflammmation parameters”.
In clinical medicine the detection of inflammation per se is usually of less interest than the detection of it’s cause, and when seeing a patient with raised inflammatory markers and suspected infection it often comes down to this: Is it a bacterial infection? Is it a viral infection? Is not infectious at all? The possibility of a fungal or parasittical infection will of course complicate this furter. Pro-calcitonin is the latest biomarker related to infectious diseases that is readibly available in a hospital setting, and although it proclaims increased specificity for detection of bacterial infections it is not sensitive enough to rule out a bacterial infection. Composite biomarkers and refined algorithms have been constructed to increase the sensitivity and specificity of the diagnostic process, and while they may be of substantial help in patients with mild and moderate disease they are of less value in patients with severe and chronic disease, and in particular in already hospitalized patients.
The increased number of patients on immunosuppressants highlights another problem with the traditional biormarkers used for detection of infectious diseases; the biomarkers rely on a proper immunological response to the invading pathogens. Patients treated with immunosuppressants or with an immunodeficiency will not necessarily respond to infections with raised inflammatory markers, at least not in the magnitude seen in immunocompetent patients. And even among immunocompetent patients, there is a wide range of inflammatory response not necessarily related to the severity of the infection. This raises the fundamental question of whether the immune response is a reliable partner for the detection of infection, and the short answer is probably closer to ”no” than ”yes”. Clinically, the distinction between sterile and non-sterile inflammation is often of vital importance. New biomarkers addressing that distinction, either by ruling out infectious agents or confirming a particular sterile component, would thus be greatly welcomed by the medical community. Theoretically, the exclusion of invading microbes could most easily be achieved through screening of blood samples even if there is a suspected focus for inflammation. As of today, patients are screened for viral infections in peripheral blood through PCR-techniques, while bacterial infections are detected through microbial culture of blood samples. The method, however, is hampered with low sensitivity, in particular in patients on antibiotic treatment. The further development of a reliable detection system of the presence of bacteria in peripheral blood is therefore vital. The identification of a particular sterile component or signature seem a less promising way to go. There are a number of causes to sterile inflammation and while some can be identified, they would be even more difficult to detect outside the inflammatory focus than microbes.
Evaluation of biomarkers is an essential and integrated part of the diagnostic process in patients with infections, with low specificity in general being a bigger problem than low sensitivity. This continues to be an issue but is challenged by the increasing number of patients with a less competent immune system, where low sensitivity of biomarkers may lead to severe complications.

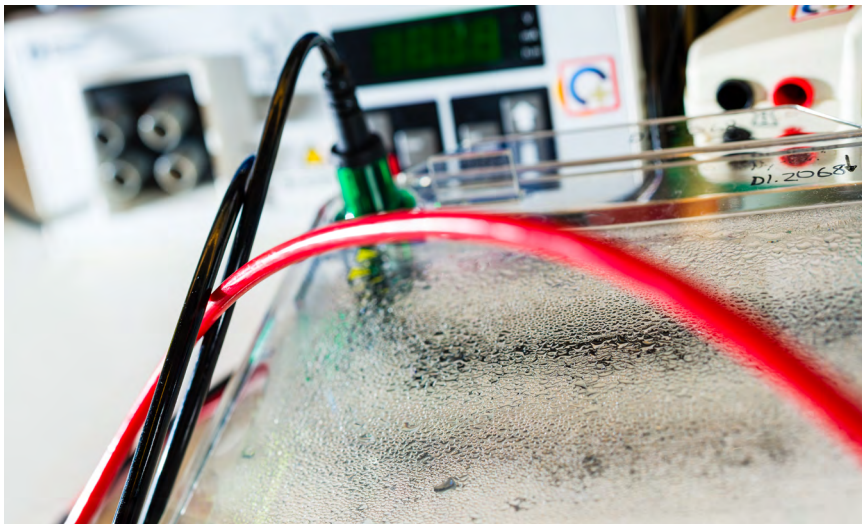

Photo: Øystein H. Horgmo, University of Oslo

Focus area - Biomarkers

Gut Microbial Biomarkers in Inflammatory Diseases

JOHANNES R. HOV AND
MARIUS TRØSEID

The gut microbiota is a metabolically highly active organ comprising more microbial cells than the body itself. The microbiota has a major impact on human health and development, probably through interaction with metabolic pathways, the immune system and even the nervous system. In several mouse models of inflammatory phenotypes, transmission of gut microbiota has been sufficient to cause disease. In multiple human diseases, gut microbiota discovery is promising as a possible source of aetiological agents or treatment targets.

Several features of the gut microbiota suggest that it may be an important source of new clinically relevant biomarkers. These may be found in the gut microbiota profile itself, e.g. microbial diversity, the abundance of specific microbes or bacterial functions, or circulating substances like microbial metabolites, e.g. trimethylamine-N-oxide, tryptophan metabolites or bile acids, or markers of inflammation or gut leakage. Importantly, the composition of the microbes and their metabolomic signatures are highly variable between individuals, making these ideal as biomarkers for personalized medicine. There are four major areas where this may be translated into biomarkers. *See figure below.*

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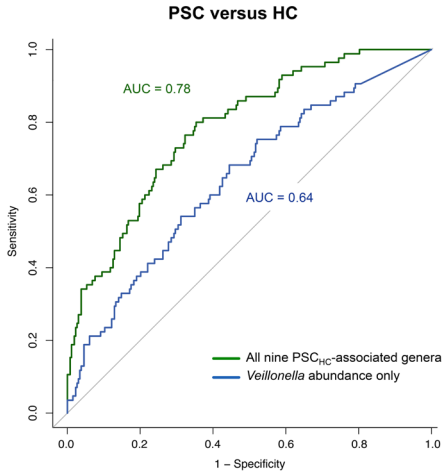

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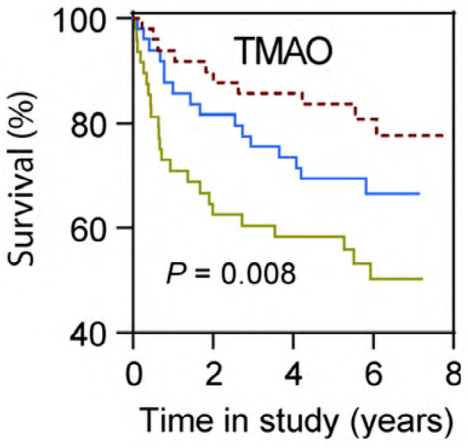

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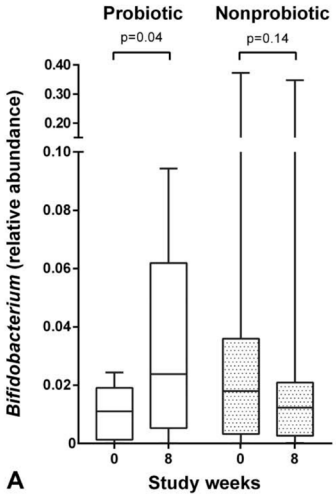

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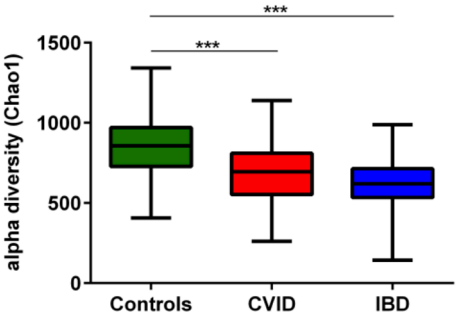

Photo: Øystein H. Horgmo, University of Oslo

1. *Diagnostic tools*. In many disease conditions, the gut microbiota profile is dramatically different in patients compared with controls. In e.g. primary sclerosing cholangitis (Panel 1) (1), the diagnostic potential is illustrated by a gut microbiota index determined from the abundance of a small number bacteria, which shows an acceptable ability to discriminate individuals with and without disease (using area under the curve/ receiver operating characteristics analysis). Similar observations in other conditions suggest that gut microbiota profile can be used to classify patients.

2. *Prognostic tools*. Several microbial metabolites are strongly associated with disease course and severity and may be used to predict disease progression, as illustrated by trimethylamine-N-oxide (TMAO) in chronic heart failure, where patients with upper tertile of TMAO levels exhibit worse outcome (Panel 2). Further studies of microbial metabolomics as well as gut microbiota profiles in relation to disease prognosis may identify further, potentially clinically relevant biomarkers.

3. *Response evaluation tools*. Several ongoing studies aim to establish proof-of-concept that manipulation of the gut microbiota influences the disease course. The prognostic biomarkers or other features of the gut microbiota or its metabolites may then be used as measures of treatment effect. In a probiotic study in HIV, adherence to treatment could be measured as an increase in relative amounts of *Bifidobacteria* in the intervention group (Panel 3), since the administered probiotic contained *Bifidobacteria*.

4. *Selection tools for personalized treatment*. In modern medicine, most treatment options are not effective in all patients. The goal of personalized medicine is to tailor the treatment by in-depth molecular characterization of the patients. Therefore, based on the experiences in the clinical studies performed, the best possible gut microbiota targeted treatment (or other types of intervention) may be selected for the optimal subgroup of patients. One possible example is shown from common variable immunodeficiency, where the group with non-infectious complications were observed to have low gut microbial diversity (Panel 4). Could these benefit from a diversity boost?

Overall, there is a clear potential for using gut microbial profile or microbial metabolites as clinical biomarkers. We hope and believe that a strong research focus on what is clinically important may shorten the typical lag time from basic discoveries to clinical translation, making clinical microbiota medicine a reality in the near future.

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Focus area - Biomarkers

A Multi-Marker Approach in Heart Failure

STÅLE NYMO AND THOR UELAND

Despite significant improvements in the management of heart failure (HF), this condition is still characterized by progressive worsening over time leading to high morbidity and mortality. Currently, only a limited number of markers are frequently used in the HF setting, with natriuretic peptides, namely BNP/NT-proBNP, being the only HF markers achieving european guideline recommendation. However, the natriuretic peptides do not reflect all underlying pathological processes in the failing myocardium, and only modestly improve well-constructed multivariable risk models. In addition to neurohormonal activation, persistent inflammation and extracellular matrix (ECM) remodeling are considered central pathogenic elements in HF progression [1]. As a result of their role in the pathogenesis of HF, circulating inflammatory and ECM markers may also be convenient, noninvasive, tools for risk stratification and prognostication in these patients. We have previously evaluated a range of inflammatory and ECM markers in elderly patients with moderate-severe ischemic HF in The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial [2]. While several of these markers alone added independent prognostic information in adjusted analyses, the improvement in prognostic discrimination, beyond established clinical risk factors and in particular NT-proBNP, was relatively modest and their clinical usefulness unclear.

While measurements of individual inflammatory and ECM markers may be unlikely to improve risk stratification of HF patients in a clinically meaningful way, modeling combinations of multiple markers could potentially identify subjects at particularly high risk and with a view to the selection of individualized therapy. Braunwald suggested selecting biomarkers reflecting seven different pathological pathways activated in HF to improve current prognostic models [3]. These are shown in Figure 1 and classifying our markers according to these categories revealed a good coverage of these "systems", although focused on inflammation and matrix remodeling.

Using this panel of 20 inflammatory and ECM biomarkers, we constructed models using different combinations of these and tested if they improved prognostication using a systematized approach according to suggested requirements for validation of new biomarkers. We found that, while there was some improvement in discriminatory power of the models, the gains were modest and clinical relevance doubtful. While this result is disappointing from prognostic view, it may illustrate the complexity of the inflammatory process. Thus, similar levels of an inflammatory cytokine may have different effects in patients depending on levels of other cytokines and activity of other systems. This interconnectedness makes the search for inflammatory biomarkers inherently difficult, and the use of more complicated systems approaches may be needed. Still, the use of such panels could still lead to new ways to categorize HF patients, and potentially aid in therapy selection.

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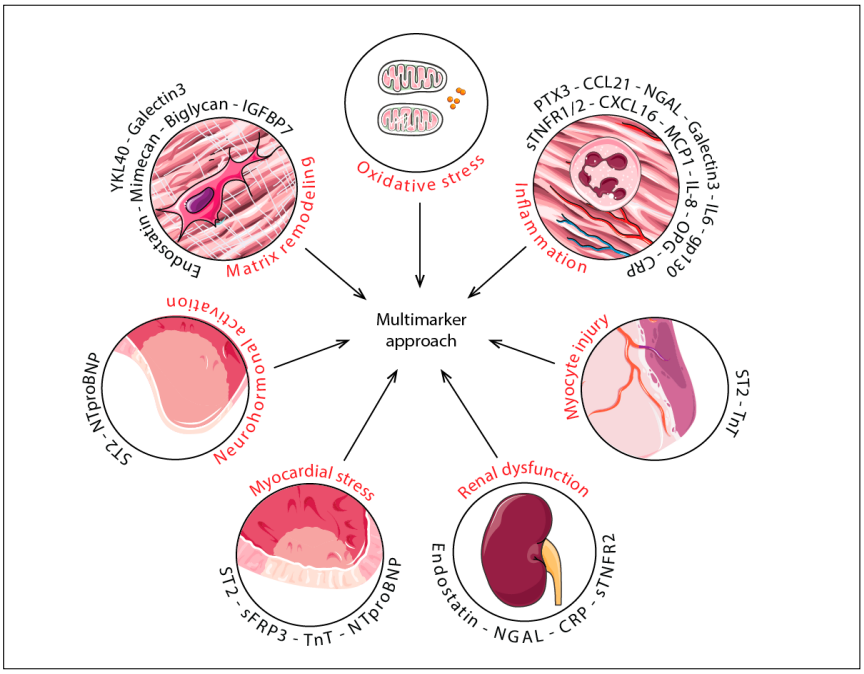

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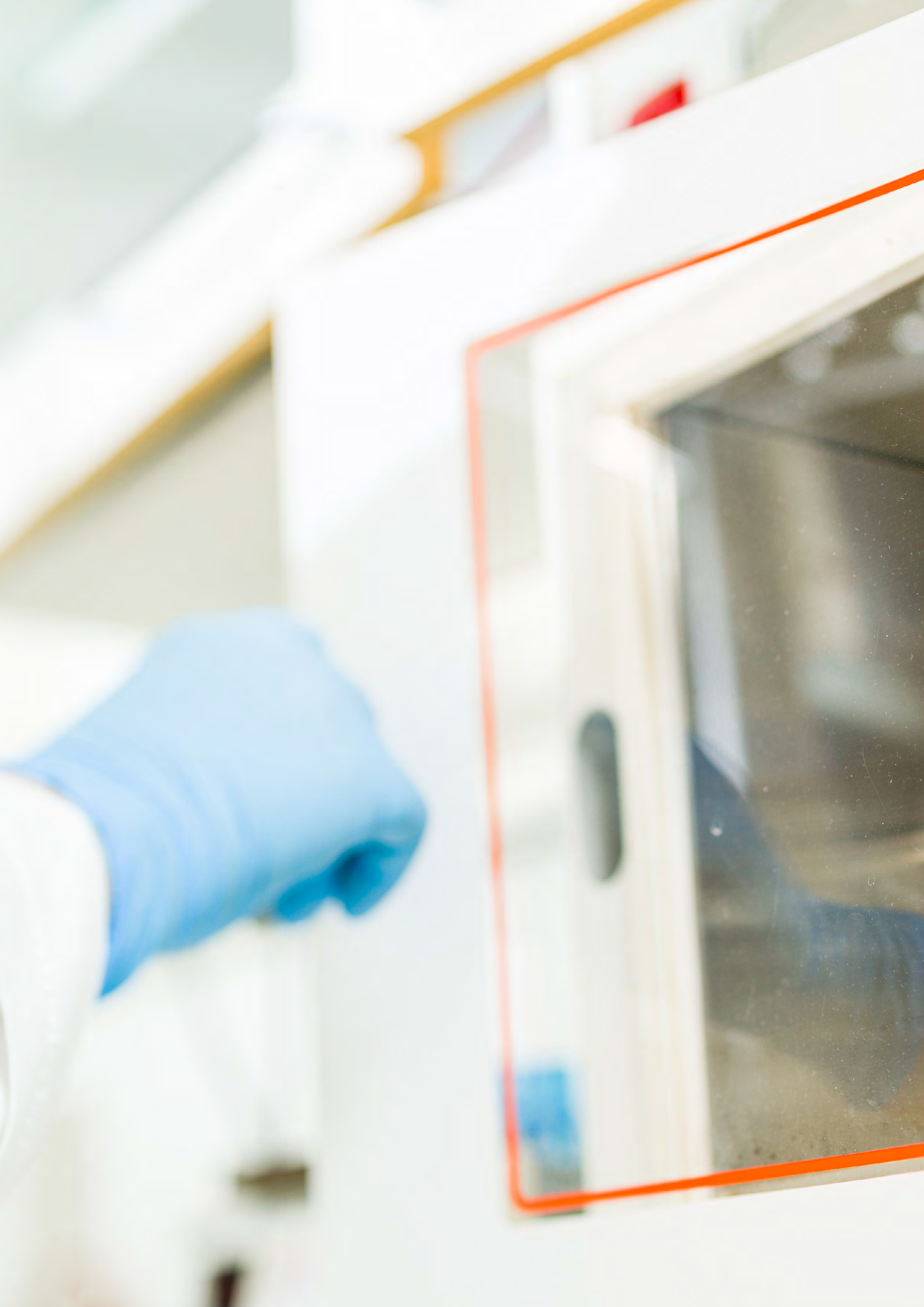

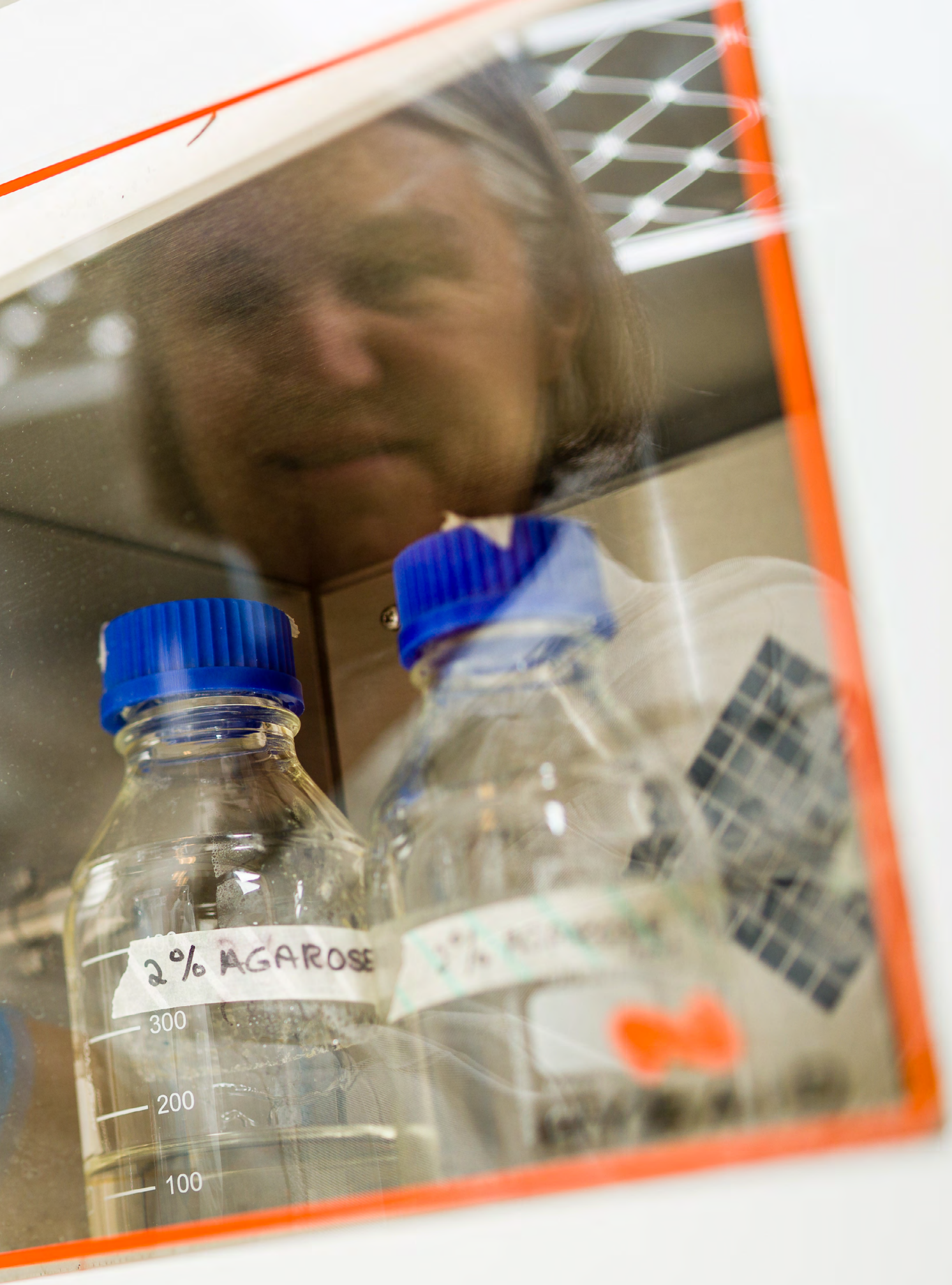

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The Research Institute of Internal Medicine

Oslo University Hospital, Rikshospitalet
P.O. Box 4950 Nydalen, 0424 Oslo, Norway

Tel: +47 23 07 00 00
Email: riim@ous-hf.no

http://ous-research.no/riim/

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