ANNUAL REPORT 2014

Institute for Surgical Research

Photo: Kristin Ellefsen, UiO

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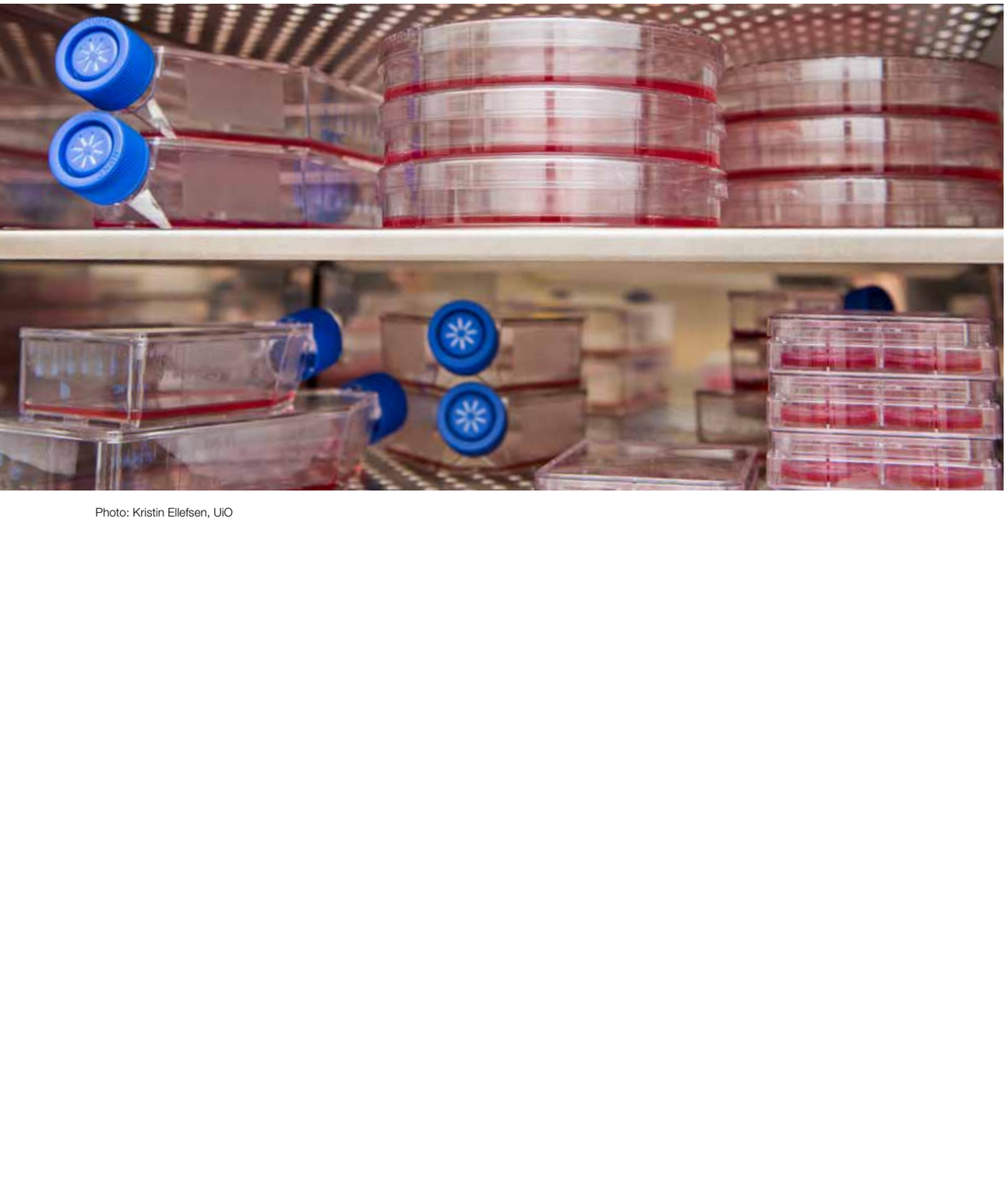


Photo: Kristin Ellefsen, UiO

Preface

2014 demarks a year of imminent changes for Institute for Surgical Research. In September 2014 Professor Ansgar O. Aasen retired from his position as Head of Institute. During his leadership Institute for Surgical Research evolved to a modern molecular medicine institute with translational research activities in many of the major clinical focus areas of the hospital. The Institute now has a multidisciplinary staff with strong expertise in gene technology and molecular biology as well as integrated physiology in both small and large animals.

By being a venue of scientists from many different fields Institute for Surgical Research has made several important contributions to clinical medicine over the years. Just to mention a few, scientists at Institute for Surgical Research played a major role in development of the Medtronic-Hall aortic valve prosthesis, over many years the most widely employed aortic valve prosthesis worldwide. Use of the Doppler principle in ultrasonography was also exploited by scientists at the Institute for assessments of heart valve defects, now implemented in all echocardiography systems.

Several of the research groups at the Institute are members of national and international research network and centers. Also several of the research groups at the Institute are members of “Focused Research Areas” appointed by Oslo University Hospital. As part of one of these research initiatives, the Institute is currently building up research activities in stem cell research and regenerative medicine. Yet, a new leadership will be required to maintain the Institute’s preeminent position in the rapidly evolving fields of life sciences.

This report provides an overview of the research groups at the Institute and their major research activities in 2014. Their strong achievements are first of all due to the dedicated and tireless 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), nurses and technicians at Section for Large Animal Research (Vivi Bull Stubberud, Sera Sebastian, and Aurora Pamplona), Roger Ødegaard (engineer/consultant – Large Animal Research) and Irene Stensrud Andersen (Housekeeping) for their relentless contribution to the smooth operation of the Institute.

The Institute maintained high productivity in 2014. Also, 5 of our students successfully defended their thesis for the PhD degree at University of Oslo in 2014.

Thanks to hard work and dedication the research groups of the institute continue to receive substantial external funding from the major funding institutions (The Research Council of Norway, The Norwegian Council on Cardiovascular disease, The Research Fund of the South-Eastern Norway Health Authority).

Institute for Surgical Research, March 2015,

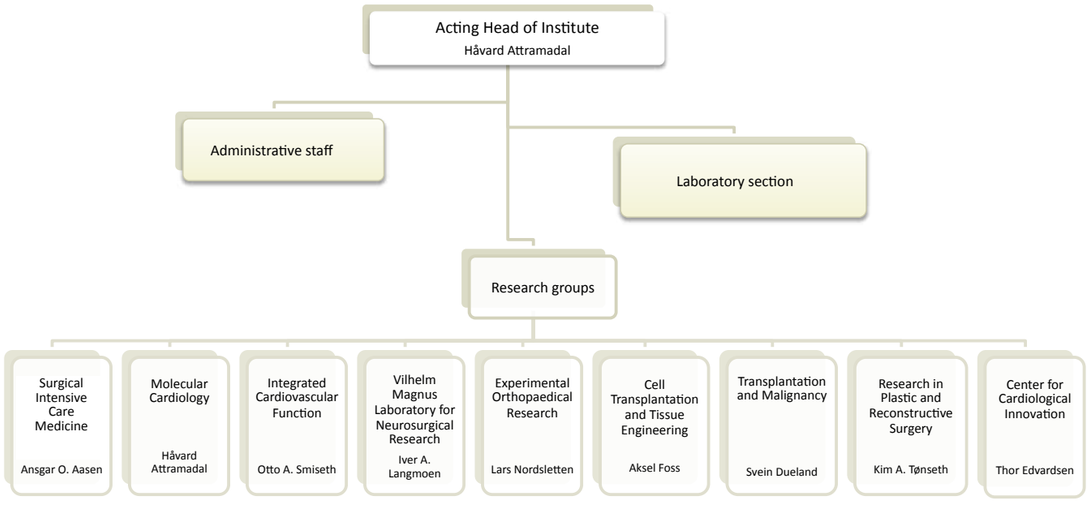
Håvard Attramadal, Professor/Acting Head of Institute

Photo: OUH

Abbreviations

AHUS	Akershus University Hospital
CAST	Cancer Stem Cell Innovation Center
CIT	Clinical Islet Transplantation Consortium
FP 7, EU	Seventh Framework Programme, European Union
LO	Lovisenberg Diaconical Hospital
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
UiT	University of Tromsø

Institute for Surgical Research



Research Groups

Photo: Øystein H. Horgmo, UiO

Surgical Intensive Care Medicine

Leader
Ansgar O. Aasen, Professor, MD, PhD (UiO/OUH)

Deputy leader
Signe Flood Kjeldsen, Head engineer, MSc (UiO)

Scientific staff
Ola Sveen, Prof. Emeritus, MD, PhD
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Yngvar Gundersen, Senior scientist, MD, PhD (OUH)
Claus Danckert Krohn, Consultant, MD, PhD (OUH)
Hamid Shegarfi, Postdoc, PhD (OUH)
Kristin Bjørnland, Consultant, MD, PhD (OUH)
Yun Yong Wang, MD, PhD (OUH)
Claus Vinter Bødker Hviid, MD, PhD-student (OUH)

Professor Ansgar O. Aasen

Research area
Infections following surgery or trauma continue to be a major clinical problem. Due to the immunological consequences of surgery and trauma, infections can develop into severe septic complications and multiple organ injuries. The problem in severe sepsis is a paradoxical and self-destructing inflammation and disturbances in the plasma protease cascade systems leading to dysfunctional host defence and injury to vital organ systems. More than one million patients are expected to die annually from severe sepsis worldwide

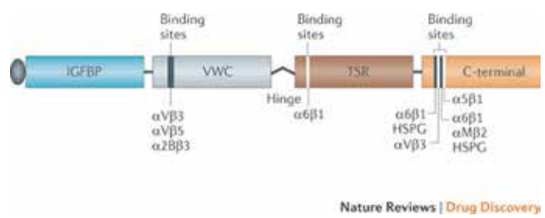
Aims
Our aim is to develop novel means to improve early detection and to prevent or ameliorate the self-destructive inflammation and the abnormal plasma proteolysis in patients with severe infection. A major focus of our work is research into the cellular mechanisms and proteins involved and to facilitate translation of new knowledge from basic re¬search into clinical practice.

Ongoing Projects in 2014

Regulation of CCN1 in septic states and Intestinal Ischemia-Reperfusion
Sepsis remains a very challenging problem estimated to claim 250,000 European lives every year. Despite great medical advances, sepsis remains the leading cause of death in intensive care medicine all over the world.
In recent years, our research group have focused on the importance of extra cellular matrix (ECM)-associated proteins, termed the CCN-family in sepsis using various experimental models.

The work has been performed in close cooperation with Professor Håvard Attramadals research group at the institute and ours colleagues at the Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria.

The CCN proteins comprise a family of six dynamically expressed and multifunctional
extracellular matrix (ECM)-associated proteins. The three initially described family members were Cyr61, connective tissue growth factor (Ctgf), and nephroblastoma overexpressed (Nov).
Later on the WNT1-inducible secreted proteins -1 through -3 (WISP1-WISP3) were identified and included in the family. Initially the proteins were studied because of their structural role in
the ECM. More recently, however, their ability to modify cellular responses to release of inflammatory cytokines, various vasoactive substances and growth factors has been studied (figure 1).



Nature Reviews Drug Discovery 10, 945-963, 2011

Figure 1. The four domains that make up the CCN protein structure and the different m ules each domain binds to.

In our studies we have shown that several members of the CCN-family of proteins are regulated in the organs of the animals with sepsis and early stages of organ dysfunction. We have also analysed sepsis induced CCN1 regulation in progressed stages of sepsis and organ dysfunction. Here we demonstrated that sepsis-induced repression of CCN1 in vital organs occurred simultaneously with a robust increase of circulating CCN1 protein levels. Furthermore we could demonstrate that circulating innate immune cells became CCN1-positive simultaneously with the increase in circulating CCN1 protein. The cells did, however, not express CCN1 mRNA. These results were published in the journal SHOCK and as illustrated in figure 2, the study was highlighted with an illustration from the article on the front-page of the journal.

Figure 2.

Figure 2. Front-page of SHOCK, 41, 233-40, 2014 highlighting our publication "THE MATRICELLULAR "CYSTEINE-RICH PROTEIN 61" IS RELEASED FROM ACTIVATED PLATELETS AND INCREASED IN THE CIRCULATIONDURING EXPERIMENTALLY INDUCED SEPSIS" with a key illustration from the article.

Our studies have also provided the first evidence that platelets carry CCN1 protein and release it upon activation. Altogether, these data strongly suggest that platelets are an important source for the observed increase of circulating CCN1 levels and that this protein targets innate immune cells.

In order to further elucidate the role of CCN proteins as potential player in the regulation of inflammatory responses, postoperative accumulation of Cyr61/CCN1 in surgical wound fluid and local cytokine activation were studied in patients undergoing major orthopaedic surgery for idiopathic thoracic scoliosis.
The study demonstrated as shown in figure 3 that CCN1 is markedly up-regulated in fluid drained from a surgical wound and revealed a connection between CCN1 accumulation and levels of the platelet activation marker sP-selectin.

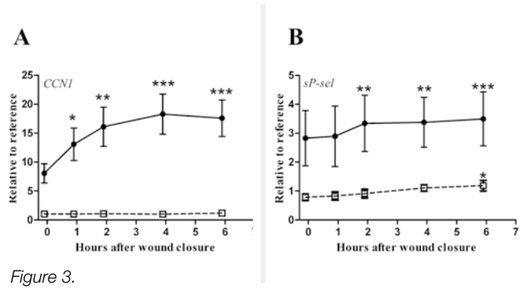


Figure 3.

Figure 3.
Relative CCN1 (A) and soluble (s)P-selectin (B) levels in the wound fluid (solid lines) and systemic
blood (punctured lines) after surgery. Values are presented as mean ± SEM. sP-sel: soluble Pselectin. Claus Vinter B Hviid et al. Postoperative accumulation of Cyr61/CCN1 in Surgical Wound Fluid Precedes Cytokine Activation and is Disparate from Systemic Alterations. J Infect Dis Ther 2014, 2:182. Doi: 10.4172/2332-0877.1000181

The CCN1 accumulation was found to precede the cytokine increases in the drained fluid. Systemic CCN1 levels, by contrast, remained at reference levels throughout the observation period.
In the fall of 2014 the Ph.D. student Claus Vinter Bødker Hviid successfully defended his thesis on CCN proteins in sepsis and acute inflammation based on the work which is partly summarized here.

During the year we have also proceeded with our investigated on the regulation of CCN1 in intestinal tissue in a porcine model subjected to long intestinal ischemia-reperfusion (IIR). In this model a section of the jejunum is subjected to ischemia-reperfusion in fully anesthetized animals. Intestine biopsies were taken from i) ischemic area (IS) ii) borderzone area (RZS) -a segment with sub-normal circulation close to the edge of the ischemic area-, and iii) non-ischemic intestine (NIS) -a segment from an area that was not subjected to ischemia as baseline control segment. CCN1 mRNA of the biopsies measured by real time PCR showed a significant upregulation in both IS and RZS segments compared with NIS. Western blotting experiments confirmed the upregulation of CCN1 at protein level.

Studies on modulation of inflammation caused by agents used for injection treatment of vascular and venous malformations

Sclerotherapy is the targeted chemical ablation of vessels by intravenous injection of a liquid sclerosing drug. The sclerosants destroy the vessel endothelium and possibly additional regions of the vessel wall. After successful sclerotherapy and in the long term, the vessels are transformed into a fibrous cord, a process known as sclerosis in which the vessels are definitely transformed into fibrous cords. The functional result is equivalent to surgical hemostasis and several studies have reported changes in coagulation as well as inflammation status after sclerotherapy.
The present studies were focused on means to attenuate the inflammatory reactions in the blood caused by sclerosing agent and to search ways to reduce the inflammatory effects which can be harmful in sclerotherapy. We have been applying an experimental whole human blood model developed by our laboratory. Its main advantage is that it is a fast and easy way to explore inflammatory responses in a human cell system with complex leukocyte interactions.
After 30 minutes of incubation at 37ºC an inflammatory response was induced in the test-tubes by adding polidocanol (Aethoxysklerol) alone or in combination with the bacterial wall component lipopolysaccharide (LPS). Modulation of this inflammatory response was then studied by addition of the anti-inflammatory corticosteroid Methylprednisolone (Solu-Medrol) and Methyl-prednisolone in combination with the anesthetic agent Xylocain (lidocaine).

As demonstrated in figure 4 a marked modulation of the inflammatory responses in various cytokines including IP-10 (Interferon gamma-induced protein 10) was found by methylprednisolone alone and interestingly an additive effect when the corticosteroid was combined with the anesthetic agent lidocaine.

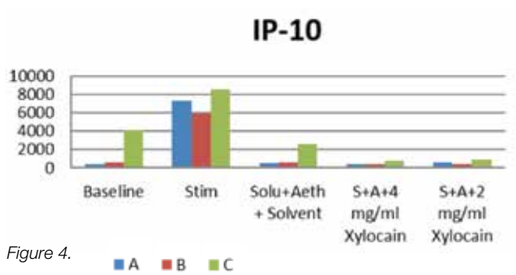


Figure 4.

Figure 4. Modulation of IP-10 response by Methyl-prednisolone (Solu-Medrol) applied alone and in combination with the anesthetic agent Xylocain (lidocaine). A, B, and C represent individual samples of human blood.

Further experiments are now in progress and the concept will be tested in in vivo experimental models in order to explore the possible significance of these observations in creating a more optimized compound for injection sclerosing treatment.

Integrated IT and mobile health systems for intensive care units and acute rescue emergency medicine

For many years we have been engaged in the development of integrated IT and mobile health systems for intensive care units. Our primary aim has been to develop systems that give decision support at early stages in such extremely complicated and time-critical situation. The research have been developed into a business operation, Ewicum, and the company have provided proof-of-concept while finishing international clinical validation with its first remote IT prototypes most recently named EWmonitoring®.
In the last few years the company has been repositioned with additional new products as EWrescue® for acute rescue emergency medicine.

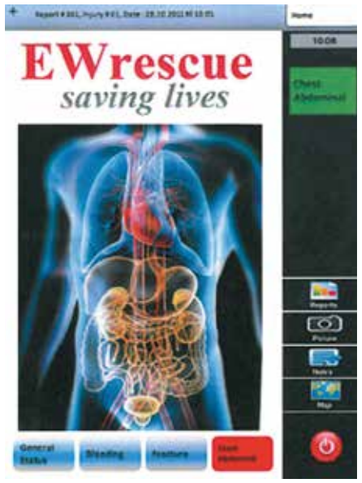


Figure 5.

Figure 5. The EWrescue® integrated IT system for improving process quality within the medical treatment chain of the acute rescue emergency medicine.

These products, based on Cloud computing technologies, generate data to help improve decision making, efficiency and reductions in cost.

The EWQ (early warning quality) platforms integrate important data from the patient with proven algorisms providing unique real time trend monitoring surveillance.

Photo: Kristin Ellefsen, UiO

Collaborators

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- Prof. Christoph Thiemermann, The William Harvey Research Institute, London, UK
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- Prof. Michael Gallimore and Dr DW. Jones, University of Kent, UK
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- Prof. Jan Olav Høgetveit, UiO/OUH, Oslo, Norway
- Prof. Håvard Kalvøy, UiO/OUH, Oslo, Norway

Molecular Cardiology

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Sima Zolfaghari Golmakani, MSc, Research Assistant

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)

Professor Håvard Attramadal

Research Area

Heart failure, a clinical syndrome of advanced cardiac disease of diverse etiologies, is a major cause of morbidity and mortality. Indeed, the incidence and prevalence of heart failure in affluent societies are increasing due to demographics with rising proportion of elderly, as well as increased survival of myocardial infarction. Despite implementation of several new treatment modalities during the last 20 years, heart failure is still a progressive and ominous condition indicating that important pathogenic mechanisms remain unmodified by the most current treatment modalities. Thus, there is an impetus for new and more effective pharmacological interventions.

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 also reflects in alterations of cardiac 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 still remain to be identified. Thus, an important focus of our research group is to unravel the signal transduction mechanisms that generate the dysfunctional signals leading to pathologic remodeling and progression of heart failure. Another important conceptual approach and aim of our research group is that of delineating 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 cells and progenitors and regeneration of myocardial tissue following tissue injury. The purpose of these investigations is to provide new knowledge of disease mechanisms enabling development of novel pharmacological interventions for heart failure.

Our research group is a multidisciplinary team of experts in gene technology, molecular and cellular biology, as well as experimental cardiovascular 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. The Institute for Surgical Research provides infrastructure with state-of-the-art equipment for gene technology, as well as high-resolution echocardiography and integrated physiologic assessment of cardiac function in both small and large animals.

Major Aim

Dysfunctional cardiac signaling mechanisms and signals astray are considered major causes of pathologic myocardial hypertrophy and predisposition to heart failure. Increasingly, dysfunctional signaling mechanisms are implicated in increased production of free oxygen radicals, mitochondrial dysfunction and reduced tolerance to hypoxia. Thus, a major goal of our research group is to dissect the function of myocardial autocrine/paracrine factors, their cognate receptors, and intracellular pathways in cardiac myocytes and fibroblasts. Of particular interest is also the cross-talk and intercellular signaling between cardiac fibroblasts and cardiac myocytes. New knowledge on the function and mechanisms of signaling pathways in the heart may provide basis for development of new and more effective therapeutic intervention in acute coronary syndromes and heart failure.

Current specific aims of the research group

1. Elucidate the function of novel G protein-coupled receptors and their signaling pathways in the heart in health and disease.

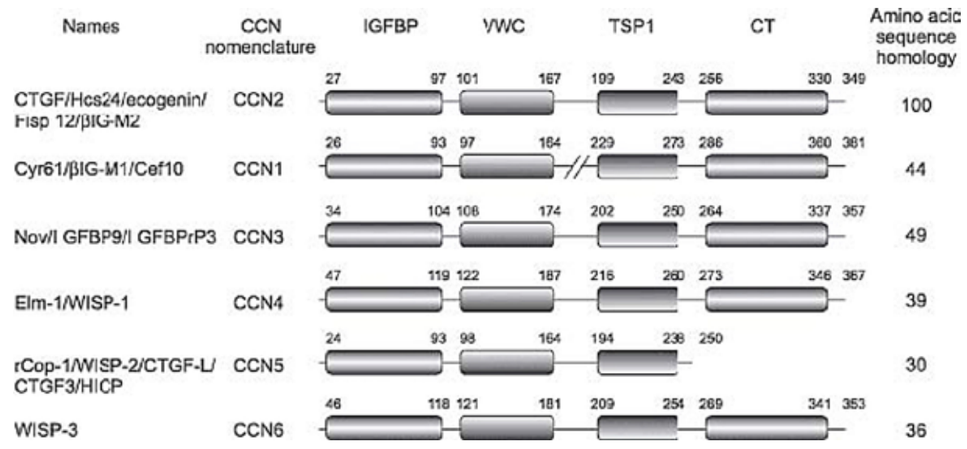
2. Another major focus of our group is to resolve how G protein-coupled receptor kinases (GRK) control the sensitivity of receptors to their cognate agonists, as well as to decipher the role of GRKs in controlling G protein-dependent versus G protein-independent signaling in the heart in health and disease, with particular focus on heart failure.

3. Uncover the function of myocardial autocrine/paracrine factors or cytokines that are activated or induced in heart failure. Current focus is on delineating the functions of secreted matricellular CCN proteins, in particular CCN1, CCN2/CTGF (connective tissue growth factor), and CCN5/ WISP-2 (Wnt-inducible secreted protein-2), secreted regulators of Wnt signaling, as well as the TGF-ß super family cytokine GDF-15 in heart failure. The CCN proteins (CCN is an acronym for the first three members 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 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 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. Cardiac myocyte GPR81 inhibits synthesis of cAMP in response to lactate. We have shown that cardiac myocyte GPR81 is upregulated in heart failure in proportion to the functional derangement. We are currently investigating the functional role of GPR81 in genetically-engineered mice.

2) Dissecting the function of cardiac G protein-coupled receptor kinases (GRKs) in health and disease.
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. Yet, the signaling pathway(s) implicated in CCN2-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 remains to be resolved.

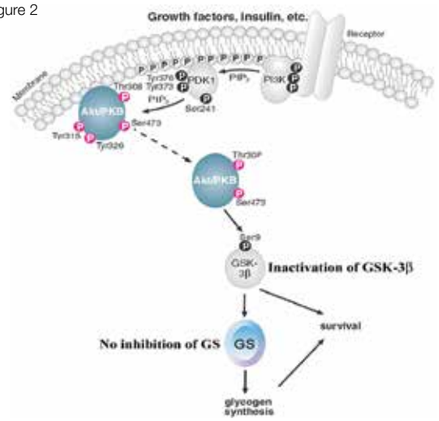


3) Role of CCN2 - connective tissue growth factor - in regulation of tolerance towards ischemia-reperfusion injury and in resisting maladaptive cardiac remodeling during chronic pressure overload.
Myocardial CCN2 is highly expressed in the developing heart in fetal life and apparently plays crucial role in cardiac development. However, myocardial expression of CCN2 is repressed in the postnatal heart under physiologic conditions. Interestingly, myocardial expression of CCN2 is reactivated or induced during evolving heart failure. Previous findings from our laboratory demonstrate that induction of myocardial CCN2 appears to be a general response to evolving heart failure, i.e. induction of myocardial CCN2 occurs in heart failure of diverse etiologies. Induction of tissue expression or increased 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. The 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 both ex vivo in Langendorff-perfused hearts as well as in vivo in mice subjected to transient ligation of the left anterior descending coronary artery in situ. 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). These findings have led to filing of patents for protection of the potential commercial development of CCN2/CTGF as a new pharmacologic treatment in acute coronary syndromes with the objective of minimizing myocardial necrosis. Verification of the data in large animal models, commercial development plans, including plans for early clinical testing, are currently being pursued in collaboration with Birkeland Innovation/ Inven2 AS, the TTO of University of Oslo and Oslo University Hospital. A recent report from our group also demonstrates that CCN2 enhances healing after myocardial infarction (Gravning, J. et al PlosOne 2012;7(12):e52120). However, the mechanisms whereby CCN2 enhances scar healing after myocardial infarction is still obscure and a matter of investigation. Interestingly, the study also reports data from patients admitted for acute ST-elevation myocardial infarction. The patient cohort segregated in two groups, one in which plasma CCN2 levels were elevated after myocardial infarction and the other in which plasma CCN2 levels remained unchanged or lower. Patients that had elevated plasma CCN2 levels after MI displayed 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 cohort was relatively small, these findings are translational evidence supporting a cardioprotective function of CCN2. Another report from our laboratory published in 2013 provides evidence that CCN2 attenuates pathologic cardiac hypertrophy associated with chronic pressure overload following aortic constriction. The diminished hypertrophic response of cardiac myocytes from transgenic mice overexpressing CCN2 was related to inhibition of NFAT transcriptional activities (Gravning, J. et al. Int J Cardiol. 168:2049-2056, 2013).

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. Furthermore, analysis of the phosphoproteome of cardiac myocytes following stimulation in the absence or presence of recombinant CCN2 revealed that the PI3 kinase/AKT/GSK-3ß pathway is a major intracellular signaling pathway of CCN2 (Figure 2).

Indeed, our data also demonstrate that this pathway is crucial for CCN2-dependent cytoprotection towards hypoxia/reoxy-

Figure 2



genation-induced cell injury. The mechanisms of the cytoprotective actions of CCN2 are currently a major endeavor in our research group. However, the cytoprotective actions of CCN2 apparently entail activation of a transcriptome that includes the gene ontology groups anti-apoptosis, oxidative stress-associated genes and hypoxia-induced genes (Moe, IT et al. J Cell Commun Signal. 7:31-47, 2013). To facilitate studies on the mechanisms of CCN protein actions in cells, our group has currently established eukaryotic expression systems for large scale production and purification of several of these proteins.

Our research group is currently member of a national consortium of research groups that in 2012 obtained funding from UNIKARD, a research program sponsored by the Norwegian Research Council and the Regional Health Authorities, on a major effort to investigate the mechanisms and implications of physical exercise on the progression heart failure. One of the focus areas of this consortium is to unravel the epigenetic role of exercise training in targeting the pathophysiologic mechanisms of heart failure

Collaborators

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- 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. Finn Olav Levy, Dept. of Pharmacology, University of Oslo.

Photo: Øystein H. Horgmo, UiO

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Sebastian Imre Sarvari, MD, PhD, Cardiologist (OUH)
Kristoffer Russell, MD, PhD, Cardiologist (OUH)
Espen Bøe, MD, PhD-student (NCCD)
Nina Eide Hasselberg, MD, PhD-student (CCI)
Jørg Saberniak, MD, PhD-student (CCI/OUH)
Petter Storsten, MD, PhD-student (OUH)
Øyvind Senstad Andersen, MD, PhD-student (SENRHA)
Ola Gjesdal, MD, PhD, Cardiologist (OUH)

Professor Otto A. Smiseth

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 idea is to develop better diagnostic understanding and solutions and to translate these into improved clinical practice. 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.

Specific objectives
1. To investigate mechanisms of left ventricular (LV) dyssynchrony and develop better methods for selecting patients for CRT.
2. To investigate mechanisms of LV diastolic dysfunction and to develop better diagnostic methods of diastolic heart failure.
3. To investigate right ventricular function in patients congenital abnormalities which involve the right ventricle.

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, Rikshospitalet, Research group: Molecular Cardiology
- Prof. Ivar Sjaastad, OUS, Institute for Experimental Medical Research
- Consultant Harald Brunvand, MD, PhD, Sørlandet hospital, Arendal.

Photo: Kristin Ellefsen, UiO

Center for Cardiological Innovation

Center Leader and Management

Thor Edvardsen, Professor, MD, PhD, Center Director SFI-CCI, Head of Department of Cardiology (OUH / UiO)
Kristina Hermann Haugaa, Associate Professor, MD, PhD, Center Director of Cardiology Research (OUH / UiO)
Eigil Samset, PhD, Center Coordinator (GE Vingmed Ultrasound AS / UiO)
Samuel Wall, PhD, Deputy Director of Scientific Computing (Simula Research Laboratory)
Piritta Nyberg, Administrative Coordinator (Oslo University Hospital)

Professor Thor Edvardsen

Scientific Staff, Oslo University Hospital

Otto Smiseth, Professor, MD, PhD, Head of Division for Cardiovascular and Pulmonary Diseases
Erik Kongsgård, MD, PhD, Head of Section for Electrophysiology
Svend Aakhus, Professor, MD, PhD, Head of Section for Echocardiography
Lars Aaberge, MD, PhD, Head of Section for Treatment and Diagnostics
Jan Olav Høgetveit, Associate Professor, PhD, Head MTA Research and Development
Håvard Kalvøy, PhD, Senior Scientist, Deputy Head of R&D for Medicine and Technology
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Helge Skulstad, MD, PhD, Consultant Cardiologist
Einar Hopp, MD, Consultant Cardiologist
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Morten Eriksen, MD, PhD, Senior Researcher
Sebastian I. Sarvari, MD, PhD
Kristoffer Russell, MD, PhD
Margareth Ribe, Research Nurse

PhD-Students

PhD and MD Students
Jørg Saberniak, MD, PhD student
Nina Eide Hasselberg, MD, PhD student
Trine S. Fink Håland, MD, PhD student
Stian Ross, MD, PhD student
Lars Gunnar Klæboe, MD, PhD student
Espen Bøe, MD, PhD student
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Ida Skrinde Leren, MD, PhD student
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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.

From left: Trine S. Fink Håland, Lars Gunnar Klæboe, Ida S. Leren, Nina E. Hasselberg and Jørg Saberniak

Ongoing projects:

Echocardiography may replace exercise testing in certain clinical settings

Main contributors: Hasselberg NE, Haugaa KH, Sarvari SI, Gullestad L, Andreassen AK, Smiseth OA, Edvardsen T.

A subset of patients suffering from heart failure have preserved ejection fraction, defined as heart failure with preserved ejection fraction (HFpEF). HFpEF patients constitute around half of the heart failure population and have as poor prognosis as those with reduced ejection fraction. However, these patients are difficult to detect and to diagnose. Cardiopulmonary exercise testing is a strong predictor of mortality but it remains underutilized clinically because of costs and lack of trained personnel and equipment. Previous studies have failed to find a relationship between cardiac pump function and exercise capacity. We explored the relationship between exercise capacity and myocardial mechanics in heart failure patients with preserved and reduced EF. We found that deformation of the left ventricle measured as strain by echocardiography was closer related to exercise capacity than EF. These results indicate that echocardiographic strain may replace cardiopulmonary exercise testing in certain clinical settings.

Athletic activity impairs myocardial function in ARVC subjects

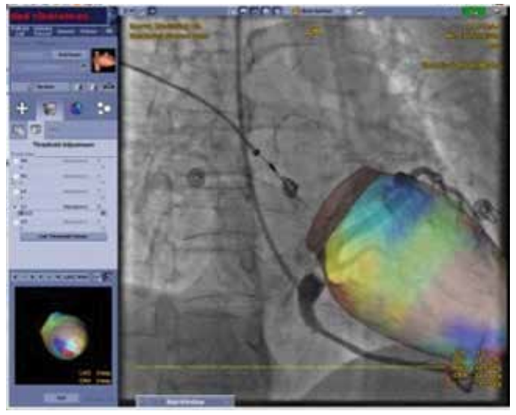
Main contributors: Jørg Saberniak, Nina E. Hasselberg, Rasmus Borgquist, Pyotr G Platonov, Sebastian I.Sarvari, Hans-Jørgen Smith, Magareth Ribe, Anders G. Holst, Thor Edvardsen, Kristina H. Haugaa

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disease with an increased risk of life threatening arrhythmias and sudden cardiac death. Sudden death may be first devastating symptom in apparently healthy young individuals, which is a tragedy for their families. The mechanism behind the disease is complex and involves dysfunction in the glue between the heart muscle cells, which ultimately leads to severe damage of the cardiac muscles with potentially severe consequences. Athletic activity may increase the risk of life threatening arrhythmias in individuals with ARVC and these individuals are recommended to restrain from competitive sports. However, the impact of high level exercise on heart function is not fully understood. We investigated 110 ARVC individuals of which almost half had a history of athletic activity. We showed that athletes with ARVC had reduced cardiac function compared to non-athletes in ARVC subjects. Interestingly, the amount and intensity of exercise activity was associated with impaired function of both heart chambers. Athletic activity may accelerate the development of heart disease in patients with ARVC. This finding adds to current guidelines for sports recommendation in ARVC patients to restrain from competitive sports.

Echo-guided placement of leads for Cardiac Resynchronization Therapy

Main contributors: Aleksandar Babic (GEVU), Hans Henrik Odland (OUH), Olivier Gerard (GEVU) and Eigil Samset (GEVU)

Patients suffering from heart failure, a condition where the heart is not able to supply the body with enough blood, can often benefit from cardiac resynchronization therapy. This therapy involves implanting a special pacemaker with leads going into the right ventricle and the coronary veins (blood vessels on the outer surface of the heart, draining blood away from the heart muscle). Despite that many patients experience very good improvements after this therapy, about 30% does not experience this benefit and some can even get worse. The reasons for this are not fully understood and are probably a combination of several factors including patient selection (some patients could have been excluded from this therapy) and failure to put the leads in the most optimal positions.



We have developed a guidance system that allows the treating cardiologist to co-visualize coronary veins (from x-ray) and which part of the heart that needs to be activated first by the pacemaker (from ultrasound strain analysis). The cardiologist can find the best position to place the lead based on echo-findings done before the implantation and image-guidance used during the implantation.

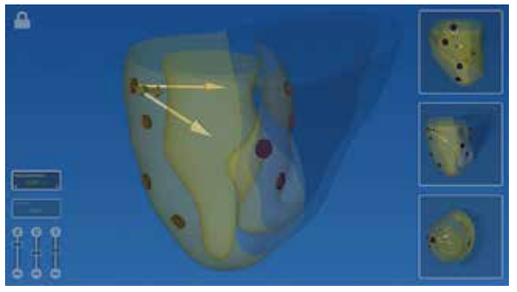
Pacertool

Main contributors: Hans Henrik Odland (OUH), Erik Kongsgård (OUH), Fred-Johan Pettersen (OUH), Morten Flattum (OUH), Joachim Berdal Haga (Kalkulo), Marek Gayer (Kalkulo), Christian Tarrou (Kalkulo)

Pacertool is software that is developed in collaboration between Kalkulo and OUH. The software is a part of a system that will provide feedback to the operator when implanting a cardiac resynchronization device (CRT) and represents the interface between measured parameters and the operator. The aim of this system is to improve the current 50-60% responder rate of CRT.

The pacertool software will allow the implanter to individualize pacing lead positions to optimize the resynchronization effect of the CRT device. Parameters that are measured during implantation will be collected and displayed to highlight the optimal site of electrode placement. Imaging from pre-implantation studies, as echocardiography and magnetic resonance imaging can be incorporated to display patient specific cardiac geometry. When coronary sinus angiography is performed during the implantation procedure, the patient specific anatomy can be segmented and utilized during the procedure. When incorporated in research different positioning can be compared and analyzed.

The data from any procedure can be used for predictive patient specific simulation. With different electrode positions data from every patient is stored together with geometry. This will allow for validation of simulation algorithms and for calculating predictive reverse remodeling. When performed during the implantation procedure, optimal sites for lead placement can be highlighted and compared to acute study hemodynamic parameters. This may provide validity to the simulation protocol and possibly provide insight into patient specific reverse remodeling processes.



When used in combination with bioimpedance studies, this system will provide the operator with acute feedback from each electrode position and allow the operator to move the electrodes into different positions until optimal sites of stimulation are found. During this process biofeedback will guide positioning in a closed-loop fashion. Bioimpedance as measured in collaboration with the medical engineering section at OUH will provide insight into hemodynamic and mechanical characteristics of the heart during each procedure.

Dissemination activities

Center for Cardiological Innovation has a notable presence at both national and international congresses. Center members from Oslo University Hospital have participated in approximately 70 dissemination activities during 2014, including abstracts.

Members have presented posters, given presentations, and had chair and judge duties in several renowned scientific conferences around the world, including the annual European Society of Cardiology Congress (ESC), American Heart Association (AHA) meeting, the annual Center for Heart Failure Symposium (CHFR), the Autumn Meeting for the Norwegian Society of Cardiology, and the EuroEcho Imaging Congress, just to mention a few.

PhD students Nina Eide Hasselberg and Ida Skrinde Leren won the Best Poster Award at the 12th Annual Center for Heart Failure Research Symposium on September 18th. PhD student Jørg Saberniak was recognized with a high scoring abstract at the EuroEcho Imaging Congress in December. He received the same recognition in 2013, along with fellow PhD students Ida Skrinde Leren and Nina Eide Hasselberg. Several of the Center's PhD students were also noted at the ESC Congress in Barcelona in August-September.

Associate Professor and Center Director of Cardiology Research, Kristina Herman Haugaa, has been interviewed by NRK.no and Cardiostim Times the past year. Both articles focused on Long QT Syndrome. Kristina Haugaa, MD, PhD is one of Norway's foremost experts on LQTS and has spent years studying this syndrome.

Center Coordinator Eigil Samset (GEVU) has been interviewed by the Research Council of Norway and Center Director, Professor Thor Edvardsen has featured in EuroEcho-Imaging

Congress News and in the Congress Reports for the European Society of Cardiology

Members of the CCI have published close to 60 articles in peer reviewed journals during the past year. These include articles from the Center Partners GE Vingmed Ultrasound AS and Simula Research Laboratory.
For the complete list of publications, other news and information regarding the CCI, visit the Center's website www.heart-sfi.no.

Vilhelm Magnus Laboratory for Neurosurgical Research

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Professor of Neurosurgery (UiO / OUH)

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Artem Fayzullin, MD, PhD Student (Norwegian Cancer Society)
Mrinal Joel, MSc, PhD Student (SENRHA)
Cecilie Sandberg, MSc, PhD Student
Håvard K Skjellegrind, MD, PhD Student (VIRUUS)
Kirsten Strømme, PhD Student
Zanina Grieg, Research Technician, MSc (NRC)
Birthe Mikkelsen, Research Technician, MSc
Emily Palmero, Research Technician, BSc
Inger Marit Stark Valstad, Assistant & Study Nurse

Network partnerships
Cancer Stem Cell Innovation Center (CAST) Norwegian Stem Cell Center

Research area
Vilhelm Magnus Lab is the translational research group for neurosurgery at Oslo University Hospital. The goal of the laboratory is to build a bridge between the basic biological sciences and clinical neurosurgery, to explore the biology underlying neurosurgical conditions, and to facilitate translation of new knowledge from basic research disciplines into the clinic. Research efforts therefore encompass both normal brain cell development and disease states such as tumours. Investigations aim to understand these processes and develop methods to treat disease as well as promote cell replacement to heal damaged brain tissue.

Aims
The goal of the laboratory is to build a bridge between the basic biological sciences and clinical neurosurgery, to explore the biology underlying neurosurgical conditions, and to facilitate translation of new knowledge from the basic research disciplines into the clinic. Research efforts therefore encompass both normal brain cell development and disease states such as tumours. Investigations aim to understand these processes and develop methods to treat disease as well as promote cell replacement to heal damaged brain tissue.

Stem cells (SC) from the adult human brain
A central dogma in neuroscience has been that the mature brain is unable to produce new neurons. Towards the end

Professor Iver A. Langmoen

of the 20th century, studies in birds and rodents came to question this doctrine as new markers for labelling neurons combined with techniques for identifying cells that had been born in adult life, suggested that new neurons sometimes may develop later in life in some species.

At the turn of the century, these findings were to some degree extended to the human brain, as a few research groups had been able to culture immature cells from the human ventricular wall and hippocampus. It was still not known, however, whether it would be possible to differentiate these cells into functional neurons, i.e. cells with typical neuronal action potentials with the ability to communicate via synapses.

The putative existence of an adult human brain stem cell type with the ability to proliferate and differentiate into mature neurons created huge interest as one could now envisage treatment of neurological diseases with either transplantation of stem cells that have been expanded in vitro or by mobilization of endogenous progenitor cells. The work on developing functional neurons from cells from the human ventricular wall was started in Professor Langmoen's laboratory at the Karolinska Institute in Stockholm by Morten C. Moe and Mercy Varghese. Human tissue was harvested from the wall of the lateral ventricle in temporal lobe specimens resected due to medically refractory epilepsy (Moe MC et al., Brain, 2005). In keeping with earlier results from other groups they were able to expand stem cells from the ventricular wall as cell clusters (neurospheres) in vitro. Following dissociation and exposure to differentiation cues these cells went through characteristic steps of morphological and electrophysiological development and developed into the three principal building blocks of the brain: astrocytes, oligodendrocytes and neurons.
Our group was first to demonstrate that it is possible to transform immature progenitor cells from the adult human ventricular zone into functional neurons, i.e. cells with typical neuronal action potentials and the ability to communicate through synapses (Figure 1). Essentially, a small nervous system could

develop from a single human stem cell in vitro. This “nervous system”, consisting of glial cells as well as a large number of neurons, communicated via synapses. These results were selected from more than 15000 abstracts for presentation at the press conference of the Society for Neuroscience 2005 (Westerlund U et al., Exp Cell Res 2003, Moe MC et al., Brain, 2005 and Neurosurgery 2005).

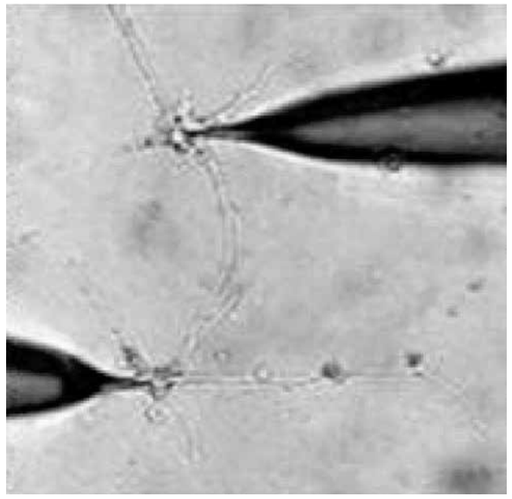

Figure 1 – Dual patch-clamp recording from neighbouring neuron- like cells, demonstrating synaptic communication between the cells.

For stem cells to be useful in the clinical setting, it must be demonstrable that after transplanting them to another adult brain they can survive and integrate into the recipient neuronal circuitry. Using rats with a selective lesion of the hippocampal CA1-region (a small part of cerebral gray matter), Håvard Ølstørn and Morten C. Moe demonstrated that stem cells from the adult human brain are not only able to survive in the rat brain, but also selectively target and migrate to the area with the lesion (Olstorn H et al., Neurosurgery, 2007). Through pre-differentiation, i.e. “pushing” the cells in a neuronal direction prior to transplant, it was possible to significantly enhance the development of neurons following transplantation. This study for the first time showed that stem cells from the adult human brain are able to survive and differentiate in another adult brain (Olstorn H et al., Neurosurgery, 2011).

Expansion of adult human brain derived stem cells

An avenue where adult human neural stem cells offer tremendous promise is in the treatment of CNS diseases such as Parkinson’s disease, stroke, Alzheimer and spinal cord damage. The advent of induced pluripotent stem cells might allow for generation of a large pool of autologous cells – but the use of such cells are still dangerous as they have the propensity to induce tumours after transplantation. The use of adult human neural stem cells avoids this issue. The main problem with such cells are however the low number of cells available from the patient. Effective in vitro expansion is a necessity both for further characterization of neural stem cells, but also for the development of further therapies.

An improved protocol for propagation of adult human neural stem cells has been developed that allows for an almost unlimited expansion of cells while maintaining stem cell characteristics like Sox2 and Oct4 expression (Murrell W et al., PLoS One 2013). In plastic adherence cultures containing the mitogens cells derived from the subventricular zone, hippocampus and white matter expand exponentially (Figure 2). Traditionally, cells derived from brain are considered to be restricted to neuroectodermal differentiation (i.e. neurons and glial cells). Interestingly, after transplantation to the primitive streak chick gastrulae we could demonstrate the incorporation of brain derived in vitro expanded cells into striated muscle, heart muscle and the brain vesicle. Thus, these brain derived cells are truly multipotent.

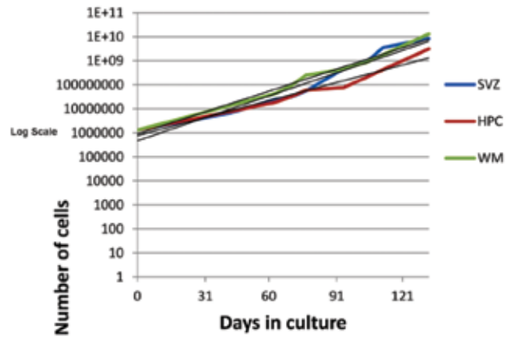

Figure 2 – Early expansion of brain derived stem/progenitor cells from the subventricular zone (SVZ), hippocampus (HPC) and white matter (WM).

Stem cells and brain cancer

Cancers of the brain and meninges are the 7th most common cancer in adults and the most common form of cancer in children. The most common form of cancer in the brain, glioblastoma, is also the most malignant. Despite the efforts of surgery, chemo- and radiotherapy the average survival is only just over nine months. In parallel with results emerging from other research institutions, our group has shown that only a subpopulation of cells in brain cancers have the ability to proliferate and initiate new tumours following transplantation to immunodeficient mice. Due to similarities between these highly malignant cells and normal somatic stem cells, these cells are coined cancer stem cells (CSCs). This cell population infiltrates surrounding brain tissue, appears resistant to both irradiation and chemotherapy, and is the likely explanation for recurrence.

Through a direct comparison of adult human neural stem cells and CSCs we showed that these cells share a number of properties (Varghese M et al., Neurosurgery, 2008). Both normal and tumour stem cells showed a high proliferation rate. Interestingly, the proliferation rate fell dramatically also in tumour stem cells when they were induced to differentiate. Normal and tumour stem cells showed a similar pattern of differentiation, i.e. in neuronal and glial directions, although differentiated cells from the tumour were clearly abnormal morphologically and differentiation in itself progressed much faster. Both cell types proliferate under identical conditions in three dimensional structures as multicellular spheres. In a follow-up study, we found that both stem cell- and CSC cultures, giving rise to neuro- and tumourspheres, contained similar cell types. The organization in these structures differed, as the rapidly expanding tumourspheres appeared to have a more organized structure (Vik-Mo et al., Exp Cell Res. 2011) (Figure 3).

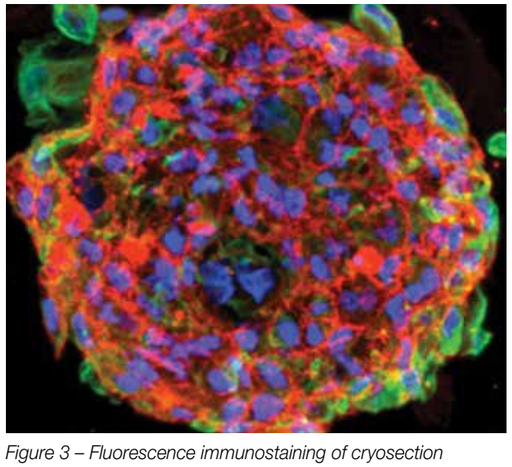

Figure 3 – Fluorescence immunostaining of cryosection of tumoursphere stained with antibodies towards the putative stem cell/tumour markers tenascin C (red) and Vimentin (green).

Cecilie Sandberg defended her PhD-thesis “A Study of Stem Cells from Gliomas and Adult human Brains – Support for a clinical role of glioma stem cells” in March 2014. Her thesis included studies that further compare adult human neural stem cells and CSCs. The transcriptomes of the two cell types were analyzed in collaboration with Winston Hides group at Harvard School of Public Health, Boston, USA. The results of this comparison show that although the two cell types share common stem- and lineage-related markers, CSCs show a more heterogeneous gene expression. We identified a number of pathways that are dysregulated in CSCs connected to regulation of focal adhesion, actin cytoskeleton, axon guidance as well as the Wnt signalling pathway (Sandberg C et al., Exp Cell Res, 2013). A subset of these pathways has previously been identified in leukemic stem cells, suggesting that CSCs of different origin may have common features. Genes upregulated in CSCs were also highly expressed in embryonic and induced pluripotent stem cells. We found that canonical Wnt- signalling plays an important role in CSCs, but not in adult human neural stem cells. As well we identified a 30-gene signature highly overexpressed in CSCs (Figure 4). The expression of these signature genes correlates with clinical outcome and demonstrates the clinical relevance of CSCs.

The transcriptome of adult human neural stem cells has also been further characterized in a separate study and identified genes, pathways and proteins that are significantly up-regulated in adult human neural stem cells compared to adult brain tissue (Sandberg C et al., PLoS One 2014).

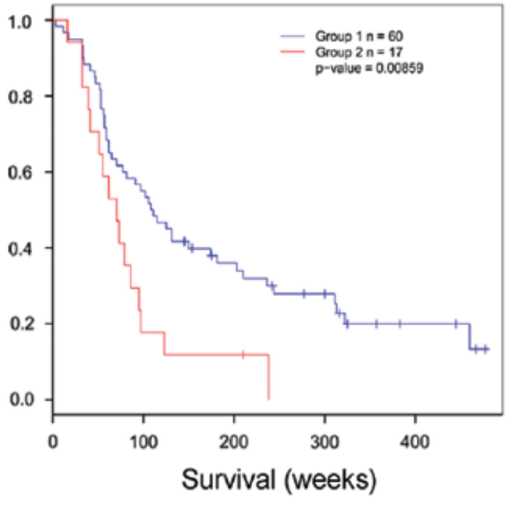

Figure 4 – The enrichment of the CSC-upregulated signature correlates with decreased survival of glioma patients. Kaplan Meier plot of patients from a publically available dataset (Phillips et al., Cancer Cell, 2006) showing significantly decreased survival of glioma patients with a high expression of the 30-gene signature (group 2, red).

Mrinal Joel has characterized glioblastoma CSCs in xenotypic tissue environments under main supervision of Professor Joel Glover of Norwegian Cancer Stem Cell Centre. To examine the effects of embryonic tissue microenvironments CSCs were transplanted into a central neural tissue microenvironment in the chicken embryo. Within the proliferative embryonic neural tissue, the cells exhibited reduced proliferation and survival, altered gene expression, and formed no tumours. This in marked contrast to their aggressive behaviour in vitro and tumour formation in other tissue microenvironments including the chorioallantoic membrane of the chicken embryo and the brain of adult severe combined immunodeficiency (SCID) mice. Surviving cells in the spinal neural tube exhibited tumour-atypical expression profiles of neuron-, glia-, stem cell-, and tumour-related genes. Thus, embryonic neural tissue provides a poor environment for glioblastoma CSC survival and tumour formation, and redirects differentiation toward a more benign phenotype. Understanding the anti-tumourigenic effects of this embryonic tissue microenvironment could provide opportunities to develop novel therapies for GBM treatment. (Joel M et al., Dev. Dynamics, 2013).

Targeting Cancer Stem Cells in Glioblastoma

Further work is now being done to identify possible genes up-regulated in glioblastoma CSCs. The identified genes are involved in cell-cycle/division, epigenetic regulation, signalling and down-regulation of tumour-suppressors. Several of the candidate genes are implicated in cancer (breast, ovary and colon), while others have no known associations to cancer or have unknown functions. The presence of these targets has been confirmed by real-time polymerase chain reaction (qPCR), Western blot and immunohistochemistry on tissue sections and cell cultures as well as publically available dataset (Rembrandt, TCGA). These data are likely to be published during 2015.

To explore the functional importance of the potential target genes the lab has established lentiviral-based shRNA delivery and started to test the potential of gene knock-downs (KDs) to inhibit growth of CSCs. After obtaining stable knockdown the cell cultures are subjected to functional studies including in vitro effects on proliferation, apoptosis and sphere- formation. The biological importance of these findings is then further investigated in vivo using our xenotransplantation model in immunodeficient SCID mice. PhD-student Awais Mughal has, under main supervision of Biljana Stangeland, investigated the role of a N-acetyltransferase (NAT12) and found that this protein plays an important role in growth and survival of glioblastoma CSCs (Mughal et al. Knockdown of NAT12 reduces tumorigenic features of glioblastoma stem cells, submitted, Molecular Cancer). Mrinal Joel has investigated the role of PDZ-binding kinase (PBK) in glioblastoma CCSs (Joel M. et al. Targeting PBK/TOPK decreases growth and survival of glioblastoma stem cells in vitro, and atteneuates tumor growth in vivo, submitted, Mol Cancer Ther).

We have also identified the Wnt-pathway as a promising target in glioblastoma CSCs. Further exploration of the Wnt-pathway is performed by MD/PhD student Kirsten Strømme. By comparing the expression of Wnt related-genes in GSCs and adult human neural stem cells, we have revealed a conserved six-gene mRNA expression pattern. The expression of three of these signature genes correlated with clinical outcome in patients with malignant glioma. As the most dysregulated of the genes identified, we chose the downregulated Wnt inhibitor sFRP1 for more in-depth analysis. We found that sFRP1 was downregulated through methylation of the sFRP1 promoter and that sFRP1 was silenced also at the protein level. Restoration of tumor suppression through treatment with recombinant sFRP1 decreased in vitro proliferation and sphere formation of three primary GSC cultures in a dose-dependent manner. Subsequent cell cycle analysis showed that treatment with sFRP1 reduced the number of cells undergoing cell division and significantly increased apoptosis. In conclusion, our results suggest that Wnt signaling is important for maintenance of the GSCs phenotype. This insight may be used for the development of new treatment strategies for malignant gliomas based on Wnt signaling inhibition.

Through collaboration with Professor Kjetil Taskéns group at Biotechnology Centre of Oslo, phospho-specific flow cytometry signal profiling of glioblastoma CSCs analysis were performed to evaluate phosphorylation status of Akt/Erk/S6 and assessment of rapamycin-mediated mTOR inhibition. This method demonstrated a potential to improve the understanding of aberrant signalling in glioblastoma and other solid tumours (Cornez et al., J. Neurooncol., 2013).

Single cell-time laps imaging

The Vilhelm Magnus Laboratory has previously studied the effects of hypoxia and glucose deprivation in brain tissue and tumour-derived cell cultures using various assessments of mitochondrial function (Larsen GA et al., Brain Research, 2006). Håvard Skjellegrind has worked on live imaging of single cells in heterogeneous normal stem cell and tumour stem cell cultures upon hypoxic conditions. This work has been done in collaboration with Professor Lars Eide, Department of Clinical Biochemistry. Upon differentiation of CSCs, the tolerance of hypoxia changes, thus implying that differentiation therapies in malignant gliomas may have to take situations of hypoxia in consideration. Skjellegrind is planned to defend his PhD thesis in 2015.

Studies on single cell behaviour of neural stem cells, CSCs and established cell lines are done by Artem Fayzullin. He is exploring the pattern of single cell movement and mitosis of GFP- expressing cells transplanted to live rodent brain slices by time-laps imaging. Such slices can be maintained alive in physiological conditions for a long time - more than 1 month - and give a good opportunity to follow the invasion in relatively “natural” conditions (Figure 5).

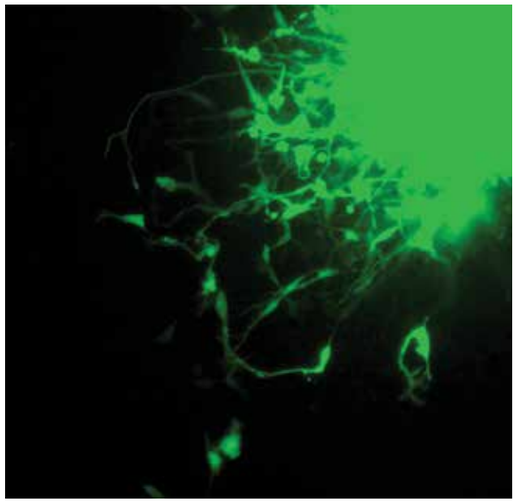

Figure 5 – Glioblastoma stem cells from a patient, grafted into brain slices, aggressively invade from tumour bulk to healthy brain.

This project is funded through the Norwegian Cancer Association, and was picked to promote their funding of research activities on the National Science Week fair in Oslo. The stand was very popular and had a very high number of visitors.

Immunotherapy against brain tumour stem cells

PhD-student Jinan Behnan has established the GL261/C57 BL6 model for brain tumour immunotherapy. This is considered one of the prime models for exploring interaction between the tumour and the hosts immune apparatus and stroma. We have described the presence of cells with mesenchymal stem cells characteristics within the GL261 cell line. Upon transplantation of such cells to C57BL6 mice similar mesenchymal cells are recruited from the host, and actually make up most of the tumour bulk. The recruited cells develop tumourigenic properties on their own (Behnan et al., Stem Cells, 2014).

Behnan has also used the established model for preclinical testing in drug development in collaboration with the biotech company Lytix Biopharma. Here we have explored the possible use of adjuvant stimulation in immunotherapeutic treatment of glioblastoma.

Clinical protocols

Based on our preclinical studies we have developed a clinical protocol for immunotherapeutic targeting of glioblastoma CSCs. Patient derived CSC are derived from the brain tumour a surgery. Such cells are cultivated under conditions allowing for clinical use of the cell product under Good manufacturing Procedures (GMP) (Figure 6). mRNA is harvested from tumourspheres and amplified in vitro, before being transfected into patient derived monocyte derived dendritic cells. Such cells are injected back to the patient as intradermal injections in combination with standard treatment for glioblastoma. This clinical trial is derived from the collaboration through the Cancer Stem Cell Innovation Center (SFI-CAST) and is collaboration between the Departments of Neurosurgery, Cell Therapy, Clinical Cancer Research and Oncology. The phase I/II trial has now completed inclusion of patients, and the results from the first eleven patients have been published (Vik-Mo et al., Cancer Immunol. Immunotherapy, 2013). Autologous CSC cultures were established from ten out of eleven tumours. High-quality RNA was isolated, and mRNA was amplified in all cases. Seven patients were able to be weaned from corticosteroids to receive DC immunotherapy. An immune response induced by vaccination was identified in all seven patients. No patients developed adverse autoimmune events or other side effects. Compared to matched controls, progression-free survival was 2.9 times longer in vaccinated patients (Figure 7).

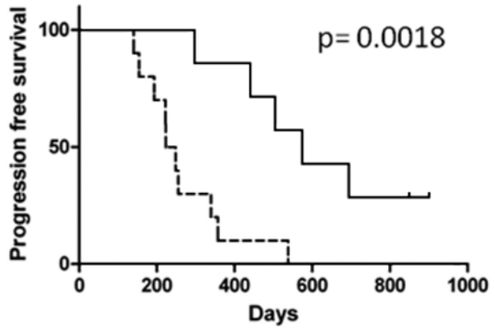

Figure 7 – Kaplan Meier plot showing progression free survival of patients treated with DCs targeting GSCs compared to matched control patients treated with standard therapy. Controls were matched by age, performance status, tumour volume, treatment modalities, and lack of corticosteroid treatment. The vaccinated patients had a significantly longer progression-free survival (median of 694 days) compared to the matched controls (median 236 days; p = 0.0018, log-rank test). Two DC-treated patients had not developed recurrence (short straight bars).

International collaborators of the Vilhelm Magnus lab

- David Tirrell, California Institute of Technology, Los Angeles, USA
- Charles Liu, University of Southern California, Los Angeles, USA
- Monica Nistér, Karolinska Institutet, Stockholm, Sweden
- Anders Björklund, Wallenberg Center/University of Lund, Sweden
- Alan Mackay-Sim, Australian National Adult Stem Cell Centre, Brisbane, Australia
- Yasuhiro Watanabe, Tottori University, Japan
- Winston Hide, Harvard University, MA
- Dolph Hatfield, NIH, Washington, USA

Figure 6 – Brain tumour biopsies cultivated under GMP conditions for enrichment of autologous tumour stem cells for vaccine production.

Experimental Orthopaedic Research

Leader

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

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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
- reduce the numbers of deficient fracture healing
- improve healing of tendon grafts in orthopaedic surgery
- delineate the best biomaterial surface for prosthesis surgery
- reveal biomechanical factors in internal fixation of hip fractures

Cartilage research

Malfunction of the knee joint is often associated with cartilage injury. Whether healing, or restoration, of lost, or

Professor Lars Norrdsletten

wounded, portions of articular cartilage with newly formed fully functional cartilage is possible remains one of the unsolved problems in orthopaedic practice. Knee patients have more problems than patients with rupture of the anterior cruciate ligament and experience severe limitations in their daily life. Despite this, knowledge about the best treatment, and if surgical treatment do offer a better outcome than the natural history, is still not documented. A better understanding of articular cartilage biology, pathophysiology, and biomechanics are definitely warranted. High priority research projects of the group have been better understanding of the cartilage repair process and assessment of the role of the mesenchymal stem cells versus chondrocytes in studies of cartilage repair.
The ongoing work of the cartilage research group can be divided into three main areas.

Experimental cell-culturing cartilage research
The group has worked intensively to provide the best cell source for cartilage repair. Mesenchymal stem cells, harvested from the bone marrow, implanted in hyaluronic- based scaffold have been studied in the laboratory for production of articular hyaline cartilage specific markers. Theoretically, these cells have a promising potential for repair of normal hyaline cartilage. The collaboration with the Ex Vivo Laboratory (Rikshospitalet) headed by Jan Brinchman has enhanced the supply of improved cells for cell based cartilage repair and the ability to test and develop new scaffolds.

Experimental cartilage research in an animal model
Experimental cartilage research in an animal model An important factor in cartilage treatment is the location of the defect in the knee and the consequences for the treatment of the defect and the risk of degenerative changes. An experimental study has been undertaken to specifically investigate this factor. The location of the defect is essential, as it is demonstrated in the current study. The difference

in treatment outcomes between microfracture and mosaicplasty has been difficult to assess clinically and another study has been conducted to evaluate some clinical assessment techniques. We observed changes in the subchondral bone and their relation to the long-term risk of degenerative changes in the joint. Mesenchymal stem cells implanted under a commercially available scaffold for repair of articular defect have been assessed experimentally to look at feasibility of this technique and at the amount of cartilage obtained in the defect.

Clinical cartilage projects

The experimental work is closely connected to the clinical studies of the group and, currently, there is an ongoing study on stem cell treatment versus chondrocyte implantation. Patients with cartilage defects of the knees treated with chondrocyte implantation have been evaluated with electron microscopy biopsies to study ultra- organization of the tissue and deaths of chondrocytes.
Results have recently been published.

Fracture and tendon-to-bone healing

Delayed fracture healing or non-union may occur in high energy fractures, in patients with systemic diseases, with hormonal or nutritional deficiencies, or in patients taking specific medications like non-steroidal anti-inflammatory drugs (NSAIDs and COXIBS). Healing of tendon material to bony surfaces is of major importance in both shoulder and knee surgery where understanding of the biology and biomechanics in this process is a key element. Rupture of the reconstructed tendon/ligament and increased laxity by repeated loading constitute the major problems.

We have previously studied fracture healing in rats on a short time medication with NSADs and COX-2-inhibitors, and in rats made severely osteoporotic by estrogen and vitamin-D depletion. We have demonstrated the potential negative effects of these drugs on bone metabolism and bone, tendon and tendon-to-bone repair. However, relevant dose, timing, and if it is safe to delay the administration is still in our scope.

Manipulation of bone resorption by osteoclast inhibitors has become possible with several drugs including monoclonal antibodies. Bone formation stimulators have been more difficult to develop, but several candidates are now available. In ligament reconstructions, stability is achieved only by solid tendon to bone healing. This may pose a clinical challenge considering the necessity of early active movement and loading to facilitate the best possible functional outcome. For both fracture and tendon to bone healing, it would be desirable to be able to speed up the healing processes. There is growing evidence that pharmacological adjuvants may have an important role to play and may be pivotal for the clinical outcome. We are currently developing our rat models and analyses are testing potential positive effects of bone formation stimulators and bone resorption inhibitors. Previous experiments on intramedullary nailing and external fixation in lower leg fractures assessed bone healing by quantitative microcomputer tomography (qmCT), in addition to mechanical testing and densitometric measurements (Figure 1). A collaboration program between EOR and the Robotics and Intelligent Systems (ROBIN) research group at the Department of Informatics is under planning. The scope is to utilize modern robot technology to standardize bone-implant and fracture-implant systems for improved experimental biomechanical evaluation of fracture fixation techniques in both composite and human cadaver bones. A pilot study included one group of standard mechanical testing of 4th generation (Figure 2) composite bones (radius) with manual osteotomy and fixation with different devices. A similar group of composite bone is now in the process of being tested in the robotic setup.

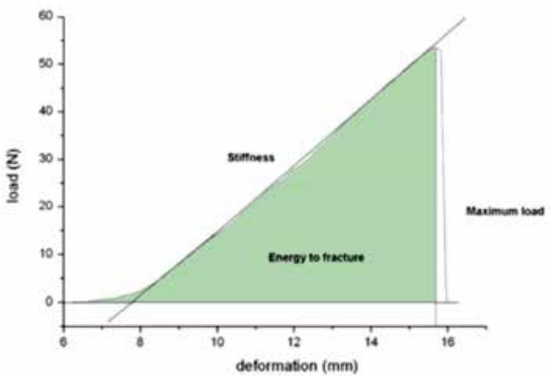

Figure 1. - In most of our fracture and tendon projects we use biomechanical tests as the primary endpoint to evaluate healing. Samples are loaded until fracture, rupture or pull-out in a highly sensitive materials testing machine (MTS). We obtain data on load, time and deformation. This figure illustrates a typical load-deformation curve from a cantilever bending test of an adult rat tibia tested to failure. It shows the biomechanical structural properties of strength,stiffness and energy to fracture.

Biomechanical studies of hip fractures

Most hip fractures are operated with reduction and internal fixation. An improvement in this procedure is thought to reduce the complications related 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 bio-mechanical 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 use bone mineral content measured by quantified CT.
As a consequence of our findings clinical trials are planned.

Innovation

The EOR group has also collaborated with AHUS in an innovation project funded by OUH and Inven2. The inventor wwas also awarded the yearly SE Health Authority Region Innovation award. Novel orthopaedic devices and implants have been mechanically tested and characterized in our laboratory as a part of the global patent seeking process. Data cannot be published yet due to patenting procedural issues.

International Collaborators

- Rob LaPrade, Steadman Philippon Research Institute Vail, Colorado, USA

Figure 2. Photograph of a 4th generation radius composite bone with a standardised osteotomy fixated with the Orthomedic DVR volar plate.

Photo: Kristin Ellefsen, UiO

Cell Transplantation and Tissue Engineering

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Deputy leader:
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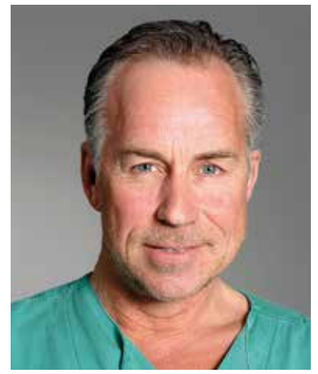
Scientific Staff Tissue Engineering:
Oslo Regenerative Medicine Initiative (ORMI) partners

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. The group has recently implemented tissue engineering as a focus research area for the next 5 years. This is a joint initiative of 11 top rated research groups at OUS and UiO (see the ORMI partners below) that are experts in their field. Islet transplantation as a therapy for type 1 diabetes (T1D) has been an important and major focus of the research group and significant progress has occurred in past years. We have established a GMP human cell processing facility approved for large-scale production of human islet product at the Department for Cellular Therapy, Radiumhospitalet in close collaboration with Professor Gunnar Kvalheim.

Aims
- The improvement and implementation of new strategies for islet isolation, engraftment of human islets in the setting of clinical islets transplantation.
- To establish a protocol for trans differentiate of human pancreatic exocrine cells to beta-like cells.
- Establish the research plan for Oslo Regenerative Medicine Initiative (ORMI).



Professor Aksel Foss

Research activity in 2014
Clinical islet transplantation
Clinical islet transplantation is an alternative therapy for those T1D patients whose disease cannot be effectively managed with current methods of exogenous insulin administration.
More than 1000 patients worldwide have received islet transplantation since the breakthrough in 2000 when the introduction of the “Edmonton protocol” occured. In terms of improving glycemic control and reducing life-threatening episodes of hypoglycemia, islet transplantation is highly successful, but the long-term efficacy is to low and further refinement of the treatment is highly needed. As outlines in Fig. 1 the most obstacles happens to be the toxicity associated with current regimens of immunosuppression, administration route of the islets and the limited supply of human organ donors available for isolation leading to that only a small fraction of the people could potentially benefit from this therapy.

Experimental Cell Transplantation
1. Investigate the intracellular immunosuppressive concentrations in human islets and the regulation thereof.
Following islet transplantation the recipients are in need of lifelong immunosuppression. Known diabetogenic side effects of immunosuppressive therapy are particularly deleterious in the situation of a reduced beta cell mass (like in islet transplantation), possibly contributing to the historically poor success rate of human islet allografts. Studies to

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

determine the right dosages and optimal combinations of available immunosuppressants for optimal islet survival are needed. We have together with the i2mc research group headed by Prof. Stein Bergan investigated the pharmacokinetics, pharmacodynamics and pharmacogenomics of the immunosuppressive drugs in human islets in vitro. Our data indicate that there is significant expression of some drug transporters and enzymes in the islets, and also that the intra-islet concentrations of immunosuppressants are significantly influenced by concomitant drugs.

2. Precondition of human adipose-derived stem cells promotes islet survival.

Mesenchymal stem cells (MSCs) are multipotent stromal cells found in many different types of tissue. MSC from bone marrow have been documented to reduce inflammation and promote islet survival both in vitro and in vivo. However, the frequency of MSC in bone marrow is reported as low. Adipose tissue yield 100-500 times more cells than bone marrow and generates less pain and morbidity for the donor. The stromal vascular fraction (SVF) can be cultured and expanded in vitro to adipose derived stem cells (ASCs). We have in close collaboration with Prof. Gunnar Kvalheims research group at Radiumhospitalet explored whether ex vivo expanded ASCs from fat can improve islet survival in vitro. We have data that support that precondition of ASC such as incubating ASCs in hypoxia (1% O2) for 48 hours increase secretion of several anti-inflammatory cytokines, including VEGF and IL-10. We have investigated whether condition media (CM) from ASCs cultured under hypoxic conditions could have beneficial effects on human islets compared to condition media from ASCs culture under normoxic (21% O2) conditions or to unconditioned media. Our data shown that human ASCs cultured in hypoxia releases factors that significantly reduce apoptosis and improve function of human islets.

3. The effects of exendin-4 treatment on human graft failure.

In collaboration with Astra Zeneca AB research team and Uppsala University, we have established a double islet transplantation model to be able to investigate the impact of new compounds on the expansion of beta cell mass and improvement of function. Briefly, two islet transplantations are performed in the same animal. First, mice islets are transplanted under the left kidney capsule to restore hyperglycemia, the second transplantation are performed after a recovery time of 2-4 weeks. A suboptimal dose of human islets are transplanted under the right kidney capsule and the grafts is allowed for a recovery period for up to 3 weeks, the first graft is removed by left sided nephrectomy which allows for followed islet function and possible proliferation in the second graft in response to different interventions in vivo. Exendin-4 has the potential to increase - cell mass either by stimulating proliferation or inhibiting apoptosis. We study the effects of exendin-4 on metabolic parameters of aged human islets in vivo and report that exendin-4 could play an important role in the first period after islet transplantation where normal levels of blood glucose are desirable to reduce glucose toxicity to the islets.

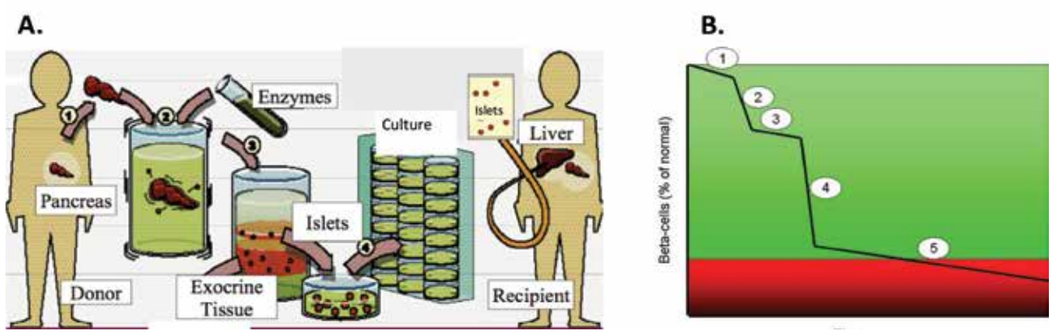


Fig.1 (A) Illustration of clinical islet transplantation (organ procurement, islet isolation and intraportal transplantation. (B) Schematic presentation of loss of islets from the time of organ retrieval (1), islet isolation (2), pre-transplant culture (3), transplantation (4), and post-transplant period (5). Green area represents insulin-independence, red area insulin dependence. From Olle Korsgren

4. Beta cell replacement vs. beta cell regeneration

Expanding the beta cell mass would greatly improve opportunities for cell-based therapy in diabetes. The fact that the beta cell mass in a person is capable of expanding in response to insulin resistance, obesity, pregnancy and trauma is the background for our research focus on conversion of non-beta cells within the pancreas to beta-like cells. The adult pancreas consists of both exocrine and endocrine parts with different functions. The acinar, ductal and pancreatic progenitor cells of the exocrine pancreas has been suggested as source for conversion into beta-like cells or to prevent hyperglycemia in diabetic animals. In addition, it is believed that other cells that belong to the endocrine part of pancreas can be transformed into beta-like cells, especially when the transformation occurs in the native microenvironment. Among the endocrine cells, the glucagon-producing alpha cells seem to be the potential source. In human T1D, random beta cells are found scattered around the pancreas. Whether this is a result of regenerating new beta cells in the adult pancreas or persistence of existing cells that have escaped from autoimmune reaction, is unknown.

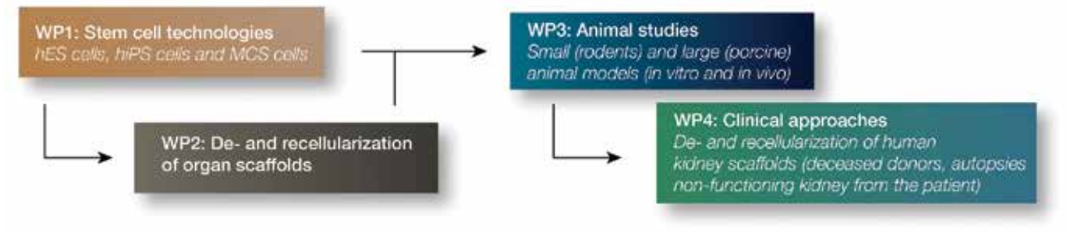
Oslo Regenerative Medicine Initiative (ORMI)

Recently, all activities on regenerative medicine and tissue engineering at OUH and UiO were joined in ORMI (see below) and the initiative was selected as Focused Area of Research at our institution for the timeframe 2014-2018.

Prof. Aksel Foss (leader) Department of Transplantation Medicine, Division of Cancer Medicine, Surgery and Transplantation.
Prof. Lars Engebretsen, Department of Orthopaedic Surgery, Division of Surgery and Clinical Neuroscience (Research area: Cartilage tissue engineering.)
Prof. Morten C. Moe, Center for Eye Research, Department of Ophthalmology, Division of Surgery and Clinical Neuroscience (Research area: Stem cells and tissue engineering in the treatment of ocular disorders.)
Prof. Joel C Glover, Norwegian Center for Stem Cell Research, OUH/University of Oslo. (Research area: Human somatic and pluripotent stem cell differentiation, characterization and genetic manipulation.)
Prof. Iver A Langmoen, Department for Neurosurgery, Division of Surgery and Clinical Neuroscience.Stem cells in the adult human brain. (Research area: Stem cells in brain cancer. Vilhelm Magnus Laboratory for Neurosurgical Research.)
Prof. Gunnar Kvalheim, Department of Cellular Therapy, Division of Cancer Medicine, Surgery and Transplantation. (Research area: Adipose tissue stem cells in tissue repair.)
Dr. Kim A Tønseth, Department of Plastic and Reconstructive Surgery, Division of Surgery and Clinical Neuroscience. (Research area: Regenerative medicine in plastic surgery.)
Prof. Stefan Krauss, SFI-CAST Biomedical Innovation Center, University of Oslo. (Research area: Chemical biology in regenerative medicine.)
Dr. Hanne Scholz, Department of Transplantation Medicine, Division of Cancer Medicine, Surgery and Transplantation. (Research area: Cell replacement and tissue engineering.)
Dr. Jan E Brinchman, Norwegian Center for Stem Cell Research and Department of Immunology (Ex vivo), Division of Diagnostics and Intervention.
(Research area: Cellular therapy.)
Prof. Jørgen J Jørgensen Department of Vascular Diseases (Oslo Vascular Centre), Division of Cardiovascular and Pulmonary Diseases. (Research area: Tissue-engineered allogenic vein valves in treatment of chronic venous insufficiency.)
Prof. S. Petter Lyngstadaas, Faculty of Dentistry, University of Oslo. (Research area: Scaffold technology and biomaterials.)
Dr. Einar Martin Andahl, Department of Transplantation Medicine, Division of Cancer Medicine, Surgery and Transplantation and the Biotechnology Center of Oslo. (Research area: Transplantation surgery, experimental immunology and tissue engineering.)

Establishing tissue engineering research at OUS

Harvard Medical School and Massachusetts General Hospital (The Ott lab) has performed the pioneering studies of tissue engineering organs (Song//Ott. Nat Med 2013, and Ott. Nat Med 2010 and 2008). ORMI will use the methods for detergent perfusion and decellularisation of whole organ developed by Harald Ott´s laboratory and adapt these technologies. The establishment of the these technologies at the Institute for Surgical Research will be the first step in this work, and will help combine life sciences and engineering expertise to determine feasibility, verify and validate in order to optimize the decellularization and recellularization process for organs.



EU Horizon 2020 proposal
A joint initiative has been to prepare an EU Horizon 2020 proposal (Program PHC 16 – 2015: Tools and technologies for advanced therapies on Tissue Engineering of Human Kidneys for Transplantation of Patients with End-Stage Renal Disease (NeoKidney Consortium). ORMI has been the Principle Investigator of the project. The research programme has been design to developing of the technologies required for bringing tissue-engineered kidneys into clinical practice through four interconnected WPs as outline below.

LIST OF PARTICIPANTS

(NeoKidney Consortium)

1. Oslo University Hospital/University of Oslo (OUH/UiO), Oslo, Norway – Foss A, Aandahl EM, Scholz H, Glover JC,
2. Karolinska Institute/Karolinska University Hospital (KI/KUH), Stockholm, Sweden – Macchiarini P, Lendahl U
3. Harvard Medical School, Massachusetts General Hospital (The Ottlab), Boston, USA – Ott HC
4. AstraZeneca R&D, Cardiovascular & Metabolic Disease Translational Medicine Unit & Discovery Science-Advanced Cell Laboratory (AZ) Mölndal, Sweden – Skrtic S, Brolén G
5. Organ Recovery Systems NV (ORS), Brussels, Belgium (SME) – De Muylder P, Kravitz D

Collaborators Cell transplantation:
The Research Group is part of several international networks of high levels such as the Nordic Network for Clinical Islet Transplantation. The strength in our organization is that the people involved are a mix of full time researchers and active clinicians who quickly can bring translational research into clinical trials and further on to clinical treatment.

- Professor Olle Korsgren, Uppsala University Hospital, Sweden
- Professor Peter Stock and Ass. Professor Qizhi Tang, University of California, San Francisco, USA
- Professor Gunnar Tufveson Uppsala University Hospital, Sweden
- Corline Systems AB
- AstraZeneca R&D Mølndal, Sweden
- Professor Pål Aukrust and Professor Bente Halvorsen, Institute for Internal Medicine, Oslo University Hospital
- Senior scientist Thor Ueland and Arne Yndestad, Institute for Internal Medicine, Oslo University Hospital
- Professor Gunnar Kvalheim, Department of Cellular Therapy, Oslo University Hospital
- Senior scientist Daniel Branhorst, Oxford Center for Diabetes, Endocrinology and Metabolism, University of Oxford

Collaborators Tissue Engineering
- ORMI partners, Oslo University Hospital and University of Oslo
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- Prof. Stephen Strom, Karolinska Institute, Stockholm, Sweden
- Prof. Paolo Macchiarini, Karolinska Institute, Stockholm, Sweden
- Prof. Harald Ott, The Ottlab Massachusetts General Hospital, Harvard Medical School, Boston, USA
- AstraZeneca (Center for Cardio Metabolic Research and Regenerative Medicine)
- Organ Recovery Systems
- Advanced Center for Translational REgenerative Medicine (ACTREM), Karolinska Institutet, Sweden

Transplantation and Malignancy

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Jihua Shi, MD (OUH)
Morten Hagness, MD, PhD- (OUH)
Jon Magnus Solheim, MD PhD-fellow (OUH)

Associate members
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Marit Andersen, MSc, PhD (OUH)
Rune Horneland, MD (OUH)


Consultant Svein Dueland

Introduction
Organ transplantation requires lifelong immunosuppression. A side effect is increased post-transplant de novo malignancy. During the last decades, the effectiveness of standard immunosuppressants in allograft transplantation has improved and so has the incidence of de novo cancer. Arecent study of 905 recipients of transplanted hearts, lungs,or both has shown a 7.1 times increase in de novo cancers compared to the general population. Cancer-related death following transplantation is increasing and accounts for 13% of post transplant mortality. Regulatory T cells (T regs) maintain self-tolerance to autoantigensand are involved in the pathogenesis of variousclinical conditions such as autoimmune diseases, chronicviral infections and cancer. T regs appear more frequentlyin peripheral blood lymphocytes of cancer patients than healthy controls and interestingly, it seems that high levels of T-regs are a prerequisite for allograft tolerance following transplantation. By manipulation of the interaction between CD4+ CD25+ T regs and dendritic cells, it may become possible to influence host offence and defense in cancer and organ transplantation. In these aspects it is of particular interest that immunosuppressive drugs used in transplantation have both an anti-rejection and anti-neoplastic activity.

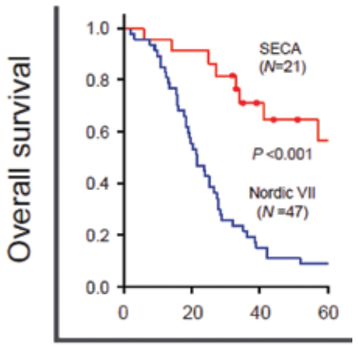
Rapamycin (Sirolimus, RapamuneR) is an established drug for prevention allograft rejection by blocking the intracellular pathway complex mTOR. It also appears that a Sirolimusbased immunosuppression protocol has beneficial effects on tumor recurrence and survival with an acceptable rate of rejection and toxicity in liver transplanted HCC patients. Rapamycin is a potent VEGF antagonist showing significant anti angiogeneic effects in addition to a direct inhibitory effect on tumor growth and proliferation. mTOR inhibitor has shown clinical effect and objective radiological responses and stabilizationof disease in different types of cancer, such as advanced breast and renal cancer that has previously progressed on other treatments. mTOR inhibitor has also shown increased survival in high risk metastatic renal cancer patients compared to interferon treatment. mTOR inhibitor is also approved for treatment of neuroendocrine tumors. Accordingly, rapamycin is an effective anticancerdrug in addition to its immunosuppressive effects.
This supports the use of the drug for patients transplanted for cancer and in patients with de novo post transplant malignancy.

The SECA study
In 2006 we acquired an ethical approval (S-05409 Regional Ethics Committee, Helse Sør-Øst) for a clinical pilot study (SECA-study) to investigate liver transplantation as treatment option for selected patients with non-resectable liver metastases after colorectal carcinoma (CRC), using themTOR inhibitor Rapamycin as standard immunosuppression from postoperative day 1.

The primary endpoint of the study was overall survival (OS) at two years after liver transplantation (Lt). Secondary endpoints are disease free survival (DFS), quality of life and complications to the procedure. By March 2012, 23 patients have been transplanted in the study. The OS at 2 years after Lt for all 23 patients included in the SECA-I trial is 91% compared to about 50% in non-resectable colorectal cancer patients receiving chemotherapy. Based on data from the first 21 patients with observation time to November 2013 with median follow-up of 65 months, Kaplan-Meier estimates of overall survival at 5 year post Lt were 56%. (Figure 1, ref 1). Four of the included patients had metachronous disease with lymph node negative primary colorectal tumor. These four patients are all alive at 5 years after Lt.

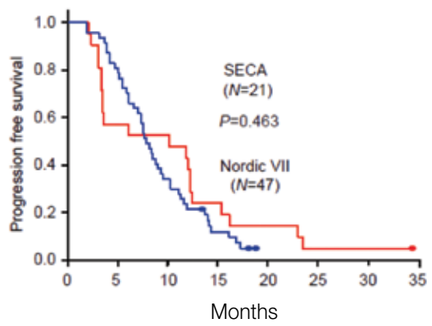
The OS after Lt is better than most studies for liver resection for colorectal metastases. Furthermore, it should be kept in mind that all SECA patients were not eligible for liver resection.

Fig. 1



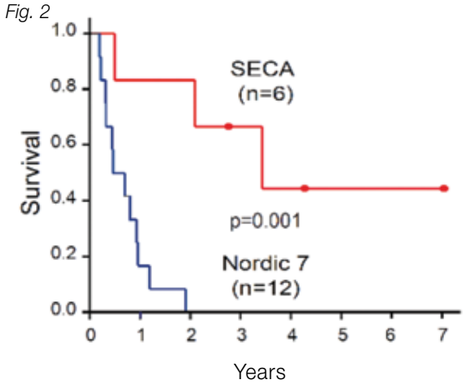
Kaplan-Meier overall survival for patients included in the liver transplantation group (SECA-study, hatched line), and the chemotherapy group (NORDIC-VII-study, solid line).
All SECA patients (n=21) vs all NORDIC VII patients (n=47).

Fig. 3



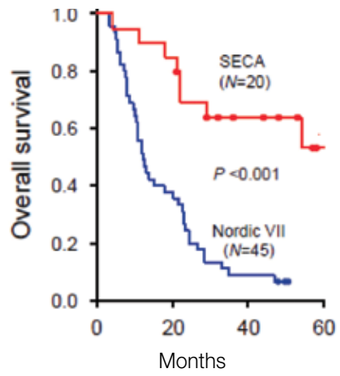
Progression-free survival for patients included in the liver transplantation group (SECA-study, hatched line, n=21), and the chemotherapy group (NORDIC-VII-study, solid line, n=47).

Fig. 2



Overall survival from time of liver transplantation (n=6, red line) and OS in NORDIC VII patients from time of terminating second line treatment in patients with KRAS mutant tumor (n= 12, blueline) p=0.001.

Fig. 4



Kaplan-Meier overall survival from time of progressive disease for patients included in the Liver transplantation group (SECA-study, hatched line, n=20), and the chemotherapy group (NORDIC-VII-study, solid line, n=45, two patients with OS=PFS were excluded from analysis).

The overall 5-year survival in liver resection studies is generally between 30-50%. For patients with larger hepatic tumor load, the OS results are even lower. The patients in the SECA study had generally a large tumor burden (the median number of liver tumors was 8 (Range 4-40) and the median size of largest metastatic lesion was 4.5 cm (range 2.8- 13cm). All patients were deemed non-resectable even when available treatment options such as liver expansion techniques, repeat resections and ex situ liver resections after chemotherapy were taken into account. If resectable, expected 5 year OS of the study population based on the clinical risk score (CRS) would have been only 25% when each patient were scored according to Fong clinical risk score for resectable colorectal liver metastases. Non-resectable colorectal liver metastases is a devastating disease with a 5-year overall survival of about 10% after start of first line chemotherapy. Sixteen of the 21 patients in the SECA study had progressed on first or later lines of chemotherapy at the time of inclusion in the study. Such patients have a median expected OS of 12 months or less.

Six patients had progressive disease on all lines of standard chemotherapy at time of Lt. They all had extensive disease with 8-35 liver metastases and largest diameter of 2.8-13.0 cm. Median OS of these 6 patients was 41 months with a Kaplan-Meier calculated 5 year OS of 44% (Figure 2, Ref 2). A woman with body weight of 60 kg had an explanted liver of 4.6kg (liver weight to body weight of 7,6%, normal ration of about 2%). She also had 5 L of ascites drained at a local hospital the day before Lt. The patient died of progressive disease 6 months post Lt. Patients with such extensive disease and reduced performance status are not candidates for Lt. If this patient is excluded from the analysis the Kaplan-Meier estimated 5 year OS is 53% compared to median OS of less than 6 months in patients with no treatment (Figure 2, Ref 2), suggesting that these patients benefited from Lt.

By end of December 2014 recurrence of disease appeared in 22 of 23 patients. Median progression free survival (PFS) was only about 10 months, relative similar to patients starting first line chemotherapy (Figure 3, Ref 1). However, most of the relapses were pulmonary and these progressed slowly untreated. Also, a significant proportion of the recurrences were accessible for surgery and several patients obtained no evidence of disease status after surgical treatment. The 5 year OS from time of relapse was 53% (Figure 4, Ref 1). Hepatic tumor load prior to liver transplantation, time from primary surgery to Lt, and progressive disease on chemotherapy at time of liver transplantation were identified as significant prognostic factors for survival. A combination of these factors can be used as prognostic factors to select patients that have a 75% probability of 5 years survival. These strategies could further improve the outcome after Lt.

Adverse events

Lt is a major surgical procedure with well known post-operative complications. The patients included in the SECA study had good performance status without liver failure and in general they had a fast recovery compared to other patients receiving Lt. However, as expected some patients had major complications.

Four patients experienced hepatic artery complications, 2 patients were retransplanted because of hepatic arterial thrombosis. Two of the patients experienced hepatic artery stenosis, one complicated with thrombosis; both were managed with interventional radiology. There were three cases with stenosis of the bile ducts, one complicated with leakage, all three were managed endoscopically. Five patients were reoperated because of deep heamatomas or hemorrhage.

There was one incident of serious unexpected suspected adverse reaction, reported to the study control committee and health authorities. This was a case of ischemic optic neuropathy which resulted in a permanent visual loss after surgery. This is an established complication to surgery and is reported at very low incidents for non-ocular surgeries. Because of Rapamycin used as immunosuppressant, there was a focus on wound complications. There were two patients reoperated because of wound dehiscence, additionally three patients were treated for superficial wound healing problems. 8 patients developed ventral hernias, all 8 among the 10 first operated.
All together 12 reoperations were performed, not counting hernia repair and operations for recurrence. No fatal incident is reported.

Quality of life

Quality of life has been reported up to 12 months after transplantation for the first 10 patients. The median reported global health status score (GHS, on a 0-100 scale were 100 is the best score) was 71 at baseline, 75 at 3 months after Lt, and 83 at 6 and 12 months postoperative, with a significant difference between baseline and 6 months scores (p=0.027). As compared to baseline, Lt resulted in sustained excellent GHS (score of 100) in one patient, improved scores in 4, and unchanged scores in 3 patients at 12 months after Lt. The scores for physical function were also good with median values of 87 at baseline, 3 and 12 months, respectively and 93 after 6 months. Although two patients had marked symptoms both before and after Lt, the patients in general reported low levels of pain and fatigue before and after surgery. Quality of life questionnaires for all 23 included patients in the SECA-I study have been collected for up to 3 years after Lt. The last questionnaire will be collected in April 2015 and the data for all patients will be analyzed.

The SECA II study

The SECA II trial was initiated on January 2011as a randomized trial where Ltx was compared to best available on-cological treatment. Because of the large difference in survival in the SECA-I study compared to all previously reported chemotherapy studies, an amendement in the protocol was approved by the Regional Ethics Committee in November 2011. This changed the objective of SECA-II study to a randomized controlled trial between Ltx and hepatic resection for patients with large but resectable colorectal metastases (arm A og the study) and a non-randomized Ltx study for patients with non-resectable liver only metastases and favorable prognostic factors arm B (metachronous disease) and arm C (synchronous disease) of the study.

Study Objectives of SECA II

- In a randomized controlled trial to explore whether liver transplantation in selected patients with liver metastases from CRC can obtain significant life extension and better health related quality of life compared to patients receiving surgical resection.
- To explore if patient selection according to risk factors from the SECA-I study and nomograms for outcome of colorectal cancer can define a subgroup of patients with a 5 year survival of at least 60% or even cure from the disease

Study endpoints

Primary endpoint

- Overall survival

Secondary endpoints

- Survival related to SECA-I risk factors and Memorial Sloan-Kettering nomograms for recurrence after liver re-section of metastatic CRC.
- Disease free survival (RECIST criteria and time to lung lesions of ≥10 mm)
- Time to start of new treatment (change in strategy)
- Quality of life (EORTC QLQ-C30), time to decrease in physical function and global health score
- Registration of symptoms (NCI-CTCAE version 4.0)
- Diagnosis of other malignancies
- Determine nomo-gram scores of patients who survive for 5 years or more
- Survival in relation to biological markers (plasma TIMP-1and TPA , circulating tumour cells and micro-metastatic disease in bone marrow biopsies at time of Ltx, different micro-arrays of liver biopsies, regulatory T-cells, infiltrating T-lymphocytes in liver biopsies and KRAS and BRAFmutations.
- Correlation between recurrence/metastases and other biological parameters (proteomics, micro array, micro me-tastases in bone marrow and lymph nodes and circulating tumour cells)

Study population

In part A of the study patients with 6 or more respectable liver lesions will be randomized between liver resection and liver transplantation since surgical resection in this group of patients have a 5 years survival of only 0-30%. Patients randomized to Lt will continue chemotherapy until Lt Patients randomized to Lt who have not received a Lt within 2 months after randomization due to donor deficiency, will be taken off the transplantation list and included in the resection arm of the study.

In part B, CRC patients with metachronous non-resectable liver only metastases with at least 10% response according to RECIST criteria on first line chemotherapy will receive liver transplantation. Further inclusion criteria in part B is having a primary pN0 disease and CEA<100 ng/ml at time of primary diagnosis as well as at time of metastatic disease. This selected group of patients is expected to obtain a 5 year survival of 60-80 %.

In part C, patients that may be included is patients with relapse of liver metastases after second liver resection or patients with liver metastases not eligible for curative liver resection, who have received chemotherapy treatment with at least 10% response (RECIST-criteria) on chemotherapy. The patients must be accepted for transplantation before progressive disease on ongoing chemotherapy and before start of chemotherapy, no lesion should be larger than 10 cm and total number of lesions should be 30 or less. Patients may also be included if they have less than 10% response on chemotherapy if they obtain at least 20% response after treatment with TACE (DEB-IRI) or by 90Y-spheres.
At time of progressive disease all patients will be considered for the best treatment options, including further chemotherapy as well as surgical resections/radiation therapy/radiofrequency ablation (RFA).

MECA-study

Ocular malignant melanoma is a rare disease. Patients who have a relapse of the disease often have metastases to the liver. In many patients liver is the only site of metastases. There are no treatment options that have shown increased survival in patients with liver metastases from ocular malignant melanoma. These patients have a dismal prognosis with median overall survival of 6-10 months in most studies. Two patients with ocular malignant melanoma have been included in the study. One patient with extensive disease at time of liver transplantation had a relapse after a few months and died 6 months post transplant with relapse at multiple sites. The other patient had a relapse in the transplanted liver 15 months after liver transplantation. The patient developed multiple liver metastases and surgery was not an option in this patients and the patient received palliative treatment. Due to lack of effective treatment of relapse in these patients and rapid progressive disease, long term survival cannot be expected after a relapse. The study has therefore been closed for further inclusion.

RAPID Study

Selected patients with nonresectable colorectal liver metastases benefit from liver transplantation and have acceptable five-year survival rates. However, allocating full sized grafts to this group of patients is difficult due to the scarcity of grafts. This could be improved by utilizing small partial grafts, which mandates effective strategies to overcome the problems regarding insufficient functional liver mass.
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.
A fifty years old male weighing 92 kg was transplanted with a graft weighing 330 g, and the portal vein to the right remnant liver was closed. The volume of the liver graft was doubled two weeks after the first procedure, and increased further after the second procedure, with extended right hepatectomy performed at day 23 after transplantation. There were no signs of liver failure or small for size syndrome.
The current protocol and ongoing study could represent a possible strategy to increase the availability of liver transplantation to patients with nonresectable liver tumors such as hepatocellular carcinoma and colorectal liver metastases. The concept has been accepted for Publication in The Annals of Surgery.

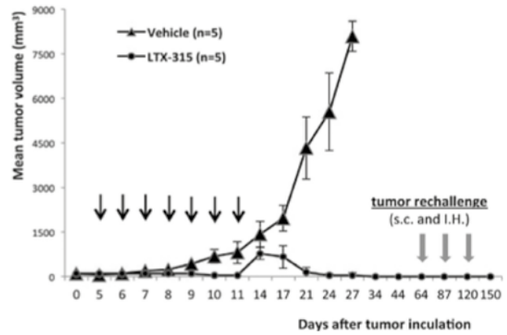


Figure 5. Treatment and protective immune responses of LTX-315 in a rat hepatocellular carcinoma model

Novel Immunotherapeutic principle for primary and secondary liver tumours – From bench to bedside

LTX-315 is a cationic peptide derived from bovine lacto-ferricin (LfcinB) that has been shown to have potent direct anti tumor effects in experimental sarcoma and lymphoma in rodents. The effect is attributable both to direct lysis of tumor cell membranes and to an activation of T-cell.
During 2012 we have cooperated with Gunnar Kvalheim and Meng Yu Wang at the Institute for Cellular therapy, Radium-hospitalet, Janne Nestvold at the Institute of Anatomy, and Prof. Øystein Rekdal and Baldur Sveinbjørnsson at the Uni-versity of Tromsø/Lytix biopharma.

The experiments performed have been focused on:

1. The effect of intratumoral LTX-315 on subcutaneous HCC tumors
2. The effect of transfer of specific immunity on growth of experimental tumor
3. The effect of preemptive vaccination with LTX-315+ tumor cell lysate before tumor implantation
4. The effect of intratumoral LTX-315 on intrahepatic HCC tumors

We have been able to show that treatment with LTX-315 kills experimental tumor in the subcutaneous tissue as well as in the liver (figure 5). Interestingly, this invokes a strong immune response, since rechallenge of the animals with tumors does not result in any tumor growth. The immune response appears to be t-cell dependent and invokes memory. Adoptive transfer of plenocytes from cured animals to total body irradiated naive animals resulted in protection from tumor when we tried to establish tumors in these animals s.c. and in the liver.

Our focus now has been to investigate whether LTX-315 treatment causes an immunogenic cell death of cancer cells. This is an important theoretical concept that opens up a range of possibilities.
Immunogenic cell death is according to Guido Kroemer and Laurence Zitvogel at Institut Gustav Roussy in Paris characterized by externalization of calreticuling, release of ATP and high mobility box group 1 (HMGB1) as illustrated in figure 6 (adapted from: *Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic Cell Death in Cancer Therapy. Annu Rev Immunol. 2013;31(1):51–72.doi:10.1146/annurev-immunol-032712-100008.)*

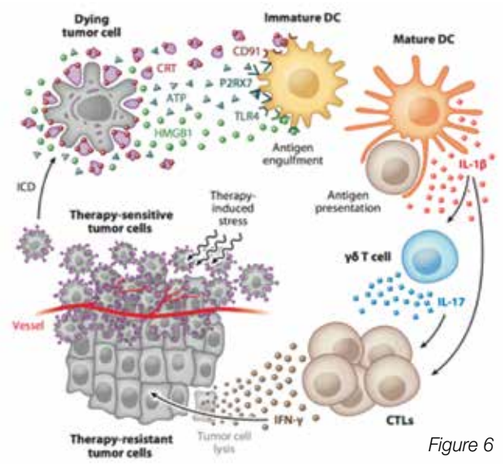


Figure 6

We have now started experiments to test the hypothesis that LTX-315 invokes immunogenic cell death in the described manner. So far, we have been able to show that LTX-315 treatment of tumor cells leads to both release of HMGB1 and ATP, and this further undlerlines and strehgthen the hypothesis that LTX-315 tratment is incoking immunogenic cell death. We have now been able to further elaborate our series of experiments on LTX-315 in the rat model. In our last experiments, we have been able to demonstrate that LTX-315 seemst to be effective in a multi-tumor model in the liver. This is created by injecting tumor cells (JM1) into the portal vein, and concomitantly injecting tumor cells under the capsule. When treating a target lesion with LTX-315, all other tumors disappear. This is most likely explained by the specific t-cell mediated immunologic response that is elicited by LTX-315 injection treatment

PhD theses

In May 2014 Morten Hagness received his Ph.D from the University of Oslo based on the thesis: "Liver transplantation for colorectal liver metastases-clinical and immunological considerations." The thesis was based on data from the SECA-I study.

In August 2014 Jihua Shi received his PhD from the University of Oslo based on the thesis: "Growth of hepatocellular carcinoma and liver regeneration"

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1. Svein Dueland , Tormod K. Guren, Morten Hagness, Bengt Glimelius, Pål-Dag Line, Per Pfeiffer, Aksel Foss, Kjell M.Tveit,: Chemotherapy or Liver Transplantation for Non-Resectable Liver Metastases from Colorectal Cancer? Ann Surg. 2014 Jun 19.
2. Svein Dueland, Morten Hagness, Pål-Dag Line, Tormod K. Guren, Kjell M.Tveit, Aksel Foss: Is Liver Transplantation an Option in Colorectal Cancer Patients with Nonresectable Liver Metastases and progression on All Lines of Standard Chemotherapy? Ann Surg Oncol. 2014 Oct 9.

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Research in plastic and reconstructive surgery

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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 area

1 Microcirculation, wound healing and microsurgery

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.

a. Microcirculatory of the Abdominal Skin in Deep Inferior Epigastric Perforator Flap procedure

No studies have assessed the perfusion of the undermined abdominal skin in breast reconstruction with deep inferior epigastric artery perforator flap. A greater understanding of the procedure's impact on the perfusion of the abdominal skin can be valuable in predicting areas susceptible to necrosis. Furthermore, it can provide us with more knowledge on perfusion dynamics in undermined skin in general. Microcirculatory changes were monitored in the abdominal skin of patients undergoing breast reconstruction with a deep inferior epigastric artery perforator flap. Quantitative mapping was performed with laser Doppler perfusion imaging at set intervals from before commencing surgery until the seventh postoperative day (Figure 1). Measurements were recorded according to four standardized zones covering the skin between the xiphoid process and the upper incisional boundary of the flap. Although perforators are divided during undermining of the abdominal skin, our results shows that, there seems to be a significant, reactive hyperemia which exceeds the blood supply delivered by the perforators. Thus, due to microcirculatory mechanisms, the undermining of the abdomen during the procedure does not seem to pose any great risk of tissue necrosis.

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

In order to investigate the distribution of blood and microcirculation in random flaps we have designed a rat model that enables us to perform multiple measurements with laser Doppler perfusion imaging (LDPI)*. A random flap is raised with width-length proportions of 1:5. The flap is monitored in 5 equally sized squares on which a LDPI measurement is performed. The circulation is evaluated for every square with regards to the blood distribution within the flap.

Several studies suggest a positive effect of prostaglandin E1 (PGE1) on the circulation of flaps. In the same rat model as described above we compare the circulation of random flaps with i.v. infusion of PGE1 (fig 1) alternative saline and perform LDPI measurement. The circulation is evaluated and comparison between the control and intervention groups is performed and verified statistically.

c. Microcirculation and wound healing
To resemble a clinical situation, we are using animals with skin structure and function similar to the human skin. Pig skin has many similarities to human skin, including histological appearance and wound healing ability. We are using Norwegian pigs (Norsk landsvin) with weight between ± 25 kg in our studies. Microcirculation and histological measurements are performed to evaluate the effect of different reconstructive procedures or other interventions on wound healing. To investigate microcirculation and wound healing in an isolated setting, we use rat models as described below.

d. Experimental perforator flaps and other rat models
Dissection of the perforator flaps preserves the muscle and minimizes the donor site morbidity. Nevertheless, the method may have undesirable effects on the muscle because of damage of its innervation, blood supply or by direct injury when dissecting the perforator. We are performing studies to evaluate the surgically technique to reduce this damage to a minimum using Wistar rats where two symmetrical abdominal lipocutaneous flaps are raised around the midline. One side is used for intervention which is compared to the other side. After dissection, the flaps are fixed to the original position by a continuous suture. Microcirculation, flap viability, wound strength and histological changes are measured preoperatively and during the first week after the operation.

To continue improvements in both a clinical and scientific setting research using animal models is important. The groin flap based on the superficial inferior epigastric artery (SIEA) is well described. We have established a new model where the SIEA flap is transposed to the back of the rat with good conditions for flap monitoring, without danger of flap autocannibalisation. This model is used when performing studies on microcirculation and histological changes where we want to compare different interventions on the flap or the animal over a longer period of time.

e. Changes in microcirculation of the skin during sepsis and cardiogenic shock
Sepsis and cardiogenic shock are diseases with high mortality. New equipment for monitoring central hemodynamics has not improved survival as expected. In 1922 Freedlander studied skin microcirculation with a microscope in patients with sepsis and found decreased capillary density and increased heterogeneity of capillary density. New studies with advanced microscopes on patients with sepsis and cardiogenic shock show microcirculatory alterations in tongue mucosa in the way Freedlander described. In addition, alterations in erythrocyte flow velocity appear without changes in central hemodynamics. These characteristic changes may be valuable in diagnosing sepsis at an earlier phase, and may also have a potential in treatment guiding. Still microcirculatory monitoring is not used as a routine in any clinical field to examine patients with sepsis or cardiogenic shock.

Our hypothesis is that systemic diseases will induce microcirculatory changes everywhere in the organism. We also believe that we will see changes with our microscope before we see them in central hemodynamics and bloodtests. In our last study we have induced fecal sepsis in eight pigs and three controls. In the model they have been measured regularly from before sepsis induction to immediately before death by four different non-invasive techniques in four areas of interest (two skin sites, eye and tongue,). The techniques are Laser Doppler techniques (LDPM, LDPI*), spectroscope (for microvascular tissue oxygenation) and an “in vivo” microscope. The analysis of microcirculatory data are done by two blinded observers and microcirculatory data will be compared to central hemodynamics and bloodchemistry and immunology.

f. Microcirculation in human perforator flaps.
The deep inferior epigastric artery perforator (DIEAP) flap from the abdomen is one of the most suitable perforator flaps used for breast reconstruction. This procedure has had a significant impact on the field of plastic and reconstructive surgery, because of the high number of women requiring breast reconstruction after cancer surgery. Based on the experimental research and clinical experience, our group is performing investigations to optimize the reconstruction technique and to minimize the donor morbidity.

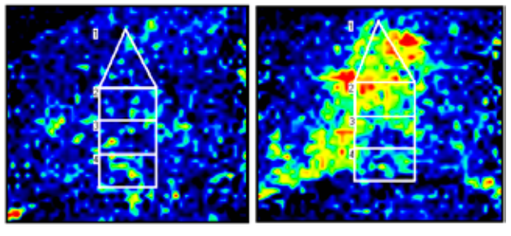

Fig. 1. Intraoperative perfusion maps with zones 1-4. After raising of the DIEAP flap (left) and after undermining of the abdominal skin (right).

Through better understanding of flap anatomy, physiology and better surgical technique the complication rate has decreased and the cosmetic outcome has improved. However, partial flap necrosis is still a recurrent complication that can affect the final cosmetic result and the patient satisfaction. In most cases this can be avoided by discarding parts with unreliable capillary refilling after transferring the flap to the recipient site. We are performing quantitative evaluation of the perfusion zones and skin areas with LDPI* in order to get a more exact picture of the microcirculatory differences in the DIEAP flap and other skin flaps.

Laser induced fluorescens of (ICG) is a new sensitive method for evaluation of tissue perfusion. In another project ICG videoangiografy is used to evaluate tissue perfusion of the DIEAP flap during conventional abdominoplasty. The perforators are isolated to investigate their effect on the microcirculation of the flap.

These studies will have major clinical impact on all surgical procedures involving flap surgery in order to improve surgical outcome of the reconstructed part and to reduce the donormorbidity.

**Measurements of microcirculation with laser Doppler perfusion imaging (LDPI)*

Measurements of microcirculation are a central part of all our animal and human experiments. It is performed with a PIM 3.0 LDPI from Perimed, Stocholm, Sweden. The LDPI generates, processes and displays colour-coded images of tissue perfusion. An optical scanner guides a low power laser beam stepwise to the tissue surface. The LDPI measures microcirculation to a depth of a few hundred micrometers. When the laser beam hit moving erytrocytes in the subepidermal plexus the light is backscattered and detected by a photodetector, this convert the light intensity to electrical signals and colour-coded images.

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. Treatment of Bell`s palsy has been a matter of debate for decades, and treatment with corticosteroids and antivirals have been the most commonly described treatments. To evaluate the treatment effect of these two drugs, the Scandinavian Bell`s palsy study has been performed at 17 different clinics in Scandinavia. This randomized, double-blind, placebocontrolled, multicenter trial included 839 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 treamtment. We will also analyze the outcome of pregnant patients whith 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

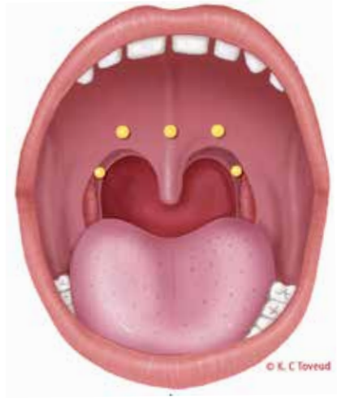

Fig. 2. Anatomical loci for fat transplantations to the soft palate and palatopharyngeal arches.

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. We have investigated the use of fat transplantation to the velum and pharynx (Figure 2) in patients with velopharyngeal insufficiency (VPI). In these patients there is an incomplete velopharyngeal closure during speech, which may give rise to hypernasality. Fat transplantation to the velopharynx has proven to reduce the velopharyngeal gap during phonation when measured by MRI..In addition, blinded perceptual speech assessments has shown a significant reduction in hypernasality.

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 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.

Cultured epidermal cells are used to treat large area burns and are a potential source of autologous epithelial cells for the regenerative treatment of limbal stem cell deficiency, as shown in animal models. Retention of undifferentiated phenotype has proved important to clinical success in both applications. Storage is critical to provide worldwide distribution of transplants and is a main issue which has been evaluated this year. Based on previous work, the storage temperatures 4°C, 8°C, 12°C, 16°C and 24°C were chosen for in-depth analysis. Preliminary results indicate that high (24°C) and low (4°C) temperatures are not suitable for the retention of viability and undifferentiated cell character. 12°C was the only temperature where these attributes were maintained and may be the preferred temperature for storage and transportation of cultured epidermal cells for 1 week.

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Training Courses

Courses

Introduksjon til nyfødtmedisinske teknikker og prosedyrer

Dato: 24. – 28.03 2014 + 13. – 17.10. 2014

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.

Temaoversikt
Følgende teknikker/prosedyrer vil bli undervist:
- Innleggelse av perifer venenål.
- Innleggelse av perifer arterienål/-"kran", inkludert etablering av trykkmåling.
- Kapillær blodprøvetagning.
- Innleggelse av navlevenekateter.
- Innleggelse av navlearteriekateter.
- Innleggelse av perkutant sentralvenekateter
  1."Peel away" teknikk
  2. Seldinger teknikk.
- Innleggelse av thoraxdren
  1. Vanlig rett dren med mandreng
  2. "Pig-tail" dren med Seldingers teknikk
  3. Bruk av drenasjekammeret.
- Spinalpunksjon.
- Endotrakeal intubering.
- Blærepunksjon (suprapubisk)
- Lokalbehandling av ekstravasering.
- Innleggelse av intraossøs nål for infusjon.

Kurskomité
Thor Willy Ruud Hansen og Vigdis Skaug (kursledere). Jannicke H. Andresen, Tor Einar Calisch, Kirsti Haaland, Gro Furset Flatekval, Astri Maria Lang, Sverre Medbø, Arild Rønnestad, Kenneth Strømmen, Inger Elisabeth Silberg, Hans Jørgen Stensvold, Henrik Rasmussen, Vivi Bull Stubberud, Per Arne Tølløfsrud, Klaus Bye, Elisabeth Lund Hansen, nne Haga, Helle Madsen Holm, Tonje Hallan Kristiansen, Lill Røisland Nybro, Hildegunn Lie Peterson, Thomas Rajka, Inger Louise Üner.
Komitéen utgår fra hhv Nyfødtavdelingen, Kvinne- og Barneklinikken; Utdanningssenteret; Institutt for Kirurgisk Forskning og Avdeling for Komparativ Medisin, alle Oslo Universitetssykehus.

Basalkurs i laparoskopisk kirurgi

Dato: 28. – 29.08.2014

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 D-boks og pop-trainere.

Temaoversikt
Laparoskopets oppbygging og vedlikehold, fysiologiske effekter av pneumoperitoneum, anestesi ved laparoskopi, laparoskopi ved akutt abdomen og galle. Praktiske øvelser under supervisjon på modeller og simulatorer vil være en vesentlig del av kurset.

Kurskomité
Trond Buanes og Arne R. Rosseland (kursledere), Anders Debes, Ronald Mårvik, Erik Trondsen, Bjørn Edwin, Ole-Christian Olsen, Marianne Berg, Vivi Bull Stubberud.

Mikrokirurgikurs. *Photo: Jorunn H. Larsen*

Thorako-/laparoskopisk kirurgi

Dato: 23. - 25.04.2014 + 26. - 28.11.2014

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

Kurskomité 1
Arne R. Rosseland (kursleder), Trond Buanes, Erik Trondsen, Bjørn Edwin, Ole Christian Olsen, John Hausken, Marianne Berg, Vivi Bull Stubberud.

Kurskomité 2
Trond Buanes og Bjørn Edwin (kursledere), Ole Christian Olsen, Thomas Moger, Hjørtur G. Gislason, Åsmund Fretland, Kristin Kjellevold, Ronald Mårvik, Vivi Bull Stubberud og Marianne Berg.

Mikrokirurgi

Dato: 23. - 25.04.2014 + 26. - 28.11.2014

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

Læringsmål
Læring av generell mikrokirugisk teknikk og praktisk ferdighet som gjør kursdeltaker i stand til å anastomosere kar med diameter ned til en mm.

Kurskomité
Pål-Dag Line (kursleder), Bjarte Fosby, Hilde Bjærke, Vivi Bull Stubberud, Sera Sebastian, Aurora Pamplona, Transplantasjonskirurgisk seksjon og Institutt for kirurgisk forskning.

Illustration photo

Publications and PhD-Theses

Publications 2010 - 2014

2014

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PhD-Theses 2014

Hans Henrik Odland

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24.01.2014
Non-invasive assessment of myocardial function in the neonate.

Cecilie J. Sandberg

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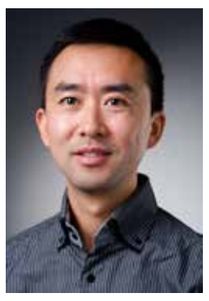

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