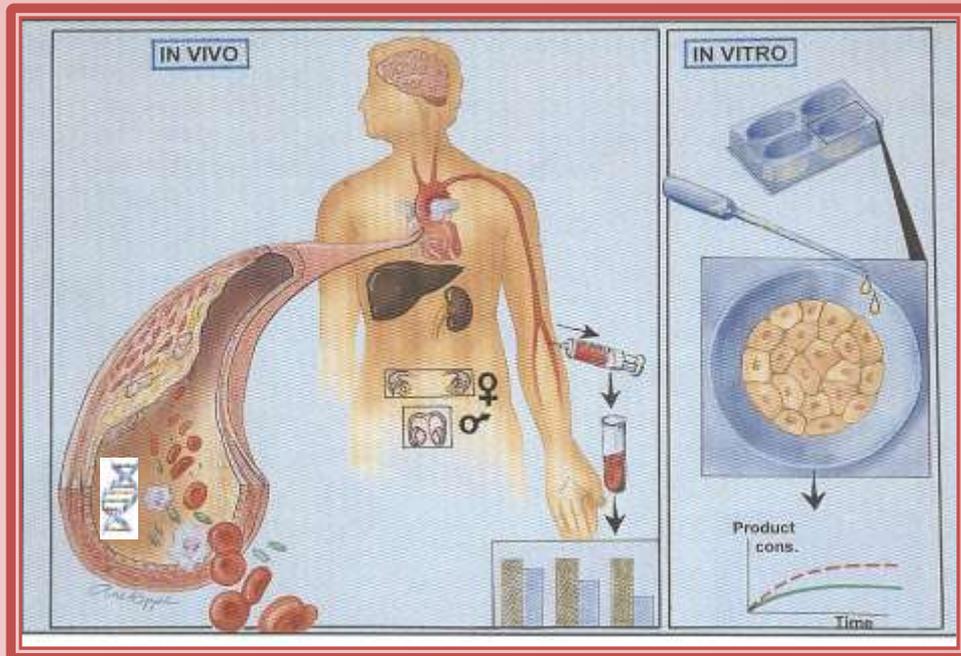


Annual Report 2020



Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital,
Ullevål

"Team building for individual excellence"

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Preface

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

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. Asker & Bærum Hospital, Akershus University Hospital and OUH Rikshospitalet and the Oslo Diabetes Research Center, are of special importance by having common projects and PhD-students.

Also in 2020 focus has been to improve methodology related to the innate immune system, microbial translocation aspects, adipose tissue inflammation and the ageing process. Due to the Corona situation, more work has been turned towards laboratory activity as patient related projects have been challenging.

However, despite Corona, the scientific activity has been almost at the same level as previous years, although delay in some projects. One PhD thesis defended and 18 internationally published papers. The number of abstract has been lower, due to postponed congresses. Although digital congresses/meetings were available the last part of 2020, the loss of integrative meetings has been challenging. That is also for our internal team-building meetings. Nevertheless, the scientific staff and PhD students have given a lot of effort into keeping a good working atmosphere and a high scientific spirit.

One PhD candidate defended his thesis January 2021, and 4 are preparing for defense during 2021.

We still had 1 candidate in The Medical Research Student Program at the university, funded by the Norwegian Council of Research in 2020. Along with other PhD candidates, this is important contribution to a young and dynamic milieu.

Our participation in the “Regional Research Network for clinical Microbiota Science”, established in 2019, led to collaboration for a PhD project in this novel field with regard to cardiovascular disease, and we are further working to strengthen our related methodology to be a core lab for some of these specialities. Also, our participation in the Norwegian Atrial Fibrillation Research Network, financed from Health South East, has given fruitful collaborations, especial with Asker & Bærum Hospital and Akershus University Hospital.

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. He will retire to be an “ex officio” member from 2021, where after MD PhD and cardiologist Svein Solheim, medical responsible at the center, will replace him from 2021. The research coordinator, Charlotte Holst Hansen, employed for administrative matters in 50% position in 2019 continue.

We are very pleased to give the annual report for 2020.

March 2021

Ingebjørg Seljeflot (sign)
Professor dr. philos
Center Head

Strategy

- Clinical studies, including studies on mechanisms/translational studies in cardiovascular medicine. Biochemical, cellular and genetic aspects especially related to the cardiovascular disease processes, focusing inflammation, remodeling, thrombosis, endothelial function and the ageing phenomenon.
 - 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 research group, including researchers at post.doc level
- To collaborate in appropriate networks as well as at the research group and individual levels

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
- 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 especially encouraged to give presentations to prepare for international conferences. In 2020 these meetings have been conducted digitally.

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 on projects/scientific matters, 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 cardiologist, and one professor emeritus, the latter has been the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUS Ullevål. Further, a research coordinator 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).

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. We strive for fundings by applications wherever we find it relevant.

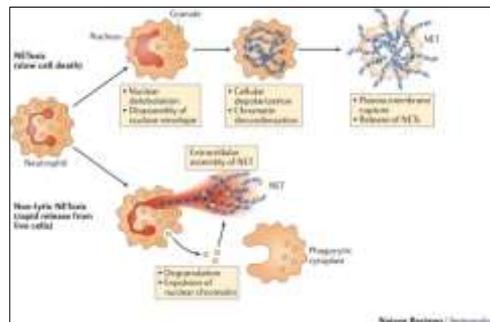
The major economic support from Stein Erik Hagens Foundation for Clinical Heart Research, anchored at Institute of Clinical Medicine, University of Oslo, has been of crucial importance for the activity also in 2020.

Scientific Activities

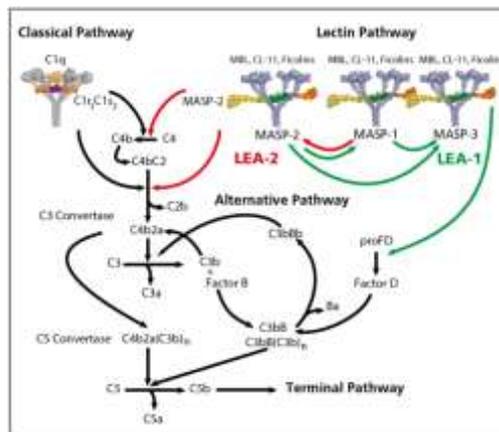
We also in 2020 had our methodological focus in the following areas, which has led to improved knowledge and several publications.

In addition to atherosclerosis, inflammation and remodeling in general,

- **Neutrophil extracellular traps**

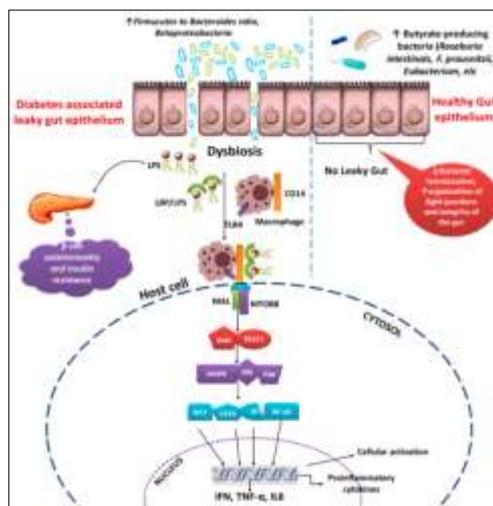


- **Complement activation**



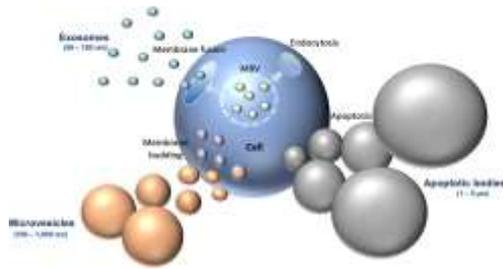
W Schwaeble, University of Leices, UK

- **Microbial translocation**



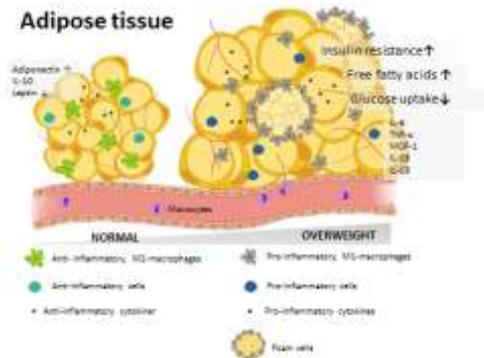
Ganesan K et al.
Int. J. Mol. Sci. 2018, 19

- **Microvesicles**



Carrino et al, Respiratory Research, 2019

- **Adipose tissue inflammation and remodeling**

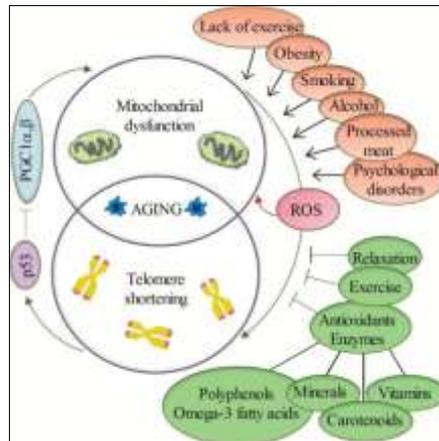


Åkra L, Åkra S. 2020

- **Omega-3 fatty acids**



- **Ageing**



J Geront: Series A, 2008;73,1

Scientific Activities

Highlights 2020

This year two randomized clinical studies were fulfilled, whereof one in collaboration with OUS Rikshospitalet, The **GutHeart study**, a part of the thesis of Ajodeji Awoyemi (vide infra), an intervention study with goal to change the microbiota with subsequent improvement of heart function.

The other one was the **OMEMI-trial**, which has been ongoing from 2012 as a multicenter study, including 1027 elderly myocardial infarction patients from 3 different hospitals (vide infra) for the effect of omega-3 fatty acid supplement on clinical endpoints. The study was conducted at CCHR, which has been the study center throughout. The study was highlighted at the American Heart Association Congress (digital), given much attention in the scientific community and media, and published in the well reputable cardiovascular journal *Circulation*, online in 2020. 4 PhD students have worked on the project, whereof 2 have finalized their thesis and 2 are in pipeline for 2021. This study has several unanswered questions and a broad biobank for future research.

PhD-theses defended 2020

Mater of Science Vibeke Bratseth:
Pro-thrombotic activity and circulating microvesicles in diabetes, with and without CAD
Special emphasis on the influence of exercise training and longitudinal changes



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

The aims of this project were 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 was 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. It was specially observed that diabetes patients with albuminuria were in a hypercoagulable state, and also shown to express cMVs related to hypercoagulability and endothelial function. No effects of 12-months exercise training on hypercoagulability and cMVs were observed. In the ACD study, childhood diabetics were compared with matched controls and followed for 5 years development, for thrombogenicity and cell activation assessed by cMVs. Four papers were included in the thesis, defended December 2020.

PhD-theses finalized primo 2021

Cand Med Ayodeji Awoyemi, PhD student

Microbial translocation and cardiovascular disease states

Emphasis on chronic heart failure, diabetes and the metabolic syndrome

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

This first part of the project focused 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. The second part was 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 intervention did not show any significant effects on the outcome variables, probably due to the well-treated population included. Four papers were included in the thesis, defended February 2021.

PhD-theses planned for 2021

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

This project is 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. Preparing for submission Spring 2021, somewhat delayed due to the corona situation.

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 2021, somewhat delayed due to the corona situation

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 supra) 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. The thesis prepared to be submitted Spring 2021.

Cand Med Are Annesønn Kalstad, PhD student

The role of n-3 fatty acids in cardiovascular diseases of ageing

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

This thesis is fully based on the OMEMI trial, commented as Highlight, and further presented (vide infra), in which the main study results from the intervention with omega-3 fatty acid supplementation are focused. In addition, the interplay between the ageing process and cardiovascular disease are important topics.

Scientific Activities

Ongoing Projects

Studies on Omega-3 fatty acids

Steering Committee: Harald Arnesen Professor em, Pål Smith Professor em, Arnljot Tveit Professor, Svein Solheim MD PhD, Dennis WT Nilsen Professor, Morten Fagerland MSc PhD, Erik Berg Schmidt Professor, Ingebjørg Seljeflot Professor.

As mentioned in the Highlights, the main OMEMI trial was finalized in 2020. The main aim was 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. The study was quite neutral with regard to clinical endpoints, and added to results from other studies in this field published in 2020. Special emphasis was paid on the incidence of atrial fibrillation and in this elderly population, in which we could show a tendency to an unbeneficial effect. There are still several unanswered questions and a broad biobank for future research is established. The study will further generate important new knowledge about the elderly with CAD. The study was 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 main results will be part of the thesis of Are A. Kalstad who prepares to submit his thesis Spring 2021, including three papers from the OMEMI cohort.

There are several sub-studies ongoing, especially with regards to dissect any importance of the different fatty acids.

Topics previously 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).

Nordic Diet and Omega-3 Fatty Acids and reduced platelet activation assessed by circulating microvesicles (Chiva-Blanche G et al. 2019)

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 (Kalstad A et al. 2020)

Ongoing:

- Studies on polymorphisms important for the effects of omega-3 fatty acids, as well as related to ageing
- Omega-3 and dietary pattern as related to microbiota translocation and regulation in adipose tissue
- The importance of n-3 fatty acid concentrations on clinical outcome
- The importance of n-6 fatty acid concentration on clinical outcome
- The relationship between omega-3 fatty acids and the occurrence of atrial fibrillation

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 products 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:

Microbial translocation and chronic heart failure

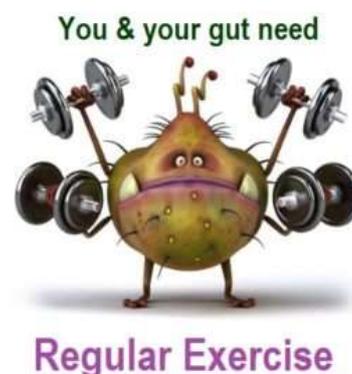
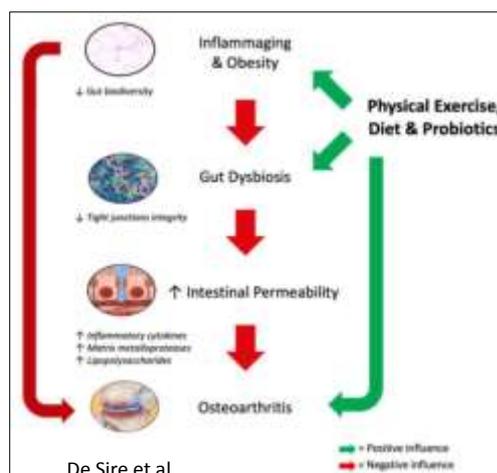
Based on the biobank from the GutHeart study, several mechanistic studies are underway to shed light on the gut-related inflammation in chronic heart failure patients. Peripheral blood mononuclear cells (PBMCs) have been isolated and give us the possibility in more depth, to explore the inflammatory 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, the effect on microbiota-related inflammation (gut leakage markers) is investigated. This first part is finalized, showing markers of gut leakage to be strongly associated with physical fitness, submitted for publication. In the second part the effects of acutely induced exercise are under investigation by use of the biobank from CADENCE (vide supra). The hypothesis is that patients with manifest CAD, assessed by coronary angiography, will have more increased leakage from the gut, compared to those without during strenuous exercise.



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=1027) 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 to 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. The first part was published in 2020, and the second part expected to be published 2021.

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 throughout the course of allogeneic hematopoietic stem cell transplantation has 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 2020).

Gut microbiota Signatures in Acute Coronary Syndromes (GutACS)

Cand Med Aasmund Nordheim PhD student

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 was quite delayed due to the corona situation, thus, started September 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 2018-2020 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 myocardial injury

Christian Shetelig MD PhD and Ragnhild Helseth MD PhD

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, and the results were published in 2020.

- Impact of Interleukin-6 receptor antagonist.

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

Beyond reducing troponin T (TnT) release, interleukin-6 receptor antagonist tocilizumab is associated 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 exerted through NETs.

- NETs in coronary thrombi from STEMI patients

Miriam Langseth, Jostein Nordeng PhD-students

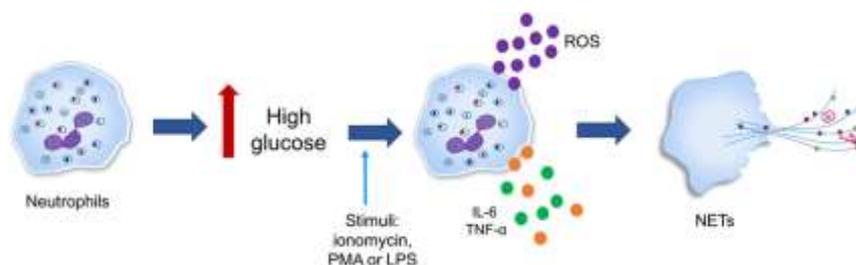
In the TASTI-study (vide infra) we aim to explore cell types and content, in addition to the genetic profile in aspirated coronary thrombus. The presence and localization of NETs markers will be examined with morphological and immunohistochemical methods and related to time from onset of symptoms to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

NETs in type-1 diabetes

Sverre Aukrust MD

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. The project delayed due to the corona situation.



Delgado Ritzo, Front Immunol 2017

NETs as related to dementia

Vibeke Bratseth MSc PhD, Ragnhild Helseth MD PhD, Leiv Otto Vatne MD PhD (Dept of Geriatric)

A collaborative study planned with Department of Geriatric. 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. These studies were postponed due to the corona situation, but will continue 2021.

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, published 2020. The BAMi-cohort (vide infra) is now used to investigate part ii). In addition, interaction between hypercoagulability and complement was explored in stable CAD, also published in 2020. The candidate is working part time in research along with his medical studies.

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 EXCAD1 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 have been investigated, related to the degree of atherosclerosis, glucose control, and to the effects of exercise training, submitted for publication 2020. Adipokines are further examined in a healthy cohort to explore such regulation in un-medicated individuals.

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 assessed 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, published 2020.

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.

Executors: In addition to the surgeons

MSc Sissel Åkra: Sample handling and drafting manuscript

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 CAD, and valvular disease for control. Laboratory examinations are almost finalized, however, search for collaborations for immune-histochemical analyses 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. Thrombus content is examined with morphological and immune-histochemical methods, as well as genetic regulation (mRNA) of selected signal molecules – all related to time from onset of symptoms to PCI, and to the degree of myocardial necrosis. Furthermore peripheral venous blood samples are analyzed 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. The laboratory work is ongoing. Main focus are on pathways related to inflammasome activation, fibrinolysis, remodeling and netosis. Some delay due to Practical issues for collaborators and the corona situation. Results from the first part were presented at the European congress of cardiology (digital) august 2020, and is submitted for publication.

Coronary thrombus and extracellular circulating microvesicles (cMVs)

Vibeke Bratseth MSc PhD, Jostein Nordeng and the TASTI-group

From the above mentioned TASTI project, we will explore the relationship between the expression of cMVs and pro-thrombotic and pro-inflammatory signals in coronary thrombi, especially related to the presence of NETs. Flow-cytometry with a renewed and more advanced method will be used to better distinguish the cMVs and their origin cells.

The importance of ADAMTS-13 on vWF regulation in patients with CAD

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 activation upon vessel wall injury. In this project we have shown reduced ADAMTS13 is of importance for clinical outcome after 2 years in patients with stable CAD. Genetic polymorphisms in the gene coding for ADAMTS-13 will further be explored for the impact on ADAMTS-13 levels as well as on clinical events. The candidate is working to finalize for her diploma as a licensed doctor, and will continue this work thereafter.

Exercise induced changes in pro-thrombotic and cardiac biomarkers in CAD patients

Charlotte Holst Hansen, Study Nurse

Patients from the CADENCE study which were tested with exercise EKG for the diagnosis of CAD, showed a hypercoagulable state after exercise. Some of these patients are re-examined after successful revascularization to explore whether they still had a tendency to be hypercoagulable, and also whether they still induced release of cardiac biomarkers. Results are underway.

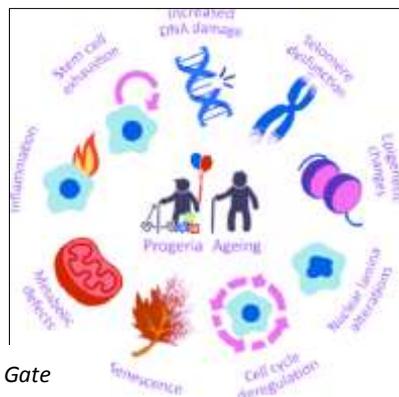
Studies on Telomere lengths and Ageing

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

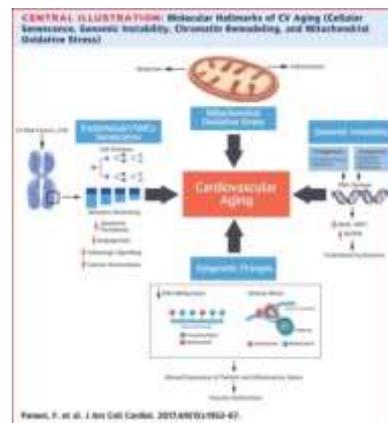
A telomere is a region of repetitive nucleotide sequences at the ends of each chromosome which protects DNA at the ends from deterioration. The telomeres become truncated during cell division and about 7 kilobases of telomere length is lost during life. The rate of shortening is thought to be greater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

Sirtuins (SIRT) 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 (from the OMEMI trial 2019)

Telomere length and Sirtuin-1 as related to the presence of atrial fibrillation (from the OMEMI trial) (2020).

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 (2019).

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 (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 (2019).

Telomere length and rejuvenating factor analyses in type- 1 diabetes compared to healthy controls have been investigated based on the biobank from the Dialong study, showing telomere length and SIRT-1 to be lower in T1DM (2020).

SIRT-1 and life style. Based on the link between longevity factors, life style and oxidative stress, an intervention study on caloric restriction has been performed, in collaboration with Department of Medicine, OUS Ullevål, showing SIRT-1 to increase beneficially with caloric restriction for one year in obese individuals (accepted for publication 2021).

CHIP (clonal hematopoiesis with indeterminate potential) is mainly affecting the elderly and suggested to be a novel link between inflammation and CVD. CHIP is caused by an age-dependent increased frequency of mutations in stem cells of the bone marrow. We have recently started out a project to explore the influence of selected TET2 and JAK2 mutations (two of the most mutated genes in CHIP) in our elderly CVD populations with regard to i) clinical status and outcome ii) telomere length, iii) degree of inflammation, SIRT-1 and NETs, iv) potential response to n-PUFA supplementation. This is a novel, but highlighted field of CVD research and thus limited knowledge in this field.

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.

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 2021.

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 and 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 MD PhD Kristine Holte

The hypothesis in this study was that patients with long-standing diabetes type-1 have late complication syndrome consisting of cheirography 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, cheirography, 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 was 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 were randomized to receive tocilizumab or matching placebo prior to PCI. The patients were followed-up for 6 months. The results, showing a beneficial effect of the drug, were presented at the European congress of cardiology (digital) august 2020, and published early 2021). 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

Cand Med Kjersti Blom PhD-student

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

A collaborative 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. A recent Norwegian epidemiological study suggested that kidney donors have an increased risk of CVD. 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. The project has been much delayed and influenced by the corona situation, but is ongoing with inclusions.

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 Loreta S. Strøm, supervised by MD PhD Harald Kjekshus and professor Kjetil Steine

The main aim of this project was 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 assess 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. As 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 results were presented at the European congress of cardiology (digital) august 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 was 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 performed at CCHR. Results showed beneficial clinical effect of the treatment, and also improved endothelial function (accepted for publication 2021).

Vascular function in Norwegian female elite runners – ongoing at OUS Aker

Karoline Kyte, Medical student in Research Program

Supervisors: Jonny Hisdal Professor, Ingebjørg Seljeflot, Professor

Increased aerobic capacity and regular aerobic exercise are well known to have a positive impact on the cardiovascular system. It has, however, been claimed that in healthy young women, the effect of high amounts of endurance training may not be that obvious. The aim in this study is to investigate especially vascular function, including the endothelial function, in female elite runners compared to inactive women. Special emphasis is given to menstrual state which may be of importance. Results are under discussion

Laboratory Methods

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

- Method for telomere length
- Biomarkers of ageing; circulating and regulated
- Method for micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers
- Biomarker of gut-leakage
- 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
- Fluoroscanner
- 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

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 Health South East 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 Health South East, and also the Norwegian Atrial Fibrillation Research Network, financed from Health South East. All contributing to fruitful meetings and collaborations.

Publications 2020

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