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Department of Surgical Sciences

Annual Report 2016

Avsändare/Fastställd av Per Hellman 2017-05-23

Introduction

Chairman's annual address/comments

The year 2016 was a year of change within the Department of Surgical Sciences, since Professor Olle Nilsson retired and was replaced by me on July 1st. Olle Nilsson was a friendly Chairman, and the Department was in good shape when I started. Even though this change, the research and educational activities continued in a fruitful manner by the teachers and staff of the Department. The Department is diversified, in its division into 15 sections, and is working in close collaboration with 9 clinics of the Academic Hospital. This organization aims to allow comparably independent sections and research groups. Thus, strategic decisions and future plans should emerge from the researchers themselves within their local organizations. Our aim is to offer a platform for the researchers and teachers by reducing their administrative duties and enabling them to focus on their main duties; research and teaching. We can do so by the contributions of our highly professional and qualitative administrative staff.

The Department has a history of being highly productive in educating research students as well as graduate students. The continuous work to create stimulating studying and working conditions for the students is high up on our agenda. We also, on a higher level, enjoy good support from the Faculty of Medicine and the Uppsala University in our daily work.

While writing this Annual Report, the work with the KOF17 is fully ongoing. This has for me as the Chairman of the Department since eight months, provided a fantastic information flow regarding all activities of the Department. I am impressed by the thorough and high-quality research that is performed at all corners of the Department. Our researchers are really dedicated their subspeciality and the number and quality of the publications are high. In fact, we are the Department, which is the most effective one, if one accounts the available research grants (including ALF) and the number and quality of publications. We squeeze a lot out of our available resources! The attraction of external grants has also increased, allowing even better results in the future.

Throughout 2016, our teachers have made outstanding contributions in clinical education. The Department has the main responsibility for several specialist education programs in nursing within the surgical field. These programs are of profound importance for both the University Hospital and for the nursing profession, *i.e*. intensive care, anesthesiology, surgical care and ambulance care. The new curriculum in our medicine program for physicians is now running smoothly, but improvements are continuously implemented in order to promote the scientific and academic career of our young and capable scholars. Teachers from the Department play an essential role in this development. The Department is now involved in teaching during semester 1, 3, 5, 6, 7, 10 and 11, with main responsibility for the curriculum taking place during semester 6, 7 and part of semester 11. Other contributions within the pedagogic field also include teaching in biomedicine, physiotherapy and nursing.

Looking forward to the remainder of 2017, we can anticipate an interesting year with numerous challenges, new colleagues, new PhD students, new graduate students, hard but hopefully rewarding and enjoyable work to look forward to. I want to thank everyone at the Department, including all teachers, researchers, administrators, students and laboratory personnel for their dedication and excellent work in 2016, as well as thanking Professor Olle Nilsson for handing over such a nice and friendly Department to me.

Per Hellman

Professor and Chairman

Table of Content

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Michaela Tollin

Emelie Karlström

Anders Lundberg

Elin Lundström

Scientific Reports

1) Anesthesiology and intensive care medicine

Research group 1: Cardiac arrest-neuroprotection

Mechanical chest compressions during cardiac arrest

Background: Every year 300,000 to 400,000 people suffer from sudden cardiac arrest outside of the hospital in Europe. Only 10 % of these patients survives and is discharged from hospital. Lately, there is a strong emphasis on chest compressions being delivered without interruptions. Manual chest compressions during CPR result in only 20-30% of normal blood flow and are difficult to perform continuously. Mechanical chest compressions with the LUCAS device have shown increased cerebral blood flow, coronary perfusion pressure and survival in experimental studies.

Questions: Can mechanical chest compressions with the LUCAS device combined with defibrillation during ongoing chest compressions improve survival? Will treatment with the LUCAS device result in more injuries in non-surviving patients.

Methods and results: Defibrillation during ongoing mechanical compressions showed promising results with a trend in increased short time survival in out of hospital cardiac arrest in a recently completed pilot study of 149 patients. Autopsy was performed in 85 non surviving patients after being treated with either mechanical chest compressions with the LUCAS device or with manual chest compressions according to guidelines. There were no injuries in one third of the patients in both groups. The most frequent injuries found were rib fractures and sternal fractures but there was no difference between the groups. No fatal injuries were found in any of the groups. The results from this pilot studies are the foundation for a multicenter study in Europe-the LINC study of 2,500 patients with out-of hospital cardiac arrest. The study started in January 2008. Patients with cardiac arrest will be randomized to either treatment with a concept using mechanical chest compressions with the LUCAS and defibrillation during ongoing compressions or treatment according to international guidelines including manual chest compressions. In May 2011, an interim analysis was performed and resulted in allowing inclusion of the entire study population. On September 1st, 2012 the last patient was included. The database has been analyzed and first article of the ITT analysis has been published in JAMA January 2014. Predefined subgroup analysis has also been performed and has been publication published in Resuscitation. Within this study, non-surviving patients in Uppsala, Gävle and Västerås have been through autopsy. This article has been published in Resuscitation.

This project has been ongoing since 2004 but has now been completed except for a couple of additional subgroup analyses that is under publication

An additional project is about to start where we are going to measure the achieved ventilation during mechanical CPR either during continuous chest compression or in the 30:2 mode. Pilot testing will be performed during spring 2017 in the ambulance service of this protocol

Members of the group during 2016

Sten Rubertsson, Professor, PI

David Smekal, MD, PhD

Erik Lindgren, MD, PhD student

In collaboration with

Steering com for the LINC trial

Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

Physio Control/Jolife AB

DISCO-trial: Direct or Subacute Coronary angiography for Out-of-hospital cardiac arrest

Background: Although the majority of cardiac arrest patients with return of spontaneous circulation do not have ECG changes indicating an acute STEMI (ST-elevation myocardial infarction), registry studies have shown that about 30% of these patients have an acute occlusion, sub-occlusion or signs of recent occlusion of any coronary artery. Results from observational studies suggest that acute coronary angiography and Percutaneous Coronary Intervention (PCI) increases survival in this group of patients. Data from randomized trials are however missing.

Aim: The overall aim of this prospective, randomized pilot study is to investigate whether immediate coronary angiography (within 120 minutes), with a predefined strategy for revascularization, is feasible and safe to implement in patients with out-of-hospital cardiac arrest. The pilot phase of this study will be terminated Aril 15, 2017 and thereafter a main study will start in which we intend to answer the important clinical question at issue; if early revascularization in this population may improve survival with good neurologic outcome.

Method: This is a national multicenter with the aim to make a larger multi-center study after the pilot phase. The pilot phase started in December 2014 and will last for about 2 years. The study is an open randomized trial. All university hospitals in Sweden are participating and during the year additional hospitals have been recruited and have started or will start recruiting during 2016-17.The study will include a total of 1006 patients *without* ST elevation with successful resuscitation after out-of-hospital cardiac arrest. The study is an open prospective randomized multicenter study with a registry follow up where out of hospital cardiac arrest without ST elevation in ECG will be randomized to immediate coronary angiography with possible intervention or the usual intensive care usually without acute coronary angiography during the first three days. Randomization takes place immediately after ECG is taken in conjunction with the first medical contact.

The study thus includes the following groups:

1. *Intervention* - Cardiac arrest where the patient regained circulation *without* ST elevation randomized to immediate coronary angiography within 120 minutes and possible PCI.

2. *Control* - Cardiac arrest where the patient regained circulation *without* ST elevation randomized to routine intensive care usually without acute coronary angiography during the first three days.

Acute 12-lead ECG taken in the ambulance or in the emergency department prior to randomization will be compared to the coronary angiography findings and follow-up biomarkers.

Survival and neurologic function

Follow-up at Discharge from ICU, Discharge from hospital, one month, six months: EQ5D-5L, Cerebral Performance Category-CPC and mRS. IQCODE at baseline and at six months. Follow-up at six months: Cognitive tests: MoCA (Montreal Cognitive Assessment), TSQ (Two simple questions) and IQCODE (Informant questionnaire), Depression and anxiety test – HADS (Hospital anxiety depression scale). The 30 day and follow up visit after six months for neurological evaluation will be performed by a person blinded for treatment.

Cardiac function endpoints

Systolic left ventricular function will be assessed by echocardiography after 72 hours and six months. Left ventricular systolic function estimated by left ventricular ejection fraction, LVEF, when patient is in the ICU. After six months, global strain will also be calculated and regional left ventricular movement estimated by the regional strain.

Members of the group during 2016

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SUS-Skåne University Hospital

Sahlgrenska University Hospital

Linköping University Hospital

Örebro University Hospital

Umeå University Hospital

Helsingborg Hospital

Gävle Hospital

Sundsvall Hospital

Karlskrona hospital

Danderyd Hospital

Agencies that support the work/Funding

Swedish HeartLung Foundation

The Laerdal Foundation for Acute Medicine

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

INTOx-A prospective measurement of serum concentrations of routine drugs in patients treated in the intensive care unit-A quality measurement/ improvement for clinical treatment and forensic assessment

Background: Patients treated in the intensive care unit (ICU) are treated with a variety of sedative and analgesic drugs to be able to undergo intensive care. The amount of drugs that each patient receives is based on standard dosages where the dose regimen is based on clinical studies with a limited number of patients included. Most patients treated in the intensive care unit have a varying degree of cardiac, renal or liver failure which affects the metabolism of the drugs administered. Possibly, the drug concentrations achieved with the standard dosages administered to these patients can vary significantly between patients. This may possibly lead to an extended hospital stay at the ICU which gives the patient an unnecessary suffering, affects the patient's family and increases the cost of health care. Intoxications treated in the ICU is common and it is often unknown what type of medication or drugs these patients have been taken and what serum concentration it may result in. Also, there are no previous studies with reliable documentation about the drug concentrations expected to be in the blood of patents that die in the intensive care unit.

The aim: is to follow up the result of a quality measurement based on the results of a new routine for drug analysis introduced during a period of time in the intensive care unit. To ensure the quality of the dose regimen of routine drugs for sedation and analgesics. The aim is also to know if the routine analysis can give information about if the self- intoxicated patients have taken drugs that were primarily not suspected. Finally to know the serum concentrations of routine drugs in patients who died and will undergo autopsy.
Methods: Blood will be drawn according to routine procedures upon the patient's arrival at the ICU and then two times per day. Extra blood samples (one tube) will be drawn in addition to routine blood samples and the extra blood samples will be sent to the Swedish National Board of Forensic Medicine unit in Linköping, Sweden. The drugs that will be analyzed are drugs used for sedation and analgesia. There will also be a screening of unknown drugs taken by self- intoxicated patients. The administration of sedative and analgesic drugs is via infusion pumps and the amount supplied is recorded daily. Routine blood samples will be drawn to measure organ function Sedation ratio by the RASS- scale will be evaluated and recorded 3 times per day. An assessment of the visual analogy scale (VAS) will be done for the patients who are awake and are able to cooperate. All physiological measurements will be measured and documented according to local routines. Age, sex, medical history, diagnose at admission and discharge, care burden measurement according to SAPS 3 score will be recorded. For patients who die at the CICU and will undergo autopsy, blood samples will be taken after death for analysis of routine drugs.

Collection of blood samples has now been completed and we have started to analyze data which hopefully during 2017 will end in starting publication of our results.

Members of the group during 2016

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In collaboration with

Swedish National Board of Forensic Medicine

Faculty of Pharmacy

Agencies that support the work/Funding

Institutional Grants, Uppsala University

Uppsala University Hospital (ALF)

Swedish National Board of Forensic Medicine

Research group 2: Injury and critical care epidemiology

Principal investigator: Rolf Gedeborg

Injuries are the most important cause of death in the young and middle aged and a common reason for ICU admission. With the aid of unique person identification numbers to link health care registers, we have excellent opportunities for population-based research. Each year approximately 100,000 people in Sweden are hospitalized because of injuries and 5,000 people die from their injuries.

Injury epidemiology is a collaborative effort involving several sections of the department, among them the sections for Anesthesiology and Intensive Care, Orthopedics, Vascular surgery and Forensic Medicine. A close collaboration has also been initiated with researchers at Linköping University.

A new comprehensive data extraction from multiple health care databases, including control individuals from the normal population and data on socio-economic factors has been finalized. A PhD project utilizing this dataset, in collaboration with the section for vascular surgery, has been finalized, involving a study that estimated incidence of traumatic vascular injury

During the year, two PhD-student projects related to trends in injury incidence and mortality has progressed in collaboration with Linköping University.

A comprehensive data extraction has also been finalized combining data from the Swedish intensive care registry with data from the national patient registry and socio-economic data. The research objective for the

critically ill population primarily aims to study factors related to probability of admission to the intensive care unit, and the impact of comorbidity and socio-economic exposures on long-term survival.

The ability to identify and study prehospital injury deaths and consequences of prehospital management remains important for the study of the injured population. The group has published methods for the use of ICISS scores that are internationally comparable. A particular focus of our efforts is also on the ability to develop reliable estimates of comorbidity in injured patients and also applied to patients in general intensive care. In collaboration with Forensic Medicine the development of prediction models for the outcome after violent crime has been finalized and submitted for publication.

Members of the group during 2016

Rolf Gedeborg, Associate Professor

Anna Aronsson, RN, PhD student

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In collaboration with

Folke Sjöberg, Professor, Linköping University

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Miklós Lipcsey, Docent

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Agencies that support the work/Funding

Uppsala University Hospital (ALF)

Research group 3: Lung function in anesthesia and intensive care

Principal investigator: Anders Larsson

The project is primarily aimed at improving ventilator treatment in the critically ill patient with acute respiratory failure (ARF). The secondary aim is to increase the understanding of respiratory physiology at spontaneous and mechanical ventilation during anesthesia and intensive care. The project is mainly performed at the Hedenstierna laboratory (a part of the Department of Surgical Sciences) and in the Central Intensive Care Unit, Uppsala University Hospital in collaboration with Professor Göran Hedenstierna as well as coworkers from Karolinska Institute, Swedish Agricultural University, University of Bari, Politecnico di Milano University, University of Magdeburg, University of Freiburg, University of Istanbul and University of Sao Paolo, University of Helsinki, Jules Verne University, Amiens,the European Synchrotron Radiation Facility (ESRF), Grenoble, Paul Scherrer Institute (PSI), Villigen, Switzerland, MAX IV, Lund and the medical technical equipment manufacturer Getinge Group.

Inflammation induced by mechanical ventilation

About 3,000 patients are treated with mechanical ventilation in the Swedish intensive care units due to ARF, a condition with mortality of about 30-40%. Although mechanical ventilation saves lives, it has

inherent side effects by inducing mechanical injury on the lungs, leading to local and systemic inflammation. In fact, the patients do not die of hypoxemia but of multiple organ failure caused by the inflammation. It has been shown that by decreasing the mechanical stress on the lungs by reducing the tidal volumes, mortality is reduced by ten absolute percent. In a present project we are studying in an experimental ARF model with positron emission tomography (PET) and immunohistology the inflammatory effects of two different ventilator modes; a conventional and a new, protective mode (low tidal volumes and lung recruitment i.e., opening of closed lung regions by applying high airway pressure). The results indicate that the experimental mode induces less severe inflammation. Another new, interesting finding is that the inflammation is mainly located in the "healthy" open parts of the lungs and not, as previously thought in the collapsed lung regions. In parallel with these studies, we will test whether a new synthetic surfactant with very stable molecular bindings will improve lung function and down-regulate pulmonary inflammation. Moreover, since the cytokine TGF-β is involved in the immunologic process, the edema formation as well as in the development of fibrosis in ARF, a blocker of this mediator will be studied in experimental ARF. Furthermore, we are studying experimental ARF with synchrotron radiation computed tomography at ESRF and PSI that has a very high resolution, and have found that the ventilatory pattern on micro-level is chaotic in ARF, but not in healthy lungs. During the coming year this research track will be expanded substantially and we will continue this research line at MAX IV (MedMax). We have a full time post-doc working in this field together with a PhD student.

Spontaneous breathing in ARF

Modes in which spontaneous breathing efforts are allowed have been shown, except improving the patient's comfort, to improve oxygenation in ARF. The underlying mechanism has previously been thought to be caused by recruitment of collapsed lung tissue located close to the diaphragm, but studies by us in an experimental model have shown that the explanation is that perfusion is redistributed to open and ventilated lungs regions during spontaneous breathing. We will now initiate a study using dual Energy CT to further explore the difference in pulmonary perfusion between spontaneous and mechanical ventilation. In a new study, we have found that the lung collapse is less during spontaneous breathing, and that this is associated with an expiratory activity in the diaphragm, indicating that the diaphragm has, in addition to its important function as the main inspiratory muscle, a protective role by stabilizing the lung during expiration Furthermore, we have performed studies of neuronal adjusted ventilatory assist (NAVA) in experimental models ,and found that positive end-expiratory pressure higher than normally is used is essential in order to avoid cyclic lung collapse.

Apneic oxygenation or low tidal volume ventilation in combination with/without extracorporeal carbon dioxide removal (ECCO2R) or a proton acceptor (THAM) in ARF

As discussed above, low tidal ventilation improves survival in ARF. The ultimate ventilation would be a mode with zero tidal ventilation, i.e. apneic ventilation. We have recently shown that apneic ventilation in combination with ECCO2R gave excellent oxygenation and blood CO2 levels in an experimental ARF model. However, to prevent alveolar nitrogen concentration/accumulation in the lungs with this technique 100% O2 (which is toxic) is thought be needed. We have now successfully explored a modified apneic ventilation technique in an experimental lung model, where the alveolar O2 concentration could be kept at non-toxic levels; we have found that a THAM is a possible method keeping normal pH during apnea and that low tidal volume ventilation combined with THAM administration might be feasible.

Lung function measurements using optoelectronic plethysmography during anesthesia

Optoelectronic plethysmography, in which the dimensions of thorax and abdomen are determined in real time by registration of the movement of reflective markers on the chest wall by several video cameras, is a non-invasive method to measure with high resolution the changes in thorax and abdomen induced by breathing and the anesthesia technique. The method has been used to study the ventilatory mechanical effects of propofol anesthesia and of different modes of jet ventilation. We found, very interestingly, that during emergence from anesthesia lung volume decreased due to increased activity of the expiratory muscles. The expiratory muscles are usually silent except at severe airway obstruction (e.g. asthma). We

will further explore whether this effect also occurs under inhalation anesthesia using different advanced methods.

Members of the group during 2016

Anders Larsson, MD, PhD, Professor

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Agencies that support the work/Funding

Swedish Research Council (VR)

Swedish Heart and Lung Foundation (HLF)

Uppsala University Hospital (ALF)

Institutional Grants, Uppsala University

Research group 4: Pain research group

Principal investigator: Torsten Gordh

Search for candidate biomarkers markers relevant to pain pathophysiology

This project aims to build knowledge about the pathophysiology of chronic pain with the goal to find new diagnostic markers for early biochemical characterization of patients suffering from chronic pain (e.g. neuropathic pain, fibromyalgia, low back pain). The outcome is believed to be essential also for the development of new diagnostic and therapeutic strategies.

We also study the effects on biomarkers of various treatments such as electrical spinal cord stimulation, or pharmacological interventions. The project is a part of Uppsala Berzelii Technology Centre for Neurodiagnostics (Uppsala Berzelii Centre), with long term support by and The Swedish Research Council (VR) and VINNOVA, having access to extremely sensitive analytic methods, in cooperation with Professor Masood Kamali (the PEA method) and the group led by Professor Jonas Bergquist (mass spectrometry). It is as a PhD student project for Anne-Li Lind (dissertation 2017) . We have found inflammatory biomarker patterns in blood and CSF that separates pain patients from healthy controls. At present we study patients suffering from trigeminal neuralgia, by analysis of biological markers in blood and in CSF, using multiplex inflammation panels, and mass spectrometry.

Visualization of peripheral pain mechanisms using PET ligands relevant to inflammation

In this project we investigate some PET ligands concerning their capacity to mark for painful processes in the body. We have found markers that distinctly accumulate in painful areas in patients suffering from chronic WAD, and following distortions. Experimental studies in “small animal PET scan”, as well as in vitro binding studies, is ongoing, in order to pin point to what cellular structure the relevant marker is

binding to. The project is carried out in close collaboration with Professor Fred Nyberg and post doc Anna Lesniak, and a PhD project for Dr. Mikko Aarnio.

Persistent postoperative pain

In this project, a genetic analysis of patients who have developed chronic pain after inguinal hernia surgery or hand surgery are compared with patients that had undergone the same type of surgery and not developed pain. About 2500 patients have been screened, resulting in 150 with persistent pain + 150 without pain who all have been investigated clinically. The results show that persistent postoperative pain in mainly of neuropathic, and that the presence of certain genetic HLA haplotypes seems to increase the risk for chronic pain following surgery. The project is led by Dr. Adriana Miclescu. We now proceed to study patients that have undergone hand surgery with nerve repair. Around 1000 patients have been identified and contacted for an questionnaire study. Of those, selected subgroups are presently be studied for characterization of phenotype and biomarker profiling, and for studies on CMP mechanisms.

Strong opioids for long term treatment of pain

We are undertaking a study on long term effects, side effects, cognitive effects, and effects on quality of life, opioid receptor polymorphism as related to effect, and nerve cell culture receptor studies after chronic opioid exposure. The “problematic use of opioids” and the possibility to restore opioid induced cognitive impairment by using growth hormone therapy, is studied in experimental models an in patients. The clinical part of the project is led by Annica Rhodin and dr Lenka Katila in close collaboration with Senior Professor Fred Nyberg.

Clinical and biochemical characterization of very complex chronic pain patients

We aim to characterize a group of very complex chronic pain patients, suffering from substantial psychiatric co-morbidity in addition to their pain problem. This group, having a very low quality of life, and consuming large amounts of health care, has not been well understood, leading to consequences with poor treatment outcome. We use PRO instruments, qualitative methods, and biochemical tools. It is a PhD project for MD Eva-Britt Hysing. The clinical characterization is now completed.

Biochemical studies on patients suffering from chronic fatigue syndrome

We study the inflammatory pattern I blood and CSF in patients suffering from chronic fatigue syndrome.

Members of the group during 2016

Torsten Gordh, MD, PhD, Professor in Clinical Pain Research, Anesthesiology

Rolf Karlsten, MD, PhD, Uppsala University

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Lena Smith, MD, PhD, Uppsala University

Anders Larsson, Professor, Uppsala University

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Mikko Aarnio, MD, PhD student, Uppsala University

Eva-Britt Hysing MD, PhD student, Uppsala University

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Agencies that support the work/funding

Agencies that support the work/funding

VINNOVA and the Swedish Research Council (Vetenskapsrådet) via Uppsala Berzelii Technology Centre for Neurodiagnostics

Uppsala University Hospital (ALF)

Regional Clinical Research Council

University of Heidelberg

Institutional Grants, Uppsala University

Research group 5: Sepsis and intensive care research group

Experimental septic shock

Principal investigator: Mats Eriksson

Septic shock is secondary to bacteria, fungi or virus entering the blood, causing an extensive systemic inflammatory reaction, characterized by disturbances in cardiac performance and blood circulation, oxygenation of blood and tissues, temperature regulation, in the number of leucocytes and platelets as well as development of metabolic acidosis. Septic shock is frequently seen in ICUs all over the world. The mortality in this condition is high and may occur suddenly and unexpectedly in previously healthy people despite extensive care. MD PhD student Ewa Söderberg presented her Licentiate thesis on “Experimental Septic Shock”, 2012. The experimental part of this work takes place at the Hedenstierna laboratory, which is a part of the Department of Surgical Sciences, Uppsala University.

Steroids and endotoxemic shock

Principal investigator: Mats Eriksson

Whether or not steroids should be given in septic shock has been an issue for decades. Despite several clinical trials in which different doses and durations of treatment have been studied, the possible benefit of hydrocortisone in septic shock has not yet been clarified. Since timing of steroid treatment could be a key to these conflicting results, we decided to examine whether hydrocortisone given at the earliest possible time point in established porcine endotoxemic shock. At the onset of endotoxemic shock, defined as the moment when the mean pulmonary arterial pressure reached the double baseline value, the pigs were randomly given a single intravenous dose of hydrocortisone at 5 mg x kg-1 or the corresponding volume of saline. Mean arterial pressure and systemic vascular resistance index were significantly higher and heart rate was significantly lower in the endotoxin + hydrocortisone group compared to the endotoxin + saline group. Body temperature and blood hemoglobin levels increased in the endotoxin + saline group, but not in the treatment group. Since there was no significant difference in the plasma levels of TNF-alpha or IL-6 between the groups, our results suggest that these effects are not mainly mediated by these pro-inflammatory cytokines. These results were published in Steroids 2012.

Renal function in critical illness

Principal investigator: Miklós Lipcsey

Kidney function is an important risk factor for cardiovascular morbidity and mortality both in intensive care patients and in a general population. Since the performance of renal biomarkers have not been investigated in a large ICU population we have now collected all creatinine and cystatin C results from Uppsala, Stockholm and Lund, Sweden, and link it to outcome from national registries. We will investigate how cystatin C and creatinine predicts ICU illness severity, short and long term mortality and development of end state renal failure. Project group: Professor Anders Larsson, Associate Professor Max Bell, Alain Dardashti, Associate Professor Johanna Helmersson-Karlqvist

We are evaluating the performance of creatinine and cystatin C based GFR estimates in critically ill patients through clearance of vancomycin and gentamycin, antibiotics with routine plasma concentration determination. The pharmacokinetic modelling is done in collaboration with Associate Professor Elisabet Nielsen. Project group: Prof Anders Larsson, Associate Professor Elisabet Nielsen, Mia Furebring, Anna-Karin Smekal.

Blood sampling and drug administration through intraosseous needles

Principal investigator: Mats Eriksson

In life-threatening emergencies, especially among children, it might be difficult to establish vascular access. When such access has been obtained, fluid regimen is frequently prioritized. Blood sampling is, of course, also an important part of the emergency treatment, since relevant information on the clinical condition aids therapy and further clinical management. Intraosseous needles, most frequently inserted through the anterior tibia, have an important mission in emergencies, since they let us create a simple and fast access to the vascular system. Fluids and drugs may be administered through these needles. They may also be used for sampling of bone marrow aspirates, fairly reflecting the conditions in the peripheral blood. However, samples obtained through aspiration from intraosseous needles may contain bone marrow particles, which may harm laboratory devices. Since tools for laboratory for laboratory analyses have been improved, and handheld devices have been developed, where the aspirate is analyzed within a cartridge that is never in contact with the device itself. Utilizing an experimental model, we have compared intraosseous bone marrow aspirates analyzed by such an instrument with conventional arterial blood samples. The aims of this study were: 1) To investigate whether intraosseous samples can be used for analysis, using a handheld, cartridge-based, point-of-care analyzer, where aspirate is never in contact with the device. 2) To determine whether these values are comparable to those in arterial blood and 3) to validate the reproducibility of the method during a six hour period. There was generally a good agreement between the two intraosseous sites with Calcium and Base Excess showing the highest coefficient of variance (CV).

Despite CVs were in the 20% range for calcium and base excess, we consider the results acceptable to use in this very acute situation. There was also in general a good agreement between intraosseous and arterial values but Base Excess, Lactate and especially PO_2 showed high CVs. This work was published 2012 in Resuscitation. We have also presented a report in: Scand J Lab Clin Invest on morphine analysis in samples taken from intraosseous needles compared to plasma samples. This work was the scientific presentation of a medical student, which is a part of their education. Present research focuses mainly on point-of-care analysis of blood gases during endotoxemic shock.

A study on analysis of blood gases, using a POCT device during experimental shock is published in Acta Anaesth Scand. We found systematic differences between IO and arterial/venous sample values in this setting. However, samples from tibia or humerus may give clinically useful information during initial evaluation and resuscitation. IO infusion seem to affect the results, thus sampling during infusion should probably be avoided. Cartridge based analyzers can be used to avoid possible instrument problems due to debris in IO samples.

Intraosseous needles and administration of antibiotics

Principal investigator: Mats Eriksson

In the patient with an acute life-threatening infection such as septic shock or meningitis, timely administration of parenteral antibiotics is paramount in order to increase the likelihood of survival. However, gaining access to the circulation could be challenging in circulatory unstable patients. A special concern is the pediatric patient, where venous access is often difficult even under stable conditions.

Thus, we aimed to investigate whether comparable antibiotic concentrations could be reached with intraosseous and intravenous administration during experimental septic shock. Cefotaxime and gentamin were used. For both antibiotics, plasma concentrations after intraosseous and intravenous administration followed similar curves throughout the observation period, and peak concentrations were comparable. Mean concentration area under the curve (AUC mg x hr x L^{-1}) for cefotaxime was 108.1 ± 19.5 after intraosseous and 116.5 ± 11.1 after intravenous administration; ratio 0,93 (95% CI 0.71 - 1,19). Mean AUC for gentamicin was 28.1 ± 6.8 for intraosseous and 32.2 ± 3.5 for intravenous administration; ratio 0.87 (95% CI 0.62 - 1.19). These results have been published in Acta Anaesth Scand. MD PhD student Gunnar Strandberg completed his half-time dissertation 2014. Further studies will focus on blood coagulation in a trauma model of exsanguination.

Evaluation of plasma calprotectin as a marker of sepsis in intensive care patients

Principal investigator: Miklós Lipcsey

This study was performed in order to determine the performance of plasma calprotectin as a marker of sepsis on intensive care unit (ICU) admission and as a marker of mortality day 30 post-ICU admission. Consecutive ICU patients were allocated to: sepsis, postoperative sterile inflammation and intoxication without inflammation groups. We found that calprotectin is a sensitive marker of systemic inflammation, is a potential sepsis marker and performed well as mortality predictor in this pilot study. Project group: Prof Jan Sjölin, Prof Anders Larsson, Associate Professor Mats Eriksson, Ewa Söderberg. This study was published in Biomark. Med. 10: 811 – 818, 2016.

Has hydrocortisone treatment an impact on neutrophil gelatinase – associated lipocalin realease in porcine endotoxemic shock?

Principal investigator: Miklós Lipcsey

A key feature of sepsis is systemic inflammatory activation that could be counteracted by steroids. In this experimental model of systemic inflammation, we sought to investigate whether septic neutrophil activation, evaluated by the plasma levels of neutrophil gelatinase-associated protein (NGAL), is modulated by the timing of hydrocortisone treatment. Sixteen anesthetized pigs were allocated to one of four equally sized groups. Three of these groups received endotoxin for 6 hours to induce endotoxemic

shock. Hydrocortisone (5 mg × kg^{-1}) was administered intravenously before endotoxemic challenge, or at the onset of endotoxemic shock. Endotoxemic pigs not receiving hydrocortisone and non-endotoxemic pigs served as control groups. Endotoxemic shock increased plasma NGAL. The increase in plasma NGAL is counteracted by hydrocortisone administration prior to endotoxemia; concomitantly, this treatment was associated with less expressed circulatory derangement. Urine NGAL did not differ between the groups, suggesting that the NGAL response was not primarily related to kidney injury. Project group: Prof Jan Sjölin, Prof Anders Larsson, Ewa Söderberg

This study is published in Intensive Care Med Exp. 5:4. doi: 10.1186/s40635-017-0117-6. Epub 2017

Intraosseous needles and thromboelastography

Principal investigator: Mats Eriksson

Laboratory analysis of coagulation is often critical in medical emergencies. If vascular access is difficult, intraosseous cannulation may be necessary. We studied the analysis of coagulation parameters in intraosseous aspirates during steady state and after major hemorrhage.

Thus, ten anesthetized pigs received intravenous and intraosseous cannulas and samples were taken for analysis of thromboelastography (TEG), prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen. Analyses were repeated after removal of 50% of the calculated blood volume and resuscitation with crystalloid. Intraosseous and venous values were compared.

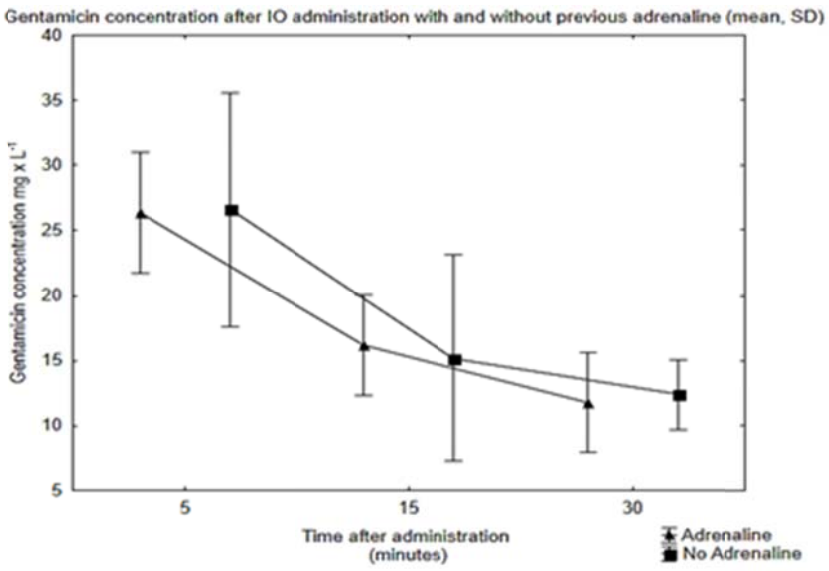
We found that bleeding and resuscitation resulted in significant hemodilution and shock. In TEG, the activation time (R) was shorter and maximal amplitude (MA) smaller in the intraosseous samples. No important differences were demonstrated for the other studied parameters. However, there was a strong tendency for the intraosseous samples to coagulate in vitro, making analysis of PT, APTT and fibrinogen difficult. After hemodilution a clinically relevant decrease was seen for MA and fibrinogen concentration.

We conclude that intraosseous samples seemed hypercoagulable, making analysis of standard coagulation parameters difficult. TEG analysis demonstrated shortened activation time. 50% hemorrhage and crystalloid resuscitation moderately affected the studied parameters. These results were published in Scand J TraumaResusc Emerg Med 2016, 24: 131-136. Heparinization of the IO device and subsequent neutralization by heparinase did not alter these results.

Intraosseous needles and administration of adrenaline

Principal investigator: Mats Eriksson

Does an intraosseous injection of adrenaline reduce the uptake of a second drug injected through the same needle? We designed an experiment, where adrenaline or saline was injected through an intraosseous needle during hemodynamic shock. A subsequent injection of gentamicin was done, as this substance may serve as a tracer in blood. As seen in the figure below, intraosseous adrenaline does not seem to impair uptake of a second drug injected through the same intraosseous needle. The results from this study are not yet finally analyzed, since the number of animals has been extended compared to our original estimation and the control group has been re-designed. Still, the results in the figure are relevant.



Comparison of intraosseous aspirates and arterial blood samples, analyzed by point – of – care during hypovolemic shock.

Principal investigator: Mats Eriksson

In hypovolemic shock, vascular access may be a challenge. In order to evaluate the usefulness of intraosseous (IO) aspirates versus arterial samples, analyzed by point – of – care – technology (POCT), anesthetized pigs were exsanguinated by 50% of the circulating blood volume. Interpretation of IO aspirates analyzed by POCT should be done with caution, this is especially true for PaO_2 and SaO_2, which are markedly lower in IO samples than in arterial blood. Still, IO samples are sufficiently close to arterial ones, to give initial information, which may help to guide therapy during the early phase of expressed blood loss.

The impact of rapid bolus administration vs. slow infusion on the extravasation of albumin

Principal investigator: Miklós Lipcsey

Albumin solutions are used for fluid resuscitation in in critical illness. Recent experimental and clinical evidence suggest that extravasation of albumin could be influenced by the rate of administration in systemic inflammatory response syndromes. The aim of this project is to determine whether rapid bolus administration of albumin leads to greater extravasation compared to a slow intravenous in experimental septic shock. Endotoxemic pigs, monitored and ventilated with standard intensive care equipment, are given 5% albumin labeled with Technetium-99m either as a rapid bolus or a 2-hour infusion. Radioactivity is monitored in muscle microdialysate, plasma, and urine as well as radioactivity in liver, spleen, kidney and lung is analyzed post mortem. Project group: Prof Jan Sjölin, Prof Anders Larsson, Magnus von Seth

Model of living bacteria and bacterial clearance by splanchnic mononuclear phagocyte system

Principal investigator: Miklós Lipcsey

In order to increase the knowledge of the interplay between bacteria and the body's immune response we have set up a model, where living E. coli bacteria are administered to the anaesthetized pig. This model may give important information on pathophysiological events and reactions, optimization of antimicrobial strategies and inflammatory markers. We have shown that during infusion of live bacteria, bacteria can be cultured despite an ongoing administration of antibiotics although termination of such an infusion causes the bacteria to disappear from the blood rapidly. The hypothesis currently investigated in this project that systemic inflammatory activation decreases the capacity of the hepatic mononuclear phagocyte system. We have now presented data showing that the ability of the liver to eliminate bacteria from the splanchnic circulation is almost total at a single pass in healthy animals, while in animals with systemic inflammatory response syndrome 60 times more bacteria reach the systemic circulation from the splanchnic bed. In the same porcine model we are currently investigated trans-splanchnic bacterial clearance and endotoxin clearance. Project group: Prof Jan Sjölin, Prof Anders Larsson, Katja Hanslin

Microcirculation and cellular energetics

Principal investigator: Miklós Lipcsey

In septic shock, hypoperfusion of the organs are of crucial importance and considered to be one of the key factors in the development of this syndrome. Lack of substrate secondary to mitochondrial insufficiency seems to be, at least partly, responsible for this phenomenon. We are aiming to evaluate the rate of the occurrence of this insufficiency, and to determine whether this deficiency is due to the metabolic disturbances caused by endotoxemic shock or whether hypoperfusion per se is sufficient to explain this condition. These experiments are performed by microdialysis in anaesthetized endotoxemic pigs where the energy consumption of cells and mitochondrial function is selectively blocked in endotoxemic and non-

endotoxemic animals to differentiate if organ failure is due to energy deficit or mitochondrial dysfunction. Project group: Prof Jan Sjölin, Prof Lars Hillered, Magnus von Seth, Alexander Otterbeck

Antibiotic concentration in critical illness (ACCIS study)

Principal investigator: Miklós Lipcsey

Early and effective antibiotic therapy is of paramount importance in septic shock. Current recommendations on antibiotic dosing are mainly based on studies in healthy volunteers. In critical illness several factors change the pharmacokinetics of drugs, such as variations in total body water, plasma protein levels, and in hepatic and renal function. Initiation of renal replacement therapy can also alter elimination of antibiotics. Given the unpredictable pharmacokinetics of antibiotics, both underdosing and overdosing of these drugs is likely in the critically ill population. Our hypothesis is that antibiotic concentrations are insufficient during the first days after starting antibiotic therapy. Given that the maximum impact on outcome is probably during the first phase of the antibiotic treatment, investigating this hypothesis is of great importance. We are planning to start a multicenter study in the Uppsala-Örebro region with, currently, nine participating ICUs aiming to include 150 patients. After initiation of antibiotic therapy (with the eight most common antibiotics in this population) plasma concentrations will be followed for three days. In the second phase of the study, based on the study data, pharmacokinetic modelling will be used to optimize dosing of the antibiotics investigated. The latter project is run in collaboration with Assistant Professor Elisabet Nielsen. This multicenter study is now running in eight centers. Project group: Mia Furebring, Anna-Karin Smekal.

The epidemiology of sepsis in Sweden

Principal investigator: Miklos Lipcsey

Recent data from Australia and the USA indicate that mortality related to sepsis and septic shock is decreasing. The crude numbers from the yearly report of the Swedish intensive care register indicates that mortality in sepsis is higher than in the two mentioned countries and that the mortality rate in sepsis is virtually unchanged over the last five years in Sweden. We are now conducting a study to investigate the crude mortality and the evolution of mortality over the last eight years in sepsis, relating this to co-morbidities, severity of illness, level of care and other variables that may affect prognosis. The project group consists of Associate Professor Johanna Hästbacka, Ing-Marie Larssom, Gunnar Strandberg and Björn Ahlström.

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RFR

Vinnova

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Research group 6: Acute Kidney Injury

Principal investigator: Robert Frithiof

Influence of the innate immune system on sepsis-induced acute kidney injury

Sepsis-induced acute kidney injury (SI-AKI) is common and associated with high mortality. Survivors are at increased risk of chronic kidney disease. The precise mechanism underlying SI-AKI is unknown and no curative treatment exists. The innate immune system is activated in response to exogenous microbial products. The result is an inflammatory reaction aimed at clearing a potential infection. However, the consequence may also be organ dysfunction as the immune response can cause collateral damage to host tissue.

The purpose of this project is to describe the basis for how activation of the innate immune system has the potential to cause renal dysfunction and the mechanisms by which this may take place in sepsis.

Studies are undertaken in large-animal models (pigs and sheep) to elucidate the influence of histones and corticosteroids on renal dysfunction as a result of infection with *Escherichia coli* or *Pseudomonas aeruginosa*.

Mitochondrial dysfunction in sepsis-induced acute kidney injury

It is not clarified if renal oxygen delivery is reduced in sepsis and in experimental studies it does not always explain the renal dysfunction that may develop. Increased anaerobic metabolism could theoretically occur despite normal oxygen delivery if mitochondrial function is impaired. Since the kidney is second only to the heart in mitochondrial density a role for mitochondrial dysfunction in septic AKI seems plausible. In ongoing studies we are aiming at describing a potentially altered mitochondrial function as a result of experimental sepsis.

Renal blood flow in human sepsis

Acute kidney injury (AKI) in intensive care patients with sepsis or septic shock is a serious and common condition. In 2013, more than 1600 patients were treated for AKI with continuous renal replacement therapy (CRRT), i.e., hemofiltration/dialysis, in the Swedish intensive care units (ICUs). Sepsis is the single most frequent underlying condition causing AKI in critically ill patients (45% of all cases). AKI, even treated with dialysis, contributes per se to mortality and is associated with longer stay in the ICU. Furthermore, about 14% of the patients surviving CRRT-treated AKI will be dialysis-dependent after discharge. Thus, it is of extreme importance to prevent AKI by improving renal blood flow and oxygenation. The most common method used for this purpose is intravenous infusion of large amount of fluids combined with norepinephrine (a vasoconstrictor) that often increases diuresis. However, there is no conclusive evidence that this method really improves renal blood flow, oxygenation and function and reduces the need of CRRT. Indeed, in contrast, there are animal studies indicating that this measure may cause kidney injury and, in addition, retrospective studies have shown that liberal fluid resuscitation is associated with increased mortality in critically ill patients. Our belief is that the dissonance between the studies and clinical practice is due to the individual response, where some patients benefit, while others do not benefit of this treatment. One way to assess whether the treatment will give a positive effect on renal blood flow and oxygenation is to measure these variables. However, it has hitherto not been possible clinically due to lack of suitable methods. But recent developments of the magnetic resonance technique (MR) by collaborators at Uppsala University, the radiology department at Uppsala University Hospital and coworkers in Nottingham have made it possible to perform such studies. Therefore we plan use the MR-technique to titrate fluids and vasoconstrictors in this patient category. Since the information, whether this routine treatment affects renal blood flow and oxygenation has not previously been obtained in septic patients we plan to report our findings.

Renal dysfunction during anesthesia and surgery

Patients that undergo surgery with general anesthesia have an 8-10% risk of developing perioperative acute kidney injury. The risk is higher if high age, diabetes, obesity, cardiovascular disease and/or hypertension are present. The underlying mechanisms contributing to renal dysfunction during surgery are largely unknown. Therefore we have three ongoing projects investigating this in experimental animals as well as humans.

In experimental animals renal sympathetic nerve activity is measured in the conscious as well as the anesthetized state and the magnitude of nerve activity is correlated to changes in urine output, glomerular filtration and renal oxygen utilization.

In another set of experiments renal function during anesthesia is investigated with and without angiotensinreceptor II antagonism.

Finally, in pediatric subjects undergoing anesthesia for general surgery the level of fluid- and electrolyte regulating hormones arginine vasopressin, angiotensin II and aldosterone is measured during different types of anesthesia.

To reduce the risk for extreme anesthesia-induced hypotension, hypertension patients are paused from their ongoing treatment a couple of days before surgery. Therefore, we investigated renal function, hemodynamics and oxygen status in pigs with/without angiotensin II inhibitor during acute procedures mimicking general anesthesia with hypovolemic chock and resuscitation.

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Dissertations 2016

Henrik Oliveiro-Reinius. Open lung concept in high risk anaesthesia: Optimizing mechanical ventilation in morbidly obese patients and during one lung ventilation with capnothorax.

Joakim Engström. Patient safety in the Intensive Care Unit: With special reference to Airway management and Nursing procedures.

Jaime Retamal Montes. Aspects on ventilation induced stress and strain on regional and global inflammation in experimental acute respiratory distress syndrome.

Ewa Söderberg. Experimental septic shock – Effects of endotoxemia with special reference to pathophysiological responses in the pig.

Staffan Höstman. Minimal volume ventilation in lung injury: With special reference to apnea and buffer treatment.

Moritz Kretzschmar. Ventilation/Perfusion Matching and its Effect on Volatile Pharmacokinetics.

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2) Endocrine Surgery

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Genetics and treatment of endocrine tumors

The Endocrine Surgical Research Group runs studies of genetics, epigenetics, diagnosis and treatment of endocrine tumors, in order to identify genes involved in tumor development and progression, and to ultimately provide possibilities for new treatment. In clinical studies genetic changes are related to the disease course of individual tumors, with the overall aim to improve diagnosis and treatment in patients with endocrine tumor disease.

Endocrine tumors are of special interest in tumor biology because of a common extended disease course, and often presence of only few specific genetic changes, which can be related to variable tumor biology. For many endocrine tumors histopathology can often not distinguish tumors with more malignant biological features, and there is a general hope that genetic differences will provide better means of discrimination. Genetic studies are expected to become of great importance for the clinical management by predicting prognosis, and genetic defects may be used as targets for new treatment. The overall aim of the studies is to identify tumor genes and other prognostic markers of importance for the development and progression of endocrine tumors, reveal gene changes with new technology, and investigate new possibilities of treatment against tumor progression, all in order to offer personalized care for each patient.

Parathyroid

In parathyroid tumors overexpression of β-catenin has been demonstrated due to a truncating mutation of the Wnt receptor LRP5. The mutation has been shown to stimulate cell proliferation in an own established parathyroid cell line, and tumor growth in SCID mice, supporting our identification of a new important receptor for Wnt-mediated tumorigenesis. The same mutation has been revealed and found to influence tumor growth in breast cancer. Accumulation of active non-phosporylated β-catenin also occurs in parathyroid carcinomas, but due to aberrant CpG methylation and lost expression of the tumor suppressor gene APC. Therefore, adjuvant epigenetic therapy should be considered as an additional option in the treatment of patients with recurrent or metastatic parathyroid carcinoma. A genome-wide analysis of parathyroid tumor DNA methylome has revealed several epigenetically deregulated genes of putative importance to benign and malignant parathyroid tumourigenesis. The HIC1 tumor suppressor gene plays a growth-regulatory role in the parathyroid glands and reduced HIC1 expression by repressive histone modification H3K27me3 rather than by CpG methylation was observed in parathyroid tumors regardless of the hyperparathyroid disease state.

The H3K27me methyltransferase EZH2 was then shown to be overexpressed in a subset of the benign and in all malignant parathyroid tumors. Overexpression was explained by EZH2 gene amplification in a large fraction of parathyroid tumors, including adenomas, carcinomas, and secondary hyperplastic parathyroid glands. This supports a possibility of a common pathway in parathyroid tumor development. It was also found that maintained expression of EZH2 in the human parathyroid cell line sHPT-1 was necessary for tumor cell growth. The results strongly support an oncogenic role of EZH2 in parathyroid disease. The epigenetic modification 5-hydroxymethylcytosine (5-hmC) is severely reduced in many cancers, as are the responsible enzymes TET1/2. Now 5-hmC and TET1 have been found at reduced levels in parathyroid adenomas and carcinomas and that 5-hmC can also discriminate between these tumor groups. Whether 5-hmC represents a novel marker for malignancy warrants further analysis in additional tumor cohorts. A growth regulatory role of TET1 in parathyroid cells was also demonstrated.

Small Intestinal Neuroendocrine Tumors (SI-NET)

Small intestinal neuroendocrine tumors (SI-NETs) have been studied with molecular methods. We have as the first group revealed presence of a suspect tumor suppressor gene for SI-NETs on chromosome 18q. Chromosome 18q was also shown to be involved in familial tumors in collaboration with Professor E Tiensuu-Janson. A candidate tumor suppressor gene at 18q, Elongin, has been thoroughly studied. Expression array has identified different clusters of tumors, and methylation as well as single nucleotide polymorphism arrays have continued the search for molecular deficits in these tumors. We have demonstrated mutations in the CDKN1B gene in 8.5% of our cohort. The large local cohort in Uppsala, but also nationally, are identified clinically and tumor markers and prognostic variables are being identified to subgroup the patients.

Pancreatic NETs

Several previous studies have investigated gene changes associated with pancreatic NETs. We have by exome sequencing identified YY1 as a gene involved in the development of insulinoma; and further studies in other tumors are being performed.

Adrenocortical tumors

We have in collaboration with researchers at Yale University and the Experimental Surgery group at Uppsala University identified novel mutation in KCNJ5 and CACNA1D (publications in Science and Nature Genetics, respectively) in aldosterone-producing adenomas in primary aldosteronism. Germline mutation of KCNJ5 was demonstrated in familial hyperaldosteronism. We have also identified beta cathenin as being important in tumorigenesis in these tumors. In continued studies, PRKACA was found mutated in a subset of cortisol-producing adenomas (published in Nature Genetics). Analysis of DNA CpG methylation genome-wide has revealed genes with putative importance to benign and malignant adrenocortical tumor development.

Graves' disease

In a translational study, also in collaboration with the Experimental Surgery Group, reasons for postoperative hypocalcemia after surgery for Grave's disease is being studied. SNP arrays, calcium-citrate clamping and studies of bone metabolism have been performed to explain the phenomenon.

Clinical studies

Clinical studies of primary hyperparathyroidism (HPT) focus on relations between calcium, aldosterone and/or parathyroid hormone (PTH), and increased mortality in cardiovascular disease, serum lipid dysregulation, insulin resistance, coagulation abnormalities, endothelial cell malfunction, which all have been linked to the metabolic syndrome. These studies are performed on patients with primary HPT, and normal individuals (from the PIVUS cohort).

Efforts are being made to investigate possible new tracers for PET, specifically targeting the adrenal cortex. In collaboration with Cambridge we are aiming for a novel tracer being sensitive for primary aldosteronism (PA), and a possible substitute for the invasive adrenal venous sampling in the diagnostic work-up of such patients. In addition we are also conducting a screening among hypertensive individuals in order to identify the prevalence of PA in the population.

Further clinical investigations study epidemiology and survival in endocrine tumors, relating gene abnormalities to prognosis of patients with endocrine tumors, with the aim to develop prognostic markers and individually designed therapy based on genetic and epigenetic aberrations. We aim to identify clinical and biochemical prognostic variables in various ways (national nested case-control study; studies of novel serum markers and, as noted above genetic abberrations). The research is translational, using methods including basic science, epidemiology, bioinformatics and clinical observations. Endocrine tumors have

variable and extended disease course, and often few specific genetic aberrations possible to relate to tumor type and tumor biology. A large collected tissue bank is used to study genes of importance for endocrine tumors using various molecular methods including RNA expression arrays, SNP arrays, exome sequencing, and concomitant studies of epigenetics.

Members of the group during 2016

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Research students 2016

John Eriksson, Epidemiological studies of small intestinal neuroendocrine tumors

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Dissertations 2016

Tobias Åkerström. Genetic Alterations and Molecular Signatures in Aldosterone Producing Adenomas.

Maria Annerbo. Calcium Homeostasis in Patients with Graves' Disease.

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Experimental Surgery

Principal investigators: Peyman Björklund and Per Hellman

The group of Experimental Surgery has started as an independent research group in January 2012, supported by a Young Investigator Award and project grants from Swedish Cancer Society.

We utilize state of the art methods such as Next Generation Sequencing (NGS), high throughput array technologies, *In Situ* sequencing and drug screening of viable primary tumour cells.

Personalized medicine, Precision Medicine

In partnership with SciLifeLab, clinical diagnostics platform and utilizing high density SNP array technology and Next Generation Sequencing, we aim to develop a fast and affordable diagnostic tool to identify genetic and epigenetic aberration in each individual tumour. Viable tumour cells are then subjected to screening for druggable targets.

Adrenal tumors; genetics, epigenetics and new therapeutic strategies

In pheochromocytoma tumours we have identified mutations in *HRAS*. This finding introduces possibilities for targeted therapy in non-resectable tumours. In parallel we have developed an NGS based mutation screening method to identify patients with hereditary pheochromocytoma and paragangliomas.

Screening of viable primary tumour cells for candidate drugs have shown induction of apoptosis by somatostatin analogues and other agents affecting the methylation activity.

In cortisol producing tumours we have identified recurrent mutations in *PRKACA* and are performing drug screening tests on primary tumour cell cultures.

Complicated Graves' disease

Even though Graves thyrotoxicosis is a common disease, complications such as disrupted calcium homeostasis and ophthalmopathy are rare. We aim to identify genetic determinants predisposing for complications.

Rare Mendelian inherited conditions

In collaboration with several international and national groups we are utilizing NGS to identify genes responsible for rare syndromes.

Endocrine disrupting chemicals and adrenal disorders

As a part of an international consortium led by Associate Professor Monica Lind UU and Professor Bruce Blumberg University of California, Irvine, we aim to determine physiological effects of Bisfenol A on adrenals and kidneys.

Clinical studies

In collaboration with other groups, we are evaluating a new target for positron-emission-tomography (PET) for diagnosis of adrenal tumours, aiming at improved diagnostic imaging procedure.

Computational Medicine

We have developed the first mobile application for assistance in decision making in the clinical genetic testing for pheochromocytoma and paraganglioma susceptibility genes (PHEGEN), available for free download.

Members of the group during 2016

Peyman Björklund, Principal Investigator

Per Hellman, Professor, Principal Investigator

Rajani Maharjan, MS, PhD student (Genetics of Adrenocortical Cancer)

Tobias Åkerström, MD, PhD (Genetics of Aldosterone producing Adrenal tumours)

Maria Annerbo, MD, PhD (Calcium Metabolism in Graves disease)

Samuel Backman, MD, PhD student (Computational Approach to Genetics of Small Intestine Neuroendocrine Tumours)

Joakim Crona, MD, PhD (Gentics of Pheochromocytoma and Paragangliomas)

Lee Starker, MD, PhD (Rare Mendelian Inherited Conditions)

Alberto Falk Delgado, MD, PhD (Rare Mendelian Inherited Conditions)

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Selanders Foundation

Publications Experimental Surgery 2014-2016

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Clinical cancer epidemiology

Principal investigator: Lars Holmberg

The group is based at the Department of Surgery, Uppsala University and affiliated to the Regional Cancer Centre in the Uppsala Örebro region. Professor Holmberg is also professor emeritus at Division of Cancer Studies, Faculty of Life Sciences and Medicine, King's College London and collaborates closely with epidemiologist, oncologists and surgeons at King's College London. The group collaborates within an EU network with Sweden, UK, Ireland and Italy. Researchers at the Dana-Farber Cancer Institute at Harvard Medical School, Boston, USA, collaborate with the group in translational research. Several of the projects involve collaborations with networks for clinical data bases in cancer in Sweden and the AMORIS group which governs a large cohort for studies of serum biomarkers and their relation to cancer.

Clinical trials

The group has participated with main functions or lead several clinical trials, among them the Scandinavian Prostate Cancer Group Study no. 4 (SPCG4), the SWEDCIS trial of breast conservation ± radiotherapy in ductal cancers in situ of the breast, the CW1 trial of breast cancer conservation ± radiotherapy in invasive

breast cancer and the HABITS study, which tested if hormonal replacement therapy in women with a previous breast cancer is safe. In a network with other researchers, the group is participating a large randomized study in active surveillance for prostate cancer (SPCG17). The group supports and gives scientific advice to a nation-wide randomized clinical trial (SCREESCO) of screening directed against colorectal cancer organized by the Swedish county authorities.

Translational research

In collaboration with the Karolinska Institute and the Department of Immunology, Genetics and Pathology at the Uppsala University Hospital the group is conducting a study of the reasons for a worse prognosis among very young women with breast cancer. The study involves utilization of a large number of bio samples. In the AMORIS cohort the group collaborates with the principal investigators of the cohort in studies on serum biomarkers and later risk and natural history of several types of cancer. One of the primary focuses is on perturbed lipid metabolism and risk of cancer progression. A research addressing the association between the metabolic syndrome and intracellular metabolomics in prostate cancer has been developed within the U-CAN cohort. The group collaborates with researchers at King's Collage London in a study addressing genome wide expression data and the pattern of breast cancer metastases. The center advices on nation-wide development of processes to combine advanced molecular pathology data with clinical outcomes.

Register-based research

In collaboration with steering groups for large clinical data bases at the Regional Cancer Centre and at King's College London, the group has conducted research on different aspects of treatment for prostate and breast cancer, among them side-effects of radiotherapy and hormonal treatment. The group has also studied the impact of local recurrence and metachronous contralateral breast cancer on breast cancer prognosis. Currently, multi register linkage for patients with bladder cancer has been developed to study aspects of clinical management and bladder cancer survival.

Methodological developments

The group participates in methodological development in advanced biostatistical tools. One main interest has been to disentangle cohort heterogeneity and its impact on long-term disease specific outcomes such as outcomes measured together with competing risks. A new method to address competing risks has been developed for the purpose of analyzing the cohort of bladder cancer patients as mentioned above. Furthermore, the new method is tested in conjunction with analyzing the outcomes for cancer patients with other chronic diseases, such as diabetes.

Senior members of the group during 2016

Lars Holmberg, Professor, Head of Regional Cancer Centre, Uppsala-Örebro Region

Sonja Eaker, Senior researcher, Head of Regional Biobank Centre, Uppsala-Örebro Health Care Region

Hans Garmo, PhD, Senior Biostatistician

Mieke Van Hemelrijck, PhD, Lecturer, Division of Cancer Studies, Medical School, King's College London

Christel Häggström, PhD, postdoc, Department of Surgical Sciences, Uppsala University

Agencies that support the work/Funding

Cancer Research UK; Swedish Cancer Society

Publications 2014-2016

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3) Gastrointestinal Surgery

The report is presented in two main parts – upper abdominal surgery and colorectal surgery. Both main parts are further subdivided into sections and research fields. Since more than one year the gastrointestinal research group has common seminars in which research projects are presented and discussed.

Upper Abdominal Surgery

The research in Upper abdominal surgery is divided in four main areas; Bariatric surgery, Esophageal- and gastric cancer, Hepatic surgery, and Biliary- and pancreatic surgery.

Bariatric surgery

In bariatric surgery, we have focused on surgical technique, postoperative changes in gastrointestinal physiology and long term results. Our research is clinical and based on operated patients with the aim to improve surgical technique and understand the altered physiology. We perform laparoscopic Duodenal Switch (DS) in patients with super obesity, i.e. BMI>50 kg/m^2, and laparoscopic gastric bypass (GBP) routinely. Almost all patients are potential research subjects, as we have many ongoing projects.

At present, we are recruiting patients for PET/MR-based studies of glucose metabolism before and after GBP, and in comparison to non-surgical weight loss with low calorie diet. The effects of bariatric surgery on bowel function are evaluated in a PhD project using manometry and validated questionnaires

Postoperatively, we are evaluating changes in appetite-regulation and gastrointestinal physiology in operated patients (DS and GBP) and controls as well as calcium homeostasis and vitamin-D levels. We are also comparing differences in inflammatory markers and gastrointestinal hormones between responders and non-responders after GBP. In super obese patients, we are studying long-term results and patient-related outcomes between DS and GBP.

Bariatric research is expanding and the number of projects performed in collaboration with other units in the hospital, e.g. The Metabolic Unit, Department of Endocrinology and Gastroenterology, or departments at the University, are increasing continuously.

Esophageal- and gastric cancer

In the field of esophageal- and gastric cancer, we are working on detailed loco-regional evaluation of esophageal cancer with PET/MRI. Patient outcome on a national level is studied in a PhD project in collaboration with the national quality register, NREV. Locally, we are studying the effect of value-based care on outcome and patient satisfaction.

Members of the Esophageal- and Gastric Surgery Group 2016

The research group is headed by Professor Magnus Sundbom.

Jakob Hedberg, Associate Professor of Surgery

David Edholm, MD, PhD

PhD students

Eduardo Sima, MD

Zakaria Bekhali, MD

Gustav Linder, MD

Martin Skogar, MD

Bjarni Vidarsson, MD

Khalid Elias, MD

Eladio Cabrera, MD

External Founding 2016

Bengt Ihre, 300,000 SEK

Bergholms fond, 250,000 SEK

Liver surgery

Principal investigator: Agneta Norén

Liver surgery for colorectal liver metastases (CRLM) has become standard treatment for patients with resectable disease. The treatment is multimodal with chemotherapy and also ablative methods as a complement to surgery. In liver surgery we have focused on defining the possible risk following liver resection induced by preoperative chemotherapy. More than half (60-70%) of the patients receive preoperative chemotherapy and some patients develop sinusoidal injury (SI) due to oxaliplatinbased chemotherapy. SI is associated with preoperative bleeding and morbidity after liver surgery. SI was initially described as simple sinusoidal dilatation, but further research revealed a full spectrum of histopathological changes including congestion in sinusoids, hemorrhage in perisinusoidal space leading to hepatocyte loss, perisinusoidal and centrilobular fibrosis, sinusoidal obstruction, nodular regenerative hyperplasia and veno-occlusive lesions

MRI studies

In an attempt to diagnose SI noninvasively a project using pre-operative 3T MR we have studied patients with and with-out pre-operative chemotherapy the day before surgery with 83 special techniques to reveal and grade steatosis, steatohepatitis, SI and portal flow. The results are related to the histopathological evaluation and to the clinical outcome. Two of the studies are published and further MR studies are ungoing.

Local registry of liver surgery

We have also studies using our local data base of data of all liver resected patients with CRLM. Clinical outcome of 500 resected patients with focus on liver specific complications related to chemotherapy (manuscript).

Liver surgery for colorectal liver metastases is unequally used in Sweden. A study of tumor burden in liver and reasons for not referring patients for liver surgery is accepted at EPN.

Liver first (liver resection before the primary tumor) has become a new treatment strategy but is not validated. We are planning to evaluate the “liver first” patients and compare with traditional strategy.

Liver tissue and cultured cells

In collaboration with Professor Per Artursson, department of pharmacy, we have studies aimed at developing a model using cultured human liver cells, obtained from waste liver tissue after resection for

liver metastases from colorectal cancer. The cultured cells will be used to study membrane transport function, the influence of preoperative chemotherapy as well as the influence of cytostatic drugs on this function. On aim is to enlighten the effect of oxaliplatin treatment for CRLM on non-tumorous liver tissue, using label-free global proteome analysis to quantify changes in proteins, associated biological process and pathways (manuscript).

Members of the liver surgery group 2016

Ulf Haglund, MD, PhD, Professor Emeritus of Surgery

Agneta Norén, MD, Associate Professor

Frans Duraj, MD

Jozef Urdzik, MD, PhD

Biliary surgery

The biliary group has focused on surgery for gall stones and ERCP. Long term results after endoscopic sphincterotomy, particularly in patients with gall stone-related pancreatitis, are under evaluation and a prospective study on Gallbladder in situ after papillotomy is ongoing. Also a study regarding the prevalens of gallstones and the patients need for medical proceedings in a specific yearsgroup of persons in Uppsala country.

In collaboration with Per Sangfelt and Fredrik Rorsman, department of Medical Sciences, studies in primary sclerosing cholangitis are ongoing and a consecutive patient material with this disease is accumulated with endoscopic cholangiographic data.

Pancreatic cancer

A project on irreversible electroporation (IRE) in patients with inoperable pancreatic cancer has started and the first phase 1 study is finished. Several (phase 2) studies are ongoing with different groups of patients, treated before or after chemotherapy, with local recurrence after pancreatic surgery.

In collaboration with Professor Peter Nygren, department of oncology, ongoing studies on chemotherapy resistance for pancreatic, duodenal and cholangiocellular cancer.

Members of the group of biliary and pancreatic surgery during 2016

The research group is headed by Britt-Marie Karlson, MD, PhD

Stefan Linder MD, Associate Professor of Surgery

PhD students

Ann Langerth, MD

Christopher Månsson, MD

Agencies that support the work/Funding

The research is funded by "ALF-medel".

Publications 2014-2016

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Colorectal surgery

The research in this field is divided into colorectal cancer, peritoneal carcinomatosis, functional bowel disorders (including proctology), and inflammatory bowel disease.

Colorectal cancer

We are continuing the effort to find prognostic markers in order to individualize surgical and oncological treatment. Analyses of the influence of genetic aspects is also performed as well as studies to improve the knowledge on the interaction between heredity and various biomarkers, like tryptophanyl-tRNAsynthetase, microsatellite instability and mismatch repair genes. We also perform several studies on the effects of several surgical and perioperative factors, like preoperative bowel preparation, intraoperative antibiotics, adhesion prophylaxis, and the importance of the patients position during abdominoperinal resections, supine versus prone for the oncological outcome. Other ongoing studies are the influence of surgical complications on recurrence and survival as well as the impact of a diverting stoma and laparoscopic surgery on outcome. We participate in a national trial exploring the effects of a nationwide colon cancer screening project with regards to compliance, polyp detection rate, complications, and disease rate reduction.

Peritoneal carcinomatosis

We have one of the largest patients cohorts treated with cytoreductive surgery and intraoperative chemotherapy worldwide. Since 2001 more than 550 patients have been treated and this large series is analyzed concerning various outcomes. One project aims at evaluating the histopathological specimens, and we have observed that neoplastic cells are absent in 15%. In a recently published study we observed that appendiceal neoplasms, low levels of tumor markers, and no preoperative chemotherapy increased the likelihood of negative histopathology. We are also studying the morbidity after surgery and HIPEC, its effect on outcome and predictors of morbidity. A study exploring the dose – efficacy relationship is also performed. A project analyzing risk factors for appendiceal neoplasms has started as well as a study exploring risk factors for development of peritoneal carcinomatosis. We have together with the other Swedish centers formed a network and a national registry as well as national multicenter studies is planned. Finally, we recently published the results of a randomized trial comparing systemic chemotherapy versus cytoreductive surgery plus intraperitoneal chemotherapy.

Functional bowel disorders and proctology

In depth analyses of bowel motility has since long been a focus of the group. We have analyzed the effect of electrical stimulation of sacral nerve roots in 42 constipated subjects. Totally 15 patients had more than 50% symptom relief and received a permanent implant. Out of these only five (12% on an ITT basis) had sustained benefit. Further studies will be performed aiming at characterizing the subgroup with treatment response.

We have also a long tradition in incontinence research and have contributed substantially to the concept of injectable bulking treatment for fecal incontinence. The active treatment group in a previously published randomized multicenter study comparing submucous injection of dextranomer in stabilized hyaluronic acid against placebo has been followed up after 3 years and the effect was essentially unchanged. We have also analyzed the long term morbidity and stability of a response. In a study of patients with systemic sclerosis, we observed that the external sphincter was affected and mainly responsible for incontinence. A randomized trial comparing injectable treatment versus sacral nerve stimulation for fecal incontinence has recently started. In addition, we participate in an industry funded multicenter trial exploring the potential benefit of autologous muscle cell implantation in the external sphincter in fecal incontinence.

A comprehensive project concerning functional outcome and secondary treatment of patients treated for anorectal malformations in childhood have been performed in collaboration with the Department of

Pediatric Surgery. Approximately 40% of the cohort of 136 subjects reported either that they had a stoma or fecal incontinence. Several treatments have been developed for this patient category.

In order to prevent iatrogenic incontinence we have investigated sphincter saving surgery for anal fistulas and observed a healing rate after intersphincteric ligation of the fistula tract in 9/15 patients with recurrent anal fistula after a median follow up of 13 months. We participate in a national randomized trial comparing plug closure versus advancement flap closure of anal fistula.

A previous study of anal sphincter function after excisional hemorrhoidectomy found fecal incontinence in 40/418 which was related to surgery. An extended anatomical and physiological analysis of this subgroup found definite signs of external sphincter injuries, reduced anal pressures and impaired sealing capacity indicating iatrogenic injuries. We are currently performing a long term follow up of 200 patients who participated in a randomized trial about twelve years ago comparing two forms of surgical technique. Another research focus is minimal invasive hemorrhoid surgery and the importance a Doppler guidance during transanal hemorrhoidal dearterialisation is explored in a randomized trial.

Inflammatory bowel disease

We have participated in the population based IBD cohort ICURE study focusing on epidemiology in Ulcerative colitis and Crohn's disease headed by the Department of gastroenterology. Incident cases of pediatric Crohn's disease are biopsied for evidence of enteral viral infections an etiological factor. This project is performed together with The Pediatric gastroenterologists. We participate in the research network: Swedish organization for inflammatory bowel disease.

Members of the group during 2016

Wilhelm Graf, Professor, Director

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4) Forensic medicine

Principal investigator Ingemar Thiblin

The research at the Division of Forensic Medicine during 2015 were in five main areas; consequences of abuse of anabolic androgenic steroids (AAS), injury interpretation, homicide injury evaluation , infant abuse, and determination of post-mortem interval in decomposed bodies found indoors.

Consequences of abuse of anabolic androgenic steroids (AAS)

This PhD project aims at identifying cardiovascular lesions and testicular lesions in deceased AAS users. The heart and testes were chosen because clinical experience suggests that the heart and reproductive organs are strongly affected by AAS. There are currently a number of clinical studies and some case reports/case series regarding deceased AAS users. There have been no previous large-scale surveys of organ pathology of the kind we currently conduct. The project is run in close cooperation with the National Board of Forensic Medicine's Forensic Medicine Department in Uppsala.

Injury interpretation

In Sweden, nearly 100,000 persons per annum receive hospital care for injuries, 3,000 die before receiving hospital care, and 1,500 die after receiving hospital care. Injuries are the main cause of death and disability below the age of 60. At present, the feedback to the public bodies responsible for injury prevention on injury-related death and complications is highly deficient. To overcome these shortcomings, we intend to cooperate with the UCR to establish an injury database that will provide a constantly updated current picture of regional injury incidence, an improved standard analysis and registration of causes of injury and injury mechanisms within the health care services and forensic medicine, methods for the reliable assessment of the causes of injuries and their levels of severity, and a data source for research within various disciplines such as medicine, law, and criminology.

So far, we (the UCR and the Division of Forensic Medicine) have focused on creating a model for the assessment of the level of severity for injuries caused by assault. This has resulted in a very sturdy model that predicts with almost 100% accuracy (AUC 0.98) whether an injury or a combination of injuries is life threatening, which is central to forensic medicine assessments. The model is based on the so-called Bayesian regression, and an extension of the model is expanded to include injuries caused by means other than assault. An adaptation into a web-based application is also planned.

The project further includes the development of new advanced methods of damage analysis. These are intended for use in forensic medicine assessments and for the indirect improvement of the quality of the injury database. The project is conducted in cooperation with Dr. Svein Kleiven's research team at the KTH Royal Institute of Technology. In short, it concerns the simulation of injuries with the help of Finite Element Analysis based on information on the injured body part (e.g. skull thickness) as well as observations made at the scene (documentation of drop heights, the shape of hard objects in the environment, etc.). This simulated image of the injury can then be compared to the true image of the injury, which allows conclusions to be drawn regarding the stated or assumed course of events. Among other things, this is central to the assessment of causes of injury (whether accident, self inflicted, or inflicted by someone else) and to injury preventive work (e.g. the development of improved motorcycle helmets). Conducted in close cooperation with the National Board of Forensic Medicine, the project has been going on for several years.

Homicide injury evaluation

This PhD project aims at *A)* develop an easy-to use and valid model for scoring the level of violence (brutality score) in homicides and *B)* examine the level of violence in homicides in a longitudinal

perspective by employing the model. This project is done in collaboration with criminologist Joakim Sturup at the Stockholm University and Department of Forensic Psychiatry, Stockholm. So far a Gold standard for the grading of "brutality" has been defined and an easy-to use model based on the Homicide Injury Scale (HIS) has been developed. The modified HIS is now used and further evaluated in a longitudinal mapping of Swedish homicides over a 40–year period.

Infant abuse

This PhD project concerns physical abuse of up to one-year old children. The project is based on registry data from the National Board of Forensic Medicine and The National Board of Health and Welfare. The previously widely accepted conception of certain findings (e.g. retinodural bleeding or metaphyseal lesions) and circumstances (e.g. no history of trauma in the presence of retinodural bleeding) in infants are virtually pathognomonic for infant abuse has been increasingly questioned during the latest years. Several alternative hypotheses have been presented. All hypotheses, both those in favour of abuse and those questioning abuse have in common that empirical verification has been hard to obtain. One major limitation of previous studies is circular reasoning, since the explanatory variables often are more or less identical to the criteria for defining cases as abuse cases. Our aim is to perform large registry based studies that test the different proposed hypothesis in an uniform manner, avoiding methodology involving circularity.

Post mortem interval

An important but difficult task is to determine the post mortem interval (PMI) in decomposed bodies. So far most research in this area has focused on bodies found out doors. This Ph.D. project aims at developing a method for PMI determination by combining classical decomposing scoring models with entomological data employing a Bayesian network software.

Members of the group during 2016

Ingemar Thiblin, Professor

Håkan Sandler, MD, PhD

Greta Ågren, Ass. Professor

Hamid Mobini-Far, PhD student

Fredrik Tamsen, PhD student

Jacob Andersson PhD student

Ann-Sofie Pålsson PhD student

Collaborations:

Svein Kleiven, Ass. Professor, Department of Neuronics, KTH Royal Institute of Technology

Joakim Sturup, PhD, Ssociologist, Swedish Board of Forensic Medicine

Anders Lindström PhD, Entomologist, SLU

Publications 2014-2016

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5) Hand Surgery

Principal investigator: Monica Wiig

1) Flexor tendons - prevention of adhesion formations

The main objective of our research is to improve the results after tendon surgery and tendon transplantation. Adhesions comprise scar-tissue that connects anatomic structures that should not normally be connected. Adhesions form after almost any type of surgery and are a significant source of post-surgical complications.

To find strategies for the prevention of post-surgical adhesion formations and decrease reruptures after suturing a ruptured flexor tendon is one of our goals. To this end we investigate the mechanism for how adhesions develop and in parallel work with the development of new drugs to prevent adhesion formation as well as identify risk factors for ruptures of the tendons.

A) In an observational study, we identified risk factors for rupture of repaired flexor digitorum profundus (FDP) Patients suffering from postoperative tendon repair rupture were compared with non-ruptures using multivariate logistic regression. Increasing age and a concomitant flexor digitorum superficialis (FDS) transection were significantly associated with increased risk of rupture of repair, while a concomitant nerve transection lowered the risk significantly. For better understanding of the effects of increasing age and combined injuries on the long-term outcome after intrasynovial flexor tendon injury and repair, we used chi square tests to check for associations between age, coexisting nerve transection, and patients with transection of both the FDP and the FDS tendons. Combined transection of the FDP tendon and transection of digital nerves or the FDS tendon did not affect digital mobility during the first 2 years after surgery. Increasing age did however impair digital mobility the first year after surgical repair but this impairment could not be detected 24 months postoperatively.

B) In a rabbit model of flexor tendon injury, we have identified tissue- and temporal-specific aspects to the flexor tendon healing process for factors involved in remodeling, inflammatory response and fibrosis.

A new therapeutic option has emerged in the form of a synthetic peptide (PXL01) structurally derived from human lactoferrin. PXL01 exhibits broad-spectrum antimicrobial properties and is shown to down-regulate inflammatory cytokines. PXL01 also inhibits plasminogen activator inhibitor type 1 (PAI-1), which is expected to increase the fibrinolytic activity after surgery and is suggested to be an additional mechanism for these peptides to reduce excessive scarring. It is presently unclear, though, which of these activities that are important for the observed anti-adhesion effect in vivo.

We have earlier performed a prospective, randomized, double-blind, multicenter trial including 138 patients admitted for flexor tendon repair surgery. PXL01 in HA, or placebo was administered locally around the repaired tendon. The study suggests that treatment with the peptide PXL01, formulated with native sodium hyaluronate carrier, in connection to the surgical flexor tendon repair after hand injury, improves the clinical outcome in terms of mobility of the affected finger. A potential for a favorable role of PXL01 to stimulate nerve regeneration is also raised.

We have now started to prepare for a phase III clinical study.

In a mechanism of action study we observed significantly higher levels of PRG4 mRNA in rabPXL01 in HA treated tendons, but not in tendon sheaths, at all-time points, which subsequently may lead to increased lubrication of the injury site and inhibition of peritendinous adhesion formations. In addition, coordinated repression of the expression of several pro-inflammatory mediators was observed in tendon sheaths. Taken together, our results indicate that adjuvant treatment with rabPXL01 in HA will increase lubricin levels and inhibit the inflammatory response. This would lead to reduced gliding resistance and adhesion formations

as well as increased tendon excursion after tendon injury and repair, and could explain the results seen in the previously reported clinical study.

C) Tissue engineering (collaboration with Simon Farnebo, Linköping University)

We are starting a project on tissue engineering, to characterize and compare the *in vivo* result after reconstruction of tendons after injury and diseases. In an animal model we are investigating what happens with tissue engineered tendons (allografts) and different tendon grafts after transplantation. Focus is on different factors included in the healing process and of importance for strength and the undesirable scar tissue. Adhesions contribute to decreased mobility and we want to avoid adhesion formations as much as possible.

2) Trigger finger study

The overall purpose of the program is to develop a new, better treatment of trigger finger, one of the most common conditions seen in the clinical practice of hand surgery. Triggering occurs as a result of a disproportion between the flexor tendons and the A-1 pulley and includes thickening of the pulley and tendon, but the pathogenesis of these changes is not clearly understood. Several factors, including inflammation, trauma, degeneration and heredity, that may initiate the pathologic process also are poorly defined in the current literature. Besides surgery, corticosteroid injections are currently used to treat trigger finger, suggesting an inflammatory response.

The first goal is to try to understand the mechanism behind the origin of trigger finger. Through histological and transcript analyses of affected fingers and control material we aim to analyze cellular and molecular changes in affected tendons, tendon sheats and the A-1 pulley. In particular we will address cells and transcripts known to be important for inflammatory and fibrotic responses.

To date140 patients have been included. Together with PharmaConsulting Group, we have developed a very extensive and useful eCRF (electronic case report form) to collect and analyze all the data collected.

Members of the research group 2016

Monica Wiig, Associate Professor, principal investigator

Sara Edsfeldt, PhD student

Björn Holm, PhD student

Eva Nordin, Research Nurse

Ylva Petterson, Ylva Gollbo Foucard, Elisabeth Källman (Fysioterapeuts)

Joint reconstruction

Principal investigator: Torbjörn Vedung

An alternative method to reconstruct an osteoarthritic joint is to use perichondrium from the rib. The method was introduced in humans in 1974 by our predecessors in Uppsala. Initially the method was used for the metacarpo-phalangeal (MCP) joint. Later it was adapted to the proximal inter-phalangeal joints of the finger and the inter-phalangeal joint of the thumb. It has been used sporadically in the elbow, the knee, carpometacarpal joint of the thumb, and the metatarso-phalangeal joint of the big toe. As results after implant arthroplasty have improved the use of the technique has declined. The second surgical site at the rib level may also be part of the reason why the technique is not widely used. However, perichondrial transplantation is still a reasonable alternative in selected cases, such as young individuals with high

manual demands. We still use the method at our unit to resurface the osteoarthritic MCP joint in such patients. Forty years after the reconstruction, the MCP joint of the carpenter mentioned above is still pain free and has normal range-of-motion. No modern implant can achieve such results. Recently we adapted the technique to the distal radio-ulnar joint, which is well known to be particularly difficult to repair. The published results are encouraging and ignited the spark to this project, which is planned to result in the doctoral thesis of Daniel Muder.

The reported results after perichondrium transplantation vary in the literature and it is unclear what kind of tissue the perichondrium produces. Some have proposed that it is articular cartilage while others argue that it is fibro-cartilaginous tissue at best. Moreover, it has not been proven that the resulting tissue actually originates from the transplant. Ingrowth from the side or from the bone marrow after preparation of the damaged joint surface has been suggested to be the origin. Rib perichondrium consists of hyaline cartilage but the environment in the rib cage is non-synovial. Previous studies suggest that cells in the perichondrium transplanted to a synovial joint differentiate into articular chondrocytes. Hence, unknown factors in the synovial fluid may trigger this differentiation. We plan to explore this hypothesis in transplant experiments using inbred rats. With modern lab techniques it is possible to answer many of these questions. Our patient cohort is unique since it is large and enables extremely long follow-up times. We also plan to compare the outcome with the results after implant surgery.

During 2016 a comprehensive review of the literature regarding perichondrium transplantation has been completed. Our aim is to publish a forty-year follow-up of the very first case together with a review of the topic. *Submitted*

The first part of the long-term follow-up of perichondrial transplantation has been completed during 2016. 48 patients went through joint reconstruction by means of perichondrium transplantation between 1974 - 1981. In the cohort, 37 patients were either found to be deceased, did not fit the inclusion criteria, or were lost to follow-up. Muder has done meticulous work during 2015 to identify and re-examine the remaining 11 patients. The final study group consisted of 11 patients, three MCP joints and eight PIP joints. The clinical outcome in the MCP group was excellent. The results in the PIP group were more variable. *In manuscript*

The second part of the long-term follow-up, with patients operated from1982 to present has been started. The outcome in this group will be compared with outcome after implant arthroplasty.

The experimental part of the project has been initiated. In January 2017 we performed a pilot study to test the surgical technique. We found that it was technically possible to transplant rib perichondrium to the knee in rats. The actual study was started in April 2017.

Members of the research group 2016

Torbjörn Vedung MD, PhD, Department of Orthopaedic and Hand Surgery

Nils Hailer MD, Professor, Department of Orthopaedic and Hand Surgery

Ola Nilsson MD, Professor, Department of Women´s and Children´s Health, Karolinska Institutet, Stockholm, Department of Medical Sciences, Örebro University and University Hospital

Daniel Muder MD, PhD-student, Department of Orthopaedic and Hand Surgery

Fracture treatment

Principal investigator: Torbjörn Vedung

Early Mobilization of Spiral Metacarpal Fractures Compared With Operative Treatment

Spiral metacarpal fractures (metacarpal II-V) can be treated conservatively or with surgery. If minimally displaced, this fracture is usually treated with immobilization in a cast or early mobilization. Fracture displacement, especially any malrotation are usually is treated with open reduction and internal fixation with plates and screws or two lag screws. Surgery is always associated with risks and eventual complications. New studies have shown that these fractures, and even displaced fractures, can be treated with early mobilization. In these cases, the fracture may heal with some shortening but usually with good function. An advantage of early mobilization is that the patient avoids all risks of an operation and the costs for the treatment are decreased markedly. The study is designed to answer the question if early mobilization is comparable to operative treatment but with lower costs and without any surgery related risks.

Study Type: Interventional

Study Design: Randomized Controlled Trial

Intervention Model: Parallel Assignment

Intervention Model Description: Prospective randomized controlled trial to compare operation and treatment with early mobilization for metacarpal fractures

Masking: No masking

Primary Purpose: Treatment

Official Title: Early Mobilization of Spiral Metacarpal Fractures Compared with Operative Treatment - a Prospective Randomized Trial

Members of the research group 2016

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Daniel Muder MD, PhD student, Department of Orthopaedic and Hand Surgery

Fredrik Peyronson, MD, Department of Orthopaedic and Hand Surgery

Publications 2014-2016

1. Ekblom A G, Dahlin L B, Rosberg H, Wiig M, Werner M, Arner M. Hand Function in Adults with Radial Longitudinal Deficiency. Journal of Bone and Joint Surgery. American volume. 2014;96(14)
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6) Nursing

Nursing research is currently a group of nurse researchers and nurse PhD students within the department rather than a research group. The nurse researchers and PhD students are members of the department's different research groups and the nursing research concerns a diversity of topics. We are just in the beginning of creating an inter-professional nurse research network within the department.

Intensive care of the ventilator treated patient

Nursing perspectives on patient safety in the ICU with special reference to ventilator treated patients. The aim is to improve safety of the nursing procedures in the severely ill ventilator treated patients.

The studies can be divides in three specific projects:

- Reducing the risk of hypoxemia in connection with endotracheal intubation
- Reducing the risk of lung complications when changing ventilator filters – a procedure, which is done daily.
- Reducing the risk of circulatory and respiratory compromise at specific nursing procedures (e.g. turning and washing) in the ventilator treated patient.

Members of the group during 2016

Joakim Engström, RN, PhD student

Camilla Fröjd, RN, PhD

Henrik Reinius, MD, PhD student

Anders Larsson, MD, Professor

Collaborations

Göran Hedenstierna, Professor

Filip Fredén, MD, PhD

João Batista Borges, MD, PhD student

Patient safety in intensive care

The intensive care unit (ICU) work system (as all high risk organizations) consists of five elements: Technology and tools, Tasks, Environment, organization and at the center the individuals, being providers and patients. The characteristics of these elements and their interactions will determine the performance of the processes, e.g. compliance to evidence-based guidelines and ward routines, which in turn may affect patient safety. The five elements co-exist and interact. To achieve patient safety, the entire work system should be well designed.

The *hypothesis* is that there is a cognitive overload in intensive care making it difficult for intensive care nurses to catch up with, and prioritize/utilize important information. Furthermore, when adding the large amount of impressions that the nurses constantly are subjected to bedside, coming from technical devices, equipment and patients' vital signs, there is a risk for cognitive overload, which may influence compliance to evidence-based guidelines and ward routines and this in turn may harm patient safety.

The study explores the nature and extent of the ICU nurses' cognitive work load and how this compromises patient safety. The aim is also to improve patient safety by interventions in the ICU work system.

Since there exists very few observational studies of the intensive care work systems from a high risk organization perspective, and rarely none in which interventions have been done to improve the intensive care work systems with regard to technology, cognitive work load and patient safety, this project will, to some extent be shaped along with the results from the study above. However, the overall intention of the project is to test which technical and environmental interventions will create a firm intensive care work system with optimal patient safety, regardless of which people are working within the system.

Members of the group during 2016

Project Leader: Camilla Fröjd, PhD, Specialist Nurse in Intensive Care, Senior Lecturer

Anders Larsson, MD, Professor Intensive Care Specialist

Johann Valtysson, MD, PhD Head of the Intensive Care Department at Uppsala University Hospital

Anders Jansson, Associate Professor, Department of Information Technology

Burn care

Resuscitation in acute burn care

Evaluates how routines for adjustment of the resuscitation fluid in acute burn care were carried out in practice and to develop a burn resuscitation protocol for improving procedures to ensure patient safety.

Members of the group during 2016

Björn Wikehult, RN, PhD

Linda Yngvesdotter, RN, MSc Burn Center Uppsala University Hospital

Bengt Gerdin, MD, Professor

Patient satisfaction with care

Evaluation of patients' experiences of care. At present the focus is on patients treated on the Burn Center.

Members of the group during 2016

Björn Wikehult, RN, PhD,

Mimmie Willebrand, Professor (Department of Neuroscience)

Working hours, sleep quality and health among intensive care unit personnel

The aims of this cross-sectional study were to examine how ICU personnel experience their sleep quality and possible links between working hours, sleep quality and perceived health. An additional aim was to study if demographic variables such as age, gender, profession, and years in the profession are associated with the experience of altered sleep quality?

Members of the group during 2016

Björn Wikehult, RN PhD

Caisa Öster, RN PhD (Department of Neuroscience)

Person-centered care and advanced practice nursing roles in acute care

Research investigator: Eva Jangland

The research area is around person-centered care, patient participation, professional development, advanced practice nursing roles and specific the implementation of Nurse Practitioner in surgical care. The research has several on-going projects.

SMAAPP research program

Seamless ***M***anagement of patients seeking care for ***A***cute ***A***bdominal ***P***ain is a Person-centered approach. The focus is on patients with acute abdominal pain and their experiences of their in-hospital care focusing on the fundamentals of care and continuity of care across the acute care episode. The research team has members in Sweden and Australia. Registered nurses, physicians, leaders, researchers, post-doc researchers, PhD students and an expert group with researchers from Sweden, Australia and Denmark are also involved in different projects.

Members of the group during 2016

Eva Jangland, PhD, RN

Åsa Muntlin-Athlin, RN, CNS, PhD (Department of Medical Sciences, Department of Public Health and Caring Sciences)

Alison Kitson, RN, Professor, the University of Adelaide, Australia

Martin Björck, MD, Professor

Claes Juhlin, MD, Associate Professor

Frank Donelly, RN, PhD, the University of Adelaide, Australia

Rebecca Feo,RN, PhD, The University of Adelaide, Australia

Tim Schultz, PhD, the University of Adelaide, Australia

Erik Elgaard Sorensen, RN, Professor University of Aalborg, Denmark

Therese Avallin, CNS, PhD student. IKV

Alexander Tegelberg, CNS, PhD student, (department of Public Health and Caring Sciences)

Research project: Implementation of Nurse Practitioner

Research Investigator Eva Jangland

The overarching aim is to study how implementation of a new expanded nursing role affects teamwork and interprofessional collaboration on a surgical ward.

Members of the group during 2016

Eva Jangland, PhD, RN

Pia Yngman Uhlin, RN, PhD

Erebouni Arakelian, CNS, PhD

Researchers at the Department of Medicine and Health, Faculty of Health Sciences, Linköping University.

Patients with hip fracture and patient safety

The research group investigates different aspect of patient safety for elderly patients with hip fracture. Two ongoing projects during 2016:

1. To investigate if cranberry capsules given preoperatively and postoperatively will decrease the incidence of bacteria's in the urine in female hip fracture patients receiving urine catheter. A Randomized Control Study.
2. Setting up a local quality register for patients with hip fracture to evaluate the care of the patients; i.e. mobilization, pressure ulcers, pain and analgetics.

Members of the group during 2016

Anna-Karin Gunnarsson, RN, PhD

Lena Gunningberg, RN, Professor

Kenneth B Jonsson, MD, Associate Professor

Sune Larsson, MD, Professor

Surgical care

Person-centered care and advanced practice nursing roles in acute care

Research investigator: Eva Jangland

The research area is around person-centered care, patient participation, professional development, advanced practice nursing roles and specific the implementation of Nurse Practitioner in surgical care. The research has several on-going projects.

SMAAPP research program

Seamless Management of patients seeking care for Acute Abdominal Pain – a Person-centered approach. The focus is on patients with acute abdominal pain and their experiences of their in-hospital care focusing on the fundamentals of care and continuity of care across the acute care episode. The research team has members in Sweden and Australia. Registered nurses, physicians, leaders, researchers, post-doc researchers, PhD students and an expert group with researchers from Sweden, Australia and Denmark are also involved in different projects.

Members of the group during 2016

Åsa Muntlin-Athlin, RN, CNS, PhD (Department of Medical Sciences, Department of Public Health and Caring Sciences)

Alison Kitson, RN, Professor, the University of Adelaide, Australia

Martin Björck, MD, Prfofessor

Claes Juhlin, MD, Associate Professor

Frank Donelly, RN, PhD, the University of Adelaide, Australia

Rebecca Feo,RN, PhD, The University of Adelaide, Australia

Tim Schultz, PhD, the University of Adelaide, Australia

Erik Elgaard Sorensen, RN, Professor University of Aalborg, Denmark

Therese Avallin, CNS, PhD student. IKV

Alexander Tegelberg, CNS, PhD student, (Department of Public Health and Caring Sciences)

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Research Investigator Eva Jangland

The overarching aim is to study how implementation of a new expanded nursing role affects teamwork and interprofessional collaboration on a surgical ward.

Members of the group during 2016

Researchers at Department of Medicine and Health, Faculty of Health Sciences, Linköping University.

Pia Yngman Uhlin, RN, PhD

Erebouni Arakelian, CNS, PhD

Anesthesia Care

Aspects of the surgical team's and patients' perception of efficiency, and the recovery process after major abdominal surgery

Aims to:

- Explore variations in how staff and leadership working in a non- team organization within an operating department understand and experience operating room efficiency.
- Explore how organized surgical team members (Peritoneal Carcinomatosis team) and their leaders understand operating room efficiency.

Members of the research group during 2016

Erebouni Arakelian, RN, CNS, PhD

Haile Mahteme, MD, Associate Professor

Lena Gunningberg, RN, Associate Professor

Jan Larsson, MD, PhD

Karin Norlén, MD, PhD

Postoperative recovery from the patients' perspective after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy- a qualitative follow up study

Same group of patients chosen strategically were followed by qualitative individual interviews before discharge, two to six months after discharge and fourteen months after discharge. The aims were:

- To study patients' descriptions of their health after cytoreductive surgery (CRS) before discharge.
- To study post-discharge, postoperative health described by patients after CRS and HIPEC and to study the patients' understanding of in-hospital efficiency and quality of care.

Members of the research group 2016

Erebouni Arakelian, RN, CRNA, PhD

Christine Leo Swenne, RN, OR Nurse, Associate Professor

Kristina Haglund, RN, Associate Professor

Maria Gustafsson, RN, Intensive Care Nurse, MSc

Eva Jangland, RN, PhD

Karin Cederholm, RN, Intensive Care Nurse, MSc

Hanna Eriksson, RN, CRNA, MSc

How to prepare patients before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is considered major surgery in patients with PC. The treatment is tough and the recovery process is long. The goal is to optimize the patients before surgery and to better prepare them for postoperative recovery.

Members of the research group 2016

Erebouni Arakelian RN, CRNA, PhD

Wilhelm Graf, Professor

Olivia Sand, Physical Therapist, BS

Mikael Andersson, Physical Therapist, PhD

The effect of perioperative dialogue on postoperative recovery for patients with peritoneal carcinomatosis- studied by quantitative variables.

The effect of perioperative dialogue was studied with quantitative variables in patients with peritoneal carcinomatosis.

Members of the research group 2016

Erebouni Arakelian RN, CRNA, PhD

Christine Leo Swenne, RN, OR Nurse, Associate Professor

Louise Hjelte, RN

Emma Härdne, RN

Carin Friberg, RN, OR Nurse, MS

When, why and how do patients with perioperative carcinomatosis read their electronic health records through *Journalen*?

Patients in Uppsala County have had access to their electronic medical and nursing records since 2012. Since patients with peritoneal carcinomatosis (PC) undergo major surgery with rough recovery process, it is interesting to study if the patients read their electronic health records through *Journalen.* In previous studies patients with PC have asked for support through internet. By finding out what, when and how patients read their electronic health records, the health care personal may better be able to help the patients with the support they need.

Members of the research group 2016

Erebouni Arakelian RN, CRNA, PhD

Åsa Cajander, Senior lecturer at Department of Information Technology, *Division of Visual Information and Interaction*, and she is associate professor of human-computer interaction and does research mainly in the field of IT and work.

Maria Hägglund | Researcher in Health Informatics

Program Director Joint Master's Programme in Health Informatics

Dept. of Learning, Informatics, Management and Ethics | Karolinska Institutet HIC, Health Informatics Centre | Karolinska Institutet

Worry in connection to surgery

1. How do nurse anaesthetists and patients estimate the level of patients' worries in connection to surgery? How well the estimates match?
2. What do patients worry about in connection to surgery and what kind of support do they need from the nurse anaesthetists?
3. How do nurse anaesthetists and anaesthesiologists assess patients' worries in connection to surgery?
4. Which instrument can be used to better assess i.e. in a more subjective manner the patients' level of worry in connection to surgery?

Members of the research group 2016

Erebouni Arakelian, RN, CRNA, PhD

Lena Nyholm, RN, ICU Nurse, PhD

Christine Leo Swenne, RN, OR Nurse, Associate Professor

Caisa Öster, RN PhD (Department of Neuroscience)

Emma Laurssen, RN, Nurse Anaesthetist

Martin Färdig, RN, Nurse Anaesthetist

Identification of genetic factors and patient experiences at the focal primary hyperhidrosis

Primary focal hyperhidrosis is a hereditary disease with unknown prognosis which can be seen in 3% of the population. The condition can occur in both younger and older people, and involves abnormal amounts of sweat in one or more locations in the body such as in the hands, feet, axillaries, and groin. Increased knowledge about how children and adults perceive their illness could lead to a more individualized and person-centred care and treatment and a goal to reduce patient suffering in a more effective manner.

Members of the research group 2016

Erebouni Arakelian, RN, CRNA, PhD

Sten-Magnus Aquilonius, Professor Emeritus at Department of Neuroscience, *Neurology*

Ellinor Lejonhufvud, MD, Department of Dermatology in Uppsala University Hospital

Laila Hellgren Johansson, MD, PhD, Associated professor, Department of Surgical Sciences, Thoracic Surgery, Head of Department of Clinical neurophysiology, Neurosurgery and Neurology in Uppsala University Hospital

Recovery, morbidity and mortality in patients undergoing CABG

Members of the research group 2016

Erebouni Arakelian, RN, CRNA, PhD

Christine Leo Swenne, RN, OR Nurse, Associate Professor

Martin Färdig, RN, Nurse Anaesthetist

Fredrik Lennmyr, MD, PhD, Associated professor, Department of Surgical Sciences, Head of Department of Thoracic Surgery and Anaesthesia in Uppsala University Hospital

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7) Oral & Maxillofacial Surgery

Oral and Maxillofacial Surgery at Uppsala University Hospital connects odontology with medicine and within our field we perform research in several areas and collaborations. We presently run 11 PhD-projects.

Oral cancer – tobacco, virus, alcohol and malignant cell transformation

Principle investigators Lars Sand and Jan Hirsch

The overall aim is to study clinical, immunological, genetic and viral parameters of importance for malignant cell transformation in a global network covering the spectrum from low to high socioeconomic standards.

We elucidate the presence of Human papilloma virus (HPV) plus quantitative gene expression of viral DNA, differential expression of apoptosis, cell cycle regulation and intermediate genes, in patients with benign and malignant oral lesions in retrospective and prospective studies locally and in a national network. Utilizing human gDNA (genomic deoxyribonucleic acid) extracted from blood- and tissue samples which are phenotyped as normal respectively malignant, a high-resolution array-based comparative genomic hybridization (HR-aCGH) approach is conducted. The aim is to generate genetic profiles, which may distinguish different phenotypes from each other in order to develop informative diagnostic and prognostic tools.

Surgery in the Cranio-maxillofacial complex

Principle investigators Andreas Thor and Jan Hirsch

A longstanding goal in cranio-maxillofacial (CMF) surgery is to develop new approaches to surgery planning and evaluation which will reduce morbidity and increase precision, leading to better function and aesthetics and ultimately to better quality of life for patients with serious congenital and acquired conditions. With a computer system that allows the surgeon to plan the surgical procedure, test alternative surgical solutions, move bone segments, and design patient-specific implants and plates, the improved patient outcome can be achieved while at the same time the costs of surgery and follow-up care can be reduced considerably. Our goal is to produce a system where the surgeon can plan a complex procedure in less than one hour, leading to a drastically reduction of time in the operating room for complex cases. In-house production of the system-designed, patient-specific devices will lead to considerable additional cost savings, and allow surgery on trauma patients within hours, rather than days that out-sourced planning and production require today. The ultimate goal is of course custom-made solutions/implants with optimal load-bearing properties that contain bone or bone substitutes and have surfaces that can work as delivery systems to promote bone regeneration and that will yield surgical results superior to what is currently achievable.

Image-Guided Planning of Cranio-Maxillofacial Surgery using Haptics and 3D Visualization, computer assisted surgery, bone regeneration and patient specific implants

Principle investigators Andreas Thor and Jan Hirsch

With development of a haptic surgical planning system, HASP, that allows for virtual planning and training of difficult surgery of skeletal congenital or acquired defects, it further includes virtual design and fitting of patient specific biomaterials. This system is now installed for in-house use for actual patient surgical planning. The algorithms for the biomaterial can be transferred for Free Form Fabrication using Electron Beam Melting techniques. The implants will be manufactured with properties fulfilling the biomechanical requirements of a specific anatomical site and with surface properties to stimulate healing, and ultimately incorporation even during non-privileged conditions. Additionally, we are engaged in the clinical

evaluation of new bone substitutes from Uppsala University; both in animal and in human studies. The new technologies are evaluated using molecular methods and PET/CT technology for in vivo study of the biology of bone formation and integration. The PET/CT technique is a promising additional method to histology and radiology that currently is explored in our group for maxillofacial purposes. Imaging for planning and for evaluating healing are therefore important areas of our research. In addition we make use of in vitro immunological data from early interaction between blood and blood derivatives with a variety of implant surface candidates. Osseointegrated implants, intra- as well as extra-oral, require a sufficient bone volume and the need for "every-day" reconstructive therapies for lost bone is immense. We are involved in long-term follow-up studies on implant and bone regenerative therapies. Furthermore we are involved in establishing a hands-on digital workflow for planning of maxillofacial surgery where computerized tomography of the face is combined by scanning technologies of the teeth and jaws. We perform an extensive project of studying the accuracy of state-of-the art intra oral scanning systems, that eventually may substitute traditional impression materials. Alloplastic reconstruction of the temporo-mandibular joint is another area where we focus and are investigating the Swedish experience in a retrospective as well as prospective fashion. The total joint reconstruction is a promising method but needs further evaluation.

Functional outcome, quality of life

Principle investigator Jan Hirsch and Andreas Thor

The aim is to conduct in-depth analyses of skull and facial fractures and their ramifications and to create a structure for research and quality assurance. The project uses computerized fracture classification systems that define fractures in great detail to facilitate documentation and web-based communication. We apply a newly developed semi-automatic system for segmenting bone structures, in particular the orbit, evaluating the precision of outcome after surgery. The system will be integrated in our haptic planning console for CMF surgery.

Experiences made from treating total edentulous patients with fixed restorations and evaluating the oral health impact the therapies have on quality of life is also studied in our group.

Members of the group during 2016

Anders-Petter Carlsson, DDS

Petter Gavelin, DDS

Lars Eriksson, DDS

Kristina Hedman

Miranda Jalouli, RN, BSc

Björn Lindell, DDS

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Christoph Riben, DDS

Jani Talvilahti, DDS

Amela Trbakovic, DDS

Bent Williger, DDS, MD

Robert Nedelcu, DDS

Research Fellows

Lena Blomstrand, DDS

Maria Erkapers, DDS

Collaborations

Ewert Bengtsson, Ingrid Carlbom, Ingela Nyström, Pontus Olsson, Fredri Nysjö, Johan Nysjö, Centre for Image Analysis Uppsala University

Omar Omar, Anders Palmquist, Peter Thomsen, BIOMATCELL, Gothenburg University

Carina B. Johansson; Fac. Of Odontology, Gothenburg University

Lars-Erik Rännar, Mikael Bäckström, Mid Sweden University

Bo Nilsson, Jaan Hong, Department of Immunology, Genetics and Pathology, Uppsala University

Håkan Engquist, Uppsala University Ångström Laboratory Department of Engineering Sciences

Jens Sörensen, Gunnar Antoni; Pet-centre Uppsala University

Daniel Nowinski; Department of Surgical Sciences, Plastic Surgery

Bengt Magnusson, Bengt Hasséus; Oral Medicine and Pathology, Sahlgrenska Academy, Gothenburg University

Hans-Florian Zeilhofer, Dep. of Cranio-Maxillofacial Surgery, University Hospital Basel, Switzerland

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Lars Rasmusson, Lars Sennerby, Göran Kjeller, Department of Oral & Maxillofacial Surgery, Sahlgrenska Academy, Göteborg University

Jöns Hilborn, Thomas Engstrand, Uppsala University, Ångström Lab Department of Materials Chemistry, Polymer Chemistry

Lena Larsson, Oral Medicine and Pathology, Sahlgrenska Academy, Gothenburg University

Patricia Hedenqvist, Marianne Jensen Waern, Swedish University of Agricultural Sciences, Uppsala

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Folktandvården, Uppsala

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Nobel Biocare

Straumann AG

OssDsign

Dissertations 2016

Miranda Jalouli. Oral cancer with special reference to virus detection and quantitative gene expression.

Kristina Edman. Epidemiological studies of Oral Health, development and influencing factors in the county of Dalarna, Sweden 1983–2013.

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8) Orthopedics

Medical epidemiology

Principal investigator: Karl Michaëlsson

The epidemiology research group is based at the Uppsala Clinical Research Center (UCR, www.ucr.uu.se). This facilitates fruitful interaction with the biostatisticians and data managers at UCR. We also collaborate with external epidemiological, nutritional, genetic, cardiovascular, injury, osteoporosis and bone density expertise. Our main research topics are osteoporotic fractures but we are involved in other areas of epidemiological research such as injuries, outcome in intensive care, cardiovascular diseases, nutrition and the impact of physical activity on disease and mortality. We also administrate a multidisciplinary network of epidemiologists at Uppsala University (www.ucr.uu.se/epinet). A one-week long course in medical epidemiology is each year held by us, normally during week 43.

We use different internationally unique cohort designs with the main overall aim to study the etiology and prevention of osteoporotic fractures:

1. The Uppsala Longitudinal Study of Adult Men (ULSAM)
2. Screening Across the Lifespan Twin study (SALT)
3. The Swedish Mammography Cohort (SMC)
4. The Swedish Mammography Cohort Clinical (SMC-C)
5. Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)
6. The Cohort of Swedish Men (COSM)
7. The Cohort of Swedish Men Clinical (COSM-C)
8. EpiHealth
9. Uppsala Family Study
10. Uppsala Birth Cohort Multi-generational Study (UBCoSmultigen)
11. Cohort of Vasaloppet

Brief descriptions of the cohorts can be found at: http://www.surgsci.uu.se/Forskning/

Members of the group during 2016

Head Karl Michaëlsson, Professor

Liisa Byberg, PhD, Associate Professor

Eva Warensjö Lemming, researcher

Carina Fredriksson, Research Nurse

Eva Strandberg, Research Nurse

Siv Tengblad, Lab technician

Mohammad Kharazmi, PhD student

Karl Stattin, PhD student

Anna Sprinchorn, PhD student

Adam Mitchell, PhD student

Agencies that support the work/Funding

The Swedish Research Council

Forte

ALF

OrthoLab

Principal investigators: Sune Larsson and Nils Hailer

OrthoLab is the platform for much of the experimental research conducted at the section of Orthopaedics. We have two main areas of interest:

1. Research on bone substitutes in order to treat critical size bone defects after fractures or bone defects in challenging revision arthroplasty.
2. Neuroprotection and neuronal regeneration after spinal cord or peripheral nerve injury.

Bone substitutes

Our main interest is to develop new cell free bone substitutes for clinical use whenever there is need for building new bone due to bone loss caused by injury or disease. A substantial part of our work is done in collaboration with the departments of polymer chemistry and material science at the Ångström laboratory, Uppsala University. Over the past years a lot of effort has been put into the development, refinement and evaluation of various hydrogel compounds intended for use as a new carrier for bone morphogenetic protein (BMP). With this new carrier, the release of the BMP molecule seems much more efficient than with previously used carriers based on bovine collagen, which means that the BMP dosage can be lowered dramatically while still gets the same amount of bone being formed. During the last years we have done studies using PET technique. By using different tracers where one binds to the BMP molecule and the other to osteoblasts it is possible to follow not only the release of BMP but also the bone formation. By the use of PET technique, we can over time correlate the release profile of BMP with bone formation, with the aim to define the most efficient release profile for BMP from a bone forming perspective. The first manuscript where this novel technique has been used has recently been submitted for publication.

A second research line is to optimize calcium phosphate compounds with respect to injectability, mechanical properties, carrier ability and resorption characteristics when used as bone substitutes for filling of bone defects. This work has been ongoing for several years using both in vivo and in vitro models. Over the last years the first preclinical studies have been completed and evaluation of a number of different implants has been done. By the use of our micro-CT equipment formation of bone tissue and the in vivo behaviour of implants can now be assessed not only ex vivo but also in living animals. The equipment allows not only more precise assessment of the bone tissue but also a substantial reduction in the number of animals needed to address a number of the questions that have to be answered.

Sune Larsson, Professor of Orthopaedics

Nils Hailer, Professor of Orthopaedics

Anders Westermark, PhD student

Britt-Marie Andersson, Laboratory Assistant

Neuro-regeneration

Spinal cord injury (SCI) is an incurable condition with devastating impact on the life of mostly young adults. The pathophysiology of spinal cord injury is characterized by two phases: In the acute phase, endogenous CNS macrophages (i.e., microglial cells) contribute to secondary neuronal damage: They release neurotoxic factors, aggravate excitotoxic damage, and induce neuronal apoptosis. In the chronic phase, microglial cells and astrocytes take part in the formation of glial scar tissue and prevent axonal regeneration.

Several immunomodulatory substances have been investigated for their capacity to inhibit microglial activation and to enhance neuronal survival following spinal cord injury, and some substances exert distinct glia-inhibitory and neuroprotective effects. We have previously shown that one very promising immunomodulatory substances, interleukin-1 receptor antagonist (IL-1RA) potently suppress microglial activation and proliferation, and has the capacity to promote both neuronal survival and preservation of a myelinated axon projection.

Different carrier compounds such as hyaluronic acid hydrogels and collagen matrices are developed together with material scientists at the Ångström lab in order to be able to carry and release immunomodulatory substances.

Main projects:

In the acute phase of SCI we follow three different strategies to prevent secondary damage to the injured spinal cord:

1. *Neuroprotective substances:* IL1RA is a competitive antagonist of IL-1α and IL-1β. IL1RA is secreted by the same cell types that produce the above-mentioned pro-inflammatory cytokines. Endogenous IL1RA is neuroprotective and inhibition of IL1RA aggravates ischemic lesions in vivo. We have in previous experiments examined the effects of IL1RA in an in vitro model of spinal cord injury and found that IL1RA can exert neuroprotective effects.
2. *Biomaterials based on hyaluronic acid (HA)*: The blood-brain barrier prevents drugs that are administered intravenously to achieve a sufficiently high concentration in the spinal cord. However, this is not the case in in vitro experiments where the BBB is disrupted. We study HA-based hydrogels (cross-linked and non-cross-linked) as carrier for IL1RA or other neuroprotective compounds. A hydrogel containing IL1RA and applied locally during surgery could provide sufficient concentrations of IL1RA during a given period, thus bypassing the BBB. Spinal cord slice cultures maintained on a hydrogel based on HA show increased neuronal survival compared to controls. In an international collaboration with Robert Nitsch (Institut für Anatomie und Mikroskopische Neurobiologie, Mainz, Germany) we conduct in vivo studies on spinal cord injury where carriers and neuroprotective compounds that were found to be efficient in vitro are tested in vivo.
3. *Small interfering RNA (siRNA)*: Small interfering RNA is a class of double-stranded RNA molecules, and the most notable function of the siRNA is to interfere and silence specific genes, which regulate protein expression. Since the first report in 1998, siRNA has been used as a type of gene therapy, especially concerning approaches for cancer treatment. Collaborators in Professor Hilborn's group have developed a type of siRNA with a specific oligonucleotic extension allowing cell penetration and endosomal release without involving any kind of carrier. Future strategies include RNA interference to silence genes that regulate the expression of various factors involved in the secondary injury process after SCI, for example IL-1β.

In the chronic phase of SCI we aim to promote functional recovery by bypassing the glial scar that has evolved subsequent to the trauma.

Two main strategies are used:

1. In collaboration with Associate Professor Anna Rostedt Punga we intend to implant a micro-array chip in the proximal site of the injury site that will amplify the electrophysiological signal coming from the cortex. The signal will subsequently be sent to a receiver implanted at the distal site of the injury, thus bypassing the glial scar. A similar setting has been tested in non-human primates. Initial steps of this experiment include maintenance of spinal cord slice cultures on microarrays and subsequent detection of signal from neurons in spinal cord slice cultures. Electrophysiological recordings in spinal cord slice cultures are performed after placing the cultures on a microarray chip and assessing neuronal excitation.
2. Transplantation of Neural Crest Stem cells into the injured spinal cord counteracts the neuronal loss observed in the ventral horns, reduces the proportion of apoptotic cells among neurons and suppresses the number of activated microglial cells and astrocytes. In vitro, stem cells migrate across the surface of spinal cord cultures and exert neuroprotective actions through the release of soluble mediators such as brain-derived neurotrophic factor (BDNF).

Collaborations:

Experiments are undertaken in close collaboration with the groups of Jöns Hilborn, the Ångström lab, Cecilia Persson, the Ångström lab, Elena Kozlova, Department of Neuroscience, and Anna Rostedt-Punga, Department of Neuroscience, all at Uppsala University.

An international collaboration with the group around Robert Nitsch, Department of Cell- and Neurobiology at the Gutenberg University in Mainz, Germany, has been established in order to pursue in vivo-experiments further.

Members of the group during 2016

Nils Hailer, Professor

Nikos Schizas, Post-Doc

Alexander Ossinger, PhD student

Andrej Bajic, PhD student

Sarah Pan, M.Sc., project student

Gilles Bert, ERASMUS student

Britt-Marie Andersson, Laboratory Assistant

Agencies that support the work/Funding 2016

4,800,000 SEK from EU for the project Biodesign

500,000 SEK ALF funding from Uppsala University Hospital

400,000 SEK from the Thureus Fund

Spinal Surgery

Principal investigator: Claes Olerud

The Spinal Surgery Research Group consists of members involved in the clinical management of patients with spine pathology which facilitates clinical research and registry based research with clinical implications. There are several different research lines both cervical and lumbar. The lumbar group presented two PhD theses on spinal stenosis during 2015 Perter Försth, Stockholm Spine Center, and Björn Knutsson, Sundsvall. One more PhD project within the same group is on its way.

The project on lumbar spinal stenosis evaluates results of different surgical methods in a multi-center RCT with the Spinal Surgery Research Group as the coordinating center. The effects of fusion in lumbar spinal stenosis are studied, and the influence of obesity and smoking on outcome after surgical treatment. The follow-up includes generic and condition-specific outcome measures as well as radiological studies. Also this project analyses registry data in epidemiological and outcome studies. This is in cooperation with the Epidemiology Group.

The cervical group held two “half time seminars” during the first semester of 2016; Yohan Robinson and Anna MacDowall. Both plan to defend their theses during 2017. The cervical spine projects comprise studies on artificial disks, dysphagia in relation to anterior cervical spine surgery, non-invasive CT-based motion analysis, complications in relation to bone graft harvesting, artificial disk fixation, degeneration of the segment adjacent to a fusion, and validation of various pain measurement instruments for cervical spine research. Another project deals with Odontoid fractures in the elderly with a clinical multi-center RCT and registry studies on epidemiology and survival as main components, but also consisting of studies on health economics and the significance of osteoporosis.

Another research lines is on traumatology of the cranio-cervical junction, CCJ. Suspected acute ligament injuries of the cranio-cervical junction are evaluated with a specific MRI technique and compared to CT – data. In another arm of this project chronic WAD-patients are investigated with both the specific MRI technique and dynamic MRI to evaluate cranio-cervical ligament insufficiency. Patients with detected injuries are treated with fusion surgery in a prospective study. Some anatomical work on the soft tissues in the CCJ is also performed.

Fractures in Anchylosing Spondylitis are studied in clinical and registry studies and the mechanical behavior of spinal fixation in the anchylosed spine is evaluated with finite element analysis in collaboration with KTH, Stockholm.

The Spine Surgery Unit at Uppsala University Hospital was 2012 as the first unit in Sweden appointed as an AOSpine Center of Excellence. Apart from being prestigious this allows the unit to accept clinical and research fellows with financial support from AOSpine.

Members of the group during 2016

Claes Olerud, Professor

Yohan Robinson, Associate Professor

Bengt Sandén, Associate Professor

Martin Skeppholm, MD, PhD, Stockholm Spine Center

Peter Försth, PhD

PhD students

Thomas Karlsson, MD

Anna MacDowall, MD

Anna-Lena Robinson, MD

Christian Carrwik, resident, PhD student

Jan Triebel, MBA, resident, PhD student

Bioimplantat

Principal investigator: Hans Mallmin

The Bioimplant research group evaluates new knee and hip implants through prospective and longitudinal studies, ie randomized, controlled trials, RCT. We have focused on the stability of fixation of uncemented implants with roentgen stereogrammetry, RSA, effects on bone mineral density, BMD, adjacent to the femoral implant with dual energy X-ray absorptiometry, positron emission tomography (PET)/Computerized Tomography (CT), clinical score systems, and gait analysis. Bone metabolic response to biological implants, especially endoprostheses of the hip, has been investigated using PET. An uncemented short-stemmed hip prosthesis, CFP®, leading to a very restricted collum osteotomy, is subject for a prospective and longitudinal study of stability and bone mineral density with an extension to eight years of follow-up. A validation of computed tomography in comparison to RSA for implant stability is performed in cooperation with the researchers at Karolinska Sjukhuset, Solna, and the section for radiology, at our institution for Surgical Sciences, Uppsala University.

The Swedish Knee Arthroplasty Register is a source for evaluation of revised knee arthroplasty (Asgeir Gudnason).

The Swedish Hip Arthroplasty Register is a source for evaluation of mortality and hip arthroplasty (Anne Garland)

The out- and inpatient Uppsala region register is a source for epidemiological studies of major osteoporotic fractures and the relation to fracture prevention (Eva Ribom och Hans Mallmin).

The local Hip Prosthesis Register, University Hospital, Uppsala, is basis for two research project. The first concerning acetabular cuprevision surgery comparing two different procedures/implants and the second infected hip and knee implants (Anders Brüggemann and Hannah Eriksson).

A single center academic non commercially sponsored Randomised Clinical Trial, phase 2,”Uncemented total hip implant and subcutaneous injections of Denosumab for patients with osteoarthritis of the hip. A randomized double blind placebo controlled study on the effects on bone evaluated with DXA, PET/CT, and biochemical markers” has been approved by the Medical Product Agency and the Regional Ethical Committee. The effect on bone metabolism and density of two subcutaneous injections of a human monoclonal antibody, Denosumab, with an osteoprotegrin-like action will be studied and followed for two years. The study has been successful and all included patient (n=64) have been followed according to the CRF. Last patient for Bone Mineral Density measurement and clinical evaluation will occur January 2017.

Members of the group during 2016

Hans Mallmin, MD, Professor

Nils Hailer, MD, Professor

Olof Nilsson, MD, Professor

Jan Milbrink, MD, Associate Professor

Eva Ribom, Physiotherapist, Associate Professor

Per Mattsson, MD, PhD

Stergios Lazarinis, MD, PhD

Asgeir Gudnason, PhD student

Anne Garland, PhD student

Andreas Nyström, PhD student

Demostenis Kiritopoulos, PhD student

Anders Brüggemann, PhD student

Hannah Eriksson, PhD student

Agencies that support the work/Funding

Skofonden 600,000 SEK

Endoklinikens forskningsstiftelse, Hamburg 400,000 SEK

Regionala Forskningsfonden 400,000 SEK

Pelvic fracture research

Principal investigator: Sune Larsson

Surgical treatment of pelvic fractures has for many years been a niche area for the department of orthopedics at Uppsala University Hospital with more than 30 hospitals referring their patients to our unit. Since January 2003 all pelvic fracture patients are followed according to a strict protocol that includes questionnaires at specific time points after surgery as well as radiographic evaluations. Even with international standards we have now reached a substantial number of patients that are followed prospectively, given the type of injury and the thorough follow-up. Two new instruments intended to be used as a self-assessment tool for patients following acetabular or pelvic injuries have been constructed and are at present in the validation phase. One problem when assessing quality of life (QoL) in patients following a trauma is the lack of information about the pretraumatic QoL in these patients. In a recent study this knowledge gap was addressed through a study that has been published last year. In a specific project we have been also compared whether the time following the trauma has any effect on how the patients assess their preinjury QoL. In an additional project we will use qualitative methods to find out what differences in QoL that can be translated into differences that are of clinical relevance, i.e. of relevance for the patients.

Members of the group during 2016

Sune Larsson, MD, Professor

Tomas Borg, MD, PhD

Björn Hernefalk, PhD student

Dissertation 2016

Karin Bernhoff. Orthopaedic Patients with Lower Limb Vascular Injuries.

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9) Oto-, rhino- laryngology and Head & Neck Surgery

Principal investigator: Göran Laurell

Research group 1: Experimental inner ear research

Pharmacokinetics, toxicicity and otoprotection

Mechanisms of damage in exogenous inner ear disorders (ototoxic drugs, acoustic overstimulation) have been analyzed with special emphasis on pharmacokinetics, metabolomics, reactive oxygen species and otoprotection.

Cisplatin and oxaliplatin are two anticancer platinum-containing drugs that differ in ototoxicity during clinical use. Cisplatin induces hearing loss at high doses while oxaliplatin therapy is not ototoxic. Recent findings suggest that redox-related effects involving cellular proteins constitute a major mechanism of action for cisplatin toxicity not being related to DNA damage. Bypass of the blood-labyrinth barrier by using cultured organs of Corti, shows comparable levels of outer hair loss induced by either cisplatin or oxaliplatin, as well as inhibition of thioredoxin reductase, demonstrating that the two drugs are similarly ototoxic if cochlea is directly exposed. However, these results could not be confirmed in vivo.

Little is known about drug transport to and within the inner ear, but it is clear that the accessibility from blood is limited by the blood-perilymph barrier and the intrastrial fluid-blood barrier. Recent studies indicate that organic cation transporters may play an important part in the influx of cisplatin to cochlear target cells. We have identified the transport protein OCT2 in the supporting cells of the organ of Corti and in the type I spiral ganglion cells. These findings suggest that OCT2 is not primarily involved in cisplatin uptake from the systemic circulation. Experimental magnetic resonance imaging is an excellent research tool to study inner ear pharmacokinetics in vivo. We have in an experimental model characterized the kinetics of four different paramagnetic contrast agents in the inner ear compartments after intravenous injection. There is an extremely low transport of all four agents to the middle compartment of the cochlea (scala media). Pretreatment with a high dose of furosemide opens up the intrastrial-fluid blood barrier for gadolinium-containing contrast agents and the uptake to scala media is found to be similar to that of the other fluid-filled compartments.

Reactive oxygen species play an important role for development of noise-induced hearing loss. Hydrogen gas has antioxidant effects and is easily administered for possible otoprotection. Inspired by the idea that hydrogen might affect noise-induced hearing loss impulse noise was given simultaneously with inhalation of hydrogen gas and an otoprotective effect of hydrogen gas was demonstrated. Furthermore, an otoprotective effect was also found in an experimental study when cisplatin was given to our in vivo model. The effects of hydrogen gas in the systemic compartment are now investigated furthern map the order to characterize the. Immunohistochemical analysis is now undertaken to characterize the protective effects of hydrogen gas in the cochlea.

There is robust evidence that cisplatin-induced hearing loss can be prevented in experimental models, while the results in humans have so far been poor. One likely reason to the futile results in humans is that a systematically administered otoprotective drug does not reach the target cells localized in the deep compartment of the inner ear in sufficient amounts unless a very high dose is used. Local treatment of the inner ear by intratympanic injection of a semi-solid gel has earlier been demonstrated by our group. It is shown that the uptake of thiosulfate to the inner ear can be improved by direct administration to the ear instead of given intravenously. Moreover, systemic administration of a nucleophile might be risky since these species are prone to react with cisplatin and thereby reduce the antineoplastic effects. We have using an experimental model investigated the blood metabolome after cisplatin treatment with or without systemic otoprotection using thiosulfate. It was found that there is a correlation between increase in reduced glutathione in serum and electrophysiological hearing thresholds.

An important factor for local administration of drugs to the middle ear aimed for inner ear treatment is the adherence of the vehicle to the round window membrane. Experimental high resolution magnetic imaging is employed in different animal models for studying distribution and eliminations of vehicles in the middle ear and contrast agents in the inner ear. In a series of experiments a new and promising vehicle with unique mucoadhesive properties is tested. These experiments include also analysis of immune responses on the middle and inner ear after intratympanic injection of a drug-loaded polymeric hydrogel formulation.

Pharmacokinetics and pharmacodynamics of drugs cannot be studied in human beings. Studies are performed in experimental models to further define drug transport inside the cochlea. We have demonstrated an early high concentration of cisplatin in the base of the cochlea and a delayed elimination of cisplatin from scala tympani perilymph compared to blood. These two findings might correlate to cisplatin-induced loss of outer hair cells in the base of the cochlea.

Prevention of ototoxicity by administration of an exogenous antioxidant in conjunction with cisplatin treatment has been successful in experimental studies. One of our goals is to prevent cisplatin ototoxicity in cancer patients by local administration of an otoprotectant. We are going to evaluate a novel pharmacological method in a randomized placebo-controlled multicentre clinical trial where a thiosulfate-containing gel is injected into the middle ear of patients undergoing cisplatin-based chemotherapy.

Proteomics of the human perilymph

Proteomic studies of the human perilymph are scarce. The goal of this project is to improve the understanding of the causes of inner ear disorders. An approach is to investigate the protein composition of the perilymph and the rough concentrations of these proteins using modern mass spectrometry-based techniques. Perilymph samples are aspirated during translabyrinthine and cochlear implant surgery for proteomic analysis at Professor Jonas Bergquist's laboratory, Department of Chemistry, Uppsala University.

Members of the group during 2016

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Agencies that support the group/Funding

Uppsala University Hospital (ALF)

Afa Insurance

Tysta Skolan

Research group 2: Head and neck cancer

Head and neck tumor targeting

Cancer cells differ from normal cells, for example by different protein expressions on the cell surface. In targeted radionuclide therapy, we take advantage of these differences, by using e.g. antibodies, antibody derivatives, or peptides to target these structures, and by arming these "missiles" with radionuclides. By delivering the radioactivity directly to the tumor cells, small metastases and disseminated tumor cells can be found and killed. By using radionuclides as warheads, multidrug resistance can be avoided, and the need to target every single tumor cell is reduced. There is great potential for targeted radionuclide therapy in the treatment of head and neck cancer. In this disease there is a vast need for a systemic treatment that is effective in locating or treating metastases at distant sites and minimal residual disease at the local and regional levels. Furthermore, head and neck cancer is intrinsically radiosensitive, and is therefore especially suitable for radiotherapy.

In the Head and Neck Tumor Targeting Group, we are studying several steps in the targeting process. Different protein structures, targeting molecules and radionuclides are assessed, and the different properties of the constructed radioconjugates are evaluated. By creating and evaluating novel tumor seeking radioconjugates, we hope to provide more sensitive and specific methods for identifying and treating head and neck cancer, and hopefully help improve long-term survival rates for this patient group in the future.

Nutrition and head and neck cancer

There is a great need to increase knowledge of nutrition in tumor disease. Long-term malnutrition is one major sequel after treatment of head and neck cancer, possibly related to muscle loss, cachexia and psychological and emotional distress. Greater weight loss during radiotherapy (RT) has been associated with postsurgical infections and wound healing problems. Weight loss has also been found to be related to increased mortality in H&N cancer patients, but the issue is controversial and debated. Two different cohorts have been studied. Patients continue to lose weight long-term after termination of therapy with a nadir at about six months. It seems that the nutritional status before treatment is of greatest importance. We have in a secondary study in patients with oropharyngeal cancer found that a high body mass index (BMI) gives significantly better 5-year survival than a low BMI.

More knowledge is needed to increase the understanding of persistent swallowing dysfunction long-term after treatment. A finding is that swallowing dysfunction is an important factor for nutritional status in head and neck cancer survivors. We found that almost 50% of surviving patients had silent aspiration.

We have started a Swedish multicentre study in collaboration between the hospitals in Uppsala, Örebro, and Umeå. The title of the study is "Diet, muscle mass and inflammatory reaction – A prospective observational study of nutritional factors in patients with head and neck cancer". With this study we expect to highlight correlations between inflammatory response induced by treatment and disease, changes in body weight composition and survival. A web-based patient case report form has been developed for a reliable long term data storage. Approximately 150 patients are now included in the study that will continue until 2020.

Effects of radiotherapy

Despite improvements in treatment of head and neck cancer during the last decades, survival rates have not significantly increased. About 70% of the patients undergo radiotherapy. There is therefore a need to better understand how the tumor and adjacent tissue react to radiotherapy. Expression of different biomarkers is studied in a consecutive cohort of patients with tongue cancer. To gain insight in the mechanisms behind oral mucositis we developed an animal model where the mucosa spontaneously heals with two weeks.

Members of the group during 2016

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Royal Institute of Technology (KTH) (Professor Sophia Hober)

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University of Dundee, Scotland, and IMCB Singapore (Professor Sir David Lane)

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Karlsruhe Institute of Technology, Germany (Dr Véronique Orian-Rousseau

University of Toronto, Canada (Dr Johan Nilvebrant)

Uppsala university (Professor Curt Pettersson, Mikael Engskog)

Örebro university (Associate Professor Svante Hugosson)

Umeå university (Professor Karin Nylander, Eva Levring Jäghagen, Krister Tano)

Agencies that support the work/Funding

IngaBritt och Arne Lundbergs Forskningsstiftelse

Swedish Cancer Society

Uppsala University Medical Faculty

Uppsala University Hospital (ALF)

Svenska Sällskapet för Medicinsk Forskning (SSFMF)

The Kamprad Family Foundation for Entrepreneurship, Research & Charity

Research group 3: Facialis

Principal investigator: Lars Jonsson

Studies on peripheral facial palsy

Each year 3,000 subjects in Sweden are struck by a peripheral facial palsy. Of these palsies, 75% are of unknown origin, so-called Bell's palsy. During 2001 to 2007, the Uppsala ENT-clinic monitored the world's largest controlled Bell's palsy study (the Scandinavian Bell's palsy study) which was performed in Sweden and Finland. A beneficial effect on time to recovery and a better outcome was present in patients treated with prednisolone whereas no convincing effect was found with anti-viral valaciclovir. The study was published in Lancet Neurology in 2008. Subsequent analyses documented the influence of time to treatment start with prednisolone, a relation between early deterioration and outcome and also a risk curve for the recovery in Bell's palsy.

Synkinesis in Bell's palsy

Facial synkinesis is troublesome squeal after facial palsy and causes facial asymmetry, functional limitations and pain which can adversely affect quality of live. The development of synkinesis in Bell's palsy is still not clear and to what degree the different facial muscles are affected. Mapping of clinical and subclinical co-contractions in synkinesis patients may further cast light of the underlying pathology and help to increase the efficiency of the treatment with botulinum toxin. In this study, the development of synkinesis in a cohort of 150 Bell's palsy patients is analyzed according to the prevalence by gender, age and location in the face. Performed in collaboration with Andres Rodriguez, MD, PhD and David Jensson, MD, Department of Plastic Surgery.

Quality-of-life in Bell's palsy

The measurement methods for the severity of Bell's palsy are today physician-ranked scales. The House-Brackmann and the Sunnybrook grading scales describe the severity of facial palsy but do not address the perception of the patient's outcome, neither or the impact of quality-of-life. We recently validated two patient-reported questionnaires in Swedish regarding quality-of-life outcomes in peripheral facial palsy patients. These two instruments, the Facial Disability Index (FDI) and the Facial Clinimetric Evaluation scale (FaCE), have been used in facial palsy studies but never evaluated in consecutive follow-up studies. The two quality-of-life measures are compared with the physician's facial rankings in an estimate of 100 consecutive patients with Bell's palsy. In collaboration with Elin Marsk, MD, PhD and Professor Malou Hultcrantz, Department of Otolaryngology, Karolinska University Hospital.

Long-term follow-up of Bell's palsy

There are no studies on the long-term effect of corticosteroids and/or anti-viral treatment with valaciclovir in Bell's palsy. In our previous (the world's largest) controlled Bell's study, altogether 1,953 patients were

examined of which 829 were included. Patients who were included and excluded in this study and examined at the University clinics in Helsinki, Stockholm, Uppsala and Lund during 2001 to 2007 will be re-examined 10 to 15 years after the onset of palsy. Difference in long-term outcome related to gender and effect of treatment will be examined. Pregnant women and patients with diabetes mellitus are reported to have a higher risk for Bell's palsy, and also a poorer outcome compared with other Bell's palsy patients. The long-term results for these patient groups have not previously been studied. It will also be examined if Bell's palsy patients have a higher incidence of other diseases, including hypertension and/or other neurologic disease. In collaboration with Elin Marsk, MD, PhD and Professor Malou Hultcrantz, Department of Otolaryngology, Karolinska University Hospital; Mervi Kanerva, MD, PhD, Department of Otolaryngology, Helsinki University Central Hospital and Sara Axelsson, MD, PhD, Department of Otolaryngology, Skåne University Hospital, Lund.

PET-MR in Bell's palsy – etiologic perspective

The etiology of Bell's palsy remains unknown. The most prevailing theory is that the nerve injury is caused by a viral inflammatory edema. In a previous pilot positron emission tomography (PET) study in 1994 we found one Bell's palsy patient with possible radionuclide uptake in the brain stem. PET in combination with high-Tesla MR (PET-MR) allows the visualization of regions with edema and increased metabolism. In this study 8-10 patients with a severe Bell's palsy will be examined with PET-MR within 7 days of onset of palsy in order to give further etiologic information on the pathogenesis of the disease. In collaboration with Professor Håkan Ahlström and Anna Grabowska, MD, Department of Radiology.

Facial reanimation and brain plasticity – a neurophysiological and functional-MR study

One of the benefits of nerve transfers is to provide a source of axons very close to the target muscle and also provide direct nerve anastomosis. There are no studies analyzing the most common donor nerves used in nerve transfers (V, XII, XI) to determine which of these transfers that has the best potential for cortical plasticity. This knowledge may establish postoperative strategies for physiotherapy to improve cortical plasticity and smile relearning. Healthy volunteers undergo electrophysiological tests and functional magnetic resonance (fMR). Determination of functional co-activity between the facial nerve and the XII, XI, and V nerve muscles are determined by electromyograms. fMR will determine the cortical areas for smiling (VII), biting (V), tongue movement (XII) and elevation of shoulders (XI) to elucidate cross activation of cortical areas during different activities (smile-moving tongue, smile-biting) to analyze ways to improve postoperative training and brain plasticity. In collaboration with Andres Rodriguez, MD, PhD, David Jensson, MD, Department of Plastic Surgery, Johan Wikström, MD, PhD, Department of Radiology and Professor Roland Flink, Department of Neurophysiology.

Members of the group during 2016

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Agencies that support the work/Funding

Uppsala University Hospital (ALF)

Landstinget i Uppsala läns FoU-medel

Research group 4: Upper Respiratory Airways

Principal investigator: Leif Nordang

Respiratory symptoms during exercise are common and might limit adolescents' ability to take part in physical activity. In a survey of of 12–13 year old in Uppsala (n=3838), where fourteen percent (n=330) reported exercise-induced dyspnea (EID), sixty-one percent (n=202) of the participants with EID did not have a diagnosis of asthma. This study was published in Respiratory Medicine. To investigate the prevalence of exercise-induced laryngeal obstruction (EILO) and exercise-induced bronchoconstriction (EIB) we tested a selected group of these children, both EIA-tests and videolaryngoscopy during exercise (CLE-test) to study the number of both EIB and EILO in this cohort. The estimated prevalence of EILO was 5.7% and of EIB 19.2%. No gender differences were found. EILO is equally common among girls and boys and can coexist with EIB. The study was published in Thorax.

In the clinic we have performed CLE-tests on more than 400 patients referred to us because of EID. Many of the patients are treated with asthma medication without effect and the CLE-test discloses a laryngeal obstruction in 40-50% of them. The results of these studies are discussed in the thesis of Katarina Norlander who will defend her thesis on March 31st with the title: *Exercise-induced laryngeal obstruction: Prevalence, laryngeal findings and evaluation of treatment*.

Members of the group during 2016

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Agencies that support the work/Funding

Uppsala University Hospital (ALF)

Research group 5: Ear research – Clinical and Experimental Investigations

Principal investigator: Helge Rask-Andersen

The research can be separated into several areas:

1. “Otostem” EU project Stem cell-based inner ear therapy to cure deafness. ”Human stem cell applications for the treatment of hearing loss". Call: FP7-HEALTH-2013-INNOVATION-1.
2. Studies of the human inner ear, round window anatomy related to EAS, Mb Meniere, cell biology of tympanic membrane and regeneration (collaboration with the University of Tuebingen, Oslo and Innsbruck).
3. Hearing Implants - audiological and surgical aspects. Hearing preservation surgery (EAS; electro-acoustic stimulation) middle ear implants (MEI) and auditory brain stem implants (ABI).
4. Micro-CT analyses of the human temporal bone.

EU Project - OTOSTEM

The EU project OTOSTEM has been running since September 2013. The project aims to develop stem cell-based therapy for inner ear diseases. It includes several European research centers including the US centers at Harvard and Stanford Universities. It will end in November 2017. Dr. Hao Li is the main researcher leading this project together with the principal investigator. Our main task is to isolate and expand adult human inner ear progenitors. The consortium has devised guidance protocols for mouse and human embryonic and reprogrammed stem cells toward inner ear cell types that make use of principles of early germ layer formation and otic induction. Purification techniques for human otic progenitors from ES/iPS cell sources and in addition from native human otic tissues from foetal and adult stages will serve the dual purpose to enable the development of novel bioassays for drug screens, as well as generating cells with decreased tumorigenicity for cell transplantation studies in in vivo animal models. It is a collaborative study, with groups having considerable experience in ES/iPS cell work, inner ear stem cell biology and in translational research. Through surgical materials we have isolated and extracted stem cell-like progenitors from the vestibular organ and successfully differentiated these cells into neurons. In addition, we have also purified epithelial cells in the inner ear and characterized them through immunohistochemistry using various molecular markers such as Lgr5, Sox2 and Nestin. Hopefully stem cell based inner ear therapy will be available in the future. First however, the role of stem cells in the human inner ear and regeneration must be established.

Regeneration and localization of stem cells in the tympanic membrane

We have analyzed the regenerative capacity of the human cochlea. Progenitor/stem cells are further analyzed in the human auditory nerve. Human cochleae are dissected and nerve tissue isolated and cultured in expansion media with growth factors. Proliferation and cell division is induced and recorded using time-lapse video technique. The laboratory first reported the isolation of mitogen-responding neural progenitors from surgical specimens. Processing of this collected tissue has hitherto resulted in new information about human cochlear structure, protein expression as well as novel discoveries regarding the presence of auditory nerve progenitor cells and self-renewal of cells in adults. Our local infrastructure is built on a well-developed cooperation between surgeons and the research unit. A project was initiated 2012 on cell, stromal activation and cell repair in the human tympanic membrane. The study is performed by Dr Nadine Schart-Moren at the ENT department in Uppsala in collaboration with Professor Magnus von Unge in Oslo. Effects of induced superficial trauma on cell activation of collected human tympanic membranes are analyzed immunohistochemically. The projected has resulted in a scientific paper recently submitted.

Human inner ear studies - Immunohistochemistry and SIM (structured illumination microscopy)

We have categorized the molecular expression of connexin 26/30 protein in human cochlea using SR-SIM technique. Localization of K-channels (kir4.1) and Na-K-ATPase, NKCC1, KCNQ1, was made in human cochlea and was published in Cell Tissue Research 2016. We studied surgical specimens for proliferation

markers, such as SOX2, Ki67 and PCNA (proliferating cell nuclear antigen); basilar membrane components, such as collagen, laminin, fibronectin; adult stem cell marker Lgr 5; voltage-gated ion channels, such as KCNQ, Nav1.6 and 1.2, as well as calcium channels. A SEM analysis of human cochlear hair cells, supernumerary hair cells have been executed and published. The findings may suggest the presence of a low-grade regeneration of inner hair cells but this must be further explored using molecular techniques. Two additional works are under publication.

ABI – Auditory Brain Stem Implant

A thesis was presented by Karin Lundin at the Audiology section concerning the use and follow-up results of ABI in children and adults. Further studies are made. These studies help to understand the effectiveness of this treatment in children with congenital inner ear malformations and ossified cochlea following meningitis. Uppsala is the only Hospital in Scandinavia performing ABI surgery.

New inner ear disease can be surgically treated – Inner ear canal dehiscence

This is a rather new disease discovered by US researcher Loyd Minor. More and more patients are discovered with symptoms indicating a dehiscence on a semicircular canal. Dr Niklas Danckwardt-Lillieström has specialized himself on this disorder and has a wide experience.

Anatomy of the human round window

Human temporal bone studies have elucidated the anatomy of the human round window and the impact of cochleostomy on the inner structures of the cochlea. These studies were performed by Dr Francesca Atturo from Rome Italy and have generated two publications. Guest researcher from China studied the vascular bone channels of the human inner ear. Her study is already accepted for publication in the European journal of Otolaryngology 2016. The results are relevant for hearing preservation surgery and cochlear implantation.

Micro-CT and 3-D rendering of human temporal bones – 3-D writer reconstruction

A technique to analyze the 3-D anatomy of the human ear was developed using micro-CT. It gave us new insight in the facial nerve course and its interaction with the cochlea. The technique makes it possible to perform so-called “cropping” or sectioning of the bones reconstructions. It allows us to study the topographic anatomy in greater detail. It gives the surgeon better knowledge about the 3-D anatomy. A book chapter for oto-surgeons is under writing together with Dr Karin Strömbäck and Nadine Schart-Moren. The CT may also be used for reconstructions using 3-D writer. These reconstructions can be used to plan difficult ear surgery.

Members of the group during 2016

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Annelies Schrott-Fischer, PhD, Department of Otolaryngology, Innsbruck University

Hao Li, PhD

Several guest researchers have visited our laboratory during 2016.

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Dissertations 2016

Karin Lundin. Experiences from Cochlear Implantation and Auditory Brainstem Implantation in Adults and Children: Electrophysiological Measurements, Hearing Outcomes and Patient Satisfaction.

Fredrik Edin. Strategies in Cochlear Nerve Regeneration, Guidance and Protection: Prospects for Future Cochlear Implants.

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10) Plastic Surgery

Plastic Surgery includes the following research areas:

- The Connective Tissue Activation Programme
- Cleft and Craniofacial Research Programme
- The Uppsala Burn Research Programme
- Reconstructive Microsurgery

The programs are primarily patient-based and success is heavily related to an adequate number of patients and consequently the size of the scientifically active staff.

Uppsala University Hospital and Uppsala University has been appointed national centers for craniofacial surgery and treatment of severe burns. This has guaranteed a solid basis for research to thrive.

Network structure

In order to optimize collaborative work the national network SwedBurn has been initiated with an initiative from our research group (http://www.swedburn.se). The purpose is to stimulate burn related projects requiring intellectual and functional resources from different departments and universities.

The Bone and Connective Tissue Activation Programme

Principal investigators: Daniel Nowinski and Bengt Gerdin

This programme is composed of two main projects: A) research around conditions where an activation or dysregulation of connective tissue cells and the connective tissue matrix are central pathophysiologic components; B) development of new degradable scaffolds for bone regeneration and research on the fundamental mechanisms behind premature fusion of the calvarial sutures in craniosynostosis. The projects include the development, use and exploitation of sophisticated culture models.

A) The project on connective tissue activation deals with two main problem areas: a) excessive connective tissue deposition in hypertropic cars/keloids; and b) formation of an aberrant connective tissue matrix in the stromal compartment of tumors.

    a. Studies have focused on interaction between epidermal cells (keratinocytes) and dermal fibroblasts. Paracrine factors from keratinocytes generally down-regulate fibrotic response. The project aims to further elucidate different mechanisms in the paracrine intercellular communication between the epithelial layer of the skin, the keratinocytes, and fibroblasts that regulate various events during the activation of the supportive loose connective tissue during tissue repair and wound healing. Keratinocyte-fibroblast interactions are investigated in organotypic cocultures. Cells from keloids and hypertrophic scars are compared to those from normal skin.

    b. Studies of interactions between malignant keratinocytes, predominantly from oral squamous cell carcinomas, and fibroblasts. Malignant keratinocyte differ in their effects on fibroblasts when compared to normal keratinocytes. The group has demonstrated that malignant keratinocytes are deficient in their capacity to downregulate profibrotic mechanisms in fibroblast. Future studies will focus on the effects of radiation on cancer cell mediated regulation of stromal cells.

B) The project on bone regeneration is conducted in close collaboration with the group around Jöns Hilborn, Chemistry, Polymer chemistry, Ångström laboratory. The aim is to develop degradable scaffolds that can be used for reconstruction of calvarial defects in the pediatric population. The project on mechanisms behind craniosynostosis will exploit the above described collagen-matrix based culture models for the investigation of molecular mechanisms behind premature fusion of calvarial sutures. A biobank with primary cells and tissue from patients operated for craniosynostosis is currently being established.

Members of the programme during 2016

Dani**e**l Nowinski, MD, PhD, Associate Professor

Bengt Gerdin, Professor

Malin Hakelius, MD

Daniel Saiepour, MD, PhD

Kristofer Rubin, Professor, IMBIM

Mikael Ivarsson, PhD, Örebro University

Mohamad Nassir, MD

Eva Lindell-Jonsson, MD

Cleft and Craniofacial Programme

Principal investigator: Daniel Nowinski

This research programme gathers clinical research projects around two principal problem areas: craniosynostosis and orofacial clefts. Projects around craniosynostosis rest on the platform generated by the national care assignment for craniofacial surgery and are conducted in close collaboration with neurosurgery, psychiatry, clinical genetics and anesthesiology.

The group is partner in an Indian-Swedish research consortium, with researches around associated Professor Anders Rydberg at the Department of Engineering Sciences, Ångström laboratory, for the development of a bone mineral density analysis system (BDAS). The system will be used to investigate the dynamics of bone formation after craniosynostosis surgery.

The part of the programme on orofacial clefts is currently mainly dealing with investigations of long-term outcomes, and predictors for outcomes, after secondary bone grafting to the cleft alveolus and after primary reconstruction of the cleft lip. Dissertation on secondary alveolar bone grafting is planned for May 20 2016.

Members of the programme during 2016

Dani**e**l Nowinski, MD, PhD, Associate Professor

Malin Hakelius, MD

Daniel Saiepour, MD, PhD

Fatima Jabbari, DDS

Alberto Delgado, MD, PhD

The Uppsala Burn Research Program

Principal investigator: Fredrik Huss

A burn injury is a good model for understanding the response to a severe trauma, viewed from a short, as well as a long, perspective. The disastrous experience of being afflicted with an extensive burn injury affects all main integrating systems in the body (i.e. nervous, endocrine, and immune). The acute phase is characterized by a relatively intense and rapidly developing physiologic inflammatory response, not only in

the immediate vicinity of injured tissue, but also in a generalized syndrome of systemic inflammation, which in general is proportional to the magnitude of injury. In the most severe cases it can lead to circulatory shock, organ dysfunction, and death.

It is quite obvious that burn care is heavily multifactorial and multiprofessional, spanning from simple wound care to advanced tissue engineering/tissue culture, from intensive care to psycho-social support.

The Uppsala Burn Research Program is an umbrella for (pre)-clinical research on burns and outcome after burns and is divided into modules containing the main parts of the treatment processes for burns:

- Resilience and Vulnerability
- Anaesthesiology and Intensive Care
- Surgery / wound healing
- Prevention
- Rehabilitation
- Family perspective
- Patient satisfaction

A few of the ongoing projects are described below.

Nosocomial infections caused by S. aureus in burn patients

Background: Staphyloccocus aureus is a bacterium that normally occurs in about 30% of the population and colonizes nose, mouth, armpit and groin, without necessarily causing infection.

Burn patients represent essentially a normal population but in which the burns themselves is a breeding ground for the establishment of infections and therefore a secondary influence on the immunological defense. Sepsis and serious wound infections due to S. aureus are very common in burn patients. According to other studies 50-60% of patients with major burns suffer infections caused by S. aureus.

Whether the infection is nosocomial or caused by the patient's own normal flora has never been investigated until now.

Resuscitation the first 24 hours. The use of a protocol to improve the adherence to a fluid treatment algorithm

An algorithm for fluid resuscitation has been developed and the adherence and outcome of the algorithm is studied.

Pain in ICU patients, subjective aspects and objective parameters

A study of objective parameters correlating to the patients' description of pain-experiences to develop a protocol to use objective parameters in sedated patients for pain treatment.

Burn blisters

The content and physiological properties of acute burn blisters are investigated.

Hydrogen peroxide, and other markers of severe sepsis and septic shock

The purpose of the study is to measure hydrogen peroxide, glutathione and other biomarkers in patients with severe sepsis and septic shock and significant burns. The concentrations of hydrogen peroxide and glutathione will be measured over time for several days to examine the variability of these markers and how these markers is influenced by usual treatment. Inflammatory mediators in the blood will also be

analyzed. Correlation with SOFA Great and SAPS 3 scores, which are clinical markers of severity of the infection and 28-day mortality after onset of illness will be investigated. The septic patients' biomarkers will be compared with the burn patients' in order to investigate any differences between SIRS±sepsis and burns.

Antibiotic concentration in critical illness (ACCIS study)

Early and effective antibiotic therapy is of paramount importance in septic shock. Current recommendations on antibiotic dosing are mainly based on studies in healthy volunteers. In critical illness several factors change the pharmacokinetics of drugs, such as variations in total body water, plasma protein levels, and in hepatic and renal function. Initiation of renal replacement therapy can also alter elimination of antibiotics. Given the unpredictable pharmacokinetics of antibiotics, both under- and overdosing of these drugs is likely in the critically ill population. Our hypothesis is that antibiotic concentrations are insufficient during the first days after starting antibiotic therapy. Given that the maximum impact on outcome is probably during the first phase of the antibiotic treatment, investigating this hypothesis is of great importance. We are planning to include 150 patients. After initiation of antibiotic therapy (with the eight most common antibiotics in this population) plasma concentrations will be followed for three days. In the second phase of the study, based on the study data, pharmacokinetic modelling will be used to optimize dosing of the antibiotics investigated. The latter project is run in collaboration with Assistant Professor Elisabet Nielsen. This multicenter study is now running in eight centers.

Epidemiology

Each year over 300 000 people die worldwide, and about 90% of burns occur in countries with low and middle incomes. The morbidity after large burns is often considerable and commonly associated with reduced quality of life. Older Scandinavian investigations have indicated that about 0.4% of the population seek medical care for burns each year. With the current population in Sweden this would extrapolate to about 38 000 burns treated each year. In several projects and from different aspects are we investigating the epidemiology of fire-related injuries and deaths in Sweden.

Intestinal flora in burn patients

A study of the intestinal flora, the presence of resistant intestinal bacteria, and the effect of faecestransplantation in patients with severe burns.

This study examines:

1) the intestinal microflora composition and the presence of resistant intestinal bacteria in patients who admitted to our burn center

2) the intestinal flora and occurrence of resistant bacteria changes during hospitalization

3) the relationship between the given antibiotic treatment and the intestinal flora as well as the risk of resistance development

4) whether faecestransplantation performed after completion of treatment has a beneficial effect on the patient's intestinal flora and risk of carriage of resistant bacteria in the longer term.

Vulnerability and resilience; medical, psychological and social adaptation after burn injury

The project is mainly concerned with three of the themes described above: resilience and vulnerability, family perspective, and patient satisfaction.

The overall aim is to investigate factors that influence outcomes after a severe life threatening physical trauma or stressor, in this case a severe burn injury. Patients treated for severe burn injuries and their associated family members have been assessed prospectively during care and several years after discharge

from hospital. Burn injury provides an excellent model for severe trauma with a protracted recovery. Therefore, the results can be generalized and facilitate the development of new treatment strategies that can improve outcome also after other severe conditions with an increased risk for psychiatric morbidity. According to the working hypothesis, several factors act, and interact, to shape the adaptation process and outcome (see Figure 1 below). Outcome is broadly defined in medical, psychological and social terms. Individual factors such as gender, psychiatric history, and psychological factors are related to acute and long-term outcome. Also, physiological stress responses during treatment for the burn injury have been studied in relation to outcome. Among adult patients we have focused much of our interest on stress response, burn-specific health status, itching, sexuality, psychiatric morbidity including posttraumatic stress disorder and alcohol consumption, cognitive factors, return to work, health-related quality of life and patient satisfaction. Adult family members, mostly spouses, have been assessed regarding psychological symptoms, health-related quality of life and their experiences during recovery and rehabilitation. In addition, the situation of parents of children with burns has been studied descriptively and with an intervention study. As parent health is of vital importance for children's health, an Internet-based information and self-help programme has been developed and is currently evaluated for parents of children with burns. Two theses have been published (2013-2015): Andreas Lindahl (2013): Neuroendocrine stress response after burn trauma, and Josefin Bäckström (2013): Family members of patients with burns - experiences of a distressful episode.

Participants (besides members stated below):

From Department of Neuroscience Professor Lisa Ekselius, Josefin Bäckström, PhD, and Emelie Gauffin PhD student. From Department of Surgical Sciences, Plastic Surgery: Professor Bengt Gerdin, and Andreas Lindahl, PhD.

Collaborators:

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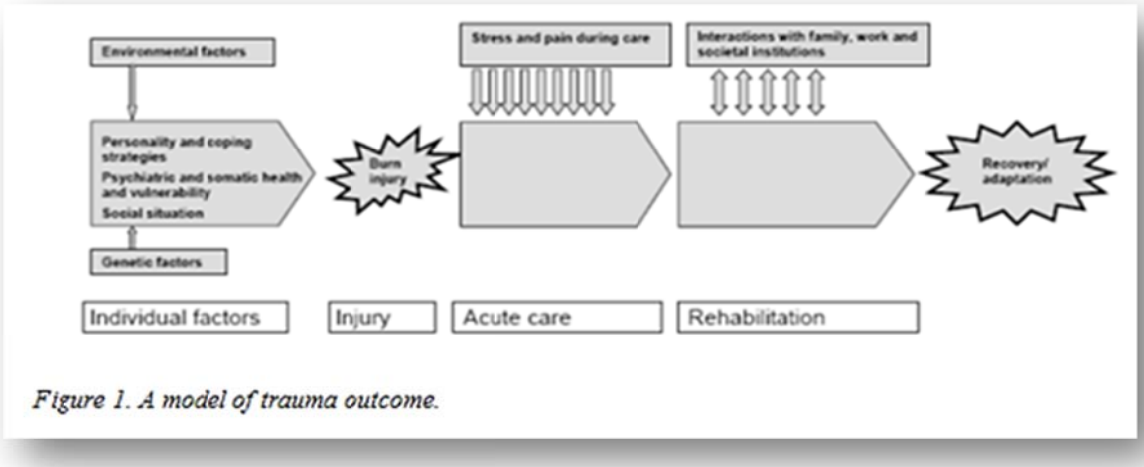

Figure 1. A model of trauma outcome.

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MSB (Swedish Civil Contingencies Agency)

Uppsala University Hospital (ALF)

The Swedish Society of Medicine (SLS)

Reconstructive Microsurgery Research Programme

Principal investigators: Andres Rodriguez and Maria Rydevik Mani

Within the area of reconstructive microsurgery several research projects are carried out.

Clinical Applied Anatomical Studies in Face transplantation and Facial Paralysis

This project is carried out in collaboration with the Department of Plastic Surgery of the University of Texas Southwestern Medical Center and University of Viena, Austria. Anatomical studies are performed to study the technical feasibility of the application of new techniques in the field of face transplantation and facial paralysis.

Virtual Planning in Microvascular Head and Neck Reconstruction

In collaboration with Maxillofacial Surgery and the Center of Image Analysis at Uppsala University a study is carried out to study the application of a new virtual planning system (UHASP) in microvascular reconstruction of the mandible using free vascularized fibula flap.

Clinical Studies in Facial Paralysis

In collaboration with the department of ENT and Electrophysiology, a study of the implications of different cranial nerves (V, XII, XI) in relation to the Facial Nerve (VII) is carried out by performing electrophysiological studies and Functional MRI to elucidate the cortical interconnections of this nerve and to analyze ways to increase the cortical plasticity after nerve transfers in facial paralysis.

Cancer Recurrence after Breast Reconstruction

Collaboration between department of general surgery (breast surgery) and department of oncology, Uppsala and Malmö, with the aim to evaluate potential risk of breast cancer recurrence after breast reconstruction. The project includes retrospective analysis of patients who was mastectomied in 1992-2009 and reconstructed between 2000 and 2009 as well as a prospective study arm.

Lymphoedema – risk of and treatment of lymphoedema

Evaluation of the risk of lymphoedema of the arm after microsurgery reconstruction of the breast and cephalic vein usage. Retrospective analysis of a cohort of already reconstructed patients as well as prospective study of patient operated 2014–2016. The project also includes evaluation of microsurgical treatment of lymphoedema by lymphnode transfer at the time of free flap reconstruction of the breast. The evaluation includes clinical measurements, displacement test, photographs and questionnaires.

A prospective,, randomised study on microsurgical treatment of lymphedema are set up and different treatment modalities are compared. Recruitment will start in 2017.

Quality of life, patient satisfaction and optimizing resources in breast reconstruction

The program includes different projects including the Swedish Breast Reconstruction Outcome (SweBRO) study which is a national study with representatives from all universities and regions in collaboration with Swedish Breast Cancer Group. The project aims to evaluate quality of life (QoL) and health economics in the long term perspective among 6 000 women with breastcancer operations in 2000, 2005 and 2010. Furthermore, in collaboration with Breast Cancer Surgery, Patient Reported and Clinical Outcomes Research Group in Bristol, United Kingdom. Development of the Swedish version of the questionnaire EORTC BRR-24. International collaboration between more than 15 countries for a common instrument to use for breast reconstruction. This project further includes studies of patients already reconstructed and comparison of different methods as well as a prospective study. Parameters evaluated are QoL, patient satisfaction, resource management and socioeconomic impact. In addition prospective studies are carried out comparing different reconstructive methods on perspectives of QoL and resourcemanagement.

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Bröstcancerfonden funding of Dr Svee´s PhD project (Risks for breastcancer recurrence) and SweBRO project including salary of post-doc

The Swedish Society of Medicine (SLS)

Bergholm och Erikssons stiftelse: Breastcancer recurrence after post mastectomy reconstruction

Thúreus Stipendium 2014 for the project “Incorporation of Fibula Flaps into a Virtual Cranio-Maxillofacial Planning System”

Nyström Amerika stipendium 2014-2016 for the research collaboration with University of Texas Southwestern Medical Center for anatomical studies in Face Transplantation.

FOU-Medel (Landstinget I Uppsala Län) 2014 for the research project “Hjärnbarkens omformbarhet vid plastikkirurgiska rekonstruktioner av leendet: En funtionell MR- och neurofysiologisk studie.

Uppsala University Hospital (ALF)

Disseration 2016

Fatemeh Jabbari. Reconstruction of the alveolar process in cleft patients.

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11) Radiology

Research group 1: PET/MR studies in metabolic and oncological diseases

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Project 1: Imiomics in PET-MR studies of the obesity-diabetes-atherosclerosis disease process

More studies about the associations between white and brown adipose tissue (amount, localization and metabolic activity) and present and future atherosclerosis (location, amount and degree of inflammation), and brain infarcts as the consequence of vulnerable plaques, are needed. The knowledge about the various genotypes and phenotypes of type 2 diabetes mellitus (T2DM), and the tissue-specific pertubations at different stages of the disease, are incomplete. Imiomics is an automated whole-body image analysis concept, including an image registration method that deforms all image data to a common coordinate system, so that the signal in each voxel is comparable between individuals and within an individual over time. It will in the present application be applied for automatic statistical analyses of whole-body data in one MRI and two PET/MR ongoing studies of T2DM and cardiovascular diseases. Whole-body PET-MRI scans will be performed for detailed analysis of the subjects' body composition, lipid homeostasis (by MRI) and tissue-specific glucose metabolism/inflammation (by FDG-PET). The image data will be integrated with the non-imaging data, including clinical and molecular data from relevant tissues and blood, using Imiomics. By this approach new findings that are difficult, or impossible, to detect with other methods, and that are important for future prevention and therapy strategies of T2DM and cardiovascular diseases, are anticipated to be found.

Project 2: Whole-body PET/MRI for detection, staging, characterization, prognostic estimation, and early therapy evaluation of tumors

Uppsala University installed a whole-body PET/MR equipment, funded by VR, in October 2014. The whole body approach has the potential to give information about different cell populations, and their response to therapy, in spread cancer. Whole-body PET/MR generates a lot of information.

The overarching aim is to improve detection, staging, characterisation, prognostic estimation and therapy evaluation of tumors by using the fully integrated whole-body PET/MR equipment. To reach this aim the following projects can be defined:

A. Validation of different whole-body PET/ MR parameters and investigation of the additional clinical value of PET/MR in oncology using data from the PET/MR equipment, the U-CAN cohort and surgery as references. Consecutive investigations with the PET/MR equipment in patients with different cancer diagnoes, i.e. gynaecological, colorectal and neuroendocrine tumours will be performed at diagnosis, during and after treatment according to the program of the U-CAN project.

B. Develop and validate a new imaging concept, Imiomics, for holistic, objective and automated analysis of whole-body imaging and non-imaging biomarkers in oncology. The first step of this project is to create a reference person. The image data must then lie in the same space, i.e. the image data has to be registered/matched/fused. This fusing process can be applied to a large number of healthy subjects, to create a mean shape or a normal reference person. Each pixel in this reference person then contains the distribution of all "normal" imaging parameters measured in the entire cohort. The idea of the open ended and a priori driven computer aided image analysis is to calculate the difference using all image data available from one patient compared to this "normal reference person" to facilitate detection of tumors. For early therapy evaluation of tumors, a similar comparison is performed between image data at diagnosis and during treatment. The introduction of molecular imaging (i.e. MRI and especially PET/CT) has caused a shift of paradigm which has lead to the possibility for measuring the biochemical activity in vivo of tumors. The whole body approach gives information of different cell populations, and their response to therapy, in spread cancer. The integrated PET/MR equipment will be used in oncological projects within U-CAN,

where PET and MRI used separately are established techniques, but the combination of modalities is anticipated to amplify the information. Validation of PET/MR methods and development of a new concept for computer aided diagnosis and therapy evaluation in oncology, using whole-body data from the PET/MR equipment, are key components for the project. PET/MR investigations will be performed within prospective protocols to guide sampling of tissues and to evaluate therapeutic strategies. We will also evaluate modern multimodality radiotherapy to explore combinations of radiation and targeted drugs in order to select the optimal therapy for individual patients and lesions within one patient. The information from the PET/MR investigations has also the protential to be of importance in supporting the national proton beam therapy facility, the Skandion Clinic, a collaboration between all counties of Sweden, which starts in Uppsala June 2015.The additional clinical value of PET/MR in oncology using data from the PET/MR equipment, the U-CAN cohort and surgery as references will be evaluated.

Members of the group during 2016

Joel Kullberg, Ass Professor

Jan Weis, docent, physicist

Tomas Bjerner, Ass Professor, MD

Charlotte Ebeling Barbier, MD

Robin Strand, Ass Professor

Filip Malmberg, Ass Professor

Lina Carlbom, PhD-student

Per Hammar, PhD-student

Emil Johansson, PhD-student

Jonathan Andersson, PhD-student

Catrin von Below, PhD-student

Simon Ekström, PhD-student

Elin Lundström, PhD-student

Therese Sjöholm, PhD-student

Research group 2: Neuroendocrine tumours (NETs) and endocrine tumours

Principal investigator: Anders Sundin

Neuroendocrine tumours (NETs) and endocrine tumours are challenging in the sense that they vary considerably in their characteristics. They may be functioning, i.e. producing hormones giving rise to clinical syndromes, or non-functioning without hormonal symptoms. The former usually present at an early stage when the tumour is small whereas the non-functioning tumours often present with local symptoms and are usually larger at diagnosis. Small-intestinal NETs may cause obstruction and venous ischemia. Most of the NETs are slow growing with low proliferation but a subgroup has higher proliferation rate and more aggressive clinical behaviour. Because of all these various characteristics the NET patients present at many varying tumour stages and, consequently, require very different imaging strategies utilising radiological and nuclear medicine imaging methods.

Based on the generally high somatostatin receptor expression in the low grade NETs and the elevated metabolic rate in the high grade NETs, imaging by positron emission tomography (PET) with 68Ga-lablled somatostatin receptor analogues and [18F]fluoro-deoxy-glucose, respectively, has become a standard during the last few years. PET is currently always performed together with diagnostic CT (PET/CT)

allowing for simultaneous functional and anatomical imaging work-up. Another PET tracer available for PET/CT is the amine precursor 11C-5-hydroxy-tryptophan, which is taken up by the NET cells and converted to serotonin, and is valuable in patients with tumours with low or absent somatostatin receptor expression.

A second area that has expanded during the last few years is Magnetic Resonance Imaging (MRI) especially with diffusion weighted imaging (DWI) and the development of whole-body imaging examination protocols. DWI in the area of NETs basically allows for imaging of high cellularity tissues, which is malignant tumours and increases the sensitivity for especially small tumour lesions. MRI has traditionally, for the sake of examination time, been restricted to examination of limited body-areas but with the current whole-body MRI protocols examination from the top of the head to the thighs may be completed within 45-60 minutes including intravenous contrast-enhancement and DWI.

Peptide receptor radio therapy (PRRT) with 177Lu-labelled somatostatin receptor analogues has become an important therapy option in patients with disseminated disease in whom conventional therapies fail. The number of therapy cycles that may be administered rely on the absorbed dose in the dose limiting normal organs – kidneys and bone marrow – and may be determined by dose calculations (dosimetry). Because 177Lu not only emits therapeutic beta radiation but also gamma that allows for gamma-camera examination (scintigraphy including SPECT) the absorbed doses to normal organs and tumours may be calculated. The original PRRT protocol of 4 cycles may because of this dosimetry whereby the accumulated absorbed doses in kidneys and bone marrow are registered, instead be personalized and about half of the patients receive more than 4 and up to about 10 PRRT cycles.

Organization

The group comprise radiologists, nuclear medicine physicians and physicists. The work is performed at the Departments of Nuclear Medicine, PETcentre and Radiology, Uppsala University Hospital involving Institutions of Surgical Sciences and Hospital Physics, Uppsala University.

Project 1: PET/CT and PET/MR diagnosis and therapy monitoring of neuroendocrine tumours

PET/CT with 68Ga-labelled somatostatin analogues, mainly 68Ga-DOTATOC, has replaced previous nuclear imaging of NETs with scintigraphy because of the better spatial resolution of the PET camera, the faster kinetics of the tracer and the better tumour-to-normal tissue image contrast. The well-established PET tracer 11C-5-hydroxy-tryptophan still has a role for patients with tumours with low or no somatostatin receptor expression. The tracers have, however, never been examined in the same patients in a head to head comparison.

The first study in this project is a retrospective evaluation of PET/CT with 11C-5-hydroxy-tryptophan in NET patients to assess its impact on primary tumour diagnosis, tumour staging and diagnosis of recurrent disease in comparison with results of surgery, histopathology, and follow-up imaging.

The second study utilises PET/MRI to compare the PET tracers 68Ga-DOTATOC and 11C-5-hydroxy-tryptophan in NET patients also in comparison with whole body MRI including DWI.

The third study constitutes a therapy monitoring trial. Firstly, a retrospective comparison is performed between 11C-5-hydroxy-tryptophan-PET/CT in patients before start and during treatment somatostatin analogue therapy to measure the therapy effects on PET as changes in 11C-5-hydroxy-tryptophan-tumour uptake (SUV) in correlation to conventional radiology (CT/MRI) with RECIST 1.1 criteria, biochemisty and clinical status. Secondly, in a prospective study patients undergoing PRRT with 177Lu-DOTATATE are examined by dynamic and static PET/CT with 68Ga-DOTATOC before therapy start and before the third cycle of PRRT in order to measure the changes in tumour transport rate (Ki) and the uptake (SUV) between examinations as a means to assess the therapy effect in relation to conventional radiology (CT/MRI) using the RECIST 1.1. criteria, biochemistry and clinical status.

Project 2: Imaging and dosimetry in PRRT with 177Lu-DOTATATE

In the first part of this project the absorbed tumour dose is related to various factors during PRRT mainly tumour shrinkage as evaluated by CT. Other aspects are the administered peptide (TATE), the specific activity of the 177Lu-DOTATATE preparation. This is performed for different NET types (pancreatic NETs, Small-intestinal NETs etc.)

In the second part, 68Ga-DOTATATE-PET/CT will be added to the dosimetry calculations based on repeated scintigraphy (including SPECT) during 177Lu-DOTATATE therapy. In order to assess the respective kinetics of the 177Lu-DOTATATE and the 68Ga-DOTATATE preparations, respectively, patients will receive both preparations and undergo scintigraphy and PET/CT during blood sampling for whole-blood and plasma pharmacokinetics. Because of the more precise absolute quantification and better spatial resolution provided by PET as compared to scintigraphy, higher precision in the dosimetry is anticipated as well as better appreciation of organ and tumour heterogeneity in this respect.

Projekt 3: PRRT in neuroendocrine tumours

The results of PRRT with 177Lu-DOTATE as monitored by organ dosimetry in order to administer the maximum number of therapy cycles to each patient are promising. A manuscript on a large study comprising 200 patients with various NETs was recently submitted for publication. However, many more patients have undergone PRRT that those in the study and it is therefore of great interest to assess also the results for these patients and to perform this for each NET type separately (pancreatic NETs, small bowel NETs etc.). Currently more than 100 patients with pancreatic NETs who have undergone PRRT are assessed for therapy outcome and, in a sub-analysis, for the relationship between absorbed radiation dose and therapy outcome. Outcome is evaluated by tumour size measurements according to RECIST 1.1. (CT/MRI) and best response, time to progression, progression free survival and overall survival will be determined. Further, the results will be assessed in patients small-intestinal NETs.

Projekt 4: Radiological and nuclear medicine imaging in adrenal tumours

Adrenal tumours are subject to imaging examinations for several reasons. CT or MRI of the abdomen/thorax, for reasons unrelated to adrenal disease, results in diagnosis of an adrenal tumour in approximately 1/25 patients and these, so called adrenal incidentalomas, needs to be assessed regarding malignancy (typically by imaging) and hormonal function (biochemistry).

One of the rare but feared tumours in the adrenals is adrenocortical cancer (ACC). In a large cohort of patients with ACC at the Uppsala, Karolinska and Sahlgrenska University Hospitals, patients who all had undergone preoperative CT were evaluated for primary tumour size, heterogeneity, contrast-enhancement, tumour invasion and patterns of metastasis.

A large cohort of ACC patients having undergone 11C-metomidate-PET/CT will be similarly assessed and the diagnostic accuracy compared to that of contrast-enhanced CT and MRI.

In patients with hypertension a subgroup suffers from aldosteronism because of adrenal hyperplasia or an adrenal tumour (Conn adenoma). In order to determine the treatment (systemic and surgical resection, respectively) the reason for aldosteronism needs to be established. Adrenal venous sampling of blood for hormonal analyses is the standard procedure to determine whether the increased aldosterone production relates to a unilateral adenoma or bilateral hyperplasia. This is an invasive, technically demanding and extremely operator dependent procedure and therefore often needs to be repeated because of failure to sample blood from both adrenals.

PET/CT with 11C-metomidate, that accumulates in adrenocortical tissues has been tried in several studies to characterise adrenal tumours and to localise Conn adenomas but is hampered by the approximately 0,5cm resolution of the PET camera that makes detection of small tumours difficult. Suppression of the

normal adrenocortical tissue by cortisone premedication has partially increased the imaging yield but further studies are necessary.

Future studies will concentrate on further developing 11C-metomidate-PET/CT, firstly in a joint project with Cambridge University, GB, to develop a 18F-labelled analogue 18F-etomidate with theoretically better imaging characteristics.

Members of the group during 2016

Anders Sundin, MD, PhD, Professor

Nicoleta Casta, PhD student

Sorgul Guven, PhD student

Ulrika Jahn, PhD student

Katarzyna Fröss-Baron, PhD, Researcher

Ezgi Elan, PhD student

Mattias Sandström, PhD Researcher

Mark Lubberink, PhD, Professor

Irina Velikyan, PhD, Ass Professor

Dan Granberg, MD, PhD, Ass Professor

Per Hellman, MD, PhD, Professor

Agencies that support the work/Funding

Start funding 1,500,000 Kr as new Professor of Clinical PET

Research group 3: Neuroradiology

Principal investigators: Elna-Marie Larsson, Johan Wikström

The neuroradiology research group performs studies on advanced imaging of central nervous system (CNS) disorders. Imaging of the CNS with magnetic resonance imaging (MRI) and computed tomography (CT) is rapidly developing in research and clinical applications. The methods allow investigation of structural as well as physiological and biochemical changes by diffusion MRI, perfusion CT and MRI and MR spectroscopy. The technique for endovascular treatment of cerebral and spinal disorders is another field of research.

The overall aim of our projects is to improve imaging for diagnosis and follow-up of disorders of the CNS with clinical application.

Members of the group during 2016

Elna-Marie Larsson, MD, Professor (and also Visiting Professor at Linköping University)
Johan Wikström, MD, Professor

Raili Raininko, MD, Professor Emerita

Sven Haller, MD, Visiting Associate Professor

Nuno Canto Moreira, MD, PhD

Ljubisa Borota, MD, PhD

Dragan Bajic, MD, PhD

David Fällmar, MD, PhD (dissertation 2016)

Ruta Nylander, MD, PhD student

Johannes Finnsson, MD, PhD (dissertation 2016)

Johanna Mårtensson, PhD student

Vilma Velickaite, PhD student

Maria Correia de Verdier, MD, PhD student

Markus Fahlström, PhD student

Niklas Hegerius, MD, PhD student

Anna Grabowska, MD, will be registered as PhD student

Ehab Mahmoud, MD

Christoffer Nyberg, MD, PhD student

Jussi Hellström, MD, PhD student

Project 1: Aging and dementia

PhD project Ruta Nylander. Assessment of white matter changes, infarctions, microbleeds and cerebral perfusion in an elderly population and comparison with cardiovascular risk factors, biochemical markers, silent myocardial infarctions, and cognitive function.

PhD project David Fällmar. Visual assessment of metabolism and perfusion in neurodegenerative dementia. Development of improved analysis of 18F-FDG PET and arterial spin labelling MR perfusion in patients with early dementia and comparison of these methods.

PhD project Vilma Velickaite. Automatic volumetry versus visual scoring of atrophy patterns in MRI of the brain in healthy aging compared with early dementia with cross-sectional and longitudinal evaluation. Comparison with cognitive testing.

Members of the project group during 2016

Elna-Marie Larsson, Ruta Nylander, David Fällmar, Vilma Velickaite, Sven Haller

Project 2: Brain tumours

PhD projects Markus Fahlström and Johanna Mårtensson. Study of advanced MRI methods for differential diagnosis between different tumour types and differential diagnosis between tumours and post therapeutic changes in the brain. Comparison of different cerebral perfusion MRI techniques for evaluation of brain tumours and normal appearing white matter preoperatively and during treatment monitoring. Improvement and evaluation of MR diffusion tractography for assessment of white matter tracts affected by brain tumours and other cerebral disorders.

Members of the project group during 2016

Elna-Marie Larsson, Johan Wikström, Raili Raininko, Markus Fahlström, Johanna Mårtensson, Nuno Canto Moreira, Jussi Hellström

Project 3: Cerebrovascular disease

PhD projects Maria Correia de Verdier and Niclas Hegerius. Development and evaluation of advanced MR-techniques for preoperative assessment and posttreatment monitoring of cerebral aneurysms and arteriovenous malformations.

Members of the project group during 2016

Johan Wikström, Maria Correia de Verdier, Niclas Hegerius, Ljubisa Borota

Project 4: Hereditary neurological diseases

PhD project Johannes Finnsson. Rare neurological hereditary disorders are studied with MRI of the brain, spinal cord and muscles including long-term longitudinal follow-up of patients and their relatives (persons-at-risk in genetic disorders).

Members of the project group during 2016

Raili Raininko, Johannes Finnsson

Miscellaneous projects

Collaboration with other clinical and pre-clinical research groups at Uppsala University

- Cortical activation studies (fMRI) of neuropsychology and psychiatric disorders.
- Trigeminal neuralgia: advanced MRI techniques at 3T and 7T
- Traumatic brain injury: PET/MRI and MRI
- MRI of hypoxic/ischemic brain injury in resuscitated cardiac arrest patients treated with hypothermia
- MRI of the brain in prematurely born babies
- Physiological MRI of patients with normal pressure hydrocephalus
- MRI of the brain and spinal cord in patients with multiple sclerosis
- MRI of the brain in epilepsy
- Endovascular treatment of cerebrovascular diseases – technical improvement and assessment
- Fetal MRI
- Advanced MRI of the placenta
- Correlative studies of MRI and protein expression in diffuse low-grade gliomas
- Subtle change detection and quantification in MRI of the brain

Members of the project group during 2016

Elna-Marie Larsson, Johan Wikström, Nuno Canto Moriea, Anna Grabowska, Dragan Bajic, Raili Raininko, Sven Haller, Ljubisa Borota, Ehab Mahmoud, Christoffer Nyberg

Collaboration with other universities in Sweden

Elna-Marie Larsson is visiting Professor and main supervisor for two PhD students at Linköping University, Sweden:
- *Ida Blystad:* Clinical applications of synthetic MRI of the brain
- *Charalampos Georgiopoulos*: Imaging studies of olfactory impairment in parkinsonism.

Agencies that support the work/Funding

The Swedish Cancer Society (Cancerfonden)

The Swedish Research Council (Vetenskapsrådet) (co-applicants)

Uppsala University Hospital (ALF)

Uppsala County

Research group 4: Uroradiology

Principal investigator: Maria Lönnemark

Research areas:

- Dose reduction at CT-examination of the urinary tract
- Optimization of radiologic examination in patients with gross hematuria
- CT-guided intervention
- CT-guided ablation of renal tumors
- Benefit of reconstructed 3D images in preoperativ planning
- Functional information in the CT-image
- Radiological follow up in patients with pancreatic transplants
- Nursing at CT examination

Members of the group during 2016

Anders Magnusson, Professor Emeritus

Pär Dahlman, MD

Allina Dimopoulou, MD

Gaute Hagen, MD

Malin Helenius, MD

Maria Lönnemark, Ass Professor, Director of Studies

Eva Lundqvist, PhD student

Monica Segelsjö, PhD student

Vanessa Acosta Ruiz, PhD student

Klara Sahlén, dr

Research group 5: Nuclear medicine and PET methodology

Principal investigator: Mark Lubberink, Jens Sörensen

Research in nuclear medicine & PET is primarily aimed at the development of new PET tracers and clinical PET methods, in order to meet clinical demands and facilitate clinical research, and at the diagnosis and treatment of neuroendocrine tumours. Our research covers the entire perspective from substance screening, through radiochemistry and pre-clinical validation, to clinical implementation (”bench to bedside”). Our clinical research focuses on the use of PET to create the prerequisites for personalised medicine, for example in relation to molecular radiotherapy and other high-cost cancer therapies. Furthermore, our research aims to increase the understanding of molecular processes related to various diseases, such as for example the development of multimodality imaging using PET-MRI in relation to metabolic diseases and cancer. To be able to offer a complete platform for the use of PET and PET-MRI in clinical research and drug development, the PET community at Uppsala University and Uppsala university hospital has a high competence in all aspects of PET methodology: chemistry, physics, data-analysis, etc. The research in the nuclear medicine & PET group at the Department of Surgical sciences is performed in close callobration with the PET-MRI group, the pre-clinical PET platform at the Department of Medicinal Chemistry, the Section of Biomedical radiation sciences at the Department of Genetics and Pathology, and the PET centre at Uppsala university hospital, as well as a number of clinical research groups at Uppsala university and Uppsala university hospital.

Members of the group during 2016

Jens Sörensen, PhD, Senior Nuclear Medicine Consultant, Professor

Mark Lubberink, PhD, Senior Medical Physicist, Professor

Irina Velikyan, PhD, Hospital Chemist, Associate Professor

Mattias Sandström, PhD, Senior Medical Physicist

Kerstin Heurling, PhD, Research Scientist

Lieuwe Appel, PhD, Research Scientist

Anders Wall, PhD, Research Scientist

Torsten Danfors, PhD, Senior Consultant in Nuclear Medicine and Neurology

Cecilia Wassberg, PhD, Senior Consultant in Radiology

Hadis Honarvar, PhD, postdoc

Enn Maripuu, Senior Medical Physicist

Tanja Kero, Senior Nuclear Medicine Consultant, PhD student

Ezgi Ilan, Medical Physicist, PhD student

My Jonasson, Physicist, PhD student

Naresh Regula, PhD student

Johan Lilja, PhD student

Jonny Nordström, Medical Physicist, PhD student

Dan Sandberg, PhD student

Joao Sousa, PhD student

Elin Lindström, Research student

Other graduate students with JS, ML or TD as advisor

David Fällmar, Radiology Resident, PhD student

Emil Johansson, Medical Physicist, PhD student

Eric Grönlund, Medical Physicist, PhD student

Lina Carlbom, Radiology Resident, PhD student

Jonathan Andersson, PhD student

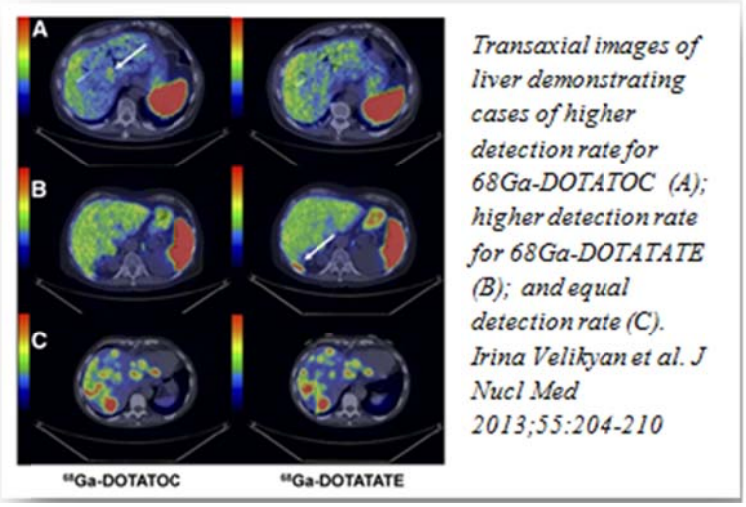
Mikko Anniko, PhD student

Andreas Tolf, PhD student

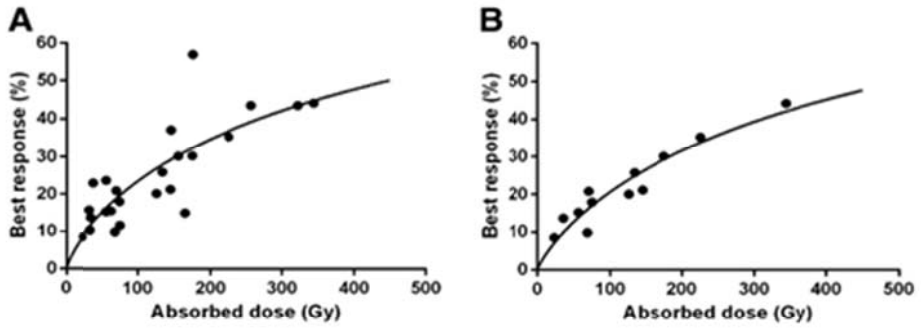
Anders Petter Carlsson, PhD student

Project 1: Diagnostics and therapy of neuroendocrine tumours

- Patient-specific dosimetry for optimization of molecular radiotherapy of neuroendocrine tumours with ^{177}Lu-DOTATATE
- Use of ^{68}Ga-DOTATOC and DOTATATE PET for patient selection, response evaluation, and improved dosimetry of ^{177}Lu-DOTATATE therapy
- Dose-response evaluation of ^{177}Lu-DOTATATE therapy



Transaxial images of liver demonstrating cases of higher detection rate for 68Ga-DOTATOC (A); higher detection rate for 68Ga-DOTATATE (B); and equal detection rate (C). Irina Velikyan et al. J Nucl Med 2013;55:204-210



Tumor dose–response relationship for patients with PNETs treated with PRRT using 177Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B). Ezgi Ilan et al. J Nucl Med 2015;56:177-182

- Evaluation of ^{11}C-5HTP and ^{68}Ga-DOTATOC PET-MRI
- Optimization of specific activity of ^{68}Ga-DOTATOC

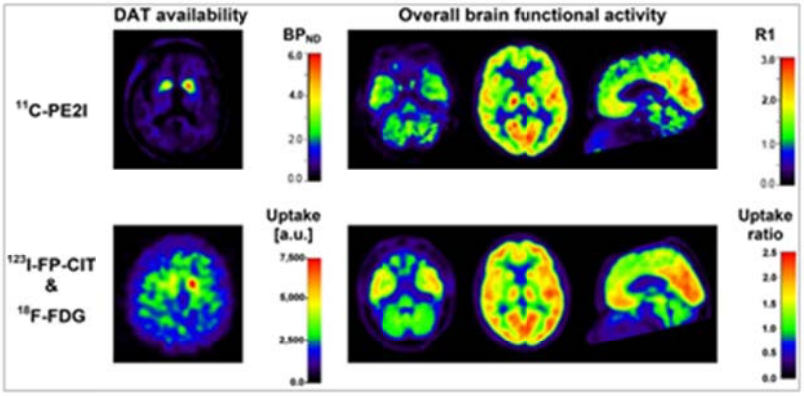
Members of the group

Anders Sundin, Mattias Sandström, Ulrike Garske, Mark Lubberink, Irina Velikyan, Ezgi Ilan, Ulrika Jahn

Project 2: PET & Neurology

Projects include:

- Evaluation of [^{18}F]THK5317 as a PET tracer for tau pathology in Alzheimer's disease, in collaboration with Professor Nordberg, Karolinska Institutet
- Development of [^{11}C]PE2I-PET in the differential diagnosis of Parkinsonism

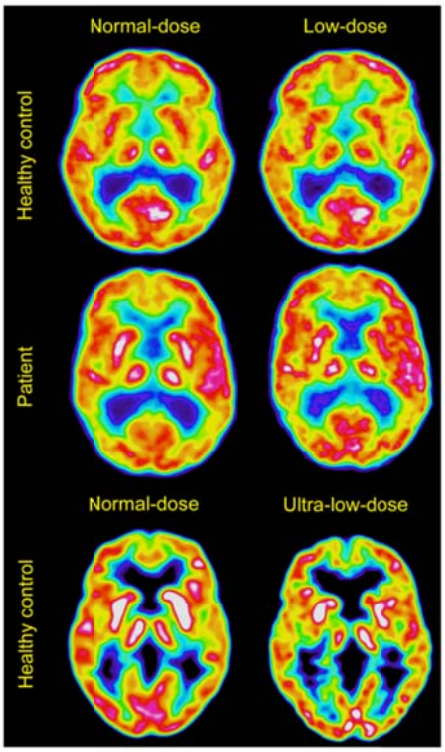


Parametric images of ^{11}C-PE2I relative delivery (R_1) and BP_{ND} compared with ^{123}I-FP-CIT and ^{18}F-FDG images, illustrating DAT availability and overall brain functional activity in a patient diagnosed with multiple systems atrophy with atrophy related to cerebellum. a.u. = arbitrary unit. Lieuwe Appel et al. J Nucl Med 2015;56:234-242 (publication 36). The images show that a single ^{11}C-PE2I scan can give the same information as a dual-scan protocol with DATscan and FDG, whilst resulting in a considerable reduced radiation dose.

- Characterization of ^{18}F-flutemetamol as a β-amyloid PET imaging ligand

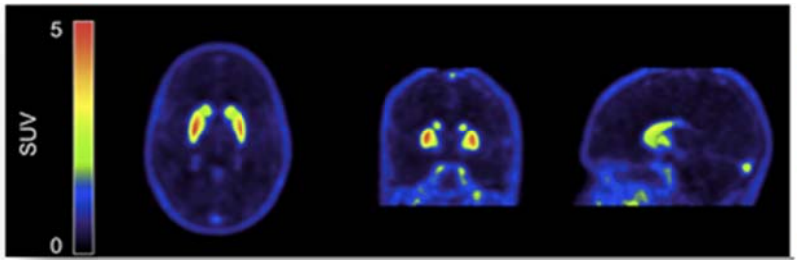
Cover of The Journal of Nuclear Medicine, July 2016: 3D-SSP maximum-intensity results of Aβ+ 18F-flutemetamol image. (Upper left) PET values only. (Upper right) PET values with threshold set so that MR information is visible in areas in which PET values are below threshold. (Lower left) PET values with opacity set to 50%, revealing patient-specific MR information. (Lower right) PET values with opacity and threshold set. Lilja et al, J Nucl Med 2016; 57: 1078-1083.

- PET and social anxiety disorder; several studies in collaboration with Professor Mats Fredrikson and Professor Tomas Furmark, Uppsala University
- Validation of true low-dose ^{18}F-FDG of the brain.



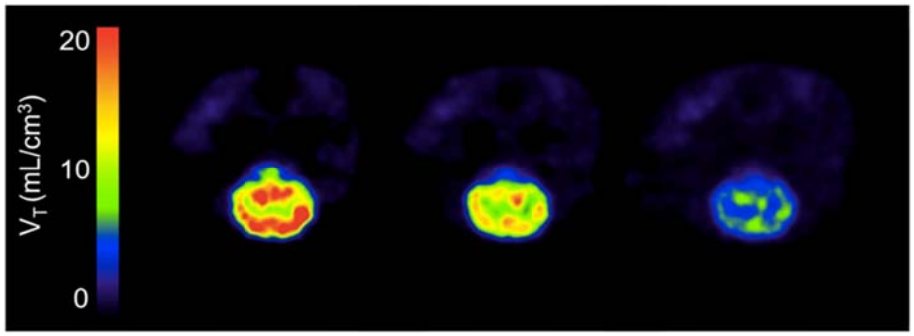
Healthy control (top), AD patient (middle) with normal dose images to the left and 25% of normal dose images to the right. Bottom row shows normal and ultra low dose (10% of normal) images of a healthy control. The images show that the dose of FDG required for evaluating cortical glucose metabolism can be reduced considerably without loss of diagnostic accuracy. David Fällmar et al, Am J Nucl Med Mol Imaging 2016; 6(5): 269-276.

- Development of ^{11}C-LuAE92686 as a PET tracer for PDE10A in collaboration with Lundbeck AS, 'Uppsala University



^{11}C-Lu AE92686 uptake in human brain (sum image 15–90 min after injection). Jan Kehler et al. J Nucl Med 2014;55:1513-1518

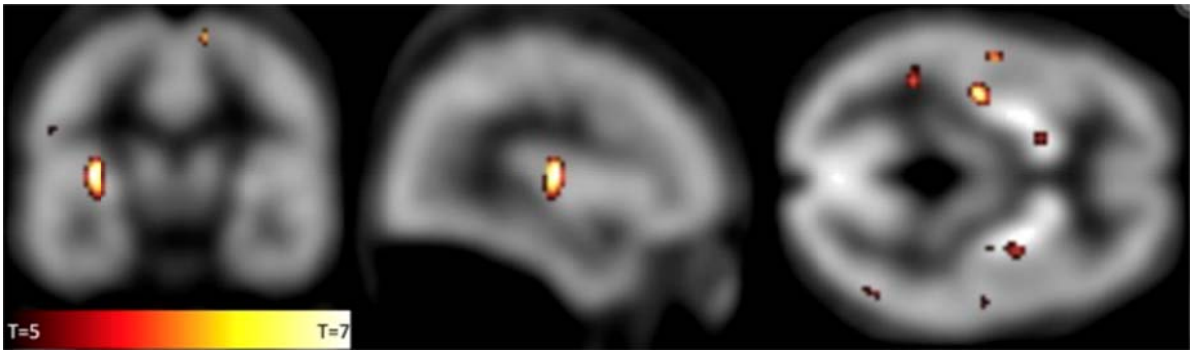
- SVCA function in epileptic patients using ^{11}C-UCBA-PET-MRI, and pre-clinical evaluation.



Parametric [11C]UCB-A Logan VT images of a single pig brain at baseline (left) and after two different doses of an SV2A-targeting drug resulting in 52% and 81% occupancy, respectively, showing dose-dependent blocking. Estrada et al, Nucl Med Biol 2016; 43:325-332.

- Evaluation of stemcell-treated MS patients with ^{11}C-Deprenyl, ^{11}C-PK11195 and ^{15}O-water, in collaboration with Joakim Burman, Uppsala University
- Neuroinflammation and tau in neurotrauma patients: ^{11}C-PK11195 and ^{18}F-THK5317, in collaboration with Professor Niklas Marklund, Uppsala University

- Brain Neurokinin-1 Receptor Availability in Chronic Tennis Elbow.



Regions with Significantly Lower NK1-receptor availability in patients with chronic tennis elbow compared to healthy controls, at a Family Wise Error Corrected p-value of <0.05 in the insula. The color bar indicates t-values. The background image is the average net uptake rate image of all patients and controls (note the absence of NK1-receptors in the cerebellum). Linnman et al, PloS ONE 2016; 11(9): e0161563.

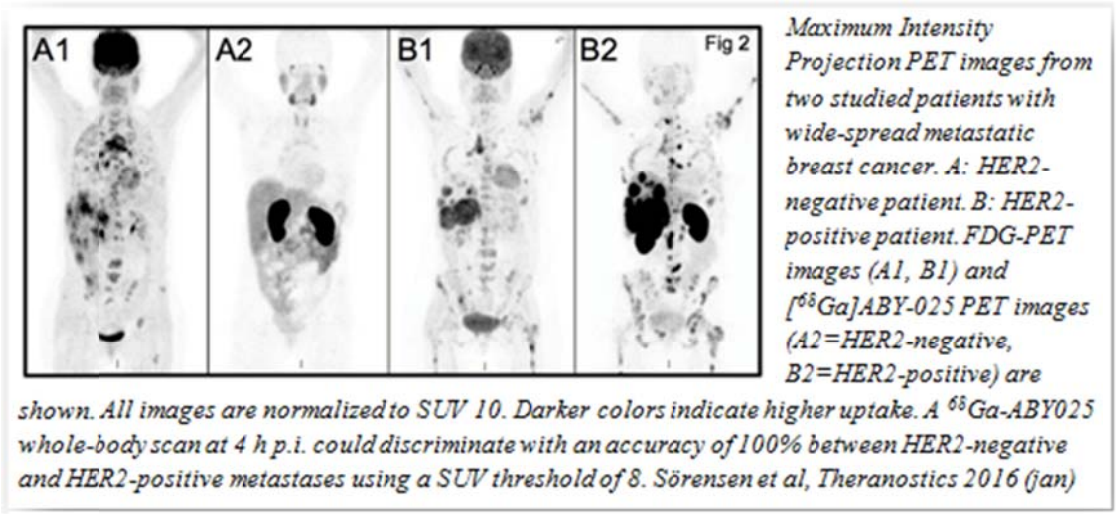
Members of the group

Jens Sörensen, Mark Lubberink, Torsten Danfors, Kerstin Heurling, Lieuwe Appel, Anders Wall, Tanja Kero, Ezgi Ilan, My Jonasson, Johan Lilja, Joao Sousa, David Fällmar

Project 3: PET & Oncology

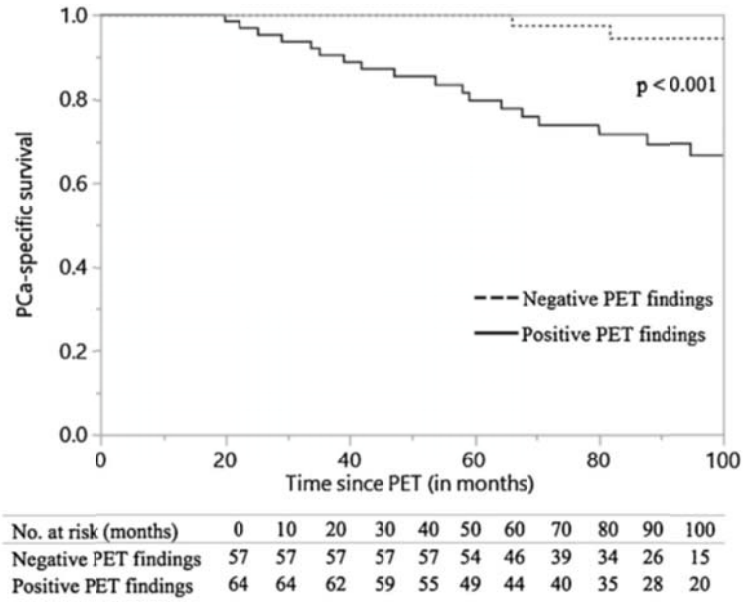
Projects include:

- Development and validation of [^{68}Ga]ABY025 Affibody molecule for diagnosis of HER2-positive breast cancer



Maximum Intensity Projection PET images from two studied patients with wide-spread metastatic breast cancer. A: HER2-negative patient. B: HER2-positive patient. FDG-PET images (A1, B1) and [^{68}Ga]ABY-025 PET images (A2=HER2-negative, B2=HER2-positive) are shown. All images are normalized to SUV 10. Darker colors indicate higher uptake. A ^{68}Ga-ABY025 whole-body scan at 4 h p.i. could discriminate with an accuracy of 100% between HER2-negative and HER2-positive metastases using a SUV threshold of 8. Sörensen et al, Theranostics 2016 (jan)

- Development of ^{68}Ga-labelled PET tracers for oncology
- Reproducibility of ^{18}F-fluoride PET
- 11C-acetate PET/CT and prostate cancer-specific survival in patients with biochemical relapse after prostatectomy



Increased survival in patients with negative ^{11}C-acetate PET: Kaplan-Meier survival curves in patients with negative and positive 11C-acetate PET findings. The time between the date of 11Cacetate PET and the date of PCa-specific death was considered PCa-specific survival. Regula et al, Eur J Nucl Med Mol Imaging 2016; 43:2131-2138.

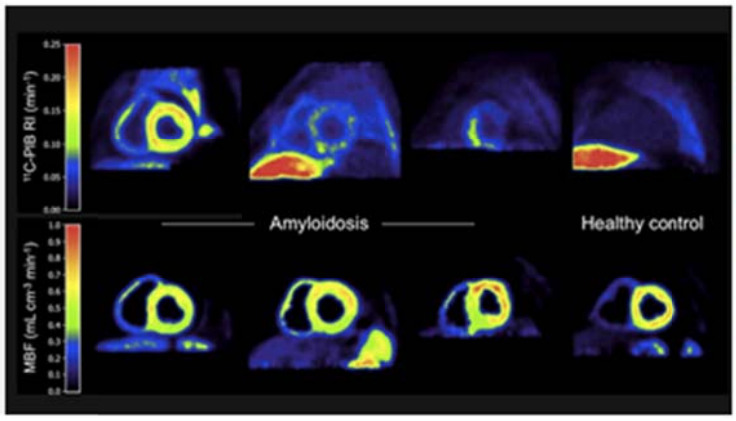
Members of the group

Jens Sörensen, Irina Velikyan, Mark Lubberink, Lieuwe Appel, Naresh Regula, Dan Sandberg, Cecilia Wassberg

Project 4: PET & Cardiology

Projects include:

- Clinical evaluation of ^{15}O-water-PET, in collaboration with VUmc Amsterdam and Århus University Hospital
- ^{11}C-PIB for diagnosis of cardiac amyloidosis. Validation of simplified methods. Sensitivity and specificity in AL and ATTR amyloidosis compared to hypertrophic myocardiopathy and healthy controls.



Short-axis images of ^{11}C-PIB RI and MBF in (left to right) cardiac amyloidosis patients with high, intermediate, and partially increased ^{11}C-PIB retention and a healthy control. Gunnar Antoni et al. J Nucl Med 2013;54:213-220

- Comparison of regadenason and adenosine in pharmacological stress ^{15}O-water PET, in collaboration with Turku PET Centre.
- Measurement of cardiac geometry and function using ^{15}O-water PET. PhD project Jonny Nordström. Collaboration with Århus University and Brigham and Women's Hospital, Boston.
- Evaluation of prognostic impact of ^{15}O-water PET in hypertropic cardiomyopathy treated with ICD. Collaboration with Peter Magnusson, Region Gävleborg.

- LVregurge: effects of regurgitation on myocardial blood flow and metabolism. PI: Frank Flachskampf.

Members of the group
Jens Sörensen, Tanja Kero, Mark Lubberink, Jonny Nordström, Gunnar Antoni (Medicinal Chemistry), Hans Harms (Århus University / Brigham and Women's Hospital Boston), Lars Tolbod (Århus University).

Project 5: Other applications of PET

Projects include:

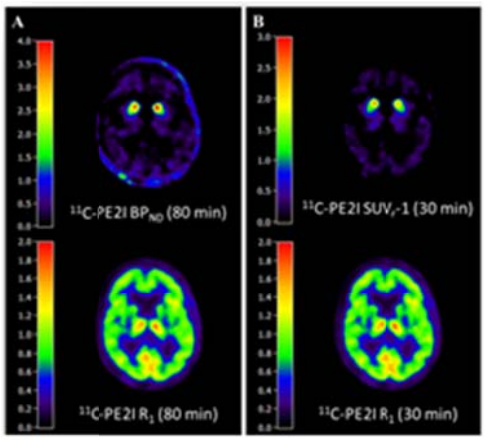
- Use of ^{18}F-fluoride PET in hip transplants, in collaboration with Gösta Ullmark (Gävle) and Professor Hans Mallmin
- Validation of ^{11}C-HTP as a marker for beta cells in the human pancreas, in collaboration with Professor Olle Korsgren and others

Members of the group
Jens Sörensen, Mark Lubberink, Enn Maripuu, Marie Berglund, Lina Carlbom

Project 6: PET methodology and physics

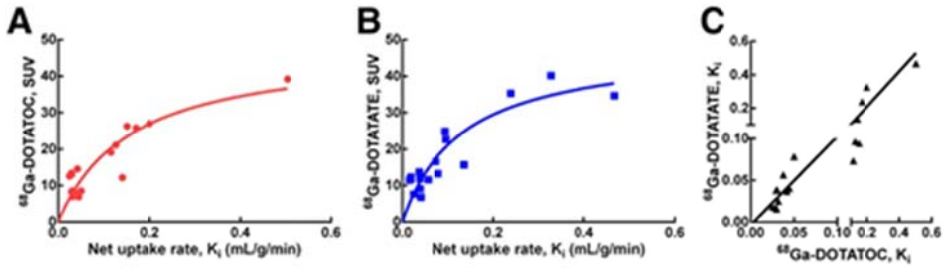
Projects include:

- A clinically feasible protocol with fully automated processing of dynamic ^{11}C-PE2I PET scans for calculation of relative cerebral blood flow and dopamine transporter availability images



Patient with clinically diagnosed multiple system atrophy. A) BP_{ND} and R_1 parametric images of an 80 min ^{11}C-PE2I scan with co-registered MRI-based cerebellum reference, B) SUV_r-1 and R_1 parametric images of a 30 min scan with automatically obtained SVCA reference. Jonasson et al, Neuroreceptor Mapping 2014

- Estimation of left ventricular ejection fraction based on parametric ^{15}O-water blood volume images: 5D PET
- Validation of quantitative dynamic PET-MRI scans in cardiology, neurology and oncology
- Development and validation of tracer kinetic analysis of various PET tracers (^{18}F-flutemetamol, ^{18}F-THK5317, ^{68}Ga-DOTATATE, ^{68}Ga-ABY025, ^{11}C-PIB in amyloidosis, etc.)



SUV is presented as function of net internalisation rate K_i, determined by tracer kinetic modelling of dynamic PET data, in tumors for ^{68}Ga-DOTATOC (A) and ^{68}Ga-DOTATATE (B). Irina Velikyan et al. J Nucl Med 2013;55:204-210. This data shows that SUV does not correlate linearly with K_i and can probably not be interpreted as a marker of somatostatin receptor density.

- Dosimetry and biodistribution of new **P**ET tracers (^{68}Ga-ABY025, ^{68}Ga-DO**T**ATOC, ^{68}Ga-DOTATATE).
- Whole-body parametric glucose consumption imaging using serial ^{18}F-FDG **P**ET-MRI scans

Members of the group

Mark Lubberink, Jens Sörensen, Tanja Kero, Jonny Nordström, Mattias Sandström, Joao Sousa, Kerstin Heurling, Ezgi Ilan, Johan Lilja, Emil Johansson, My Jonasson

Agencies that support the work/Funding

Cancerfonden

Parkinsonfonden

Hjärt-Lungfonden

Bröstcancerfonden

ALF

Research group 6: Interventional Radiology

Principal investigator: Rickard Nyman

Members of the group during 2016

Rickard Nyman, Professor

Pär Gerwins, Professor

Charlotte Ebeling Barbier, MD PhD

Lars-Gunnar Eriksson, MD PhD

Hampus Eklöf, MD PhD

Kerstin Rosenqvist, MD

Collaboration

MD PhD Dan Granberg Endokrinonkology

MD PhD Per Sangfelt och MD PhD Fredrik Rorsman Gastroenterology

Professor Hans Lennernäs, MD Elsa Lilienberg, Doktorand Ilse Dubbelboer Farmacology institution. Professor Per Stål, Gastoenterology, Dr Omar Karalli, Radiology, Huddinge sjukhus.

DD PhD Teus van der Laar, UMCG, Groningen. MD PhD Dag Nyholm, Neurologen.

Professor Magnus Sundbom och MD Mikael Ljungdahl, MD Eladio Cabrera kirurgen

Professor Bengt Fellström, MD PhD Hans Furuland, njurmedicin

Project 1: Radio embolization of liver tumors – effect and knowledge

Background: Liver tumors can be treated with local radiological interventional technique. Arteria hepatica is catheterized and embolic agent is infused closed to the tumor. High doses can be local administrated, which minimize the systemic effect. Chemoembolization has been performed for decades, but radio embolization is a quiet recent method.

Aim: Analyze the treatment effect of radio embolization.

Material and methods: All patients who have had radio embolization with Yttrium-90-microspheres during the period 2006-2013 are included. Retrospective evaluation of survival, tumor response, liver function and complications will be analyzed.

Members of the group during 2016

Charlotte Ebeling Barbier, Med PhD

Rickard Nyman, Professor

Ulrike Garske, Med PhD

Dan Granberg, Med PhD

Project 2: Treatment with transjugular intrahepatic portosystemic shunt (TIPS) in patients with portal hypertension.

Background: In liver cirrhosis the blood flow through the portal vein and liver is reduced resulting in portal hypertension. This will result dilated collateral veins in the abdomen and around the esophagus, which can cause life threatening bleeding. The portal hypertension can also cause substantial problem with ascites. By creating a shunt between the portal vein and the inferior vena cava (TIPS) the pressure in the system can be reduced with less risk of bleeding and reduction of the ascites. The result has been improved due to improved technique and better covered stents. More knowledge is needed to better understand which patient will benefits the most and when the treatment should be given. Hepatic encephalopathy is common seen after the procedure and there is a need to better understand how this can be avoided.

All patients are registered in a nationwide register, the Swedish portal hypertension registry (SPHT-register). The effect on rebleeding, reintervention, ascites, liver function, survival, encephalopathy, complications will be studied.

Members of the group during 2016

Rickard Nyman, Professor

Fredrik Rorsman, PhD

Per Sangfelt, PhD

Charlotte Ebeling-Barbier, PhD

Lars-Gunnar Eriksson, PhD

Kerstin Rosenqvist, MD

Reza Sheikhi, MD

Project 3: In vivo Drug Delivery Performance of Lipiodol-based Emulsion or Drug-eluting Beads in Patients with Hepatocellular Carcinoma

Primary liver cancer is in 90 % of the cases hepatocellular carcinoma (HCC) and is strongly associated with liver cirrhosis. The incidence is increasing in the industrial countries due to obesity and steatosis. The disease has a bad prognosis and is the third cause to cancer related death in the world.

Doxorubicin (DOX) delivered in a lipiodol-based emulsion (LIPDOX) or in drug-eluting beads (DEBDOX) is used as palliative treatment in patients with intermediate-stage hepatocellular carcinoma (HCC). The primary objective of this study was to evaluate the in vivo delivery performance of DOX from LIPDOX or DEBDOX in HCC patients using the local and systemic pharmacokinetics of DOX and its main metabolite doxorubicinol (DOXol). Urinary excretion of DOX and DOXol, and their short-term safety and anti-tumor effects were also evaluated. In this open, prospective, non-randomized multi-center study, LIPDOX (n=13) or DEBDOX (n=12) were injected into the feeding arteries of the tumor. Local (vena cava/hepatic vein orifice) and systemic (peripheral vein) plasma concentrations of DOX and DOXol were determined in samples obtained up to 6 h and 7 days after treatment. Tumor response was assessed using computed tomography or magnetic resonance imaging. The Cmax and AUC0–24 h for DOX was 5.6-fold and 2.4-fold higher, respectively, in LIPDOX vs DEBDOX recipients ($p < 0.001$). After 6 h, the respective mean proportions of the dose remaining in the liver or drug-delivery system (DDS) were 49% for LIPDOX and 88% for DEBDOX. LIPDOX releases DOX faster than DEBDOX in HCC patients and provides more extensive local and systemic exposure (AUC) to DOX and DOXol initially (0–7 days). DEBDOX formulation has a release and distribution of DOX that is more restricted and controlled than LIPDOX.

Members of the group during 2016

Hans Lennernäs, Professor, Farmakological institution

Elsa Lilienberg, MD, Farmakological institution

Ilse Dubbelboer, MD, Farmakological institution

Per Stål, Professor, Gastoenterology, Huddinge sjukhus

Omar Karalli, MD, Radiology, Huddinge sjukhus.

Charlotte Ebeling Barbier, MD

Project 4: Post Market Clinical Follow-Up study on the T-Port® Enteral Access System

Multicenter, non-randomized, open labelled, observational study where Parkinson patients who have been prescribed the T-Port as the access system for delivery of Duodopa to the jejunum will be monitored carefully and systemically the first year following the implantation.

Members of the group during 2016

Teus van der Laar, MD PhD, UMCG, Groningen.

Dag Nyholm, MD PhD, Neurologen.

Rickard Nyman, Professor

Project 5: Percutaneous Endoscopic Gastrostomy (PEG) compared with Radiological inserted Gastrostomy (RIG): A prospective, randomized study.

In patients with swallowing problems a gastrostomy might be a necessity in order to be able to give enough nutrition. Earlier this was done through open surgery, but since several decades this has been performed by minimal invasive technique with either percutaneous endoscopic gastrostomy (PEG) or radiological inserted gastrostomy (RIG). In PEG gastroscopy and in RIR x-ray is used for placing the tube. Both methods have its advantage and disadvantage, but there is not enough evidence for choosing the best method for a certain patient group.

This is a prospective randomized study in 150 patients during a 3 year period. The two methods efficacy and complications will be evaluated.

Members of the group during 2016

Magnus Sundbom, Professor

Mikael Ljungdahl, MD PhD

Eladio Cabrera kirurgen, MD

Rickard Nyman, Professor

Project 6: Pilot Study on the Use of a Novel Hemodynamic Access System for patient on Haemodialysis. The HAS-01 Study

The hemodynamic access port (HAS-port) for hemodialysis has been developed to address some of these problems. The development of the product builds upon the experience from the clinical use of the CE-marked product T-Port© Enteral Access System (T-Port), which was developed for catheter access to the stomach and small intestine. The T-port has mainly been used for continuous infusion of L-Dopa to the small intestine in patients with severe symptoms of Parkinson's disease. The port has a perforated plate that lies subcutaneous allowing the tissue to grow into it and stabilizing the port with creation of a tissue seal against bacterial invasion. The HAS-port will replace the catheter penetration of the skin and thereby possibly reducing the risk for bacteria invasion around the catheter. With the special designed mechanism to open and close the port before and after dialysis the risk of bacterial contamination during handling of the connection is believed to be reduced. Therefore, it is believed that the port can facilitate the dialysis and reduce the risk for serious infection. If functional problems occurs with the catheter the port can be easily opened in an aseptic way allowing for investigation of the cause with exchanged of catheter and/or performing procedures such as thrombolysis, balloon dilation or stripping of fibrous sheath. As the opening of the port means no interference with the skin the risk for bacteria contamination is believed to be reduced.

The hypothesis is that the port will heal in uneventfully during the first month and that the central venous catheter (CVC) will maintain acceptable blood flow (> 300 ml/min) on the dialysis machine during 6 months. The number of complications (inflectional or functional) that results in hospitalization or intervention during 6 months due to the use of HAS-port for hemodialysis will be analyzed and compared with historical data of conventional CVC catheters. Incidence for bacteremia is at an average to be between 2-6/1000 catheter days, which means that the number of bacteremia with 10 HAS-port during 6 months should not be more than 10 and most likely stay less than 5 episodes.

Members of the group during 2016

Bengt Fellström, Professor, njurmedicin

Hans Furuland, MD PhD, njurmedicin

Rickard Nyman, Professor

Johan Ryden, Transcutan AB

Research group 7: Musculoskeletal Radiology

Principal investigator: Adel Shalabi

Project 1: Low-dose CT in comparison with plain x-ray of musculoskeletal disorders.

Spine and pelvic fractures are usually caused by high-energy trauma, frequently following motor vehicle, equestrian accidents, or falls from heights. Primary investigation after high-energy trauma in our hospital is a CT scan with separate reconstructions of the pelvic bone. This investigation is usually sufficient for a detailed description of any pelvic fracture, i.e. both acetabular fracture and injuries involving the pelvic ring. CT with thin slices and multi-planar reconstructions has a significantly higher sensitivity for detection and correct classification of fractures than plain radiographs, CR. Postoperative radiology is performed to verify reduction of joint surfaces, reconstruction of ring integrity, and placement of hardware. CR exposes patients to a low radiation dose. However, the technique is problematic as evaluation of malalignment and screw placement is projection dependent. Furthermore, implanted hardware may obscure important structures. Conventional CT scanning has a higher sensitivity for detection of articular hardware penetration of the joint space and residual loose fragments as well as detecting non-anatomical articular reduction. On the other hand the major drawback is the higher radiation exposure compared to CR. Low dose CT, LDCT, has proven effective in postoperative evaluation in spine surgery. Similarly, postoperative evaluation after pelvic fracture involves mainly bone and hardware why LDCT could be of value also for these patients.

The aims of this study were to compare LDCT with CR for postoperative evaluation after operated pelvic fractures in terms of hardware positioning, fracture reduction, image quality and time required for reviewing. The radiation exposure was also calculated for the two techniques.

Project 2: long term (20-25 years) Follow-up Study of Anterior Cruciate Ligament reconstruction. Radiological findings compared with clinical outcome.

The anterior cruciate ligament (ACL) is commonly injured, with a reported injury rate of 0.38 per 1000 individuals. ACL injury often causes knee joint laxity and instability, leading to pain and varying levels of disability ranging from limited sports participation to difficulties performing activities of daily living. An ACL injury is also associated with meniscal tears and posttraumatic osteoarthritis (OA) of the knee. The prevalence of reported osteoarthritis (OA) after anterior cruciate ligament (ACL) injuries ranges between 10% and 90% in different studies, and it is unclear how ACL reconstruction affects the prevention of OA. When the prevalence of OA after ACL reconstruction is compared between the reconstructed and the healthy noninjured knee, most authors have found more cases of OA in the reconstructed knee . However, the cause of OA is multifactorial, and long-term outcomes after an ACL injury are largely influenced by the presence of associated injuries, such as meniscus and cartilage injuries. It has been reported that meniscus injuries requiring resection increase the risk of an inferior functional result and OA after ACL reconstruction. High body mass index (BMI) might also influence the risk of OA after an ACL injury. Whether the time elapsed between injury and ACL reconstruction affects the prevalence of OA is not clear. The choice of graft for ACL reconstruction has been discussed as one of the factors influencing long-term morbidity. Bone–patellar tendon–bone (BPTB) grafts have been reported to result in more cases of patella

infera and to cause more problems with kneeling and other patellofemoral problems, including OA, compared with hamstring tendon grafts. However there are no clear consensus regarding radiographic OA differences between grafttypes. Today people are living longer and it is therefore interesting to see how the cruciate ligament surgery affect knee function in the longer term.

The major purpose is to report a long follow-up evaluation of ACL reconstruction and comparing radiological findings on plain x-ray and MRI with IKDC, KT 1000, Werner score, KOOS (clinical assessment).

Project 3: Anatomy and function of Anterior Cruciate Ligament and thigh muscles in healthy elite female handballs players examines with CT, MRI and clinical examinations.

Anterior cruciate ligament (ACL) tears are common among younger persons involved in different sports activity. These injuries are functionally disabling and predispose to subsequent injuries and early onset of osteoarthritis in the knee. The ACL-deficient knee has an impaired muscle function with diminished muscle strength, often measured as maximal torque. The reasons for this are both neuromuscular, with impaired muscular activation discussed in a review article by Ingersoll et al 2008, and muscular atrophy. It is therefore of importance to assess the effect of ACL-injuries on muscular development not at least to develop the best strategies for rehabilitation. ACl-injuries are often accompanied by meniscal tear which like ACL-injuries per se can induce atrophy of quadriceps.

Contralateral leg for comparison: lateral asymmetry and dominance

Most studies use the contralateral limb as comparison in evaluating changes in muscle size and strength following ACL rupture. This is not without problems. The underlying assumption that both limbs were equal in size and muscle strength prior to injury is not fully justified. There are indications that there might be a difference related to limb dominance. The concept of limb dominance in the lower extremity is however controversial. Van der Harst et al in a study of leg kinematics and kinetics in landing from a single-leg hop defined the dominant leg as the leg with the biggest horizontal hop distance. This is in accordance with the view that the heaviest and probably strongest leg is considered as dominant. Most investigators on the other hand, seem to consider the leg preferred for kicking a ball as the dominant leg. If the leg preferred for kicking, which for the majority of people is the right leg, is defined as dominant, the contralateral leg would serve as supporting and weight bearing which might explain why the left leg often is heavier. Considering the different views of leg dominance it is not surprising that there is no consensus regarding difference in muscle cross sectional area (CSA) or volume comparing dominant and non-dominant leg.

The reduction in maximal voluntary contraction force (MVC) of quadriceps in the ACL-deficient knee is not only due to atrophy but also to arthrogenic muscle inhibition with the effect of reduced maximal voluntary muscular activation (MVA) and it has been shown that this reduction is bilateral.

Asymmetry due to limb dominance implies that the effect of ACL-injury might be different in right-sided and left-sided injuries which should be taken in account when analyzing the effects. Moreover there is growing evidence that gender differences in muscular strength and activation impacts the risk of attaining an ACL-injury and therefore gender difference is of interest in evaluating the effect of an injury

Purpose of study

The purpose of the study is to study muscle using CT and MRI measured CSA of the thigh muscles. We also wanted to analyze the feasibility of using the contralateral limb as control in studies of the effect of ACL-injuries. In doing this we had to take into consideration the effect of limb dominance. Furthermore we wanted to identify any gender differences in the effect of ACL-injury and to investigate if there were any correlations between the degree of atrophy and concomitant meniscal injury, time from injury or the subjects' physical activity level after injury.

Members of the group during 2016

Mari Hänni, MD, PhD

Thomas Eriksson, PhD student

Tomas Söderman, PhD student

Pär Holmer

Moaz Shalabi

Research group 8: Imaging renal metabolic changes in systemic disease with focus on diabetic nephropathy

Principal investigator: Per Liss

The mechanisms behind the renal impairment in systemic disease are unclear. In diabetes mellitus about 30% of patients will develop a renal impairment that may end in dialysis and renal transplantation. In our own prior experimental studies we have shown that hypoxia may play an important role. The aim of our project is to investigate the changes in regional renal blood flow, oxygenation and fibrosis in especially diabetic patients, and other systemic conditions, using non-invasive functional magnetic resonance imaging (MRI) techniques. The studies aim to ~~i~~nvestigate if non-invasive MR techniques can be used to find patients at risk for developing renal impairment due to diabetes.

Project 1: Mechanisms of renal impairment in diabetic and hyperthyroid patients.

Project 2: Mechanisms of renal impairment in septic patients.

Project 3: Mechanisms of renal impairment in renal obstruction.

Project 4: Mechanisms of renal impairment in patients after injection of contrast media

Members of the group during 2016

Per Liss, Associate Professor

Peter Hansell, Professor

Fredrik Palm, Professor

Per Eckerbom, MD, PhD student

Robert Fritjof, Associate professor

Ebba Sivertsson, MD, PhD student

Michael Häggman, Associate Professor

Sam Ladjavardi, MD, PhD

Daniel Espes, MD, PhD

Anca Dragomir, Associate Professor

Susan Francis, Professor

Organization

The group comprise researcher from the Departments of Radiology, Internal Medicine, Anestesiologi, Pathology and Physiology

Collaboration with other universities

Anders Persson, Professor, Linköping

Susan Francis, Professor, Nottingham,

Agencies that support the work/Funding

The Swedish Diabetes Foundation

The Swedish Child Diabetes Foundation

Uppsala University Hospital (ALF)

The Ernfors Foundation

Uppsala County

Dissertations Radiology 2016

Catrin von Below. PET and MRI of Prostate Cancer.

Johannes Finnsson. Radiological studies of LMNB1-related autosomal dominant leukodystrophy and Marinesco-Sjögren Syndrome.

David Fällmar. Visual assessment of perfusion and metabolism in neurodegenerative dementia.

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12) Thoracic Surgery

Principal investigator: Elisabeth Ståhle

Project 1. Hemostasis in cardiac patients

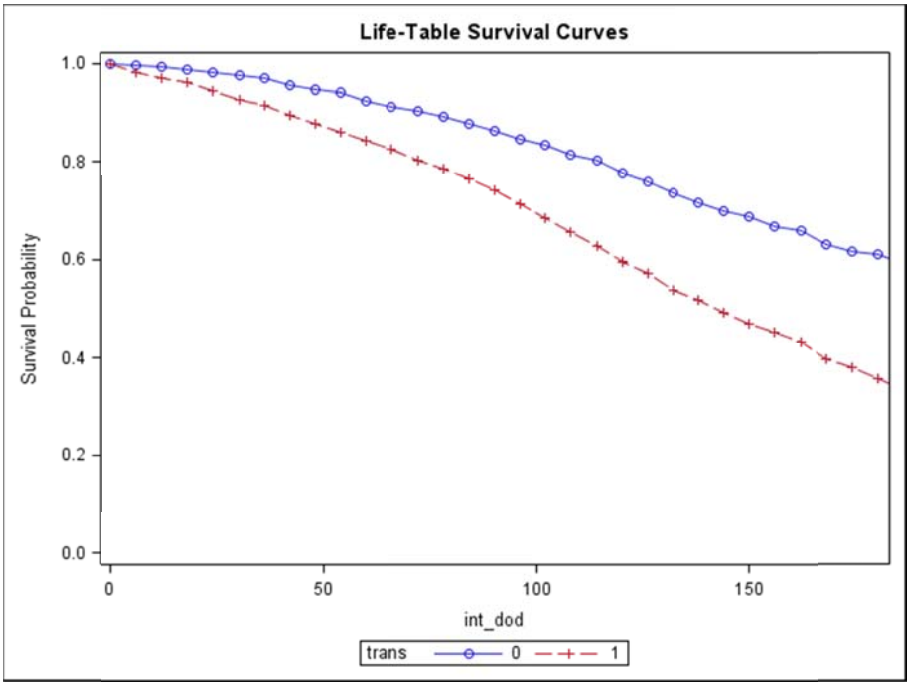
Effects of blood transfusion in relation to open heart surgery.

Cardiac surgery especially if including extra corporeal circulation is associated with bleeding and blood loss, despite efforts to curtail the frequency of blood transfusions in cardiac operations, the frequency remains high and reported to vary from 27% to 90. The decision to transfuse patients is invariably done to promote hemostasis or improve the carrying capacity of oxygen in the blood. However, there is still limited consensus on who needs to be transfused. Deciding when a patient requires transfusion of blood products varies significantly among surgeons, anesthesiologists and intensivists, even those at the same institution. Moreover, there are studies suggests that a substantial proportion of given transfusions may be clinically inappropriate. Adverse reactions are associated with transfusion and although many reactions appear to be benign, also serious complications occur e.g. renal dysfunction, severe sepsis, increased hospital and long-term mortality. The association between blood transfusion and adverse events has been thoroughly studied regarding the short-term effect. There are only few studies evaluating the effects of transfusion on long-term survival after cardiac operation and none of them report truly long-term effects i.e. after 5 or 10 years.

Long-term effects of transfusion was evaluated among were 3248 patients who underwent undergoing primary aortic valve surgery (AVR) with or without concomitant coronary artery bypass grafting (CABG) at the Department of Cardiothoracic Surgery, Uppsala University Hospital, Uppsala, Sweden. Patients were included from January 1996 through December 2012 and survived the initial chain of care i.e. the hospital admission chain including the index surgery.

2291 (71 %) of the patients received at least one unit of red blood cells (RBC). The proportion who got RBC transfusion was stable over the study period (before 1st January 2000; 63% vs. 1st January 2000-31st December 2005; 79 % vs. 1st January 2005-31st December 2012; 69 %, Cochran-Armitage Trend Test p=0.5180) while the incidence of transfusion of plasma and thrombocytes increased (before 1st January 2000; 23 % vs. 1st January 2000-31st December 2005; 34 % vs. 1st January 2005-31st December 2012; 32 %, Cochran-Armitage Trend Test p= 0.0007 regarding plasma; 12 % vs. 18 % vs. 22 % Cochran-Armitage Trend Test <.0001 regarding thrombocytes). Two-hundred fifty seven patients (11 % of patients transfused) received just one unit of RBC. In mean transfused patients received 4.6 $\pm$4.4 Units (Q_2=3; range=1-46). 1105 (31 %) received plasma in mean 4.0$\pm$4.4 Units (Q_2=2; range 1-47). Corresponding figures for thrombocyte transfusion that were given to 681 patients (19 %) in mean 2.5 $\pm$1.9 Units (Q_2=2; and range=1-18).

833 (26 %) received no foreign blood product. 1,262 (39 %) patients received solely RBC, 90 (2.8 %) patients received solely plasma and 34 solely thrombocytes (1.0 %). 911 (28 %) receive both plasma and RBC and 2390 (74 %) received either RBC or plasma transfusion. Patient´s characteristics according to transfusion of either erythrocytes or plasma are depicted table 1.



Legend Total survival according to transfusion of red blood cells or plasma in relation to aortic valve surgery.

Our study confirms that transfusion of blood products in relation to open heart surgery is harmful. The effect on survival is substantial with a relative risk increase of 20 to 30 percent after adjustment for other relevant risk-factors. This harmful effect of blood transfusion persists at the same magnitude also more than five and ten years after surgery. We could not confirm that the negative effects blood transfusion is restricted to low risk groups as proposed by others. Instead we report a significant interaction between transfusion and age so that transfusion was especially harmful in younger individuals. The observed increase in mortality was due to a number of conditions, many heart related e.g. myocardial infarction and heart failure. An independent impact by transfusion on deaths related to diseases of the circulatory system was verified in multivariate models. More precise conclusion regarding less common causes of death need to be confirmed with extended follow-up and by others. Nevertheless the finding of increased incidence rates of deaths due to relatively rare causes of death e.g. cerebrovascular disease, sepsis and chronic renal failure, among transfused patients may shed some light to the search for an underlying mechanism for a harmful effect of blood transfusion.

Future work

We plan to analyze the effect of transfusion of different blood products in relation to open heart surgery in an extended patient cohort. If a negative effect of transfusion can be reproduced by us and others the strategy is to work towards a national randomized registry study.

Biomarkers and risk factors associated with bleeding in aortic valve surgery

Symptomatic narrowing of the aortic heart valve, aortic valve stenosis, is preferably treated with surgical valve replacement. This generally requires an open-heart surgical procedure using a heart lung machine. Bleeding is a common associated problem, and up to 7 % of patients need a subsequent acute operation to stop hemorrhage. Excessive bleeding after surgery is associated with an increased risk of adverse outcome, including death. Valve surgery has more bleeding complications when compared to coronary bypass surgery, another of the most common types of cardiac surgery. Patients are treated with different anticoagulant and anti-platelet drugs before, during and after surgery, which can contribute to increased risk for bleeding. Identification of patients at risk of bleeding complications through blood tests would be of benefit, enabling early individualized procoagulative medical treatment and transfusions.

Mechanistic studies on coagulation and hemostasis in cardiac patients with focus on aortic valve disease, in collaboration with Professor Agneta Siegbahn and Christina Christersson

A prospective study focusing on bleeding after heart valve surgery was initiated in 2013. The main purpose is to investigate causes of abnormal bleeding after valvular heart surgery. 104 patients with aortic valve stenosis and 67 with coronary artery disease planned for surgery have been included. Blood samples drawn before, at the end and after surgery have been stored and analyzed. The two patient groups are compared, in order to identify biomarkers and risk factors that could explain and foresee an increased risk of bleeding in the valve surgery group.

In this study, biomarkers present in blood, patient related risk factors and effects of prior medical treatment are analyzed. The hemostatic blood components proteins, platelets and the cells lining the inside of blood vessels are known to describe the condition of the coagulation system. Levels of fibrinogen, von Willebrand factor, micro-RNA and cell fragments reflecting the degree of platelet activation. All these markers could correlate to excessive bleeding or inadequate thrombus formation.

To further evaluate perioperative changes in the coagulation system, thrombin generation assessed with CAT (Calibrated Automated Thrombography) is analyzed in stored plasma. Thrombin is the coagulation factor that converts fibrinogen to insoluble fibrin, and the method quantifies the total amount of thrombin that the patient's plasma is capable of producing upon activation. Preliminary results in the aortic valve replacement group show that thrombin generation is significantly decreased during surgery. Our data shows no correlation between postoperative bleeding and thrombin generation ability. Aortic stenosis patients displayed higher thrombin generation in both thrombin peak with mean (interquartile range) 252 nM (187–319) and endogenous thrombin potential with mean 1552 nM·min (1340-1838) as compared to in coronary artery disease patients where thrombin peak was mean 174 nM (147-229), and endogenous thrombin potential mean 1247 nM·min (1034–1448) (both $p<0.001$). Differences persisted after adjustment for age, gender, comorbidity and antithrombotic treatment.

In addition, thromboelastography analyze ROTEM (Rotational Thromboelastometry) is performed before and directly after surgery. The test measures time until blood clotting begins and the firmness of the produced clot. Our results show small but statistically significant differences in clot formation between aortic stenosis patients and coronary artery disease patients. However, other patient related factors such as gender, inflammation and the ratio between plasma volume and erythrocytes seem to have more impact on variations in clot formation in both groups. The clot firmness before surgery correlates to the volume of early postoperative bleeding (r=-0,23). However, the minor differences in thromboelastometry clotting detected between patient groups did not persist after adjustment for baseline characteristics.

Fibrinogen is converted by thrombin into fibrin, which constitutes the building block of the blood clot. During major bleeding, fibrinogen is the first coagulation factor that reaches a critically low level where clotting is impaired. Our data shows equal mean fibrinogen levels in aortic stenosis and coronary artery disease patients. However, fibrinogen levels estimated by thromboelastography test ROTEM with deactivated platelets indicate higher levels of fibrinogen in aortic stenosis patients. Fibrinogen plasma levels preoperative and at the end of surgery display a weak correlation to postoperative bleeding amount (r=-0.18 and -0.28 respectively)

Postoperative median bleeding amount during the first 12 hours was lower in aortic stenosis patients with median 290 ml than in coronary artery disease patients median 410 ml ($p=0.001$). Postoperative bleeding amount showed no relationship to thrombin generation, but a weak association to thromboelastometry (r-square max 0.06).

Conclusions: Aortic stenosis patients exhibited a preoperatively increased thrombin generation as compared to patients with stable coronary artery disease. Even though further studies are warranted, the evaluation of thrombin generation in elective low risk groups seems not to add information of postoperative bleeding risk.

Platelet proteins

Platelet protein content in preoperative blood samples from a subcohort pilot study of 10 patients from the previous study has been examined. We have identified differences in several proteins involved in platelet skeleton and adhesion between patients planned for aortic valve and coronary artery surgery.

Method:

Platelets were purified from whole blood from AS (n=10) and CAD (n=10) upon admission before surgery. After preparation the proteins were analyzed by mass spectrometer. Whole blood was activated ex vivo by CRP-XL and ADP and the expression of fibrinogen, CD62P, and CD63 on platelets were evaluated.

Results:

A total of 1567 protein groups were included in the quantitative analysis and 16 proteins were downregulated in the AS compared to CAD groups and 12 proteins were upregulated. Uppreglated proteins were; CVD3 homolog, Dematin, Septin-6, Bifunctional ATP-dependent dihydroxacetone kinase/FAD-AMP lyase, ATP synthase subunit d. mitochondrial, Hematopoetic lineage cell-specific prrotein, Filamin-A, cGMP-dependent protein kinase, Protein G6b, Platelet endothelial aggregation receptor 1, Microtubule-associated protein RP/EB family member 1, Rho GDP-dissociation inhibitor 2, Ras-related protein Rab-1B and 1C, Tubulin alpha-8 chain, HLA class I histocompatibility antigen, Integrin alpha-6, Ras-related protein protein Rab-27B, HLA class I histocompatibility antigen and Glycine-tRNA ligase.

Warfarin sensitivity after aortic valve surgery

Following valve surgery, patients are prescribed warfarin to prevent thrombosis and stroke. The dose requirement varies more than ten times between patients, and over-treatment can lead to life threatening bleedings. Therefore the anticoagulative effect, measured as INR, is monitored daily with blood tests. Genetic variances in the vitamin K cycle protein VKORC1 have been identified as the main determinant of warfarin sensitivity.

This study aims to investigate the impact of these genetic variances on bleeding complications and concentrations of coagulation factors and other biomarkers after aortic valve surgery. 104 aortic valve patients from the first study have been genotyped for variations in VKORC1. Our results show that patients with a sensitive type of VKORC1 receive too high doses, and non-sensitive too low doses, of warfarin even though treatment is guided by daily INR measurements. A future objective would be to develop an algorithm for safer and easier warfarin dosage after cardiac surgery.

Risk factors associated with reexploration due to bleeding after aortic valve surgery

Following valve surgery, patients are prescribed warfarin to prevent thrombosis and stroke. The dose requirement varies more than ten times between patients, and over-treatment can lead to life threatening bleedings. Therefore the anticoagulative effect, measured as INR, is monitored daily with blood tests. Genetic variances in the vitamin K cycle protein VKORC1 have been identified as the main determinant of warfarin sensitivity.

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Future work

Extended analysis regarding mechanisms for hemostasis in aortic stenosis versus ischemic heart disease.

Analysis of proteomics reflecting known cellular processes for inflammation, apoptosis, hemostasis etc as a response på open heart surgery, in relation to operative complications and long-term prognosis.

Influence of pharmaceutical treatments on heart failure after surgery for aortic stenosis versus ischemic heart disease.

Members of the group during 2016

Elisabeth Ståhle

Ulrica Alström

Axel Dimberg

Christina Christersson

Project 2. Management of right heart failure during LVAD-therapy and ECMO

Members of the group during 2016

Laila Hellgren

Petter Schiller, MD

Per Vikholm, MD

Project 3. Arrhythmia surgery

The Cox-Maze III operation in Sweden: registry-based and clinical long-term follow-up in 536 patients

This is a multicenter collaborative study between cardiac arrhythmia surgeons and cardiologists in Uppsala, Stockholm and Gothenburg. The study has been granted support by the Swedish Heart-Lung foundation. The Cox-Maze III operation was introduced in Sweden in 1992 and performed in four different centers. It is an open heart procedure for treatment of medically refractory and highly symptomatic atrial fibrillation, in which multiple incisions are made in both atria to block re-entrant circuits causing atrial fibrillation. Initially it was used in patients with lone atrial fibrillation but has subsequently been performed in conjunction with other heart surgery. From 1992-2009, 536 patients in Sweden underwent this procedure. Early results were good with up to 90% of patients free of atrial fibrillation. However, long-term results have not been thoroughly evaluated in Sweden. This project is an effort to determine patient outcomes through Registry-based studies of mortality and stroke/TIA as well as individual patient surveys of quality of life, actual rhythm and on-going medication.

Part 1:"Early and Long-Term Mortality in 536 Patients After the Cox-Maze III Procedure: A National Registry-Based Study" Albåge A et al. Ann Thorac Surg. 2013;95(5):1626-32.

This recently published study showed low early and long-term cardiovascular mortality and no stroke-related mortality after the Cox-Maze III procedure.

Part 2: "Long-Term Follow-Up of Cardiac Rhythm in 320 Patients After the Cox-Maze III Procedure for Atrial Fibrillation" Albåge A et al. Ann Thorac Surg. 2015.

This recently published study showed that when assessing rhythm by 12-lead ECG, 82% of patients were in sinus rhythm or other regular supraventricular rhythm more than 9 years after the Cox-Maze III procedure. There was no difference in rhythm outcome by gender, type of AF or type of operation (stand-alone CM-III or concomitant procedure).

Part 3: "Long-term risk of ischemic stroke after the Cox-maze III procedure for atrial fibrillation" Albåge et al. Accepted.

Registry-based evaluation of in-hospital care for postoperative ischemic stroke/TIA after the Cox-Maze III procedure in Sweden. This study is in collaboration with associate Professor Ulrik Satirpy, Stockholm. The results show a very low incidence of perioperative and late postoperative ischemic stroke/TIA, with an association between preoperative CHA_2DS_2-VASc score and stroke outcome. This manuscript is accepted for publication in The Annals of Thoracic Surgery 2017.

Part 4:"Long-Term Evaluation of Quality of Life in 339 Swedish Patients after the the Cox-Maze III Procedure for Atrial Fibrillation" Jidéus et al. Manuscript.

This follow-up study of the same patients as in Study 2, showed QoL-scores in patients with regular supraventricular rhythm equal to the general population, more than 9 years after the Cox-Maze III procedure. This manuscript is in submission process. This study has been reported at SATS in Gothenburg 2014 and was awarded best presentation.

National research group, SRAK

The research group is collaborating closely with arrhythmia surgeons from all cardiac surgical units in the country, in an organization called ***SRAK*** (Svenska Referensgruppen för Arytmikirurgi). This national workgroup is quite unique in cardiac surgery in Sweden and its purpose is to address and unify clinical issues and research projects in the field of arrhythmia surgery. The group has recently produced guidelines in this field:

1. "A Swedish consensus on the surgical treatment of concomitant atrial fibrillation". *THE SWEDISH ARRHYTHMIA SURGERY GROUP. Scand Cardiovasc J. 2012 Aug;46(4):212-8.*

2. Kirurgisk behandling av förmaksflimmer i samband med hjärtkirurgi. Konsensusrapport från Sveriges arytmiansvariga hjärtkirurger. *Läkartidningen 2012 Feb 1-7;109(5):214-7.*

In addition, there are several on-going collaborative projects including the start-up of a national registry for atrial fibrillation surgery, which will be included in the SwedeHeart registry.

Another ongoing project is forming a consensus statement regarding anticoagulant treatment in connection with postoperative atrial fibrillation.

Local follow-up of patients undergoing surgical treatment of atrial fibrillation at the Department of Cardiothoracic Surgery, University Hospital, Uppsala

The Cox-Maze III procedure has been further developed and at present most of the surgical incisions in the atria of the original procedure has been replaced by cryoablation. This allows for a faster and safer procedure and this therapy of atrial fibrillation can be offered to older and sicker patients. There is a completed local long-term follow-up study of patients who were operated between 2009 and 2012 for *structural heart disease (valves or CABG) and concomitant cryo-Maze procedure.* Follow-up of quality of life, rhythm and medication has been performed in 50 patients and the study is in the data analysis phase. Cardiac rhythm has been evaluated by handheld trans-telephonic monitoring (Zenicor "thumb-ECG") in

each patient. This has been presented by medical student Kristina Dalin in January 2015. This study is continuing including patients prospectively.

In another collaborative project between Uppsala and Karolinska, we are performing long-term follow-up of patients who have undergone *open heart patch closure of atrial septal defect and concomitant surgical ablation of atrial fibrillation* between 2000 and 2012. This study is in the start-up phase and end points are quality of life, rhythm and present medication. In an era of increased use of catheter-based therapies for ASD, we hope to show consistent and good results with open surgical treatment in the ASD-patients who also have atrial fibrillation.

Minimal invasive surgical ablation

This is a collaborative project between cardiac arrhythmia surgeons and cardiologists in Uppsala. It is a total thoracoscopic bilateral procedure for treatment for treatment of medically refractory and highly symptomatic atrial fibrillation, in which multiple epicardial ablation lines are made on the left atrium to block re-entrant circuits causing atrial fibrillation. From 2008 to 2013, 100 patients in Uppsala underwent this procedure. Early results were good with up to 90% of patients free of atrial fibrillation. Long-term results have been presented by medical student Josef Larsson in January 2016.

"Thoracoscopic Epicardial Left Atrial Ablation in Symptomatic Patients with Atrial Fibrillation" Probst J et al. Europace 2016;18(10):1538-1544. This recently published study is included in an ongoing project and further data are in analysis phase.

"An echocardiographic study of left atrial size and function in relation to the extensiveness of epicardial off-pump pulmonary vein isolation and vagal denervation in patients with atrial fibrillation" Bagge L et al. Submitted. **This submitted study is included in a**nother ongoing project and further data are in analysis phase.

Miscellaneous

Research group members have participated actively as lecturers in various Symposia at Svenskt Kardiovaskulärt Årsmöte, in 2008, 2013 and 2014 in the field of surgical treatment of atrial fibrillation. We have also participated actively as lecturers at Svensk Thoraxkirurgiskt Årsmöte, in 2011, 2012, 2014 and 2015 in the field of surgical treatment of atrial fibrillation.

We are also co-authors in the recently published Swedish textbook of cardiac arrhythmias, *"Arytmier - Mekanismer, utredning och behandling"* ISBN 978-91-44-09534-9.

We have also participated at STS 2017 in Houston, USA with the poster ""*Long-term risk of ischemic stroke after the Cox-maze III procedure for atrial fibrillation".*

Members of the group during 2016

Lena Jidéus (Group Leader)

Anders Albåge

Vitas Zemgulis

Project 4. Heart surgery; indications, complications and long-term outcome

Atrial fibrillation after heart surgery – prediction and outcomes

The most common complication after cardiac surgery is atrial fibrillation (AF). Approximately one third of all patients have an episode of AF after coronary artery bypass grafting (CABG), so-called postoperative atrial fibrillation (POAF). This arrhythmia has been associated with an adverse outcome after surgery, but the causes behind POAF as a negative prognostic factor are not fully understood.

This project was designed to identify predictors and early complications associated with POAF after CABG, as well as its associations with early and late mortality and cause of death. Further, we wanted to monitor the heart rhythm of patients with and without POAF to see to what extent recurrent or new AF occurred after discharge.

The first two studies and the fourth study included approximately 7,000 CABG patients that underwent surgery at the Department of Cardiothoracic surgery, Uppsala University Hospital, during the years 1996 through 2012. Data was collected from the Department's database, the Swedish Cause of Death Register, and the National Patient Register.

The first study revealed several predictors of POAF, including increasing age, which was the strongest risk factor. Other predictors were decreased kidney function, male gender, symptoms of heart failure, smoking, history of myocardial infarction, and absence of hyperlipidemia. Patients with POAF had an increased length of hospital stay, included stay in the intensive care unit. There was also an association between POAF and early complications after surgery, such as heart failure and infection, and stroke.

In a second study we found an association between POAF and late cardiac death, and death related to arrhythmia, heart failure, and cerebrovascular death. The effect remained after adjusting for age and other pre- and perioperative variables. More than eight years after surgery, POAF was till associated with a 30% to 80% increase in mortality. The results indicate a negative prognosis associated with POAF in a long-term setting.

A third, prospective study examined heart rhythm after CABG, with a mobile ECG device. A total of 67 patients were followed for 30 days following discharge. The incidence of AF was highest among patients with POAF. More than half of the POAF patients experienced post-discharge AF, with six times the odds of developing AF compared with non-POAF patients. There was, however, a surprisingly high number (almost 20%) of patients without POAF who registered post-discharge AF. A third of the patients with post-discharge AF did not experience any symptoms related to AF. There seems to be room for a more active treatment of POAF, and a more thorough follow-up of heart rhythm after CABG.

The fourth study examines the association between POAF and morbidity, were information was collected regarding what diagnoses patients are treated for after discharge after CABG, and up to 18 years postoperatively. The examined diagnoses were AF, myocardial infarction (MI), heart failure (HF), ischemic stroke, thrombosis, hemorrhagic stroke, and bleeding. Medical history data was also examined for five years prior to surgery. Preliminary results show a high overall incidence of MI, HF, ischemic stroke, and AF during follow-up. The incidence of ischemic stroke (11%) was higher than hemorrhagic stroke (2%). A higher overall mortality was seen among POAF patients, as well as a higher incidence of MI, HF, and ischemic stroke. Most prominent was the association between POAF and AF during follow-up, where patients with POAF had three times the hazard of future AF compared to non-POAF patients. Further analyses are in progress.

In summary, the overall purpose of this project is to identify risks associated with POAF after CABG, and hopefully find ways to minimize these risks in the future.

Future work

Extended analysis regarding long-term effects of open heart surgery in patients with permanent atrial fibrillation – rationales for pulmonary vein ablation, left atrial appendix closure etc. Influence of non-sinus rhythm on prognosis after open heart surgery.

Influence of pharmaceutical treatments on outcome with regard to pre- and postoperative atrial fibrillation.

Analysis of proteomics reflecting known cellular processes for inflammation, apoptosis, hemostasis etc in relation to pre- and postoperative atrial fibrillation and long-term prognosis.

Members of the group during 2016

Elisabeth Ståhle

Emma Thorén

Project 5. Surgery in lung cancer treatment

Aspects on lymph node metastasis in lung cancer

This projects focus on molecular analysis of lymph nodes, lymph node metastasis and primary tumors with special reference to lymphangiogenesis. Surgical, radiological and pathological implications.

Lung cancer kills 1.2 million people in the world every year. It is one of the cancers with the worst prognosis. Only 10-20% of the patients can be subject to the only possible cure that is surgery. Thus, in the majority of cases, at the time of diagnosis, the disease has progressed too far to be able to cure, usually through metastatic spread to lymphnodes or distant organs. Among those patients subjected to surgery, the mean five year survival is around 50%, worse in those with larger tumors with signs of local lymph node spread and better in those with smaller tumors and no evidence of metastatic lymph node spread. However, the five year survival in these patients, with a totally radical removal of a small tumor and no signs of lymph node spread, i still far from 100%. This could indicate that there in some cases still could be, although with today's methods unrecognizable, a very low degree of metastatic spread present at the time of surgery. To be able to understand the basic driving mechanisms and earlier find such a spread would help to better help these patients to a longer life.

This is a joint venture between the departments of thoracic surgery, oncology, radiology and pathology, still in an early phase. The goal is to:

With the use of advanced surgical, molecular and radiological methodology, increase our understanding of lymph node metastasis in non-small cell lung cancer in order to be able to better diagnose, operate and prognosticate patients with this disease. This includes to:

- In detail, from an anatomical surgical level down to a basic molecular level, study and map the metastatic spread in lymph nodes in patients with NSCLC.
- In detail, from an anatomical surgical level down to a basic molecular level, study and map the concept of lymphangiogenesis in patients with NSCLC.
- Try to find methods for earlier and more precise detection of lymph node metastasis and lymphangiogenesis in patients with NSCLC.

Detection of Mutations in Epidermal Growth Factor Receptor and Monitoring of Therapy in Non-Small Cell Lung Cancer

The objective of this study is to identify predictive markers for EGFR inhibitors and drug resistance in blood samples from patients with non-small cell lung cancer. The overall aim is to obtain optimal staging prior to surgery.

Background

A rapid development of molecular biology has opened new possibilities for the staging and corresponding treatment of non-small cell lung cancer (NSCLC) and the receptor for epidermal growth factor receptor (EGFR) has lately been the focus of targeted therapy of NSCLC. EGFR has been shown to be commonly expressed in lung tumors and be important for the growth of lung cancer. Gefitinib (Iressa) and erlotinib (Tarceva) are small molecule tyrosine kinase inhibitors (TKIs) blocking the activity of EGFR and in clinical studies have demonstrated clinical activity in lung cancer patients resulting in tumor reduction and prolonged survival. Research groups have subsequently identified somatic mutations in the tyrosine kinase domain of EGFR associated with response to EGFR TKIs. The most common EGFR sensitizing mutations, which account for approximately 85% of all EGFR mutations in NSCLC, include deletions in exon 19 and a point mutation, L858R, in exon 21. Both gefitinib and erlotinib are now approved for treatment of advanced NSCLC patients with sensitizing EGFR mutations. Resistance development is a major clinical problem, and this is also true for EGFR targeted therapies. In 50% of patients resistant to gefitinib or erlotinib a mutation in exon 20 of the EGFR, leading to the substitution of the amino acid threonine to methionine at position 790 (T790M) in the kinase domain of the receptor has been found. Attempts are now underway to develop irreversible EGFR TKIs to overcome this resistance mechanism.

Department of Thoracic Surgery at Uppsala University Hospital has since 2002 collected consecutive blood samples (plasma, whole blood) from surgical lung cancer patients, up to date 728 lung cancer patients in all. Linked to these patients are full clinical data including tumor stage, sex, age, survival, EGFR mutation status (from 2009). This database is planned to be used as a basis for collaboration with the SciLifeLab in Uppsala in order to:

1. Using the proximity ligation assay technique (PLA) for high-performance DNA -assisted protein analyses to find sensitizing EGFR mutations in blood from lung cancer patients in order to easily identify the optimal patients for EGFR TKI treatment using only a blood test instead of tumor tissue.
2. Using the same PLA technique to monitor lung cancer patients being treated with EGFR TKIs by looking at levels of sensitizing EGFR mutations in blood and correlate that to treatment response as determined by radiological evaluation. The intention would be to replace laborious monitoring using radiological exams with easy monitoring using blood tests.
3. With the help of PLA technique detect the emergence of EGFR resistance mutations during treatment with EGFR TKIs in blood samples from lung cancer patients. This would be helpful in early detection of resistance and guiding further therapeutic decisions.
4. The same methodology as described in 1-3 above can be applied to other novel targeted therapies in lung cancer where there is a predictive biomarker for treatment response. One example already in routine clinical use is the ALK gene rearrangement in a subpopulation of NSCLC patients where the targeted agent crizotinib (Xalkori) is used to treat these patients.

Analyses of proteomics with SciLife cancer panel has been performed during 2015. The patient cohort consisted of 176 patients operated due to primary adenocarcinoma of the lung. Statistical analyses have been initiated.

A similar analysis of patients with squamous cell carcinoma and patients operated due to non-cancer causes are planned spring 2016.

A prospected study of lymphnode micrometastases in patients with adeonocarcinom in the lung is started 2016-03-10.

Members of the group during 2016

Per Landelius

Elisabeth Ståhle

Collaboration:

Patrick Micke, department of immunology, genetics and pathology, Uppsala University

Project 6. Clinical and experimental studies of malperfusion of the Central Nervous System in conjunction with cardiovascular surgery

Cerebral perfusion during surgery of the thoracic aorta

Description of the research: Irreversible neurological injuries are a major complication to complex cardiovascular surgery. There is to date no treatment available for these patients, only therapies that aim at minimizing the consequences of established injury.

The goals of the current project are to both develop potential therapeutic strategies and also identify analytic tools to be applied in a clinical setting where ischemic injury to the central nervous system (CNS) could have occurred. The research is translational, with a clinical and an experimental arm. The clinical material consists of a well characterized cohort of patients where blood and more importantly cerebrospinal fluid samples, which is unusual, have been collected from patients that have undergone open cardiovascular surgery. The experimental part is carried out in a porcine model, implying that the results obtained likely are of more clinical relevance than those from murine models.

The aim of developing an active strategy to treat ischemic CNS injury in the clinical setting is realistic on selected patients undergoing cardiovascular surgery, as the operative strategy already today isolates and cannulates the major vessels supplying the CNS with blood. In the longer term, a similar treatment could be relevant also in situations with major cerebrovascular infarctions or following cardiac arrest, but this is more speculative. In order to be a candidate for intervention early identification of ischemic injury needs to be possible. As it is difficult to detect brain injury in the early phase following extensive surgery that could have put the brain at risk, there is a need to develop better biomarkers that can improve the diagnostics in this setting.

Members of the group during 2016

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Detection of markers of neurologic injury in cerebrospinal fluid and blood following complex aortic surgery

Description of the project: It is challenging to detect and quantify neurologic injury in the early post-operative setting following extensive aortic surgery, as the patient as a rule is sedated or under general anesthesia for many hours, sometimes even days due to circulatory and respiratory instability. This means that the patient is bound to the intensive care unit, making detailed radiological examinations difficult. Also, radiological examinations of the brain early following suspected ischemic injury are not always reliable with regard to sensitivity [1].

In other neurological diseases, such as Multiple Sclerosis or Alzheimer's disease biomarkers of disease activity have been developed in cerebrospinal fluid (CSF). However, these are diseases with chronic course, and it is therefore not evident that the markers identified [2,3], which correlate with degree of nerve injury are applicable on acute ischemic injuries. After acute traumatic brain injury, it has been demonstrated that levels of certain CSF proteins correlate with degree of survival [4], and recently it was identified that elevated levels of several proteins in CSF following aortic surgery to a certain extent correlated with the degree of neurologic injury [5]. However, it is not known if these proteins also are detectable in blood. Blood sampling is an easier and safer technique than sampling from the intradural cavity. It would therefore be of great value to in a simple, fast and reliable way detect acute ischemic neurological injury in order to rapidly undertake adequate treatment.

All patients at the Department for Cardiothoracic Surgery at Uppsala University Hospital admitted for either open or endovascular operative treatment of complex disease of the thoracic aortic that have a spinal catheter introduced are included, on condition of written consent. The criterion of getting a spinal catheter is that the planned procedure carries a significant risk of disturbing the circulation to the CNS, which could cause ischemic injury to the brain or spinal cord. CSF and blood samples are collected concomitantly during the perioperative phase, until the catheter is removed. In the current material, where 27 patients are included at this stage, there are patients without injuries, with transient CNS symptoms and also permanent CNS injury. The paired sampling, of blood and CSF simultaneously, enables a kinetic characterization of when neurological proteins are possible to detect in the blood compartment. It can also help establish the degree of potential blood-brain barrier defect caused by the surgery. Proteomic analysis of the serum and CSF has been carried out, in collaboration with SciLife and Professor Ulf Landegren. Initial analysis will examine a panel of 90 proteins linked to neurological processes.

Initial results identify several significant differences in the levels of multiple proteins in both cereum and cerebrospinal fluid from patients that suffered ischemic spinal cord injury or delirium postoperatively. The results will be presented as an abstract at AATS (American association of Thoracic Surgery) aortic symposium in NY, May 2016.

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Experimental studies of global cerebral ischemia and controlled reperfusion

Description of the project: Inadequate blood supply to the brain is harmful, but the exact mechanisms leading to tissue injury following ischemia are not fully understood. It is likely the combination of ischemia with the uncontrolled reperfusion that occurs once the circulation is re-established that causes the damage. It has been demonstrated in both heart [6] and lungs [7] that a controlled reperfusion following ischemia can reverse and minimize tissue injury. However, it is important how this reperfusion occurs, since a number of parameters can be manipulated, for instance velocity, pressure and temperature of the reperfusate, as well as its content with regard to immunologic factors, balance of electrolytes and content of anti-oxidants or other drugs [8].

Recently, an extensive research series performed in pig demonstrated that a controlled reperfusion was able to salvage a brain exposed to a 30 minute long global, normothermic ischemia [9,10,11]. But a number of questions remain even after this pioneering work- for instance; what is the most important parameter in the controlled reperfusion? And also, after how long ischemia is it possible to prevent permanent injury from affecting the brain?

In the current project, an animal model (pig) has been developed where we by surgically identifying all vessels that supply the brain with blood are able to induce a global, reproducible cerebral ischemia. In the control group all brain vessels are occluded for 30 minutes, after which they are opened and the regular circulation resumes. This is what we term uncontrolled reperfusion. In the interventional group ischemia is induced in the same way, but after the 30 minute ischemic period a controlled reperfusion of the brain is performed during 20 minutes, using extra-corporeal circulation and heart-lung machine connected to the cerebral vessels. This is the controlled reperfusion, as we are able to modulate the pressure, flow, temperature and content of the reperfusate. After the controlled reperfusion, the vessels are opened and the regular circulation again takes over. During the experiment extensive monitoring and regular taking of blood and tissue samples is performed. At the end of the experiment the brains of the animals are examined by experts in neuropathology at Uppsala University Hospital. The aim is to evaluate and develop an optimal reperfusion strategy that minimizes, or perhaps altogether hinders development of brain injury following ischemia.

The results are currently under submission to the journal Resuscitation.

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Project 7. Treatment of severe Acute Respiratory Distress Syndrome (ARDS) with allogeneic bone marrow-derived Mesenchymal Stromal Cells (BM-MSCs)

Background: Patients suffering from acute respiratory distress syndrome (ARDS) continue to have a high mortality and high costs related to often-prolonged intensive care unit (ICU) and hospital stay (1-4). In addition, ARDS survivors often have long-term neuromuscular, cognitive symptoms and diminished quality of life (2, 3). ARDS is caused by a variety of disorders that either directly or indirectly affect the lungs as part of a systemic inflammatory process. Respiratory viral infections like influenza A H1N1, the severe acute respiratory syndrome (SARS) coronavirus, and the Middle East respiratory syndrome coronavirus all cause pandemic ARDS and multiple organ failure with a high mortality (4-6). Current treatment options are limited to supportive care with appropriate use of mechanical ventilation (7). The addition of extracorporeal membrane oxygenation (ECMO) has been used in patients with severe ARDS, particularly H1N1-induced forms, nevertheless in a systematic review and meta-analysis of current evidence, no association with improved outcomes could be demonstrated (4). As such, new therapeutic approaches are needed.

Bone marrow-derived mesenchymal stromal cells (BM-MSCs) have proven to be successful in the treatment of experimentally induced acute lung injury in pre-clinical models (8, 9). While not completely understood, the mechanism of MSCs in these models include release of paracrine anti-inflammatory and anti-bacterial peptides as well as mitochondrial transfer from MSCs into damaged alveolar epithelial cells in the absence of stable MSC engraftment (8-11). Another important characteristic of BM-MSCs is their retention in injured lungs after systemic administration (12). Infusion of non-HLA-matched allogeneic MSCs has already been demonstrated to be safe and potentially effective in a widening range of clinical applications, including lung diseases, suggesting that this approach may be beneficial in ARDS patients (13, 14). In a recent phase I dose-escalation safety study demonstrated the safety of a single i.v. administration of 1–10 million cells per kilogram of MSCs in 9 patients with moderate to severe ARDS, and a phase II efficacy trial is currently underway (15).

We have treated two patients with severe ARDS on ECMO support by systemically administer BM-MSCs and correlate clinical improvement with *in vivo* anti-inflammatory actions (16). Both patients received 2 million cells per kilogram body weight, and each subsequently improved with resolution of respiratory, hemodynamic, and multiorgan failure. In parallel, a decrease was seen in multiple pulmonary and systemic markers of inflammation, including epithelial apoptosis, alveolar-capillary fluid leakage, and proinflammatory cytokines, microRNAs, and chemokines. *In vitro* studies of the MSCs demonstrated a

broad anti-inflammatory capacity, including suppression of T-cell responses and induction of regulatory phenotypes in T cells, monocytes, and neutrophils. Some of these *in vitro* potency assessments correlated with, and were relevant to, the observed *in vivo* actions. These experiences highlight both the mechanistic information that can be gained from clinical experience and the value of correlating *in vitro* potency assessments with clinical effects. The findings also suggest, but do not prove, a beneficial effect of lung protective strategies using adoptively transferred MSCs in ARDS.

We are now planning a clinical follow-up of these two patients and investigate if the initial positive effects seen after treatment with allogeneic MSCs sustains over time and prevents development of lung fibrosis, pulmonary hypertension, reduced physical capacity, reduced quality of life and chronic systemic inflammation.

Aims for the clinical follow-up of already treated patients
To make a follow-up of the two patients treated with allogeneic MSCs for severe ARDS in order to assess:

Pulmonary function in relation to normal values

- Pulmonary function in relation to normal values
- Development of lung fibrosis
- Heart, liver and kidney function
- Physical capacity
- Systemic inflammatory response and immunomodulatory memory
- Sensitisation to the previously administered allogeneic MSCs

Significance
This study will be the first long-term clinical follow-up of patients with severe ARDS on ECMO support that are treated with allogeneic MSCs. This information will be of importance for planning of a Phase I clinical trial, where ten patients with severe ARDS on ECMO support will be treated with allogeneic bone marrow-derived MSCs.

Aims for the Clinical Trial

Primary Endpoint:

Is infusion of BM-MSCs concomitant to ECMO support safe?

Secondary Endpoints related to in vitro experiments:

Can therapeutic efficacy be predicted by monitoring of signs of lung epithelial destruction?

Can *in vitro* assays of recipient Myeloid-Derived Suppressor Cells (MDSC) and regulatory T cells predict therapeutic efficacy?

Secondary Endpoints related to the clinical study:

BM-MSCs effect on:

1. Adverse events (ie. infection, fever, effect on end-organ function)
2. Increase in pulmonary compliance and tidal volumes
3. Recovery of organ functions (lung, kidney, liver, heart)

Clinical Study Design
In the clinical phase I/II study (Ethical permit 2013/1908-31/2), patients that have diagnosed ARDS (according to CDC criteria) and are on cardiopulmonary support with ECMO due to respiratory insufficiency with or without concomitant circulatory problems will be included. At the time of inclusion, the patients can also have multi-organ failure, which further strengthens indication for therapeutic intervention.

In total 10 patients will be enrolled. Informed consent will be received from the closest relatives, since the patient will be on a respirator and on ECMO and thereby is unable to give concent. The patient and relatives can decide to discontinue the study at anytime.

Blood samples and bronchioalveolar lavage (BAL, 60cc x 2 each time point) will be harvested before infusion of the BM-MSCs. The patient will receive 2 million allogeneic BM-MSCs/ kg body weight through a central venous catheter. At the time of MSCs infusion, the pump flow in the ECMO circuit will be reduced for 20 seconds in order to get the highest retention of cells in the lungs. This has marginal hemodynamic effects. All patients will be at an ECMO unit and will be well monitored (arterial pressure, central venous pressure, oxygenation, saturation, ventilation, kidney function, neurology), which is part of the normal surveillance of these patients.

Blood samples will be harvested 1h, 3h, 24h, 48h, 72h, and then on weekly basis during the follow-up at the intensive care unit. BAL will be performed 1 day, 2 days, 3 days post infusion and then on weekly basis during the follow-up period. The blood and BAL fluid will be analysed for cytokines and microRNAs as well for the activity of the circulating inflammatory cells. Changes in lung compliance and tidal volumes will be evaluated on daily basis for the duration of time on the respirator. This is also part of the standard care of these patients.

X-rays of the chest will be performed pre-infusion and then daily during the first three days post infusion and then at least weekly until discharge.

Spirometry, 6 minute walk tests and blood samples (for the above analysis) will be performed at 3 months, 6 months and 12 months (end of study) after discharge from the intensive care. SF36, quality of life, will also be evaluated at these appointments.

In vitro analysis
Levels of pro- and anti-inflammatory cytokines in serial samples of BAL fluid and serum are assessed using a multiplex cytokine assay (Millipore, MA, US) on a Luminex machine (Luminex, Millipore). In BAL fluid, surfactant protein B concentration is determined by enzyme-linked immunosorbant assay (ELISA) (Uscn Life Science Inc, Houston, US). Caspase-cleaved K18 (ccK18) and total K18 are measured using M30-Apoptosense® ELISA (Peviva AB, Bromma, Sweden) and M65 EpiDeath® ELISA (Peviva AB), respectively to study epithelial cell apoptosis, necrosis and functional activity.

MDSC and regulatory T cells will be isolated from peripheral blood samples by magnetic bead separation. MDSC will be co-cultured with patient dendritic cells and expression of MHC, costimulatory receptors, IDO, HLA-G isoforms, IL-10 and TGF-beta are measured by ELISA and flow cytometery. Generation of regulatory T cells is measured by flow cytometery of co-cultures with patient naïve T cells together with MDSC and dendritic cells where the proportion of CD4+CD25+CD127low cells (regulatory T cells) are quantified.

CD4+CD25+CD127low cells from the patient blood samples are quantified and cultured with naïve T cells and activated dendritic cells. Activation of naïve T cell proliferation is quantified. In this way biological activity in the patient's immune system can be monitored before and after MSC therapy.

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Project 9: Derivation of multi-potent cardiac progenitors from mesenchymal stromal cells of different origin

We have previously developed a feeder-free protocol for generation of Isl1+ cardiac progenitors co-expressing c-kit, Tbx5, Pdgfr-alpha and Tbx18 from MSCs of human fetal hearts (1). Now we want to evaluate different sources of human MSCs in order to identify an allogeneic source that is easily available in order to generate enough cells for clinical use. The sources that should be tested are: Bone-marrow mesenchymal stromal cells (BM-MSCs) from healthy donors; Wharton´s Jelly MSCs. We have an organization for harvesting Wharton´s Jelly cells at Karolinska Institutet/Karolinska University Hospital.; MSCs from adult heart biopsies.

In all projects, Isl1+ cells will be generated from the MSC-fractions by culturing these cells according to the protocol developed for human fetal cardiac MSCs. The read-out will be Isl1 expression after 3 to 4 weeks in culture. These cells will be further characterized by their expression of SSEA-1, c-kit, Tbx5, Tbx18, Nkx2.5, TnT, sarcomeric actin and Ki67 (Staining and FACS). Full-genomic sequencing as well as proteomics will be performed on cells from the different passages in order to characterize if the Isl1+ progenitors are derived through a phenotype switch or dedifferentiation process.

Further characterization will be to identify the subpopulations responsible for generation of endothelial cells, smooth muscle cells and cardiomyocytes using a combination of FACS sorting and differentiation strategies. The exosome profile as well as their immunomodulatory capacities will also be evaluated using third party cytotox tests as well as analysing expression of IDO and HLA-G5 after interferon gamma stimulation.

The final aim is to develop clinically applicable cardiac progenitors derived from bone marrow or Wharton´s Jelly MSCs in order to treat or prevent heart failure after myocardial infarction.

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Project 10: The development cell-encapsulation systems and cell-extracellular patches for heart regeneration

A major concern in cell-therapy is that implanted stem cells cannot survive the shear stress during cell injection, which in addition to the toxic effects of ischemic tissue causes cell death. Cell-encapsulation will be performed with GFP-labeled Isl1 cardiac progenitors (see Project 9) in agarose in combination with gelatin and chemical cross-linkers and ECM proteins in order to receive the best combination for cell survival, differentiation and cell release. Cell survival and differentiation capacity will be evaluated in

myocardial ischemia models in mice and rats. By using the In Vivo Imaging System (IVIS) it will also be possible to compare the biodistribution.

In order to identify which ECM proteins that are important for cell survival and differentiation, we will use the decellularized heart model, first developed by Doris A. Taylor in 2008 (1). Different decellularization protocols (ions, chelating molecules, detergents, enzymes, freeze-thawing and buffers) will be compared. The resulting ECM scaffolds will be assessed histologically, with immunohistochemistry (IHC) and with Förster resonance emission tomography (FRET). The FRET technology will be used to assess the presence and composition of laminins, while routine histology and IHC will be used to detect fibronectin, heparan sulfates, collagens and other ECM components. Once a suitable scaffold has been obtained, it will be used for *in vitro* cell seeding studies to assess the ability of Isl1+ cells to survive and differentiate to the different components of the heart. This information will be used for the encapsulation studies of the Isl1+ cells but also for generation of ECM patches. These will be used for bridging the infarcted regions of the heart and thereby replace the scar tissue with healthy myocardium. Unfortunately, this approach is not clinically applicable since it is very time consuming and there will always be a risk of bacterial or viral contamination when preparing the ECM. Therefore, electrospinning will be performed with different biomaterial and polymers (PCL, collagen) together with conductive and anti-microbial agents like gold and silver nanoparticles/nanowires. The thickness of the mesh and the fiber-orientation can be manipulated to mimic the mechanical and biochemical properties of the ECM of the heart. This means that we can control the differentiation of implanted cells by modeling the composition of the nano-/microfibers. In cell culture studies using Isl1+ cells cultured on different electrospun meshes, the differentiation of the cells will be studied and compared to the results from the decellularized heart ECM. This will guide the mesh composition that should be used for implantation studies. In ischemic mice models, the electrospun patches with Isl1+ cells will be tested for their capacity to repair remodeled myocardium. Ingrowth of endothelial

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Project 11. De- and recellularization of aortic roots

Decellularized aortic root scaffolds have been used either as nude ECM-scaffolds for *in vivo* repopulation by autologous cells, or recellularized with various cell lineages. However, the histology of the resulting graft has always been abnormal, with intimal hyperplasia and lack of smooth muscle cells (1), adventitial hyperplasia (2), incomplete media and adventitial recellularization (3), or with no evidence of differentiation (4). We will carry out the decellularization of the aortic roots of rats comparing different protocols and solvent systems (ions, chelating molecules, detergents, enzymes, freeze-thawing and buffers) as discussed under project 10. Once a suitable scaffold has been obtained, it will be used for *in vitro* cell seeding studies to assess the ability of Isl1+ cells to differentiate into adult aortic root cell phenotypes. By using antibodies, mRNA interference or enzymes to disrupt specific cell-matrix interactions, we seek to study how different ECM components affect cell behavior in the decellularized scaffold.

Next we will analyze the structural integrity and mechanical properties of the decellularized aortic valve. In the final step, the decellularized as well as the recellularized aortic valves will be implanted into the abdominal aorta of rats in order to study if the bioengineered aortic root can improve its mechanical

characteristics, which would imply that this strategy could be used to generate new biological aortic valves for patients.

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13) Transplantation Surgery

Principal investigator: Tomas Lorant

Transplantation research is based on clinical need but encompasses both clinical and experimental research.

Most of the research is done in a collaborative fashion within the University in particular with the Departments of Immunology, Genetics and Pathology (Clinical Immunology, Clinical Pathology and Clinical Oncology), Medical Sciences (Nephrology), Surgical Sciences (Anesthesiology and Radiology) and Neurosciences (Neurosurgery) are involved.

The field of transplantation research is very heterogeneous but it has a common focus of clinical need.

Although the topics can be listed as separate items these may in several aspects be interrelated either by technology or goal. Under the broad heading *transplantation immunology* we conduct clinical research overcome the anti-HLA antibody as well as AB0-barrier barriers. The former is dependent on the use of complement inactivation or IgG-degradation.

The second topic may be assembled under the broad heading of *increasing organ quality before transplantation*. The common denominator is the knowledge that organs transplanted are damaged all the way through the procedure until after reperfusion. The following damaging events have been identified: brain death, harvesting procedure, storage with ischemia and finally reperfusion injuries. It is also recognized that all these factors together generate rather non-specific damages, which may switch the organs from a neutral to a pro-inflammatory state. Further, it is recognized that especially the storage period with cold storage or machine perfusion, warm or cold, may offer an opportunity of repair by endothelial or perfusion solution modulation to improve the long-term transplant outcome. More specifically ischemia reperfusion is studied in renal transplants in small and large animal models.

Patient and live donor management are important areas for both technical and psychological development. Thus, we have research and developmental programs for management of malignancies after transplantation, clinical islet transplantation, live donor kidney donation and clinical pancreas transplantation.

Members of the group during 2016

Henrik Benoni, MD, PhD student

Alireza Biglarnia, MD, PhD, Associate Professor (until February 2016)

Lars Bäckman, MD, PhD, Associate Professor (until May 2016)

Malin Dackborn, Research Nurse (until October 2016)

Maria Elofsson, Research Nurse

Aksel Foss, MD PhD (from May 2016)

Pål Foyn Jørgensen, MD PhD (from May 2016)

Janniz Jönsson, MD, PhD student (from December 2016)

Vivian Hellström, MD, PhD (dissertation June 2016)

Anna Högvall, Research Nurse

Tomas Lorant, MD, PhD, Associate Professor, Principal Investigator

Helene Malm, MD, PhD

Amir Sedigh, MD, PhD

Tim Scholz, MD PhD (from May 2016)

Maria Svenaeus Lundgren, Research Nurse

Gunnar Tufveson, MD, PhD, Professor, Principal Investigator (until January 2016)

Shinji Yamamoto, MD, PhD

Bengt von Zur-Mühlen, MD, PhD

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The Kidney Foundation 350,000 SEK

Novartis Sweden (unrestricted grant) 200,000 SEK

Swedish Surgical Society 200,000 SEK

Uppsala University Hospital (ALF) 750,000 SEK

Vinnova 2,000,000 SEK

Disseration 2016

Vivan Hellström. The clinical perspective on malignancies in renal transplanted patients.

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14) Urology

Identification of biomarkers for clinical management of patients with urinary bladder carcinoma

Principal investigator: Per-Uno Malmström

The purpose of this project is to identify a panel of biomarkers that can improve the clinical management of patients with bladder cancer. Their function would be to predict response to specific therapies and also to find new targets for therapy. To achieve this, our specific aims are to;

- Screen a large well categorized biobank consisting of frozen tissue, blood and urine for candidate markers
- Validate these candidates in an independent biobank consisting of formalin fixed tissue from five large prospective randomized trials.
- Incorporate these markers in a prospective evaluation through our international network.
- Translate use of biomarkers to the clinical management

Our lab, headed by Ulrika Segersten PhD, is located in the Rudbeck building facilitating cooperation with preclinical research groups.

External cooperation

We participate in an international study funded by EU/FP7 of gene-signature classifiers (Uromol). This is a prospective trial validating our retrospective results with molecular classifications for the clinical outcome of non-muscle invasive bladder cancer.

Members of the group during 2016

Per-Uno Malmström, Professor

Ulrika Segersten, PhD

Polat Turker, MD

Tammer Hemdan, Specialist

Agencies that support the work/Funding

Cancerfonden 500,000 SEK

Prostate cancer: Epidemiology, Survival and Quality of Life

Principal investigator: Anna Bill-Axelson

SPCG-4 main study: The SPCG-4 randomized study between radical prostatectomy and watchful waiting in localized prostate cancer has been analysed every third year since the first analyses in 2002 regarding differences in risk of overall mortality, prostate cancer mortality and risk of metastases. The first and second analyses were published in NEJM 2002, 2005 and the third in JNCI 2008 and the forth in NEJM 2011. The research group is a collaboration where the first authors Anna Bill-Axelson and Professor Lars Holmberg are from Uppsala University and the PI is from Örebro University. The fifth analysis was

undertaken in 2013 and published in NEJM mars 2014. We collaborate with the British study ProtecT about PSA as a marker for intervention and with Harvard Medical School in a project of biomarkers. The monitoring is on-going and next follow-up will be in 2017.

SPCG-4 Quality of life study: The included men in SPCG-4 have twice been asked to participate in a separate quality of life study. They have been sent a questionnaire with multiple questions concerning urinary, sexually function as well as psychological and quality of life questions. Results from the first round were published in NEJM 2002 and European Urology 2006. We have now collected new data with an extended questionnaire, where the first manuscript has been published concerning hernias in European Urology 2010 and the manuscript concerning long-term symptoms and quality of life after radical prostatectomy versus watchful waiting was published in Lancet Oncology 2011 (Eva Johanssons thesis work with main supervisor Anna Bill-Axelson). Further studies from this material are ongoing.

PcBaSe: Based on the National Prostate Cancer Register (including 98 percent of all prostate cancer cases) and a number of other linked registers. (Anna Bill-Axelson is in the steering committee, Pär Stattin is the PI). PCBaSe enables us to look at uncommon but important consequences of a prostate cancer diagnosis. We have published a number of studies among them we have investigated the risk of androgen deprivation therapy after curative treatment published, in European Journal of Cancer with Ph.D. student Magdalena Lycken as first author. She has also investigated patterns of palliative treatment and possible socio-economic or regional differences; three years before death in prostate cancer. Together with Karl-Johan Lundström we have looked at the incidence of infections following prostate biopsies and different risk factors, published in the Journal of Urology. We have also investigated the risk of small bowel obstruction and abdominal pain after robotic versus open radical prostatectomy and the manuscript is submitted. Eva Johansson is studying functional outcomes in correlation to prescribed drugs for erectile dysfunction published in Journal of sexual medicine and sick leave after radical prostatectomy.

U-Care is an initiative where cancer patients with signs of depression according to HADS score will be randomized between standard care or internet based cognitive therapy.

Low-risk prostate cancer and quality of life: All men diagnosed with low-risk prostate cancer in 2008 were asked to participate in the quality of life study. A study specific questionnaire was sent out in 2015 and in November 2015 we had a 75% response rate. This study is the base for Dr Oskar Bergengren thesis work. In the first study we investigate predictors for high satisfaction with healthcare. We will also investigate predictors for high quality of life and reasons for early stopping in active surveillance.

PSA database Uppsala-Örebro: The linkage of Uppsala-Örebro PSA data from 2005-2015. PSA data has been linked to a number of other databases to investigate patterns of testing for diagnosis, curative treatment and palliative treatment.

SPCG-17. A multi-center randomized study, Scandinavian Prostate Cancer Group nr 17 where we randomize between current practice and standardized triggers for prostate cancer. Today a large proportion of men are diagnosed with low-risk prostate cancer and currently over-treated. The Swedish guidelines for prostate cancer advocate active surveillance for these men (where treatment is postponed until there are signs for tumor progression). However, due to lack of evidence of when tumor progression occurs with evidence based triggers for treatment, a large proportion unnecessarily switch to curative treatment. The study started in October 2016 with Anna Bill-Axelson as study PI.

Eva Johansson is further working with Quality of Life in three large projects, one is a prospective study concerning active surveillance in prostate cancer (SAMS) and the other is a randomized study between surgery and radiotherapy for locally advanced prostate cancer (SPCG-15). The third is as participant in the SPCG-17 QoL-group.

Members of the group during 2016

Anna Bill-Axelson MD, Associate Professor

Eva Johansson, MD, PhD

Magdalena Lycken, MD, PhD student

Oskar Bergengren MD, PhD student

Hans Garmo, statistician

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Swedish Cancer Foundation

Percy Falk foundation

Prostate Cancer foundation

Uppsala University Hospital (ALF)

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Dissertation 2016

Tammer Hemdan. Prognostic and Predictive Factors in Bladder Cancer.

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15) Vascular Surgery

Principal investigator: Anders Wanhainen, Professor

The research group uses several different methods including prospective clinical studies, registry-based research, data-simulation (Markov-analysis), animal experiments, biochemical analyses and complex imaging techniques. The PhD projects normally include several different scientific methods. The activity of the research group is high, illustrated by the list of publications. The most important research projects focus on aneurysmal disease.

Aneurysmal disease, in particular abdominal aortic aneurysm (AAA)

1) Etiology/pathogenesis with multiple translational research projects that are implemented in collaboration with other research groups. They are focused on inflammation (studied with PET/CT, MRI and PET/MRI imaging), SNP analyses, infectious agents, micro RNA, long non-coding RNA and possible auto-immune reactions. A population-based blood- and tissue-bank has been created, as well as a blood-bank from patients with multiple aneurysms. One project focus on women with AAA, others on circulating vascular basement membrane fragments and metabolomics, related to aneurysm growth. The research group has organized an investigator driven multicentre randomized controlled trial, studying if growth of AAA can be inhibited by the platelet inhibitor ticagrelor, which is sponsored by AstraZeneca.

2) Prevention by screening, where the role of Uppsala as pioneer in Sweden is exploited in various projects. Three PhD students and one post-doc are engaged in evaluating different aspects of the screening program. The prevalence of, and risk factors for, the disease in different risk groups are being studied in a multicentre collaboration. The cost-effectiveness of different screening strategies is evaluated. Methodological aspects of ultrasound measurement are studied as well as the importance of the definition of AAA. One project focuses on screening women and another project on how to help patients with small AAA to stop smoking. The issue of how to invite 65 year old men to screening in a balanced and objective way, to facilitate an informed consent to participate or not in screening, is studied with qualitative research methodology.

3) Improvement of treatment results including methods how to prevent and treat the abdominal compartment syndrome and intestinal ischemia, and evaluating new endovascular and hybrid operative techniques. The group is involved in several projects related to the dynamic endovascular development within vascular surgery, including treatment of diseases of the thoracic aorta, and infected aneurysms. Uppsala is one of few European hospitals that can perform total endovascular repair of the entire aorta, from the ostiae of the coronary arteries to the bifurcation. Many clinical research projects are developed in collaboration with other major centres in Europe and in the USA. Epidemiological studies on treatment of AAA include international comparisons through registries. Kevin Mani is chairing the Vascunet collaboration (12 registries in Europe, Australia and New Zeeland) and Martin Björck is part of the International Consortium of Vascular Registries (also including USA and Japan).

There most important international collaborators are: Hamburg, Nürnberg, Zürich, London, Oxford, Leicester, Lisbon, Paris, Tarttu, Helsinki, and Rotterdam. Anders Wanhainen is co-chairing a working group revising evidence-based international Guidelines on AAA, under the auspice of the European Society of Vascular Surgery. Martin Björck is president in that same society.

Peripheral arterial occlusive disease

4) Several projects focusing on carotid artery stenosis, and surgery to prevent stroke, are under evolution. One project studies population based screening of carotid artery stenosis in 65-year old men, profiting from the screening organization for AAA, another focuses on the importance of contra-lateral occlusion when

operating on patients with carotid artery stenosis, and a third one analyses symptoms occurring between a qualifying symptoms and surgery. The possible association between asymptomatic carotid artery stenosis and later development of dementia is explored in a large database created by a previous international multi-center RCT.

5) Intestinal ischemia is studied with both epidemiological and translational methodology. Martin Björck is chairing a working group developing evidence-based international Guidelines on Mesenteric vessel diseases, under the auspice of the European Society of Vascular Surgery, and participates in the development of similar guidelines developed by the Society for Vascular Surgery (USA).

6) Iatrogenic vascular injuries are studied in different registries with the aim of defining preventive strategies, and in collaboration with the orthopedic department popliteal artery injuries after both elective orthopedic surgery and knee trauma are studied.

7) Lower extremity arterial occlusive disease and popliteal artery aneurysm is studied in different projects. New imaging techniques (in particular CT angiography with direct puncture of the artery) to improve treatment of especially patients with diabetic foot ulcer are tested. New endovascular treatment modalities for lower extremity ischemia are evaluated.

Members of the group during 2016

Principal investigator

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Kim Gunnarsson, Gävle
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Hamid Gavali, Uppsala
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External PhD students (to whom senior members of the research group are co-tutors)

Sofia Bohlin, Surgical Nursing, Uppsala
Magnus Jonsson, Vascular Surgery, SÖS, Stockholm
Mari Holsti, Vascular Surgery, Umeå
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Heart and Lung Foundation: 200,000SEK/year 2014-2017
AstraZeneca: 4,900,000 SEK, sponsored RCT on ticagrelor and AAA
Konung Gustaf V's och Drottning Victorias Frimurarestiftelse: 200,000 SEK/year 2014-2017

Disseration 2016

Karl Sörelius. Aortic infections: The Nadir of Vascular Surgery.

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New PhDs

Surgery

Tobias Åkerström	7/5 2016	Endocrine Surgery
Fatemeh Jabbari	20/5 2016	Plastic Surgery
Maria Annerbo	2/6 2016	Endocrine Surgery
Karl Sörelius	22/10 2016	Vascular Surgery

Anesthesia

Henrik Oliveiro-Reinius	12/2 2016	Anesthesiology
Joakim Engström	22/4 2016	Anesthesiology
Jaime Retamal Montes	6/9 2016	Anesthesiology
Ewa Söderberg	28/10 2016	Anesthesiology
Staffan Höstman	2/12 2016	Anesthesiology
Moritz Kretzschmar	8/12 2016	Anesthesiology

Orthopedics

Karin Bernhoff	23/9 2016	Orthopedics

Radiology

Catrin von Below	30/9 2016	Radiology
Johannes Finnsson	22/11 2016	Radiology
David Fällmar	7/12 2016	Radiology

Oral and Maxillofacial Surgery

Miranda Jalouli	18/3 2016	Oral and Maxillofacial Surgery
Kristina Edman	27/4 2016	Oral and Maxillofacial Surgery

Oto-, rhino- laryngology and Head & Neck

Karin Lundin	15/4 2016	Oto-, rhino- laryngology and Head & Neck Surgery
Fredrik Edin	28/4 2016	Oto-, rhino- laryngology and Head & Neck Surgery

Thorax Surgery

Vilyam Melki	15/9 2016	Thoracic Surgery

Transplantation Surgery

Vivan Hellström	4/6 2016	Transplantation Surgery

Urology

Tammer Hemdan	30/5 2016	Urology

Undergraduate Teaching

A list of programs at the Department of Surgical Sciences can be seen below.

- Speech and Language Pathology Programme (Logopedprogrammet) 240 c
- Medicine Programme (Läkarprogrammet) 330 c
- Physiotherapy Programme (Fysioterapeutprogrammet) 330 c
- Radiography Programme (Röntgensjuksköterskeprogrammet), 180 c
- Specialist Care in Nursing (Specialistsjuksköterskeprogrammet) 60c
- Emergency Medicine (Akutsjukvård) SAKU 60 c
- Ambulance Care/ Pre-hospital Emergency Care (Ambulanssjukvård) SAMB 60 c
- Specialist Nursing Programme Anaesthesia Care (Anestesisjukvård) SANE 60 c
- Specialist Nursing Programme Intensive Care (Intensivvård) SINT 60 c
- Specialist Nursing Programme Surgical Care (Kirurgisk vård) SKIR 60 c
- Specialist Nursing Programme Theatre Care (Operationssjukvård) SOPE 60 c

Centres and Facilities

Hedenstierna Laboratory

The Hedenstierna laboratory is a university core facility for large animal experimental research. The main users are researchers from the departments of anesthesiology and intensive care, infectious diseases, cardiothoracic surgery, vascular surgery, clinical physiology and the medical technical industry, as well as SLU, the Swedish university of agricultural sciences. The laboratory staff consists of four full time laboratory technicians/engineers and one director. About 250 large animal studies are performed in the laboratory each year contributing to about 40 scientific articles, mainly within the fields of respiratory physiology and infectious disease. The laboratory is recognized both nationally and internationally and attracts many foreign scientists; at present researchers from Germany, Spain, Italy, Brazil, Chile and Japan are working in the laboratory. The economic turnover is approximately four million SEK/year. The laboratory is financed by contributions from Uppsala University and via grants to the researchers, from the Swedish Research Council and the Swedish Heart and Lung Foundation.

Awards and Appointments 2016

Anne Garland

First prize winner, oral presentation

International Congress of Arthroplasty Registries Manchester 2016

"Early mortality and morbidity after total hip arthroplasty in patients with femoral neck fracture"

List of Authors

For lists of Authors, se each research group.