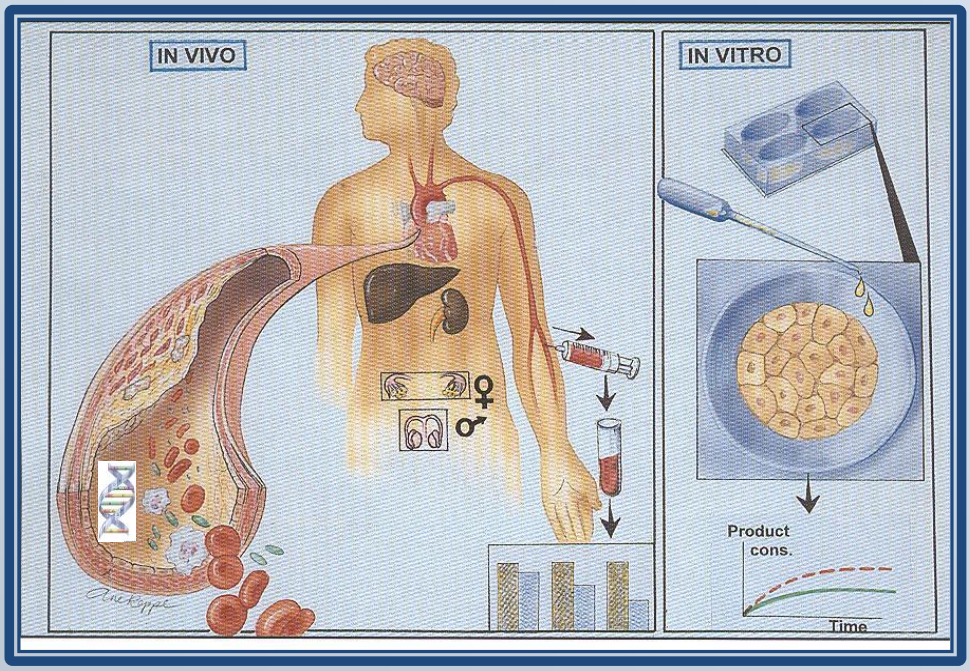


Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital,
Ullevål

"Team building for individual excellence"

Annual Report 2019

http://research.no/clinicalheartresearch/

Oslo University Hospital
UiO : University of Oslo
Center for Clinical Heart Research, OUH, Ulleval

Content

Preface

Center for Clinical Heart Research (CCHR), organized within Department of Cardiology, OUH Ullevål, is located close to the patients, which is crucial for the scientific activity. The Center plays an important role as a core laboratory for other research groups in the Department as well as for the many collaborators.

The trademark is researcher-initiated clinical, randomized intervention trials including translational studies on pathophysiological mechanisms in cardiovascular disease states.

The Center has close and fruitful collaborations with other milieus, of special notice, with the research group at the ICCU within the department, as well as with other institutions. Asker & Bærum Hospital, Akershus University Hospital and OUH Rikshospitalet are of special importance by having common PhD-students.
In 2019 further development of laboratory methods related to improved understanding of the innate immune system, the microbial translocation aspects, adipose tissue inflammation and to the ageing process was undertaken.

The high scientific activity has this year resulted in defend of 1 PhD thesis in collaboration with others, 19 internationally published papers and 25 published congress abstracts.
One PhD candidate defended his thesis January 2020, 4 are preparing for defending in 2020.
In 2019 we again received grant from the Norwegian Counsil of Research for a project in The Medical Research Student Program at the university. Along with other PhD candidates, this is important contribution to a young and dynamic milieu.
Especial also to be mentioned is our participation in the "Regional Research Network for clinical Microbiota Science", established in 2019, giving the opportunity to a broader collaboration in this still novel field of research with regard to cardiovascular disease, as well as a strategy for further laboratory methodological development that give strength to the center as a core lab for some specialities.
In 2019 we also had the possibility for collaboration with a highly reputated research milieu in Barcelona where MD PhD Ragnhild Helseth, one of our engaged and creative post.doc researchers, stayed for a period to perform a project on innate immunity which still is in process.
The 6th Scientific Symposium "Team building for individual excellence", was organized October 2019 at Noreheim, Norefjell, also this year with international and national guests.

Professor emeritus Harald Arnesen has continued as our delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, in addition to take part in the strategy. MD PhD and cardiologist Svein Solheim has continued as medical responsible and also as responsible for several projects. A research coordinator, Charlotte Holst Hansen, was employed for administrative matters in 50% position in 2019.

We are very pleased to give this annual report for 2019.

March 2020

Ingebjørg Seljeflot (sign)
Professor dr. philos
Center Head

Strategy

- Main issues: Studies on mechanisms/translational studies, on biochemical, cellular and genetic aspects especially related to inflammation, remodeling, thrombosis and endothelial dysfunction – all that can lead to development of novel treatment options in cardiovascular medicine
    - Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUS
    - Projects related to acute myocardial infarction, chronic arterial disease, heart failure and atrial fibrillation
    - Especial focus on ischemic heart disease in diabetics and in the elderly
    - Biobanking, standardized sampling and processing of blood and tissue
      About 90 % of all publications are based on biobanks
- To perform research in line with the strategy for research in Department of Cardiology
- To be an interdisciplinary composed group, including researchers at post.doc level
- To collaborate in appropriate networks as well as at an individual level

Main Goals

The main goal is to develop novel treatment options in cardiovascular medicine

- to increase the understanding of disease mechanisms, pathogenic factors, and effects of interventions in patients with cardiovascular disease
- to design and carry out randomized clinical trials, and to further expand on translational research in light of new knowledge and by use of new technology in materials from extended biobanks

Other scientific goals

- to constitute a dynamic research group with highly motivated participants where group adherence and common efforts lead to progression – for the research group as well as for the individual researcher ("Team building for individual excellence"
- to exert research of high quality, aiming at publications in high rated international journals
- to create an arena for scientific discussions, and for structured research supervision and teaching
- to educate competent PhD candidates a.o. who contribute to academic skill in clinical medicine and research
- to contribute to extended research skill at a post doc level
- to strengthen collaboration with national and international research groups

Organization

Administration and organizational aspects are undertaken by the Center leader. Our most important activity is still the regular 2-hour-scientific meetings every 2-3 weeks with PhD fellows, post.docs, laboratory staff, professors and seniors, presentation and discussion on the progress in all projects. External experts on special relevant topics and co-workers from other groups and institutions are often invited as lecturers. The PhD fellows are specially encouraged to give presentations to prepare for international conferences.

Individual supervision of the single PhD fellows is in addition undertaken, with a ”supervisor-open-door-policy”, and specific projects are separately discussed in smaller groups.
Decisions and contracts for collaboration with other research groups are based on common scientific interests.

Personnel

Leadership: The leader is also the Head of the R&D Section at Department of Cardiology, 100% position, and professor II at University of Oslo (UiO). In addition, medical responsible is a previous post.doc and cardiologist, and one professor emeritus, the latter the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUS Ullevål. In 2019 a research coordinator was employed in 50% position, for administrative matters.

Employees: 2 medical technologists, of which one with a Master of Science in Biomedicine, 1 post.doc researcher (PhD) and 1 research coordinator.

10 PhD fellows, 5 post.docs/seniors participate in the milieu and 1 student from the research program for medical students, funded by the Norwegian Research Council via UiO. In addition, the scientific milieu and the laboratory facilities are open for several other PhD-fellows, mainly supervised in collaboration with other groups at the Department of Cardiology, but also from other collaborating groups.

Finances

Budgets for the single projects, including salary for PhD-fellows, technical personnel and running laboratory expenses are based on external fundings from different sources.

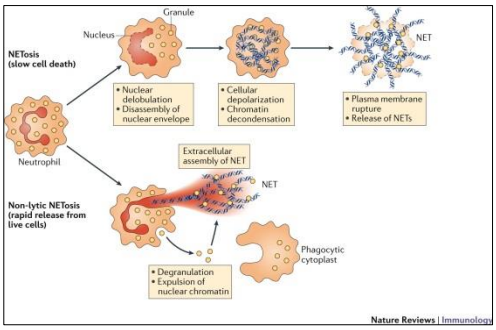
The Head is financed from the Department of Cardiology, OUS, Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department.

The major economic support from Stein Erik Hagens Foundation for Clinical Heart Research, anchored at Institute of Clinical Medicine, University of Oslo, has been of crucial importance for the activity also in 2019.

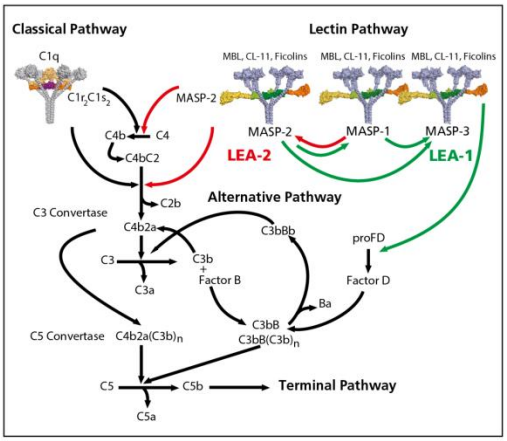
Scientific Activities

Our main focus areas this year have been very successfully developed, methodologically and with several publications, contributing to new knowledge in these fields.
In addition to atherosclerosis, inflammation and remodeling in general,

- **Neutrophil extracellular traps**

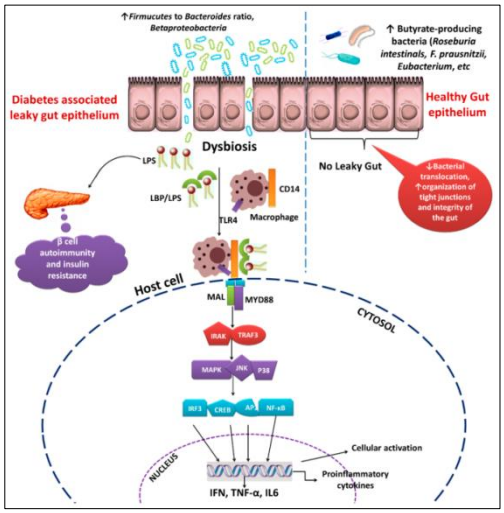


- **Complement activation**



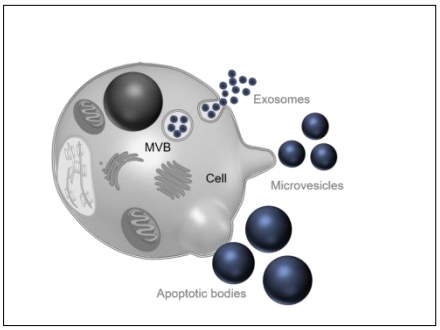
W Schwaeble, University of Leices, UK

- **Microbial translocation**



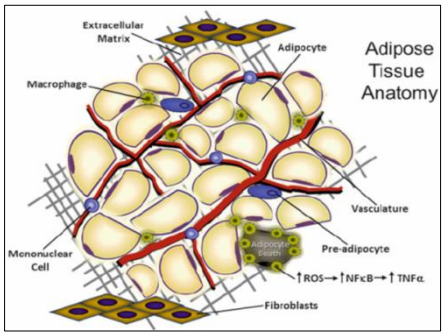
Ganesan K et al.
Int. J. Mol. Sci. 2018, 19

- **Microvesicles**



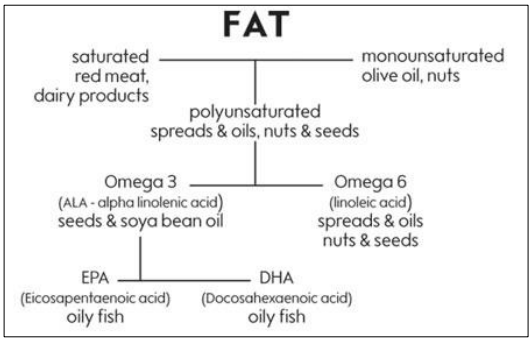
Journal of Extracellular Vesicles, 2014, 26913.

- **Adipose tissue inflammation and remodeling**

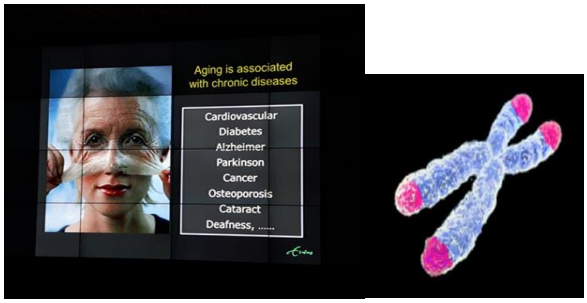


González F et al. Book chapter 2014

- **Omega-3 fatty acids**



- **Ageing**



Scientific Activities
PhD-theses defended 2019

Cand. Med. Kristine Holte:

Coronary artery disease and musculoskeletal complications in long-term survivors of type-1 diabetes: Associations with long-term glycation, oxidationand lipid markers

Supervisor: Professor Tore Julsrud Berg, Professor em. Kristian Hanssen, MD PhD Svein Solheim

The hypothesis in this study was that patients with long-standing diabetes type-1 have late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and macrovascular complications, including coronary artery disease. Markers of glycaemic burden, HbA1c and AGE's, as well as markers of inflammation and endothelial dysfunction are associated with this syndrome. The study consists of 100 patients with a duration of diabetes type-1 for 40 years in comparison to age-matched controls without any signs of related disease, for the presence of coronary heart disease assessed by CT coronary angiography, cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors. Three papers on the topic were included in the thesis which was defended for PhD June 2019.

Cand. Med. Christian Shetelig:

Inflammation and ischemia/reperfusion injury in STEMI patients treated by PCI and ischemic postconditioning

Supervisors: Geir Ø. Andersen MD PhD Jan Eritsland MD PhD, Ingebjørg Seljeflot Professor

From the POSTEMI study on the effect of post-conditioning in the treatment of acute MI (vide infra), the purpose of this investigation was to identify novel inflammatory pathways involved in acute MI, reperfusion injury and cardiac remodelling. The main objectives were to specifically explore potential chemokines/growth factors, which, based on previous research may be involved in both reperfusion damage but also potential salvage of the vulnerable re-perfused myocardium. Studies on osteoprotegerin (OPG), a member of the TNF receptor superfamily, Interleukin-8, and CTGF have been explored. Three papers on the topic were included in the doctoral thesis, submitted Spring 2019 and defended January 2020.

Scientific Activities
PhD-theses planned finalized spring 2020

Cand Med Ayodeji Awoyemi, PhD student
Microbial translocation, metabolic syndrome and chronic heart failure
Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Marius Trøseid Professor

This first part of the project focuses the potential role of microbial translocation and gut leakage (vide infra) in metabolic syndrome (MetS) and the prognostic importance for clinical endpoints. Significant associations between LPS-binding protein (LPB), CD14 and lifestyle factors (especially obesity) were found, and LBP was found to be significantly associated with clinical endpoints. Two papers published.
The second part is an intervention study on patients with chronic heart failure in collaboration with OUS Rikshospitalet (GutHeart) on the effect of treatment with antibiotics and/or probiotics on heart function (ejection fraction), the gut leakage markers as well as changes in the gut microbiota per se. The follow up of patients was finalized October 2019, and the main results are preparing for international presentation early 2020. Four papers will be included in the thesis, prepared for submission Spring 2020.

Cand Med Miriam S. Langseth, PhD student
NETs in acute and stable coronary heart disease
Supervisors: Ragnhild Helseth MD PhD, Trine B. Opstad MSc PhD, Ingebjørg Seljeflot Professor

The main part of this project is finalized, exploring the importance of markers of neutrophil extracellular traps (NETs) and NETosis (vide infra) in i) stable coronary artery disease as related to hypercoagulability and clinical endpoints ii) patients with ST-elevation myocardial infarction undergoing coronary angiography with percutaneous coronary intervention (PCI) and the relation to myocardial injury and left ventricular function (from the BAMI-biobank (vide infra)) and iii) exploring NETosis in patients with post-MI heart failure and cardiogenic shock. Two papers are published. Additionally, in the TASTI-study (vide infra) any presence and location of NETs will be explored in aspirated coronary thrombi from STEMI patients. Four papers are planned to be included in the thesis, prepared for submission Spring 2020.

Cand Med Sjur Hansen Tveit, PhD student (at AUH)
Troponins in the diagnosis of different stages of CAD
Supervisors: Torbjørn Omland Professor, Peder Langeland Myhre MD PhD, Ingebjørg Seljeflot Professor

The overall aim for the thesis was to compare two different type and different methods of troponins in evaluation for the diagnosis of coronary artery disease (stable angina and acute coronary syndroms). The CADENCE-population (vide infra) is one of the populations studied. The candidate has, in addition, been the main contributor to the OMEMI-study (vide infra) at AHUS, for patient inclusion and follow-up.

MSc Vibeke Bratseth, PhD student

Hypercoagulability, thrombin generation and microvesicles in diabetes - with and without coronary artery disease

Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em.

The aims of this project are to assess the importance of glucose control on the hypercoagulable state and on circulating microvesicles (cMVs) in patients with type 1 diabetes and in type-2 diabetes combined with CAD, and further any association with the degree of atherosclerosis and disease severity. This has been explored in two different cohorts: the EXCADI-biobank of patients with CAD and type-2 diabetes (vide infra) and the Atherosclerosis in Childhood Diabetes study (ACD) (vide infra) including type-1 diabetics.

In the EXCADI study special attention has been paid to diabetes patients with albuminuria in whom we previously have shown to be in a hypercoagulable state, and also to the effects of 12-months exercise training on hypercoagulability and cMVs. In the ACD study, childhood diabetics are compared with matched controls, for the development of thrombogenicity and cell activation assessed by cMVs. Four papers, all published/accepted for publication will be included in the thesis, prepared for submission Spring 2020.

Cand Med Joanna Cwikiel, PhD student

Markers of Coronary Artery Disease During Exercise Testing (CADENCE)

Supervisors Arnljot Flaa MD PhD, Eivind Berge MD PhD, Ingebjørg Seljeflot Professor

The aim of the CADENCE study (vide infra) was to examine whether changes in cardiac markers during exercise ECG will improve the accuracy of exercise ECG in the diagnosis of CAD. All subjects (n=300) are examined with coronary angiography, which is regarded as the gold standard for diagnosing CAD. The study furthermore aimed to clarify mechanisms related to sudden cardiac death as related to exercise by studying whether ischemia may potentiate increase in biomarkers of thrombosis and inflammation. The results add importantly to diagnosing CAD, and shed important insights into mechanisms responsible for exercise-related myocardial infarction. The results are presented in three accepted papers, and one paper submitted for publication. All papers are planned to be included in the doctoral thesis, planned to be submitted for evaluation during Spring 2020.

Scientific Activities
Ongoing Projects

Studies on Omega-3 fatty acids

Cand med Are Annesønn Kalstad at OUS
Cand med Sjur Hansen Tveit at AUH
Responsible/supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em, Pål Smith Professor em, Arnljot Tveit Professor

The ongoing clinical trial (OMEMI), started out in 2013 based on the suspected beneficial effects of omega-3 fatty acid supplementation and the limited knowledge about elderly with CAD. The aim is to investigate the effects of supplementation with 1.8 g/day of n-3 PUFAs on top of modern therapy, on cardiovascular morbidity and mortality during a follow-up period of 2 years in an elderly population (≥70-82 years) after having experienced an acute MI. Special emphasis are paid on the incidence of atrial fibrillation and heart failure in this elderly population. In addition, the study will generate important new knowledge about the elderly with CAD.
The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR. Participating centers are OUS Ullevål, Akershus University Hospital, Asker and Bærum Hospital and Stavanger University Hospital. Aalborg University Hospital, Denmark, participates by running important fatty acid analyses, in addition to scientific contribution by their top expertise in omega-3 research. The last patient for follow-up will be Spring 2020. A large biobank is established for studying mechanisms related to the intervention principle as well as to the process of ageing (vide infra).

Ongoing: Serum fatty acid measures (Aalborg) as compliance to the intervention, monitoring of the project, the endpoint committee controlling the clinical endpoints.
The main results are planned finalized during 2020 and prepared for international conferences and publication.

Topics addressed:
Omega-3 fatty Acids as related to traditional CVD risk factors and co-morbidities in elderly patients with myocardial infarction, and ***Omega-3 Fatty Acids*** and the importance for myocardial function and cardiac remodeling, both part of the thesis by Kristian Laake (2017).

Diet and Omega-3 Fatty Acids according to "Leukocyte Telomere Length", a suggested marker of longevity as well as proneness for CVD (Kalstad A et al. 2019).

Markers of Ageing / Senescence (telomere length, sirtuins) (vide infra), as related to the presence of atrial fibrillation in the elderly (Submitted)

Ongoing:
- Studies on polymorphisms important for the effects of omega-3 fatty acids, as well as related to ageing
- Omaga-3 and dietary pattern as related to microbiota translocation and regulation in adipose tissue

Studies on Microbial Translocation

An altered gut microbiota has been linked to several chronic disease states, including obesity, type-2 diabetes and chronic heart failure. Translocation of parts of the gut microbiota, and in particular endotoxins or lipopolysaccharides (LPS) to the systemic circulation, has been proposed to be an early trigger of inflammation, insulin resistance and subsequent cardiovascular risk. LPS promotes inflammation mainly by signaling through Toll like receptor (TLR) 4 on cells of the innate immune system, and CD14 plays a central role by transferring LPS to the TLR4 receptor complex.
In addition to the aforementioned work by Ayodeji Awoyemi, other studies are ongoing/started out 2019:

Microbial translocation and chronic heart failure

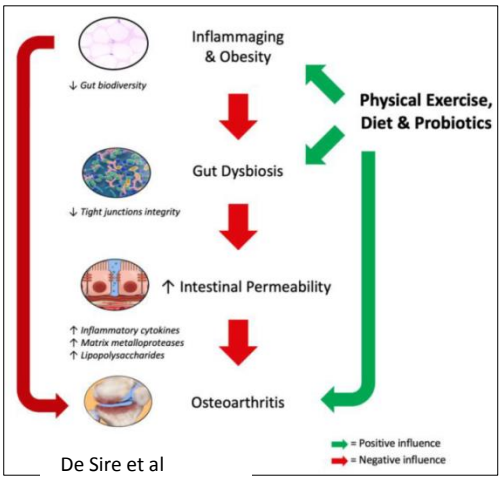
Based on the biobank from the GutHeart study, several mechanistic studies are underway to shed light on the gut-related inflammation in chronic heart failure patients. Peripheral blood mononuclear cells (PBMCs) have been isolated and give us the possibility in more depth, to explore the inflammatory pathways involved; especially the TLR4 induced inflammation.

Microbial translocation and lifestyle factors

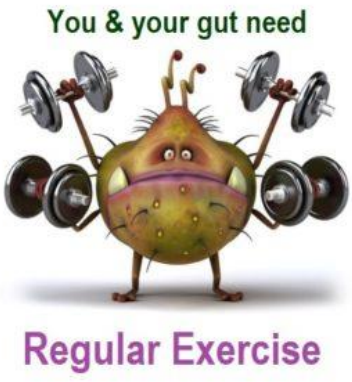
Cand med Susanne Kristine Aune PhD student

Supervisors: Ragnhild Helseth MD, PhD, Marius Trøseid Professor, Svein Solheim MD PhD, Ingebjørg Seljeflot Professor

Based on existing biobank from the EXCADI study, a randomized controlled study in patients with combined type 2 diabetes and CAD on the effects of long-term exercise training on atherosclerosis, we aim to study any effect on microbiota-related inflammation (gut leakage markers), in parallel with any relation to physical fitness.
The effects of acutely induced exercise will be explored based on the biobank from CADENCE (Markers of Coronary Artery Disease during Exercise testing), with the hypothesis that patients with manifest CAD, assessed by coronary angiography, will have increased leakage from the gut, compared to those without.



De Sire et al
Nutrients 2020, 12



Furthermore, from the OMEMI trial in which adipose tissue samples are available, TLR4 regulation, important for the effect of LPS, will be explored and related to dietary habits and intake of long-chain fatty acids.
In the total OMEMI trial (n=1026 AMI pts followed for 2 years) any prognostic value of gut leakage markers will be explored.

Microbial translocation in HIV. Effects of probiota treatment

Main investigator MD PhD Dag H. Reikvam, Dept of Infection diseases OUS Ullevål

Patients with HIV-infection who do not respond on antiviral treatment, so-called immunological non-responders (INR) have an increased low-grade inflammation and systemic immune activation. The hypothesis is that these patients have reduced mucosal barrier, and thus an increased leakage from the gut. We investigate such patients in comparison with responders to antiviral treatment as well as the effect of probiota treatment for 8 weeks. Preliminary results were published at a conference spring 2019.

Microbial translocation in primary sclerosing cholangitis

Main investigator MD PhD Johannes Hov, OUS Rikshospitalet

Primary sclerosing cholangitis is a chronic inflammatory liver disease of unknown etiology affecting both intrahepatic and extrahepatic bile ducts, eventually progressing to end-stage liver disease. Recent studies have identified an altered gut microbiota in PSC patients, and the gut leakage hypothesis could be relevant in the pathogenesis. We could show that circulating markers of gut barrier function were elevated in PSC compared with controls and elevated levels associated with reduced liver transplantation-free survival; published 2019 (Dhillon A et al).

Microbial diversity and translocation in stem cell transplantation (allogeneic hematopoietic cells)

Main investigator: Professor Per Ole Iversen, Dept of Haematology OUH and Dept of Nutrition, UiO and PhD Student Kristin Skaarud.

The diversity of the gut microbiota and throughout the course of allogeneic hematopoietic stem cell transplantation have been associated with survival and outcome of acute graft-versus-host disease. We have investigated whether markers of gut barrier function could predict survival and/or acute graft-versus-host disease among stem cell recipients, and also any reaction to nutritional intervention. Minor associations were found (Submitted for publication 2019).

Gut microbiota Signatures in Acute Coronary Syndromes (GutASC); (started 2020)

In collaboration with MD PhD Geir Ø. Andersen, ICCU Research group and professor Marius Trøseid, Dept of Infectious Disease, OUH Rikshospitalet.

In an observational longitudinal study we want to define a signature of gut microbiota composition and related metabolites in patients with ST-elevation MI (STEMI), non-STEMI and stable coronary heart disease (CAD) and relate such a signature to systemic inflammation and troponin release. The hypothesis is that they differ significantly and that AMI patients will normalize after 3 months. A huge biobank of stool and blood samples will be prepared. The inclusion of patients starts April 2020.

Studies on Neutrophil extracellular traps (NETs)

It has become evident that neutrophils upon activation are able to release parts of their nuclear content with residing neutrophil granule proteins into the extracellular space to form spindle-like networks, called neutrophil extracellular traps (NETs), which is thought to induce thrombosis. We have during 2018-2019 in patients with stable angina and STEMI published on the relationship between the surrogate markers of NETs, double-stranded deoxyribonucleic acid (dsDNA) and nucleosomes (DNA-histone complexes) and the thrombotic state, its importance for MI-complications and clinical outcome in these patients. In addition to these aforementioned studies by Miriam Langseth, other studies on NETosis are ongoing

NETs in acute myocardial infarction

- ***Impact of glucose regulation***

Post doc MD Ragnhild Helseth and MD PhD Eva C Knudsen

An early event during NETs release is decondensation of nuclear chromatin by the enzyme peptidylarginine deiminase (PAD4). In experimental studies NETosis is suggested to be glucose dependent. We could show that acute increase in glucose by an oral glucose tolerance test in STEMI patients lead to upregulated NETosis by PAD4 mRNA levels, indicating glucose to take part in the process (Published 2019).

NETs in acute myocardial infarction

- ***Impact of myocardial injury***

Cand med Christian Shetelig and post doc MD PhD Ragnhild Helseth

To further explore any impact of NETs on the degree of myocardial injury and left ventricular function assessed by coronary magnet resonance imaging, we have used of the biobank from the POSTEMI study (vide supra), and the results were published in 2019, Further in vitro studies were performed in collaboration with the ICC Cardiovascular Research Center in Barcelona.

NETs in acute myocardial infarction

- ***Impact of Interleukin-6 receptor antagonist.***

post doc MD PhD Ragnhild Helseth; in collaboration with OUS Rikshospitalet and NTNU

Beyond reducing troponin T (TnT) release, interleukin-6 receptor antagonist tocilizumab are associate with a reduction in neutrophil cell count in patients with non-ST elevation myocardial infarction (NSTEMI). We explore whether the effect on myocardial injury is excerted through NETs.

NETs in acute myocardial infarction

- ***NETs in coronary thrombi from STEMI patients (vide infra)***

Miriam Langseth, Jostein Nordeng PhD-students

In the TASTI-study (vide infra) we aim to explore cell types and content, in addition to the genetic profile in aspirated coronary thrombus. The presence and localization of NETs markers will be examined with morphological and immunohistochemical methods and related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis.

NETs as related to dementia

is planned in a collaborative study with Department of Geriatry. Hypotheses to be explored are whether innate immunity is important for the development of dementia and whether netosis can be used to distinguish between subtypes of dementia; whether patients with delirium have elevated NETs levels; whether NETs in cerebrospinal fluid are comparable with

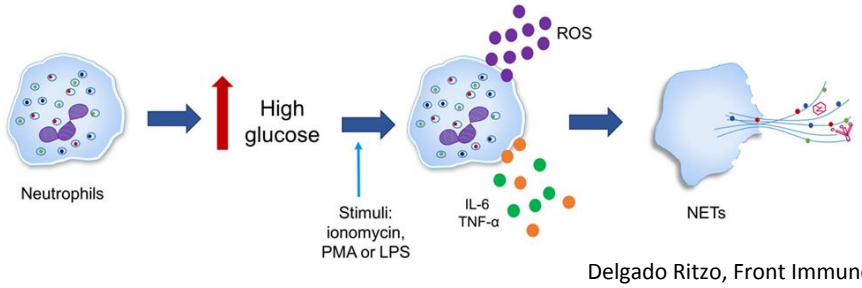
serum levels. We have performed a pilot study, showing NETs markers to be present in cerebrospinal fluid. To be continued in 2020.

NETs in type-1 diabetes

MD student Sverre Aukrust

Supervisors: Ragnhild Helseth MD, PhD, Ingebjørg Seljeflot Professor

Based on the findings of netosis to potentially be glucose dependent, the Dialong biobank (vide infra) are used to explore any differences in NETs markers between individuals with long-standing type-1 diabetes and age-matched healthy controls, and
potential differences in the diabetics who have developed coronary artery disease vs those who have not.



Delgado Ritzo, Front Immunol 2017

Studies on Complement activation

The complement system is a complex system, interacting with both inflammation and coagulation. Although experimental studies suggest interplay between these systems and also with activation and NETs in atherosclerosis, the relevance in patients with CAD is unclear.

Complement activation in association with NETs

Karsten Kluge, Medical student in Research Program

Supervisors: Ragnhild Helseth, MD PhD and, Ingebjørg Seljeflot, Professor

We here aim to study the associations between complement activation, NETs and hypercoagulability and the role of complement activation on clinical outcome in i) patients with stable CAD and ii) patients with acute myocardial infarction.

The first part was finalized in 2019, showing total complement complex to some degree to be associated with NETs and to future myocardial infarction /Submitted 2019; accepted for publication 02.2020).

The BAMI-cohort (vide infra) will be used to investigate part ii).

Studies on Adipose Tissue inflammation and remodeling

We have for several years focused on inflammation and remodeling in the metabolic syndrome, adipose tissue, atherosclerosis and cardiovascular disease states, also with respect to genetic expression of inflammatory and remodeling mediators, visualized in several previous and ongoing projects. Furthermore, differences in fat compartments are focused.

Adipose tissue inflammation and remodelling in patients with CAD and type 2 diabetes - effects of exercise training. Based on the EXCADI biobank

Cand Med Hani Zaidi PhD-student

Supervisors: Trine B. Opstad, MSc PhD, Senior Scientist, Ingebjørg Seljeflot Professor, Rune Byrkjeland MD PhD

In this project with patients with CAD and Type-2 diabetes, combined, the adipose tissue regulatory mechanisms of remodeling (MMP-9/TIMP-1/EMMPRIN/axis) were explored and related to glucose control, and to the effect of exercise training (published 2019). Further studies on the importance of certain adipokines from adipose tissue will be investigated, related to the degree of atherosclerosis, glucose control, and to the effects of exercise training.

Adipose tissue and remodeling as related to insulin sensitivity in healthy men

MSc Sissel Åkra.

In collaboration with MD PhD Tonje A. Aksnes, Section of Cardiovascular and Renal Research, OUS Ullevål

In a cross sectional study on middle-aged men we have previously shown strong association between insulin sensitivity assessed by glucose clamp, and inflammatory genes of proteins in the inflammasome pathway, expressed in adipose tissue as well as circulating levels, and further that these mediators are related to the amount of abdominal adipose tissue assesses by CT-scan. Studies on the impact of glucose regulation on adipose tissue remodelling are performed, showing early overweight and insulin resistance to be of importance for glucose regulation also in a healthy non-obese population *(Submitted for publication).*

Inflammatory activity in various compartments of adipose tissue in patients with coronary heart disease (ATICH). In collaboration with Department of Thoracic surgery

Steering Committee: Professor Ingebjørg Seljeflot, MD PhD Svein Solheim, Professor em Harald Arnesen, Professor Theis Tønnesen, MD PhD Bjørn Braathen.

Executers: In addition to the surgeons

MSc Sissel Åkra: Sample handling

Study nurse Charlotte Holst Hansen: Patient information

Different compartments of adipose tissue like subcutaneous, visceral, perivascular, pericardial and epicardial fat have been claimed to exert different proinflammatory profiles with different associations with cardiovascular disease states.

The aims of this project are to study differences in inflammatory genes expressed and protein secretion in various compartments of adipose tissue being exposed during open cardiac surgery on patients with coronary heart disease, and valvular disease for control. Laboratory examinations are ongoing.

Studies on Thrombogenicity

Thrombus Aspiration in acute ST-elevation myocardial Infarction (TASTI)

Cand Med Jostein Nordeng PhD Student

Supervisors: Ingebjørg Seljeflot Professor, Ragnhild Helseth MD, Bjørn Bendz Professor, Svein Solheim MD PhD

Based on results from a previous study "Coronary thrombus genes in acute myocardial infarction", we aim to further explore the cell types and content, in addition to the genetic profile in the aspirated coronary thrombus. Both cellular and non-cellular content of the thrombus will be examined with morphological and immunohistochemical methods and related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis. Furthermore, mRNA expression of selected signal molecules will be performed. In addition, peripheral venous blood samples will be analysed for signaling molecules and corresponding mRNA expression in circulating leukocytes. The study is in close collaboration with Department of Radiology and Department of Pathology, OUS Ullevål. Collection of thrombi are finalized and laboratory work is ongoing. Main focus will be on pathways related to inflammasome activation, fibrinolysis, remodeling and Netosis. Results from the first part will be submitted for publication and presented at conferences 2020.

The importance of ADAMTS-13 on von Willebrand factor regulation in patients with coronary artery disease – with special reference to aspirin treatment

MD Ellen M. K. Warlo (previous Medical Student in Research, University of Oslo)

Supervisors: MD PhD Alf-Åge Pettersen, Trine B. Opstad, Professor Ingebjørg Seljeflot

ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin 1 repeats) is a member of the ADAMTS family of metalloproteinases, responsible for the regulation of von Willebrand factor (vWF), which is reported to be a risk factor for coronary artery disease. VWF has pro-thrombotic properties and plays a central role in platelet adhesion and aggregation upon vessel wall injury. Deficiency of ADAMTS-13 promotes vWF-induced platelet aggregation. In this project we have shown reduced ADAMTS13 is of importance for clinical outcome after 2 years in patients with stable coronary artery disease. Genetic polymorphisms in the gene coding for ADAMTS-13 are further explored for the impact on ADAMTS-13 levels as well as on clinical events.

Biomarkers of inflammation and haemostasis: welders under exposure to high-grade pollution

In collaboration with National Institute of Occupational Health (Professor Dag Ellingsen)

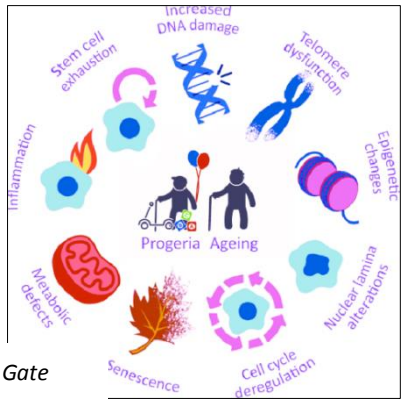
Increased mortality due to pulmonary and cardiovascular diseases by increasing pollution in the external environment has been documented. The mechanisms behind the cardiovascular and pulmonary systems vulnerability to such pollution, are not known. Tunnel construction workers and welders are especially exposed to particulate and gaseous components during work. We have previously shown (2017) that Norwegian tunnel workers have increased endothelial activation, but reduced inflammation and platelet activation during the work exposition. We have further investigated a population of russian welders, before and after a 3-year period of daily/weakly work, and could show a pro-thrombotic state with increased thrombin generation and increased endothelial /platelet activation compared to controls (published 2019).

Studies on Telomere lengths and Ageing

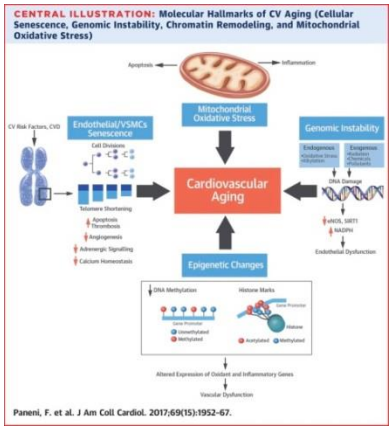
Trine B. Opstad MSc PhD, Are A. Kalstad MD PhD student a.o

A telomere is a region of repetitive nucleotide sequences at the ends of each chromosome which protects DNA at the ends from deterioration. The telomeres become truncated during cell division and about 7 kilobases of telomere length is lost during life. The rate of shortening is thought to be greater in men than in women. Lifestyle and environmental factors have been reported to influence the rate of telomere shortening.

Sirtuins (SIRTs) are a family of NAD+ dependent protein deacetylases, and are highly conserved across species. Sirtuin-1 (SIRT1) is linked to longevity through several pathways of the aging process, including protection from oxidative stress.
We have addressed studies for understanding some mechanisms behind the ageing process in different populations.



Research Gate 2017



Telomere length *as related to myocardial injury and dysfunction in acute myocardial infarction*, as well as to the presence of atrial fibrillation (from the OMEMI trial) (vide supra).

Telomere length *in a population of patient with stable coronary artery disease*, we observed significantly shorter leukocyte telomere length in patient with previous myocardial infarction.

Telomere length *related to other rejuvenating factors in patients with coronary artery disease.*
We observed that higher levels of the growth differentiating factor GDF11 and SIRT1 associated with longer telomeres, accompanied by a reduced pro-inflammatory state.
(Published 2019).

Telomere length *and rejuvenating factors in young and older healthy people*
In healthy young and elderly individuals, we explored the association between leukocyte telomere lengths and other longevity factors and pro-inflammatory markers and their influence of life-style factors and presence of hereditary coronary heart disease, showing especially telomere length to be associated with cardiovascular heredity (Published 2019).
The biobank from the Dialong-study (vide infra) has been used.

Telomere ***length*** *and rejuvenating factor analyses in type- 1 diabetes* compared to healthy controls are ongoing, based on the biobank from Dialong (vide infra).

Scientific Activities - Other

BAMI ("Biobanking in patients with Acute Myocardial Infarction")

A Steering committee for BAMI is established (Professor em. Harald Arnesen, MD PhD Geir Øystein Andersen, Professor Sigrun Halvorsen, MD PhD Jan Eritsland, MD PhD Reidar Bjørnerheim, Professor Ingebjørg Seljeflot)

In this joint project between the Intensive Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and are basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI and NSTEMI were included after consent. A total of 2150 pts (1790 STEMI; 360 NSTEMI) are included. The biobank of selected biomarkers has been used in 2 defended PhD projects and in 2 ongoing (vide supra).
Further projects are planned, including genetic studies. All logistics for processing of blood samples in the acute phase and the biochemical analyses research are undertaken by CCHR.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

*A project initiated by **Professor Kjetil Sunde**, Department of Surgical Intensive Care Unit in close collaboration with the Intensive Coronary Care Unit **by MD PhD Geir Ø. Andersen** ao. The project has daily been taken care of by PhD-student Henrik Stær-Jensen, also supervised by MD PhD **Espen Rostrup Nakstad**.*

Combined clinical-neurological, neurophysiological, neuroradiological and biochemical markers in prognostication after cardiac and/or respiratory arrest. In this multidisciplinary study performed in acute seriously ill patients, 250 patients have been included. Blood samples are collected and processed at CCHR for analysis of a series of biomarkers especially related to neuro-inflammation and thrombotic risk markers in the very acute phase and also after 3 days in those staying alive.
The patients are followed for three years, the last patient during 2018. The main study results were published 2019. Due to lack of man power, the biobank has not yet been used, but planned through 2020.

Diabetes in children and atherosclerosis development

Aida Simeunovic MD PhD-student

Supervisors: MD PhD Hanna Dis Margeirsdottir, MD PhD Martin Heier, Professor Knut Dahl-Jørgensen

Patients with type-1 diabetes from childhood have 20-30 times increased risk for premature death from cardiovascular diseases compared to non-diabetics. In this follow-up study, initiated from Department of Pediatrics/Oslo Diabetes Center, 330 children/youth with type-1 diabetes are compared with 120 healthy controls matched for age and gender to investigate early signs of atherosclerosis as measured with various methods (anatomical, physiological, biochemical). Both groups have been followed for 5 years and 10 years and will be further followed. All blood sampling/processing and facilities for biochemical translational research (biobanking, analyses) are undertaken at CCHR. Two PhD theses have been based on data from this study so far, and one is ongoing. In addition, part of this study is the basis for the PhD-project of Vibeke Bratseth (vide supra) on hypercoagulability and micro-vesicles in diabetics.

DIALONG (Diabetes type-1: long-term survivors with a new syndrome of late complications)

Main responsible: Professor Tore Julsrud Berg and PhD Kristine Holte

In addition to the work performed by MD PhD Kristine Holte (vide supra; PhD thesis defended 2019) is the biobank a source for several ongoing studies (vide infra)

The hypothesis in this study is that patients with long-standing diabetes type-1 have late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and macrovascular complications. Markers of glycaemic burden, HbA1c and AGE's, as well as markers of inflammation and endothelial dysfunction are associated with this syndrome. The study consists of 100 patients with a duration of diabetes type-1 for 40 years in comparison to age-matched controls without any signs of related disease, for the presence of coronary heart disease assessed by CT coronary angiography, cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors. Blood sampling/biobanking and analyses of biomarkers are performed at CCHR, and the biobank is also used for investigation of the ageing aspects and NETs aspects (vide supra).

ASSAIL-MI (ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction)

Main responsible: professor Lars Gullestad OUS, Rikshospitalet, Professor Rune Wiseth, NTNU and MD PhD Geir Ø. Andersen, OUS Ullevål

The study is mainly aimed to examine whether a single administration of the IL-6 receptor antagonist tocilizumab can reduce myocardial injury in patients with acute ST-elevation myocardial infarction (STEMI). A randomized, double blind, placebo-controlled trial conducted at three high-volume percutaneous coronary intervention (PCI) centers in Norway. 200 patients with first-time STEMI presenting within 6 hours of the onset of chest pain, are randomized to receive tocilizumab or matching placebo prior to PCI. The patients are followed-up for 6 months. All patients are included by 01.2020. A biobank is established based on blood sampling at several time points during the acute phase and after 6 months. CCHR is heavily involved in the biobank work.

CENS - Cardiovascular remodeling in living kidney donors with reduced glomerular filtration rate

Kjersti Blom MD PhD-student

Supervisors: MD PhD Jon Arne Birkeland, Department of Nephrology and Professor Ivar Sjaastad, Institute of Experimental Medical Research, OUS

A collaboratory study between many departments, initiated by the supervisors

Patients with advanced chronic kidney disease (CKD) are known to have a high risk of developing cardiovascular disease (CVD). However, little is known about the cardiovascular risk in patients with mildly reduced kidney function, affecting up to 10% of the general population; and importantly, also affecting living kidney donors. Until recently it has been believed that donating a kidney does not represent any health hazard. However, a recent Norwegian epidemiological study suggested that kidney donors have an increased risk of CVD. The pathogenesis linking reduced kidney function to CVD is not known. The main purpose of this project is to investigate the mechanisms underlying the development of

cardiovascular remodelling induced by reduced kidney function. This is a prospective longitudinal parallel group study including persons selected as living kidney donors according to the Norwegian donor criteria and accepted for surgery at Rikshospitalet, Norway and a control group. The project will use state of the art imaging combined with advanced molecular biology, to investigate cardiac, vascular and renal remodelling. The project has the potential to identify mechanisms linking reduced kidney function to CVD, identify predictors for adverse CV outcome, and recognize potential targets for risk lowering intervention. A huge biobank of blood, urine and stool samples are established at CCHR.

PROACTIA PRediction and detection of Occult Atrial fibrillation in patients after acute Cryptogenic stroke and Transient Ischemic Attack (PROACTIA) Sub-study on biomarkers

The project is ongoing at Akershus university hospital by PhD student Loteta S. Strøm, supervised by MD PhD Harald Kjekshus and professor Kjetil Steine

The main aim of this project is to build and evaluate a novel composite scoring system to predict the occurrence of atrial fibrillation (AF) during follow-up in patients admitted for first time cryptogenic stroke or TIA. The scoring system is based on measurements performed during the initial hospitalization (age, CHA2DS2-VASc, ECCO findings, biomarkers and OSA screening), and its purpose is to reliably asses the risk of occult AF in each individual patient. 270 patients have been included and followed for at least 1 year, and episodes of AF have been registered by implanted loop recorders.
AF is associated with left atrial remodelling and fibrosis, and several biomarkers of cardiac remodelling and fibrosis are studied as candidates to be of importance for AF, as well for left ventricular function and heart failure. Analyses of such candidates have been performed and the results will be available during 2020.

To improve blood flow in patients with peripheral artery disease; by intermittent negative pressure (INP) – ongoing at OUS Aker

Cand Med Henrik Hoel PhD student

Supervisors; Jonny Hisdal Professor, Gunnar Sandbæk MD PhD, Iacob Mathiesen PhD

The main goal of the project is to evaluate a novel method for improving blood flow in patients with reduced peripheral arterial circulation (PAD-patients), and to identify and optimize the level of negative pressure to improve blood flow in patients with varying degrees of PAD. A double blinded randomized placebo-controlled trial. All patients receive standard medical treatment; randomized to either INP treatment with pressure level of -10 mmHg (placebo group), or to INP treatment with pressure level of -40 mmHg (Intervention), for 12 weeks. A biobank, focusing endothelial activation/function is established and analyses are ongoing at CCHR.

Laboratory Methods

has been further established according to recent knowledge, available equipments and focused issues.

- Method for micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers
- Method for telomere length
- Biomarkers of ageing; circulating and regulated
- Biomarker of gut-leakage and related
- Biomarkers of netosis
- Arrays for gene regulation
- Flow cytometry
- Adipose tissue sample handling/embedding

Methods, equipments

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and –80°C))
- Platelet function testing (aggregometry and ”bedside” screening tests (PFA100, VerifyNow))
- Flowcytomtry (BD Accuri C6)
- ELISA’s
- Fluoroscan
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied Biosystems)
- Fume cupboard, moveable
- HPLC (Located at Institute for Experimental Medical Research, OUH Ullevål)

Cell-culture studies and Luminex analyses

In collaboration with Department of Medical Biochemistry, R&D Unit OUS Ullevål

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Networks

CCHR has been a part of Center for Heart Failure Research, a National network that was established in 2002, financed by Helse Sør-Øst and University of Oslo, ending in 2019. PhD candidates and other employees are still members of NORHEART, which is a National PhD network for cardiovascular research. CCHR is a part of the Regional Microbiota Network, established in 2019, funded by the Norwegian Council of Research and Helse Sør-Øst.

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