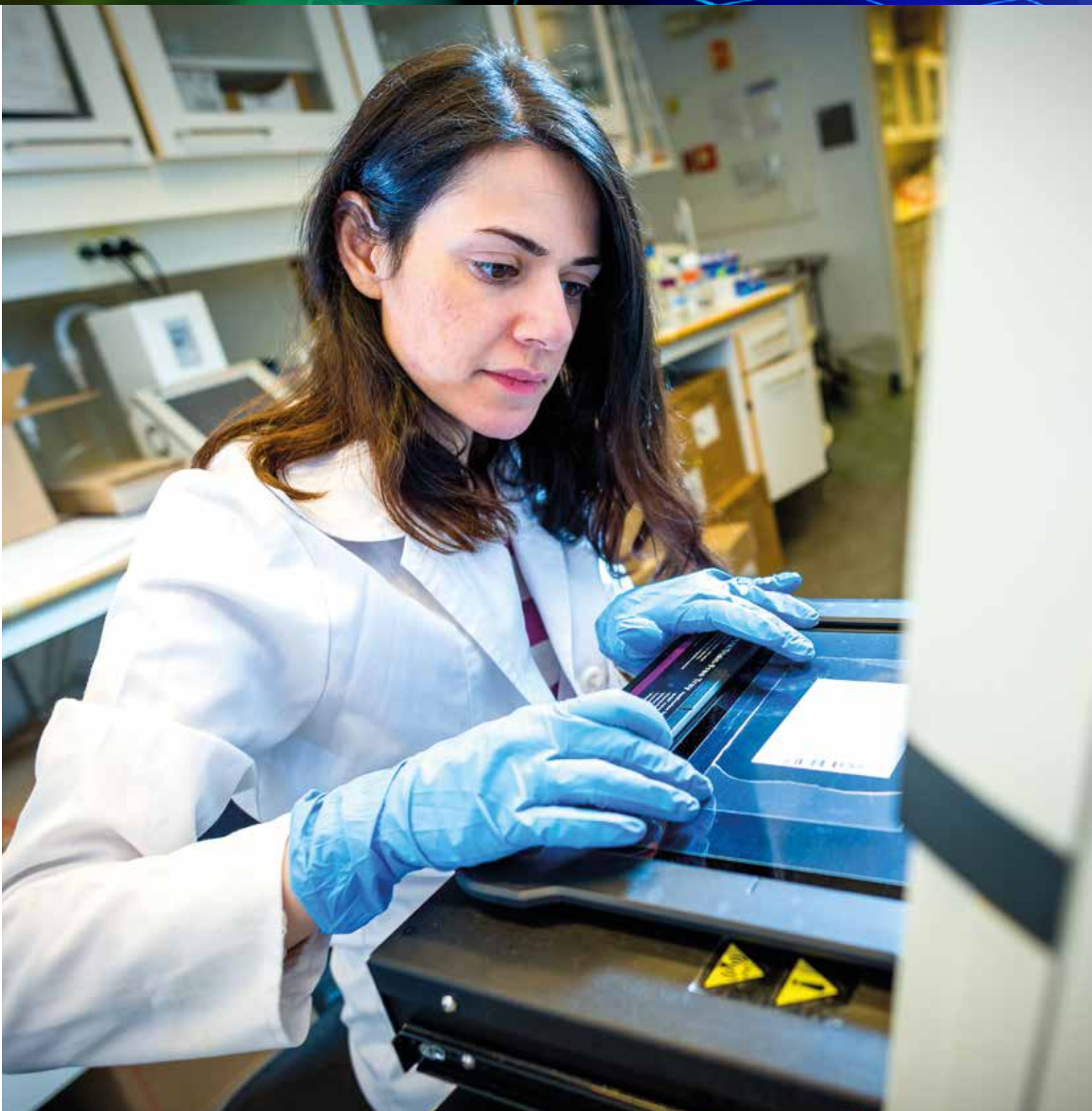
# ANNUAL REPORT 2015

## Institute for Surgical Research



# Annual Report 2015

## Institute for Surgical Research

Oslo University Hospital

UiO : University of Oslo

Photo: Øystein H. Horgmo, University of Oslo

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# Preface

It is a pleasure to present the Annual Report of Institute for Surgical Research for 2015. Institute for Surgical Research is a venue of research groups and scientists that focus on translational research in several of the major clinical areas of Oslo University Hospital. Strategic and hard work has positioned the Institute as a contemporary molecular medicine institute with a multidisciplinary staff of biochemists, molecular biologists, physiologists, physicists, medical doctors and clinical scientists. The institute currently has strong research programs in cardiovascular research, cancer research, transplantation research, and stem cell research. The institute also operates Core Facility for Large Animal Research together with Institute for Experimental Medical Research, a core facility supported by the South-Eastern Norway Regional Health Authority. The core facility provides infrastructure and staff to help scientists from hospitals in South-Eastern Norway and University of Oslo conduct large animal research.

This report provides an overview of the research groups at the Institute and their major research activities in 2015. Their strong achievements are first of all due to the dedicated and relentless efforts of both group leaders and staff. In addition, I would like to thank our administrative staff (Jorunn Hestenes Larsen, Signe Flood Kjeldsen, Magali Remy-Stockinger and Ismail Abdi), the staff at Core Facility for Large Animal Research (Roger Ødegård, Vivi Bull Stubberud, Sera Sebastian, and Aurora Pamplona), and Irene Stensrud Andersen (Housekeeping) for their relentless contribution to the smooth operation of the Institute.

Thanks to hard work and dedication the research groups of the Institute have maintained their forefront scientific position and have been well funded from the major external funding institutions for science in Norway (The Research Council of Norway, The Norwegian Council on Cardiovascular disease, The Cancer Society, The Research Fund of the South-Eastern Norway Health Authority).

*Institute for Surgical Research, March 2016,*

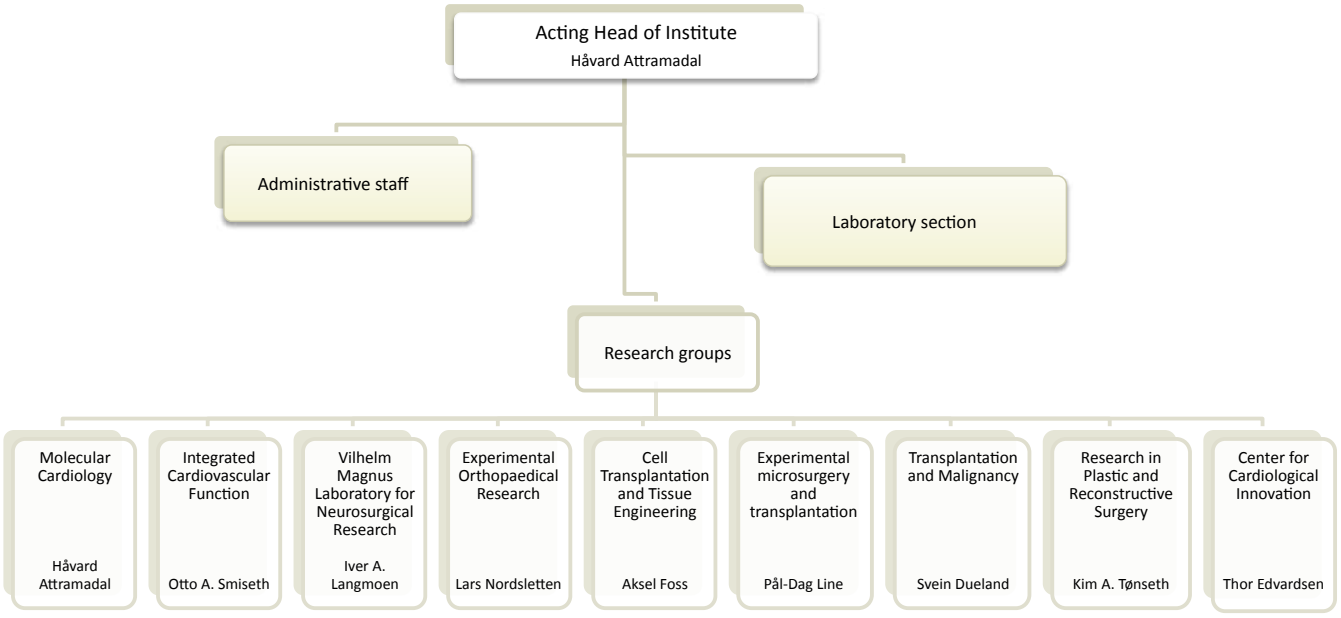
*Håvard Attramadal, Professor/Acting Head of Institute*


Photo: OUH

# Abbreviations

| | |
|---|---|
| AHUS | Akershus University Hospital |
| CAST | Cancer Stem Cell Innovation Center |
| CCI | Center for Cardiological Innovation |
| NCCD | The Norwegian Council on Cardiovascular Diseases |
| NRC | The Research Council of Norway |
| OC | Orthopaedic Centre, Oslo University Hospital |
| OUH | Oslo University Hospital |
| SENRHA | South-Eastern Norway Regional Health Authority |
| UiO | University of Oslo |

# Institute for Surgical Research



# Research Groups

Photo: Øystein H. Horgmo, University of Oslo

# Molecular Cardiology

## Leader

Håvard Attramadal, MD, PhD, Professor (OUH/UiO)

## Scientific staff

M. Shakil Ahmed, PhD, Senior Scientist (OUH)
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Jørgen A. Gravning, MD, PhD, Consultant (AHUS)
Ingvild Tronstad Moe, MD, PhD, (OUH)
Tuyet Anh Pham, MD, PhD-Student (SENRHA)
Ole Jørgen Kaasbøll, MD, PhD-Student (OUH)
Liv Kvistad Klemetsaune, MSc, PhD-Student (NCCD)
Sima Zolfaghari Golmakani, MSc, PhD-student (SENRHA)
Signe Flood Kjeldsen, Senior Engineer, (UiO)
Hemaseh Bideli, Engineer (UiO)
Umer Anayyat, MSc, Research Associate

Professor Håvard Attramadal

## Networks

- Center for Heart Failure Research (University of Oslo/ South-Eastern Norway Regional Research Network)
- UNIKARD (National Network – Treatment of Heart Failure through Exercise Training)

## Research Area

The overriding goal of our research group is to resolve the molecular mechanisms of increasing myocardial dysfunction in evolving heart failure. Heart failure is a clinical syndrome of advanced cardiac disease of diverse etiologies that may occur many years after the index event, e.g. myocardial infarction or onset of hypertension. Despite implementation of several new treatment modalities during the last 30 years, heart failure is still a progressive and ominous condition indicating that important pathogenic mechanisms remain unmodified by the most current treatment modalities. Indeed, the incidence and prevalence of heart failure in affluent societies are increasing due to demographics with rising proportion of elderly, an upsurge of patients with metabolic syndrome, as well as increased survival of myocardial infarction. Thus, there is an impetus for new and more effective pharmacological interventions.

Our research group is a multidisciplinary team of experts in gene technology, molecular and cellular biology, and in experimental animal research. The research efforts comprise studies of isolated cardiac myocytes and fibroblasts, integrated physiology in genetically engineered mice, large animal studies, as well as clinical investigations. Our research group is member of Center for Heart Failure Research, University of Oslo (www.heartfailure.no ), a thematic research initiative and focus area of research selected by the Faculty of Medicine. Center for Heart Failure Research is also a regional research network supported by the Helse Sør-Øst Regional Health Authority. Institute for Surgical Research provides infrastructure with state-of-the-art equipment for gene technology and generation of recombinant viral vectors, as well as high-resolution echocardiography and integrated physiologic assessment of cardiac function in both small and large animals.

## Major Aim

In evolving heart failure multiple compensatory mechanisms are triggered in order to maintain cardiac output, among which is activation of the sympathetic nervous system, the renin-angiotensin system, as well as a number of autocrine/ paracrine factors synthesized in myocardial tissue. Prolonged activation of these compensatory mechanisms eventually reflects in alterations of myocardial structure both at cellular and tissue levels, collectively called cardiac remodeling. The most important structural alterations are cardiac myocyte hypertrophy and myocardial fibrosis. Although cardiac remodeling may initially balance loss of contractile force, the continuum of these structural alterations often feeds into vicious circles leading to progression of cardiac dysfunction. Despite substantial new insights into the mechanisms of cardiac remodeling, many of the nodal points that orchestrate these structural alterations remain to be identified. Thus, an important focus of our research group is to unravel the autocrine/paracrine factors and signal transduction mechanisms that generate the dysfunctional signals leading to pathologic remodeling and progression of heart failure. Dysfunctional signaling mechanisms have been implicated in increased production of free oxygen radicals, mitochondrial dysfunction, and reduced tolerance to hypoxia and/or free oxygen radicals per se. Accordingly, another important aim of the group is to delineate the mechanisms that either increases or decreases the tolerance of cardiac myocytes to hypoxia or free oxygen radical injury, i.e. potential mediators of cardiac myocyte damage in evolving heart failure. Finally, we have also initiated studies aimed at resolving to what extent autocrine/ paracrine factors may stimulate resident cardiac stem cell-/ progenitor-mediated regeneration of myocardial tissue under chronic tissue injury. The purpose of these investigations is to

provide new knowledge on disease mechanisms enabling development of novel and more effective pharmacological interventions in acute coronary syndromes and heart failure.

## Current specific aims of the research group

1. Elucidate the function of the hydroxycarboxylic acid receptor GPR81/HCA1 and its cognate ligand (L-lactate) in the heart under physiologic conditions and evolving heart failure.

2. Resolve the role of G protein-coupled receptor kinases (GRK) in regulation of G protein-dependent versus G protein-independent (biased) signaling in the heart in health and disease, with particular focus on heart failure.

3. Uncover the function of myocardial autocrine/paracrine factors or cytokines in the pathophysiology of heart failure. Current focus is on delineating the functions of secreted matricellular CCN proteins, in particular CCN1/Cyr61, CCN2/CTGF (connective tissue growth factor), and CCN5/WISP-2 (Wnt-inducible secreted protein-2), as well as the TGF-ß superfamily cytokine GDF-15 in heart failure. The CCN proteins (CCN is an acronym for the first three mem bers of this gene family; Cyr61, CTGF, Nov) are non-structural proteins in the extracellular matrix (Figure 1) considered to interact with structural extracellular matrix proteins, other growth factors, or cognate receptors on the cell surface. Yet, the mechanisms of CCN protein actions are poorly understood. We have established eukaryotic expression systems for production and purification of recombinant human CCN1, CCN2, and CCN5 in order to investigate the signaling mechanisms and biologic functions of these proteins in cardiac myocytes and cardiac fibroblasts. In addition, we are working with genetically-engineered mice in order to unravel the functions of CCN proteins in the cardiovascular system in vivo in health and in evolving heart failure.

## Recent data reported from the group

*1) Unraveling the functions of GPR81, a novel G protein-coupled receptor for lactate, in the heart and its putative involvement in the pathophysiologic mechanisms of heart failure.*
We have recently demonstrated that cardiac myocytes express GPR81 and lactate inhibits synthesis of cAMP in cardiac myocytes via activation of GPR81. We have also shown that cardiac myocyte GPR81 is upregulated in heart failure in proportion to the functional derangement. Currently, we are investigating the role of GPR81 in heart failure using genetically-engineered mice.

*2) Dissecting the function of cardiac G protein-coupled receptor kinases (GRKs) in health and disease.*
Previous studies from our laboratory have revealed that GRK2 and GRK3 in cardiac myocytes display striking specificity at G protein-coupled receptors controlling different aspects of cardiac function. Overall, our data have uncovered the novel findings that GRK3 has substantially higher potency and efficacy than GRK2 at endogenous endothelin receptors (ET-R) and $\alpha_1$-adrenergic receptors ($\alpha_1$-AR). This did not seem to be the

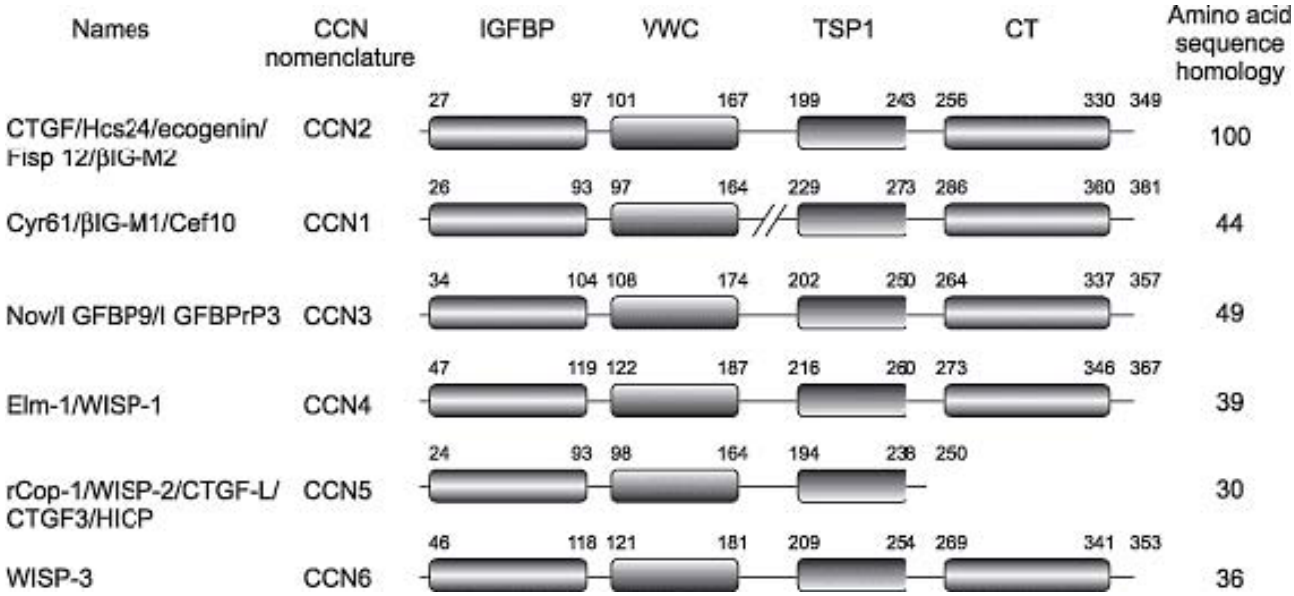


***Figure 1.*** *Schematic demonstrating the modular structure of the CCN family proteins (CCN1-6). IGFBP; insulin-like growth factor binding protein homology domain, VWC; von Willebrand factor homology domain, TSP1; thrombospondin-1 homology domain; CT; cysteine knot homology domain.*

case for the ß1-adrenergic receptor as GRK3 potency at this receptor appeared much weaker than for the ET-R, and was equipotent with GRK2. Thus, GRK3 emerges as a primary regulator of ET-R and of $\alpha_1$- AR-signaling in cardiac myocytes. The distinct receptor specificity of GRK3 may have important implications in cardiac function. These functional differences are currently subject of investigations in transgenic and gene-targeted mice.

Another ongoing effort is aimed at resolving the role of GRK5 in regulation of tolerance to ischemia/reperfusion injury as well as in the pathophysiology of heart failure. In a report from our laboratory published in 2013 (Gravning J et al. Mol Pharmacol 84:372-383,2013) we disclosed the novel findings that myocardial GRK5 is upregulated in transgenic mice with cardiac-restricted overexpression of CCN2/CTGF, as well as in cardiac myocytes pretreated with recombinant human CCN2, causing reduced sensitivity of cardiac ß-adrenergic receptors to endogenous agonists. Furthermore, increased GRK5 in the heart initiates G protein-independent signaling by recruitment of ß-arrestin to the receptor allowing ß-arrestin to act as a scaffolding protein for signaling complexes at the plasma membrane such as the mitogen-activated protein kinase ERK1/2. These findings have been recapitulated in cardiac myocytes pretreated with recombinant human CCN2/CTGF. Yet, the signaling pathway(s) implicated in CTGF-induced induction of GRK5 expression in cardiac myocytes is yet to be characterized. Furthermore, the relative contribution of GRK5 to the cardioprotective actions afforded by CCN2/CTGF remains to be resolved.

*3) Role of CCN proteins in regulation of tolerance towards ischemia-reperfusion injury and in the pathophysiology of heart failure.*

Myocardial CCN1, CCN2 and CCN5 are highly expressed in fetal life and apparently plays crucial role in cardiac development. However, myocardial expression of these proteins is repressed in the postnatal heart under physiologic conditions. Interestingly, myocardial expression of CCN1, CCN2 and CCN5 appears to be reactivated or induced during evolving heart failure. Previous findings from our laboratory demonstrate that induction of myocardial CCN2, the most extensively studied CCN protein, appears to be a general response to evolving heart failure of diverse etiologies. Currently less knowledge is available regarding regulation of myocardial CCN1 and CCN5 in evolving heart failure.

Increased tissue expression or plasma levels of CCN2 is often associated with diseases in which fibrosis is an important morphologic characteristic. However, to what extent CCN2/ CTGF actually elicits fibrosis is yet to be demonstrated. Indeed, the physiologic and/or pathophysiologic functions of CCN2 in myocardial tissue have not yet been resolved. Thus, a major focus of our research effort is to elucidate the function of CCN2 in the heart. Does CCN2 exert salutary actions in heart failure, or does CCN2 contribute to progression of heart failure? Does CCN2 cause myocardial fibrosis? In order to elucidate to the physiologic actions of CCN2 in the heart and to investigate how the actions of CCN2 may contribute in the pathophysiology of heart failure, we are currently investigating various genetically engineered models with constitutive or conditional overexpression of CCN2 in the heart. Transgenic mice with cardiac-restricted, constitutive overexpression of CCN2/CTGF displayed marginal increase of myocardial collagen contents despite 70-fold overexpression of CCN2/CTGF (Ahmed, MS et al. Am J Physiol Heart Circ Physiol. 300: H1291-1302, 2011). This finding appears to be consistent with data from transgenic overexpression of CCN2/CTGF in other tissues or organs. Thus, the interpretation of the available data both from our and other research groups is that additional factors are required for CCN2 to induce fibrosis. A surprising, novel finding in our laboratory was that CCN2 exerts striking cardioprotective actions, increasing tolerance towards ischemia-reperfusion injury in Langendorff-perfused hearts ex vivo as well as in vivo in mice subjected to transient ligation of the left anterior descending coronary artery. A recent report from our laboratory also provides evidence that cardiac myocytes are direct targets of recombinant human CCN2 (rec-hCCN2), and that rec-hCCN2 also increases the tolerance of cardiac myocytes to hypoxia/reoxygenation-induced injury and oxidative stress (Moe, IT, et al. J Cell Commun Signal. 7:31-47,2013). However, a cognate receptor for CCN2 or any of the other CCN proteins has not yet been properly characterized. Despite several reported interactions between CCN proteins and extracellular matrix-associated proteins, data from our laboratory indicate that CCN2 may also act directly on cells by binding to receptors at the surface of the plasma membrane. Major efforts of our laboratory are being focused on identification and characterization of a cognate receptor for CCN2. To facilitate studies on the mechanisms of CCN protein actions in cells, we are currently also broadening our scope by concurrent investigations of the three major CCN proteins, CCN1, CCN2 and CCN5. We have established eukaryotic expression systems for large scale production and purification of these recombinant proteins in order to study their signaling mechanisms and actions in primary cardiac cells in vitro. Furthermore, genetically engineered mice with targeted deletion of these proteins are being studied in order to disclose the role of these proteins in the pathophysiology of heart failure.

We have previously also reported that CCN2 enhances scar healing after myocardial infarction (Gravning, J. et al PlosOne 2012;7(12):e52120). However, the mechanisms whereby CCN2 enhances scar healing after myocardial infarction (MI) is still obscure and a matter of investigation. The article also reported data from patients admitted for acute ST-elevation myocardial infarction among which plasma CCN2 levels recorded at time points after MI segregated in two cohorts, one in which plasma CCN2 levels were rising after MI and the other in which plasma CCN2 levels remained unchanged or lower. Patients that had elevated plasma CCN2 levels after MI displayed

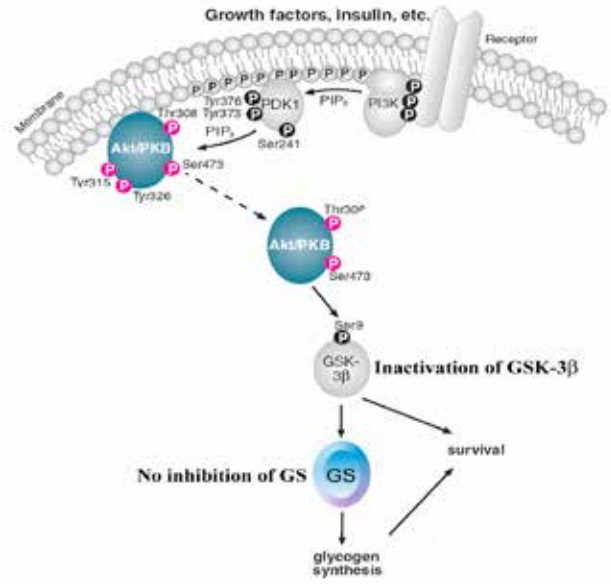


***Figure 2.*** *Schematic illustrating the intracellular signaling pathways of CTGF/CCN2 in cardiac myocytes. A cognate receptor for CTGF upstream of PI3 kinase has not yet been characterized.*

improved healing of the infarction and enhanced myocardial function one year after the event (Gravning, J. et al PlosOne 2012;7(12):e52120). Although the patient cohorts were relatively small, these findings are translational evidence supporting a cardioprotective function of CCN2.

## Collaborators

- Prof. Walter J. Koch, Dept. of Pharmacology and Center for Translational Medicine, Temple University School of Medicine, Philadelphia, PA, USA.
- Prof. Erhe Gao, Dept. of Pharmacology and Center for Translational Medicine, Temple University School of Medicine, Philadelphia, PA, USA.
- Professor Jon Storm-Mathisen, Institute of Basic Medical Sciences, Dept of Anatomy, University of Oslo.
- Professor Linda Hildegaard Bergersen, Institute of Basic Medical Sciences, Dept of Anatomy, University of Oslo.
- Professor Øivind Ellingsen, Department of Circulation and Medical Imaging Norwegian University of Science and Technology, Trondheim, Norway.
- Prof. Terje S. Larsen, Dept. of Medical Physiology, University of Tromsø, Norway.
- Assoc. prof. Ellen Aasum, Dept. of Medical Physiology, University of Tromsø, Norway.
- Prof. Pål Aukrust, MD, PhD, Research Inst. for Internal Medicine, Oslo University Hospital.
- Dr. Arne Yndestad, PhD, Research Inst. for Internal Medicine, Oslo University Hospital.
- Prof. Otto A. Smiseth, Dept. of Cardiology/Inst. for Surgical Research, Oslo University Hospital.
- Prof. Thor Edvardsen, Dept. of Cardiology/Inst. for Surgical Research, Oslo University Hospital
- Prof. Ivar Sjaastad, Inst. for Experimental Medical Research, Oslo University Hospital
- Prof. Geir Christensen, Inst. for Experimental Medical Research, Oslo University Hospital.
- Prof. Finn Olav Levy, Dept. of Pharmacology, University of Oslo.

Photo: Øystein H. Horgmo, UiO

# Integrated Cardiovascular Function

## Leader

Otto A. Smiseth, MD, PhD, Professor (OUH/UiO)

## Deputy leader

Thor Edvardsen, MD, PhD, Professor (OUH/UiO)

## Scientific staff

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Jørg Saberniak, MD, PhD-student (CCI/OUH)
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John Aalen MD, PhD-student (NCCD)
Camilla K. Larsen, PhD-student (SENRHA)
Ola Gjesdal, MD, PhD, Cardiologist (OUH)
Aurora Pamplona, Operating Theatre Nurse (OUH)
Thomas Muri Stokke, MD-student, UiO

## General objectives

The Integrated Cardiovascular Function Group studies cardiac mechanics in experimental models and in patients. The general objective is to gain new insights into mechanisms of cardiovascular disease and to develop new imaging modalities which quantify disease processes and cardiac function. The group participates in the Center for Cardiological Innovation (CCI) which focuses on improving diagnostic methods for patients with heart failure and patients at risk of sudden cardiac death. The group also participates in the KG Jebsen Cardiac Research Center which focuses mainly on left ventricular dyssynchrony and diastolic heart failure.

## Current research is focused on the following:

- How to diagnose heart failure with normal LV ejection fraction
- Pathophysiology of ventricular dyssynchrony
- How to identify responders to cardiac resynchronization therapy
- Novel methods for imaging of myocardial function
- Work efficiency as diagnostic tool
- Mathematical modeling of cardiac function

Professor Otto A. Smiseth

## Collaborators

- Prof. Joao A.C. Lima, Johns Hopkins University, Baltimore, Maryland, USA
- Prof. Frits Prinzen, Maastricht University, Maastricht, The Netherlands
- Prof. Sherif Nagueh, Methodist DeBakey Heart and Vascular Center, Houston, Texas
- Dr. Martin Penicka, OLV Hospital Aalst, Belgium
- Prof. Jens-Uwe Voigt, Katholieke Universiteit Leuven, Belgium.
- Prof. Hans Torp, NTNU, Trondheim
- Prof. Håvard Attramadal, OUH, Institute for Surgical Research
- Prof. Ivar Sjaastad, OUH, Institute for Experimental Medical Research
- Consultant Harald Brunvand, MD, PhD, Sørlandet hospital, Arendal.

Members from our group published 55 journal articles and held 38 invited lectures at international meetings in 2015. Over the years, our group has pioneered experimental and clinical testing of new echocardiographic imaging technology. The most recent innovation is a non-invasive clinical method to estimate the LV pressure curve and its application to assess regional cardiac work.

A growing number, currently about half of heart failure patients, falls into the category of so called heart failure with preserved ejection fraction, indicating that their main problem is in the diastolic function of the heart. Our group has world leading expertise in the evaluation of diastolic function. Figure 2 is from a review article showing some of the basics parameters that can be used in the evaluation of diastolic function by cardiac imaging.

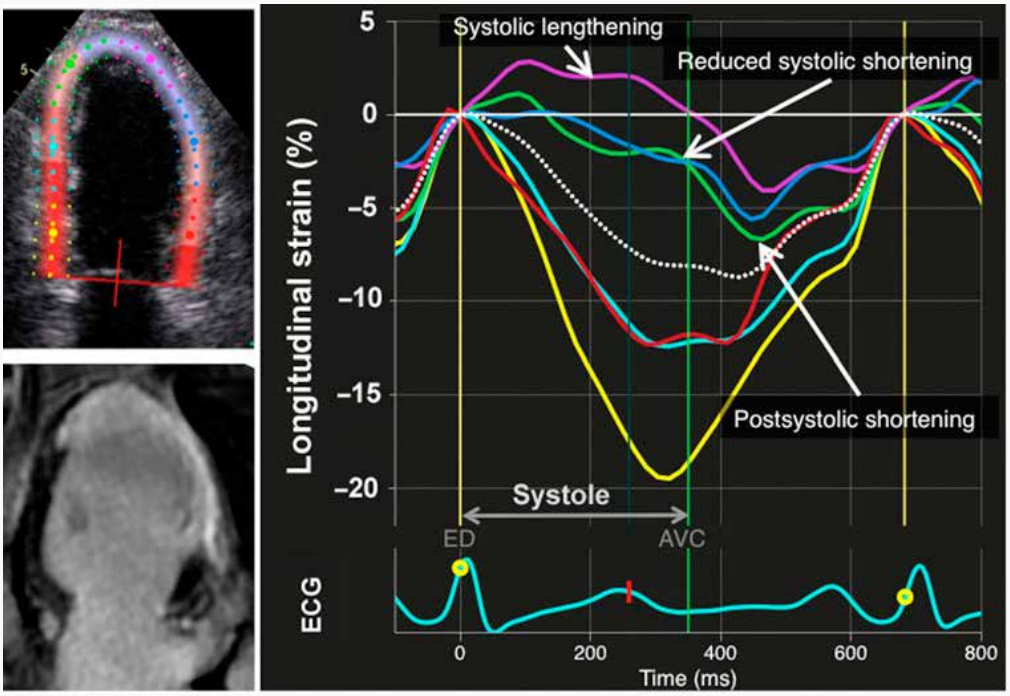


***Figure 1.*** *Strain imaging in myocardial infarction. Color-coded regions are superimposed on the ultrasound image in the top left panel. The corresponding strain traces are shown on the right where purple trace is from the center of the infarct region, while the dark blue and green segments are also ischaemic as can be seen from the white scarred myocardium in the late enhancement MRI image in the bottom left panel. The ischaemic segments shorten less than the non-ischaemic segments. Note that strain is percent change of segment length; hence the more negative number means greater shortening. (From OA Smiseth et al. Eur Heart J 2015.)*

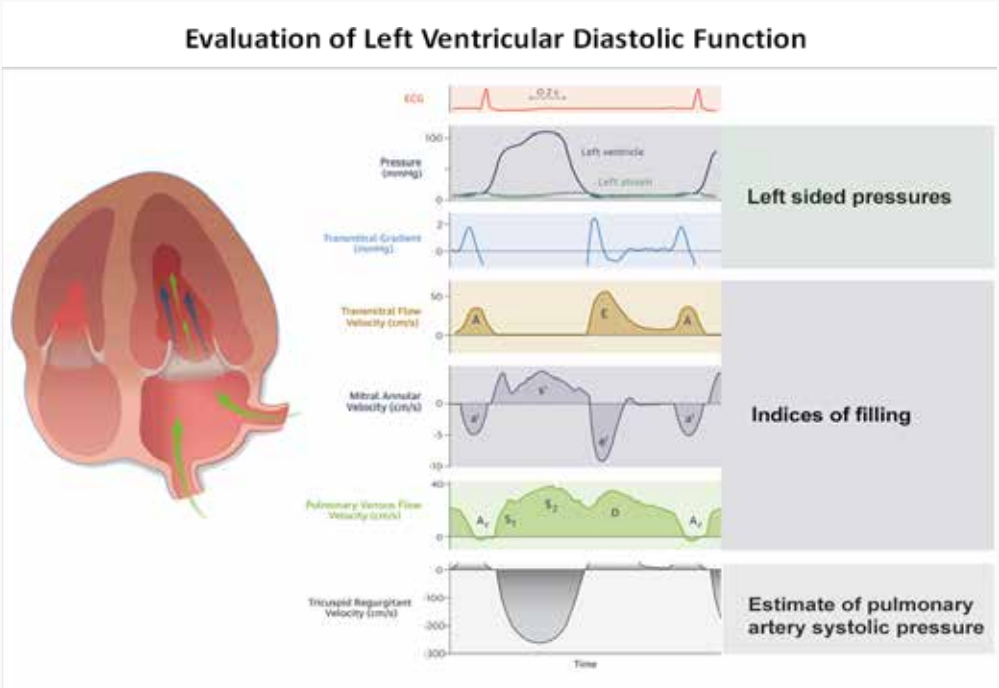


***Figure 2.*** *Schematic drawing of diastolic left ventricular filling. Diastolic left ventricular (LV) filling is shown with simultaneous recordings of left atrial (LA) and LV pressures, the diastolic transmitral pressure gradient, pulmonary venous, transmitral, and transtricuspid flow velocity, and mitral annular velocity. Flow velocity and mitral annular velocity data, together with LA size and systolic pulmonary pressure, are used in echocardiography to infer diastolic LV pressures and hence diastolic LV function. (Modified from Flachskampf/Smiseth et al., J Am Coll Cardiol Img 2015)*

# Center for Cardiological Innovation

## Center Director and Management

Thor Edvardsen, MD, PhD, Professor,
Center Director SFI-CCI (OUH / UiO)
Kristina Hermann Haugaa, MD, PhD, Associate Professor,
Center Director of Cardiology Research (OUH / UiO)
Piritta Nyberg, Administrative Coordinator (OUH)

## Scientific Staff during 2015, Oslo University Hospital

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Svend Aakhus, MD, PhD, Professor, Head of Section for Echocardiography
Morten Flattum, MS, Lead Engineer at Department of Cardiology
Hans Henrik Odland, MD, PhD, Consultant Cardiologist
Espen Remme, Dr. Ing., Senior Scientist
Helge Skulstad, MD, PhD, Consultant Cardiologist
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Einar Hopp, MD,PhD, Consultant Radiologist
Ole-Gunnar Anfinsen, MD, PhD, Consultant Cardiologist
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Jan Erik Otterstad, MD, PhD, Consultant Cardiologist
Finn Hegbom, MD, PhD, Consultant Cardiologist
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Margareth Ribe, Research Nurse

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Jørg Saberniak, MD, PhD student
Stian Ross, MD, PhD student
Lars Gunnar Klæboe, MD, PhD student
Lars Dejgaard, MD, PhD student
Øyvind Haugen Lie, MD, PhD student
Alessia Quattrone, MD, PhD student
Espen Bøe, MD, PhD student
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Vidar Ruddox, MD, PhD student, UiO
Sigve Karlsen, MD, PhD student, UiO
Thomas Dahlslett, MD, PhD student, UiO
Thomas Muri Stokke, MD student, UiO

## Aim of the Center

The center was established to enable the creation of the next generation of ultrasound technology, combining expertise in industrial development, clinical science, and advanced mathematical techniques. The main objectives of the center are focused on developing new tools to help the triage of patients suffering from heart failure (HF) or at risk of sudden cardiac death (SCD). Two OUH patents regarding Mechanical Dispersion and Regional Cardiac Work Estimation have already been licensed to GEVU. Partners contributing to the Center are; Oslo University Hospital, Simula Research Laboratory, the University of Oslo, GE Vingmed Ultrasound AS, Kalkulo AS, CardioSolv LLC and Medtronic Bakken Research Center B.V.

## Ongoing projects:

### Prevalence and cardiac penetrance of Lamin A/C mutation

*Hasselberg NE, Haland TF, Saberniak J, Berge KE, Edvardsen T, Haugaa KH*

Lamin A/C gene (LMNA) mutations cause familial dilated cardiomyopathy with a more severe phenotype than dilated cardiomyopathy of other origin.
In Norway the LMNA mutation positive patients are diagnosed through genetic testing performed at the Department of Medical Genetics and patients receive regular clinical follow-up at the Department of Cardiology at Oslo University Hospital, Rikshospitalet.

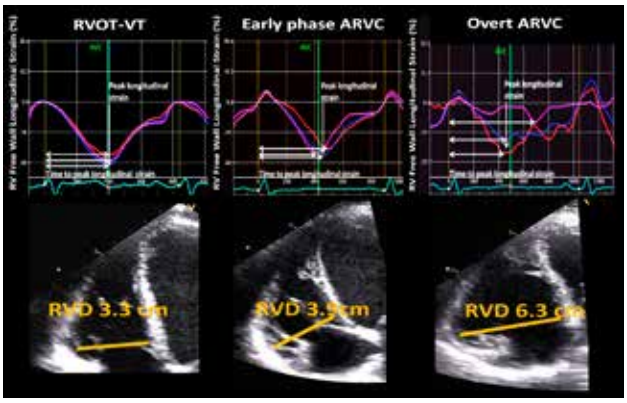
In this descriptive study the authors have collected genetic data from the start of genetic testing of cardiomyopathies in Norway in 2003. Furthermore, the authors have documented the phenotype of the LMNA mutation positive subjects.
In summary, LMNA mutation was a rare cause of familial dilated cardiomyopathy in Norway. Nevertheless, the cardiac phenotype was severe with a high incidence of life-threatening arrhythmias and heart transplantations and with poor prognosis. Importantly, the results uncover a high cardiac penetrance among LMNA mutation positive family members without symptoms. The study highlights importance of early family screening and cardiologic follow-up in LMNA mutation positive subjects.

This study was awarded Best Poster and presented by first author phd-student Nina Eide Hasselberg, MD, in the session "Genetic aspects of arrhythmias" at the ESC 2015 congress in London. Nina also presented this work and won the Best Poster Award in her moderated poster session entitled "Diagnostic and therapeutical strategies for cardiac disease" at the 13th Annual Center for Heart Failure Research Symposium in Oslo.


*Prizewinner for best poster at ESC 2015, Nina Hassselberg (first author) and associate professor Kristina H. Haugaa (last author)*

**Comparison of patients with early phase arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract ventricular tachycardia**
*Saberniak J, Leren IS, Haland TF, Beitnes JO, Hopp E, Borgquist R, Edvardsen T, Haugaa KH*

Right ventricular outflow tract ventricular tachycardia (RVOT-VT) is supposed to be a relatively benign condition, while arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy predisposing to ventricular arrhythmias, heart failure and sudden cardiac death and therefore a far from a benign condition. Both entities may become symptomatic with the same type of arrhythmias from the outflow tract of the RV. Discrimination between overt ARVC and RVOT-VT may be obvious, however, comparison between early phase ARVC and RVOT-VT can be challenging and correct diagnosis is crucial. Totally, we included 165 patients: 44 consecutive RVOT-VT and 121 ARVC patients. Of the ARVC patients, 77 had overt ARVC and 44 had early phase ARVC disease. We investigated if ECG and cardiac imaging can help to discriminate early phase ARVC from RVOT-VT patients.
We showed that patients with early phase ARVC had structural abnormalities with lower RV ejection fraction, increased RV basal diameter and pronounced RV mechanical dispersion in addition to lower frequency of PVC by Holter compared to RVOT-VT patients. These parameters may help correct diagnosis in patients with unclear phenotypes




*Upper panels: Echocardiographic longitudinal strain curves from RV free wall. Lower panels: Measures of RV basal diameters*

**Echocardiography and Signal Averaged ECGs Help to Predict Ventricular Arrhythmias in Subjects with Early ARVC**
*Leren IS, Saberniak J, Haland TF, Edvardsen T, Haugaa KH*

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disease with an increased risk of life threatening arrhythmias and sudden cardiac death. Ventricular arrhythmias (VAs) in ARVC are difficult to predict, particularly in early phase of disease. The aim of the study was to investigate early markers of VAs and improve risk stratification. We included 163 ARVC subjects (75 with early disease) and performed ARVC diagnostics by 2010 Task Force Criteria, in addition to new echocardiographic parameters. In early ARVC, signal averaged ECG and two novel echocardiographic parameters (RV diameter and RV mechanical dispersion) were markers of arrhythmias. A combination of new echocardiographic and electrical parameters was superior to electrical parameters alone in predicting VAs in early ARVC.

**Overweight may aggravate early disease in hypertrophic cardiomyopathy (HCM) mutation positive family members**
*Dejgaard LA, Haland TF, Lie OH, Massey R, Edvardsen T, Haugaa KH*

Overweight has been associated with increased left ventricular (LV) mass and progression of heart failure in hypertrophic cardiomyopathy (HCM). HCM is caused by inheritable genetic mutations in 60- 70% of cases.This study aims to explore the association between overweight and cardiac changes in HCM genotype positive (G+), phenotype negative (P-) family members. 134 familymembers were identified by cascade genetic screening and evaluated with echocardiography. We found that there was a significant correlation between overweight and LV mass and overweight and left atrial diameter. LV diastolic parameters were altered in overweight subjects. Our results suggest that overweight status might be unfavourable for HCM G+P- subjects.

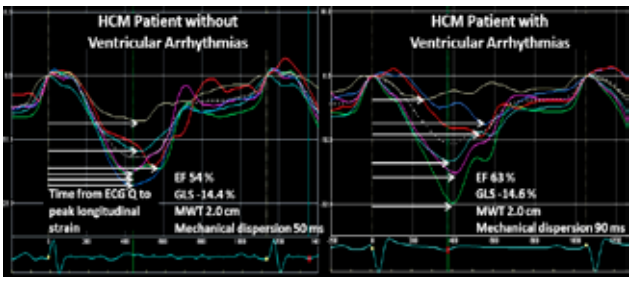
**Influence of exercise on disease progression in hypertrophic cardiomyopathy and genotype positive family members.**
*Dejgaard LA, Haland TF, Ribe M, Lie OH, Leren IS, Grøteig T, Berge KE, Edvardsen T, Haugaa KH*

Physical exercise is associated with left ventricular hypertrophy (LVH) and other cardiac changes in normal subjects, but the impact on hypertrophic cardiomyopathy (HCM) subjects or their mutation positive (G+) family members is not known. We aim to investigate the impact of physical exercise on cardiac changes and disease status in HCM subjects and their G+ family members. We hypothesize that exercise has a negative impact on disease progression. A total of 200 subjects will be included in this study. All will undergo echocardiography and a detailed history of physical exercise will be obtained.

**Strain echocardiography is related to Fibrosis and Ventricular Arrhythmias in Hypertrophic Cardiomyopathy**
*Haland TF, Almaas VM, Hasselberg NE, Saberniak J, . Leren IS, Hopp E, Edvardse T, Haugaa KH*

Hypertrophic cardiomyopathy patients (HCM) are at risk of ventricular arrhythmias. We aimed to explore if systolic function by strain echocardiography is related to ventricular arrhythmias (VAs) and to the extent of fibrosis by cardiac magnetic resonance imaging.
We included 150 HCM patients and 50 healthy individuals. We found that global longitudinal strain, pronounced mechanical dispersion and fibrosis were markers of VAs in HCM patients (Figure 1). Mechanical dispersion was a strong independent predictor of VAs and related to the extent of fibrosis. Strain echocardiography may improve risk stratification of VAs in HCM.

**Cardiac Volumes and Systolic Function in Hypertrophic Cardiomyopathy**



*Mechanical dispersion by strain echocardiography in two patients with hypertrophic cardiomyopathy.*

*Haland TF, Hasselberg NE, Almaas VM, Saberniak J, Leren IS, Berge KE, Haugaa KH, Edvardsen T*

Ejection fraction (EF) is typically normal in patients with hypertrophic cardiomyopathy (HCM). We explored how systolic function is related to cardiac volumes in HCM patients with hypertrophy (HCMP+) and mutation positive patients without hypertrophy (HCMG+P-). We included 180 HCMP+, 100 HCMG+P- patients and 80 healthy. By echocardiography, end-diastolic (EDV) and end-systolic (ESV) volumes and EF were calculated by Simpson's formula and indexed by body surface area. Left ventricular (LV) global longitudinal strain (GLS) was calculated as the average peak longitudinal strain. Cardiac volumes were smaller in the HCMP+ patients maintaining a normal EF despite reduced systolic longitudinal function by strain echocardiography. HCMG+P- patients had
reduced cardiac volumes and worse GLS compared to healthy individuals, indicating a continuum of volumetric and systolic changes from the healthy to HCMG+P- and HCMP+ patients.

**Echocardiographic comparison between Left Ventricular Non-Compaction and Hypertrophic Cardiomyopathy**
*Haland TF, Saberniak J, Leren IS, Edvardsen T, Haugaa KH*

Modern imaging technology has improved detection of left ventricle non-compaction cardiomyopathy (LVNC). Hypertrophic cardiomyopathy (HCM) shares genetic and morphological features with LVNC, while prognosis and treatment strategies differ. We aimed to compare echocardiographic parameters in LVNC and HCM. We studied 25 patients with LVNC according to Jenni criteria, 50 with HCM and 50 healthy individuals. Increased number of trabeculations, thinner maximal wall thickness and lower ejection fraction were echocardiographic characteristics of LVNC disease. The LVNC patients showed worse apical strain compared to HCM, while basal strain did not differ. Left ventricular function by strain increased from base to apex in HCM ($p<0.001$) and in healthy controls ($p<0.001$) as opposed to a more homogeneously decreased function in LVNC ($p=0.26$) (Figure). These characteristics may help may help discrimination between these two cardiomyopathies in overlapping phenotypes.

**Prediction of Clinical Outcome in Patients with Aortic Steno-**

**sis by new echocardiographic parameteres**
*Klaeboe LG, Haland TF, Leren IS, Haugaa KH, Edvardsen T*

Aortic stenosis is a prevalent valvular heart disease and a major health concern. There are strong recommendations for aortic valve replacement when aortic stenosis causes symptoms or myocardial impairment. Clinical assessment of these patients can however be complicated. There is evidence for that the aortic stenosis-related maladaptive myocardial changes that result in fibrosis and ultimately impaired left ventricular function may persist and affect clinical outcome after aortic valve replacement. These observations indicate that current echocardiographic assessment of left ventricular function is insufficient and that new robust parameters of subtle myocardial impairment may improve risk stratification and predict outcome in patients with aortic stenosis. In this study we explore the prognostic value of left ventricular mechanical dispersion by strain echocardiography.

**Strain Echocardiographic Assessment of Left Atrial Function Predicts Recurrence of Atrial Fibrillation**
*Sarvari SI, Haugaa KH, Stokke TM, Ansari HZ, Leren IS, Hegbom F, Smiseth OA, Edvardsen T*

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with an estimated prevalence of 0.4% to 1% in the general population, increasing with age to 9% in those above 80 years. We evaluated if a dispersed left atrial (LA) contraction pattern was related to AF in patients with normal left ventricular (LV) function, and normal or mildly enlarged LA.
We included 61 patients with paroxysmal (PAF). Of these, 30 had not while 31 had recurrence of AF after radiofrequency ablation (RFA). Twenty healthy individuals were included for comparison. Echocardiography was performed in patients in sinus rhythm the day before RFA. LA function by strain was reduced in both patients with and without recurrent AF after RFA compared to controls (Figure ). We found a dispersed LA contraction pattern and reduced LA deformation in patients with paroxysmal AF and normal or only mildly enlarged LA, and apparently normal LV structure and function when comparing to healthy individuals. LA dispersion before RFA treatment was most pronounced in AF patients who experienced recurrence of AF after RFA. We propose that LA dispersion by strain echocardiography may be useful as a marker of paroxysmal AF and as a predictor of AF recurrence after RFA.

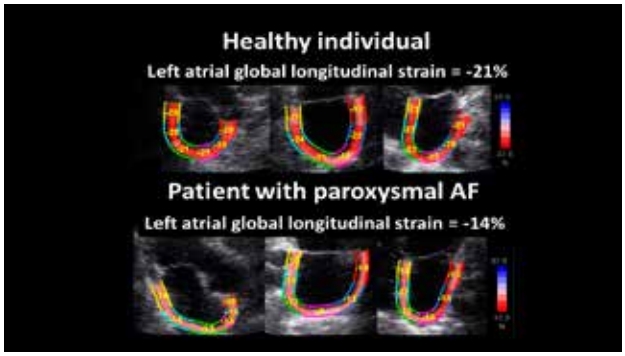



*Figure 1. LA strain curves from a healthy individual and a patient with paroxysmal AF. LA function by strain was reduced in AF patients compared to controls*

## Dissemination activities:

Members of the CCI have published 71 articles in peer reviewed journals during the past year.
For the complete list of publications, other news and information regarding the CCI, visit the Center's website www.heart-sfi.no.
The CCI had totally 38 media performances. Center members from Oslo University Hospital have participated in approximately 136 dissemination activities during 2015, including 64 abstracts. Members have presented posters, given presentations, and had chair and judge duties in several renowned scientific conferences around the world.
PhD student Ida Skrinde Leren was recognized with a high scoring abstract at the EuroEcho Imaging Congress in December. PhD students Jørg Saberniak and Ida Skrinde Leren won each the best article award at the Oslo University Hospital, respectively in april and desember 2015.

*Jørg Saberniak won the best article award in april 2015 together with associated professor Kristina H. Haugaa (last author).*

*Ida Skrinde Leren (in the middle) won the best article award in December 2015 together with associated professor Kristina H. Haugaa (last author) and professor Thor Edvardsen*

# Vilhelm Magnus Laboratory for Neurosurgical Research

## Leader

Iver A. Langmoen, MD, PhD, Professor (OUH/ UiO)

## Management staff

Cecilie Jonsgar Sandberg, MSc, PhD, Lab manager/HR/Daily activities (OUH)
Einar O. Vik-Mo, MD, PhD, Deputy Leader (OUH)

## Scientific Staff

Jinan Behnan, PhD-student (SENRHA)
Artem Fayzullin, MD, PhD-student (NRC)
Zanina Grieg, MSc, Research Technician (OUH)
Kirsten Strømme Kierulf-Vieira, MD, PhD-student (UiO)
Birthe Mikkelsen, BSc, Research Technician (OUH)
Awais Mughal, MD, PhD-student (OUH)
Wayne Murrell, PhD, Senior Scientist (OUH)
Emily Palmero, BSc, Research Technician (OUH)
Erlend Skaga, MD, PhD-student (Norwegian Cancer Society)
Håvard Skjellegrind, MD, PhD-student
Biljana Stangeland, PhD, Scientist (CAST, NRC)

## Network Partnerships

- Cancer Stem Cell Innovation Center (CAST)
- Norwegian Stem Cell Center

## Research area

The Vilhelm Magnus Laboratory (VML) is the translational research group for neurosurgery at Oslo University Hospital. We explore the biology underlying neurosurgical conditions and our research efforts encompass both normal and cancer cells from the human brain. The studies on brain cancer are focused on glioblastoma which is both the most frequent and most deadly brain cancer (median survival in unselected series ≈10 months).

## Aims

- To characterize human brain stem cells and develop cell types for neurodegenerative disorders
- To characterize glioblastoma stem cells
- To develop therapeutic strategies against glioma stem cell

## Ongoing Projects

**Characterization of adult human brain stem cells**

A major obstacle in studying adult human neural stem cells has been the very limited amount of cells available. In keeping with work we have published earlier on new protocols to improve harvesting and cell culturing methods (Westerlund U et al, Exp Cell Res 2003; Moe MC et al, Brain 2005; Westerlund et al, Neurosurgery 2005; Varghese M et al, Stem Cells Dev 2009; Vik-Mo EO et al, Exp Cell Res 2011; Murrell W et al, PlosOne 2013) we have optimized methods to further increase cellular yield (Behnan and Vik-Mo, in progr). We have continued the work on identifying genes, pathways and proteins that are differentially regulated in adult human neural stem cells compared to adult brain tissue (Sandberg et al, PlosOne 2014).

Professor Iver A. Langmoen

**Targeting brain cancer stem cells in glioblastoma**

It is thought that stem cells in glioblastoma are critically important in resistance to therapy. Therefore, there is a strong rationale to target these cells in order to develop new molecular therapies. For more than a decade an important aim of the lab has been a systematic comparison of adult human neural stem cells and glioblastoma stem cells (GSC). We have identified differentially expressed cell properties (Varghese M et al, Neurosurgery 2008, Vik-Mo EO et al, Neuro Oncol 2010 ), and genes and signaling proteins that may have potential as new and specific targets for treatment of glioblastoma (Sandberg C et al, Exp Cell Res 2013).
Transcriptional analysis of GSCs identified the Wnt pathway as a promising target in glioblastoma cancer stem cells (Sandberg C et al, Exp Cell Res 2013). We have found that inhibition of Wnt signaling with recombinant SFRP1 protein down-regulated nuclear β-catenin and decreased in vitro proliferation and sphere formation in a dose-dependent manner. Furthermore, expressional and functional analysis of SFRP1-treated GSCs revealed that SFRP1 halts cell cycling and induces apoptosis. These observations demonstrate that Wnt signaling is dysregulated in GSCs, and that inhibition of the Wnt pathway could serve as a therapeutic strategy in the treatment of GBM (Kierulf-Vieira KS et al, Expr Cell Res 2016).

Based on our micro-array study (Sandberg C et al, Exp Cell Res 2013) we selected 20 genes that were consistently expressed in GSC cultures and consistently not expressed in NSC cultures. Through combined analysis of gene and protein expression in GSCs, we identified nine genes for further investigations

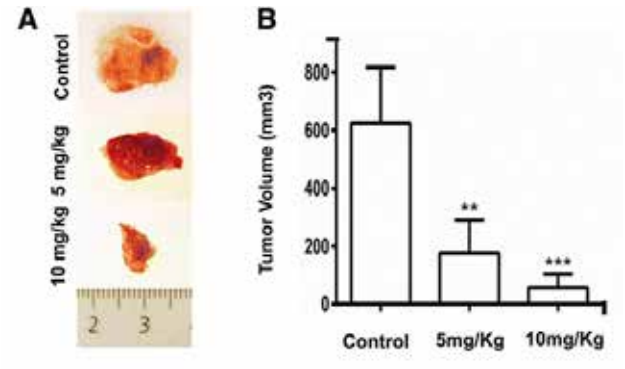



***Fig. 1 PBK:***
*Anti-tumor effects in tumor xenografts upon inhibition of PBK through administration of HI-TOPK-032 (A) The tumors were extracted after 4 weeks of treatment and a representative tumor from each group is shown. (B) Mean tumor volume was calculated. Error bars= SD.*

as targets for treatment of GBM. The genes were highly co-expressed in all GBM subtypes and part of the same protein-protein interaction network (Stangeland et al Oncotarget, 2015). Knockdown of one of these genes, the PDZ-binding kinase (PBK), led to decreased viability and sphere formation in GSCs. Treatment of experimentally induced GBM tumours in mice resulted in a significant reduction of tumour growth (Joel M et al, Molecular Cancer 2015). We have also investigated the role of N-acetyltransferase (NAT12) in GSCs. Knockdown studies of the NAT12-gene resulted in markedly reduced cell viability and sphere-forming ability of GSCs. Intracranial transplantation of GSCs featuring NAT12 knockdown into severe combined immunodeficient mice resulted in a significant prolongation of animal survival compared to controls (Mughal A et al, Molecular Cancer, 2015).

**Characterization of invasive glioblastoma stem cells**
Glioblastomas are characterized by diffusely infiltrative growth. To investigate the invasive properties of glioblastoma cells we film cells while they invade into rodent brain slices or 3D-biomatrixes. Our time-lapse microscopy data reveals distinct phenotypic subtypes among invasive cells as well as specific movement patterns of invasion guided by tumour core signaling (Fayzullin A et al, Exp Cell Res, subm). In addition, to get comprehensive data on mechanisms of invasion we work on transcriptome analysis of invasive glioblastoma cells.

**Cancer stem cell differentiation and tolerance to hypoxia**
Tolerance to hypoxia may be an important feature in cancer progression. We have previously shown that GSCs can be differentiated to more mature cell types. We have now investigated how differentiation influences tolerance to hypoxia. The results suggest that undifferentiated GSCs are oxygen dependent, and that limited differentiation induces relative hypoxia tolerance. This warrants a careful approach to differentiation as a glioblastoma treatment strategy (Skjellegrind H et al, Neurochem Res 2016).

**Immunotherapy against cancer stem cells in glioblastoma**
We have earlier developed an autologous dendritic cell (DC) based vaccine therapy that specifically target the cancer stem cells in glioblastoma and conducted a first-in-man study of this therapy (Vik-Mo EO et al, CII 2013). This study gave very promising results: the therapy resulted in the development of specific immune response, associated with shrinking tumour volume and 2.3 times increased progression free-survival. Working with our collaborating partners (Gunnar Kvalheim – partner in the Stem Cell Center, and professor Dolores Schendel in Munich) we have optimized several aspects of the vaccine during 2015. This includes improved mRNA amplification, more efficient production and modifications of the vaccine that has resulted in a stronger immune response. We have by now been granted money to perform a larger randomized controlled phase II/III clinical study, evaluating the benefit of adding the new version of the vaccine to current standard care. The study is planned to enroll 30 patients in each group, and will evaluate both progression-free and overall survival.

**Individualized systems medicine strategy to target cancer stem cells in patients with recurrent glioblastoma**
In a collaboration with our partners at the Finnish Institute for Molecular Medicine, we are combining the novel technical pos-

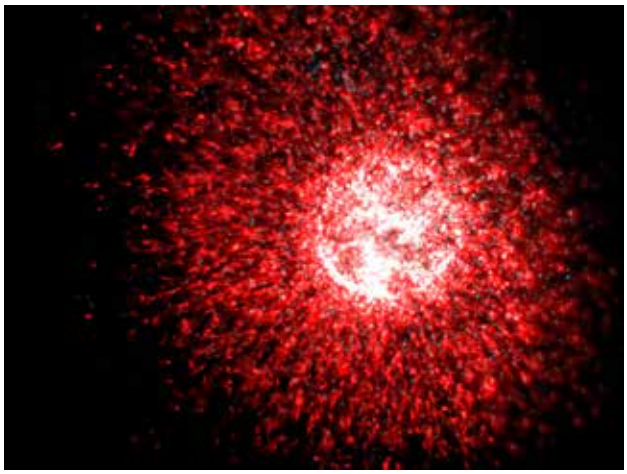
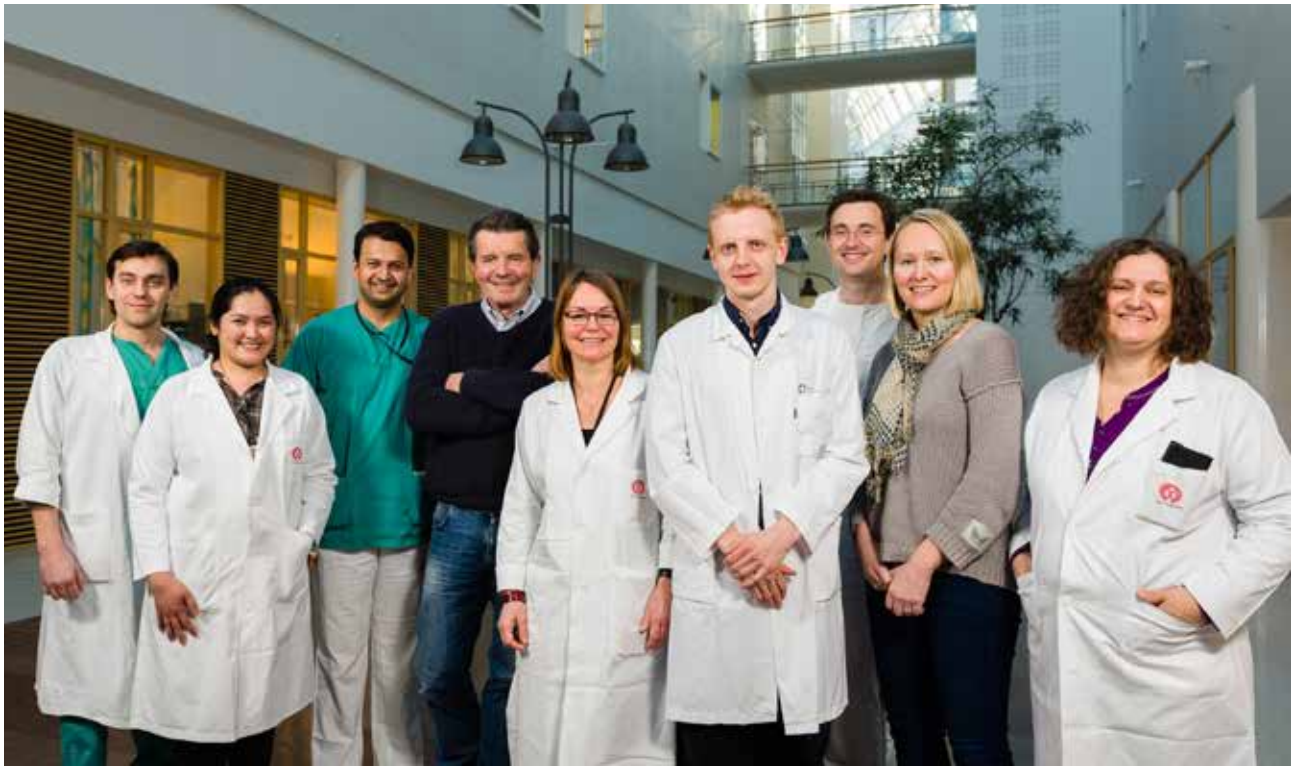


***Fig. 2 Invasive cells:***
*To investigate the invasive properties of glioblastoma stem cells we perform the filming of the brain cancer invasion in 3D-biomatrixes. When a sphere of glioblastoma cells is transplanted into a collagen matrix, it invades intensively mimicking the in vivo process. After real-time video-filming of the invasion process for 48 hours the sample was fixed and immune-labeled for BIII-tubulin (red) and nuclei (blue).*

sibilities of high-throughput screening and deep sequencing with our established know-how on individualized patients specific tumour stem cell cultures. Exploring a panel of 450 drugs established in clinical use, as well as targeted therapy drugs in early-phase studies, we are screening individualized tumour stem cells for drug sensitivity. This approach has recently been coined Individualized Systems Medicine. The preclinical pipelines have been established in 2015 and these results will allow the approach to be used to treat patients. Treatment of patients is planned to start in 2016.

## International collaborators

- Krishna Bhat and Frederick Lang , MD Anderson Cancer Center, Houton, USA
- Krister Wennerberg and Markus Perola, Institute for Molecular Medicine Finland, University of Helsinki
- Aki Laakso and Emilia Gaàl-Paavola, Helsinki University Hospital, Finland
- Deni Galileo, University of Delaware, USA
  Charles Liu, University of Southern California, Los Angeles, USA
- Yasuhiro Watanabe, Tottori University, Japan
- Winston Hide, Harvard University, MA
- Rainer Glass, Klinik der Universität München, Germany



***Our research group:***
*The Vilhelm Magnus Lab 2016. From the left: Artem Fayzullin, Emiliy Palmero, Awais Mughal, Iver A. Langmoen, Birthe Mikkelsen, Erlend Skaga, Einar Vik-Mo, Cecilie Sandberg, Zanina Grieg.*

Photo: Øystein H. Horgmo, UiO

# Cell Transplantation and Tissue Engineering

## Leader

Aksel Foss, MD, PhD, Professor (OUH/UiO)

## Deputy leader

Hanne Scholz, MSc, PhD, Senior Scientist (OUH)

## Scientific Staff Cell Transplantation

Simen W. Schive, MD, PhD student (OUH)
Shadab Abadpour, Msc, PhD student (OUH)
Kristine Kloster-Jensen, MD, PhD student (OUH)
Afaf Sahraoui MD, PhD student (OUH)
Merete Høyem, Research technician (OUH)
Ragnhild Fjukstad, Bioengineering (OUH)
Trond Jenssen, MD, PhD, Professor (OUH/UIT)
Karsten Midtvedt, MD, PhD (OUH)
Geir Hafsahl, MD, PhD (OUH)
Stein Bergan, MSc, PhD, Professor (OUH/UiO)

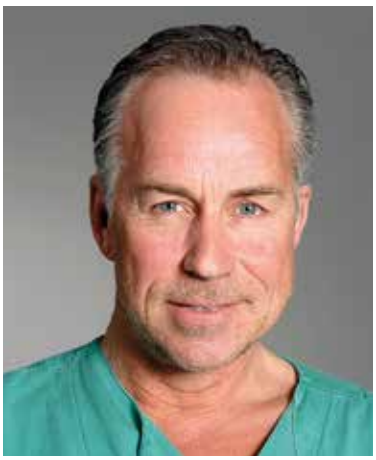
## Scientific Staff Tissue Engineering

Oslo Regenerative Medicine Initiative (ORMI) partners

## Research topics

Cell Transplantation and Tissue Engineering research group combines research within cellular biology and cellular transplantation with material and engineering science to develop biologic substitutes. The goal is to restore and maintain normal cell or organ function that has been damaged due to disease, trauma, and cancer therapy and/or by other causes.

Clinical islet transplantation is an alternative therapy for those T1D patients whose disease cannot be effectively managed with current methods of exogenous insulin administration. In terms of improving glycemic control and reducing life-threatening episodes of hypoglycemia, islet transplantation is highly successful, but the long-term efficacy is still too low and further refinement of the treatment is highly needed. The research group is responsible for human islet isolation from deceased donors for clinical islet transplantation in type 1 diabetes patients with brittle diabetes in collaboration with the Nordic Network for Clinical Islet transplantation (NNCIT). The research group has a clear translational approach with projects ranging form clinical trials and outcome studies, experimental islets and cell transplant in small animal models, and advanced in vitro studies.



Professor Aksel Foss

## Current Research Focus

- The improvement and implementation of new strategies for islet isolation, engraftment of human islets in the setting of clinical islets transplantation.
- Endogenous repair/regenerative medicine using the non-en docrine compartment of the pancreas.
- Non-Immunosuppressive Dual-Encapsulation Method for Islet Cell Transplantation and Insulin Delivery
- Comparison of adipose tissue- and bone marrow-derived mesenchymal stem cells for treatment of diabetes.

*Human islet isolation at ex vivo laboratory, Depart. for Cellular Therapy, Radiumhospitalet*

## The group has presented abstracts on the following meeting

- 5th EPITA Winter Symposium & 34th AIDPIT Workshop, Jan 25-27´15 Igls, Austria
- IPITA-IXA-CTS 2015 Nov 15-19, 2015 Melbourne, Australia.
- 12th National Stem Cell Networking Conference, Sept 29-30´15 Oslo, Norway
- 50th Annual Meeting of the Scandinavian Society for the Study of Diabetes (SSSD), April 23-26, 2015 Oslo, Norway

## Oslo Regenerative Medicine Initiative (ORMI)

All activities on regenerative medicine and tissue engineering at OUH and UiO have been joined in ORMI and the initiative was selected as Focused Area of Research at our institution for the timeframe 2014-2018. Main purpose for ORMI is to develop technologies platforms in combination with biomaterials for tissue engineering and regenerative medicine for stem-cell based therapy to move forward into new clinical application.

## Steering Committee

Attramadal, Smiseth, Vartdal, S. Smeland.

## Working Group

Kvalheim, Foss, Scholz, Engebretsen, Langmoen, Krauss, Glover.

## Core Facility

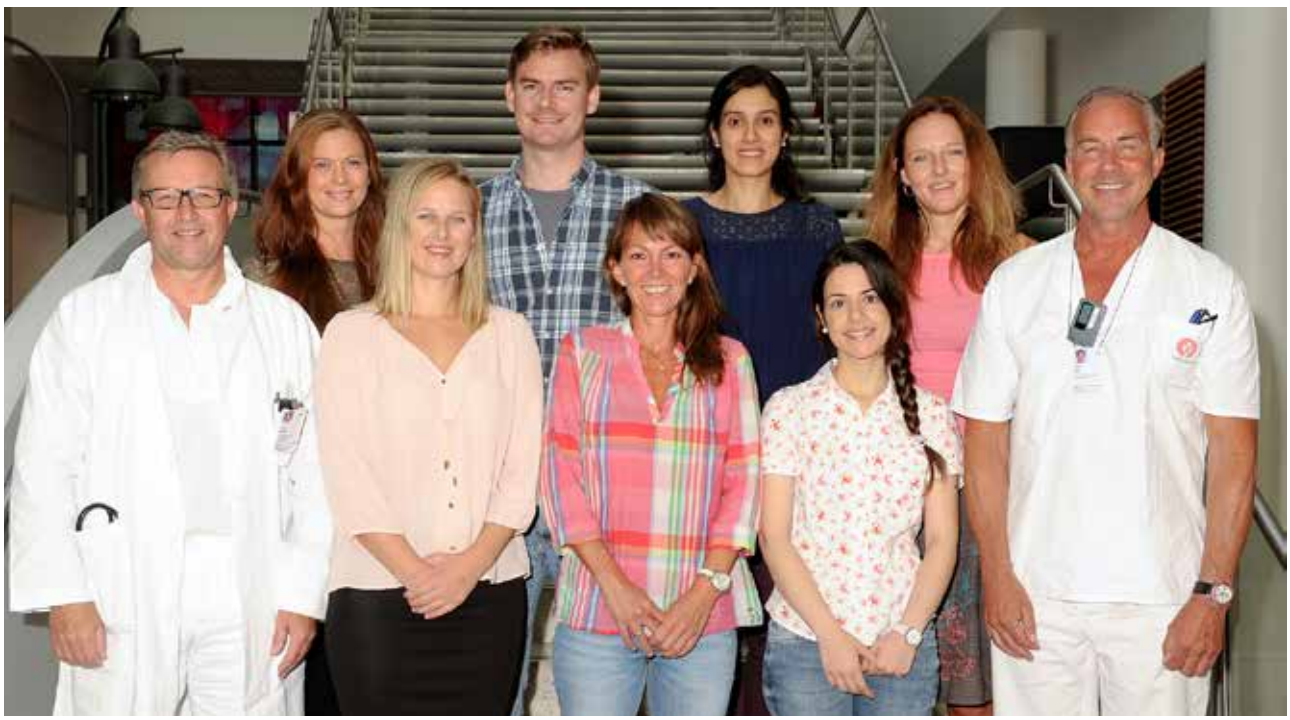
GMP-certified Ex Vivo Laboratories, Norwegian Center for Stem Cells Research, Institute for Surgical Research (TE Laboratories)

## Research Groups

Cartlige (Engebretsen), Ocular (Moe), hePS/hiPS (Glover/Sullivan), Adipose stem cells (Kvalheim), Plastic Surgery (Tønseth), Chemical Biology (Krauss), Diabetes (Scholz), Cartilage and stem cells (Brinchman), Artery and vein substitute (Jørgensen/Sundhagen), Tissue Engineering (Foss), Biomaterials (Lyngstadaas/Haugen)

## ORMI has been focus on the two following projects in 2015

- Tissue engineering of allogeneic scaffolds. Group: Jørgensen/Sundhagen
- Large-scale production under GMP condition and Comparison study of mesenchymal cells from bone marrow and adipose tissue from healthy individuals and patients with type 1 diabetes. Group: Kvalheim/Scholz



*Cell Transplantation and Tissue Engineering group.* *Photo: Bjørn Ohnstad, UiO*

# Experimental Orthopaedic Research

## Leader

Lars Nordsletten, MD, PhD, Professor (OC/UiO)

## Scientific staff

Lars Engebretsen MD, PhD, Professor (UiO/OC)
Olav Reikerås, MD, PhD, Professor (UiO/OUH)
Jan Erik Madsen, MD, PhD, Professor (UiO/OC)
Harald Steen, MD, PhD, Professor (OUH)
Stig Heir MD, PhD (Martina Hansens Hospital)
Sanyalak Niratisairak, PhD, Head Engineer (UiO/OUH)
Sverre Løken MD, PhD (OC)
Ulf Sigurdsen MD, PhD (UiO/AHUS)
Sigbjørn Dimmen, MD, PhD (LO)
Finn Reinholt, MD, PhD, Professor (UiO/OUH)
Jan Brinchmann, MD, PhD, Professor (UiO/OUH)
Stein Erik Utvåg, MD, PhD (UiO/AHUS)
Geir Hjorthaug, MD, PhD-student (OUH)
Jan-Egil Brattgjerd, MD, PhD-student (OUH)

## International Collaborators

Rob LaPrade, Steadman Philippon Research Institute Vail, Colorado, US

## Research areas

Musculoskeletal injuries are main causes of disability in the community and are often subjected in both younger and older age groups. It induces large socioeconomic costs, and improved health care in this area is important for both the individual quality of life and how the society handles increasing health expenditures. The Experimental Orthopaedic Research (EOR) group applies experimental methods on different aspects of orthopaedics. This includes research on human substances (biopsies, joint fluid, and retrievals), animal experiments and cell culture studies. Mechanical testing of structures, including live anaesthetized animals, and materials has been one of the main research methods. The experimental work in the laboratory is closely connected to ongoing or planned clinical studies, aiming to improve orthopaedic care of these patients in the community. Involvement of the clinicians is one of the strengths of the group.

## Aims

- To develop a novel treatment of focal cartilage defects
- To reduce the numbers of deficient fracture healing
- To reveal biomechanical factors in internal fixationof hip fractures
- To improve healing of tendon grafts in orthopaedic surgery
- To delineate the best biomaterial surface for prosthesis surgery

Professor Lars Norrdsletten

This year´s contribution to the research at the institute were performed at the biomechanical lab. Most hip fractures are operated with reduction and internal fixation. An improvement in this procedure is thought to reduce the complications related


Photo: Øystein H. Horgmo, University of Oslo

*Photograph of a human cadaveric femur with a standardised osteotomy fixated with the Swemac Pinloc®.*

to fracture healing. However, there is a lack of documentation of the concept and the effect of optimal reduction and fixation. On the choice of implant for hip fractures, no clear conclusions can be made. Our hypothesis is that a new implant design provides higher stiffness in fixation of intracapsular hip fractures, and that for extracapsular hip fractures, a new constellation of a well-known implant will increase stiffness and reduce fracture healing complications. We are performing biomechanical studies on synthetic and cadaveric femurs to analyze the stiffness of different fixations in different types of hip fractures as well as deformation during dynamical testing. To correct for osteoporosis in cadaveric femurs we are using bone mineral content measured by quantified CT. As a consequence of our findings clinical trials are started.

# Experimental Microsurgery and Transplantation Group

## Leader:

Pål-Dag Line, MD, PhD, Professor (OUH/UiO)

## Scientific staff

Jihua Shi, MD PhD, Post Doc-fellow (SENRHA)
Bjarte Fosby, MD (OUH)
Henrik Huitfeldt, MD, PhD, Professor (OUH)
Vivi Bull Stubberud, RN (OUH)
Geir Ivar Nedredal, MD, PhD (OUH)
Einar Martin Aandahl, MD, PhD (OUH)
Bjørn Lien, MD (OUH)
Brynjar Mauseth, MSc (OUH)

Professor Pål-Dag Line

## Introduction

Our group has for many years established various experimental transplantation models and other surgical models in order to form a solid platform that allow us to explore our main fields of interest: transplantation immunology, organ preservation, hepatic regeneration and the interaction between growth of hepatic tumours, liver regeneration induced by surgery and the immune system. Furthermore, we test new surgical technical concepts in liver surgery in rodent models before bringing them to clinical studies

## The transplantation models

For basic transplant immunological studies the cuff-based cervical heterotopic transplantation technique with transplantation of a donor heart to the neck of the recipient rat has been utilized. We have also established liver transplantation models in the rat. This entails both a non arterialized, full size model, and a partial graft, fully arterialized model where graft size can be varied.

## Tumour immunology

Through close cooperation with the Biotechnology Centre of Oslo we are able to investigate mechanisms that suppress anti-tumour immunity. Regulatory T cells is a subset of T cells that inhibits immune reactivity and thereby allow the tumour to grow and metastasize. To develop therapeutic strategies for immune modulation in cancer, we are studying how the regulatory T cells operate, and how they suppress conventional effector T cells.

- Study the mechanisms of immune suppression by regulatory T cells.
- Assess the frequency and strength of immune suppression by regulatory T cells on conventional T cells isolated from peripheral blood and spleen.
- Perform detailed phenotypic analyses of the T cell repertoire and the phenotypic plasticity that occur in the tumour microenvironment that diverts an efficient T cell mediated anti-tumour immunity towards a pro-inflammatory and immunosuppressive T cell repertoire. We have recently shown that phenotypic plasticity occurs in both the CD4 and CD8 T cell compartment.
- Perform immunohistopathological and flowcytometric studies of the cellular constituents in the tumour microenvironment. We will assess the presence and frequency of subsets of regulatory T cells and subsets of CD4 and CD8 T cells.

## Immunotherapy of experimental liver tumors

For the last two yeas we have worked with the Direct Transduction Targetide peptide LTX-315 from Lytix Biopharma. LTX-315 is derived from bovine lactoferricin (LfcinB), and we have investigated its potential as a treatment of experimental hepatocellular carcinoma in the rat. We have been able to show that treatment with LTX-315 kills experimental tumor and invoke a strong T-cell mediated anti-tumour immune response. Our group is now part of a multidisciplinary team of national and international experts working on the cutting edge of cancer biology and immunotherapy In order to verify new lead peptide candidates that can be brought to preclinical and clinical studies of patients with primary and secondary liver tumours.

## Liver preservation

To alleviate the shortage of donors, potential source of organs are patients with irreversible brain damage on continuing life support. These patients do not fulfil the brain death criteria. Withdrawal of life support will cause their death, hence referred to as donation after cardiac death (DCD), or non-heart beating donors (NHBD). The time from withdrawal of support to death,

implies a time of no oxygen to the liver and renders therefore these organs for potential damage. Preservation of livers by machine perfusion improves liver function. We are now in the process of establishing a pig model of liver perfusion in order to assess how liver warm ischaemia followed by 12 hrs. of normothermic machine perfusion. influence bile production, generation of free-oxygen radicals, release of transaminases, and of oxygen-consumption.

## Clinical studies

We have developed a protocol incorporating previously reported experiences from living donor transplantation and recent developments in liver surgery, facilitating transplantation of very small liver grafts. At the time of transplantation, segments 1-3 are resected in the recipient, and orthotropically replaced by a segment 2-3 allograft. Portal inflow is modulated by redirecting the portal flow to the graft with concomitant focus on keeping the portal vein pressure below 20 mmHg. A second stage hepatectomy is performed as soon as the graft has regenerated to a sufficient volume. Various aspects of the technique are simultaneously tested in rodent models.

# Transplantation and Malignancy

## Leader

Svein Dueland, MD, PhD, Consultant, (OUH)

## Main Members

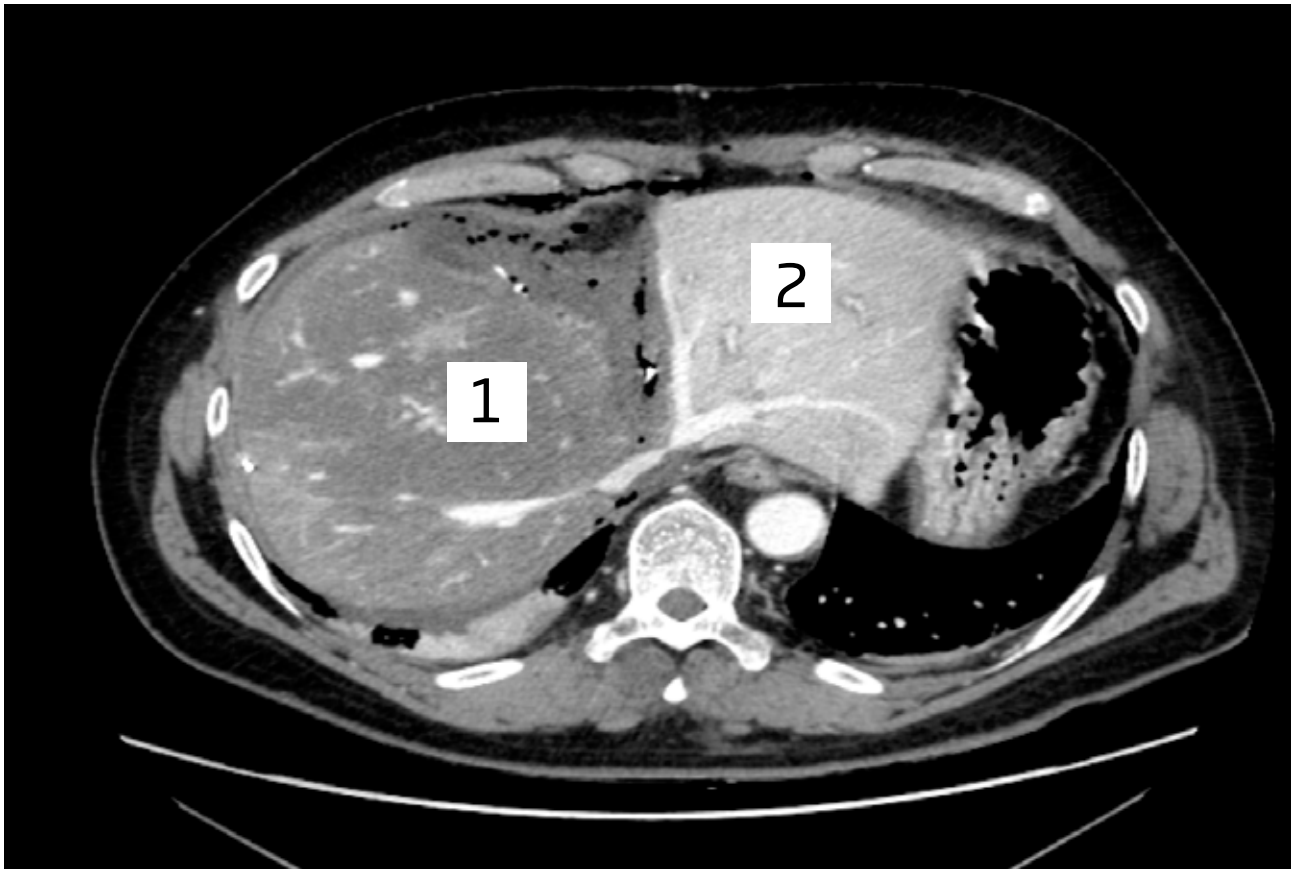
Aksel Foss, MD, PhD, Professor (OUH/UiO)
Pål-Dag Line, MD, PhD, Professor (OUH/UIO)
Jihua Shi, MD (OUH)
Morten Hagness, MD, PhD, (OUH)
Jon Magnus Solheim, MD PhD-student (OUH)

## Associate members

Einar Martin Aandahl, MD, PhD (OUH)
Marit Andersen, MSc, PhD (OUH)
Rune Horneland, MD (OUH )

Consultant Svein Dueland

Our research group has focused on liver transplantation in patients with non-resectable liver only metastases from colorectal cancer (CRC) and ocular malignant melanoma. In patients with non-resectable colorectal cancer liver metastases (CLM) palliative chemotherapy is the only treatment option. It is well established based on results from many studies that CLM patients have a median overall survival (OS) of about 2 years from time of starting chemotherapy and about 12 months from starting second line treatment. Five year OS from start of chemotherapy is about 10%. In a study with more than 50% of the patients having received more than first line chemotherapy 5 year OS was 56% in patients receiving a liver transplant. In resectable patients with a median number of liver metastases of one lesion and median size of about 2.5 cm 5 years OS was about 50%. In comparison, in our liver transplantation study in non-resectable CLM patients median number of lesions were 8 and median size of 4.5cm. Based on CEA levels, time form diagnoses, response to chemotherapy at time of liver transplantation, and size of largest lesion



we were able to obtain a 5 year OS of 75% which is similar to patients with hepatocellular carcinoma receiving a liver transplant at our institution. Furthermore, we have shown that CRC patients receiving a liver transplant had good quality of life. The side –effects of immunosuppressive treatment is only minor compared to chemotherapy. No other treatment has shown a similar increase in OS in CRC patients compared to liver transplantation, except for surgical treatment of the primary tumor in patients without metastases.

Colorectal cancer is one of the most common malignant diseases in the western world with about 4000 new cases diagnosed in Norway every year. About 50% of CRC patients have metastatic disease at time of diagnoses or will develop metastatic disease. The primary metastatic site is the liver. Therefore there will be many CRC patients that will likely benefit from a liver transplant. In Norway as well as internationally there is limited excess to donor livers for transplantation of patients with malignant liver diseases.

To be able to increase the number of patients that may be offered a liver transplant we initiated a study transplanting liver segment 2+3 only and partial hepatectomy (resection of liver segment 1-4) in the first operation and about 3 weeks later, at a time when the donor liver segment 2+3 had increase to a sufficient size the second part of the hepatectomy removing segment 5-8 were performed. Transplantation of a donor liver representing only 0.36% of total body weight had never been performed before. Normally a donor graft of 1% of body weight is considered necessary. With the surgical technics used in this study to split a donor liver in two parts may save the lives of two patients. When more mature data from this study is available and if successful survival is obtained, this may open up the possibility of living donor liver transplantation with minimal risk to the donor. Compared to other treatment options the ongoing liver transplantation projects must be considered as a huge improvement for the patients.

## Reference

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## Legend to figure

Partial hepatectomy and donor segment 2+3 transplantation (1= remaining liver segments, 2= donor liver segments 2+3).

# Research in Plastic and Reconstructive Surgery

## Leader

Kim Alexander Tønseth, MD, PhD, Head of Department of Plastic and Reconstructive Surgery (OUH/UiO)

Head of Department Kim Alexander Tønseth

## Scientific staff

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Torjus Wester, MD, PhD-student (OUH)
Haris Mesic, MD, PhD-student (OUH)
Michael Schneider, MD (OUH)
Therese Halvorsen Bjark, MD (OUH)
Christoffer Aam Ingvaldsen (OUH)
Tor Utheim, MD, PhD (OUH/UiO)
Cathrine Wold Knudsen, MD, PhD (Bærum Hospital)

## Introduction

Plastic and reconstructive surgery is performed to restore normal anatomy and function in patients with congenital and acquired disorders, and in patients with tissue defects after trauma or cancer surgery. During the last decades research in plastic and reconstructive surgery has led to development of a large number of treatment options for patients with different kinds of disorders and defects. These methods are often based on experimental research which has been refined through clinical procedures. The main outcome is improved quality of life and patient satisfaction based on restoration of anomalies and dysfunction.

## Research areas

**1. Microcirculation, microsurgery and wound healing**

Free tissue transfer is a technique which has revolutionized the field of reconstructive surgery over the past four decades. Tissueflaps, based on small vascular vessels (±1mm), can be transposed from a distant part of the body (donor site) to a location where reconstruction is needed and the vessels can be anastomosed to the recipient artery and vein. A new area of free flap surgery was initiated with the introduction of flaps based on perforator vessels. This technique improved reconstruction by reducing donor site morbidity and by allowing new alternative flap designs. There is a constant need for optimising the reconstruction techniques to give the best possible result with minimal disadvantages at the donor site. Our main projects are:

a. *Microcirculatory of the Abdominal Skin in Deep Inferior Epigastric Perforator Flap procedure (fig.1)*

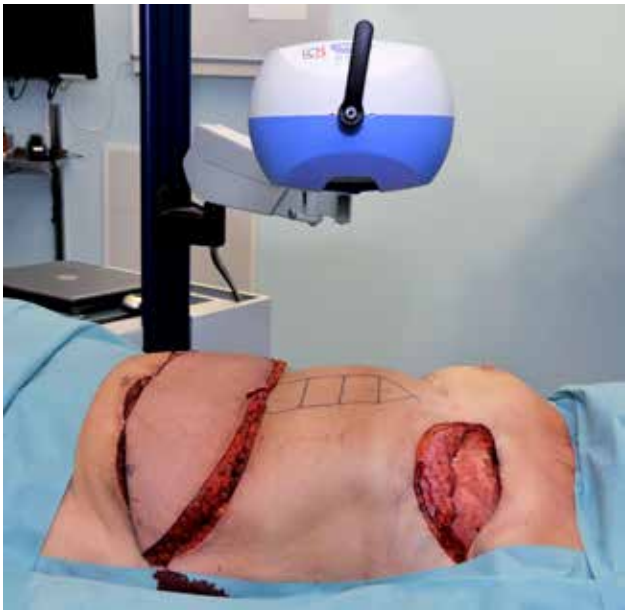

***Figure1.*** *Microcirculatory evaluation with laser Doppler perfusion imaging of the undermined abdominal skin during breast reconstruction surgery using autologous tissue (DIEP flap).*

b. *Microcirculation in random flaps on rats and the effect of prostaglandin E1*

c. *Quality of life and patient satisfaction after breast reconstruction with autologous tissue*

d. *Experimental perforator flaps and other rat model*

e. *Changes in microcirculation of the skin during sepsis and cardiogenic shock*

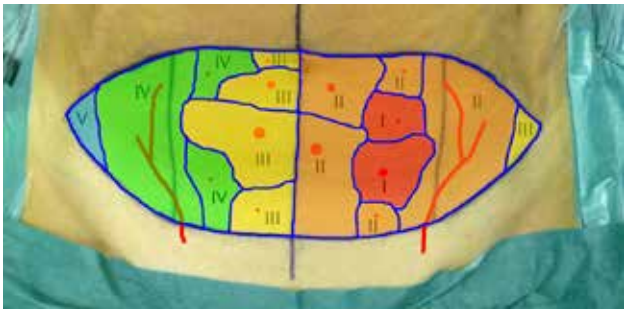

***Figure 2.*** *Evaluation of the angiosomes of the abdominal flap used for breast reconstruction. Based on the location of the perforator (zone I) the viability of the flap can be estimated and the zones IV and V should be removed before transposing the flap to the breast.*

*f. Microcirculation in human perforator flaps (fig. 2)*

**2. Treatment of facial palsy**

*a. 3-dimentional evaluation of outcome after surgical reanimation of facial palsy.*
Patients with persistent facial palsy are evaluated for surgical treatment. One of the treatment options is dynamic reconstruction with cross-facial nerve grafting and subsequent gracilis muscle transfer to the face. In cooperation with the department of plastic surgery in Vienna, Austria, we are analysing the 3-dimentional outcome of these surgical procedures.
*b. Medical treatment of Bell`s palsy*
Bell`s palsy is an acute, idiopathic, unilateral peripheral facial palsy of unknown cause with an incidence of 30 per 100,000 inhabitants per year. The Scandinavian Bell`s palsy study is a randomized, double-blind, placebocontrolled, multicenter trial including patients with Bell`s palsy with a 12-month follow-up. Patients were randomized to treatment with prednisolone plus placebo, valacyclovir plus placebo, prednisolone plus placebo, and placebo plus placebo. The primary endpoint and several secondary endpoints have already been published showing significantly higher recovery among prednisolone treated patients. We are still analyzing some secondary endpoints to evaluate which patient groups benefit the most of prednisolone. Furthermore we will evaluate the long term result of patients who were excluded from the study and not received treatment. We will also analyze the outcome of pregnant patients with Bell's palsy.

**3. Regenerative medicine**

Regenerative medicine is of great interest in plastic surgery due to the possibility to reconstruct defects which has been difficult or impossible to handle with traditional surgery. Still, there are many aspects of the techniques which have to be improved before they can replace the methods used to day. Our group has focused on the following areas:

*a. Fat transplantation*
Transplantation of autologous fat has been performed for many decades. Improvements in harvesting techniques and advantages such as availability and biocompatibility have led to its widespread application. In addition, potential positive effects of regeneration on the surrounding cells have been described. We are using fat transplantation in a number of different clinical conditions. However, there are still areas where the use of fat transplantation has not been sufficiently described, and where the longterm outcome of the procedure is unknown. These issues are analysed in our group.

*b. Cultured urothelial cells*
In reconstructive surgery within the genitourinary tract, autologous urothelial cells cultured in vitro could be of considerable value. To acquire urothelial cells for in vitro engineering of urothelium, bladder washings from adult patients as well as children can be performed. These samples will contain enough proliferative and colony-forming uroepithelial cells to regenerate urethral mucosa in vitro. The cultures could be expanded to confluent, stratified sheets, which can be used for reconstruction of the urethra in urogenital anomalies or in patients with other needs (transsexuals, reconstruction after trauma or cancer surgery). The laboratory work will give a large improvement in the clinical treatment of these patients.

*c. Cultured epidermal cells*
This project, in cooperation with department of medical biochemistry, focus on how cultured epidermal epithelial cells can be (1) successfully cultured on electrospun scaffolds, (2) optimally stored within a small temperature interval, (3) successfully stored in a tailor-made medium, and (4) reliably transported under specific conditions.

**4. Other projects**

*a. Evaluation of patients treated for lymphatic malformations*
*b. Lymphedema Treatment with Supermicrosurgical Lymphovenous Bypass. Clinical - and patient reported outcome during a five year follow-up (in cooperation wieth STHF)*
*c. Mothers' experiences of feeding infants with cleft lip and palate (CLP) and the effects of a follow-up program on parental information needs, parental stress and growth in infant with CLP*

# Regional Core Facility for Large Animal Research

*The new C-arm for interventional cardiology at Institute for Surgical Research.* *Photo: Kristin Ellefsen, UiO.*

# Regional Core Facility for Large Animal Research

The core facility for large animal research is a regional technological core facility supported by the South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF). The purpose of the core facility is to provide facilities (fully equipped operation theatres), expertise and assistance in planning and conducting large animal research (rabbit, pig, piglet, dog). The aim of the core facility is to help scientists who request large animal research as part of their projects and to make large animal research feasible and affordable for those who are not proficient in large animal research. The core facility provides service on equal conditions to scientists from both local and regional institutions within the South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF) as well as to scientists from University of Oslo.

The core facility is comprised of two nodes both located at Oslo University Hospital; Section for Large Animal Surgery, Institute for Surgical Research (ISR – Gaustad) and Section for Preclinical Physiology, Institute for Experimental Medical Research (Ullevål). Both nodes have state-of-the-art equipment, and leading expertise and capabilities in conducting large animal research, including anaesthesia, hemodynamic monitoring, and surgery. The researchers at both nodes of the core facility have extensive experience in cardiovascular physiology and pathophysiology (including cardiac ischemia), gastrointestinal physiology and pathophysiology and cerebral ischemia. The core facility will also be working to provide methodologies (vectors) for gene transfer (e.g. adeno-associated virus) and to provide robust and validated disease models (e.g. ascending aortic constriction in pigs for chronic pressure overload of the heart) in large animals. For more information go to website: http://ous-research.no/lar/

Scientists seeking help to plan and conduct large animal research as part of their research projects at the core facility at Institute for Surgical Research may contact Professor Håvard Attramadal for more information (Ph. 23071396 (direct)/23073520 (reception) or e-mail: havard.attramadal@rr-research.no).

## Projects perfomed at the Core Facility (ISR – Gaustad) 2015:

| Project title | Project leader / department |
|---|---|
| Assessment of cerebral perfusion with contrast enhanced ultrasound during malposition of the Odón deviceTM (Piglet) | Rønnaug Solberg, Charlotte De Lange, Ola Didrik Saugstad, Dept. of Pediatric Research, OUH |
| Neuroprotection and cooling after birth asphyxia (Piglet) | Rønnaug Solberg, Dept. of Pediatric Research, OUH |
| Neuroprotection after birth asphyxia (Piglet) | Rønnaug Solberg, Dept. of Pediatric Research |
| Validation of echocardiographic 3D VSAP (Virtual Semi-Transparent Annulus Plane) in acute animal experiments (Pig) | Stig Urheim, Dept. of Cardiology, OUH |
| Effects of alterations in load, contractility and heart rate on cardiac function in left bundle branch block | Otto Smiseth, Dept. of Cardiology, OUH |
| Needle-i, Detection of intraneural needle-placement with multiple frequency bioimpedance monitoring (Pig). | Håvard Kalvøy, Clinical and Biomedical Engineering, OUH |

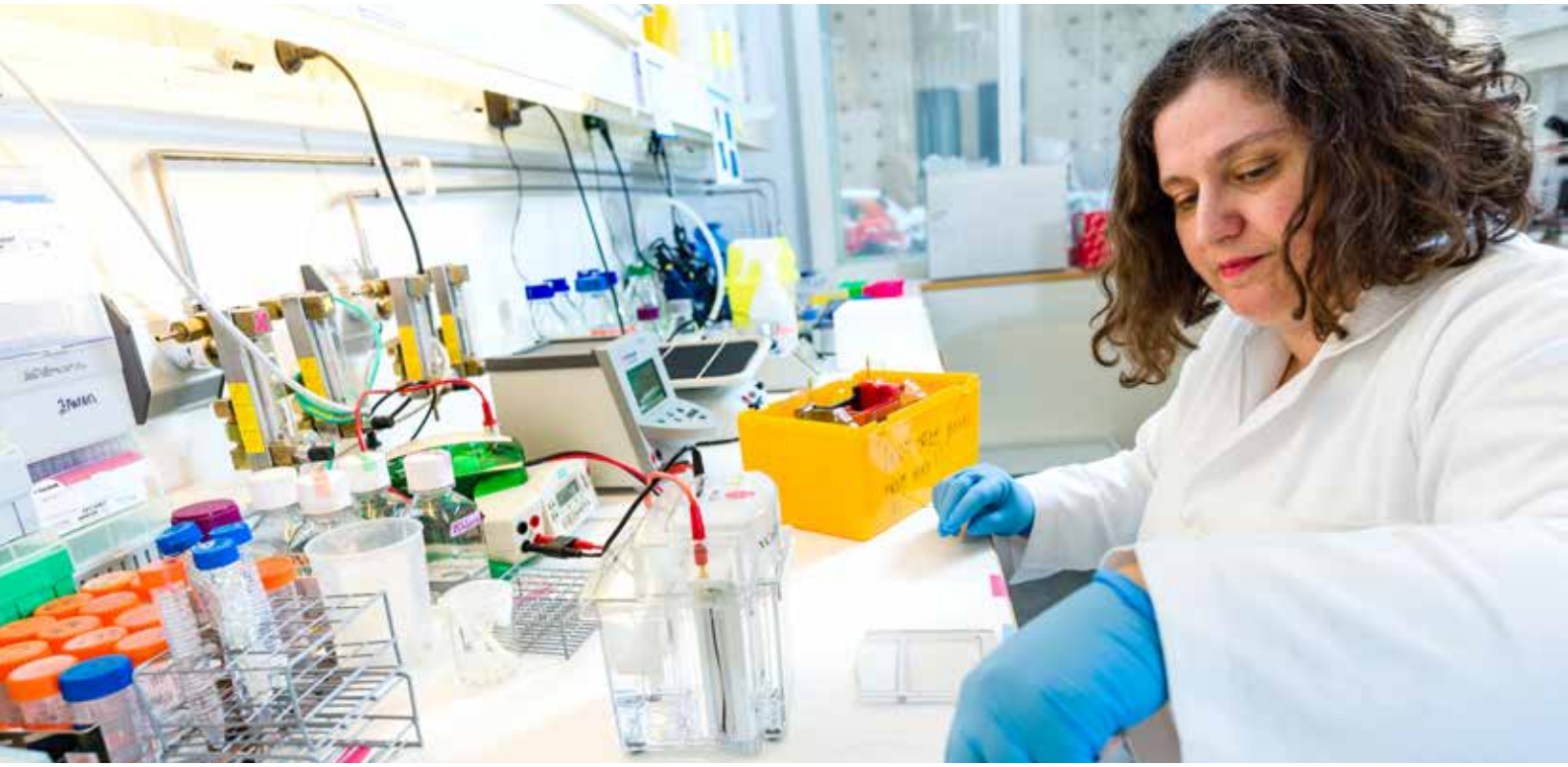

Photo: Øystein H. Horgmo, UiO

# Training Courses

# Courses

## Introduksjon til nyfødtmedisinske teknikker og prosedyrer

***Dato: 09.-12.03.2015 + 12.-15.10.2015 + 23.03.2015 (Bakvaktkurs)***

**Målgruppe**

Leger under utdanning i barnesykdommer med særlig fokus på de helt ferske og uerfarne. Kurset kan også ha interesse for andre kolleger i det barnemedisinske faget som arbeider ved avdelinger der visse typer nyfødtmedisinske prosedyrer utføres svært sjelden. Videre vil kurset være relevant for anestesileger som arbeider ved avdelinger der akuttbehandling av nyfødte ivaretas av anestesiolog.

**Læringsmål**

Deltakerne skal i løpet av kurset få demonstrert teknikker og selv få utføre praktiske øvelser. Målsettingen er å gi deltakerne grunnleggende kunnskaper og ferdigheter slik at de med større trygghet kan utføre prosedyrer på syke nyfødte.

**Arbeidsmåter**

Kurset vil ta for seg de vanligst forekommende teknikker og prosedyrer som brukes i nyfødtmedisinen. For hver teknikk/ prosedyre vil det først bli gitt en kort teoretisk introduksjon. Deretter vil teknikken bli demonstrert av kurslærerne. Demonstrasjonen vil bli fulgt av øvelse på modell. For de fleste teknikker vil det bli brukt anesteserte dyr som modeller. Det er lagt opp til at deltakerne skal få flere muligheter til repetisjon av ferdighetene. Kurset vil også omfatte en dag i simuleringslaboratorium for trening i teamarbeid.

**Kurskomite**

- Thor Willy Ruud Hansen (Kursleder)
- Vigdis Skaug (Kursleder)
- Jannicke Andresen
- Tor Einar Årstad Calisch
- Astri Maria Lang
- Sverre I. Medbø
- Vivi Bull Stubberud
- Per Arne Tølløfsrud
- Henrik Rasmussen

## Mikrokirurgiske teknikker

***Dato: 02.03. - 06.03.2015***

**Målgruppe**

Leger under videreutdanning/ spesialisering i barnekirurgi, karkirurgi, urologi, bryst - og endokrinologi, nevrokirurgi, plastikkirurgi, øre-nese-halssykdommer og valgfrie kurs.

**Læringsmål**

Mikrokirurgiske teknikker har fått en stadig større plass innenfor en rekke kirurgiske spesialiteter slik som transplantasjonskirurgi, plastikkirurgi, ortopedi, ØNH, kjevekirurgi, m.m. Mikrokirurgiske teknikker brukes i økende grad ved rekonstruktive inngrep etter skader, kreftbehandling og ved medfødte misdannelser. Teknisk sett er dette krevende prosedyrer, og for pasienten kan konsekvensene av mangelfull eller manglende mikrokirurgisk kompetanse være alvorlige. Samlet sett er pasientmaterialet ved hver institusjon lite i forhold til de fleste andre kirurgiske prosedyrer, og det er derfor meget viktig at leger som skal praktisere innenfor dette feltet kan lære grunnleggende mikrokirurgiske teknikker i en kontrollert forsøkssituasjon. Kurset gir deltagerne anledning til å lære og skjøte sammen blodkar og nerver med diameter ned mot en millimeter og sikrer at kandidatene får en viss mengdetrening innenfor området før de foretar lignende prosedyrer på pasienter.

**Arbeidsmåter**

Teori, teknikker blir demonstrert av kurslærere og følges av praktiske øvelser på modell (anesteserte dyr). All trening gjøres med mikroskop.

**Kurskomite**

- Pål-Dag Line
- Bjarte Fosby (Kursleder)
- Hilde Brunvold Bjærke (Kursleder)
- Vivi Bull Stubberud

## Thorako-/laparoskopisk kirurgi

***Dato: 15.04 - 17.04.2015***

**Målgruppe**

Leger under utdanning i generell kirurgi og gastroenterologisk kirurgi.

**Læringsmål**

Indikasjoner, operasjonsmetoder, resultater og kvalitetssikring innen laparoskopisk kirurgi. Kurset vil omhandle teoretisk undervisning og praktiske øvelser på simulatorer samt demonstrasjonsoperasjoner.

**Temaoversikt**

Laparoskopets oppbygging og vedlikehold.
Fysiologiske effekter av pneumoperitoneum.
Anestesi ved laparoskopi.
Laparoskopi ved akutt abdomen.
Cholecystecomi Antirefluxkirurgi.

*From the practical course in neonatology.* *Photo: Øystein H. Horgmo, University of Oslo*

Laparoskopisk cancerkirurgi.
Laparoskopi i urologien.
Thoracoskopisk kirurgi.
Praktiske øvelser under supervisjon, på modeller og anestesert gris vil være en vesentlig del av kurset.

**Kurskomite**

- Åsmund Fretland (kursleder),
- Trond Buanes,
- Bjørn Edwin,
- Ole Christian Olsen,
- John Hausken,
- Marianne Berg,
- Vivi Bull Stubberud.

## Laparoskopisk kirurgi for spesialiteten gastroenerologisk kirurgi

***Dato 20.05 - 22.05.2015***

**Målgruppe**

Legerunder utdanning i subspesialiteten gastroenterologisk kirurgi

**Læringsmål**

Kirurgisk strategitenkning innenfor gastroenterologisk kirurgi, slik dette konkretiseres innen laparoskopisk og åpen gastrokirurgi. Indiksjonsstilling, operasjonsmetodikk og postoperativ oppfølging klargjøres teorestisk (forelesninger). Kurset bruker i stor utstrekning pasienteksempler som gjennomgås etter modell av multidisiplinære møter (MDT). Et viktig læringsmål er skriving av gode MDT-referater. Om lag halvparten av undervisningstiden brukes til praktisk trening, der læringsmålet er at hver deltaker skal kunne forbedre sine praktisk, kirurgiske ferdigheter under veiledning.

**Kurskomite**

Trond Buanes og Bjørn Edwin (kursledere), Åsmund Fretland, Ole C. Olsen, Thomas Moger, Hjørtur G. Gislason, Kristin Kjellevold, Ronald Mårvik, Vivi Bull Stubberud og Marianne Berg.

Photo: Øystein H. Horgmo, UiO

# Publications

# Publications 2011 - 2015

## 2015


1. Bersvendsen J, Orderud F, Massey RJ, Fossa K, Gerard O, Urheim S, Samset E
Automated Segmentation of the Right Ventricle in 3D Echocardiography: A Kalman Filter State Estimation Approach
IEEE Trans Med Imaging, (2015); 35 (1): 42-51

2. Bøe E, Russell K, Eek C, Eriksen M, Remme EW, Smiseth OA, Skulstad H
Non-invasive myocardial work index identifies acute coronary occlusion in patients with non-ST-segment elevation-acute coronary syndrome
Eur Heart J Cardiovasc Imaging, (2015); 16 (11): 1247-55

3. Broch K, Urheim S, Lønnebakken MT, Stueflotten W, Massey R, Fosså K, Hopp E, Aakhus S, Gullestad L
Controlled release metoprolol for aortic regurgitation: a randomised clinical trial
Heart, (2015); 102 (3): 191-7

4. Dhondup Y, Sjaastad I, Scott H, Sandanger Ø, Zhang L, Haugstad SB, Aronsen JM, Ranheim T, Holmen SD, Alfsnes K, Ahmed MS, Attramadal H, Gullestad L, Aukrust P, Christensen G, Yndestad A, Vinge LE
Sustained Toll-Like Receptor 9 Activation Promotes Systemic and Cardiac Inflammation, and Aggravates Diastolic Heart Failure in SERCA2a KO Mice
PLoS One, (2015); 10 (10); e0139715

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Mitral valve analysis adding a virtual semi-transparent annulus plane for detection of prolapsing segments
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6. Espe EK, Aronsen JM, Eriksen GS, Zhang L, Smiseth OA, Edvardsen T, Sjaastad I, Eriksen M
Assessment of regional myocardial work in rats
Circ Cardiovasc Imaging, (2015); 8 (2): e002695

7. Estensen ME, Grindheim G, Remme EW, Godang K, Henriksen T, Aukrust P, Aakhus S, Gullestad L, Ueland T
Elevated inflammatory markers in preeclamptic pregnancies, but no relation to systemic arterial stiffness
Pregnancy Hypertens, (2015); 5 (4): 325-9

8. Flachskampf FA, Biering-Sørensen T, Solomon SD, Duvernoy O, Bjerner T, Smiseth OA
Cardiac Imaging to Evaluate Left Ventricular Diastolic Function
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9. Hals IK, Bruerberg SG, Ma Z, Scholz H, Björklund A, Grill V
Mitochondrial Respiration in Insulin-Producing -Cells: General Characteristics and Adaptive Effects of Hypoxia
PLoS One, (2015); 10 (9): e0138558

10. Hasselberg NE, Haugaa KH, Bernard A, Ribe MP, Kongsgaard E, Donal E, Edvardsen T
Left ventricular markers of mortality and ventricular arrhythmias in heart failure patients with cardiac resynchronization therapy
Eur Heart J Cardiovasc Imaging (2015); published online ahead of print 11 July 2015; doi:10.1093/ehjci/jev173

11. Haugaa KH, Bundgaard H, Edvardsen T, Eschen O, Gilljam T, Hansen J, Jensen HK, Platonov PG, Svensson A, Svendsen JH
Management of patients with Arrhythmogenic Right Ventricular Cardiomyopathy in the Nordic countries
Scand Cardiovasc J, (2015); 49 (6): 299-307

12. Haugaa KH, Haland TF, Leren IS, Saberniak J, Edvardsen T
Arrhythmogenic right ventricular cardiomyopathy, clinical manifestations, and diagnosis
Europace (2015); published online ahead of print 25 October 2015; doi:10.1093/europace/euv340

13. Hyde ER, Behar JM, Claridge S, Jackson T, Lee AW, Remme EW, Sohal M, Plank G, Razavi R, Rinaldi CA, Niederer SA
Beneficial Effect on Cardiac Resynchronization From Left Ventricular Endocardial Pacing Is Mediated by Early Access to High Conduction Velocity Tissue: Electrophysiological Simulation Study
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14. Joel M, Mughal AA, Grieg Z, Murrell W, Palmero S, Mikkelsen B, Fjerdingstad HB, Sandberg CJ, Behnan J, Glover JC, Langmoen IA, Stangeland B
Targeting PBK/TOPK decreases growth and survival of glioma initiating cells in vitro and attenuates tumor growth in vivo
Mol Cancer, (2015); 14: 121

15. Kierulf-Vieira KS, Sandberg CJ, Grieg Z, Günther CC, Langmoen IA, Vik-Mo EO
Wnt inhibition is dysregulated in gliomas and its re-establishment inhibits proliferation and tumor sphere formation
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Impaired dynamics and function of mitochondria caused by mtDNA toxicity leads to heart failure
Am J Physiol Heart Circ Physiol, (2015); 309 (3): H434-49

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Cardiac Mechanical Alterations and Genotype Specific Differences in Subjects With Long QT Syndrome
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18. Leren IS, Saberniak J, Majid E, Haland TF, Edvardsen T, Haugaa KH
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The lactate receptor, G-protein-coupled receptor 81/hydroxycarboxylic acid receptor 1: Expression and action in brain
J Neurosci Res, (2015); 93 (7): 1045-55

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Knockdown of NAT12/NAA30 reduces tumorigenic features of glioblastoma-initiating cells
Mol Cancer, (2015); 14, 160

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Factors determining the magnitude of the pre-ejection leftward septal motion in left bundle branch block
Published online ahead of print 26 November 2015;
Europace (2015); doi:10.1093/europace/euv381

23. Risøe PK, Rutkovskiy A, Ågren J, Kolseth IB, Kjeldsen SF, Valen G, Vaage J, Dahle MK
Higher TNF responses in young males compared to females are associated with attenuation of monocyte adenylyl cyclase expression
Hum Immunol, (2015); 76 (6): 427-30

24. Sahraoui A, Winzell MS, Gorman T, Smith DM, Skrtic S, Hoeyem M, Abadpour S, Johansson L, Korsgren O, Foss A, Scholz H
The effects of exendin-4 treatment on graft failure: an animal study using a novel re-vascularized minimal human islet transplant model
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33. Heir, S. Focal cartilage defects in the knee. ISBN: 978-82-8072-557-8, Thesis, University of Oslo, 2011

34. Solberg, R. Resuscitation of the newborn. An experimental study of toxic effects of supplementary oxygen in newborn piglets. ISBN: 978-82-8264-131-9 Thesis, University of Oslo, 2011

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# PhD-Theses and Awards 2015

## PhD-Theses

Ingvild Tronstad Moe

**Ingvild Tronstad Moe**
**26.02.2015**
Investigations on signaling pathways and functions of CCN2 in the heart.

## Awards

### Article from Institute for Surgical Research Among Articles Awarded Best Article from Oslo University Hospital during the first half-year of 2015

Cardiac Mechanical Alterations and Genotype Specific Differences in Subjects With Long QT Syndrome.

Leren IS, Hasselberg NE, Saberniak J, Håland TF, Kongsgård E, Smiseth OA, Edvardsen T, Haugaa KH. JACC Cardiovasc Imaging. 2015 May;8(5):501-10. doi: 10.1016/j.jcmg.2014.12.023.
Epub 2015 Apr 15. PMID: 25890583


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